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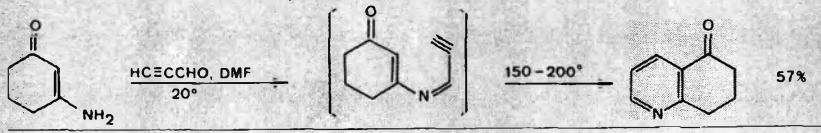
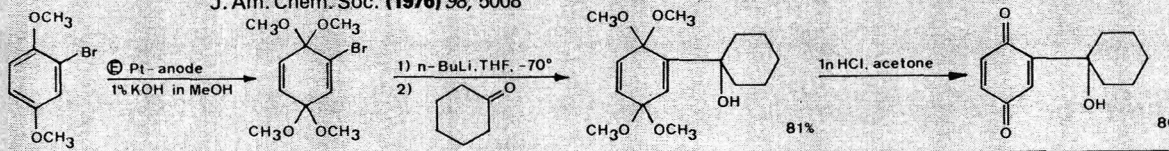
07625 **3-Amino-2-cyclohexen-1-one purum** >98%(NT); MP 134-135°
$CH_2CH_2CH_2C(NH_2):CHCO$ C_6H_9NO MW 111.15
5 g sFr. 29.– US$ 14.50
25 g sFr. 120.– US$ 60.00

Versatile enamine; e.g. for the preparation of quinoline derivatives: F. Zymalkowski, J. Rimek, Arch. Pharm. **(1961)** *294,* 759



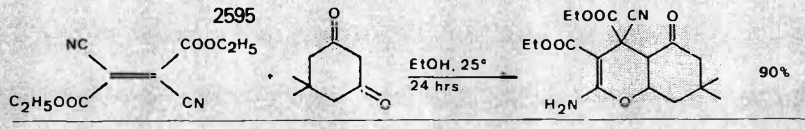
16910 **2-Bromo-1,4-dimethoxy-benzene purum** $BP_{0.3}$80°; n_D^{20} 1.5712
$BrC_6H_3(OCH_3)_2$ $C_8H_9BrO_2$ MW 217.08
1 lt ≈ 1.05 kg
5 ml sFr. 34.– US$ 17.00
25 ml sFr. 145.– US$ 72.50

An "Umpolung" reagent for quinones: M.J. Manning, P.W. Reynolds, J.S. Swenton, J. Am. Chem. Soc. **(1976)** *98,* 5008



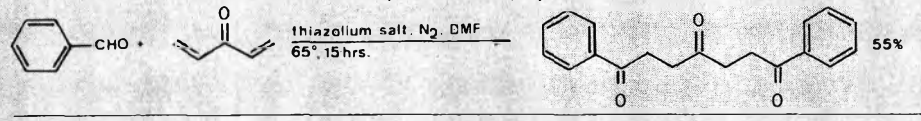
36610 **Diethyl 2,3-dicyano-2-butenedioate purum** MP 116-117°
$C_2H_5OCOC(CN):C(CN)COOC_2H_5$ $C_{10}H_{10}N_2O_4$ MW 222.20
10 g sFr. 22.– US$ 11.00
50 g sFr. 90.– US$ 45.00

A versatile electrophilic olefin: Z. Rappoport, D. Ladkani, J. Chem. Soc. Perkin I **(1974)** 2595



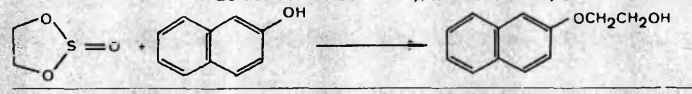
40697 **3,4-Dimethyl-5-(2-hydroxyethyl)thiazolium iodide purum** >98%(I); MP 87-88°
$C(CH_3):C(CH_2CH_2OH)SCH:NCH_3(I)$ $C_7H_{12}INOS$ MW 285.10
10 g sFr. 15.– US$ 7.50
50 g sFr. 63.– US$ 31.50

Catalyst for the addition of aromatic and heterocyclic aldehydes to α,β-unsaturated ketones (e.g. divinylketone, dibenzylideneacetone, difurfurylideneacetone). Syntheses of tri- and polyketones: H. Stetter, W. Basse, H. Kuhlmann, A. Landscheidt, W. Schlenker, Chem. Ber. **(1977)** *110,* 1007; preparation of unsymmetrical acyloins and α-diketones: H. Stetter, G. Dämbkes, Synthesis **(1977)** 403



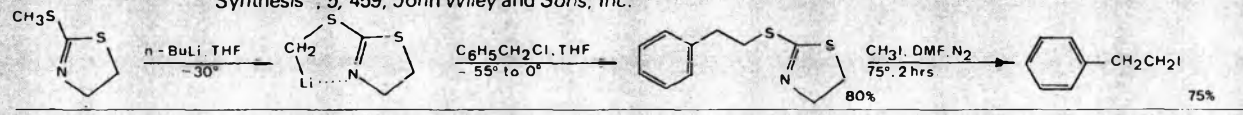
03920 **Ethylene sulfite purum** >98%(GLC); BP_{20}71-72° (Glycol sulfite)
OCH_2CH_2OSO $C_2H_4O_3S$ MW 108.12
1 lt ≈ 1.43 kg
100 ml sFr. 18.– US$ 9.00
500 ml sFr. 75.– US$ 37.50

Versatile intermediate; reagent for the hydroxyethylation of phenols and carboxylic acids: W.W. Carlsson, L.H. Cretcher, J. Am. Chem. Soc. **(1947)** *69,* 1952



67830 **2-Methylthio-2-thiazoline purum** ~97%(GLC); n_D^{20} 1.5925
$CH_2CH_2SC(SCH_3):N$ $C_4H_7NS_2$ MW 133.24
1 lt ≈ 1.23 kg
10 ml sFr. 15.– US$ 7.50
50 ml sFr. 63.– US$ 31.50

Reagent for the iodomethylation of alkyl halides: K. Hirai, Y. Kishida, Tetrahedron Lett. **(1972)** 2743; Org. Synth. **(1976)** *56,* 77; L. Fieser, M. Fieser, "Reagents for Organic Synthesis", *5,* 459, John Wiley and Sons, Inc.



90275 **1-Triacontanol purum** MP 86-87°
$CH_3(CH_2)_{29}OH$ $C_{30}H_{62}O$ MW 438.80
100 mg sFr. 18.– US$ 9.00
1 g sFr. 145.– US$ 72.50

A new naturally occuring plant growth regulator: S.K. Ries et al., Science **(1977)** *195,* 1339, and ref. cited therein

23259 **2,2,2-Trichloro-tert-butyl chloroformate, TCBOC puriss.** >99%(Cl); MP 32-34°
$ClCOOC(CH_3)_2CCl_3$ $C_5H_6Cl_4O_2$ MW 239.91
10 g sFr. 22.– US$ 11.00
50 g sFr. 90.– US$ 45.00

For the introduction of the TCBOC-amino-protection which is stable towards basic and acidic conditions but cleaved by "super-nucleophiles" or by zinc in acetic acid: H. Eckert, M. Listl and I. Ugi, Angew. Chem. **(1978)** *90,* 388

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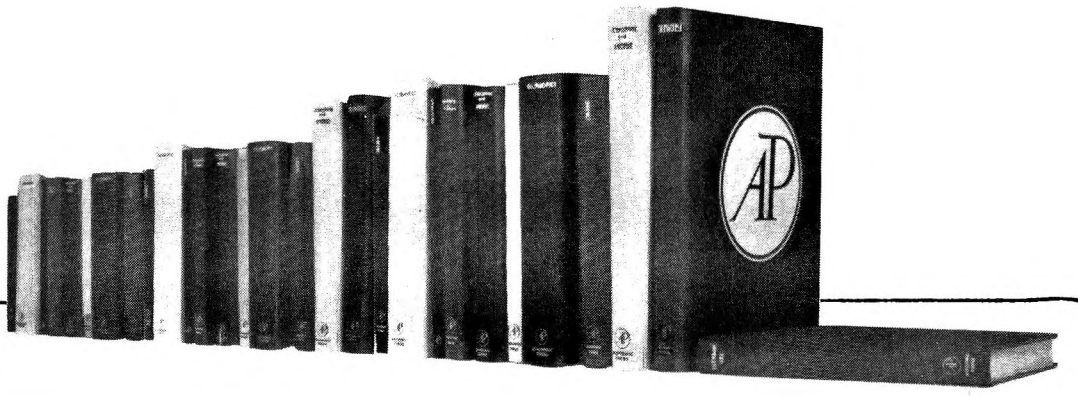

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Chemical Evolution. 31. Mechanism of the Condensation of Cyanide to HCN Oligomers[1]

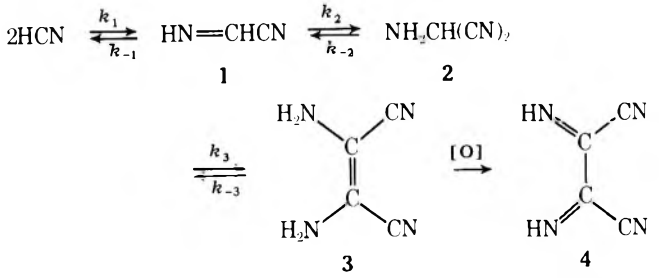
J. P. Ferris* and E. H. Edelson[2]

Contribution from the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

Received July 5, 1978

Diaminomaleonitrile undergoes a rapid Ni(II)-catalyzed or a much slower uncatalyzed decomposition to yield 2 equiv of cyanide. This is not an equilibration between diaminomaleonitrile and the dimer and trimer of HCN as shown by the absence of incorporation of $H^{13}CN$ when incubated with diaminomaleonitrile. The formation of urea and oxalic acid is enhanced and the steady-state concentration of diaminomaleonitrile is decreased when the oligomerization of HCN is performed in the presence of oxygen as compared to a pure nitrogen atmosphere. Small but significant yields of oxalic acid and urea were observed when oxygen was eliminated from the reaction solution. An oligomerization pathway is proposed which is consistent with these data. These findings are not consistent with the proposal that HCN condenses to heteropolypeptides via azacyclopropenylidene imine.

Hydrogen cyanide oligomers are believed to have had a significant role in the prebiotic synthesis of purines, pyrimidines, and amino acids.[1,3] HCN condenses in a stepwise fashion to the dimer **1**, trimer **2**, and tetramer **3**. It was postulated that one or more of these simple HCN derivatives condenses further to yield HCN oligomers, a complex mixture of substances with a molecular weight of 500–1000. Purines, pyrimidines, and amino acids are released on hydrolysis of these oligomers. The oligomerization reaction is dependent only on the pH of the reaction mixture and is independent of added nucleophile.[4] Urea and oxalic acid are also products of the oligomerization reaction. An investigation of the mechanism of formation of the oligomers was undertaken because these substances may have had a central role in the formation of biomolecules on the primitive earth.



Results and Discussion

The Proposed Equilibrium between Diaminomaleonitrile (3) and Aminomalononitrile (2). We proposed previously that the monomer, dimer (**1**), trimer (**2**), and tetramer (**3**) of HCN readily equilibrate in aqueous solution.[4] The formation of a precipitate of AgCN when Ag^+ is added to an aqueous solution of **3** provided support for this hypothesis.[5] The observation that diaminomaleonitrile releases cyanide rapidly when treated with Ni^{2+} in NH_4OH solution, a method for the determination of cyanide ion, prompted a reinvestigation of the equilibrium proposed between **1**, **2**, and **3**. The catalyzed decomposition of diaminomaleonitrile requires the presence of both Ni^{2+} and NH_3 if it is to proceed at a rapid rate. Approximately 2 equiv of cyanide are released per mole of diaminomaleonitrile. If diaminomaleonitrile is in equilibrium with HCN, 4 equiv of cyanide would be detected as the $Ni(CN)_4^{2-}$ complex. The same yield of cyanide is obtained when the hydrolysis proceeds 4×10^{-3} times slower in the absence of Ni^{2+}. The similar yields of HCN in the catalyzed and uncatalyzed reactions suggest that overall decomposition pathways are the same in both reactions.

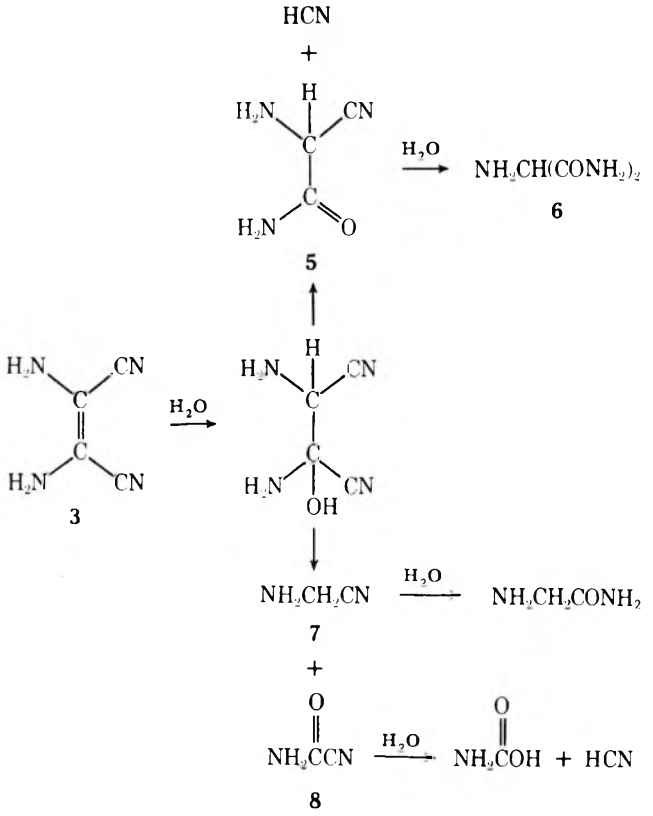
The mechanisms of both the Ni^{2+}-catalyzed and -uncatalyzed decomposition of diaminomaleonitrile are unclear. Hydrolysis of **3** yields either the monoamide of the aminomalononitrile (**5**) and 1 equiv of cyanide or aminoacetonitrile (**7**) and the monoamide of cyanogen (**8**). The monoamide of cyanogen may cleave as does cyanogen to yield 1 equiv of cyanide; however, it appears unlikely that a second equivalent of cyanide will be formed by either reaction pathway. The monoamide of aminomalonitrile is known to hydrolyze to the diamide **6**, and it does not eliminate cyanide.[6] Further work is required to determine the pathway for the decomposition of **3**; however, it is not the stepwise dissociation of **3** to give 4 equiv of HCN. The isotope exchange studies given below eliminate the possibility of the dissociation of **3** to **1** and 2 equiv of HCN.

The proposed equilibrium between cyanide and the dimer, trimer, and tetramer was investigated further by isotope exchange, a technique which has the advantage that the position of the equilibrium is not perturbed as it is by metal ions such as Ag^+ and Ni^{2+}, which form essentially nondissociating cyanide complexes. None of the added $^{13}CN^-$ will condense to

Table I. Reaction of Diaminomaleonitrile and Potassium [^{13}C]Cyanide at pH 7–8

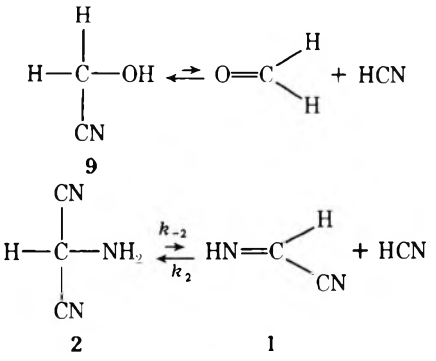
reaction time, days	yield of product, mg	number of scans	area ratio (peak 2/peak 1)[c]	mean ratio ± standard deviation
0[a]		4 000	0.3418	0.3129 ± 0.0743
			0.3967	
			0.2909	
			0.2223	
0.17	246	4 000	0.2417	0.3425 ± 0.0968
			0.3510	
			0.4347	
1.0	230	4 000	0.4223	0.3205 ± 0.0709
			0.3251	
			0.2338	
			0.3007	
4.0	210	6 000	0.3500	0.2857 ± 0.0511
		7 000	0.2329	
		8 000	0.2594	
		8 000	0.3006	
10.0	173.2	10 000	0.3478	0.3666 ± 0.0702
		10 000	0.4426	
		10 000	0.2788	
		20 000	0.3973	
31.0	53.4	20 000	0.7861[b]	

[a]Control solution: 250 mg of diaminomaleonitrile in 2 mL of dimethyl-d_6 sulfoxide. [b]After 31 days, the concentration of diaminomaleonitrile was too low to obtain reliable data. With 20 000 scans, the signal/noise ratio was less than 2. [c]Mean shifts: peak 1, 117.80 ppm; peak 2, 106.90 ppm.



form [^{13}C]diaminomaleonitrile if the $^{13}CN^-$ concentration is less than 0.01 M.[6] The exchange of $^{13}CN^-$ with diaminomaleonitrile was monitored by ^{13}C NMR. Diaminomaleonitrile exhibits two peaks at 106.49 and 117.71 ppm when its ^{13}C NMR spectrum is determined in dimethyl sulfoxide solution. If the proposed equilibrium between the trimer and tetramer exists, then the addition of $^{13}CN^-$ to an aqueous solution of diaminomaleonitrile should result in an increase in the relative intensity of the ^{13}C NMR signal at 117.71 ppm due to the nitrile carbons of diaminomaleonitrile.[7,8] If the equilibrium resulted in appreciable concentrations of the dimer and trimer, then a proportional increase in intensity would be expected in both the nitrile and olefin ^{13}C NMR signals.

When the cyanide exchange experiment was performed in aqueous solution at pH 7 and 9.2 using <0.004 M $^{13}CN^-$, no $^{13}CN^-$ incorporation was observed over a 1- and 3-day time period, respectively, as evidenced by the lack of change of the nitrile/olefin intensity ratios (Tables I and II). These data demonstrate that the equilibrium for the formation of diaminomaleonitrile from aminomalononitrile is so strongly shifted to the side of tetramer in aqueous solution that it is essentially irreversible; i.e., the rate of the reverse reaction (k_{-3}) is very small compared to the rate of the forward reaction (k_3). This conclusion is consistent with the observation that aminomalononitrile (2) reacts rapidly with HCN to yield diaminomaleonitrile.[9] It was estimated that there is a steady-state concentration of 10^{-5}–10^{-6} M aminomalononitrile in the presence of 1 M cyanide.[6,9] One might argue that significant amounts of 1 might be present if it were as stable as 3. But several lines of evidence suggest that k_2 is much greater than k_{-2}. The equilibrium constant for the dissociation of glyconitrile (9) to formaldehyde and HCN has been measured, and



it is far on the side of the glyconitrile as shown by the equilibrium constant of 2.1×10^{-6} at 25 °C.[10] This reaction is analogous to the dissociation of aminomalononitrile to iminoacetonitrile; the two reactions would be expected to have similar equilibrium constants. Furthermore, the facile conversion of N-substituted iminoacetonitrile derivatives to N-substituted derivatives of diaminomaleonitrile, a reaction which presumably takes place via the aminomalononitrile derivative, provides added support for k_2 being greater than

Table II. Reaction of Diaminomaleonitrile and Potassium [^{13}C]Cyanide at pH 9.2

reaction time, days	yield of production, mg/mL	number of scans	area ratio (peak 2/peak 1)[c]	mean ratio ± standard deviation
0[a]		1 500	0.2907	0.3787 ± 0.0717
		2 000	0.4530	
		3 000	0.3800	
		4 000	0.3250	
		5 000	0.4450	
0.5	0.9662	5 000	0.2541	0.3711 ± 0.0701
		7 000	0.4415	
		7 500	0.3974	
		8 000	0.3750	
		20 000	0.3878	
3.0	0.3900	15 000	0.3423	0.3578 ± 0.0718
		15 280	0.4472	
		18 000	0.3983	
		25 730	0.3465	
		50 000	0.2547	
10.0[b]	0.0306			

[a]Control solution: 400 mg of diaminomaleonitrile in 2 mL of dimethyl-d_6 sulfoxide. [b]The concentration of diaminomaleonitrile was insufficient to obtain a spectrum. [c]Mean shifts: peak 1, 117.80 ppm; peak 2, 106.90 ppm.

Table III. ^{13}C NMR Study of the Reaction of Diaminomaleonitrile and Potassium [^{13}C]Cyanide in Dimethyl Sulfoxide

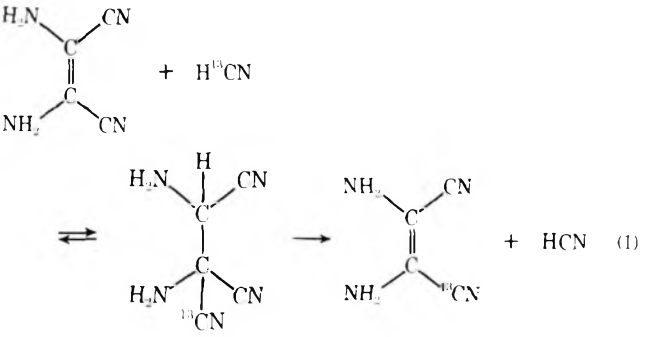
reaction time, days	relative peak area			area ratio (peak 1/peak 2)
	peak 1[a]	peak 2[b]	peak 3[c]	
0[d]	1.18	2.30		0.512
0.67[e]	4.94	4.25	14.26	1.162
1.83[e,f]	7.33	4.71	9.22	1.554
2.67[e,f]	6.40	3.35	5.70	1.910
3.67[e,f]	7.34	4.19	6.07	1.749
10.0	2.56	1.23	7.60	2.151

[a]Average shift, 117.20 ppm. [b]Average shift, 106.50 ppm. [c]Average shift, 158.20 ppm (CN^-). [d]Control solution: 500 mg of diaminomaleonitrile in 2 mL of dimethyl-d_6 sulfoxide. [e]Additional small peak at 145.50–145.79 ppm. [f]Additional small peak at 161.75–161.90 ppm.

k_{-2}.[11,12] Finally, molecular orbital calculations predict that iminoacetonitrile should be more susceptible to a nucleophilic attack than either aminomalononitrile or diaminomaleonitrile.[13] Since we have shown that k_3 is much greater than k_{-3}, it follows from these calculations, as well as from the experimental observations cited above, that k_2 is much greater than k_{-2}.

We conclude from this study that the steady-state concentration of the *dimer and trimer* of hydrogen cyanide is exceedingly low in dilute aqueous solution. This conclusion is supported by the reported inability to isolate the dimer or trimer from an oligomerizing hydrogen cyanide solution.[6] Diaminomaleonitrile is the predominant species present when cyanide is added to either the dimer or trimer. Consequently, the formation of the HCN oligomers must be via the reaction of diaminomaleonitrile with HCN or less likely by the condensation of two or more diaminomaleonitrile moieties and not via reactions involving the dimer or trimer. This conclusion is supported by the observation that the products released on hydrolysis of HCN oligomers appear to be formed by the condensation of diaminomaleonitrile or its trans isomer with cyanide.[1,3]

We did observe exchange of $^{13}CN^-$ with diaminomaleonitrile in dimethyl sulfoxide solution (Table III). The signal at 117 ppm intensified 2-fold after 16 h and 3–4-fold after 30 days relative to the signal at 106 ppm. This change in peak intensities corresponds to an extent of exchange which is 67% of complete exchange. At the same time, the $^{13}CN^-$ signal at 158 ppm decreased in intensity. The equilibrium between **2** and **3** may be shifted toward **2** in this solvent. On the other hand, these findings may reflect the greater nucleophilicity of cyanide in dimethyl sulfoxide.[14,15] The exchange may proceed via the Michael addition–elimination pathway shown in eq 1 rather than by the dissociation of diaminomaleonitrile.



(1)

The Effect of Oxygen on the Oligomerization of HCN. It was reported by Volker[16] that oxygen has no effect on the oligomerization of hydrogen cyanide. The observation that diaminomaleonitrile is readily air-oxidized[17] prompted a reinvestigation of the oligomerization reaction in the absence of oxygen. It was essential to determine if the cyanide oligomerization proceeds in the absence of oxygen because it is generally agreed that there was little or no molecular oxygen on the primitive earth.[18]

The effect of molecular oxygen was investigated by comparing the loss of cyanide, the formation of urea, and the formation of diaminomaleonitrile in the following 0.1 M cyanide solutions: (1) no precautions were taken to remove air from the solution; (2) the solution was degassed by a freeze–pump–thaw procedure followed by the addition of sufficient nitrogen to give atmospheric pressure in the reaction vessel; (3) the solution was purged with molecular oxygen. The oligomerization reactions were periodically sampled and analyzed over a 6-month period.

The yield of urea was found to be significantly greater in the oxygenated solutions (Figure 1). This is attributed to the oxidation of diaminomaleonitrile to diiminosuccinonitrile (**4**), a compound which is rapidly hydrolyzed to urea by dilute NH_4OH.[17] The observation that the amounts of diaminomaleonitrile are significantly less in the presence of molecular oxygen (Figure 2) is consistent with the above result. The

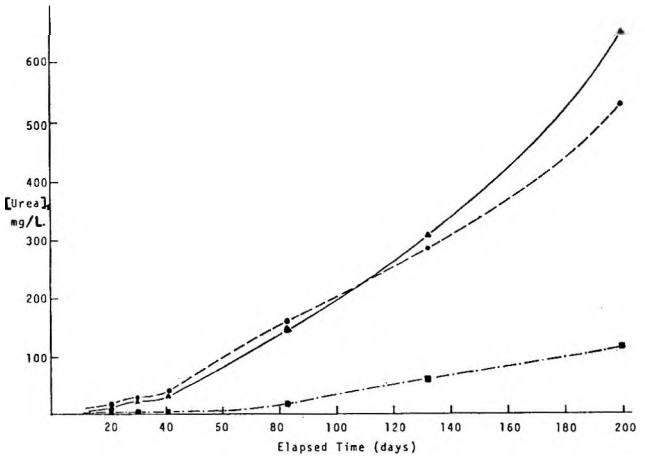


Figure 1. Effect of oxygen on urea formation in HCN oligomerization solutions: solution 1 (control), –▲–; solution 2 (degassed), –■–; solution 3 (oxygenated), –●–.

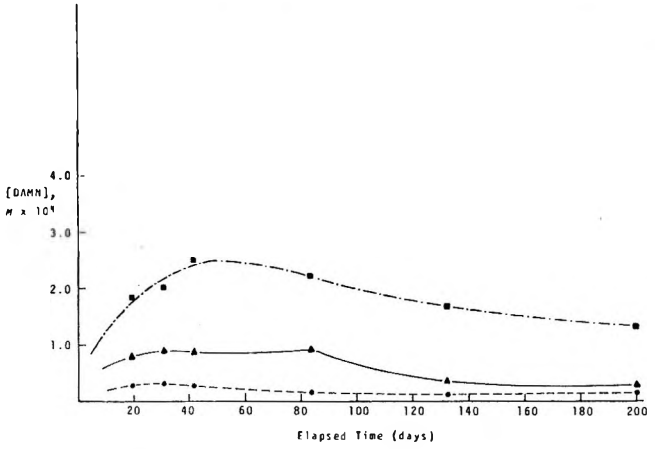


Figure 2. Effect of oxygen on diaminomaleonitrile concentration in HCN oligomerization solutions: solution 1 (control), –▲–; solution 2 (degassed), –■–; solution 3 (oxygenated), –●–.

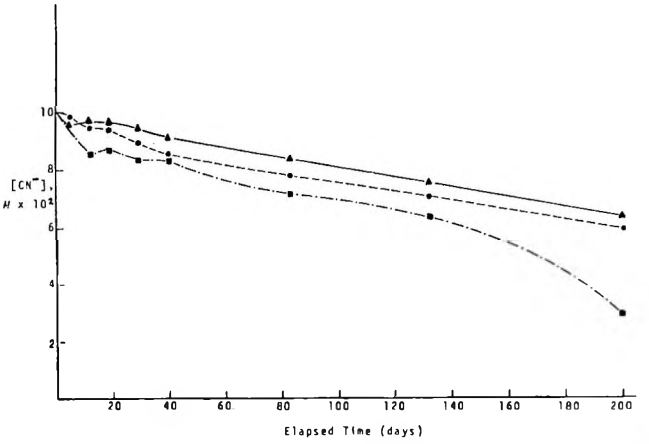


Figure 3. Effect of oxygen on cyanide concentration in HCN oligomerization solutions: solution 1 (control), –▲–; solution 2 (degassed), –■–; solution 3 (oxygenated), –●–.

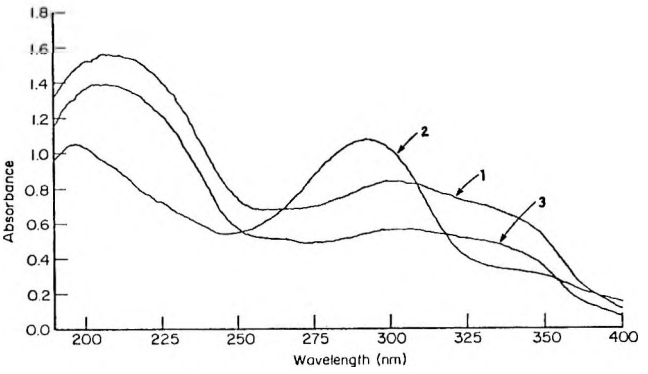


Figure 4. Ultraviolet spectra of the HCN oligomerization mixture after 83 days: (1) solution 1 (control); (2) solution 2 (degassed); (3) solution 3 (oxygenated). Samples were diluted 5× from original concentrations.

principal effect of molecular oxygen is apparently the oxidation of diaminomaleonitrile since the rate of oligomerization of HCN, as monitored by the loss of cyanide, was not significantly different in the absence or presence of oxygen in the early stages of the reaction (Figure 3). The previously reported difference in rate may reflect the differences observed here near the end of the oligomerization.[17]

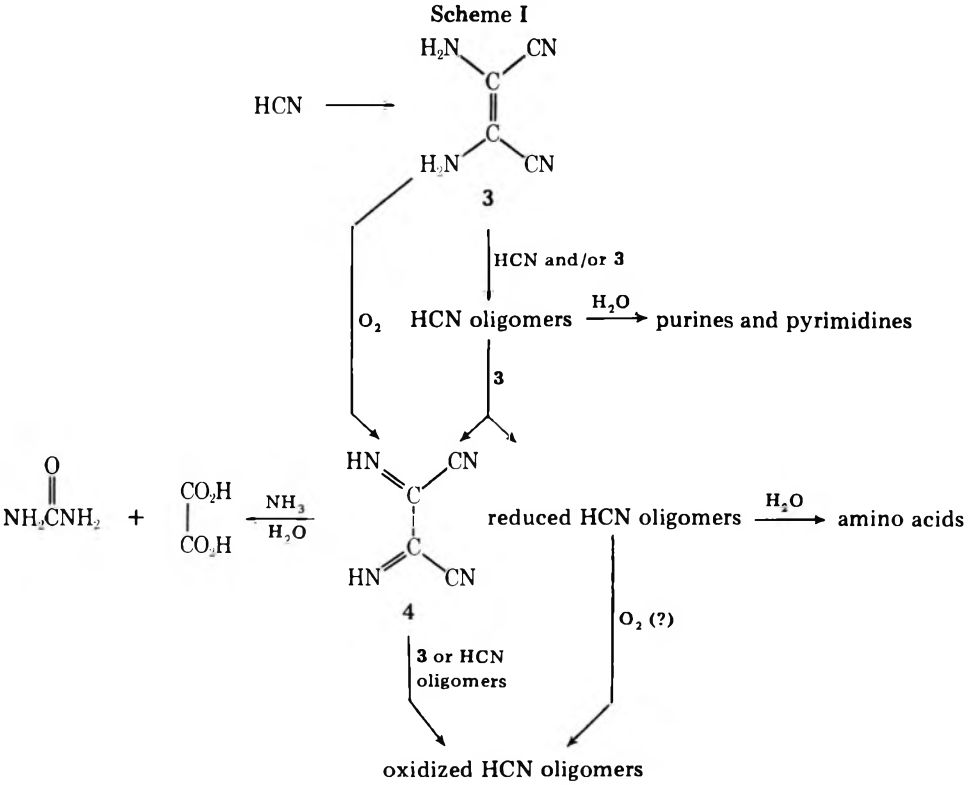
It is significant that urea is formed in the absence of oxygen. This result demonstrates that oxidation reactions are a normal part of the oligomerization reactions in the absence of oxygen. Consistent with this conclusion is the detection in the HCN oligomer hydrolysate of the amino acids glycine, diaminosuccinic acid, aspartic acid, and alanine. A reduction step is required to account for the formation of alanine, diaminosuccinic acid, or aspartic acid from HCN or HCN oligomers such as diaminomaleonitrile.[1,19] The urea may be formed by the oxidation of **3** to **4** by other HCN oligomers. Hydrolysis of **4** yields urea while the hydrolysis of the reduced oligomers yields amino acids. We cannot eliminate the possibility that urea is formed from cyanogen, which is produced by the oxidation of cyanide with aminomalononitrile,[4] but we think that the oxidation of **3** to **4** has more literature precedent.[17]

The ultraviolet spectra of the oligomerization mixtures formed in the absence of oxygen are much simpler than the spectra of those oligomers formed with molecular oxygen present (Figure 4). This suggests that the presence of oxygen may result in the oxidation of the oligomers or their precursors. This is probably a partial oxidation since the general shape of the UV curves is the same; only the intensity of the absorption differs.

Oxalic acid is formed in large amounts during the oligomerization of HCN in the presence of oxygen.[17,20] Since the conversion of hydrogen cyanide to oxalic acid requires an oxidative reaction, the role of oxygen in this oxidation was investigated by measuring the yield of oxalic acid released by hydrolysis of HCN oligomers which had been prepared in the absence of molecular oxygen.[1] The yield of oxalic acid formed by acid hydrolysis was 8.1 mg/L (3% of the HCN oligomer) from the oligomers prepared in a nitrogen atmosphere and 85 mg/L from the oligomers prepared in the presence of molecular oxygen. This dramatic increase in yield demonstrates that molecular oxygen is directly involved in the oxidation of HCN oligomers or a precursor to them. Since it is known that diiminosuccinonitrile (**4**) yields oxalic acid on hydrolysis,[21] compound **4** is the most likely source of free oxalic acid in the oligomerization mixture. The oxalic acid released on hydrolysis is probably formed from **4**, or related structures at the same oxidation state, which became incorporated into the HCN oligomers. The previously discussed differences observed in the ultraviolet spectra of the oligomerization mixtures formed in the presence and absence of oxygen probably reflect a greater percentage of incorporation of these more highly oxidized units when oxygen is present.

The hydrolytic release of oxalic acid from oligomers prepared in a nitrogen atmosphere is further evidence that redox reactions are taking place in the HCN oligomerization reaction. Both the formation of urea and oxalic acid probably

Scheme I



proceed by the oxidation of diaminomaleonitrile (3) to diiminosuccinonitrile (4), which in turn either undergoes hydrolysis to oxalic acid and urea or is incorporated into the HCN oligomers (Scheme I). Of particular interest is the absence of urea on hydrolysis of the HCN oligomers, although it is found in the oligomerization mixture. Ammonia is required for the formation of urea from 4 or its derivatives.[17] Ammonia is present in the oligomerization mixture, but none is used for the hydrolysis of the HCN oligomers. The absence of urea as a hydrolysis product is consistent with the proposed oxidative formation of 4 in the HCN oligomerization. After compound 4 is formed, it either reacts with water or NH_3 to yield simpler hydrolytic products or with other organic compounds to yield HCN oligomers.

Conclusions

The chemical transformations which may take place during HCN oligomerization are summarized in Scheme I. HCN undergoes a rapid, essentially irreversible, condensation to diaminomaleonitrile, which in turn condenses with additional HCN or possibly other diaminomaleonitrile units to give HCN oligomers. Redox reactions take place during the oligomerization to yield reduced HCN oligomers and diiminosuccinonitrile. The diiminosuccinonitrile either hydrolyzes to urea and oxalic acid or reacts with diaminomaleonitrile[22] or HCN oligomers to give oxidized HCN oligomers. Although the oxidized and reduced HCN oliglomers are shown as separate entities in Scheme I, there is no reason to exclude the possibility that there will be both oxidized and reduced units in the same molecule. Diiminosuccinonitrile and the oxidized HCN oligomers may also be formed by oxidation with molecular oxygen.

The amino acids, with the exception of glycine, must be formed by the hydrolyses of reduced oligomers. Glycine may be formed by the hydrolytic cleavage of diaminomaleonitrile[6] or by the hydrolysis of the HCN oligomers. Reduction reactions are not required for the formation of purines or pyrimidines since many of them are at the same oxidation state as HCN. Oxidation by molecular oxygen would be expected to decrease the yields of purines, pyrimidines, and amino acids since they are either at the same oxidation level or at a more reduced state than HCN.

Our findings on the mechanism of HCN oligomerization are not consistent with Matthew's proposal that azacyclopropenylidene imine, a dimer of HCN, is the monomer unit which condenses to give the HCN oligomers.[23,24] First, it seems unlikely that azacyclopropenylidene imine is formed from HCN since recent calculations suggest that the iminoacetonitrile structure is considerably lower in energy.[25] Furthermore, there must only be a low steady-state concentration of the HCN dimer produced since a dimer has never been detected in the presence of HCN. Such a dimer, be it iminoacetonitrile or azacyclopropenylidene imine, will undergo nucleophilic addition reactions with the large excess of cyanide that is present much more rapidly than it will undergo self-condensation reactions. The addition of cyanide to *N*-alkyl derivatives of iminoacetonitrile, yielding N-substituted diaminomaleonitrile derivatives, has been shown to proceed more rapidly than the oligomerization of *N*-alkyliminoacetonitriles.[11]

A modified version of Matthew's proposed mechanisms,[23] the dissociation of diaminomaleonitrile to a dimeric species which undergoes polymerization, was also ruled out in the present study. In this proposal diaminomaleonitrile would be the thermodynamically stable oligomer, but there would still be sufficient amounts of dimer and trimer in equilibrium with it to permit the polymerization of a portion of the dimer, the remainder being reconverted to diaminomaleonitrile in the equilibration process. The lack of incorporation of $H^{13}CN$ in diaminomaleonitrile demonstrates the absence of the equilibrium and eliminates this possibility.

Diaminomaleonitrile, and not the HCN dimer, must be the direct precursor to the HCN oligomers. This work establishes that the formation of diaminomaleonitrile from the HCN dimer and trimer is essentially irreversible. Support for this conclusion is the observation that the structures of the hydrolysis products of the HCN oligomers, glycine, diaminosuccinic acid, aspartic acid, 4,5-dihydroxypyrimidine, and oxalic acid, are readily understood if it is assumed that they are derived from diaminomaleonitrile structural units in the HCN oligomers.[1,3]

Table IV. Reaction of Diaminomaleonitrile with Ni(II) and NH_4OH[a]

reaction time, min	absorbance × 100 (corrected[b])
0	129
1.70	104.4
3.15	89.1
4.33	76.8
5.63	65.6
7.87	51.2
10.13	39.5
12.87	29.75
17.30	18.00
23.33	9.3
42.13	1.6
121.25	0
∞	0

[a] [Diaminomaleonitrile] = 10^{-4} M, [$NiCl_2$] = 9×10^{-4} M, and [NH_4OH] = 0.45 M. [b] Absorbance corrected as discussed in the text.

Experimental Section

General Procedures.[26] Ultraviolet and visible spectra were recorded on a Unicam SP800A spectrophotometer. Carbon-13 NMR spectra were obtained on a Bruker WP-60 spectrometer. Analytical thin-layer chromatography (TLC) was performed on silica gel plates containing a fluorescent indicator (Eastman Chromagram no. 13181), and the compounds were visualized under UV light or with specific color tests. Diaminomaleonitrile (Aldrich) was purified by recrystallizing three times from warm (65 °C) water using a small amount of decolorizing charcoal. Cyanide analyses were performed by silver nitrate titration,[27] the UV absorption of the tetracyanonickelate(II) complex,[28] and the methods of Schilt[29] and Bark and Higson.[30] Urea was analyzed by the procedure of Ormsby.[31] $K^{13}CN$ (90% ^{13}C) was lot MZ from Stohler Isotope Chemicals.

Oligomerization of Hydrogen Cyanide. Pure hydrogen cyanide was prepared from sodium cyanide using a modification of the method of Ziegler.[26,32] Dilute aqueous solutions (0.1 N) of HCN were prepared and adjusted to pH 9.2 with dilute NH_4OH. The solutions were stored in stoppered glass bottles in the dark for at least 1 year, and then filtered and fractionated by ion-exchange chromatography.[26] The term HCN oligomer in this paper is used synonomously with the acid and amphoteric oligomer fractions[1,26] unless otherwise noted.

Hydrolysis of Diaminomaleonitrile with $NiCl_2$ and NH_4OH. A 10^{-3} M diaminomaleonitrile solution was prepared, and a 1-mL aliquot was mixed with 9 mL of freshly prepared nickel(II) chloride (10^{-3} M) in 0.5 M NH_4OH.[28] The UV spectrum was recorded using a thermostated cell maintained at 25 °C and a solution with the same concentrations of nickel(II) ion and ammonia in the reference cells. The UV spectrum was scanned repeatedly until the absorbance at 296 nm remained constant. The tetracyanonickelate ion which formed during the reaction also had some absorbance at 296 nm. The absorbance of the diaminomaleonitrile at 296 nm was therefore corrected to account for this residual absorbance due to tetracyanonickelate ion. The resulting data (Table IV) were found to conform to a first-order kinetic plot (k = 0.112 min^{-1}, $t_{1/2}$ = 6 min).

Hydrolysis of Diaminomaleonitrile with NH_4OH. The UV spectrum of a 10^{-4} M solution of diaminomaleonitrile in 0.45 M NH_4OH was monitored for a 3-h period in a cell thermostated at 25 °C. The half-life of 3 was approximately 1 day (Table V).

Longer term hydrolyses at pH 9.2 in which the HCN concentration was followed by the method of Bark and Higson[30] and the diaminomaleonitrile concentration was followed by the UV absorption at 296 nm indicated that 2 equiv of HCN were formed for every equivalent of diaminomaleonitrile which was hydrolyzed. The same cyanide yield was observed when the hydrolyses were performed in distilled water.

Hydrolysis of Diaminomaleonitrile with $NiCl_2$. An aliquot (1 mL) of 10^{-3} M diaminomaleonitrile solution was mixed with 9 mL of 10^{-3} M $NiCl_2$ solution. The UV spectrum of the mixture was monitored for 24 h in a cell thermostated at 25 °C. No change was observed in the absorbance at 296 nm. In a control experiment it was observed, from the absorption maximum at 267 nm, that CN^- reacts quantitatively with $NiCl_2$ to form the tetracyanonickelate complex.

Reaction of Diaminomaleonitrile with $K^{13}CN$ in Aqueous Solution at pH 7–8. Diaminomaleonitrile (1.5 g) and potassium [^{13}C]cyanide (150 mg, 0.0023 mol) were dissolved in 1 L of distilled water. The solution was then divided into five 200-mL portions which were shaken at 30 °C in stoppered flasks in a shaker bath. The pH of these solutions was in the 7–8 range. Each solution was filtered and extracted with five 100-mL portions of ethyl acetate, and the ethyl acetate solutions were then combined and evaporated to dryness. The product was dissolved in 2 mL of dimethyl-d_6 sulfoxide and the ^{13}C NMR spectrum recorded. The intensity ratio (peak 2/peak 1) was calculated in each case. Each spectrum was run at least 3 times, and the average intensity ratio for all runs was calculated. Results are shown in Table III.

Table V. Decomposition of Diaminomaleonitrile in Ammonium Hydroxide

reaction time, h	absorbance (A) (296 nm)
0	1.29
0.5	1.19
1.0	1.12
1.5	1.08
2.0	1.04
2.5	1.01
3.0	0.98

Reaction of Diaminomaleonitrile with $K^{13}CN$ in Aqueous Solution at pH 9–9.5. In another study, a solution was prepared containing diaminomaleonitrile (2.5 g) and potassium [^{13}C]cyanide (250 mg, 0.0038 mol) in 2 L of distilled water. The pH was adjusted to 9.2 with sodium hydroxide solution and thereafter maintained at 30 °C and pH 9.2. Aliquots were periodically withdrawn and extracted with ethyl acetate as previously described. The results are given in Table II.

Reaction of Diaminomaleonitrile with $K^{13}CN$ in Dimethyl Sulfoxide. A solution containing diaminomaleonitrile (1 g) and potassium [^{13}C]cyanide (100 mg) in 4 mL of 50% dimethyl sulfoxide–50% dimethyl-d_6 sulfoxide was prepared. The ^{13}C NMR spectrum of the black solution was recorded at time intervals up to 10 days, and the intensity ratio (peak 1/peak 2) was calculated in each case. Results are shown in Table V.

Effect of Oxygen on the Oligomerization of HCN. A 3-L solution of 0.1 M HCN was adjusted to pH 9.2 with NH_4OH and was then divided into three equal parts. Solution 1 was simply stoppered and allowed to stand in the dark. Solution 2 was degassed by four freeze–pump–thaw cycles and then stored in an N_2 atmosphere in the dark. Oxygen was bubbled through solution 3 for 15 min before it was stoppered and stored in the dark. Solutions 1 and 3 were subjected to the same freeze–thaw cycles as was solution 2, but they were not pumped to remove air. Aliquots of each solution were taken for analysis immediately after the preparation of the solutions and at regular intervals thereafter. Oxygen was passed through solution 3 and nitrogen was bubbled through solution 2 after each sample was withdrawn. The rate of darkening and precipitate formation was fastest in solution 2 and slowest in solution 3.

Aliquots of the three solutions were monitored for urea, diaminomaleonitrile, and cyanide. Urea was measured by the method of Ormsby,[31] and the results are given in Figure 1. Diaminomaleonitrile formation was measured by the UV absorption of the oligomerization mixture at 296 nm.[6] These spectra showed the formation of a variety of UV-absorbing compounds, especially in solutions 1 and 3 (Figure 4). It was necessary to separate the diaminomaleonitrile from these other substances by TLC using butanol saturated with water and then determine the UV absorption of the eluted diaminomaleonitrile. The amount of diaminomaleonitrile was calculated from the absorbance of standard samples of pure diaminomaleonitrile which were subjected to the same chromatographic and elution procedure. The yields of diaminomaleonitrile are given in Figure 2. Cyanide loss was monitored by silver nitrate titration[27] and the method of Scoggins.[28] The former method gave more reproducible data, and these are given in Figure 3.

Oxalic Acid Analyses. Oxalic acid is a major product formed by the hydrolysis of the HCN oligomers.[33] This result was confirmed by GC/MS analysis of the trimethylsilyl derivative.[34] The yield of oxalic acid was estimated by converting the oxalic acid in the acidic and neutral fractions[1] of the sublimed oligomer acid hydrolysate to its trimethylsilyl derivative. Quantitation was accomplished by comparing the area of the oxalic acid peak with that of standard samples of oxalic acid which were carried through the same procedures. The yield of oxalic acid from the oligomers prepared in the presence of air

and from the oligomers prepared in the presence of nitrogen was found to be 85 and 8.1 mg/L of the oligomerization mixture, respectively.

Urea Analysis of HCN Oligomer Hydrolyzates. Sublimed HCN oligomers (50 mg) were hydrolyzed with 6 N HCl, and half of the hydrolysate was subjected to paper chromatography on Whatman 3MM paper using ethyl acetate/formic acid/water (7:2:1 by volume) as the developing solvent. One-quarter of the hydrolysate was analyzed by TLC using butanol/acetic acid/water (12:3:5 by volume) as the developing solvent. Both chromatograms were sprayed with the *p*-dimethylaminobenzaldehyde reagent.[35] No urea was detected in either chromatogram above the limit of detection of 2–5 μg. It was determined that urea is stable under the acid hydrolysis conditions used.

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Registry No.—**1**, 1726-32-5; **2**, 5181-05-5; **3**, 1187-42-4; hydrogen cyanide, 74-90-8; cyanide, 57-12-5; urea, 57-13-6.

References and Notes

(1) For the previous paper in this series, see J. P. Ferris, P. C. Joshi, E. Edelson, and J. Lawless, *J. Mol. Evol.*, in press.
(2) Present address: NASA Ames Research Center, Extraterrestrial Biology Division, Moffett Field, Calif. 94035.
(3) J. P. Ferris, P. C. Joshi, and J. Lawless, *BioSystems*, **9**, 81 (1977).
(4) J. P. Ferris, D. B. Donner, and A. P. Lobo, *J. Mol. Biol.*, **74**, 511 (1973).
(5) W. Lotz, unpublished work from this laboratory (1971).
(6) R. A. Sanchez, J. P. Ferris, and L. E. Orgel, *J. Mol. Biol.*, **30**, 223 (1967).
(7) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(8) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(9) J. P. Ferris and R. A. Sanchez, *Org. Synth.*, **48**, 60 (1968).
(10) G. Schlesinger and S. L. Miller, *J. Am. Chem. Soc.*, **95**, 3729 (1973).
(11) J. P. Ferris, D. B. Donner, and W. Lotz, *J. Am. Chem. Soc.*, **94**, 6968 (1972).
(12) J. P. Ferris, D. B. Donner, and W. Lotz, *Bioorg. Chem.*, **2**, 95 (1972).
(13) G. H. Loew, S. Chang, and D. Berkowitz, *J. Mol. Evol.*, **5**, 131 (1975).
(14) L. Friedman and H. Schechter, *J. Org. Chem.*, **25**, 877 (1960).
(15) R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960).
(16) T. Volker, *Angew. Chem.*, **72**, 379 (1960).
(17) J. P. Ferris and T. J. Ryan, *J. Org. Chem.*, **38**, 3302 (1973).
(18) S. L. Miller and L. E. Orgel, "The Origins of Life on Earth", Prentice-Hall, Englewood Cliffs, N.J., 1974.
(19) J. P. Ferris, J. D. Wos, D. W. Nooner, and J. Oro, *J. Mol. Evol.*, **3**, 225 (1974).
(20) J. P. Ferris, D. B. Donner, and A. P. Lobo, *J. Mol. Biol.*, **74**, 499 (1973).
(21) R. W. Begland and D. R. Hartter, *J. Org. Chem.*, **37**, 4136 (1972).
(22) R. W. Begland, D. R. Hartter, D. S. Donald, A. Cairncross, and W. A. Sheppard, *J. Org. Chem.*, **39**, 1235 (1974).
(23) C. N. Matthews, J. Nelson, P. Varma, and R. Minard, *Science*, **198**, 622 (1977).
(24) R. Minard, W. Yang, P. Varma, J. Nelson, and C. Matthews, *Science*, **190**, 387 (1975).
(25) J. B. Moffett, *J. Chem. Soc., Chem. Commun.*, 888 (1975).
(26) Detailed procedures are given in the Ph.D. Thesis of E. H. Edelson, Rensselaer Polytechnic Institute, 1977.
(27) H. H. Willard, N. H. Furman, and C. E. Bricker, "Elements of Quantitative Analysis", Van Nostrand, Princeton, N.J., 1956, pp 133–135.
(28) M. W. Scoggins, *Anal. Chem.*, **44**, 1294 (1972).
(29) A. A. Schilt, *Anal. Chem.*, **30**, 1409 (1958).
(30) L. S. Bark and H. G. Higson, *Talanta*, **11**, 621 (1964).
(31) A. A. Ormsby, *J. Biol. Chem.*, **146**, 595 (1942).
(32) K. Ziegler in "Organic Syntheses", Collect. Vol. 1, J. B. Conant and A. H. Blatt, Ed., Wiley, New York, N.Y., 1941, p 314.
(33) J. P. Ferris, J. D. Wos, and A. P. Lobo, *J. Mol. Evol.*, **3**, 311 (1974).
(34) J. P. Ferris, P. C. Joshi, and J. G. Lawless, unpublished data.
(35) R. A. Heathcock and N. E. Mahon, *J. Chromatogr.*, **17**, 338 (1965).

Steric Effects. 13. Composition of the Steric Parameter as a Function of Alkyl Branching

Marvin Charton

Department of Chemistry, Pratt Institute, Brooklyn, New York 11205

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The υ steric parameters for alkyl, alkoxy, thioalkyl, dialkylamino, and oxyalkyl groups and the υ' values of alkyl groups were correlated with equations derived from the relationship $\upsilon = an_\alpha + bn_\beta + cn_\gamma + dn_\delta + i$, with excellent results. The parameters n_α, n_β, n_γ, and n_δ represent the number of α, β, γ, and δ carbon atoms, respectively. The correlation equations make possible the estimation of υ values for a very large number of groups. The E_S^c values of Hancock and the E_S^o values of Palm are simply steric parameters with different values of a from that obtained for the υ values. Rate constants for nucleophilic substitution of benzyl chloride by alkoxide ions, of allyl bromide and of 1-chloro-2,4-dinitrobenzene by alkylamines, of alkaline hydrolysis of ethyl 4-nitrophenyl alkyl phosphonates, C-substituted amides, O-substituted esters, and dialkylphenylacetonitriles, of acidic hydrolysis of C-substituted amides, and of the reaction of alcohols with 4-nitrobenzoyl chloride have been successfully correlated with the equation $Q_{Ak} = an_\alpha + bn_\beta + cn_\gamma + i$. Evaluation of the effect on branching shows clearly that for alkyl groups which are not symmetric, no one set of steric parameters will be effective in all types of reactions.

We have calculated in our previous work in this series[1–5] υ steric parameters for 232 substituents and υ' steric parameters for nine substituents.[6,7] In this paper we investigate the dependence of the steric parameter, υ, on the degree of branching in the alkyl group. We would also like, if possible, to be able to estimate υ values for many additional groups.

In commencing this work, we note that Bowden and Woolridge[8] have reported a poor but significant correlation of E_S values with the equation

$$E_S = m_1 n_C + m_2 n_H + m_3 \quad (1)$$

where n_C and n_H are the number of carbon and hydrogen atoms in the sixth position (with the carbonyl oxygen atom in the ester used to define E_S being considered atom number 1). Let us define the following quantities: $n_\alpha \equiv$ the number of C atoms bonded to the α carbon atom of an alkyl group; $n_\beta \equiv$ the number of C atoms bonded to the β carbon atoms; $n_\gamma \equiv$ the number of C atoms bonded to the γ carbon atoms; $n_\delta \equiv$ the total number of carbon atoms bonded to the δ carbon atoms. Thus, for example, the group *t*-BuCH(Me(CH(Et)CMe$_2$– has values of 3, 2, 3, 3 for n_α, n_β, n_γ, n_δ, respectively, while for the cyclohexyl group, the corresponding values are 2, 2, 1, 0.

Newman[9] had suggested long before that the "six number", n_6, is the major factor in the steric effect. This quantity is defined by the equation

$$n_6 = 3n_\beta \quad (2)$$

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Table I. υ Values Used in the Correlations

1. Alkyl groups: Me, 0.52; Et, 0.56; Pr, 0.68; Bu, 0.68; $BuCH_2$, 0.68; $BuCH_2CH_2$, 0.73; $Bu(CH_2)_3$, 0.73; $Bu(CH_2)_4$, 0.68; *i*-Pr, 0.76; *sec*-Bu, 1.02; c-$C_6H_{11}CH_2$, 0.97; *i*-Bu, 0.98; *t*-Bu, 1.24; *t*-$BuCH_2$, 1.34; Et_2CH, 1.51; Pr_2CH, 1.54; Bu_2CH, 1.56; *t*-$BuCH_2Me_2C$, 1.74; *t*-BuMeCH, 2.11; *i*-PrEtCH, 2.11; *t*-$BuMe_2C$, 2.43; Et_3C, 2.38; *i*-$PrCH_2CH_2$, 0.68; *t*-$BuCH_2CH_2$, 0.70; $(i\text{-}PrCH_2)_2CH$, 1.70; $(t\text{-}BuCH_2)_2CH$, 2.03; *t*-$BuCHEtCH_2CH_2$, 1.01; c-$C_6H_{11}CH_2CH_2$, 0.70; c-$C_6H_{11}(CH_2)_3$, 0.71; *sec*-$BuCH_2$, 1.00; *t*-$BuCH_2CHMe$, 1.41; MePrCH, 1.05; Me-*i*-PrCH, 1.29; *i*-$BuCH_2CH_2$, 0.68; MeBuCH, 1.07; Me-*i*-BuCH, 1.09; EtBuCH, 1.55; *n*-C_9H_{19}, 0.68; *n*-$C_{11}H_{23}$, 0.68; *n*-$C_{13}H_{27}$, 0.68; *n*-$C_{15}H_{31}$, 0.68; *n*-$C_{17}H_{35}$, 0.68; c-C_4H_9, 0.51; c-C_5H_9, 0.71; c-C_6H_{11}, 0.87; c-C_7H_{13}, 1.00
2. Alkoxy groups: Me, 0.36; Et, 0.48; Pr, 0.56; *i*-Pr, 0.75; Bu, 0.58; *i*-Bu, 0.62; *sec*-Bu, 0.86; *t*-Bu, 1.22; CH_2Bu, 0.58; CH_2-*sec*-Bu, 0.62; CH_2-*i*-Bu, 0.62; CH_2-*t*-Bu, 0.70; $CHEt_2$, 1.00; CHMePr, 0.90; CHMe-*i*-Pr, 0.91; CMe_2Et, 1.35; CH_2CH_2Bu, 0.61; CHEtPr, 1.04; CH_2CH_2-*t*-Bu, 0.53; CH_2CHEt_2, 0.71; CH_2CMe_2Et, 0.78; CH_2CHMe-*i*-Pr, 0.64; CHEt-*i*-Pr, 1.18; CEt_2Me, 1.52; $CPrMe_2$, 1.39; CHMe-*t*-Bu, 1.19; $CHMeBuCH_2$, 0.90; CH_2CHEt-*i*-Pr, 0.76; CH_2CHMe-*t*-Bu, 0.66; CH_2CMeEt_2, 0.82; *n*-C_8H_{17}, 0.61; $CH_2CHEtBu$, 0.76; $CHMe(BuCH_2CH_2)$, 0.92; CH_2CHEt-*t*-Bu, 0.96; CH_2CH-*i*-Pr_2, 0.89; CH-*i*-Bu_2, 1.28; *n*-$C_{12}H_{25}$, 0.65; c-C_5H_9, 0.77; c-C_6H_{11}, 0.81; CH_2-c-C_3H_5, 0.48; CH_2-c-C_5H_9, 0.58; CH_2-c-C_6H_{11}, 0.65; CH_2CEt_3, 0.97
3. Alkylamino and dialkylamino groups: NHMe, 0.39; NHEt, 0.59; NHPr, 0.64; NH-*i*-Pr, 0.91; NHBu, 0.70; NH-*i*-Bu, 0.77; NH-*sec*-Bu, 1.12; NH-*t*-Bu, 1.83; $NHCH_2Bu$, 0.64; $NHCH_2$-*i*-Bu, 0.65; $NHCH_2CH_2Bu$, 0.66; NMe_2, 0.43; NMeEt, 0.87; NEt_2, 1.37; NPr_2, 1.60; $NiPr_2$, 2.01; $NHcC_6H_{11}$, 0.92
4. Alkylthio groups: Me, 0.64; Et, 0.94; *i*-Pr, 1.19; Pr, 1.07; Bu, 1.15; *i*-Bu, 1.15; *sec*-Bu, 1.36; *t*-Bu, 1.60
5. Oxyalkyl groups: $MeOCH_2$, 0.63; $EtOCH_2$, 0.61; $PrOCH_2$, 0.65; *i*-$PrOCH_2$, 0.67; $BuOCH_2$, 0.66; *i*-$BuOCH_2$, 0.62; EtCHOMe, 1.22; PrCHOMe, 1.22; BuCHOMe, 1.20; CH_2OH, 0.53; MeCHOH, 0.50; EtCHOH, 0.71; PrCHOH, 0.71; BuCHOH, 0.70; $BuCH_2CHOH$, 0.71; *t*-$BuCH_2OCMe_2$, 1.23
6. Alkyl groups: Me, 0.35; Et, 0.38; Pr, 0.42; Bu, 0.42; *i*-$PrCH_2$, 0.55; *i*-Pr, 0.62; *t*-Bu, 1.23; *sec*-Bu, 0.66

while

$$n_C = n_\gamma \tag{3}$$

Furthermore,

$$n_6 = nC + n_H \tag{4}$$

Thus, from eq 2, 3, and 4, we obtain

$$n_H = 3n_\beta - n_\gamma \tag{5}$$

Substituting eq 3 and 5 in eq 1 gives

$$E_S = 3m_2n_\beta + (m_1 - m_2)n_\gamma - m_3 \tag{6}$$

Thus, the work of Bowden and Woolridge indicates a dependence of the Taft steric parameter, E_S, on the degree of branching. This work is extended by a report of Rybkov, Gankin, and Gurevich,[10] which states that the rate of esterification of RCO_2H is dependent on n_5 as well as n_6, as n_5 is given by the equation

$$n_5 = 3n_\alpha \tag{7}$$

It seemed reasonable, therefore, to examine the correlation of all available υ values for alkyl groups with the equation

$$\upsilon = an_\alpha + bn_\beta + cn_\gamma + dn_\delta + i \tag{8}$$

The υ values were taken from our previous work.[1,2] The groups studied are set forth in Table I (set 1). The cyclopropyl group was not included in this correlation as we have already suggested that υ for this group includes a significant resonance effect contribution. The results of the correlation by least mean squares with eq 8 are reported in Table II (set 1A). The results are significant at the 99.9% confidence level (CL). The value of r^2, however, is only 0.7909. Thus, only about 79% of the data are accounted for by the correlation. Seven of the 46 data points are apparently outliers. These points include Me, Et, *t*-$BuEtCHCH_3CH_2$, c-C_4H_7, c-C_5H_9, c-C_6H_{11}, and c-C_7H_{13}. The deviation of the cyclic substituents is reasonable as the steric effect of these groups is undoubtedly different from that of the corresponding open chain analogues. Comparing *sec*-Bu with c-C_4H_7, the υ values are 1.02 and 0.51, respectively. This is certainly due to greater freedom of motion in an acyclic group than is possible in a cyclic group. The υ values for the Me and Et apparently deviate because they are not substituted sufficiently compared to the other groups studied. The deviation of υ for the *t*-$BuEtCHCH_2CH_2$ group may be due simply to experimental error.

A further point is that the "student t" test shows that *d* is not significant and therefore n_δ is not required. The remaining 39 data points were therefore correlated with the equation

$$\upsilon = an_\alpha + bn_\beta + cn_\gamma + i \tag{9}$$

with excellent correlation (set 1B). Again, the correlation was significant at the 99.9% CL. The value of r^2 obtained was 0.9722. Thus, the correlation accounts for about 97% of the variation. The success of eq 9 led us to applying this method to υ values for alkoxy, dialkylamino, and alkylthio substituents. Values of the υ constants used in the correlations are set forth in Table I and results of the correlations in Tables II and III. The υ values for the alkoxy groups were correlated with the equation

$$\gamma = bn_\beta + cn_\gamma + dn_\delta + i \tag{10}$$

This equation was obtained by dropping the n_α term in eq 8. The n_α term is not required for alkoxy groups as the α atom is the oxygen atom which of course can form only one bond to a carbon atom. Correlation of all 44 available υ values for alkoxy groups gave a result (set 2A) significant at the 99.9% CL with a value for r^2 of 0.8633. Thus, the correlation accounted for about 86% of the variation. Examination of the calculated υ values showed that the OMe, OCH_2CH_2-*t*-Bu, OcC_5H_9, OcC_6H_{11}, OCH_2-c-C_3H_5, OCH_2-c-C_4H_7, and OCH_2-c-C_5H_9 groups deviate considerably from the experimental values. Exclusion of these values gave an excellent correlation (set 2B) which was again significant at the 99.9% CL with an r^2 value of 0.9491. Thus, the correlation accounts for about 95% of the variation. The most probable cause for the deviation of the groups indicated above from the correlation is experimental error with the exception of the OME groups. The deviation of the OMe group is reasonable in view of the deviation of the υ value for the Et group from the correlation line for alkyl groups.

It must be noted that the successful correlation obtained with eq 10 shows that the n_δ term is required. We believe that this is due to the fact that the alkoxy groups available had much more variation in n_δ than did the alkyl groups available. Thus, seven alkoxy groups had n_δ values ≥ 3 whereas only one alkyl group had such a value. We believe that if υ values for suitably substituted alkyl groups were available, the n_δ term would have been significant.

Since the dialkylamino and alkylamino groups can undergo variable substitution at N, we have correlated υ values for them with eq 8. An excellent correlation was obtained (set 3A), significant at the 99.9% CL, with an r^2 value of 0.0258, thereby accounting for about 93% of the variation. Examination of calculated υ values showed that those for the NHMe, NH-*i*-Pr, and NH-c-C_6H_{11} groups deviated considerably from the experimental υ values. The deviation of the NHMe group is in agreement with the previously observed deviations of the OMe and Et groups. The NH-*i*-Pr and NH-c-C_6H_{11} groups pre-

Table II. Results of Correlations

set	a	b	c	d/b'	e	i	R^a	F^b
1A	0.397	0.347	0.0614	0.0158		−0.101	0.889	38.76[e]
1B	0.497	0.409	0.0608			−0.309	0.986	408.0[e]
2A		0.372	0.0787	0.0528		0.0795	0.929	84.18[e]
2B		0.406	0.108	0.0594		−0.0084	0.974	204.9[e]
3A	0.227	0.415	0.0467	−0.0737		0.0357	0.962	37.41[e]
3B	0.200	0.453				0.0407	0.969	85.58[e]
4		0.318	0.108	0.0897		0.635	0.999	476.9[e]
5A	0.262	0.186	−0.0153	0.417	−0.0551	0.309	0.957	21.91[e]
5B	0.303	0.255		0.484		0.159	0.997	612.9[e]
6A	0.280	−0.0127				0.202	0.900	10.65[f]
6B	0.386	0.0760				−0.0502	0.950	18.53[g]
6C	0.349					0.0638	0.935	34.87[h]
11	0.346					0.345	0.997	397.7[e]

set	$s_{est}{}^c$	$s_a{}^c$	$s_b{}^c$	$s_c{}^c$	$s_d{}^c/s_{b'}$	$s_{c'}{}^c$	$s_i{}^c$	n^d
1A	0.249	0.616[e]	0.0497[e]	0.0303[i]	0.0483[j]		0.118[k]	46
1B	0.0927	0.0230[e]	0.0199[e]	0.0118[e]			0.0457[e]	39
2A	0.103		0.0240[e]	0.194[e]	0.0140[e]		0.0543[l]	44
2B	0.0623		0.0167[e]	0.0128[e]	0.00934[e]		0.0400[m]	37
3A	0.151	0.0896[i]	0.0388[e]	0.0534[k]	0.0716[k]		0.143[m]	17
3B	0.136	0.0779[i]	0.0380[e]				0.114[j]	14
4	0.0197		0.00854[e]	0.00903[e]	0.0212[n]		0.0161[e]	8
5A	0.0936	0.0471[e]	0.0875[o]	0.0786[m]	0.0584[e]	0.0559[k]	0.0595[e]	16
5B	0.0230	0.0119[e]	0.0148[e]		0.0146[e]		0.0165[e]	15
6A	0.0148	0.0621[g]	0.0764[m]				0.117[l]	8
6B	0.112	0.0681[g]	0.0709[k]				0.146[j]	7
6C	0.114	0.0590[e]					0.102[j]	7
11	0.0145	0.0141[e]					0.0184[e]	6

[a] Correlation coefficient. [b] F test for significance of regression. Superscripts indicate confidence levels (CL). [c] Standard errors of the estimate and the regression coefficients. Superscripts indicate confidence level of the "student t" test. [d] Number of points in set. [e] 99.9% CL. [f] 97.5% CL. [g] 99.0% CL. [h] 99.5% CL. [i] 95.0% CL. [j] 20.0% CL [k] 50.0% CL. [l] 80.0% CL. [m] <20.0% CL. [j] 98.0% CL. [o] 90.0% CL.

Table III. Partial Correlation Coefficients [a]

set	r_{12}	r_{13}	r_{14}	r_{23}	r_{24}	r_{34}
1A	0.372[b]	0.042	0.369[b]	0.106	0.195	0.126
1B	0.265	0.009		0.096		
2A	0.109	0.344[c]		0.247		
2B	0.241	0.421[b]		0.280		
3A	0.218	0.264	0.387	0.052	0.187	0.369
3B	0.228					
4	0.145	0.114		0.061		
5A	0.552[d]	0.422	0.269	0.764[e]	0.358	0.313
5B	0.523[d]	0.395		0.472		
6A	0.183					
6B	0.520					

set	r_{15}	r_{25}	r_{35}	r_{45}
5A	0.406	0.633[b]	0.484	0.556[c]

[a] Superscripts indicate significance of partial correlation coefficients. Lack of superscripts indicates less than 90% CL. [b] 98.0% CL. [c] 95.0% CL. [d] 90.0% CL. [e] 99.5% CL.

sumably deviate due to experimental error. The correlation obtained with eq 8 shows (from the "student t" tests) that c and d are not significant and therefore the n_γ and n_γ terms are not required. We have therefore correlated the data, after the exclusion of the values for NHMe, NH-*i*-Pr, and NH-c-C_6H_{11}, with the equation

$$v = an_\alpha + bn_\beta + i \qquad (11)$$

once more resulting in a correlation (set 3B) significant at the 99.9% CL, with an r^2 value of 0.9396, accounting for about 94% of the variation.

The v values for alkylthio groups were correlated with eq 10 as no n_α term is required, as was the case for alkoxy groups, and for the same reason. An excellent correlation was obtained, significant at the 99.9% CL, with r^2 equal to 0.9972. Surprisingly the SMe group does not deviate greatly from the correlation line for thioalkyl groups, in contrast to the behavior of the Et, OMe, and NHMe groups.

We have also examined the effect of branching on oxyalkyl groups of the type $CR^1R^2(OR^3)$. We first attempted correlation with

$$v = an_\alpha + bn_\beta + cn_\gamma + b'n_{0\beta} + c'n_{0\gamma} + i \qquad (12)$$

where $n_{0\beta}$ is the number of carbon atoms bonded to O (either 0 or 1, keeping in mind that the lettering of C atoms is as shown in (I) with the oxygen atom replacing Cβ), and $n_{0\gamma}$ is the number of γ carbon atoms attached to the β carbon atom, which is bonded to an oxygen atom.

Table IV. Values of υ_{CHX_2} and υ_{CX_3}

X	H	Me	F	Cl	Br	I
υ_{CHX_2}	0.52	0.76	0.68	0.81	0.89	0.97
υ_{CX_3}	0.52	0.24	0.91	1.38	1.56	1.79

$$\underset{\alpha\ \beta\ \gamma\ \delta}{\text{-C-C-C-C-C-}} \quad \text{(I)}$$

The result obtained from correlation with eq 12 (set 5A) was significant at the 99.9% CL, with a value of r^2 of 0.9164, accounting for about 92% of the variance. The "student t" tests showed that c and c′ were not significant. Furthermore, the calculated value of υ for the CH_2OH group deviated greatly from the experimental value. This is in accord with our previous results for the Et, OMe, and NHMe groups. The remaining 12 values of υ were correlated with the equation

$$\upsilon = an_\alpha + bn_\beta + b'n_{0\beta} + i \quad (13)$$

with excellent results (set 5B). Once again, the correlation was significant at the 99.9% CL, with an r^2 value of 0.9941, accounting for essentially all the variation.

Finally, we have examined the few available values of υ' for alkyl groups. As no υ' values were available for groups with significant values of n_γ or n_δ, the data were correlated with eq 11 (set 6A). The correlation obtained was good and the results were significant at the 95% CL with an r^2 value of 0.8099, accounting for about 81% of the variation. A "student t" test showed that b was not significant. Exclusion of the υ value for Me gave an improved correlation with eq 11, significant at the 99.0% CL, with an r^2 value of 0.9026, accounting for about 90% of the variation. Again, however, b was not significant. Data were therefore correlated with the equation

$$\upsilon' = an_\beta + i \quad (14)$$

giving an excellent correlation, significant at the 99.5% CL with an r^2 value of 0.8746, accounting for about 87% of the variation. The lack of significance of b is probably due to the small number of points in the set.

The successful correlation of υ values with the degrees of alkyl branching makes possible the estimation of ν values for a large number of substituents and thereby greatly expands the utility of the modified Taft equation. The preferred equations for the estimation of new υ constants are:

$$\upsilon_R = 0.497n_\alpha + 0.409n_\beta + 0.0608n_\gamma - 0.309 \quad \text{(i)}$$

$$\upsilon_{OR} = 0.406n_\beta + 0.108n_\gamma + 0.059n_\delta - 0.00839 \quad \text{(ii)}$$

$$\upsilon_{NR^1R^2} = 0.200n_\alpha + 0.453n_\beta + 0.0407 \quad \text{(iii)}$$

$$\upsilon_{SR} = 0.318n_\beta + 0.108n_\gamma + 0.089n_\delta + 0.635 \quad \text{(iv)}$$

$$\upsilon_{CR^1R^2(OR^3)} = 0.303n_\alpha + 0.255n_\beta + 0.484n_{0\beta} + 0.159 \quad \text{(v)}$$

Our results also shed light on the composition of the "corrected" E_S^c values of Hancock and co-workers[11] and E_S^o values of Palm.[12]

Let us establish the freedom of the υ parameters for alkyl groups from resonance effects. We propose to do this by showing that they are obtained by calculation from van der Waals radii, or by linear relationships with υ values which were calculated from van der Waals radii. It will be convenient to review at this point the difference between electrical and steric effects. Both effects are of course electrical in orgin. The electrical effect of a substituent is due to the charge (usually partial) on the substituent. It is conveniently factored into a localized effect and a delocalized effect. The steric effect is dependent on the size and shape of the substituent, whereas the electrical effect is not. Thus, it is quite possible to have groups which are isoelectronic (have a constant electrical effect) and show a widely varying steric effect, or are isosteric and have a widely varying electrical effect. The origin of the steric effect lies in repulsions between nonbonding atoms. The origin of the electrical effect lies in the effect of the substituent upon the electron distribution at the active site (the atom or group of atoms at which some measurable phenomenon occurs). As van der Waals radii are a measure of size, not charge, we believe that υ parameters which are calculated from these radii or are a linear function of parameters calculated from these radii are pure steric parameters.

The υ values for Me and t-Bu were directly calculated from van der Waals radii and are therefore pure steric parameters. The values of υ for i-Pr and $CHCl_2$ lie on the correlation line of the equation

$$\upsilon_{CHX_2} = m\upsilon_{CX_3} + c \quad (15)$$

All of the υ values for the CX_3 groups involved were obtained by calculation from van der Waals radii. The υ values used are given in Table IV and results of the correlation in Table II (set 11). The results of the correlation are excellent; it was significant at the 99.9% CL with $r^2 = 0.9936$. Thus, the υ_{CHX_2} parameters are completely accounted for by a relation with pure steric parameters and are therefore themselves pure steric parameters. We have previously shown[1] that when X = Cl, an excellent correlation with the equation

$$\upsilon_{CX_nH_{e-n}} = m\upsilon_{CMe_nH_{3-n}} \quad (16)$$

was obtained, significant at the 99.9% CL with $r^2 = 0.9986$.

We have also pointed out above that υ_{Me}, υ_{CHCl_3}, υ_{CHMe_2}, and υ_{CMe_3} are pure steric parameters. Since the point for υ_{CH_2Me}, υ_{CH_eCl} lies on this line, both of these υ values must be pure steric parameters. Thus, we have now shown that the ν values for Me, Et (or CH_2Me), i-Pr (or $CHMe_2$), and t-Bu (or CMe_3) are all related to van der Waals radii and may therefore be considered pure steric parameters.

Significant correlations obtained with eq 16 when X = Pr or Et suggest that υ values for the CH_2Et, CH_2Pr, $CHEt_2$, and $CHPr_2$ groups are also pure steric parameters. We feel, therefore, that as all of these alkyl groups are pure steric parameters, and as they cover the complete range of number of α hydrogen atoms, the υ parameters for alkyl groups are free of hyperconjugative effects in particular and electrical effects in general. We conclude therefore that as the left side of eq 8 represents only steric effects, the right side of eq 8 must also represent only steric effects. Let us now consider the "corrected" E_S^c values of Hancock. They are defined by the equation

$$E_S = E_S^c + h(n_{H\text{-}3}) \quad (17)$$

where n_H is the number of α hydrogen atoms. From the definition of E_S values and that of υ values it can be seen that neglecting errors in the definition of E_S, $E_S = s\upsilon$. Furthermore, $n_H = 3 - n\alpha$. Thus,

$$E_S^c = E_S - h(n_{H\text{-}3}) \quad (18)$$

$$E_S^c = s\upsilon - h(3 - n_{\alpha-3}) \quad (19)$$

$$E_S^c = s\upsilon + hn_\alpha \quad (20)$$

From eq 8

$$E_S^c = s(an_\alpha + bn_\beta + cn_\gamma + i) + hn_\alpha \quad (21)$$

$$E_S^c = (sa + h)n_\alpha + sbn_\beta + scn_\gamma + si \quad (22)$$

It follows then that the E_S^c values are not freer of electrical effects than E_S or υ, as claimed by Hancock, but are steric parameters which differ from υ in the coefficient of n_α. Thus, they are not better or worse steric parameters, they are steric

Table V. Composition of the υ Parameters

type of group	a	b	c	d	b'
R	0.497	0.409	0.0608		
OR		0.406	0.108	0.0594	
NR^1R^2	0.200	0.453			
SR		0.318	0.108	0.0897	
$CR^1R^2(OR^3)$	0.303	0.255			0.484
R[a]	0.348				

[a] υ^1 values.

parameters which differ from E_S or υ in their sensitivity to branching at the first carbon atom of the alkyl group. The same treatment can be applied to the E_S^o values of Palm

$$E_S = E_S^o - j(n_{H\text{-}3}) - kn_C \quad (23)$$

where n_H is the number of α hydrogen atoms and n_C the number of α carbon atoms. With $E_S = s\upsilon$, $n_H = 3 - m_\alpha$, $n_C = n_\alpha$, we obtain

$$E_S^o = s\upsilon + j(3 - n_\alpha - 3) - kn_\alpha \quad (24)$$

$$E_S^o = s - (j + k)n_\alpha \quad (25)$$

From eq 8

$$E_S^o = s(an_\alpha + bn_\beta + cn_\gamma + i) - (j + k)n_\alpha \quad (26)$$

$$E_S^o = (sa - j - k)n_\alpha + sbn_\beta + scn_\gamma + si \quad (27)$$

Again, E_S^o is not more or less free of electrical effects than is υ. It differs from E_S and υ in its sensitivity to branching at the first carbon of the alkyl group. As to the use of the E_S^c and E_S^o values, it is certainly true that different reactions may have a different composition of the steric effect. Differences in the geometry of the transition state would lead us to expect this. Thus, for example, the υ values for many groups were defined from rates of esterification of carboxylic acids and have a value of a in eq 8 of 0.497 while the υ values defined from a bimolecular nucleophilic substitution have a value of a in eq 14 of 0.348. It is entirely likely that for some particular reaction a correlation with E_S^o or E_S^c (or their equivalents, υ^o or υ^c) would be best. As more data become available, we expect to find a wide variation in a, b, and c with reaction type.

It is of interest to compare the composition of the various types of υ values studied here. Values of a, b, c, d, and b are given in Table V. The values of a are easily understandable for the υ_R, $\upsilon_{NR^1R^2}$, and $\upsilon_{CR^1R^2(OR^3)}$ parameters, all of which are determined from analogus reactions (esterification or acid catalyzed amide hydrolysis). The υ_R values in which hindrance to α substitution is greatest show the highest sensitivity to n_α. The $\upsilon_{CR^1R^2(OR^3)}$ values should be less senitive than the υ_R values to n_α because the oxygen atom is significantly smaller than a CH_2 group and this is indeed the case. The $\upsilon_{NR^1R^2}$ values should be the least sensitive to n_α because only two N-C bonds can be formed, the remaining tetrahedral orbital being occupied by a pair of nonbonding electrons. Again, this is what is observed.

The υ_R, υ_{OR}, and $\upsilon_{NR^1R^2}$ values all show about the same sensitivity to n_β. The υ_{SR} values are less sensitive to n_β, possibly due to the longer C–S bonds which would tend to remove the alkyl moiety of the thioalkyl group from the vicinity of the reaction site. We are unable at the present time to account for the smaller sensitivity to n_γ of υ_R as compared with υ_{OR}. The value of b' obtained for $\upsilon_{CR^1R^2(OR^3)}$ values is somewhat larger than but comparable to the values of b obtained for the υ_R, $\upsilon_{NR^1R^2}$, and υ_{OR} constants.

Our rests suggest the possibility, when a sufficiently large data set is available, of correlating the data with the equation

$$Q = S(an_\alpha + bn_\beta + cn_\gamma + dn_\delta + i) + h \quad (28)$$

where Q is some quantity to be correlated, such as the logarithm of a rate or equilibrium constant. This equation simplifies to

$$Q = a'n_\alpha + b'n_\beta + c'n_\gamma + i \quad (29)$$

Table VI. Data Used in Correlation with (30)

1. k_r, AkPhCHCN + OH^- in isoamyl alcohol at 99.8 °C:[a] Pr, 0.121; *i*-Pr, 0.013; Bu, 0.082; *sec*-Bu, 0.013; *i*-Bu, 0.095; $BuCH_2$, 0.137; *i*-$PrCH_2CH_2$, 0.095; c-C_5H_9, 0.019; $BuCH_2CH_2$, 0.119; c-C_6H_{11}, 0.010
2. k_r, AkPhCHCN + OH^- in isoamyl alcohol at 117 °C:[a] Pr, 0.250; *i*-Pr, 0.044; Bu, 0.256; *sec*-Bu, 0.045; *i*-Bu, 0.225; $BuCH_2$, 0.423; *i*-$PrCH_2CH_2$, 0.260; c-C_5H_9, 0.058; $BuCH_2CH_2$, 0.308; c-C_6H_{11} 0.018
3. k_r, $AkNH_2$ + $CH_2{=}CHCH_2Br$ in PhH at 100 °C:[b] H, 1.380; Me, 8,302; Et, 3.807; Pr, 3.783; Bu, 3.896; $BuCH_2$, 3.790; $Bu(CH_2)_3$, 3.537; *i*-Pr, 1.257; *sec*-Bu, 1.240; *i*-Bu, 2.759; *i*-$PrCH_2CH_2$, 2.985; *i*-PrMeCH, 0.586; *t*-Bu, 0.314
4. k_r, AkO^- + $PhCH_2Cl$ in AkOH at 50 °C:[c] Pr, 0.530; Bu, 0.460; $BuCH_2$, 0.350; $BuCH_2CH_2$, 0.270; *i*-Pr, 0.334; Bu, 0.229; *t*-Bu, 0.132
5. k_r, AkO^- + $PhCH_2Cl$ in AkOH at 60 °C:[c] Pr, 1.31; Bu, 1.02; $BuCH_2$, 0.830; $BuCH_2CH_2$, 0.620; *i*-Pr, 0.662; *sec*-Bu, 0.458, *i*-Bu, 0.907; *i*-$PrCH_2CH_2$, 0.697; *t*-Bu, 0.250
6. k_r, AkO^- + $PhCH_2Cl$ in AkOH at 70 °C:[c] Pr, 2.96; Bu, 2.33; $BuCH_2$, 1.77; $BuCH_2CH_2$, 1.33; *i*-Pr, 1.43; *sec*-Bu, 0.845; *i*-Bu, 1.89; *i*-$PrCH_2CH_2$, 1.54; *t*-Bu, 0.523
7. k_r, AkO^- + $PhCH_2Cl$ in AkOH at 80 °C:[c] Pr, 6.39; Bu, 4.96; $BuCH_2$, 3.65; $BuCH_2CH_2$, 2.77; *i*-Pr, 2.55; *sec*-Bu, 1.60; *i*-Bu, 3.92; *i*-$PrCH_2CH_2$. 3.35; *t*-Bu, 0.910;
8. k_r, $AkNH_2$ + 1-Cl-2,4-$(NO_2)_2C_6H_3$ in EtOH at 25 °C:[d] Et, 9.2; Pr, 9.6; *i*-Pr, 1.0; Bu, 10.0; *sec*-Bu, 0.91; *t*-Bu, 0.038; Me, 31.6; *i*-Bu, 6.8; $Bu(CH_2)_3$, 10.0; H, 0.04
9. k_r, Ak(PO)(O-$C_6H_4NO_2$-4)(OEt) + OH^- in water (pH 8.3) at 37.5 °C:[e] Me, 24.2; Et, 5.06; Pr, 4.17; Bu, 4.23; $BuCH_2$, 3.62; $BuCH_2CH_2$, 3.56; *i*-Pr, 1.07; *i*-Bu, 2.34; *i*-$PrCH_2CH_2$, 2.45; *i*-$Pr(CH_2)_3$, 3.62; *t*-Bu, 0.032; *t*-$Bu(CH_2)_3$, 3.41; c-C_6H_{11}, 0.307
10. k_r, $PhCAK^1AK^2CN$ + OH^- in isoamyl alcohol at 99.8 °C:[a] H, H, 0.505; Me, H, 0.411; Et, H, 0.316; Pr, H, 0.121; Bu, H, 0.082; Me, Me, 0.148; Et, Me, 0.057; Pr, Me, 0.073; Bu, Me, 0.058; Et, Et, 0.046; Pr, Et, 0.021; Bu, Et, 0.007
11. k_r, $PhCAk^1Ak^2CN$ + OH^- in isoamyl alcohol at 117 °C:[a] H, H, 1.221; Me, H. 0.695; Et, H, 0.600; Pr, H, 0.250; Bu, H, 0.256; Me, Me, 0.341; Me, Et, 0.107; Pr, Me, 0.141; Bu, Me, 0.134; Et, Et, 0.109; Pr, Et. 0.056; Bu, Et, 0.035;
12. 10^4 k_r, $AkCONH_2$ + H_3O^+ in H_2O at 75 °C:[f] Me, 10.3; Et, 12.0; Pr, 5.99; Bu, 5.93; *i*-Bu, 1.29; *t*-$BuCH_2$, 0.193; *i*-Pr, 6.06; Et_2CH, 0.176; *sec*-Bu, 1.51; *t*-Bu, 2.26
13. 10^4k_r, $AkCONH_2$ + OH^- in H_2O at 75.0 °C:[g] Me, 13.6; Et, 13.1; Pr, 7.05; Bu, 5.52; *i*-Bu, 1.97; *sec*-Bu, 1.65; *i*-Pr, 6.61; *t*-Bu, 2.57
14. k_r, AkOBz + OH^- in 56% w/w MeAc–H_2O at 25 °C:[h] Me, 9.022; Et, 2.891; Pr, 1.932; Bu, 1.667; $AmCH_2$, 1.274; $Am(CH_2)_3$, 1.263; *i*-Pr, 0.4644; *i*-Bu, 1.429; *sec*-Bu, 0.2259; *t*-Bu, 0.01327; *i*-$BuCH_2$, 1.200; MePrCH, 0.1487; Me_2EtC, 0.005024
15. 10^3k_r, AkOH + 4-$O_2NC_6H_4COCl$ in Et_2O at 25 °C:[i] Me, 184; Et, 84.5; Pr, 65.9; *i*-Pr, 10.1; Bu, 70.3; *sec*-Bu, 7.35; *t*-Bu, 2.70; *i*-Bu, 30.8; Am, 79; $AmCH_2$, 85; $Am(CH_2)_2$, 69; *sec*-$BuCH_2$, 36; *i*-$BuCH_2$, 73; *i*-$Bu(CH_2)_2$, 68; MePrCH, 5.9; MeBuCH, 65; Et_2CH, 36; Pr_2CH, 2.7

[a] D. Zavoianu, *Ann. Univ. Bucuresti. Ser. Stiint. Natur. Chim.*, **17**, 41, 123 (1968); *Chem. Abstr.*, **71**, 112064, 112065. [b] Menschutkin, *Z. Phys. Chem.*, **17**, 193 (1895); *Ber.*, **30**, 2775, 2966 (1897). [c] I. G. Murgulescu and D. Dancea, *Rev. Roum. Chim.*, **16**, 1625 (1971). [d] O. L. Brady and W. H. Cropper, *J. Chem. Soc.*, 507 (1950). [e] T. R. Fukuto and R. L. Metcalf, *J. Am. Chem. Soc.*, **81**, 372 (1959). [f] P. D. Bolton, *Aust. J. Chem.*, **22**, 527 (1969); **24**, 471 (1971). [g] P. D. Bolton and G. L. Jackson, *ibid.*, **24**, 969 (1971). [h] E. Tommila, *Ann. Acad. Sci. Fenn., Ser. A3*, **59**, 3 (1942); *Chem. Abstr.*, **38**, 6172b (1944). [i] J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925); J. F. Norris and F. Cortese, *J. Am. Chem. Soc.*, **49**, 2340 (1927).

Table VII. Results of Correlation with (30) [o]

set	−a	−b	−c	i	R[a]	F[b]	r_{12}[c]	r_{13}[c]
1	0.985	0.0606	0.0374	0.114	0.9882	55.67[g]	0.577	0.518
2	0.815	0.0531	−0.0242	0.305	0.9798	32.00[g]	0.577	0.518
3	0.500	0.0688	−0.0329	1.056	0.9779	58.36	0.542	0.291
4	0.384	0.164	0.188	0.282	0.943	8.026[l]	0.806[l]	0.679
5	0.410	0.136	0.143	0.628	0.956	17.67[g]	0.732[l]	0.526
6	0.452	0.176	0.145	1.05	0.949	14.97[i]	0.732[l]	0.526
7	0.487	0.165	0.135	1.39	0.954	16.86[g]	0.732[l]	0.520
8	0.968	0.0822	−0.148	1.74	0.981	43.60	0.204	0.218
9	0.940	0.0955	0.0284	1.59	0.974	49.50	0.306	0.221
10	0.328	0.330	0.227	−0.101	0.926	18.12	0.536[l]	0.187
11	0.341	0.291	0.181	0.200	0.962	33.38	0.548	0.258
12	0.308	0.561	−0.322	1.320	0.951	18.92[g]	0.125	0.167
13	0.281	0.353	−0.0815	1.294	0.937	9.577[m]	0.183	0.165
14	1.04	0.106	0.0505	1.346	0.971	49.84	0.098	0.255
15	0.809	0.220	0.0545	2.704	0.959	53.66	0.000	0.082

set	r_{23}[c]	s_{est}[d]	s_a[d]	s_b[d]	s_c[d]	s_i[d]	$100r^2$[e]	n[f]
1	0.000	0.0867	0.112	0.0832[h]	0.0570[h]	0.231[h]	97.66	8
2	0.000	0.100	0.130[i]	0.0962[h]	0.0660[h]	0.268[j]	96.00	8
3	0.158	0.0993	0.0402	0.0423[k]	0.0475[h]	0.0759	95.63	12
4	0.548	0.0951	0.0951[m]	0.135[h]	0.0990[k]	0.247[j]	88.92	7
5	0.159	0.0783	0.0705[i]	0.0734[k]	0.0487[m]	0.176[n]	91.38	9
6	0.159	0.0909	0.0818[i]	0.0852[l]	0.0565[l]	0.205[i]	89.98	9
7	0.159	0.0973	0.0876[i]	0.0913[k]	0.0605[l]	0.219[i]	91.00	9
8	0.267	0.215	0.0910	0.113[j]	0.182[j]	0.174	96.32	9
9	0.383	0.178	0.0793	0.0966[j]	0.0877[h]	0.145	94.89	12
10	0.454	0.224	0.116[m]	0.120[n]	0.140[k]	0.166[h]	85.79	13
11	0.471	0.145	0.0777[i]	0.0777[i]	0.0952[l]	0.108[h]	92.60	12
12	0.000	0.251	0.101[m]	0.0801	0.269[j]	0.195	90.44	10
13	0.204	0.164	0.0695[n]	0.0862[n]	0.181[h]	0.133	87.88	8
14	0.292	0.255	0.0869	0.129[j]	0.120[h]	0.187	94.32	13
15	0.375	0.190	0.0663	0.0725[i]	0.0728[j]	0.126	92.00	18

[a] Multiple correlation coefficient. [b] F test for significance of correlation. [c] Partial correlation coefficients of n_α on n_β, n_α on m_γ, and n_β on n_γ. [d] Standard errors of the estimate, a, b, c, and i. [e] Percent of data accounted for by correlation equation. [f] Number of points in set. [g] 99.5% CL. [h] 20.0% CL. [i] 99.0% CL. [j] 50.0% CL. [k] 80.0% CL. [l] 90.0% CL. [m] 95.0% CL. [n] 98.0% CL. [o] Superscripts indicate confidence levels of F, "student t" test of a, b, c, i, and of r. No superscript indicates 99.9% CL for F or the "student t" test, <90.0% CL for r.

Table VIII. Values of P_n

set	P_a	P_b	P_c
1	91.0	5.60	3.45
2	93.9	6.1	
3	87.9	12.1	
4	52.2	22.3	25.5
5	59.5	19.7	20.8
6	58.5	22.8	18.8
7	61.9	21.0	17.2
8	92.2	7.8	
9	88.4	8.98	2.67
10	35.5	40.0	24.5
11	41.9	35.8	22.3
12	35.4	64.6	
13	44.3	55.7	
14	86.9	8.86	4.22
15	74.7	20.3	5.03

We may now examine the application of equations such as eq 29. In order to provide a good test of the applicability of this type of correlation we have examined a wide range of reaction types. They include rate constants for nucleophilic substitution of benzyl chloride by alkoxide ions and of allyl bromide and 1-chloro-2,4-dinitrobenzene by alkylamines for alkaline hydrolysis of ethyl 4-nitrophenyl alkyl phosphonates, C-substituted amides, O-substituted esters and $PhCAk^1Ak^2CN$, acidic hydrolysis of C-substituted amides, and finally for reactions of alcohols with 4-nitrobenzoyl chloride.

The data used in the correlations are set forth in Table VI. As the data available were insufficient to provide a test of the effect of branching at the δ atom, the correlation equation used was

$$Q = a'n_\alpha + b'n_\beta + c'n_\gamma + i' \qquad (30)$$

Results of the correlations are set forth in Table VII. In the case of sets 10 and 11, a justification of this equation is necessary. In these sets the substrate has the form XCN where CN is the active site and X may be written $Z^0Z^1Z^2C$ where Z^1 and Z^2 are alkyl groups or H and Z^0 is a constant substituent, in this case a phenyl group.

We have shown elsewhere that a single sp^3-hybridized carbon atom suffices to prevent the existence of a delocalized electrical effect. Then we may write as a correlation equation for these sets

$$Q_X = L(\sigma_{I,Z^0} + \sigma_{I,Z^1} + \sigma_{I,Z^2}) + s\upsilon_X + h \qquad (31)$$

We have presented evidence which indicates that $\sigma_{I,Ak}$ is constant, with an average value of -0.01 ± 0.02,[13] that is, alkyl groups do *not* have a variable localized electrical effect.[13,14] For H, $\sigma_I \equiv 0.00$. Thus, $\sigma_{I,Ak}$ and $\sigma_{I,H}$ are essentially equal. It then follows that $\sigma_{I,Z^1} = \sigma_{IZ^c}$ = constant. As S^0 is constant throughout, σ_{I,Z^0} is constant and $L\sum\sigma_{IZ}$ is constant, then

$$Q_X = S\upsilon_X + h \qquad (32)$$

where $h' = h + L\sum\sigma_{IZ}$.

We have demonstrated that for a substituent of the type WZ^1Z^2 we may write

$$\upsilon_{WZ^1Z^2} = m\upsilon_{CHZ^1Z^2} + b \qquad (33)$$

where W is some constant atom or group of atoms. Extending this relationship we obtain

$$\upsilon_{Z^0Z^1Z^2C} = m\upsilon_{Z^1Z^8CH} = b \quad (34)$$

Substituting eq 34 in eq 32 we obtain

$$Q = Sm\upsilon_{Z^1Z^3CH} + Sb + h' \quad (35)$$

or

$$Q = S'\upsilon_{X^1} + h'' \quad (36)$$

where X^1 is Z^1Z^2CH. Then on substituting eq 8 into eq 36 we obtain, after simplification, eq 30.

All of the sets studied gave significant correlations with eq 30. Significant branching effects at the α carbon atom were observed in all of the sets studied. Six sets (6, 10–13, 15) showed significant branching effects at the β carbon atom, and sets 5–7 and 11 showed significant branching effects at the γ carbon atom. The first conclusion we may reach is that for the use of eq 30 in determinating the effect of alkyl branching on reactivity, sufficient variation at the β and γ carbon atoms is required to permit conclusions to be drawn. The interpretation of the branching effects can be simplified by considering the quantities:

$$P_n = \frac{n \cdot 100}{\Sigma n} \quad (37)$$

where n is a', b', or c'. These quantities are reported in Table VIII. When c differed in sign from a' and b' we assumed that it was an artifact and considered only a' and b' in the calculations of P_n. Those sets which differed only in temperature provide a test for the variation in P_n to be expected when steric requirements of the transition state are essentially the same. Consideration of the P_n values for sets 1 and 2, 4–7, and 11 and 12 indicates that P_n values for reactions passing through the same type of transition state may differ by as much as about 10%. Certain patterns of behavior emerge from our examination of the P_n values. Thus, the reactions of alkylamines with allyl bromide and with 1-chloro-2,4-dinitrobenzene show the same type of behavior with substitution at the α carbon atom being by far predominant in determining the steric effects. The acid- and base-catalyzed hydrolysis of amides show about the same dependence of the steric effect on branching. The reaction of alkoxide with benzyl chloride shows predominance of α substitution with significant and equal effects of β and γ substitution. Overall, the results show that the steric effect of an alkyl group depends on the degree of branching, and the nature of the dependence varies from one reaction to another. This observations supports the concept that the steric effect of an alkyl group is dependent on the geometry of the transition state. It leads to the very important conclusion that *no one set* of steric parameters for alkyl groups will work for all types of reactions.

References and Notes

(1) M. Charton, *J. Am. Chem. Soc.*, **97**, 1552 (1975).
(2) M. Charton, *J. Org. Chem.*, **41**, 2217 (1976).
(3) M. Charton, *J. Org. Chem.*, **42**, 3531 (1977).
(4) M. Charton, *J. Org. Chem.*, **42**, 3535 (1977).
(5) M. Charton and B. I. Charton, *J. Org. Chem.*, **43**, 1161 (1978).
(6) M. Charton, *J. Am. Chem. Soc.*, **97**, 3694 (1975).
(7) M. Charton and B. I. Charton, *J. Org. Chem.*, **43**, 2383 (1978).
(8) K. Bowden and K. R. H. Woolridge, *Biochem. Pharmacol.*, **22**, 1015 (1973).
(9) M. S. Newman, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956.
(10) V. A. Rybkov, V. Y. Gankin, and B. L. Gurevich, *Zh. Prikl. Khim. (Leningrad)*, **48**, 694 (1975); *Chem. Abstr.*, **82**, 138869 (1975).
(11) C. K. Hancock, E. A. Myers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211 (1961).
(12) V. A. Palm, "Fundamentals of the Quantiative Theory of Organic Reactions", Khimiya, Leningrad, 1967.
(13) M. Charton, *Prog. Phys. Org. Chem.*, in press.
(14) M. Charton, *J. Am. Chem. Soc.*, **99**, 5687 (1977).
(15) A correlation of gas phase relative proton affinities of alkylamines with $\sigma_{I,alkyl}$ values has been reported: R. W. Taft and L. S. Levitt, *J. Org. Chem.*, **42**, 917 (1977). We suspect the validity of the σ_I constants used in this correlation because they were not derived from data sets which included substituent types other than alkyl groups.

Alkaline Hydrolysis of Methyl Carboxylates, Alkyl Acetates, and Alkyl Carboxylates. Steric Effects in Carboxylic Acid Derivatives and Related Systems[1]

John P. Idoux*

Department of Chemistry, Florida Technological University, Orlando, Florida 32816

James O. Schreck

Department of Chemistry, University of Northern Colorado, Greeley, Colorado 80639

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The second-order alkaline hydrolysis rate constants for nine methyl carboxylates (RCOOMe), nine alkyl acetates (MeCOOR'), and nine identically substituted alkyl carboxylates (RCOOR', R = R') have been determined in 40% aqueous *p*-dioxane at 20 and 50 °C. The variation in reactivity in these series is controlled predominantly by steric effects of the R and R' groups. These effects are as significantly represented in terms of E_s as in terms of ν_R for variable substitution in the acyl portion of ester molecules. Similar results are observed when previously reported data on a variety of other acyl substituted carboxylic acid derivatives are evaluated in terms of E_s and ν_R. The effect of variable substitution in the nonacyl portion of ester molecules is as adequately represented in terms of E_s^c-type parameters as in terms of ν-type parameters. However, for most carboxylic derivatives RCXGR' (X = O or S and G = O, S, or NH), the influence of nonacyl groups on acyl group properties is in general more significantly represented in terms of corrected steric parameters (E_s^c-type) than in terms of individual $\nu_{GR'}$ parameters where ν values change as G changes. Thus, the necessity for sets of steric parameters derived from a variety of defining basis sets appears to be questionable.

The study of steric substituent effects and their influence on molecular properties have been of interest for a considerable period of time.[2-4] The quantification of these effects was proposed originally by Taft[2] in terms of the steric substituent parameter E_s as determined from rate studies on the acid hydrolysis of acyl substituted esters (RCOOR', R' is constant). In an attempt to refine the steric substituent parameter, Hancock and his co-workers[5] determined a set of steric parameters (E_s^c) corrected for hyperconjunction effects and applicable to the alkyl portion of carboxylate esters. The application of the E_s and E_s^c parameters to a variety of chemical systems has since provided a considerable amount of information regarding the influence of steric effects, and many of these studies have provided useful quantitative relationships in terms of these parameters.[3] More recently, Charton[6a] has demonstrated the linearity of Taft's original E_s values with van der Waals radii and has defined[6b] new steric substituent constants (ν_x) in terms of the van der Waals radii of the X groups. These new values have then been used to assess the effect of steric factors on a variety of rate, equilibria, and physical data.[7a,b] However, while the latter results are of interest, no assessment of the validity or necessity of the more established steric parameters has been attempted relative to the new ν_x values. Such an assessment is particularly important relative to carboxylic acid derivatives which are the defining basis set for all of the steric parameters. That is, while all E_s-type parameters are derived from acyl substituted carboxylate esters, ν_x values were calculated initially for groups substituted only in the acyl portion of carboxylate esters with additional sets of values (ν_{GX}) being required for the nonacyl portion of these derivatives and for each different type of nonacyl G moiety. Thus, it appeared to be of interest to investigate the applicability of the various steric parameters via data on closely related carboxylate systems under identical reaction conditions. The present paper reports the results of such a study based on our determinations of the alkaline hydrolysis rate constants in 40% aqueous *p*-dioxane at 20 and 50 °C for a series of identically substituted alkyl acetates (MeCOOR'), methyl carboxylates (RCOOMe, R = R' of acetates), and alkyl carboxylates (RCOOR', R = R'). Also included for comparison is the evaluation in similar terms of previously reported data on other carboxylic acid derivatives.

Results and Discussion

The second-order alkaline hydrolysis rate constants (log k, L mol^{-1} min^{-1}) at 20 and 50 °C in 40% aqueous *p*-dioxane for the methyl carboxylates, alkyl acetates, and alkyl carboxylates are reported in Table I along with a number of steric parameters for various R and R' groups.

Effect of Variable Steric Factors in the Acyl Portion of Carboxylic Acid Derivatives. Inspection of the data in Table I for the methyl carboxylates (RCOOMe) indicates a relative order of reactivity in accord with the variable steric factors of the R groups as represented by E_s or ν_R. Correlation analyses[3,8] of these data give eq 1 and 2 (for data at 20 °C) and eq 3 and 4 (for data at 50 °C).

$$\log k = 0.83 + 0.93E_s,\ r^2 = 99.3\%,\ s = 0.045 \quad (1)$$
$$(<0.001)$$

$$\log k = 1.86 - 1.99\nu_R,\ r^2 = 99.1\%,\ s = 0.052 \quad (2)$$
$$(<0.001)$$

$$\log k = 1.55 + 0.91E_s,\ r^2 = 98.3\%,\ s = 0.071 \quad (3)$$
$$(<0.001)$$

$$\log k = 2.56 - 1.95\nu_R,\ r^2 = 98.0\%,\ s = 0.075 \quad (4)$$
$$(<0.001)$$

The significance of the various equations is essentially identical and indicates that variable steric effects in the acyl portion of this particular series are as adequately represented in terms of E_s as in terms of ν_R. Additional confirmation of this result is provided by the correlations reported in Table II which involve rate data for for the formation or hydrolysis of a variety of carboxylic acid derivatives RCOGR' (R variable, R' constant, G = O, S, or NH). That is, inspection of these data reveals that the effect of variable steric factors from the acyl portion of carboxylic acid derivatives is independent of the nature of G and can be represented as significantly by E_s as

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Table I. Second-Order Alkaline Hydrolysis Rate Constants (log k, L mol^{-1} min^{-1}) at 20 and 50 °C in 40% Aqueous p-Dioxane and Steric Parameters for R and R′ for Methyl Carboxylates (RCOOMe), Alkyl Acetates (MeCOOR′), and Alkyl Carboxylates (RCOOR′)

R or R′	log k for RCOOMe at registry no.	20 °C	50 °C	log k for MeCOOR′ at registry no.	20 °C	50 °C	log k for RCOOR′ (R = R) at registry no.	20 °C	50 °C	E_s(R)[a]	E_s(R′)[b]	E_s(CH$_2$R′)[c]	ν_R[d]	$\nu_{OR'}$[e]
Me	79-20-9	0.9028	1.6555		0.9028	1.6555		0.9028	1.6555	0	0	−0.38	0.52	0.36
Et	554-12-1	0.7651	1.4600	141-78-6	0.5858	1.2718	105-37-3	0.3879	1.0660	−0.07	−0.38	−0.67	0.53	0.48
n-Pr	623-42-7	0.4754	1.2648	109-60-4	0.4530	1.1300	105-66-8	−0.0981	0.6086	−0.36	−0.67	−0.70	0.68	0.56
i-Pr	547-63-7	0.3560	1.0483	108-21-4	−0.1267	0.6175	617-50-5	−1.1440	−0.4468	−0.47	−1.08	−1.24	0.73	0.75
n-Bu	624-24-8	0.4267	1.1045	123-86-4	0.3788	1.0649	591-68-4	−0.2574	0.4486	−0.39	−0.70	−0.71	0.68	0.58
i-Bu	556-24-1	−0.0795	0.6726	110-19-0	0.2742	0.9927	589-59-3	−0.8755	−0.1728	−0.93	−1.24	−0.74	0.98	0.62
s-Bu	868-57-5	−0.2012	0.5419	105-46-4	−0.4167	0.3412	869-08-9	−2.2205	−1.2931	−1.13	−1.74	−1.36	1.02	0.86
t-Bu	598-98-1	−0.5700	0.1838	540-88-9	−1.4553	−0.5583	16474-43-4	−3.7768	−3.1838	−1.54	−2.46	−2.05	1.24	1.22

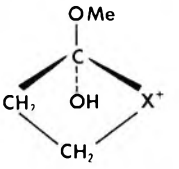
[a] Reference 2. [b] Reference 5. [c] Calculated from E_s(R′) assuming -O- equivalent to -CH$_2$-. [d] Reference 7. [e] Reference 19.

Table II. Results of Correlation Analysis of Rate Data for the Formation and Hydrolysis of Carboxylic Acid Derivatives, RCOGR′ (R variable, R′ constant, G = O, S, or NH)[a]

set	parameter coefficient	r^2, %	s	t_s	n[b]
1X[c]	−1.83	98.8	0.047	<0.001	9
1Y	0.984	99.6	0.029	<0.001	9
2X[d]	−1.95	99.9	0.016	<0.001	17
2Y	0.90	99.1	0.054	<0.001	17
3X[e]	−1.25	97.5	0.061	<0.001	6
3Y	−0.59	98.7	0.044	<0.001	6
4X[f]	−2.20	99.0	0.052	<0.001	9
4Y	0.93	99.0	0.051	<0.001	9
5X[g]	−2.59	97.5	0.157	<0.001	8
5Y	1.28	98.5	0.122	<0.001	8
6X[h]	−2.59	98.6	0.137	<0.001	8
6Y	1.28	98.7	0.129	<0.001	8
7X[i]	−1.75	96.8	0.091	<0.001	9
7Y	0.93	96.9	0.090	<0.001	9
8X[j]	−1.87	94.8	0.082	<0.001	10
8Y	0.86	93.4	0.093	<0.001	10
9X[k]	−2.13	98.0	0.083	<0.001	8
9Y	0.99	98.0	0.084	<0.001	8

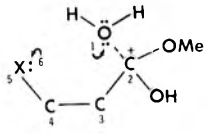
[a] Correlations using ν are designated X and those using E_s are designated Y. [b] Number of compounds in data set. [c] RCOOEt + H_2O in 70% MeAC–H_2O at 44.7 °C/HCl from G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940). [d] RCOOH + MeOH at 50 °C/MeOH–HCl from H. A. Smith, *J. Am. Chem. Soc.*, **61**, 254 (1939); **62**, 1136 (1940). [e] RCOOC$_6$H$_4$NO$_2$-4 + H_2O at 30 °C/H_2O from T. H. Fife and D. M. McMahon, *ibid.* **91**, 7481 (1969). [f] RCOOMe + H_2O in MeOH–H_2O at 25 °C/HCl from M. H. Palomaa et al., *Ber.*, **69B**, 1338 (1936); **68**, 887 (1935); *Suom. Kemistil. B*, **19**, 85 (1946); *ibid.*, **19**, 53 (1946). [g] RCOOEt + HO$^-$ in 70% MeAc/H_2O at 35 °C from G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940). [h] RCOOEt + HO$^-$ in 85% EtOH–H_2O at 25 °C from H. A. Smith et al., *J. Am. Chem. Soc.*, **61**, 1172 (1939); **62**, 1556, 2324, 2733 (1940); **64**, 2362 (1942). [i] RCONH$_2$ + H_3O^+ in H_2O at 75 °C from A. Bruylants and F. Kezdy, *Rec. Chem. Prog.*, **21**, 213 (1960); P. D. Bolton, *Aust. J. Chem.*, **19**, 1013 (1966). [j] RCONH$_2$ + HO$^-$ in H_2O at 75 °C from P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 969 (1971). [k] RCOSMe + HO$^-$ in 40% dioxane–H_2O at 35 °C from J. P. Idoux, P. T. R. Hwang, and C. K. Hancock, *J. Org. Chem.*, **38**, 4239 (1973).

by ν_R. An additional point of interest concerning the comparison of E_s and ν_R involves R groups of the type XCH$_2$CH$_2$ where X = O, S, Cl, and I. Such groups have been described[13] as having "unexpectedly large ν_R values" (compared to XCH$_2$ and X(CH$_2$)$_3$ groups) due to the importance of a structure such as I in which the protonated ester is assumed to be stabilized and thus less reactive to attack by a water molecule.



I

However, when such groups are viewed in terms of E_s, this explanation is unnecessary. For carboxylic acids and esters, Newman[14] has demonstrated that the six number of a substituent (i.e., the number of atoms in the six position from the carbonyl oxygen atom as atom number one) makes a large contribution to the total steric effect of that substituent and is thus an important factor in considering the esterification of carboxylic acids and the hydrolysis of the corresponding esters. The E_s value for a substituent, as defined by Taft,[2] is the total steric effect for a substituent and includes the steric six-number effect. The influence of a six-number effect on reactions which involve addition to a carbonyl function has been expanded[15] to include the attacking group so that groups in the substrate which interfere with the addition reaction are separated from the attacking group in the transition state by four atoms. Thus the influence of XCH$_2$CH$_2$ groups is not unexpectedly large but rather, as shown in structure II, is



II

expected when considered in terms of a six-number effect between unshared electron pairs on the oxygen of a water molecule as position 1 and unshared electron pairs on X as position 6. For XCH$_2$ and X(CH$_2$)$_3$ groups in an aliphatic chain with normal bond lengths and bond angles,[16,17] unshared electron pairs on X would occupy the less effective 5 or 7 positions. Other interesting examples of the influence of six-number effects on esterification by alkylation of carboxylate salts[17] and on esterification of alkyl substituted acetic acids[18] have recently been reported.

Effect of Variable Steric Factors in the Nonacyl Portion of Carboxylic Acid Derivatives. Inspection of the data in Table I for the alkyl acetates (MeCOOR′) indicates that the relative order of reactivity (with the exception of R′ = i-Bu) is identical to that for the methyl carboxylates while the absolute reactivity of any particular acetate is less in each case (with the exception of R = R′ = i-Bu) than that of the corresponding carboxylates. As expected, the quantitative analysis of the acetate data in terms of E_s or $\nu_{R'}$ leads to poorer overall correlations than that in terms of E_s^c (Table III). However,

Table III. Results of Correlation Analysis of Alkyl Acetate Data (Table I) with E_s, $\nu_{R'}$, and E_s^c

steric parameter	parameter coeff	r^2, %	s	t_s
E_s	1.24[a]	81.9	0.34	0.003
	1.15	82.1	0.31	0.003
$\nu_{R'}$	−2.66	81.3	0.35	0.004
	−2.45	81.5	0.32	0.004
E_s^c	0.91	92.9	0.21	<0.001
	0.84	93.7	0.18	<0.001

[a] The first set of values in each case is for data at 20 °C and the second set is for data at 50 °C.

the latter correlation is considerably improved when the variable steric factors of the R′ group are assessed in terms of $E_s^c(CH_2R')$ (eq 5 and 6, 20 and 50 °C, respectively).

$$\log k = 1.42 + 1.37E_s^c(CH_2R'),\ r^2 = 98.5\%,\ s = 0.098 \quad (5)$$
$$(<0.001)$$

$$\log k = 2.05 + 1.26E_s^c(CH_2R'),\ r^2 = 98.3\%,\ s = 0.095 \quad (6)$$
$$(<0.001)$$

The latter constant is simply calculated from $E_s^c(R')$ assuming that the interposition of an oxygen between the carbonyl carbon and the R′ group is approximately equivalent to that of a CH_2 group. In a similar manner, $\nu_{OR'}$ values have been determined by Charton[19] for the R′ group in the nonacyl portion of an ester. Analysis of the alkyl acetate data in terms of $\nu_{OR'}$ (eq 7 and 8, 20 and 50 °C, respectively) also leads to significantly improved correlations relative to that with $\nu_{R'}$.

$$\log k = 1.96 - 2.77\nu_{OR'},\ r^2 = 99.7\%,\ s = 0.042 \quad (7)$$
$$(<0.001)$$

$$\log k = 2.55 - 2.55\nu_{OR'},\ r^2 = 99.8\%,\ s = 0.028 \quad (8)$$
$$(<0.001)$$

Similarly, either $E_s^c(CH_2R')$ or $\nu_{OR'}$ provides the best representation of variable steric effects from the nonacyl portion of a carboxylate ester for the acid-catalyzed hydrolysis of alkyl acetates (set 1, Table IV) and for the formation of alky benzoates (set 2, Table IV). However, because of corresponding differences in bond lenghts and bond angles, the use of $E_s^c(CH_2R')$ or $\nu_{OR'}$ does not adequately represent variable steric effect changes from the R′ group for other carboxylic acid derivatives, RCOGR′, in which R is constant, R′ is variable, and G ≠ O. For example, for N-monosubstituted amides (G = NH in RCOGR′) we have demonstrated previously[20] that R′ groups exert a steric influence on the acyl portion of the molecule which is not accounted for solely by E_s^c. That is, groups in the seven position of R′ (from the carbonyl oxygen as position one) affect the acyl portion of these molecules and provide an additional factor of importance when considering properties associated with the acyl portion. In a similar manner, $\nu_{NHR'}$ constants have been determined[21] for the R′ group in the nonacyl portion of amides. Correlation analysis of a variety of chemical and physical properties of N-monosubstituted amides (RCONHR′, R constant, R′ variable) in terms of E_s^c + H-7-no (the seven position effect of R′ in terms of the number of hydrogen atoms in the seven position of R′) or in terms of $\nu_{NHR'}$ are reported in Table IV (sets 3–8). In general, variable steric effects from the R′ portion of these molecules are as or more meaningfully represented in terms of E_s^c + H-7-no than in terms of $\nu_{NHR'}$. Presumably, one could determine $\nu_{GR'}$ values for the R′ group of any RCXGR′ derivative, but those values would be applicable only to the defining basis set or to closely related systems. For example, a case in point is the correlations reported in set 8 of Table IV for the H^1 NMR substituent chemical shifts (SCS) of the acyl

Table IV. Results of Correlation Analysis of Rate and Physical Data for Carboxylic Acid Derivatives, RCOGR′ (R constant, R′ variable, G = O, NH, or S)

set	steric parameters	parameter coeff	r^2, %	s	t_s	n[a]
1[b]	$E_s^c(CH_2R')$	0.47	98.5	0.045	<0.001	5
	$\nu_{OR'}$	−0.94	99.5	0.026	<0.001	5
2[c]	$E_s^c(CH_2R')$	1.15	93.1	0.16	<0.001	10
	$\nu_{OR'}$	−2.32	89.9	0.20	<0.001	10
3[d]	E_s^c + H-7-no	0.64 + 0.051	97.1	0.060	<0.001 + 0.005	8
	$\nu_{NHR'}$	−1.33	97.3	0.052	<0.001	8
4[e]	E_s^c + H-7-no	0.90 + 0.056	98.4	0.056	<0.001 + 0.010	6
	$\nu_{NHR'}$	−1.94	98.4	0.049	<0.001	6
5[f]	E_s^c + H-7-no	2.25 + 0.42	91.5	0.36	<0.001 + 0.003	8
	$\nu_{NHR'}$	−3.97	70.7	0.61	0.008	8
6[g]	E_s^c + H-7-no	−1.53 + 0.48	90.4	0.49	<0.001 + <0.001	14
	$\nu_{NHR'}$	−2.43	77.1	0.57	0.001	10
7[h]	E_s^c + H-7-no	−4.52 + 0.52	99.8	0.17	<0.001 + <0.001	5
	$\nu_{NHR'}$	15.38	98.6	0.42	<0.001	5
8[i]	E_s^c + H-7-no	2.62 + 0.70	90.0	0.64	0.005 + 0.005	6
	$\nu_{NHR'}$	−3.79	38.7	1.35	0.200	6
9[j]	E_s^c	0.30	92.0	0.076	<0.001	8
	$\nu_{SR'}$	−0.87		defining basis set for $\nu_{SR'}$		
10[k]	E_s + E_s^c	0.99 + 0.42	99.0	0.12	<0.001 + 0.001	7
	ν + $\nu_{SR'}$	−2.00 + 1.27	99.5	0.09	<0.001 + <0.001	7

[a] Number of compounds in data set. [b] MeCOOR′ + H^+ in H_2O at 30.1 °C from T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 1, W. A. Benjamin, New York, N.Y., 1966, p 272. [c] ROH + 4-$O_2NC_6H_4COCl$ in Et_2O at 25 °C from J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925); **49**, 2340 (1927). [d] MeCONHR′ + H_3O^+ in H_2O at 75 °C from P. D. Bolton, J. Ellis, R. D. Frier, and P. C. Nancarrow, *Aust. J. Chem.*, **25**, 303 (1972). [e] MeCONHR′ + HO^- in H_2O at 75 °C from T. Yamana, Y. Mizukami, A. Tsuji, Y. Yasuda, and K. Masuda, *Chem. Pharm. Bull.*, **20**, 881 (1972). [f] MeCOOMe + RNH_2 in dioxane 5 M in $(CH_2OH)_2$ from E. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950). [g] ^1H NMR substituent chemical shifts for the acyl methyl protons of MeCONHR′ from J. P. Idoux, J. M. Scandrett, and J. A. Sikorski, *ibid.*, **99**, 4577 (1977). [h] Angle of rotation ϕ about the N_1–C_α bond of $MeCON_1(H)$–$C_\alpha HR'CONHMe$ from M. T. Cung, M. Marraud, and J. Neel, *Jerusalem Symp. Quantum Chem. Biochem.*, **5**, 69 (1973). [i] ^1H NMR substituent chemical shifts for the acyl methyl protons of MeCSNHR′ from J. P. Idoux and A. Davis, unpublished results. [j] MeCOSR′ + HO^- in 40% dioxane–H_2O at 35 °C from J. P. Idoux, P. T. R. Hwang, and C. K. Hancock, *J. Org. Chem.*, **38**, 4239 (1973). [k] RCOSR′ + HO^- in 40% dioxane–H_2O at 35 °C from reference in footnote *j*.

methyl protons of a series of N-monosubstituted thioacetamides (MeCSNHR'). That is, the variation in SCS in this series is adequately represented in terms of E_s^c + H-7-no for R' while evaluation in terms of $\nu_{NHR'}$ constants gives a very poor correlation. In addition, a comparison of these data with those of set 6 in Table IV provides a direct assessment of the influence of 7-position R' groups in these systems. The latter effects are obviously not accounted for by $\nu_{NHR'}$ and thus tend to be obscured by correlation analysis using $\nu_{NHR'}$. If the G heteroatom in RCXGR' is sulfur (MeCOSR', set 9 and RCOSR', set 10), there is an increase in distance between the acyl center and R' due to the larger van der Waals radius of the connecting sulfur atom. Thus, 7-position influence of R' becomes minimal and correlations simply in terms of E_s^c provide a good indication of the effect of R' groups which can then be compared directly to other RCXGR' systems.

The examples cited above establish the usefulness of E_s^c-type parameters but more importantly serve to emphasize the use of correlation analysis as only a "guide" or "tool" in assessing the influence of variable steric effects without at the same time neglecting the comparison of individual groups or systems.

Effect of Simultaneous Variable Steric Factors in the Acyl and Nonacyl Portion of Carboxylic Acid Derivatives. Inspection of the data in Table I for the alkyl carboxylates (RCOOR', R = R') indicates, as expected from analysis of the corresponding MeCOOR' and RCOOMe derivatives, that simultaneous, variable steric factors from the acyl and nonacyl portions of the molecules have a magnified effect on the reactivities. Correlation analyses of these data give eq 9 and 10 (for the data at 20°) and eq 11 and 12 (for data at 50°) and confirm the earlier assessments in terms of E_s and ν_R for R and $E_s^c(CH_2R')$ and $\nu_{OR'}$ for R'.

$$\log k = 1.49 + 1.31E_s + 1.61E_s^c(CH_2R'), \quad (<0.001) \quad (<0.001)$$
$$R^2 = 99.9\%, s = 0.064 \quad (9)$$

$$\log k = 3.31 - 1.72\nu_R - 4.14\nu_{OR'}, R^2 = 99.6\%, s = 0.12 \quad (0.008) \quad (<0.001) \quad (10)$$

$$\log k = 2.26 + 1.22E_s + 1.71E_s^c(CH_2R'), \quad (<0.001) \quad (<0.001)$$
$$R^2 = 99.7\%, s = 0.096 \quad (11)$$

$$\log k = 4.02 - 1.48\nu_R - 4.42\nu_{OR'}, R^2 = 99.9\%, s = 0.034 \quad (<0.001) \quad (<0.001) \quad (12)$$

However, while the significance of the various equations is statistically high and essentially identical, the differences between the coefficients of ν_R and $\nu_{OR'}$ in eq 10 and 12 are substantially larger than the corresponding differences from eq 2 and 7 and from eq 4 and 8. Thus, based solely on eq 10 and 12, one would predict a substantial difference in the importance and degree of simultaneous, variable steric effects from the acyl and nonacyl portions of these esters. A similar assessment in terms of E_s and $E_s^c(CH_2R')$ from eq 9 and 11 leads to more reasonable acyl/nonacyl contributions when compared to eq 1 and 5 and eq 3 and 6.

Summary

The comparative correlations reported in this study demonstrate that the influence of variable steric effects in the acyl portion of a carboxylic acid derivative can be assessed as well in terms of E_s as in terms of ν. However, certain substituents (e.g., flexible XCH_2CH_2, X = O, S, Cl, and I) appear to have an exhalted steric influence when considered in terms of ν values. For these groups, their influence is better treated in terms of E_s and individual considerations of six-number effects. On the other hand, the influence of variable steric effects originating from the nonacyl portion of a carboxylic acid derivative and the influence of simultaneously variable steric effects from the acyl and nonacyl portions of these derivatives are more properly treated in terms of E_s-type parameters. In particular, the validity and importance of E_s^c-type parameters, as proposed by Hancock,[5] appear to be clearly established. These parameters have the additional advantages (relative to the various ν values) of having been derived from a single, common defining basis set and of being applicable to the study of variable steric effects in non-carboxylic acid systems.[3] Thus, the necessity for sets of steric parameters derived from a variety of defining basis sets appears to be questionable. More importantly, the nature of the correlations reported in this study serves to emphasize the fact that correlation analysis should be relied upon only as a "guide" or "tool" in assessing variable steric effects and should not be relied upon to replace the direct comparison of groups or systems whereby more meaningful indications of differences and/or deviations can often be obtained.

Experimental Section

The esters used in this study were either obtained commercially or were prepared by well known procedures. All of the esters were purified by distillation to constant boiling points in agreement with previously reported values.[22]

The second-order alkaline hydrolysis rate constants reported in Table I are the average of at least three determinations and were determined conductiometrically as described previously in detail.[5] The average deviation from the mean of replicate rate constant values did not exceed 1.5% except in the following cases: at 20 °C, EtCOOEt (1.6%), *s*-BuCOO-*s*-Bu (3.2%), *t*-BuCOO-*t*-Bu (3.8%); at 50 °C, *n*-PrCOOMe (2.0%), *i*-PrCOOMe (3.4%), *n*-BuCOOMe (2.1%), MeCOO-*n*-Bu (2.8%), EtCOOEt (2.7%), *n*-PrCOO-*n*-Pr (1.6%).

The statistical calculations were performed on an IBM 360-75 computer using the Ohio State University interactive regression program MULREG.

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References and Notes

(1) Presented in part at the Florida American Chemical Society Meeting-in-Miniature, Lakeland, Fla. May 12–14, 1977. Part 4 of Proximity Effects. Part 3: *Tetrahedron*, **33**, 2369 (1977).
(2) R. W. Taft in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 3.
(3) N. B. Chapman and J. Shorter, Ed., "Advances in Linear Free Energy Relationships," Plenum Press, New York, N.Y., 1972.
(4) S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, **12**, 91 (1976).
(5) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211 (1961).
(6) (a) M. Charton, *J. Am. Chem. Soc.*, **91**, 615 (1969); (b) M. Charton, *Prog. Phys. Org. Chem.*, **10**, 81 (1973).
(7) (a) M. Charton, *J. Am. Chem. Soc.*, **97**, 1552 (1975); (b) M. Charton, *J. Org. Chem.*, **41**, 2906 (1976), and earlier references cited therein.
(8) J. Shorter, "Correlation Analysis in Organic Chemistry", Clarendon Press, Oxford, 1973. For all of the correlations reported in this paper, r^2 represents the square of the correlation coefficient[9a] expressed as a percentage (provides an indication of the percent variation in the correlated property which is accounted for by the particular relationship) and s[9a] represents the standard deviation from regression. The t_s values (Tables II–IV) and the values in parentheses (eq 1–12) are the significance levels of the coefficient of the particular parameter as determined by "Student's" t-test[9b] and, as recommended by other chemists,[10-12] serve as an appropriate goodness of fit criterion for expressing the confidence with which a regression coefficient is known.
(9) G. W. Snedecor, "Statistical Methods", 5th ed, The Iowa State University Press, Ames, Iowa, 1956: (a) Chapter 14; (b) pp 46, 418, and 441.
(10) C. K. Hancock, *J. Chem. Educ.*, **42**, 608 (1965).
(11) R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 3142 (1963).
(12) W. H. David, Jr., and W. A. Pryor, *J. Chem. Educ.*, **53**, 285 (1976).
(13) M. Charton, *J. Org. Chem.*, **41**, 2217 (1976).
(14) M. S. Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950).
(15) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N. Y., 1959.
(16) K. L. Loening, A. B. Garrett, and M. S. Newman, *J. Am. Chem. Soc.*, **74**,

3929 (1952).
(17) P. E. Pfeffer and L. S. Silbert, J. Org. Chem., 41, 1373 (1976).
(18) P. J. Sniegoski, J. Org. Chem., 41, 2058 (1976).
(19) M. Charton, J. Org. Chem., 42, 3531 (1977).
(20) J. P. Idoux, J. M. Scandrett, and J. A. Sikorski, J. Am. Chem. Soc., 99, 4577 (1977).
(21) M. Charton, J. Org. Chem., 42, 3535 (1977).
(22) The literature references, physical properties, and a description of the synthetic methods used for the preparation of the various esters can be obtained upon request to the corresponding author.

Solvolysis of 2-Oxiryl-2-propyl *p*-Nitrobenzoate. Evidence on the Mode of Stabilization of the Oxirylcarbinyl Cation

Edward N. Peters

Union Carbide Corporation, Chemicals and Plastics, One River Road, Bound Brook, New Jersey 08805

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The effect of a neighboring oxiryl group on the stability of an adjacent developing cationic center is minor in comparison to a cyclopropyl group. Thus, a neighboring oxiryl group increases the rate of solvolysis by a factor of 10 over an acyclic analogue. By comparison, a neighboring cyclopropyl provides a rate enhancement of 10^5 over an acyclic control.

There has been considerable interest in the solvolytic behavior of heterocyclic analogues of cyclopropylcarbinyl systems. The effect of a neighboring oxirane has been studied by several workers.[1-6] The oxirane ring can theoretically stabilize an adjacent cationic center by conjugative stabilization through its strained bonds and/or by participation of the nonbonded electrons on oxygen.[1-6]

However, the degree to which a neighboring oxirane group stabilizes an adjacent cationic center is in doubt. Reports have varied from a lack of significant participation to an oxirane group being almost as effective as a cyclopropyl group in stabilizing a cationic center.[1,5,6] Therefore, a comparison of the rates of solvolysis of the 2-oxiryl-2-propyl system with a suitable reference system, 2-methyl-3-methoxy-2-butyl, which allows for the estimation of inductive effects and the participation by lone pair electrons on a β oxygen, and the 2-cyclopropyl-2-propyl system with the 2,3-dimethyl-2-butyl system was undertaken.

Results

Synthesis. 2-Oxiryl-2-propyl *p*-nitrobenzoate (1) was prepared by the epoxidation of 2-methyl-3-buten-2-yl *p*-nitrobenzoate with *m*-chloroperbenzoic acid at 0 °C in methylene chloride. At higher temperatures the oxiryl ring is opened by the *m*-chlorobenzoic acid which is formed in the reaction.

Rates. Rates of solvolysis were determined titrimetrically in 80:20 acetone–water (v/v) by the procedure previously reported.[7] The compounds followed first-order kinetics except for 2-oxiryl-2-propyl *p*-nitrobenzoate (1) which exhibited a decrease in rate after 20% reaction. Therefore, the initial rate constant was determined during the first 20% of the reaction. This deviation was due to side reactions as described below in the product study. The rate data appear in Table I.

Products of Solvolysis. Oxiranes undergo facile reactions with both electrophilic and nucleophilic reagents. As noted in the synthesis of 1, the presence of benzoic acid derivatives leads to opening of the oxiryl ring. Thus, during solvolysis of 1, ≥50% rearranges to a secondary *p*-nitrobenzoate (via NMR). The formation of relatively unreactive secondary esters results in a decrease in rate.

Kinsman has reported that solvolysis of 2-oxiryl-2-propyl dinitrobenzoate gives a complex mixture of products.[9] Between 65 and 80% rearranges to 2,2-dimethyl-3-oxetanyl dinitrobenzoate. The products arising from solvolysis are 2,2-dimethyl-3-oxetanol and polymer (polyether). 2-Oxiryl-2-propanol rearranges to triols under solvolytic conditions; however, none was reported in the reaction products.[9]

These results suggest that 2-oxiryl-2-propyl derivatives react via ring expansion to give secondary esters (ion pair return) and oxetanols (hydrolysis by an ionizing mechanism in which the dinitrobenzoate acts as a leaving group).[3,9]

Discussion

The strained bonds in an oxiryl group have been reported to be almost as effective as the strained bonds of the cyclopropyl group in stabilizing a cationic center.[1,5] However, the strain energy in the oxiryl group is substantially less than in a cyclopropyl group.[10]

If neighboring group stabilization is important in a system, the rate of solvolysis must be greater than the unassisted rate of solvolysis estimated from reference compounds.[11] Clearly the choice of a reference system which reacts without stabilization is critical.[7,12] The isopropyl group is a suitable model system for the cyclopropyl group because of similar steric requirements.[13] On the other hand, the isopropyl group is a

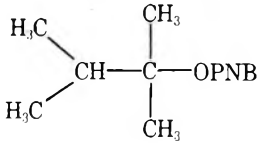
Table I. Rate Constants in 80% Acetone

p-nitrobenzoate	temp, °C	k_1, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
2,3-dimethyl-2-butyl[a] (3)	25.0	2.15×10^{-10}[b]	28.5	−7.3
2-cyclopropyl-2-propyl[a] (2)	25.0	3.75×10^{-5}	20.8	−9.0
2-methyl-3-methoxy-2-butyl (4)	150.0	1.97×10^{-5}		
	125.0	1.66×10^{-6}		
	25.0	1.32×10^{-12}[b]	32.5	−3.8
2-oxiryl-2-propyl (1)	150.0	1.49×10^{-4}[c]		
	125.0	1.31×10^{-5}[c]		
	25.0	1.33×10^{-11}[b]	(32)	(−1)

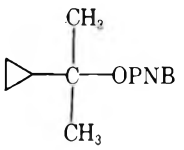
[a] Reference 8. [b] Calculated from data at other temperatures. [c] Initial (20%) rate constants.

poor reference system for the oxiryl group because of the greater electronegativity of the oxygen which can decrease the rate as well as any participation by the nonbonded electrons on oxygen. Although neighboring alkoxy participation has been reported to be unimportant, it can decrease the rate of solvolysis.[14] Therefore, the 1-methoxy-1-ethyl group was used as a reference system for the oxiryl group.

2-Cyclopropyl-2-propyl *p*-nitrobenzoate (**2**) solvolyzes 175 000 times faster than 2,3-dimethyl-2-butyl *p*-nitrobenzoate (**3**). Thus, the strained carbon–carbon bonds in cyclo-



3

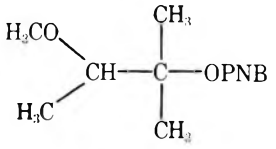


2

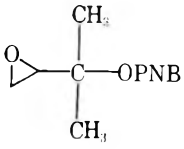
relative rate	1.0	175 000

propyl are playing a substantial role in the stabilization of the developing cationic center.

2-Oxiryl-2-propyl *p*-nitrobenzoate (**1**) reacts 10 times faster than 2-methyl-3-methoxy-2-butyl *p*-nitrobenzoate (**4**).



4



1

relative rate	1.0	10.1

Clearly the strained bonds in the oxiryl group are only contributing a minor amount of stabilization to the developing cationic center.

Conclusions

Using **4** as a model system for an indication of the inductive effect of the oxygen and any participation by the nonbonded electrons of oxygen[14] on the rate, the strained oxirane bonds in **1** increase the rate of solvolysis by a factor of 10. Thus, these results indicate that the oxiryl group is substantially less effective than a cyclopropyl group in stabilizing an adjacent cationic center. Indeed, the rate of solvolysis of **1** is 10^5 times slower than the rate of solvolysis of **2** under similar conditions.

Experimental Section

2-Methyl-3-buten-2-yl *p*-nitrobenzoate was prepared from 2-methyl-3-buten-2-ol (Aldrich Chemical Co.) via the lithium alkoxide method[7] (89% yield), mp 115.5–116.5 °C.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.38; H, 5.62; N, 6.05.

2-Oxiryl-2-propyl *p*-Nitrobenzoate. A 1-g (4.25 mmol) amount of 2-methyl-3-buten-2-yl *p*-nitrobenzoate in 50 mL of methylene chloride was reacted with 7.42 mmol of *m*-chloroperbenzoic acid at 0 °C for 41 days. The precipitated *m*-chlorobenzoic acid was filtered, and the residue from the methylene chloride was recrystallized from hexane to a constant melting point: mp 62–63 °C; NMR ($CDCl_3$) δ 1.63 (s, 6 H, CH_3), 2.86 (d, J = 2 Hz, 1 H, epoxy CH), 3.43 (t, J = 2 Hz, 2 H, epoxy CH_2), 8.27 (d, 4 H, OPNB).

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.21; N, 5.58. Found: C, 57.43; H, 5.30; N, 5.47.

2-Methyl-3-methoxy-2-butyl *p*-nitrobenzoate was prepared from 2-methyl-3-methoxy-2-butanol[15] via the lithium alkoxide method (85% yield): mp 90.0–91.0 °C; NMR ($CDCl_3$) δ 1.23 (d, J = 7 Hz, 3 H, CH_3), 1.60 (s, 6 H, CH_3), 3.43 (s, 3 H, OCH_3), 3.80 (q, J = 7 Hz, 1 H, CH), 8.23 (d, 4 H, OPNB).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.41; N, 6.41; N. 5.24. Found: C, 58.36; H, 6.37; N, 5.21.

Registry No.—**1**, 67382-29-0; **2**, 23437-9902; **3**, 55705-64-1; **4**, 67382-28-9; 2-methyl-3-buten-2-yl *p*-nitrobenzoate, 35945-67-6; 2-methyl-3-buten-2-ol, 115-18-4; 2-methyl-3-methoxy-2-butanol, 67382-30-3.

References and Notes

(1) W. C. Danen, *J. Am. Chem. Soc.*, **94**, 4835 (1972).
(2) D. L. Whalen, *J. Am. Chem. Soc.*, **92**, 7619 (1970).
(3) H. G. Richey, Jr., and D. V. Kinsman, *Tetrahedron Lett.*, 2505 (1969).
(4) H. Morita and S. Oae, *Tetrahedron Lett.*, 1347 (1969).
(5) M. Santelli, *J. Chem. Soc., Chem. Commun.*, 214 (1974).
(6) (a) D. L. Whalen, S. Brown, A. M. Ross, and H. M. Russell, *J. Org. Chem.*, **43**, 428 (1978); (b) D. W. Whalen and J. D. Cooper, *ibid.*, **43**, 432 (1978).
(7) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **97**, 1927 (1975).
(8) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **99**, 1712 (1977).
(9) D. V. Kinsman, Ph.D. Thesis, The Pennsylvania State University, University Park, Pa., 1969.
(10) R. A. Nelson and R. S. Jessup, *J. Res. Natl. Bur. Stand.*, **48**, 206 (1952).
(11) S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *J. Am. Chem. Soc.*, **75**, 147 (1953).
(12) E. N. Peters, *J. Org. Chem.*, **42**, 3015 (1977).
(13) H. Hart and P. A. Law, *J. Am. Chem. Soc.*, **84**, 2462 (1962).
(14) (a) S. Winstein, E. Ajbed, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958); (b) S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948); (c) G. T. Kwiatkowski, S. J. Kavarnos, and W. D. Closson, *J. Heterocycl. Chem.*, **2**, 11 (1965).
(15) S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc.*, **74**, 1160 (1952).

Protoadamantyl–Adamantyl Rearrangement. Methyl-d_3 Isotope Effects and Product Compositions in the Solvolysis of 4-*endo*- and 4-*exo*-4-Methylprotoadamantyl and 1-Methyl-2-adamantyl Derivatives. Evidence for Bridging

Darinka Kovačević,[1a] Bogdan Goričnik,[1b] and Zdenko Majerski*[1c,2]

Rudjer Bošković Institute, 41001 Zagreb, Croatia, Yugoslavia, and INA-Naftaplin, 41001 Zagreb, Croatia, Yugoslavia

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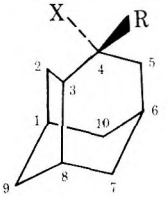
Methyl-d_3 isotope effects and product compositions in the solvolysis of 4-*endo*- (**1b**) and 4-*exo*-4-methylprotoadamantyl dinitrobenzoate (**2b**) and 1-methyl-2-adamantyl tosylate (**3b**) were determined in 60% aqueous dioxane. All three esters yield the same four products, 4-methyl-4-protoadamantene, 4-methyleneprotoadamantane, 4-*exo*-4-methylprotoadamantanol, and 1-methyl-2-adamantanol, but in significantly different ratios. The substitution product with the skeleton of the starting ester is formed preferentially. The titrimetrically determined isotope effects of **1b** (1.47) and **2b** (1.30) are larger than the "true" secondary isotope effects, owing to the primary isotope effect contribution. The calculated "true" values of the secondary methyl-d_3 effects of **1b** (1.37), **2b** (1.16), and **3b** (1.05) are consistent with an anchimerically unassisted solvolysis of **1b** and anchimerically assisted solvolyses of **2b** and **3b**. The substitution products are probably formed by collapse of the solvent-separated ion pairs rather than by nucleophilic attack on these ion pairs. The endo ester (**1b**) appears to solvolyze through a "classical" cationic species which turns subsequently into the same bridged intermediate as formed from the exo ester (**2b**). This intermediate is similar to, but not identical with, the intermediate arising from **3b**.

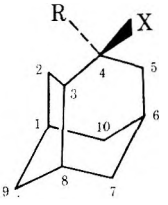
Interconversions of 2-adamantyl and 4-protoadamantyl substrates are well documented,[3-8] but the mechanism of these reactions is still controversial. Thermodynamically controlled reactions of 2-adamantyl and 4-protoadamantyl derivatives exclusively yield 2-adamantyl products[3-5,8] since the protoadamantane skeleton is 11 kcal/mol more strained than the adamantane skeleton.[5,9] However, kinetically controlled reactions produce both 2-adamantyl and 4-protoadamantyl products.[3-7] Schleyer,[4,5] Whiting,[3] and Lenoir[6] postulated the intermediacy of a common bridged 2-adamantyl cation in the solvolyses of 2-adamantyl and 4-*exo*-protoadamantyl substrates, the degree of bridging being highly dependent on the substituent at positions 1 and 4, respectively. The solvolysis of unsubstituted 4-*endo*-protoadamantyl substrates may be anchimerically assisted,[4] while the solvolysis of 4-*endo*-4-methylprotoadamantyl substrates appears to be unassisted[5] but may lead indirectly by "leakage" to the bridged 1-methyl-2-adamantyl cation. Recently, Fărcaşiu[7] questioned the intervention of bridged ions in the solvolyses of 1-substituted 2-adamantyl derivatives and suggested, as at least an equally plausible alternative, a rapidly equilibrating pair of the corresponding "classical" 2-adamantyl and 4-protoadamantyl ions formed by limiting ionization (k_c). Both of these interpretations are based on the product analyses and the substituent influence on the solvolysis rates of 2-adamantyl and 4 protoadamantyl substrates. However, the reaction mechanism can be significantly altered by replacement of substituents in the neighborhood of the reaction center, so that a direct comparison of the results obtained with different substituents could be misleading.

In this work we studied the solvolysis mechanism of 4-*endo*- and 4-*exo*-4-methylprotoadamantyl and 1-methyl-2-adamantyl substrates by methyl-d_3 isotope effects in combination with product analyses. Isotopic substitution induces only small changes in rates and mechanisms[10a] compared with the gross effects caused by replacement of one substituent by another.

Methods and Results

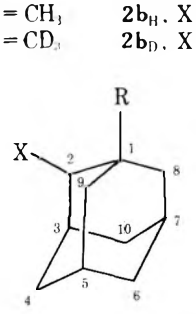
The starting materials 4-*endo*- ($\mathbf{1b_H}$) and 4-*exo*-4-methylprotoadamantyl dinitrobenzoates ($\mathbf{2b_H}$) and 1-methyl-2-adamantyl tosylate ($\mathbf{3b_H}$), as well as their methyl-d_3 analogues ($\mathbf{1b_D}$, $\mathbf{2b_D}$, and $\mathbf{3b_D}$), were obtained from the corresponding alcohols by standard procedures.[11] The purities of all esters were ≥96% (by ^{1}H NMR). 4-*endo*- ($\mathbf{1a_H}$,$\mathbf{1a_D}$) and 4-*exo*-4-methylprotoadamantanols ($\mathbf{2a_H}$,$\mathbf{2a_D}$) were prepared by methyl Grignard addition[8a,b] to 4-protoadamantanone[12] followed by column chromatography separation. Both 1-methyl-2-adamantanol ($\mathbf{3a_H}$) and 1-methyl-d_3-2-adamantanol ($\mathbf{3a_D}$) were obtained by sulfuric acid catalyzed isomerization





$\mathbf{1a_H}$, X = OH; R = CH_3
$\mathbf{1a_D}$, X = OH; R = CD_3
$\mathbf{1b_H}$, X = ODNB; R = CH_3
$\mathbf{1b_D}$, X = ODNB; R = CD_3

$\mathbf{2a_H}$, X = OH; R = CH_3
$\mathbf{2a_D}$, X = OH; R = CD_3
$\mathbf{2b_H}$, X = ODNB; R = CH_3
$\mathbf{2b_D}$, X = ODNB; R = CD_3



$\mathbf{3a_H}$, X = OH; R = CH_3
$\mathbf{3a_D}$, X = OH; R = CD_3
$\mathbf{3b_H}$, X = OTs; R = CH_3
$\mathbf{3b_D}$, X = OTs; R = CD_3

of the respective mixtures of 4-*endo*- and 4-*exo*-4-methylprotoadamantanols.

Esters $\mathbf{1b_H}$, $\mathbf{1b_D}$, $\mathbf{2b_H}$, $\mathbf{2b_D}$, $\mathbf{3b_H}$, and $\mathbf{3b_D}$ were solvolyzed in 60% aqueous dioxane at 60 °C. The solvolysis rates were measured potentiometrically on an automatic recording pH-stat. For the product studies, the esters were solvolyzed through 8 half-lives in the presence of 2,6-lutidine; the resulting solutions of the products were diluted with dioxane and directly analyzed by a gas chromatograph coupled to a data processor using authentic samples as standards. The

solvolysis rates and the methyl-d_3 isotope effects are given in Table I, while the compositions of the solvolysis products are shown in Table II. Esters **1b** and **3b** produced the same four products, 4-methyl-4-protoadamantene (**4**), 4-methyleneprotoadamantane (**5**), 4-*exo*-4-methylprotoadamantanol (**2a**), and 1-methyl-2-adamantanol (**3a**), in almost quantitative total yields. However, **2b** produced, in addition to the solvolysis products **4, 5, 2a,** and **3a,** 15–20% (by ^{1}H NMR) of 1-methyl-2-adamantyl dinitrobenzoate[13] by the internal-return reaction. In no case was 4-*endo*-4-methylprotoadamantanol (**1a**) detected in the product mixture. All products were stable under the reaction conditions used.

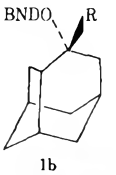
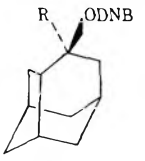
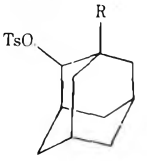
Discussion

The methyl-d_3 isotope effect of 4-*endo*-4-methylprotoadamantyl dinitrobenzoate (**1b**; Table I) is one of the largest methyl-d_3 effects ever observed, comparable with that of 2-methyl-2-adamantyl chloride.[14a] The effect of the exo dinitrobenzoate (**2b**) is considerably smaller, while the effect of 1-methyl-2-adamantyl tosylate (**3b**) is very small but still "normal" (not inverse)! Such methyl-d_3 isotope effects are consistent with the postulated[5] intermediacy of an incipient bridged cation(s) in the solvolysis of **2b** and **3b** and the anchimerically unassisted solvolysis of **1b.** However, the product compositions (Table II) indicate that the mechanism is more complex. All three esters (**1b, 2b,** and **3b**) yield the same four solvolysis products, i.e., 4-methyl-4-protoadamantene (**4**), 4-methyleneprotoadamantane (**5**), 4-exo-4-methylprotoadamantanol (**2a**), and 1-methyl-2-adamantanol (**3a**), but in significantly different ratios, contrary to the results reported[5,15] previously. Consequently, solvolyses of **1b, 2b,** and **3b** cannot lead to the same intermediate either directly from **2b** and **3b** or indirectly from **1b** ("leakage").

The elimination/substitution product ratio of the dinitrobenzoates (**1b** and **2b**) is approximately three times larger than the ratio for the tosylate (**3b**; see Table II). This strongly indicates that some elimination occurs in the tight ion pairs of **1b** and **2b,** involving the rather basic dinitrobenzoate leaving group as a proton acceptor. With the tosylate (**3b**), the low basicity of the counterion should highly reduce the elimination in the tight ion pair. This is consistent with the ratio of 4-methyleneprotoadamantane (**5**)/4-methyl-4-protoadamantene (**4**) determined in the solvolysis of the endo (**1b**) and exo dinitrobenzoates (**2b**). The ratio **5/4** is considerably larger for **2b,** which is expected[5] to solvolyze through the bridged transition state and intermediate. Owing to the bridging in the tight ion pair of **2b,** the methyl group should be tilted toward the exo side, coming close to the dinitrobenzoate group and favoring elimination. In the case of the endo dinitrobenzoate (**1b**), where no bridging is expected,[5] the distance between the methyl and the dinitrobenzoate group is larger. In addition, the dinitrobenzoate group in the tight ion pair of **2b** is more removed from the methylene hydrogen at postion 5 than in the case of **1b.** All of these effects should be considerably less pronounced in the solvent-separated ion pairs.

The relative amounts of 4-methyleneprotoadamantane (**5**) formed from the deuterio esters ($\mathbf{1b}_D$, $\mathbf{2b}_D$, and $\mathbf{3b}_D$) are, because of the primary isotope effect, twice smaller than those formed from the protio analogues ($\mathbf{1b}_H$, $\mathbf{2b}_H$, and $\mathbf{3b}_H$). All other products (**2a, 3a,** and **4**) arise in approximately equal amounts from both the deuterio and protio esters. If the elimination leading to **5** is a rate-determining process, the experimentally determined values of the isotope effects (Table I) are larger than the "true" methyl-d_3 secondary isotope effects. Since the tosylate group is a very weak base, it may be assumed that essentially all elimination from 1-methyl-2-adamantyl tosylate (**3b**) occurs in the solvent-separated ion pair and is not a rate-determining process. Elimination from the dinitrobenzoates (**1b** and **2b**) occurs in both the tight and

Table I. Solvolysis Rates and Methyl-d_3 Isotope Effects in 60% Aqueous Dioxane at 60 °C

Compd	R	$k \times 10^4$, s^{-1} [a,b]	$(k_H/k_D)_{exptl}$ [b]
 1b	CH_3	0.397 (5)	1.47 (5)
	CD_3[c]	0.270 (8)	
 2b	CH_3	4.62 (9)	1.30 (3)
	CD_3[c]	3.56 (6)	
 3b	CH_3	1.22 (1)	1.05 (1)
	CD_3[c]	1.16 (1)	

[a] Average values of 7–9 individual rate constants. [b] The uncertainties are standard errors; e.g., 0.397 (5) = 0.397 ± 0.005 and 1.47 (5) = 1.47 ± 0.05. [c] Deuterium content was 99.5%.

solvent-separated ion pairs, while the substitution products of all three esters (**1b, 2b,** and **3b**) are derived exclusively from the solvent-separated ion pairs (see later). Assuming that the fractions of the elimination products arising from the solvent-separated ion pairs of all three esters are essentially equal, fractions of the solvolysis products formed from the tight (x) and solvent-separated ion pairs ($1 - x$) of dinitrobenzoates **1b** and **2b** can be calculated by

$$f_{DNB} = x + (1 - x)f_{Ts} \quad (1)$$

where f_{DNB} and f_{Ts} are the experimentally determined fractions of the elimination products (Table II) derived from the corresponding dinitrobenzoates (**1b** and **2b**) and tosylate **3b,** respectively.

The "true" values of the methyl-d_3 secondary isotope effect, $(k_H/k_D)_{true}$, of 4-*endo*- (**1b**) and 4-*exo*-4-methylprotoadamantyl dinitrobenzoates (**2b**) can be calculated from the experimentally determined isotope effects, $(k_H/k_D)_{exptl}$ (Table I), using the modified Shiner's[14a] expression:

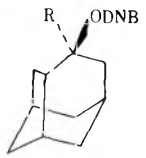
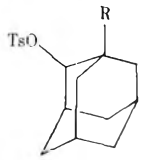
$$(k_H/k_D)_{true} = (k_H/k_D)_{exptl}\,(1 - x_H)/(1 - x_D) \quad (2)$$

Fractions of the solvolysis products derived from the solvent-separated ion pairs of the respective protio ($1 - x_H$) and deuterio ($1 - x_D$) dinitrobenzoates have been computed by expression 1. The obtained "true" values of the isotope effects (Table III) are in good agreement with the values of the methyl-d_3 secondary isotope effects estimated from the solvolysis rate constants[4,5] of the methyl-substituted (k_{CH_3}) and unsubstituted (k_H) esters using the SBS correlation:[14]

$$\log (k_H/k_D)_{SBS} = 0.02024 \log (k_{CH_3}/k_H) \quad (3)$$

The "true" values of the methyl-d_3 β-secondary isotope effect of 4-*endo*- (**1b**) and 4-*exo*-4-methylprotoadamantyl dinitrobenzoate (**2b**) are lower than the titrimetrically determined isotope effects (Table III), owing to the contribution of the rate-determining elimination. The magnitude of the "true" isotope effect of **1b** is close to the "limiting value" [16] for the methyl-d_3 β-secondary isotope effect and considerably larger compared with the "true" isotope effect of **2b.** The β-secondary isotope effects are generally reduced by positive charge delocalization in a solvolysis transition state since the

Table II. Solvolysis Products in 60% Aqueous Dioxane at 60 °C

Starting Material	R	Products, %[a] 4	5	2a	3a
 1b	CH_3	9.2 (3)	14.3 (3)	44.5 (4)	32.0 (4)
	CD_3[b]	10.3 (3)	6.5 (3)	45.4 (4)	37.8 (4)
 2b	CH_3	5.8 (2)	23.0 (2)	46.4 (2)	24.8 (4)
	CD_3[b]	6.9 (2)	11.3 (2)	52.2 (3)	29.6 (3)
 3b	CH_3	3.0 (2)	7.8 (4)	33.2 (9)	56.0 (7)
	CD_3[b]	4.2 (3)	5.2 (3)	42.5 (6)	48.1 (3)

[a] Average values of 2–4 independent experiments with 5–10 GLC analyses of each product mixture. The uncertainties are standard errors; e.g., 9.2 (3) = 9.2 ± 0.3. [b] Deuterium content was 99.5%.

Table III. Methyl-d_3 Isotope Effects of 4-*endo*-(1b), 4-*exo*-4-Methylprotoadamantyl Dinitrobenzoate (2b), and 1-Methyl-2-adamantyl Tosylate (3b) Corrected for the Primary Isotope Effect Contribution [$(k_H/k_D)_{true}$]

Compd	(k_H/k_D)-exptl[a]	$1 - x_H$[b]	$1 - x_D$[b]	$(k_H/k_D)_{true}$[c]	(k_H/k_D)-SBS[d]
1b	1.47	0.86	0.92	1.37 (6)	1.39
2b	1.30	0.80	0.90	1.16 (4)	1.19
3b	1.05	1.0	1.0	1.05 (1)	1.06

[a] Methyl-d_3 isotope effects determined titrimetrically in 60% dioxane at 60 °C (see Table I). [b] Computed by eq 1. [c] Computed by eq 2. [d] Methyl-d_3 secondary isotope effects estimated by the SBS correlation (eq 3); k_{CH_3} and k_H are calculated from the values[4,5] at other temperates using for **1b** the conversion factor[4] $k_{OTs}/k_{ODBN} = 2 \times 10^7$.

hyperconjugative interaction is better the larger the electron deficiency at the reaction center.[16] Factors, other than σ participation, which might possibly influence positive charge location in the transition state of 4-*endo*- and 4-*exo*-methylprotoadamantyl substrates, would be essentially equal. Consequently, positive charge in the transition state of the exo dinitrobenzoate (**2b**) should be more strongly delocalized than that in the endo isomer (**1b**). Both the exo C_4–ODNB bond in **2b** and the endo C_4–ODNB bond in **1b** are stereochemically well situated for σ participation, i.e., antiperiplanar relative to the C_2–C_3 and C_3–C_8 bonds, respectively. However, σ participation is far more favored for the exo dinitrobenzoate (**2b**) since the bridging resulting from the C_3–C_8 bond participation would require a considerable distortion of the skeleton and the resulting bridged species would be a highly unfavorable intermediate between a secondary and a tertiary 4-protoadamantyl cation.[17,18]

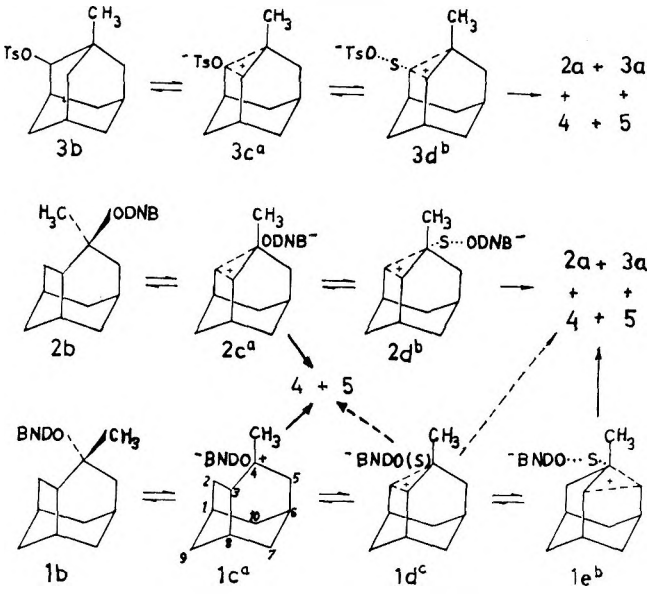
The γ-secondary deuterium isotope effect is generally inverse ($k_H/k_D < 1$) if there is no special mechanistic complication associated with the solvolysis.[10] However, the methyl-d_3 γ-secondary isotope effect of 1-methyl-2-adamantyl tosylate (**3b**) is significantly higher than unity; i.e., the effect is "normal", not inverse! Since the reaction center is at the γ position relative to the deuterium atoms, no contribution of the primary isotope effect to the measured effect should be expected. (Elimination occurs in the solvent-separated ion pair and is not rate determining; see the preceding text.) Consequently, some positive charge must be located at the β carbon relative to the deuterium atoms in the transition state of **3b.** In other words, positive charge is delocalized between the carbon atoms at positions 1 and 2; the solvolysis of **3b** is assisted by σ participation involving the C_1–C_8 (C_1–C_9) bond anti to the C_2–OTs bond.

Contrary to the solvolysis of 4-*endo*-4-methylprotoadamantyl substrate (**1b**), the solvolyses of both 4-*exo*-4-methylprotoadamantyl (**2b**) and 1-methyl-2-adamantyl (**3b**) substrates are anchimerically assisted, but fractions of positive charge located at the carbon atom adjacent to the methyl group in the transition states of **2b** and **3b** are rather different.

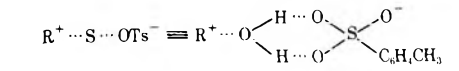
The substitution products, 4-*exo*-4-methylprotoadamantanol (**2a**) and 1-methyl-2-adamantanol (**3a**), of all three esters (**1b, 2b,** and **3b**) are formed from the solvent-separated ion pairs. Nucleophilic attack on the tight ion pairs arising from tertiary substrates as well as from secondary 2-adamantyl substrates[19] is unlikely to occur owing to steric hindrance. The ratio of the substitution products **2a/3a** depends on the structure of the starting ester (Table II). This ratio is considerably higher for 4-methyl-4-protoadamantyl dinitrobenzoates (exo, 1.9; endo, 1.4) than for 1-methyl-2-adamantyl tosylate (0.6), indicating a "memory" effect.

Both 1-methyl-2-adamantyl tosylate (**3b**) and 4-*exo*-4-methylprotoadamantyl dinitrobenzoate (**2b**) solvolyze through tight and solvent-separated ion pairs involving a common bridged cationoid[19a] resulting from the C_1–C_8 and

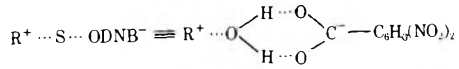
Scheme I



[a] The tight ion pairs. [b] The solvent-separated ion pairs:

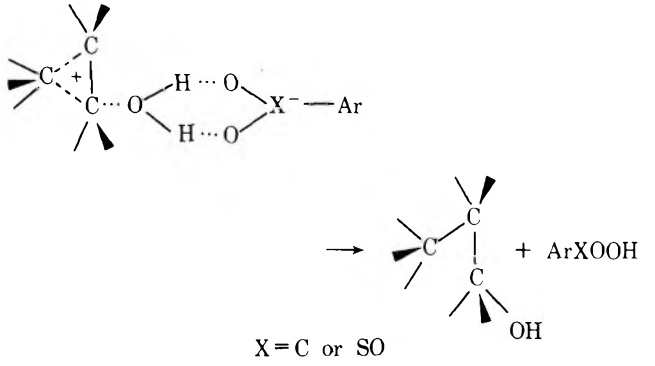


and



[c] The solvent may be "incorporated" into the ion pair.

C_2–C_3 bond participation, respectively (see the preceding text and Scheme I). The preferential formation of the substitution product with the same structure as the starting ester (Table II) may be explained by the influence of the leaving group location in the solvent-separated ion pairs. The substitution products are probably formed by collapse of the solvent-separated ion pairs rather than by nucleophilic attack on these ion pairs. This is consistent with the prevailing retention of the configuration observed in the solvolyses of secondary 2-adamantyl derivatives.[20]



The relative amounts of the substitution products, **2a** and **3a**, arising from the endo and exo dinitrobenzoates (**1b** and **2b**) are almost equal, suggesting that these products are formed from similar intermediates, solvent-separated ion pairs. The solvolysis course of 4-*endo*-4-methylprotoadamantyl dinitrobenzoate (**1b**) could be interpreted (see Scheme I) by the initial formation of an essentially "classical" cationic intermediate (**1c**), which turns subsequently into a more stable bridged species **1d** by formation of the C_2–C_4 bond and simultaneous weakening of the C_2–C_3 bond. The leaving group is located on the "wrong", endo side of the cationoid. However, this intermediate may isomerize rapidly into the isomer **1e** with the leaving group on the exo side, which is "identical"[21] to the solvent-separated ion pair **2d** formed from the exo dinitrobenzoate (**2b**). Therefore, it should yield the same substitution products as **2b**.[22] The small difference in the substitution product compositions of **1b** and **2b** indicates that the substitution products of **1b** arise preferably (but not exclusively) from the intermediate **1e**.

The formation of no 4-*endo*-4-methylprotoadamantanol (**1a**) in the solvolyses of all three esters, **1b, 2b,** and **3b,** is consistent with the bridging on the endo side and cannot be explained by the steric hindrance resulting from the hydrogen and carbon atoms neighboring the reaction center. Reduction of 4-protoadamantanone by $LiAlH_4$,[4] as well as methyl Grignard addition to this ketone,[5] do not involve the bridged intermediates and yield both the exo and endo products.

Internal return generally occurs at the tight ion pair stage. According to the mechanism proposed, the internal return to 1-methyl-2-adamantyl dinitrobenzoate should be expected to be more important for the exo dinitrobenzoate (**2b**) than for the endo ester (**1b**) since the cationoid in the tight ion pair arising from **2b** is bridged and that of **1b** is essentially "classical". The experimental results agree well with these predictions; solvolysis of **2b** gave 15–20% of 1-methyl-2-adamantyl dinitrobenzoate, while solvolysis of **1b** yielded less than 2% (if any) of the rearranged ester.

In conclusion, we would like to point out that contrary to the solvolysis of 4-*endo*-4-methylprotoadamantyl substrate, the solvolyses of both 4-*exo*-4-methylprotoadamantyl and 1-methyl-2-adamantyl substrates are anchimerically assisted. Our results are consistent with the mechanism proposed by Schleyer[5] and Lenoir[6] and cannot be explained by the equilibrating pair of the "classical" 1-methyl-2-adamantyl and 4-methyl-4-protoadamantyl ions as suggested by Fărcaşiu.[7] However, the real solvolysis mechanism is more complex than that postulated by Schleyer. All three substrates yield the same solvolysis products, but in significantly different ratios, contrary to the results reported[5] previously. The substitution products with the skeleton of the starting substrate are produced preferentially; these products are probably formed by collapse of the solvent-separated ion pairs rather than by nucleophilic attack on these ion pairs. The dinitrobenzoates yield considerably more elimination products than the tosylate, indicating that some elimination occurs in the tight ion pairs of the dinitrobenzoates involving the leaving group as a proton acceptor.

Experimental Section

General. Dioxane (p.a.) was purified as described previously.[23] Methyl-d_3 iodide (Merck) contained ≥99% of the theoretical amount of deuterium. All other chemicals were analytical grade. Melting points were determined on a Perkin-Elmer 1B differential scanning calorimeter and are uncorrected. ^1H NMR spectra were recorded on a Varian A-60A spectrometer using $CDCl_3$ as solvent, IR spectra were taken on a Perkin-Elmer 377 spectrophotometer, and mass spectra were obtained on a Varian CH-7 mass spectrometer. GLC analyses were carried out on a Varian Aerograph 1440 gas chromatograph coupled to a Perkin-Elmer processor PEP-1. Deuterium contents were determined by mass spectroscopy.

4-*endo*-4-Methylprotoadamantanol ($1a_H$) and 4-*exo*-4-Methylprotoadamantanol ($2a_H$). A crude mixture of epimeric 4-methyl-4-protoadamantanols ($1a_H$, 37%; $2a_H$, 63%) was obtained in 98% yield by methyl Grignard addition to 4-protoadamantanone[12] using the standard procedure.[8a,b] The mixture of alcohols (226 mg) was chromatographed on 40 g of silica gel using benzene with 1% of ether as eluent. Pure epimeric alcohols $1a_H$ and $2a_H$ (≥98% by GLC) were obtained in 27 (61 mg) and 65% (147 mg) yield, respectively. The ^1H NMR and the mass spectral data were in complete agreement with those reported previously[5] for these alcohols. $1a_H$: mp 86–88 °C (after sublimation in vacuo); IR (KBr) 3300 (s), 2924 (s), 1462 (m), 1372 (m), 1322 (m), 1130 (m), 1117 (s), and 917 (s) cm^{-1}. $2a_H$: mp 82–83 °C (after sublimation); IR (KBr) 3360 (s), 2920 (s), 1458 (m), 1370 (m), 1100 (m), 1090 (m), 914 (m), and 846 (m) cm^{-1}.

4-*endo*-4-Methyl-d_3-protoadamantanol ($1a_D$) and 4-*exo*-4-methyl-d_3-protoadamantanol ($2a_D$) were prepared in the same

manner as the protio analogues. The purity of $1a_D$ and $2a_D$ was higher than 99 and 97% (by GLC), respectively; the deuterium content of both alcohols was 99.5% of the theoretical amount of deuterium.

1-Methyl-2-adamantanol ($3a_H$). A crude mixture of $1a_H$ and $2a_H$ (90 mg, 0.54 mmol) was dissolved in 4 mL of 80% aqueous acetone; one drop of concentrated H_2SO_4[24] was added, and the reaction mixture was refluxed for 30 min. The resulting solution was concentrated in vacuo and extracted with ether (3 × 20 mL), the combined extracts were washed with water and dried, and the solvent was evaporated. The crude product was sublimed to give 80 mg (89%) of pure $3a_H$ (≥97% by GLC): mp 158–160 °C; IR (KBr) 3450 (s), 2900 (s), 2822 (s), 1452 (m), 1050 (m), 1034 (m), 980 (m), and 940 (m) cm^{-1}. The ^1H NMR and mass spectral data were in good agreement with those reported previously[8a] for this compound.

1-Methyl-d_3-2-adamantanol ($3a_D$) was obtained in the same manner as the protio analogue; the purity was higher than 97% (by GLC), and the deuterium content was 99.5% of the theoretical amount.

4-*endo*-4-Methylprotoadamantyl 3,5-Dinitrobenzoates ($1b_H$ and $1b_D$) and 4-*exo*-4-Methylprotoadamantyl 3,5-Dinitrobenzoates ($2b_H$ and $2b_D$). The protio and the methyl-d_3 dinitrobenzoates were prepared from the corresponding alcohols by the standard 3,5-dinitrobenzoyl chloride–pyridine method.[11a] Freshly recrystallized 3,5-dinitrobenzoyl chloride and pyridine dried over CaH_2 were used. The crude dinitrobenzoates were recrystallized twice from a 1:1 ether–pentane mixture at −80 °C (dry ice–acetone). Pure esters were obtained in the following yields: $1b_H$, 61% (mp 130–131 °C); $1b_D$, 74% (mp 131–133 °C); $2b_H$, 72% (mp 113–114 °C); and $2b_D$, 65% (mp 114–115 °C). The IR spectra (KBr) of all four dinitrobenzoates showed no absorption owing to the OH group [$1b_H$ 3111 (m), 3100 (m), 2917 (s), 1718 (s), 1630 (m), 1540 (s), 1175 (s), 742 (s), and 712 (s) cm^{-1}; $2b_H$ 3120 (m), 3099 (w), 2910 (s), 1720 (s), 1548 (s), 1342 (s), 1200 (m), 723 (s), and 711 (s) cm^{-1}]. The ^1H NMR spectral data of $1b_H$ and $2b_H$ agree with those reported previously[5] for these compounds.

1-Methyl-2-adamantyl Tosylates ($3b_H$ and $3b_D$). The protio and the methyl-d_3 tosylates were obtained by the pyridine method[11b] from the corresponding alcohols. The crude tosylates were recrystallized twice from 1:1 ether–pentane at −80 °C. Pure $3b_H$ was obtained in 69% yield (mp 113–114 °C) and $3b_D$ in 60% yield (mp 114–116 °C). The IR spectra (KBr) of both tosylates showed no absorption owing to the OH group [$3b_H$ 3060 (w), 2905 (s), 2851 (m), 1601 (m), and 1452 (m) cm^{-1}]. The ^1H NMR spectral data of $3b_H$ agree with those reported[5] for this tosylate.

Kinetic Measurements. The solvolysis rates were determined by continuous potentiometric titration using a Radiometer Copenhagen SBR2/TTT11 pH-stat, maintaining the pH of the reaction solution at 6.8. The initial concentration of the starting ester was ca. 0.004 M (20 mg in 15 mL of solvent) in all kinetic measurements. The protio and deuterio analogues were titrated at random in order to minimize the influence of temperature variations in the isotope effects. At least seven individual measurements were conducted for each ester. The rate constants were calculated from the standard integrated first-order law using a nonlinear least-squares program.

Product Studies. In a typical experiment, ester (120 mg, 0.33 mmol) was dissolved in 12 mL of 60% aqueous dioxane, an equivalent amount of 2,6-lutidine was added, and the resulting solution was stirred for 8 half-lives at 60 °C. The reaction mixture was allowed to cool down, diluted with 12 mL of dioxane, and then analyzed directly by gas chromatography on a 6 ft × ⅛ in 10% Carbowax 20M (Chromosorb W 100/120) column at a temperature programmed from 70 to 180 °C at a rate of 6 °C/min. The product study of each ester was performed at least twice. Each product mixture was analyzed by GLC 5–10 times, giving a total of at least 10 analyses for each ester.

All three esters (**1b**, **2b**, and **3b**) yielded the same four solvolysis products, 4-methyl-4-protoadamantene (**4**), 4-methyleneprotoadamantane (**5**), 4-*exo*-4-methylprotoadamantanol (**2a**), and 1-methyl-2-adamantanol (**3a**), but in significantly different ratios (see Table II). No other products were detected in the solvolyses of **1b** and **3b**, but **2b** produced, in addition to the solvolysis products, 15–20% of 1-methyl-2-adamantyl dinitrobenzoate by the internal return reaction. The solvolysis products were identified by GLC comparison with authentic samples, and the products were proved to be stable under the solvolytic conditions used, as well as on the GLC column. Samples of pure compounds **2a**, **3a**, **4**, and **5**, with an adequate quantity of 2,6-lutidine added, were treated separately with an equivalent amount of *p*-nitrobenzoic acid in the same manner as the esters in the product studies. In all cases, the gas chromatograms revealed only the compound tested.

For the internal return studies of dinitrobenzoates **1b** and **2b**, the crude solvolysis product mixture was concentrated to a small volume in vacuo at 25 °C and then saturated with Na_2CO_3 and extracted with ether. The extracts were dried, and the solvent was evaporated. The ^1H NMR spectrum of the residue was compared with the spectrum of an authentic sample of 2-methyl-2-adamantyl dinitrobenzoate (3-ODNB). The spectrum of the crude product mixture of **2b** indicated the presence of 15–20% of 3-ODNB, while essentially no 3-ODNB (less than 2%) was detected in the product mixture of **1b**.

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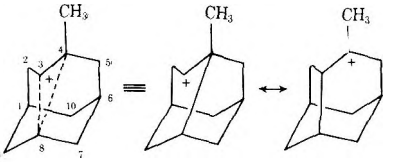
Registry No.—$1a_H$, 52746-23-3; $1a_D$, 66900-44-5; $1b_H$, 28846-71-1; $1b_D$, 66842-11-3; $2a_H$, 28840-89-3; $2a_D$, 66842-15-7; $2b_H$, 29845-45-2; $2b_D$, 66900-43-4; $3a_H$, 28786-69-8; $3a_D$, 66842-16-8; $3b_H$, 28786-70-1; $3b_D$, 66842-12-4; 4_H, 66842-13-5; 4_D, 66842-14-6; 5_H, 39762-63-5; 5_D, 66901-80-2.

References and Notes

(1) (a) Kemijski Kombinat, 41001 Zagreb; (b) INA-Naftaplin; (c) Rudjer Bošković Institute.
(2) To whom correspondence should be addressed.
(3) M. L. Sinnott, H. J. Storesund, and M. C. Whiting, *Chem. Commun.*, 1000 (1969); H. J. Storesund and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1452 (1975); J. R. Pritt and M. C. Whiting, *ibid.*, 1458 (1975).
(4) D. Lenoir, R. E. Hall, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 2138 (1974); D. Lenoir, P. Mison, E. Hyson, P. v. R. Schleyer, M. Saunders, P. Vogel, and L. A. Telkowski, *ibid.*, **96**, 2157 (1974).
(5) D. Lenoir, D. J. Raber, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 2149 (1974); D. Lenoir and P. v. R. Schleyer, *Chem. Commun.*, 941 (1970).
(6) D. Lenoir, *Chem. Ber.*, **106**, 2366 (1973).
(7) D. Farcaşiu, *J. Am. Chem. Soc.*, **98**, 5301 (1976).
(8) This has ingeniously been used in the preparation of 1,2- and 2,4-disubstituted adamantanes: (a) D. Lenoir, R. Glaser, P. Mison, and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 1821 (1971); (b) B. D. Cuddy, D. Grant, and M. A. McKervey, *J. Chem. Soc. C*, 3173 (1971); (c) J. K. Chakrabarti, T. M. Hotten, D. M. Rackham, and D. E. Tupper, *J. Chem. Soc., Perkin Trans. 1*, 1893 (1976).
(9) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(10) (a) V. J. Shiner, Jr., *ACS Monogr.*, **No. 167**, 90, (1970); (b) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).
(11) (a) For example, see K. B. Wiberg, J. E. Hiatt, and K. Hseih, *J. Am. Chem. Soc.*, **92**, 544 (1970); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1962, p 1180.
(12) 4-Protoadamantanone can be readily prepared in 70–80% overall yield from 1-adamantanol by the modified hypoiodite thermolysis–cyclization sequence: Z. Majerski, Z. Hameršak, and D. Škare, *Tetrahedron Lett.*, 3943 (1977); Z. Majerski and Z. Hameršak, *Org. Synth.*, submitted for publication.
(13) The solvolysis rate of 1-methyl-2-adamantyl dinitrobenzoate in 60% dioxane at 60 °C was estimated to be 6×10^{-12} s^{-1} from $k_{3b} = 1.2 \times 10^{-4}$ s^{-1} using the conversion factor[4] $k_{OTs}/k_{ODNB} = 2 \times 10^7$.
(14) (a) R. D. Fisher, R. C. Seib, V. J. Shiner, Jr., I. Szele, M. Tomić, and D. E. Sunko, *J. Am. Chem. Soc.*, **97**, 2408 (1975); (b) K. L. Servis, S. Borčić, and D. E. Sunko, *Tetrahedron*, **24**, 1247 (1968).
(15) Schleyer et al.[5] analyzed the solvolysis products of **1b**, **2b**, and **3b** in 60% acetone and reported just the total amounts of olefins (2–7%). These amounts were 3–4 times smaller than those we found in 60% dioxane. In addition, the ratio of the substitution products **2a**/**3a** was reported[5] to be essentially independent of the starting ester.
(16) D. E. Sunko, I. Szele, and W. J. Hehre, *J. Am. Chem. Soc.*, 99, 5000 (1977), and references therein.
(17)



(18) Supposing there was no contribution of the rate-determining elimination to the values of the methyl-d_3 isotope effect of 4-*endo*- (**1b**) and 4-*exo*-4-methylprotoadamantyl dinitrobenzoate (**2b**), the "true" methyl-d_3 β-secondary isotope effects of *both* **1b** and **2b** would be proportionally larger (and equal to the corresponding titrimetrically determined isotope effects). Consequently, the discussion and conclusions based on the values of the titrimetrically determined isotope effect would be essentially the same as those reached from the corrected ("true") values of the β-secondary effects.
(19) Cf. (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2538 (1970); (b) J. M. Harris, J. F. Fagan, F. A. Walden, and D. C. Clark, *Tetrahedron Lett.*, 3023 (1972).

(20) J. A. Bone, J. R. Pritt, and M. C. Whiting, *J. Chem. Soc., Perkin Trans.* **2**, 1447 (1975); J. A. Bone and M. C. Whiting, *Chem. Commun.*, 115 (1970).
(21) In fact, (*R*)-4-*endo*- and (*R*)-4-*exo*-4-methylprotoadamantyl substrates would give essentially identical solvent-separated ion pairs, which are mirror images of the ion pairs arising from the (*S*)-4-*endo* and (*S*)-4-exo enantiomers.
(22) Such isomerizations of bridged intermediates are well known, for example, see J. E. Baldwin and W. D. Foglesong, *J. Am. Chem. Soc.*, 90, 4303 (1968), and references therein.
(23) Autorenkollektiv, "Organikum", VEB Deutscher Verlag, Berlin, 1967, p 615.
(24) When concentrated HCl was used[8a] instead of H_2SO_4, some 1-methyl-2-chloroadamantane was also produced.

Roles of Heteroatoms in Solvolytic Reactions. 4. Solvolysis of the Exo and Endo Esters of 2-Thiabicyclo[2.2.1]heptan-6-ols[1]

Jun-ichi Ohishi, Kazuko Tsuneoka, Shiro Ikegami,* and Sanya Akaboshi[2]

Division of Pharmaceutical Sciences, National Institute of Radiological Sciences, Anagawa, Chiba-shi, Japan

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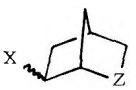
Diels–Alder cyclization of cyclopentadiene with thiophosgene yielded 3,3-dichloro-2-thiabicyclo[2.2.1]hept-5-ene, which was directly converted to 2-thiabicyclo[2.2.1]hept-5-ene in high yield by reduction with lithium aluminum hydride. Hydrochlorination of the olefin, followed by hydrolysis in a neutral or basic medium, gave 2-thiabicyclo[2.2.1]heptan-6-*exo*-ol in satisfactory overall yield. Acidic hydrolysis of 6-*exo*-chloro-2-thiabicyclo[2.2.1]heptane resulted in the major formation of a dimeric ether. The alcohol was oxidized with *tert*-butyl chromate, followed by reduction, to afford pure endo alcohol. Both alcohols were converted to esters, *p*-nitrobenzoate for the exo and tosylate for the endo, and the esters were solvolyzed. An exo/endo rate ratio of 3.7×10^{14} was observed, after correction for a leaving group as well as the solvent system, and 3.1×10^{10} and 1/43, respectively, for the rate ratios of the exo and endo esters against the corresponding parent carbon systems. This unusually high exo/endo rate ratio is attributed to β-S participation for the exo ester and the rate-retarding effect for the endo ester. In a product study, only an exo isomer was found as the solvolysis product from both esters. Isolation of a tricyclic episulfonium ion, 1-thioniatricyclo[1.1.1.$0^{2,6}$]heptane perchlorate, a solvolysis intermediate from the exo ester, was possible; its structure was confirmed by ^1H and ^{13}C NMR spectra.

Generally, it is well known that the amount of neighboring-group participation in solvolytic reactions varies with the spatial circumstances of molecules. C_2–C_6 interaction in the norbornyl system (**1**) has been observed in many kinetic, mechanistic, and structural studies.[3]

In the solvolysis of the 2-oxabicyclo[2.2.1]hept-6-*exo*-yl system (**2**), a relatively large amount of β-O-participation has



1 Z = CH_2
2 Z = O
3 Z = S

been observed.[4] It is considered that the structural peculiarity of the bicyclo[2.2.1]heptyl system gives rise to this unusual neighboring-group participation. Usually the effect of a β-oxygen atom resulting from direct nucleophilic participation is extremely small,[5] although the precise evaluation of the effect is difficult because of the large inductive character of oxygen.

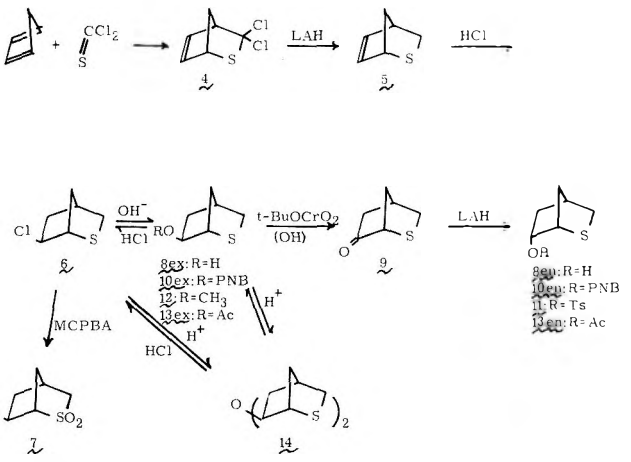
The 2-thiabicyclo[2.2.1]heptyl system (**3**) may exhibit a large amount of neighboring-group participation in solvolytic reactions and allow the isolation of a stable episulfonium ion when a carbocation is formed at the 6 position. This work was designed to examine mechanistic and structural effects in the solvolysis of the exo and endo stereoisomers of 2-thiabicyclo[2.2.1]heptan-6-ol esters and to isolate a tricyclic episulfonium ion.

Results

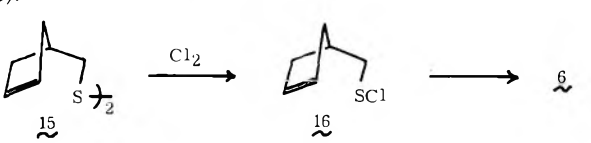
Synthesis. Originally the 2-thiabicyclo[2.2.1]heptane skeleton was prepared by Middleton[6] and several analogues were studied by Johnson and co-workers[7] in an investigation of stereochemical aspects.

As shown in Scheme I, 3,3-dichloro-2-thiabicyclo[2.2.1]-hept-5-ene (**4**), prepared according to the known procedure,[6] was directly reduced with lithium aluminum hydride ($LiAlH_4$)

Scheme I



to give 2-thiabicyclo[2.2.1]hept-5-ene (**5**) in high yield; chemical shifts of **5** in the ^1H NMR spectrum were consistent with those of reported values.[7] Hydrochlorination of the olefin (**5**) in methylene chloride with dry hydrogen chloride at −30 ~ −50 °C gave a single isomer (**6**), in which the configuration of the chlorine atom was determined to be exo on the basis of its reactivity, stereochemistry on HCl addition, and the NMR pattern of the 6-endo proton (4.74 ppm, doublets of doublet, $J_{5en,6}$ = 6.5 Hz, $J_{5ex,6}$ = 3.0 Hz) of the corresponding sulfone (**7**). This chloride was also prepared quantitatively by the intramolecular addition of sulfenyl chloride (**16**) generated in situ from the reaction of 3-cyclopentenylmethyl disulfide (**15**).[8]



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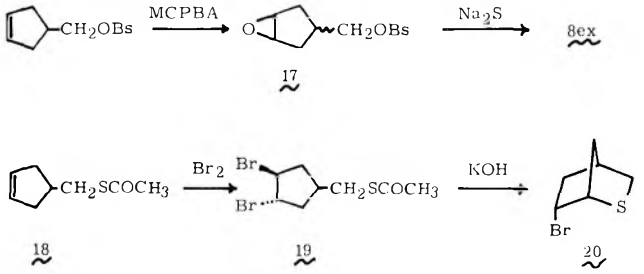
Hydrolysis of **6** in a weakly alkaline medium gave the 6-*exo*-hydroxy derivative (**8ex**) in 93% yield. When the hydrolysis was carried out without a base, a mixture of the alcohol (**8ex**) and the dimeric ether (**14**) was obtained in various ratios depending on reaction conditions used, indicating the facile conversion of **8ex** into **14** in an acidic medium.

The formation of the dimeric ether (**14**) from **8ex** was also examined by treatment of **8ex** with various concentrations of acid and by heat treatment. However, the complete conversion of **8ex** to **14** was not observed; both systems must be present in the equilibrium mixture. Treatment of **8ex** or **14** with concentrated hydrochloric acid afforded the corresponding 6-*exo*-chloro derivative (**6**).

Oxidation of β-hydroxy sulfides to the corresponding β-oxo derivatives is usually troublesome because of the high sensitivity of a sulfur atom to oxidation. The Oppenauer procedure failed. Common procedures using chromic anhydride–pyridine or *tert*-butyl chromate–pyridine in carbon tetrachloride[9] gave the desired result. However, the former procedure was accompanied with large loss of product because of difficulty in isolating product. The best yield (69%) of ketone **9** was obtained from the latter procedure. Interestingly, in the UV spectrum of **9**, a charge-transfer (CT) band at 258 (ε 478 in cyclohexane), 258 (ε 478 in acetonitrile), 260 (ε 589 in methanol), and 260 nm (ε 600 in 70% aqueous ethanol) was observed as an independent absorption.[10] The attack of a hydride on the keto group of **9** by $LiAlH_4$ or $NaBH_4$ took place exclusively on the exo side and only isomer **8ex** was obtained in moderate yield.

Infrared (IR) spectra (1×10^{-3} M solution in CCl_4) of the alcohols reveal a striking difference between the exo and endo alcohols (**8ex** and **8en**). Alcohol **8ex** exhibits an absorption at 3620 cm^{-1} due to a dissociated hydroxy group, while in **8en**, only an absorption due to an associated alcohol was observed at 3474 cm^{-1}, indicating the presence of a strong intramolecular H bond.

The exo alcohol (**8ex**) from the epoxide (**17**) has alternatively been prepared according to the following scheme by Johnson and co-workers.[7] In our experiment, however, the distillation of **8ex** under reduced pressure was accompanied by the formation of the dimeric ether (**14**) attributable to the intermolecular dehydration of the alcohol (**8ex**).

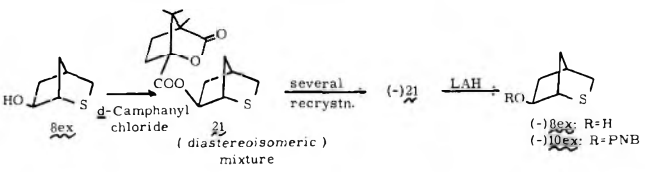


The 2-thiabicyclo[2.2.1]heptane skeleton could also be synthesized from the intramolecular nucleophilic substitution by a thiol group generated by hydrolyzing the dibromo thiolacetate (**19**) which was easily derived from the thiolacetate (**18**). Because of the great stability of 6-*endo*-bromo-2-thiabicyclo[2.2.1]heptane (**20**), with properties similar to those of 4-*endo*-bromo-6-thiabicyclo[3.2.1]octane,[11] it was not a useful compound for the stereochemical and mechanistic studies in the present systems.

The exo and endo alcohols (**8ex** and **8en**) were converted to the corresponding *p*-nitrobenzoates (**10ex** and **10en**) and the tosylate (**11**) for the endo derivative in the usual manner. ^1H NMR data of all thiabicyclic compounds are shown in Table I.

Synthesis of Optically Active 2-Thiabicyclo[2.2.1]-heptan-6-exo-ol. An optically active ester was needed to scrutinize the true effect of the sulfur atom in solvolysis of the 2-thiabicyclo[2.2.1]hept-6-yl system. Fortunately, if the system involves a stable episulfonium ion, the ion must be symmetrical, affording an optically inactive intermediate. Thus, the rate of the ionization step can be determined by the polarimetric method. By comparison with the recent report by Tabushi and co-workers[12] in which an attack of a solvent is a step determining the rate in solvolysis of 2-*endo*-chloro-7-thiabicyclo[2.2.1]heptane (**24**), it is important to determine which step is rate determining in such systems having an effective participating group as a neighboring sulfur atom.

Scheme II



The successful optical resolution was done through the separation of diastereoisomers by repeated recrystallization, followed by the reduction of the resulting diastereoisomer of the ester with metal hydride (Scheme II).

Diastereoisomeric esters (**21**) were prepared from the alcohol (**8ex**) and *d*-camphanyl chloride derived from *d*-camphanic acid[13] in the usual manner and (−)-**21** was isolated as a single pure diastereomer after several recrystallizations from ethyl acetate. Reduction with sodium bis(methoxyethoxy)-aluminum hydride in benzene gave (−)-**8ex**, $[\alpha]^{24}_D$ −16.8 (EtOH, *c* 2.5). Routine esterification procedure yielded an optically active ester [(−)-**10ex**], $[\alpha]^{28}_D$ −26.2 ($CHCl_3$, *c* 2.65).[14]

Kinetics. Measurement of solvolysis rate was carried out by the titrimetric method for racemic esters;[15] hydrolysis in 80% aqueous acetone and methanolysis in methanol for **10ex** and acetolysis in acetic acid containing 1 mequiv of sodium acetate for **11**. Since the remarkable stability of the 6-endo ester (**10en**) made its rate measurement impossible, the tosylate (**11**) was used for the determination of solvolysis rate as an endo isomer. Exact rate of hydrolysis and/or methanolysis for **11** could not be determined because the decomposition of ester took place in these solvents. The rate of the optically active ester [(−)-**10ex**] was measured in the same solvents by a polarimetric procedure by which polarimetric rate constants (k_α) at 25 and 35 °C were determined.[16] The calculation of rates and physical parameters were carried out by the usual first-order expression using a computer programmed with least squares. The results of solvolysis rate are summarized in Table II along with kinetic data for 2-norbornyl (**1**) and 2-oxabicyclo[2.2.1]hept-6-yl (**2**) derivatives.

The exo ester (**10ex**) solvolyzed 3.7×10^{14} times faster than the endo isomer (**10en**) and 3.1×10^{10} times faster than the corresponding carbon system. These factors are the greatest values among β-S-participation of various systems observed until the present.

The endo isomer (**11**) underwent solvolysis 43 times slower than the *endo*-norbornyl system. This retardation might be attributed to steric hindrance in the ionizing step caused by the endo-lone pair electrons of the sulfur atom, rather than the inductive effect of sulfur.[17]

Polarimetric rate measurement of the optically active exo ester [(−)-**10ex**] provides the true rate of the ionizing step (k_1).

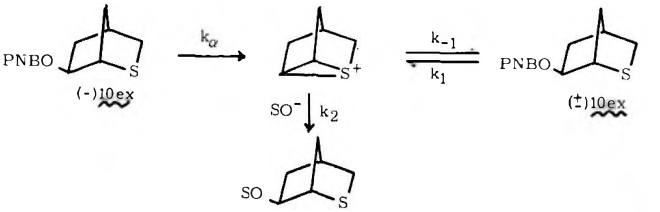
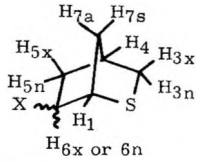


Table I. ^{1}H NMR Assignments of 2-Thiabicyclo[2.2.1]hept-6-yl Derivatives (100 MHz)[a]



registry no.	compd	1	3x	3n	4	5x	5n	6	7a	7s	other protons	J, Hz
67338-11-8	**4**	4.40 m			3.99 m	6.24 dd		6.65 dd	2.05 td	2.35 d		$J_{4,5}$ = 3.5 $J_{1,6}$ = 2.5 $J_{1\&4,7}$ = 3
						$J_{5,6}$ = 5.5 (AB)			J = 10 (AB)			
67338-12-9	**5**	4.06 m	3.22 dd	2.25 md	3.48 m	5.80 dd or		6.28 dd	1.39 md	1.61 md		$J_{4,5}$ = $J_{1,6}$ = 3 $J_{3x,4}$ = 4
			J = 9 (AB)			$J_{5,6}$ = 6 (AB)			J = 9 (AB)			
67338-13-0	**6**	3.37 bs	2.83 md	2.40 md	2.80 m	2.34 md	1.65 md	4.29 m	2.00 m			
			J = 7 (AB)			J = 11 (AB)						
67360-73-0	**7**	3.54 bs	3.04 md	2.74 md	3.00 m	2.46 qd	2.15 md	4.74 dd	2.44 m			$J_{5n,6n}$ = 7 $J_{5x,6n}$ = 3
			J = 12 (AB)			J = 14 (AB)						
67338-14-1	**8ex**	3.14 bs	2.78 md	2.35 d	2.77 m[b]	1.42 md[b]	1.82 qd	4.21 d	2.15 md	1.57 md[b]		$J_{5n,6n}$ = 6.5 $J_{5n,7}$ = 2
			J = 9 (AB)			J = 14 (AB)						
67338-15-2	**9**	3.44 bs	3.06 md	2.75 md	3.04 m	2.16 md	1.82 md		2.11 bs			
			J = 10 (AB)			J = 11 (AB)						
67338-16-3	**10ex**[c]	3.50 s	2.88 md	2.50 d	2.91 m	1.79 md	2.30 qd	5.27 d	2.17 md	1.72 md	8.23 (arom)	$J_{5n,6n}$ = 6.5
			J = 9 (AB)			J = 14 (AB)			J = 11 (AB)		J = 11 (AB)	
67338-17-4	**12**	3.32 m	2.78 md	2.36 dd	2.74 m	1.50 md	1.72 qd	3.71 md	2.04 md	1.54 md	3.30 s (CH_3)	$J_{5n,6n}$ = 7 $J_{3n,7a}$ = 1.5 $J_{5n,7s}$ = 2
			J = 9 (AB)			J = 14 (AB)			J = 11 (AB)			
67338-18-5	**13ex**	3.34 bs	*b*	*b*	2.84 m	1.64 md[b]	1.88 qd	5.00 md	2.16[b]	1.60 md	2.02 s (CH_3)	$J_{5n,6n}$ = 6.5 $J_{6n,7}$ = 2
						J = 14 (AB)			J = 11 (AB)			
67338-19-6	**14**	3.25 s	2.78 md	2.34 md	2.73 m	1.72 mdd	1.41 md	3.86 md	2.03 md	1.62 md		$J_{5n,6n}$ = 7
			J = 9 (AB)			J = 14 (AB)			J = 11 (AB)			
67338-20-9	**8en**	3.46 m	2.89 td	2.55 d	2.70 m	2.10 md	0.90 td	4.31 td	2.00 md	1.79 md		$J_{5x,6x}$ = 10 $J_{5n,6x}$ = $J_{1,6x}$ = 4
			J = 10 (AB)			J = 14 (AB)			J = 11 (AB)			
67338-21-0	**10en**	3.74 m	3.01 md	2.60 d	2.81 m	2.30 md	1.34 td	5.36 td	2.09 md	1.86 md	8.26 s (arom)	$J_{5x,6x}$ = 10 $J_{5n,6x}$ = $J_{1,6x}$ = 4
			J = 10 (AB)			J = 14 (AB)			J = 11 (AB)			
67338-22-1	**11**	3.34 m	2.91 td	2.59 d	2.69 m	2.08 md	1.26 md	4.99 td	1.91 md	1.71 md	2.45 s (CH_3) 7.59 q (arom) J = 8.5 (AB)	$J_{5x,6x}$ = 10 $J_{5n,6x}$ = $J_{1,6x}$ = 4
			J = 9 (AB)			J = 14 (AB)			J = 11 (AB)			
67338-23-2	**13en**	3.64 m	2.96 td	2.63 d	2.74 m	2.18 md	1.20 md	5.08 td	2.02 md	1.78 md	2.10 s (CH_3)	$J_{5x,6x}$ = 10 $J_{5n,6x}$ = $J_{1,6x}$ = 2.5
			J = 10 (AB)			J = 14 (AB)			J = 11 (AB)			
67338-24-3	**20**	3.51 m	2.93 td	2.62 d	2.70 m	2.34 md	1.47 qd	4.50 qd	1.95 m			$J_{5x,6x}$ = 10 $J_{5n,6x}$ = 6 $J_{1,6x}$ = 4
			J = 9 (AB)			J = 14 (AB)						

[a] All ^{1}H NMR spectra were measured in $CDCl_3$. Chemical shifts (ppm from Me_4Si) and coupling constants (Hz) were determined by the aid of shift reagent (Eu(fod)$_3$) and/or by decoupling technique. The following abbrevations are used: AB, AB pattern signal; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, doublets of doublet; td, triplets of doublet; qd, quartets of doublet; md, multiplets of doublet. [b] The precise assignment could not be obtained because of overlap of signals. [c] Spectral data taken by a Varian HR-220 spectrometer (220 MHz). We thank Professors T. Yonezawa and I. Morishima, Department of Hydrocarbon Chemistry, Kyoto University, for ^{1}H NMR spectrometric analysis.

Table II. Rate Data for Solvolysis in 80% Aqueous Acetone (A), in Buffered Acetic Acid (B), and in Methanol (C)

compd	procedure	solvent	$k \times 10^6$ s^{-1} (°C)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	exo/endo rate ratio		rel rate		
10ex	titrimetric	A	420 (50)	21.4	−8.0					
			23.7 (25)							
			Ts, 7.25×10^{11}(25)[b]			3.7×10^{14}	3.1×10^{10}			
	polarimetric	A	349 (35)	14.1	−32					
			35.4 (25)							
	titrimetric	C	27.9 (25)							
	polarimetric	C	45.7 (25)							
11	titrimetric	B	303 (125)	27.4	−6.3					
			27.8 (100)							
			1.94×10^{-3} (25)[a]					1/43		
exo-2-norbornyl			Ts, 23.3 (25)[a,c]			280	1.0			
			Bs, 88.2 (25)[a,d]	21.6	−7.2	350			1.0	
endo-2-norbornyl			Ts, 8.28×10^{-2}(25)[a,c]	25.8	−4.4			1.0		
			Bs, 2.52×10^{-1} (25)[a,d]	26.0	−1.5					1.0
exo-2-oxa-6-norbornyl			Ts, 38 (25)[e]	23.4	−0.3					
			Bs, 218 (25)[e]			7×10^7			2.5	
endo-2-oxa-6-norbornyl			Bs, 2.9×10^{-6} (25)[a,e]	30.5	−9.4					1/87 000

[a] Rate extrapolation from rates at higher temperatures. [b] Rate for the tosylate calculated using a factor of $k_{Ts}(B)/k_{PNB}(A) = 3.06 \times 10^{10}$ reported by Peters [E. N. Peters, *J. Am. Chem. Soc.*, **98**, 5627 (1976)]. [c] Reference 22. [2] S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1127 (1952). [e] Reference 4.

Internal return of the *p*-nitrobenzoate ion forms the optically inactive exo ester (**10ex**) because the intermediary episulfonium ion is symmetrical. According to the usual treatment of kinetics, the titrimetric rate is

$$k_t = k_1k_2/(k_{-1} + k_2)$$

Rearrangement of the equation and replacement of k_1 by k_α gives

$$k_{-1}/k_2 = k_\alpha/(k_t - 1)$$

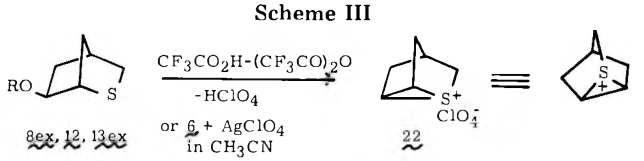
Since k_{-1}/k_2 reveals the rate ratio of internal return and solvolysis product formation, the amount of internal return in this solvolysis can be obtained.

Calculation by the introduction of the rate data observed in the present system resulted in $k_{-1}/k_2 = 33/67$ (80% aqueous acetone, 25 °C) and 39/61 (methanol, 25 °C), showing, even in the system which has a huge amount of neighboring-group participation, moderate internal return as observed in the solvolysis of carbon systems. It is concluded that the attack of solvent on an intermediary ion is not a step determining the rate, but the ionizing step determines the rate in this system.

Isolation and NMR Spectrum of the Intermediary Tricyclic Episulfonium Salt (22). Stereochemical and geometrical aspects of the 2-thiabicyclo[2.2.1]hept-6-yl system (**3**) offer the possibility of isolating a tricyclic episulfonium ion. Treatment of a solution of the chloride (**6**) in acetonitrile with 1 mequiv of silver perchlorate yielded a salt, which was found to be the tricyclic episulfonium salt (**22**) by NMR analysis. This is a common procedure for the preparation of sulfoniun salts[18] (Scheme III).

The addition of 70% perchloric acid to a solution of 6-*exo*-acetoxy-2-thiabicyclo[2.2.1]heptane (**13ex**) in trifluoroacetic acid–trifluoroacetic anhydride, followed by evaporation of the solvent, left pure **22**, which was equivalent with the salt prepared by the former method on comparison by NMR spectroscopy. The use of the other exo derivatives such as 6-hydroxy (**8ex**) and 6-methoxy (**12**) compounds also yielded the same results. This observation is a first example for trapping an episulfonium ion as a reaction intermediate.

Scheme III



The typical ^{1}H NMR and ^{13}C NMR spectra of the perchlorate (**22**) measured in trideuterionitromethane are shown in Figure 1 (Supplementary Material). Both spectra reveal that the ion (**22**) has a symmetric structure. The same spectrum was also observed in direct measurement of **6**, **8ex**, **12**, and **13ex** in trifluoroacetic acid.

As a reflection of the symmetric structure of the tricyclic episulfonium ion (**22**), its ^{1}H NMR spectrum was observed to be a simple pattern; in trideuterionitromethane, the protons of C_1 and C_6 resonated at 4.72 ppm as a singlet peak, that of C_4 at 3.24 ppm as a broad singlet, those of C_3 at 2.88 ppm as a sharp doublet ($J_{3,4}$ = 1.5 Hz), and those of C_5 and C_7 as an AB type pattern (J = 14 Hz) centered at 2.22 ppm. Each stereochemically different proton was split with the C_4 proton ($J_{5ex,7ex,4}$ = 2.5, $J_{5en,7en,4}$ = 0.5 Hz). The ^{13}C NMR spectrum of the salt (**22**) also reveals the four different carbon atoms, indicating the symmetric character of the ion (**22**).

Product of Solvolysis. Solvolyses for product studies were undertaken under the same conditions as used in rate measurements. After usual workup, products were analyzed by VPC. The 6-exo ester (**10ex**) yielded the 6-exo alcohol (**8ex**) in 97.6% yield. On the other hand, the 6-*exo*-acetoxy derivative (**13ex**) was obtained in 85.4% yield from the acetolysis of the 6-*endo*-tosylate (**11**).

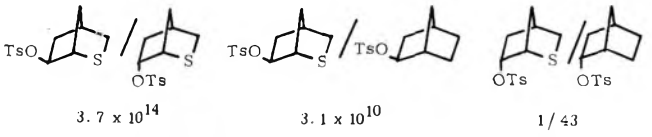
As expected from the fast rate of solvolysis of **10ex**, the reaction gave rise to an exo attack on the tricyclic episulfonium ion (**22**) by a solvent, resulting the exclusive formation of an exo derivative. The fact that only the exo product (**13ex**) was produced from the solvolysis of the less reactive **11** indicates intervention of the stable tricyclic episulfonium ion (**22**). It should be noted that no endo product nor olefin could be detected by VPC and NMR analyses.

Discussion

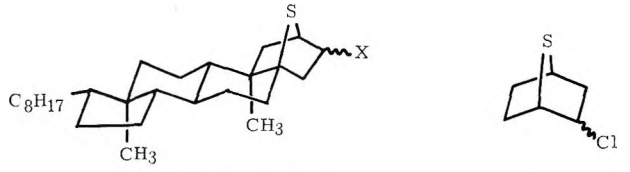
The solvolytic behaviors of the isomeric esters (**10ex** and **11**) provide valuable information on the role of a neighboring sulfur atom in solvolysis of the 2-thiabicyclo[2.2.1]hept-6-yl system. The exo isomer should have an advantage in forming a relatively stable episulfonium ion by β-S-participation.

The rate observed for the exo ester (**10ex**), 3.1×10^{10} times faster than the corresponding carbon system, reveals clearly

that the sulfur of this system highly stabilizes the transition state. An extremely high exo/endo rate ratio, 3.7×10^{14}, rises primarily from strong β-S-participation for the exo isomer (**10ex**). This value is the greatest among rate ratios of two stereoisomers observed until the present.

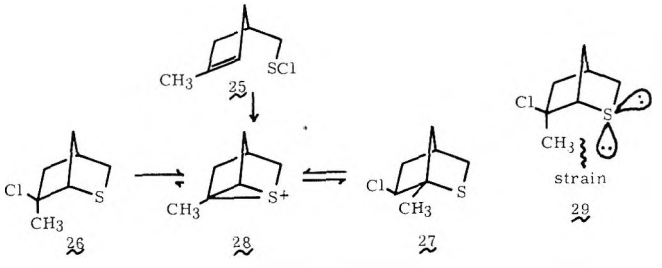


In the recent solvolytic studies of the similar systems, Tanida[19] and Tabushi[12] have examined independently the solvolytic behavior of **23** and **24**. In both systems faster rate is observed with the endo isomer: endo/exo rate ratios 1.2×10^8 (25 °C) for **23** in 70% aqueous dioxane and 4.7×10^9 (25 °C) for **24** (in acetic acid for the endo and in 50% aqueous dioxane for the exo) after correction for the solvent as well as the leaving group. Although there are observed high rate ratios of both systems, they fail to overcome the rate ratio of the 2-thiabicyclo[2.2.1]hept-6-yl system, indicating that the amount of neighboring-group participation strongly depends on the structural factors such as geometry, stereochemistry, and skeletal mobility of molecules in the transition state.[20]



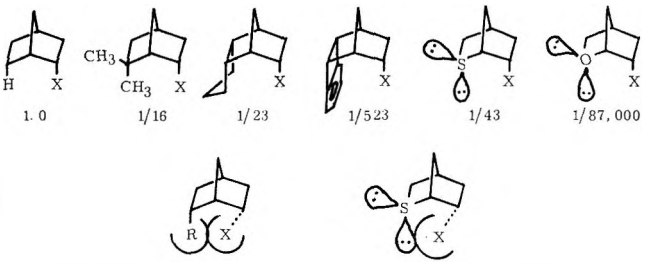
On the other hand, the endo isomer (**11**) undergoes its solvolysis somewhat slower than *endo*-2-norbornyl derivative, 1/43. This rate retardation may be attributed to the inductive character of a sulfur atom.[17]

The concept of "steric hindrance to ionization", proposed by Brown[3a] in the norbornyl system, may account for the retardation of the solvolysis rate of an endo isomer. As we reported previously,[8] the tricyclic episulfonium ion (**28**), derived



by intramolecular sulfenyl chloride addition of **25** formed in situ from the reaction of the corresponding disulfide with chlorine, should be in equilibrium with **26** and **27** at elevated temperature. However, we could not establish the presence of the tertiary chloride (**26**), although **26** is expected to be thermodynamically more stable than **27** as is usually the case with β-chloro sulfides.[21,22] The remarkable instability of the tertiary chloride (**26**) when compared with the other equilibrated isomer (**27**) indicates the presence of steric repulsion between the 6-*endo*-methyl group and the lone pair electrons of the endo side of the sulfur atom, as shown in **29**. This fact is interesting in the evaluation of the spatial requirements of lone pair electrons.

In the norbornyl system, endo-6 substituents are operative in increase of steric repulsion in ionization, and the amount of retardation depends on the spatial environment of molecules.[4,23-26] Considering the inductive rate-retarding factor of 2000 observed for solvolysis of 2-*exo*-chloro-7-oxabicyclo[2.2.1]heptane,[4] this factor being considered to be applicable to the 2-oxabicyclo[2.2.1]hept-6-*endo*-yl analogue, the factor of 1/44 attributable to steric hindrance in an ionizing step is obtained. This value is similar to that obtained for the endo isomer of the thia analogue, indicating that the steric requirement between the oxa and thia analogues, especially in relation of steric repulsion of lone pair electrons with a leaving group in the transition state, is quite equivalent.

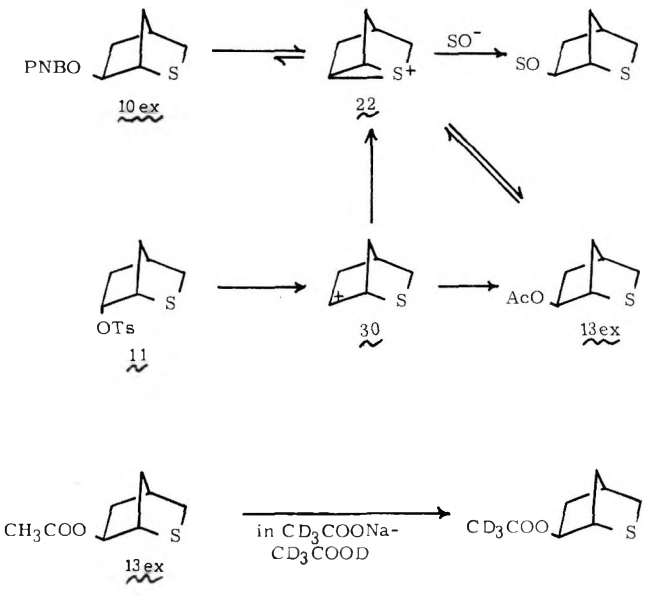


Among the solvolytic studies involving β-S-participation, an example in which a solvent-attacking step is the step determining a rate is known;[12] this may arise from a large amount of neighboring-group participation. On the basis of our results, however, the differences of rate-determining steps are not attributable to the amount of participation by neighboring groups, but to the character of the leaving groups.

The intervention of the optically inactive tricyclic episulfonium ion obtainable from the solvolysis of an ester of optically active 2-thiabicyclo[2.2.1]heptan-6-*exo*-ol makes this point unequivocal. The observation of 30–40% internal return at the first ionizing step of solvolysis, calculated from titrimetric (k_t) and polarimetric (k_α) determinations of rates, leads to the conclusion that ionization is the rate-determining step; the attack of solvent on the ion does not affect the rate.

The mechanistic considerations of solvolysis of the exo and endo esters (**10ex** and **11**) are illustrated in Scheme IV. The acetoxy group of **13ex** [the solvolysis product of the endo ester (**11**)] was readily exchangeable. The 6-*exo*-trideuterioacetoxy compound was isolated from the solvolytic reaction of the 6-*exo*-acetoxy derivative in buffered trideuterioacetic acid, so that the initially formed acetoxy product from the endo ester could be present in an equilibrium under the solvolytic condition. Thus, the presence of the direct process to **13ex** from the open carbonium ion (**30**) could not be explored independently from more plausible process via the episulfonium ion produced by overlapping of the vacant 2p orbital at the 6 position of **30** with the lone pair electrons of the sulfur atom.

Scheme IV



The intervention of the σ-sulfurane structure[18c,d,e,27,28] may be eliminated in this solvolytic reaction because of the low nucleophilic ability of a *p*-nitrobenzoate anion. The presence of σ-sulfurane as an intermediate is more plausible in reactions of β-halo sulfides.

β-Halo sulfides are often present in equilibrium with episulfonium ions even in aprotic solvents. In these cases, rates are considered to be affected by the nucleophilic character of nucleophiles and not by the ionizing ability of solvents.

Success in isolating the tricyclic episulfonium ion, 1-thioniatricyclo[1.1.1.^{2,6}]heptane perchlorate (**22**), as the intermediate ion is attributed to its structural stability when compared with usual episulfonium salts observed by Helmkamp and co-workers.[18]

The 2-thiabicyclo[2.2.1]hept-6-yl system (**3**) supplies not only matters of mechanistic interests in solvolytic reactions, but also structural interests. We are currently pursuing the role of a divalent sulfur atom in comparison with other thiabicyclic systems.

Experimental Section

All melting points are corrected and boiling points are uncorrected. IR spectra were taken on a Hitachi-Perkin-Elmer Model 225 (Grating) spectrometer. ^{1}H NMR spectra were recorded on a Varian 100-MHz spectrometer (HA-100) in deuteriochloroform and the ^{13}C NMR spectrum of the tricyclic episulfonium salt (**22**) on a JEOL FX-100 spectrometer using a 10-mm tube. Chemical shifts are indicated by parts per million from a tetramethylsilane internal standard. Mass spectra were measured on a Hitachi mass spectrometer Model RMS-4 performed with a target current of 70 μA and a chamber voltage of 70 eV. Gas chromatographic analyses were carried out with a Varian 1440 instrument equipped with a flame ionization detector and with glass tubing columns. Conditions used for analysis are given at an appropriate position.

3,3-Dichloro-2-thiabicyclo[2.2.1]hept-5-ene (4) This compound was prepared from the cycloaddition of cyclopentadiene with thiophosgene according to the procedure reported by Middleton[6] or Johnson[7] and stored in a dry-ice box.

2-Thiabicyclo[2.2.1]hept-5-ene (5). To a suspension of $LiAlH_4$ (15.5 g, 0.41 mol) in 250 mL of gently refluxing anhydrous ether was added dropwise a solution of 45 g (0.25 mol) of **4** dissolved in 150 mL of anhydrous ether. The mixture was stirred at reflux for an additional 2 h. The excess hydride was destroyed by careful addition of water. The ether solution was filtered and the residue was washed with 100 mL of ether. Both solutions were combined, dried over $MgSO_4$, and concentrated at 60 mmHg while cooling in an ice bath. Finally, the solvent was removed at room temperature to leave 25.3 g (90%) of a faint yellow oil, which solidified on cooling. The NMR spectrum of the waxy solid thus obtained was identical with that reported by Johnson and co-workers.[7] Sublimation provided pure material of a white waxy solid: mass spectrum (*m/e*) 112 (M^+), 79 ($M^+ - SH$), 66 ($C_5H_6^+$, base peak).

6-*exo*-Chloro-2-thiabicyclo[2.2.1]heptane (6). Into a solution of 11.6 g (0.103 mol) of **5** dissolved in 25 mL of anhydrous methylene chloride was passed dry hydrogen chloride gas at −50 ~ −60 °C. After the solution was saturated with HCl, the flow of the gas was stopped and then the mixture was stirred for 30 min at −50 °C. The light brown solution was washed three times with 50 mL of cold water, dried over anhydrous K_2CO_3, and concentrated at room temperature to give 13.6 g (89%) of a yellow oil. This crude material was spectroscopically pure and could be used as a synthetic intermediate. Distillation under reduced pressure gave a colorless oil, bp 36.5–37 °C (1 mmHg).

m-Chloroperbenzoic acid (MCPBA) oxidation of **6** yielded the corresponding sulfone derivative (**7**), which was recrystallized from ether to give white needles, mp 99.0–99.5 °C. Anal. Calcd for $C_6H_9ClO_2S$: C, 39.89; H, 5.02; Cl, 19.62; S, 17.75. Found: C, 39.82; H, 5.11; Cl, 19.51; S, 17.66.

2-Thiabicyclo[2.2.1]heptan-6-*exo*-ol (8ex). The chloro derivative (**6**) (5.2 g, 35 mmol) was dissolved in 400 mL of 50% aqueous acetone containing 2.1 g (20 mmol) of sodium carbonate and a solution was allowed to stand at room temperature for 10 h. Acetone was evaporated in vacuo and products were extracted with ether, then the extract was dried over $MgSO_4$ and concentrated to leave 4.3 g (93%) of a pale yellow viscous oil. The oil solidified under cooling. Purification was carried out by column chromatography over neutral or basic alumina because purification by sublimation or distillation resulted in formation of dimeric ether (**14**). When **6** was hydrolyzed without a base, products were contaminated with the dimeric ether (**14**); 34/66 as a ratio of **8ex/14**. Vigorous shaking of **8ex** or **14** in methylene chloride with concentrated hydrochloric acid resulted in the conversion into **6**: mass spectrum (*m/e*) 130 (M^+), 85 ($C_4H_5S^+$, base peak).

The *p*-nitrobenzoate (**10ex**) of **8ex** was prepared in the usual esterification procedure with *p*-nitrobenzoyl chloride and pyridine; recrystallization from a 4:1 mixture of hexane–benzene yielded pale yellow needles, mp 108.5–109.5 °C. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.02; S, 11.48. Found: C, 56.02; H, 4.93; N, 4.88; S, 11.55.

2-Thiabicyclo[2.2.1]heptan-6-one (9). A cold solution of 2.15 g (16.5 mmol) of **8ex** dissolved in 30 mL of carbon tetrachloride and a *tert*-butyl chromate reagent (32 mL, 23 mmol) freshly prepared according to the reported procedure[9] were mixed and left overnight at −10 °C. To the reaction mixture, 4 mL of a saturated tartaric acid solution in ethanol was added and the mixture was stirred for 2 h at room temperature. After filtration, the filtrate was washed several times with a 5% sodium bicarbonate solution, dried over $MgSO_4$, and then evaporated to leave 1.42 g (67.1%) of a pale brown oil, which was spectroscopically pure. An attempt to obtain pure material was carried out by column chromatography over silica gel. An elution with a 1:3 mixture of hexane–benzene provided a single isomer, which was sublimed at 60–70 °C (3 mmHg) to give a colorless waxy solid: this material melted at 100–120 °C; IR ($CHCl_3$) 1740 cm^{-1} (C=O); mass spectrum (*m/e*) 128 (M^+), 85 ($C_4H_5S^+$).

The 2,4-dinitrophenylhydrazone, recrystallized from a 1:1 mixture of hexane–benzene, had mp 175–176 °C. Anal. Calcd for $C_{12}H_{12}N_4O_4S$: C, 46.75; H, 3.92; N, 18.17; S, 10.40. Found: C, 47.02; H, 3.98; N, 18.17; S, 10.21.

2-Thiabicyclo[2.2.1]heptan-6-*endo*-ol (8en). To a cold suspension of 312 mg (8.2 mmol) of $LiAlH_4$ in 40 mL of anhydrous ether was added an ethereal solution (10 mL) of 1.05 g (8.2 mmol) of **9**. The mixture was stirred at reflux for 1 h and the usual workup was carried out. Evaporation of the solvent left 850 mg (79.6%) of a white solid, which was recrystallized from hexane or pentane to afford a white waxy solid, mp 164–167 °C. Alternatively, purification by sublimation also gave the same material: mass spectrum (*m/e*) 130 (M^+), 85 ($C_4H_5S^+$, base peak).

The *p*-nitrobenzoate (**10en**) of **8en** was prepared from the reaction of **8en** with *p*-nitrobenzoyl chloride in pyridine and recrystallized from hexane to give pale yellow needles, mp 102.5–103.5 °C. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.02; S; 11.48. Found: C, 55.78; H, 4.92; N, 4.86; S, 11.77.

The *p*-toluenesulfonate (**11**) of **8en** was prepared in the same procedure as used for the ester (**10en**). As an effort to solidify the ester (**11**) failed, the sample was purified by column chromatography over silica gel. Chromatographed material, whose purity was confirmed spectroscopically, was used for the kinetic measurements without further purification.

6,6′-*exo,exo*-Oxybis(2-thiabicyclo[2.2.1]heptane) or Di(2-thiabicyclo[2.2.1]hept-6-*exo*-yl) Ether (14). (A) To a solution of 130 mg (1mmol) of **8ex** in 2 mL of anhydrous tetrahydrofuran was added a 2 *n*-BuLi solution in hexane (0.5 mL, 1 mmol, Merck reagent) in a dry ice–acetone bath (−30 ~ −40 °C) under a nitrogen stream. The mixture was stirred for 30 min at −30 °C and then a solution of 148 mg (1 mmol) of **6** in 2 mL of tetrahydrofuran was added. After standing overnight at room temperature, the solution was concentrated and a residue was dissolved in 10 mL of ether. The ether solution was washed with water, dried over $MgSO_4$, and then evaporated to leave 210 mg (86.6%) of a viscous oil, which was sublimed at reduced pressure to give a waxy solid: mass spectrum (*m/e*) 242 (M^+), 129 ($C_6H_9OS^+$), 113 ($C_6H_9S^+$, base peak), 85 ($C_4H_5S^+$).

(B) In a small-scale experiment, the exo alcohol (**8ex**) containing a trace amount of *p*-toluenesulfonic acid was refluxed in benzene for 3 h. The mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and then evaporated. There was obtained fairly pure dimeric ether **14** quantitatively. Spectral data were consistent with those of the product prepared according to method A.

6-*exo*-Methoxy-2-thiabicyclo[2.2.1]heptane (12). A solution of 1.1 g (8.4 mmol) of **8ex** dissolved in 30 mL of anhydrous methanol containing 30 mg of *p*-toluenesulfonic acid was refluxed for 1 h. The solution was concentrated carefully and 20 mL of ether was added. The ether solution was washed with saturated $NaHCO_3$ solution and with saturated NaCl solution, and dried over anhydrous K_2CO_3. Evaporation of the solvent under atmospheric pressure left 1.1 g (90.8%) of a pale brown oil, which was distilled to give a colorless oil: bp 50–53 °C (3 mmHg); mass spectrum (*m/e*) 144 (M^+), 112 ($M^+ - CH_3OH$), 97 ($M^+ - CH_3S$), 85 ($C_4H_5S^+$).

Likewise, by the use of dimeric ether (**14**), the same product (**12**) was obtained in a high yield. Alternatively, the methanolysis of **6** or **10ex** in methanol containing sodium methoxide gave the corresponding methoxy derivative (**12**) quantitatively.

2-Thiabicyclo[2.2.1]heptan-6-*exo*-ol Acetate (13ex). To a stirred solution of 780 mg (6 mmol) of **8ex** in 4 mL of anhydrous pyridine was added 817 mg (8 mmol) of acetic anhydride under ice cooling. The usual workup gave 940 mg (91%) of a pale yellow oil, which was spectroscopically pure. Distillation provided a colorless oil: bp 82–83 °C (2 mmHg); n^{20}_D 1.5066; IR (film) 1740, 1232 cm^{-1} ($COCOCH_3$); mass spectrum (*m/e*) 172 (M^+), 129 ($M^+ - CH_3CO$), 113 ($M^+ - CH_3COO$), 85 ($C_4H_5S^+$, base peak), 43 (CH_3CO).

2-Thiabicyclo[2.2.1]heptan-6-*endo*-ol Acetate (13en). The alochol (**8en**) (26 mg, 0.2 mmol) was acetylated in the usual manner. There was obtained 34 mg of a colorless oil, which showed to be a single peak in VPC analysis and pure in NMR spectrum. IR (film) 1733, 1243 cm^{-1} ($COCOCH_3$).

1-Thioniatricyclo[1.1.1.$0^{2,6}$]heptane Perchlorate (22). To a stirred solution of 1.5 g (10.1 mmol) of **6** dissolved in 10 mL of anhydrous acetonitrile was added dropwise a solution of 2.09 g (10.1 mmol) of silver perchlorate dissolved in 10 mL of acetonitrile under ice cooling. A solid preceipitated, which consists of a sulfonium salt and silver chloride, was assembled by filtration, and extracted three times with 50 mL of hot acetontrile. Evaporation of the solvent gave 1.77 g of a pale violet solid, which was recrystallized from acetonitrile to yield 1.32 g (61.2%) of while crystals, mp 216–218 °C dec. Anal. Calcd for $C_6H_9ClO_4S$: C, 33.89; H, 4.27; S, 15.08. Found: C, 33.85; H, 4.19; S, 15.29. The IR spectrum showed a broad band at 1100 cm^{-1} assignable to perchlorate. This compound is slightly soluble in acetonitrile and nitromethane, and insoluble in such solvents as chloroform, dichloromethane, carbon tetrachloride, dimethyl sulfoxide, dimethylformamide, tetranitromethane, and nitrobenzene.

Trapping of the Tricyclic Episulfonium Ion (22) under Solvolytic Conditions. To a stirred solution of 130 mg (1 mmol) of the exo alcohol (**8ex**) dissolved, at 0 °C, in 2 mL of a 1:1 mixture of trifluoroacetic acid and trifluoroacetic anhydride was added 0.17 mL of 60% perchloric acid solution with the aid of a microsyringe. After stirring for 30 min at 0 °C, the mixture in which small amount of colorless needles appeared was concentrated under reduced pressure to leave pale brown crystals. Decolorization of a solution of the crystals dissolved in acetonitrile with active carbon and evaporation of the solvent gave 210 mg (99%) of white crystals, which was recrystallized from acetonitrile to yield white prisms, mp 216–218 °C dec. The ^1H NMR spectrum in trideuterionitromethane showed the typical pattern of the structure of the episulfonium ion.

(−)-2-Thiabicyclo[2.2.1]heptan-6-*exo*-ol[(−)-8ex]. To a stirred solution of 11.56 g (53.4 mmol) of *d*-camphanyl chloride, derived from *d*-camphanic acid[13] [mp 202–203 °C; $[\alpha]^{25}_D$ −6.9 (EtOH, c 1.13)], dissolved in 100 mL of anhydrous pyridine was added dropwise a solution of 6.95 g (53.4 mmol) of the racemic alcohol (**8ex**) dissolved in 10 mL of anhydrous pyridine under ice cooling. The mixture was stirred overnight and poured into a mixture of 100 mL of concentrated hydrochloric acid and 300 g of ice. This treatment was essential to obtain the corresponding camphanic acid ester. When the mixture was poured into cold water, the yield of the ester decreased dramatically as a result of rapid hydrolysis of the ester. A viscous oil separated from the cold acidic medium was extracted with chloroform and the extract was washed twice with cold water, dried over $MgSO_4$, and then evaporated to give 14.9 g (90.3%) of a pale brown oil. Scratching the oil after adding 5 mL of ether gave 2.2 g of crystals, which were recrystallized from ethyl acetate seven times to afford 560 mg of colorless needles: mp 136–137 °C; $[\alpha]^{24}_D$ −29.2 ($CHCl_3$, c 3.01). Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 61.79; H, 7.28; S, 10.28. No more increase of $[\alpha]_D$ could be observed on further recrystallization.

The ester (530 mg, 1.7 mmol) was dissolved in 15 mL of benzene and 3.2 mL (11 mmol) of 70% sodium bis(methoxyethoxy)aluminum hydride solution in benzene was added at 5–10 °C with magnetic stirring. The solution was allowed to stand at room temperature overnight and complexes and/or an excess hydride was destroyed by careful addition of 1.2 mL of 0.5 N NaOH. The clear upper layer was decanted, dried over $MgSO_4$, and evaporated to leave 982 mg of a viscous oil, which was purified by column chromatography over alumina. Elution with benzene gave 220 mg (~100%) of a white waxy solid. This product was shown to be pure in ^1H NMR spectroscopy and thin-layer chromatography, $[\alpha]^{24}_D$ −16.8 (EtOH, c 2.5).

(−)-2-Thiabicyclo[2.2.1]heptan-6-*exo*-ol *p*-Nitrobenzoate [(−)-10ex]. Optically active *p*-nitrobenzoate (−)-**10ex** was prepared from the reaction of the optically active **8ex** (226 mg, 1.73 mmol) with 321 mg (1.73 mmol) of *p*-nitrobenzoyl chloride in the usual manner. Recrystallization from isopropyl ether gave 402 mg (83.1%) of pale yellow needles: mp 107–108 °C; $[\alpha]^{28}_D$ −26.2 ($CHCl_3$, c 2.65). Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.02; S, 11.48. Found: C, 55.86; H, 4.87; N, 4.89; S, 11.57.

Exchange of an Acetoxy Group in the Solvolysis of 2-Thiabicyclo[2.2.1]heptan-6-*exo*-ol Acetate (13ex). A solution of 17.2 mg (0.1 mmol) of **13ex** and 8.5 mg (0.1 mmol) of sodium trideuterioacetate dissolved in 2 mL of trideuterioacetic acid was heated in a sealed ampule at 125 °C. for 380 min (10 half-lives). The solution was concentrated and extracted with ether. The extract was washed with 10% sodium carbonate solution three times and then water, and dried over anhydrous potassium carbonate. Evaporation of the solvent left 12 mg of an oil whose ^1H NMR spectrum showed no methyl signal. Mass spectrum indicated a molecular ion peak at *m/e* 175 corresponded to trideuterioacetate of **8ex** and no peak at *m/e* 172.

3-Cyclopentenemethanethiol Acetate (18). To a solution of 5.5 g (48 mmol) of potassium thiolacetate dissolved in 40 mL of methanol was added a solution of 13.9 g (44 mmol) of 3-cyclopentenemethanol brosylate dissolved in 80 mL of methanol at room temperature with stirring. The mixture was stirred at 60 °C for 2 h and then evaporated. After adding 30 mL of water to a residue, the mixture was extracted with ether and the extract was washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to leave 7.5 g of an oil, which was distilled under reduced pressure to afford 5 g (73%) of a colorless oil: bp 50–53 °C (3 mmHg); IR (film) 1695 cm^{-1} (CH_3COS); mass spectrum (*m/e*) 156 (M^+), 113 ($M^+ - COCH_3$).

3,4-Dibromocyclopentanemethanethiol Acetate (19). The basic procedure of bromine addition was similar to that used for the addition to 3-cyclohexanemethanethiol acetate reported by Johnson and Billman.[11] There was obtained the dibromo derivative (18) in 85.6% yield. Purification was carried out by column chromatopraphy over silica gel: IR (film) 1696 cm^{-1} (CH_3COS); mass spectrum (*m/e*): 194, 192 ($M^+ - CH_3CO - Br$), 113 ($M^+ - CH_3CO - 2Br$).

6-*endo*-Bromo-2-thiabicyclo[2.2.1]heptane (20). To a solution of potassium hydroxide (1.25 g. 18.8 mmol) in 30 mL of methanol was added a solution of 1.7 g (5.4 mmol) of the dibromide (18) dissolved in 20 mL of methanol, with stirring at room temperature, over a period of 20 min. Then the reaction was continued for 2 h and evaporated. To the residue was added 100 mL of ether and the solution was washed with water until the water layer became neutral, dried over $MgSO_4$, and evaporated to leave 910 mg (87.3%) of a pale yellow oil, which was highly pure on TLC analysis. Purification was run by silica gel column chromatography: mass spectrum (*m/e*) 194, 192 (M^+), 113 ($M^+ - Br$), 85 ($C_4H_5S^+$).

Measurement of Rates. (A) Titrimetric Method. The procedure was similar to those used for monocyclic heterocycles previously reported.[15] The 80% aqueous acetone used for the hydrolysis of the exo ester (**10ex**) was prepared by mixing 80 parts by volume of purified acetone with 20 parts of purified water at 20 °C and adjusted to yield a rate of solvolysis identical, within the experimental uncertainty of ±3%, with that observed for 1-phenylcyclohexyl *p*-nitrobenzoate. Acetic acid containing 0.01 N sodium acetate used for the acetolysis of the endo ester (**11**) was prepared according to Winstein's procedure[29] and titration was carried out with 0.01 N perchloric acid solution in acetic acid using bromophenol blue as an indicator. Rate constants were calculated by least-squares linear-regression analysis to first-order rate expression. The physical parameters were obtained by Eyring's absolute rate equation using a computer (TOSBAC 3400).

(B) Polarimetric Method. The polarimetric measurement of rates was carried out with a JASCO automatic polarimeter model DIP-SL in a micro 1-dm polarimeter tube of ~4.3 mL capacity equipped with an outer jacket. Water from a 25.00 ±0.03 °C thermostat was continuously circulated through the outer jacket during the course of the racemization runs. In each racemization rate run, solvent first brought to temperature in the 25 °C thermostat was used to dissolve the weighed quantity of the otpically active ester [(−)-**10ex**] to the mark in a 5-mL volumetric flask. The resulting 0.029–0.03 M solution was then transferred as rapidly as possible to the polarimeter tube and immersed into the thermostat. When readings were taken at appropriate intervals, the polarimeter tube was carefully located in place in the polarimeter trough. The optical rotation vanished at the completion of the reaction.

Analysis of Solvolysis Product. Solvolytic techniques were similar to those used for rate measurements. The solvolysis of the exo ester (**10ex**) was taken in 80% aqueous acetone. To a solution immersed in a temperature-controlled bath at 50 °C for more than 10 half-lives was added an equimolar amount of benzophenone as an internal standard for VPC analysis and the solution was dehydrated by adding anhydrous potassium carbonate. The resulting solution was analyzed

by VPC using a short glass column (1 ft × 1/8 in.) packed with 5% diethylene glycol adipate supported on acid-washed 80–100 mesh Chromosorb W. The column was maintained at 100 °C with a flow rate of 25 mL/min of N_2. Under the VPC condition, only one peak was observed at 28 min of retention time as a produce of solvolysis, which was consistent with that of the exo alcohol (**8ex**). Quantitative analysis by comparison with an internal standard was done by the use of a reporting integrator (Hewllet Packard Model 3880) and gave 97.6% yield as a result of a corrected value.

When the exo alcohol was analyzed using a 6 or 8 ft × 1/8 in. column, another new peak appeared. It was consistent with the dimeric ether **14**, which was attributed to the formation of **14** by thermal conversion of **8ex** on a column.

The solvolysis of the endo ester (**11**) was done in acetic acid containing an equimolar amount of sodium acetate. A solution heated in a sealed ampule at 125 °C for more than 10 half-lives was transferred to a small flask and an equal volume of water and acetone, then an equivalent of benzophenone as an internal standard for VPC analysis was added. The solution which was neutralized and dehydrated by adding anhydrous potassium carbonate was analyzed by VPC performed under the same conditions as used for the exo derivative. There was observed a single peak at 19 min retention time, which was consistent with that of the *exo*-acetate (**13ex**), and no other peaks were detected even under conditions capable of detecting at least 0.2% impurity. Quantitative analysis resulted in 85.4% yield.

Moreover, products from the two isomers (**10ex** and **11**) were isolated respectively and their structures were characterized by ^1H NMR and mass spectra.

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Registry No.—(−)-**8ex**, 67338-25-4; (−)-**8ex** *d*-camphonate, 67338-26-5; (−)-**8ex** trideuterioacetate, 67338-27-6; **9** DNP, 67338-28-7; (−)-**10ex**, 67338-29-8; **17**, 67338-30-1; **18**, 67338-31-2; **19**, 67338-32-3; **22**, 67338-34-5; *p*-nitrobenzoyl chloride, 122-04-3; *d*-camphanyl chloride, 67375-29-5; sodium trideuterioacetate, 14044-94-1; 3-cyclopentenemethanol brosylate, 18593-39-0.

Supplementary Material Available: Figure 1, showing the NMR (^1H and ^{13}C) for the tricyclic episulfonium perchlorate, **22** (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) Part 3 in this series: K. Uoji, Y. Fukunaga, and S. Ikegami, *Chem. Pharm. Bull.*, **22**, 1706 (1974).
(2) Ohta Seyaku Co., Ltd., Kamijujo, Kita-ku, Tokyo, Japan.
(3) For recent reviews see: (a) H. C. Brown and P. v. R. Schleyer," The Nonclassical Ion Problem", Plenum Press, New York, N.Y., 1977; (b) H. C. Brown, *Tetrahedron*, **32**, 179 (1976); (c) *Acc. Chem. Res.*, **6**, 377 (1973); (d) "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972; (e) *Chem. Eng. News*, **45** (5), 87 (1967); (f) G. D. Sargent, *Carbonium Ions*, **3**, 1099–1200 (1972); (g) P. D. Bartlett, "Nonclassical Ions", W. A. Benjamin, New York, N.Y., 1965; (h) J. A. Barson, "Molecular Rearrangements", Part 1, P. de Mayo, Ed., Interscience, New York, N.Y., 1963, pp 111–231.
(4) L. A. Spurlock and R. G. Fayter, Jr., *J. Am. Chem. Soc.*, **94**, 2707 (1972).
(5) For reviews see: (a) B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964); (b) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, pp 16–18, 113–114.
(6) W. J. Middleton, *J. Org. Chem.*, **30**, 1390 (1965).
(7) C. R. Johnson, J. E. Keiser, and J. C. Sharp, *J. Org. Chem.*, **34**, 860 (1969).
(8) S. Ikegami, J. Ohishi, and Y. Shimizu, *Heterocycles*, **6**, 387 (1977); details will be reported soon.
(9) (a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, pp 86–87; (b) E. Menini and J. K. Norymberski, *Biochem. J.*, **84**, 195 (1962).
(10) For the charge-transfer absorption of β-oxo sulfides see: L. A. Paquette and L. D. Wise, *J. Am. Chem. Soc.*, **89**, 6659 (1967).
(11) C. R. Johnson and F. L. Billman, *J. Org. Chem.*, **36**, 855 (1971).
(12) I. Tabushi, Y. Tamaru, Z. Yoshida, and T. Sugimoto, *J. Am. Chem. Soc.*, **97**, 2886 (1975).
(13) O. Aschan, *Acta Soc. Sci. Fenn.*, **21** [V], 214 (1895).
(14) (a) If the exciton chirality method[14b] based on the strong $\pi \rightarrow \pi^*$ transitions of para-substituted benzoate chromophores (Me_2N, H_2N, MeO, Cl, H, CN) is applied to that of *p*-nitrobenzoate, the absolute configuration of the optically active ester [(−)-**10ex**] would be indicated, from its CD spectrum, as the structure of (−)-**10ex** shown in Scheme II. We thank Union Giken Co., Ltd., for measurement of the CD spectrum. (b) N. Harada, Mo. Ohashi, and K. Nakanishi, *J. Am. Chem. Soc.*, **90**, 7349 (1968); N. Harada and K. Nakanishi, *ibid.*, **96**, 7352 (1974); N. Harada and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257 (1972); N. Harada, S. L. Chen, and K. Nakanishi, *J. Am. Chem. Soc.*, **97**, 5345 (1975).
(15) S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura, and S. Akaboshi, *Tetrahdron*, **30**, 2087 (1974).
(16) For the polarimetric rates of a carbonium ion see: (a) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **74**, 1154 (1952); (b) H. L. Goering, T. D. Nevitt, and E. F. Silversmith, *ibid.*, **77**, 5026 (1955). For a system involving β-O-participation see: (c) L. A. Paquette, I. R. Dunkin, J. P. Freeman, and P. C. Storm, *ibid.*, **94**, 8124 (1972).
(17) (a) P. R. Wells, "Linear Free Energy Relationships", Academic Press, New York, N.Y., 1968 p 35; (b) R. W. Alder, R. Baker, and J. M. Brown, "Mechanism in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1971, p 28.
(18) For isolation and reactivities of episulfonium ions, see: (a) D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, **28**, 2932 (1963); (b) *ibid.*, **29**, 2702 (1964); (c) D. C. Owsley, G. K. Helmkamp, and S. N. Spurlock, *J. Am. Chem. Soc.*, **91**, 3606 (1969); (d) D. C. Owsley, G. K. Helmkamp, and M. F. Rettig, *ibid.*, **91**, 5239 (1969); (e) G. K. Helmkamp and D. C. Owsley, *Mech. React. Sulfur Compd.*, **4**, 37 (1969); (f) E. Carbin and G. K. Helmkamp, *Int. J. Sulfur Chem., Part A*, **2**, 129 (1972).
(19) T. Tsuji, T. Komeno, H. Itani, and H. Tanida, *J. Org. Chem.*, **36**, 1648 (1971).
(20) L. A. Paquette, G. V. Meehan, and L. D. Wise, *J. Am. Chem. Soc.*, **91**, 3231 (1969).
(21) For review see W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969).
(22) For an equilibrium of cyclic systems see S. Ikegami, J. Ohishi, and Y. Shimizu, *Tetrahedron Lett.*, 3923 (1975).
(23) (a) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **71**, 2953 (1949); (b) *ibid.*, **74**, 1147, 1154 (1952).
(24) P v. R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, **87**, 375 (1965).
(25) K. Takeuchi, T. Oshika, and Y. Koga, *Bull. Chem. Soc. Jpn.* **38**, 1318 (1965).
(26) R. Baker and J. Hudec, *Chem. Commun.*, 929 (1967).
(27) For the nomenclature and definition of σ-sulfurane, see B. M. Trost and S. D. Ziman, *J. Org. Chem.*, **38**, 932 (1973).
(28) J. A. J. M. Vincent, P. Schipper, Ae. de Groot, and H. M. Buck, *Tetrahedron Lett.*, 1989 (1975).
(29) (a) S. Winsteln, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 812 (1948); (b) S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

Heterocyclic Studies. 46. Reaction Pathways of the 2-Acyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one System

James A. Moore* and Ben Staskun[1]

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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The 2,6-diazabicyclic carbinolamine **17** has been isolated from the reaction of the 1,2-diazabicyclic ketone **1** in methanol plus Et_3N; **17** gives the same products (**13** and **14**) on further reaction in methanol as does **1**. The reaction of ketone **1b** with base gives the enamino ketone **30** plus glycine, indicating attack at the carbonyl group. Four reaction pathways of **1** are summarized.

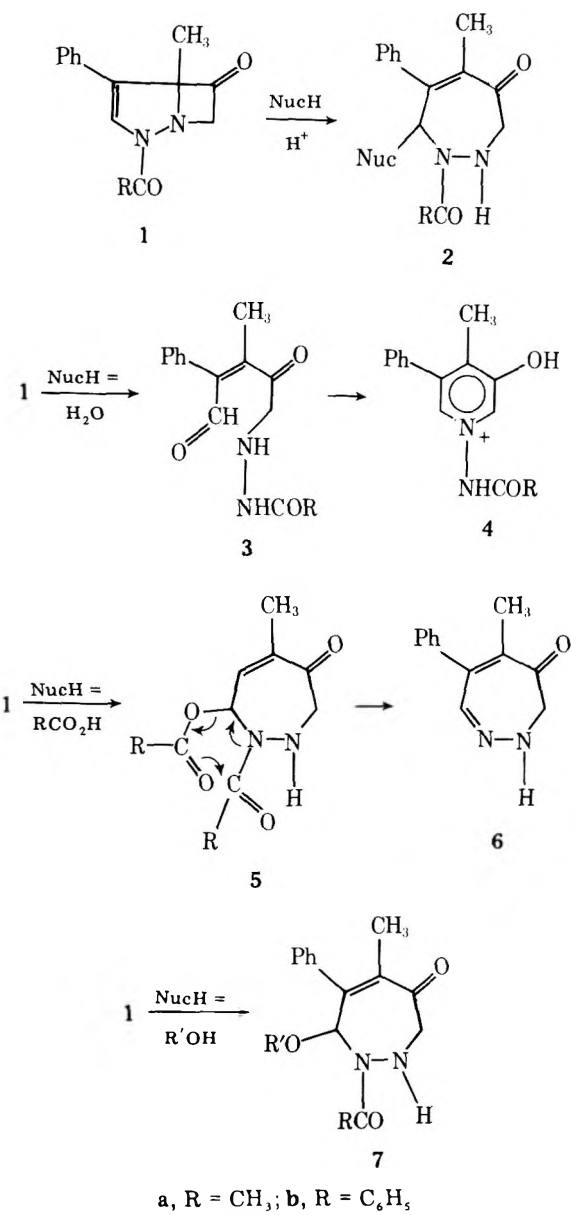
The chemistry of the bicyclic ketones **1** (Scheme I) is unusually rich and varied. Thus, different products are obtained on warming the compounds in methanol, methanol plus acid, methanol plus base, and in methanol–benzene mixtures. Moreover, the product mixtures in higher alcohols differ significantly at reaction temperatures of 60 and 70 °C.[2] In an earlier paper,[3] we described a number of the reactions in methanol and offered some speculation on their pathways. We now report further work on the reactions of **1** in alcohols which confirms some of the earlier ideas, disproves others, and clarifies the situation considerably.

Taking together the previous findings and new results, the chemistry of **1** can be discussed in terms of four groups of reactions, each arising by a different primary event.

Group 1. Acid-Catalyzed Reactions. These reactions are summarized in Scheme I. The products can be accounted for in each case by protonation of N-1 and attack of a nucleophile at C-3. In aqueous media the final product is the pyridinium system **4**.[4] In acetic acid the dihydrodiazepinone **6** is obtained, probably by cyclic elimination of an anhydride. In methanol containing a small amount of a carboxylic acid, the 7-methoxytetrahydrodiazepinones **7** (R′ = Me) are produced.[4] In the present work we have found that the corresponding 7-ethoxydiazepine (**7a**; R′ = Et) can be obtained from the acetyl ketone in ethanol under comparable conditions, but not from the benzoyl ketone. Nucleophilic addition is slower, apparently due to steric factors, and the reactions of Group 3 occur (vide infra). However, the 1-benzoyl-7-ethoxy compound **7b** (R′ = Et) can be readily isolated after warming the benzoyl ketone in ethanol in the presence of magnesium sulfate.

Group 2. Thermal Reactions. The initial step in these reactions is opening of the bicyclic system to the diazepinium betaine **8** (Scheme II), followed by recyclization to the dipolar valence isomer **9**.[2] Further reactions of **9** lead to **12** in benzene or to the pyridazinones **10** or pyrrolinones **11** in alcohols. This sequence is the major pathway followed in reactions of **1** in anhydrous ethanol at temperatures above 70 °C and in higher alcohols. With methanol the formation of **10** is observed only

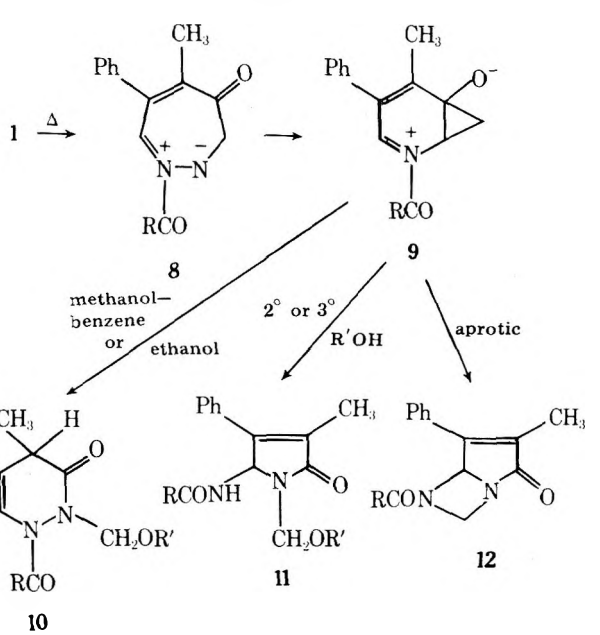
Scheme I



1 2 3 4 5 6 7

a, R = CH_3; b, R = C_6H_5

Scheme II



8 9 10 11 12

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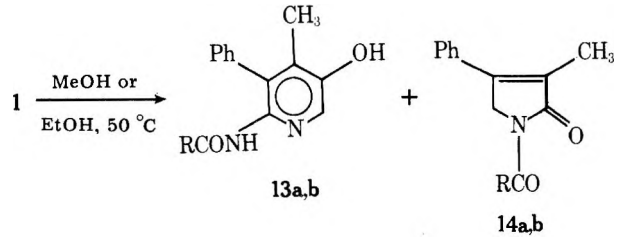
if the polarity of the medium is reduced (and the temperature is increased) by diluting the methanol with benzene; otherwise the reactions of Group 3 occur.

Group 3. Alcoholysis Reactions. The main products in this group are the 6-acylamidopyridines **13** and 1-acylpyrrolinones **14.** When a solution of the benzoyl ketone in methanol is warmed to 50 °C for 1.5 h, **13b** and **14b** are obtained in a



a, R = CH_3; b, R = C_6H_5

ratio of about 2:1 in a total yield of 80%; ammonia and trimethyl orthoformate are byproducts in the formation of **14.**[3] Partial deacylation of **14b** occurs on prolonged reaction time.

By NMR examination of product mixtures from numerous small-scale experiments, we have obtained information on the boundaries for the reaction conditions leading to **13** + **14** and products from Groups 1 and 2. In ethanol solution, **13** and **14** are produced together with the "thermal product" **10** (R′ = Et; Scheme II). The proportion of **10** increases steadily from 50 to 75 °C, and only minor amounts of **13** and **14** are formed in refluxing absolute ethanol. The presence of 1% of water in ethanol causes a marked decrease in the amount of **10,** and the disappearance of **1** is more rapid.

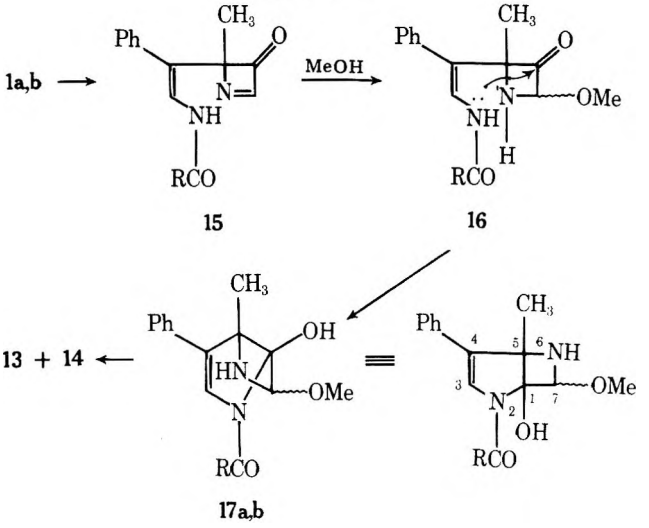
Addition of a trace of acetic acid to the alcohol causes a marked increase in the proportion of the pyrrolinone **14** relative to pyridine **13;** with the acetyl ketone **1a** the 7-alkoxydiazepinone **7** (Scheme I) then becomes a major coproduct. Correspondingly, the addition of a trace of tertiary amine suppresses the formation of **14** relative to **13.**

To summarize, the distribution of products arising from **1a** and **1b** in alcohols depends on both the temperature and the reaction medium. In a given solvent, e.g., ethanol, an increase in temperature favors the thermal reaction (Group 2). On the other hand, an increase in the polarity of the solvent (methanol vs. ethanol and wet ethanol vs. anhydrous ethanol) promotes the process of Group 3, leading to **13** and **14.** The addition of acetic acid effects both the partitioning of **1** between Groups 1 and 3 and also the ratio of products within Group 3, indicating that a step subsequent to the initial reaction in the Group 3 sequence is susceptible to acid.

The pathway to **13** and **14** was previously postulated[3] to involve elimination in the acylhydrazino ketone system of **1** to give the azetinone **15** and subsequent addition of methanol to give **16** (Scheme III). We have now isolated this latter intermediate in the form of bicyclic carbinolamine **17.**

When the reaction of the benzoyl bicyclic ketone **1b** was followed by NMR spectroscopy in CD_3OD–$CDCl_3$ solution, peaks due to an intermediate appeared and then subsided to give the spectrum of **13** + **14.** After adjusting the conditions, **17b** was obtained in large colorless crystals by a 15-min treatment of **1b** at 36 °C with a solution of methanol and chloroform containing a trace of triethylamine. The IR (3550 cm^{-1} for OH and 3360 cm^{-1} for NH), ^1H NMR, and ^{13}C NMR spectra all support structure **17b.** The proton-decoupled ^{13}C NMR spectrum contained a peak at 92.8 ppm, which in a SFORD spectrum was resolved into a singlet at 92.9 ppm due to C-5 and a doublet at 92.7 ppm due to C-7. The configuration of the methoxy group in **17b** is not assigned. Acetylation of **17b** gave an *N*-acetyl derivative. The ethoxy compound analogous

Scheme III



to **17b** was obtained by treatment of **1b** with ethanol and triethylamine in chloroform.

The bicyclic carbinolamine **17b** is a highly reactive compound, and it rapidly decomposes in solution to give the 6-benzamidopyridine **13b** and benzoylpyrrolinone **14b.** In methanol, ethanol, or benzene, the pyridine is the major product. In C_6D_6 solution at 55 °C, $t_{1/2}$ for the conversion of **17b** to **13b** plus methanol is about 45 min; a small amount (<10%) of the pyrrolinone **14b** can be detected by NMR. Addition of a trace of acetic acid to the benzene results in a large increase in the amount of **14b.** Thus, it seems quite clear that **17b,** arising via **15b** as previously suggested, is an intermediate in the low temperature alcoholysis reactions of **1b.**

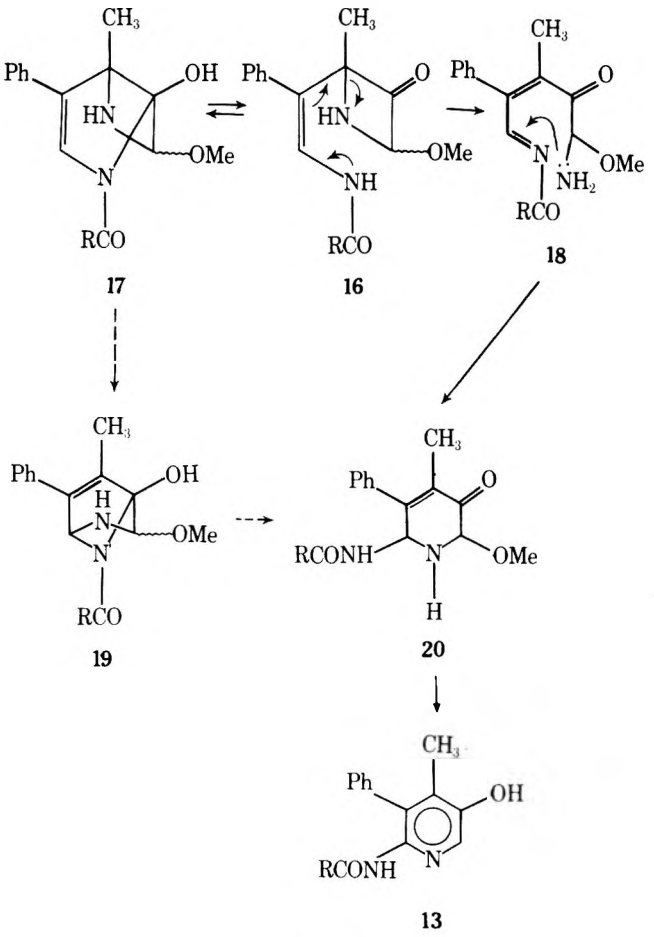
For the subsequent steps leading from **17** to the pyridine **13,** we originally suggested[3] an elimination from the ketone **16** to an acyclic structure followed by ring closure. An alternative which might be considered for the thermal reaction of **17** is a 1,3-sigmatropic rearrangement to the bicyclo[2.2.1] structure **19** (Scheme IV). Although an analogous [3.2.0] → [2.2.1] process is observed in carbocyclic systems at 300 °C,[5] there is no precedent for such a rearrangement of nitrogen and the elimination–cyclization path, perhaps modified as shown in Scheme IV, seems as satisfactory a rationalization as any.

The formation of the pyrrolinone **14** also involves breaking the C_5–N bond. This reaction can be depicted as in Scheme V, with the cation **21** as an intermediate. Loss of methyl formimidate then leads to the hydroxypyrrole which can tautomerize to the Δ^4-pyrrolinone **23** and finally to the more stable Δ^3-pyrrolinone **14.** When the carbinolamine **17b** was treated with aqueous methanolic HCl under conditions such that the product precipitated directly from solution, a mixture was obtained whose NMR spectrum showed the presence of the Δ^4 isomer **23b** [δ 1.45 (d, J = 7 Hz), 3.78 (q, J = 7 Hz), 6.80 (s)]. Further treatment of the mixture with acid converted **23b** to **14b.**

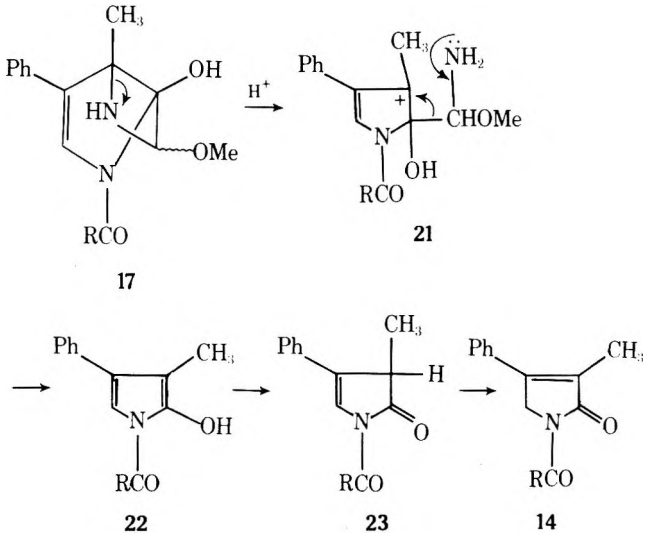
The reaction of **17b** in base takes a different course. The compound dissolved rapidly in 2 N aqueous NaOH, and after standing at 25 °C for 2 h the benzamido ketone **25** was isolated in 41% yield. This compound, previously[3] identified among the products of **1b** in aqueous base, may arise by attack of hydroxide at the carbonyl group of the ketonic tautomer **1b** to give the enamine **24** followed by hydrolysis to **25** and methoxyglycine (Scheme VI).

In the acetyl series, a compound assigned the carbinolamine structure **17a** was obtained from **1a** under the same conditions used for **17b.** The ^1H NMR spectrum at 25 °C of the initial crystalline product showed two sets of peaks of approximately equal intensities for the CH_3CO, OCH_3, H-7 and H-3 signals.

Scheme IV



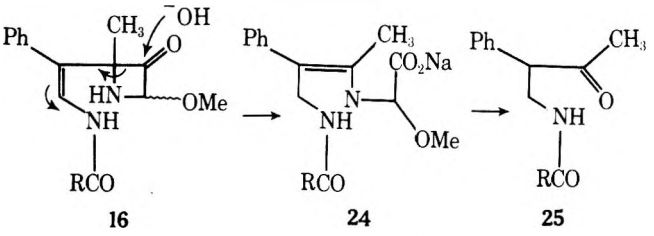
Scheme V



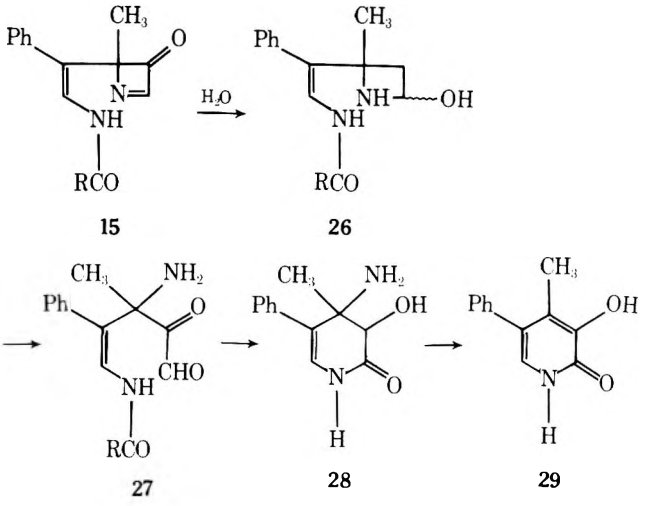
At 35 °C these peaks began to coalesce; at 45 °C coalescence was complete. The NMR observations and the fact that **17a** redissolved quite slowly in organic solvents suggest that the compound may be in equilibrium with a dimeric or higher oligomeric form. At 40 °C peaks due to the pyrrolinone **14a** began to appear; after 1 h about 40% of the mixture was **14a**.

The pyrrolinone **14a** was the main product (from NMR of total reaction mixtures) in the reactions of **17a** in methanol and in benzene; pyridine **13a** was present in smaller amounts. These reactions were not as clean as those of the benzoylcarbinolamine **17b**, and significant quantities of decomposition products were also present. Surprisingly the pyrrolinone was

Scheme VI



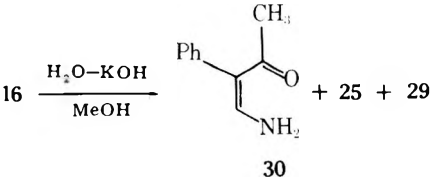
Scheme VII



also obtained from the reaction of **17a** in aqueous base, and there was no indication of ketone **25**. The relatively larger proportion of pyrrolinone to pyridine in the acetyl series was also observed in the reaction of the ketone **1a** in methanol,[3] and the data are thus consistent with **17a** being an intermediate in the reactions of **1a** in alcohol. However, the picture with the acetyl compounds is less clear than that in the benzoyl series, and the reason for the differences in product composition is obscure.

Group 4. Reactions in Base. In aqueous KOH the acetyl ketone **1a** gives the aminopiperidone **28** with a trace of the pyridone **29**, which is formed by loss of ammonia from **28**.[3] These products are presumed to arise by addition of water to the azetinone **15** with subsequent ring opening, deacylation, and recyclization (Scheme VII); their isolation provided the major basis for the original suggestion of azetinone **15** as an intermediate in reactions of the bicyclic ketones.

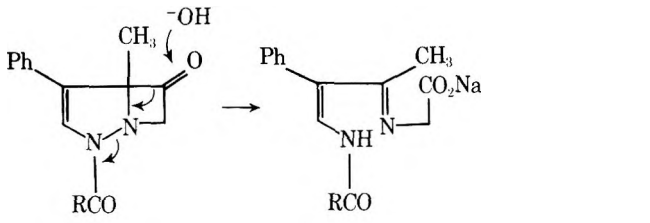
In the benzoyl series, the reaction of **1b** in aqueous methanolic base gave a complex mixture from which traces of the pyridone **29** and the benzamido ketone **25** (Scheme VI) were isolated.[3] The product obtained in largest amount (35%) was the enamino ketone **30**. Pathways were proposed with **27** (R



= Ph) as an intermediate for all three products.[3] In view of the isolation of **25** from the methoxy intermediate **17b** ⇄ **16b**, the route **1b** → **16b** → **24** (Scheme VI) now seems a more likely source of **25** in the product mixture from **1b** in H_2O–CH_3OH–KOH.

The question of the origin of the major product **30** remains. The pathway suggested[3] via **27** requires the elimination of $(CHOHCO_2H)^-$ and poses several difficulties. An alternative was suggested by the reaction of **17b** ⇄ **16b** to give **25** with loss

Scheme VIII



of a two-carbon fragment (Scheme VI). Similar attack by hydroxide at the carbonyl group of **1b** would lead to the intermediate **31** by heterolytic fragmentation,[6] and the final products would be the enamino ketone **30** and glycine (Scheme VIII). To test this possibility, the aqueous solution from the reaction of **1b** in aqueous methanolic base was subjected to amino acid analysis, and glycine was found in 24% yield. Thus, carbonyl attack appears to represent still another mode of reaction of the bicyclic ketone.

In summary, evidence now indicates that the diverse products obtained to date from the diazabicycloheptenones **1a,b** involve four different initial reactions rather than the two types proposed previously.[3] These four pathways occur under conditions which differ only slightly from one to another, and their rates are very delicately balanced, as seen in the concurrence of reactions in Groups 1, 2, and 3 and Groups 3 and 4.

Experimental Section

NMR spectra designated FT 90 MHz were recorded on a Bruker HFX 90 instrument; other NMR spectra were obtained on a Perkin-Elmer R-12B instrument.

1-Acetyl-7-ethoxy-5-methyl-6-phenyl-1,2,3,7-tetrahydro-4*H*-1,2-diazepin-4-one (7a; R′ = Et). A solution of 240 mg of **1a** in 20 mL of ethanol containing about 0.5 mL of acetic acid was allowed to stand for 2 days at 25 °C. After evaporation to a gum and reevaporation of added solvent to remove AcOH, crystallization from ether gave 130 mg of **7a** (R′ = Et) as a white solid which was recrystallized from ethanol: mp 129–130 °C; NMR δ 1.05 (t, 3, J = 7 Hz), 1.83 (s, 3), 2.28 (s, 3), 3.48 (q, 2, J = 7 Hz), 3.7–4.0 (m, 2, CH_2), 5.0 (brd, NH), 6.45 (s, 1, H-7), 7.35 (brd s, 5).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99. Found: C, 66.85; H, 6.72.

Under the same conditions, the benzoyl ketone **1b** gave mainly **14b** with a small amount of **13b** and no **7b** (based on NMR).

1-Benzoyl-7-ethoxy-5-methyl-6-phenyl-1,2,3,7-tetrahydro-4*H*-1,2-diazepin-4-one (7b; R′ = Et). A solution of 110 mg of **1b** in 10 mL of absolute ethanol plus 330 mg of anhydrous $MgSO_4$ was kept at 50 °C for 22 h. After filtration, the solution was evaporated to a gum which crystallized from ethanol–water to give 60 mg of **7b** (R′ = Et): mp 117–118 °C; NMR δ 1.05 (t, CH_3CH_2, J = 6.6 Hz), 1.84 (s, CH_3), 3.55 (q, $-CH_2-$, J = 6.6 Hz), 3.90 (brd s, CH_2), 5.0 (v brd, NH), 6.4 (brd s, H-7), 7.3–8.0 (m, Ar) (similar broadening of peaks at ambient probe temperature is also seen in the NMR spectrum of the 1-benzoyl-7-methoxytetrahydrodiazepinone[4]).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33. Found: C, 71.92; H, 6.38.

The corresponding 1-benzoyl-7-methoxytetrahydrodiazepinone was similarly formed, together with traces of **13b** and **14b**, in methanol with $MgSO_4$.

2-Benzoyl-5-methyl-4-phenyl-7-methoxy-2,6-diazabicyclo-[3.2.0]-3-hepten-1-ol (17b). A 200-mg amount of the benzoyl bicyclic ketone **1b** was dissolved by stirring in 4 mL of a mixture of chloroform, methanol, and triethylamine (5:10:0.1 v/v). After standing for 15 min in a 36 °C water bath, the solution was evaporated *in vacuo* to a pale yellow oil. CCl_4 (2 mL) was added, and the solution was again evaporated; this step was repeated, and the residue, after evaporation, was a pale cream foam. The addition of ether and brief stirring caused the crystallization of **17b** as dense colorless prisms: 120 mg (60%); 90–93 °C decomposes; IR ν ($CHCl_3$) 3550 (OH), 3360 (NH), 1620, 1640 cm^{-1} [after shaking the $CHCl_3$ solution with D_2O, small peaks appeared at 2620 and ~2500 cm^{-1}, indicating OD and ND]; ^1H NMR δ 1.60 (s, 3), 3.56 (s, 3), ~4.0–4.6 (v brd; in D_2O → O), 5.08 (s, 1, H-7), 7.02 (s, 1, H-3), 7.3 and 7.6 (brd, Ar); ^{13}C NMR (FT 90 MHz, 8% in $CDCl_3$) δ 19.3 (q, CCH_3), 54.9 (q, OCH_3), 70.3 (s, C-5), 92.7 (d, C-7), 92.9 (s, C-1), 125.8 (d, C-2 (ortho) of 4-Ph group), 127.2 (d, C-4 of 4-Ph plus C-3), 128.0 (d, C-2 of PhCO ring), 128.7 (d, C-3 (meta) of both Ph), 129.0 (s, C-4), 131.4 (d, C-4 of PhCO), 131.8 (s, C-1 of 4-Ph), 134.0 (s, C-1 of PhCO), 167.2 (C=O).

Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.58; H, 5.97; N, 8.43.

Reaction of 17b in Acid. A. In Methanol. To a solution of 80 mg of **17b** in 0.8 mL of methanol plus 0.2 mL of H_2O was added 0.4 mL of 1.0 N HCl. A mass of colorless crystals separated within a few seconds. The mixture was extracted with CH_2Cl_2, and the organic solution was washed, dried, evaporated, and reevaporated with CCl_4. The NMR spectrum of the solid residue contained predominant peaks at δ 2.08 (t, J ~ 1 Hz), 4.84 (q, J ~ 1 Hz), and 7.54 (brd), corresponding to the Δ^3-pyrrolinone **14b**, and a very small doublet at δ 1.43 ($J \cong 7$ Hz) due to the Δ^4 isomer **23b**. Crystallization of the product from ether gave 34 mg of **14b** as colorless prisms, mp 145–147 °C (lit.[3] mp 145–146 °C), and 11 mg of a lower melting material.

B. In Water. To a suspension of 110 mg of **17b** in 2 mL of water was added 0.5 mL of 1 N HCl. The mixture immediately became milky; a yellow oil separated and partially crystallized on stirring. After 30 sec, the mixture was extracted with CH_2Cl_2; the residue, after evaporation with CCl_4, showed peaks for the Δ^3-pyrrolinone (as above) and the Δ^4 isomer **23** in a ratio of roughly 2:1. The complete spectrum of the Δ^4 isomer was δ 1.45 (d, J = 7 Hz), 3.78 (q, J = 7 Hz), 6.80 (s), and 7.45 (s). Several crops of low melting crystals were obtained, the NMR spectra of which indicated mixtures.

A solution of the pyrrolinone mixture in $CDCl_3$ containing a drop of CF_3CO_2H and CH_2Cl_2 as an internal standard was allowed to stand for 14 h, and the NMR spectrum was recorded. The peaks due to **23** were no longer present, and the intensity of the peaks due to **14b** had increased relative to the CH_2Cl_2 peak, establishing the conversion **23** → **14b**.

Acetylation of 17b. To a solution of 500 mg of **17b** in 6 mL of CH_2Cl_2 was added 1 mL of acetic anhydride and 1 mL of pyridine. After 40 min, the CH_2Cl_2 was evaporated and the oily residue was triturated with water to give a solid which was washed and air-dried, 560 mg (mp 147–150 °C). Recrystallization from methanol–water gave colorless crystals of the *N*-acetyl derivative: mp 155–156 °C, IR ν ($CHCl_3$) 3530 (OH), 1660, 1610 cm^{-1}; NMR δ ($CDCl_3$) 1.76 (s, 3), 2.06 (s, 3), 3.75 (s, 3), 5.40 (s, 1), 5.7 (brd, s; in D_2O → O), 7.08 (s, 1), 7.4, 7.6 (m, Ar).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.85; H, 5.88; N, 7.25.

7-Ethoxy Analogue of 17b. A solution of 200 mg of **1b** in 4 mL of EtOH–$CHCl_3$–Et_3N (10:5:0.1) was kept at 36 °C for 15 min and then evaporated. After addition and removal of CCl_4, addition of ether gave white crystals: mp 60–70 °C; NMR δ 1.30 (t, 3), 1.58 (s, 3), 3.78 (q, 2), 5.15 (s), 7.05 (s, 1), 7.4 (m).

Thermal Reaction of 17b. A. A solution of 128 mg of **17b** in 2 mL of benzene was kept at 50 °C for 3.5 h and then evaporated to give 63 mg of the benzamido pyridine **13b**: mp 210–211 °C; NMR 1.9 (s, CH_3), 7.4 (m, Ar), 8.0 (s, H-2). The NMR spectrum of the mother liquor showed peaks for **13b** and the pyrrolinone **14b**.

B. A solution of **17b** in benzene-d_6 containing Me_4Si was placed in a 55 °C bath, and the NMR spectrum was scanned at 15-min intervals. Peaks due to the pyridine **13b** and methanol were present after 15 min. After 45 min, the CH_3O peaks due to starting material **17b** and methanol were of equal intensity. After 75 min at 55 °C and 12 h at 25 °C, the spectrum showed peaks due to **13b** and methanol and a trace (~5%) of the pyrrolinone **14b**.

C. A solution of **17b** in benzene containing 0.5% acetic acid was allowed to stand at 25 °C for 150 min and then evaporated. The NMR spectrum showed roughly equal amounts of **13b** and **14b** and no **17b**.

Reaction of 17b in NaOH. A 100-mg sample of **17b** was added to 1 mL of 2 N NaOH. The solid dissolved rapidly to give a clear pale yellow solution. After 90 min, the solution was diluted with 2 mL of water, giving an oily precipitate which became crystalline on addition of a few drops of methanol. Acid was then added to neutralize part of the base, and after standing for 2 h the solid was collected, washed, dried, and recrystallized from ether to give 36 mg (45%) of the benzamido ketone **25**, mp 125–126 °C (lit.[3] mp 125–126 °C); semicarbazone, mp 172–175 °C (lit.[3] mp 172–174 °C).

2-Acetyl-5-methyl-4-phenyl-7-methoxy-2,6-diazabicyclo-[3.2.0]-3-hepten-1-ol (17a). A solution of 400 mg of **1a** in 4.5 mL of $CHCl_3$–MeOH–Et_3N (5:10:0.1) was kept at 31 °C for 12 min and then evaporated. The white solid residue was stirred with ether, and 213

mg (47%) of white crystals was collected. The melting point was 93–100 °C with decomposition and partial resolidification. The compound was recrystallized by dissolving it in CH_2Cl_2 (several minutes of warming required); the solution was filtered to clarify and then evaporated at reduced pressure to a solid which was rinsed with ether. This material decomposed with softening and slight darkening at 95–100 °C.

Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61. Found: C, 65.67; H, 6.42.

The 90 MHz FT proton NMR ($CDCl_3$) spectrum at 25 °C showed the following: δ 1.51 (s, 5-CH_3), 2.19 and 2.25 (two s, CH_3CO), 3.45 and 3.47 (two s, CH_3O) 4.86 and 4.94 (two s, H-7), 6.87 and 7.52 (two s, H-3), 7.26 and 7.28 (two s, C_6H_5). At 45 °C, the spectrum showed peaks due to **17a** at δ 1.50, 2.20, 3.45, 4.90, and 7.27 (the coalesced peaks due to H-3 were merged with the large C_6H_5 peak at δ 7.27) and peaks due to pyrrolinone **14a** at δ 2.10 (t, 3-CH_3), 2.61 (CH_3CO), 4.59 (CH_2), and 7.47 (s, C_6H_5) [lit.[3] δ 2.08 (t), 2.60 (s), 4.58 (q), 7.48 (s)]. After 20 min at 45 °C, integration of the CH_3 peaks indicated 23% of **14a**, after 30 min, 30% of **14a**, and after 1 h, 42% of **14a**.

Identification of Glycine from Reaction of 1b and KOH. A 30-mg (100-μmol) amount of the benzoyl bicyclic ketone **1b** was dissolved in 0.2 mL of 10% aqueous KOH containing a drop of methanol. After 2 h, the solution was diluted with water, and 10.5 mg of serine plus 11.7 mg of valine (100 μmol) were added as standards. The pH was adjusted to 6, causing a yellow gum to separate. After filtration through Darco, the solution was further diluted and analyzed on a Beckman 120C amino acid analyzer.[7] The ratio of standards/glycine was 4.15, indicating a 24% yield of glycine based on **1b**.

Registry No.—**1a**, 5109-37-5; **1b**, 5109-45-5; **7a** (R′ = Et), 67350-78-1; **7b** (R′ = Et), 67350-77-0; **13b**, 10137-10-7; **14a**, 10147-13-4; **14b**, 10137-11-8; **17a**, 67328-94-3; **17b**, 67328-95-4; **17b** *N*-acetyl derivative, 67328-96-5; **17b** 7-ethoxy analogue, 67328-97-6; **23b**, 67328-98-7; **25b**, 10137-17-4.

References and Notes

(1) Visiting professor at the University of Delaware from the University of Witwatersrand, Johannesburg, S. Afr.
(2) J. A. Moore, B. Staskun, and J. F. Blount, *J. Org. Chem.*, **41**, 3156 (1976).
(3) J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. J. Creegan, *J. Org. Chem.*, **32**, 1353 (1967).
(4) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).
(5) J. A. Berson, *Acct. Chem. Res.*, **5**, 406 (1972).
(6) For a recent review and precedents, see K. B. Becker and C. A. Grob in "Chemistry of Double-Bonded Functional Groups", S. Patai, Ed., Wiley, New York, N.Y., 1977. A relevant example is the fragmentation of 3-quinuclidinone with hypochlorite to give piperidine-4-carboxylic acid: W. H. Dennis, L. A. Hull, and D. H. Rosenblatt, *J. Org. Chem.*, **32**, 3783 (1967).
(7) We thank Professor J. Wriston and Mrs. Jean Denis for this determination.

^{13}C-Labeled Benzo[*a*]pyrene and Derivatives. 1. Efficient Pathways to Labeling the 4, 5, 11, and 12 Positions[1,2]

Richard S. Bodine, Mark Hylarides, Guido H. Daub,* and David L. VanderJagt

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

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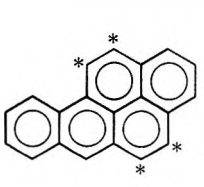
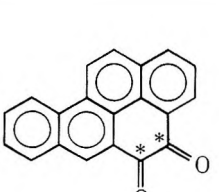
Efficient pathways leading to the synthesis of benzo[*a*]pyrene labeled with ^{13}C in the 4, 5, 11, or 12 positions are described. A method of synthesis of the benzo[*a*]pyrene-4,5- and -11, 12-quinones leading to labeling in the 4 or 5 and 11 or 12 positions, respectively, is also presented, allowing ready access to the labeled 4,5- and 11,12-oxides. The values of the ^{13}C NMR chemical shifts for C_4, C_5, C_{11}, and C_{12} of benzo[*a*]pyrene were determined using the labeled compounds.

Discussion

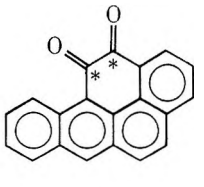
As part of a program to develop efficient syntheses of the potent carcinogen benzo[*a*]pyrene labeled with ^{13}C (90%) at each one of the peripheral carbon atoms of the ring system we have successfully developed such routes to the 4-, 5-, 11-, and 12-labeled benzo[*a*]pyrenes (**1a**, **1b**, **1c**, and **1d**). In addition, the benzo[*a*]pyrenequinones **2** and **3** have been prepared as intermediates for the synthesis of the corresponding arene oxides **4** and **5**.



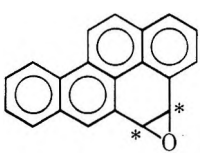
1a, label at C_4
1b, label at C_5
1c, label at C_{11}
1d, label at C_{12}



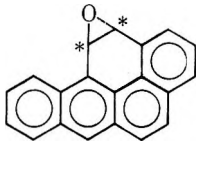
2a, C_4 label
2b, C_5 label



3c, C_{11} label
3d, C_{12} label



4a, C_4 label
4b, C_5 label

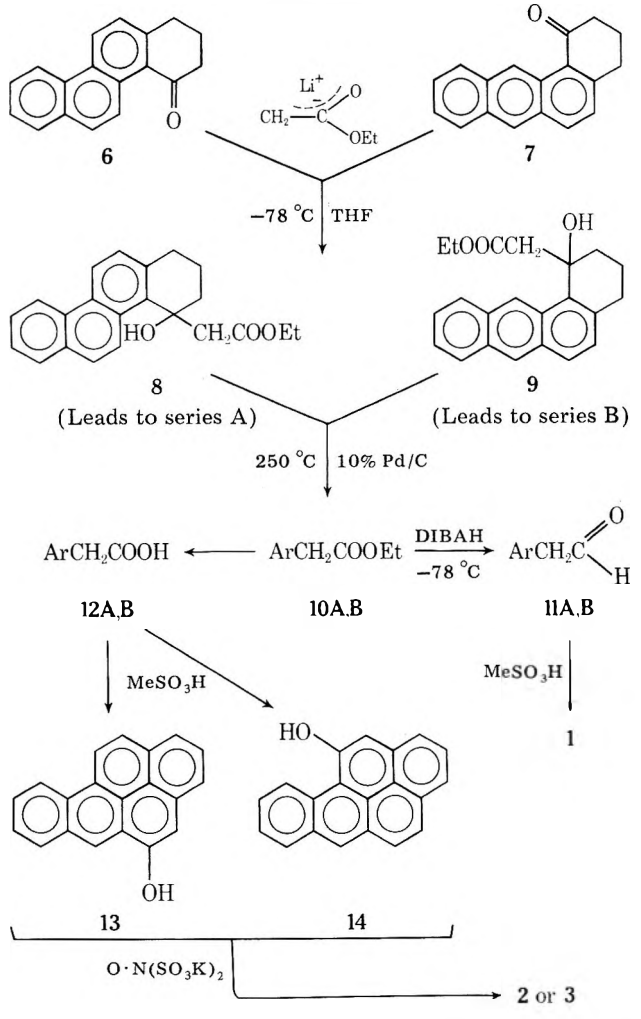


5c, C_{11} label
5d, C_{12} label

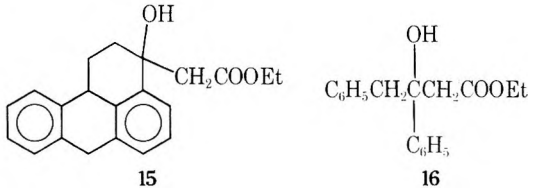
The synthesis of benzo[*a*]pyrene (**1**) from 1,2-dihydrochrysen-4(3*H*)-one (**6**)[3a] and from 3,4-dihydrobenz[*a*]anthracen-1(2*H*)-one (**7**)[4] was studied (Scheme I), since these ketones are relatively easily synthesized and have been shown previously to undergo the Reformatsky reaction[3b,4] in moderate yield. Furthermore, these two approaches would allow the introduction of the ^{13}C label at the 4 or 5 and the 11 or 12 positions, respectively, late in the synthesis depending on the position of the label in the starting ester. It was felt that the Reformatsky reaction as carried out earlier[3b,4a] would be unsuitable for labeling studies, since an excess of bromo ester was used, and in the case at hand this would contain the label. Attempts to prepare the hydroxy esters **8** and **9** via the Reformatsky reaction failed to give satisfactory yields using equimolar ratios of the ketones **6** or **7** and ethyl bromoacetate even under conditions reported to give excellent yields for selected ketones.[5-7] However, when the ketone **6** or **7** was allowed to react with the lithium enolate of ethyl acetate[8] in THF at −78 °C, the hydroxy ester **8** or **9** was obtained in 82% yield. The hydroxy esters **8** and **9** rapidly revert to the respective ketones if the reaction mixture is allowed to warm to room temperature before acidification; thus, acidification of the reaction mixtures had to be carried out at −78 °C in order for the hydroxy esters to survive.

0022-3263/78/1943-4025$01.00/0

Scheme I



Indeed, the esters **8**, **9**, **15**, and **16** undergo rapid retroaldol reactions when treated with lithium isopropylcyclohexylamide in THF at 15–25 °C, and we are currently studying the generality of this reaction.



Dehydration and dehydrogenation of the hydroxy esters **8** or **9** was accomplished by heating with Pd/C at 250 °C to afford the arylacetic esters **10A** or **10B** in 82 and 89% yields, respectively. Saponification of either ester with ethanolic potassium hydroxide gave the corresponding acid **12A** or **12B** in excellent yield. Reduction of the esters with DIBAH at −78 °C in toluene afforded the respective aldehydes **11A** and **11B**, which were directly cyclized to benzo[*a*]pyrene (**1**) by treatment with methanesulfonic acid in overall yields of 85 and 82%, respectively, from **10A** and **10B**.

Cyclization of either of the arylacetic acids, **12A** or **12B**, with methanesulfonic acid[9] gave the respective phenols, **13** or **14**, which were directly oxidized with Fremy's salt [10] in buffered aqueous acetone to the corresponding quinones, **2** and **3**.

The overall yield of benzo[*a*]pyrene from the ketone **6** was 52% and from the ketone **7** was 55–60%. The overall yields of the quinones **2** and **3** from the ketones **6** and **7** were 51 and 52–57%, respectively. These overall yields are sufficiently good to render these approaches to benzo[*a*]pyrene useful for the synthesis of the ^{13}C-labeled compounds **1a–d**. In addition, the route via the quinones **2** and **3** to the respective arene oxides **4a, b** and **5c, d** represent excellent paths for the synthesis of such labeled systems.[11–13]

We have utilized the sequences described above in synthesizing benzo[*a*]pyrene-*5*-^{13}C (**1b**) and -*11*-^{13}C (**1c**) using ethyl acetate-*1*-^{13}C (**17**) and benzo[*a*]pyrene-*4*-^{13}C (**1a**) and -*12*-^{13}C (**1d**) from ethyl acetate-2-^{13}C (**18**). Both labeled esters **17** and **18** were prepared in better than 90% yield by allowing labeled sodium acetate to react with triethyl phosphate at 180 °C.[14] The labeled quinones **2a, b** and **3c, d** have also been prepared.

Carbon-13 NMR spectra of the benzo[*a*]pyrenes **1a–d** have allowed us to identify the chemical shifts for the carbon atoms in the 4, 5, 11, and 12 positions of benzo[*a*]pyrene. Indeed, the correct chemical shifts for C_4, C_5, and C_{12} of benzo[*a*]pyrene are 127.63, 128.00, and 127.33 (δ_C from Me_4Si), respectively, and not 127.33, 127.66, and 128.00, respectively, as assigned by Buchanan and Ozubko[15] based on model compounds, empirical correlations, and deuterium substitution. The chemical shift for C_{11} was identified as 122.00, in agreement with the value assigned by these workers. The ^{13}C NMR spectra were measured by spiking a 0.24 M solution of benzo[*a*]pyrene in $CDCl_3$ successively with small amounts of the labeled products **1a, 1b, 1c,** and **1d,** and running the spectrum at 32 °C after each addition.

Experimental Section

Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are reported boiling points. Elemental analyses were performed by Mrs. Ruby Ju of the Department of Chemistry. IR measurements were obtained on a Perkin-Elmer Model 337 spectrophotometer. ^1H NMR spectra at 60 MHz were recorded on a Varian A-60 or Varian EM-360 instrument at ambient temperature. ^{13}C NMR spectra were obtained in a pulse Fourier transform Varian XL-100 or Varian CFT-20 spectrometer. Product purity and reaction progress were detected with analytical thin-layer chromatography using 2.5 × 10 cm Analtech plates coated with silica gel GF.

Ethyl 2-(1-Hydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracen-1-yl)acetate (9). To a mixture of 2.33 g (16.5 mmol) of *N*-isopropylcyclohexylamine and 15 mL of anhydrous THF, cooled to −78 °C and under a N_2 atmosphere, was added 9.4 mL of 1.6 M *n*-butyllithium (15.0 mmol) in hexane. This mixture was cooled again to −78 °C, and 1.32 g (15.0 mmol) of ethyl acetate in 15 mL of anhydrous THF was added dropwise at a rate to maintain the temperature of the reaction mixture below −75 °C. After addition was complete, stirring was continued for 15 min, after which time 3.69 g (15.0 mmol) of 3,4-dihydrobenz[*a*]anthracen-1(2*H*)-one (**7**), mp 113.5–114.5 °C, dissolved in 45 mL of anhydrous THF was added at a rate which maintained the temperature below −75 °C. After the addition was complete, stirring at −78 °C was continued for 1 h. The orange complex was hydrolyzed by the dropwise addition of 2 mL of concentrated HCl in 10 mL of THF at such a rate as to maintain the reaction mixture at a temperature below −70 °C. The mixture was allowed to warm to room temperature, and 50 mL of water and 50 mL of ether were added. The layers were separated, and the ether layer was extracted with two 20-mL portions of 5% HCl. The aqueous layer was extracted with 25 mL of ether, and the combined ether extracts were dried over $MgSO_4$. Removal of the ether afforded an orange oil which solidified on trituration with ethanol. Crystallization of this solid from 95% ethanol gave 4.02 g (80% yield) of pale yellow crystals, mp 114.5–115.5 °C (reported mp 114–115 °C).[16] In subsequent runs it was found that trituration of the crude product with hexanes in the cold afforded good hydroxy ester, mp 114–116 °C, in 82% yield (4.12 g): IR (KBr) 3465 (OH), 1710 (C=O), 1295, 1195, 1165, 1090, 1050, 1000, 890, 740 cm^{-1}.

Ethyl 1-Benz[*a*]anthraceneacetate (10B). In a dehydrogenation tube fitted with a ground-glass cold finger condenser and gas inlet and outlet tubes was placed 2.00 g (6.0 mmol) of ethyl 2-(1-hydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracen-1-yl)acetate (**9**), mp 114.5–115 °C, 0.20 g of 10% Pd/C, 1.20 g (6.6 mmol) of 1,1-diphenylethene, and 10 mL of 1-methylnaphthalene. The reaction mixture was placed in a preheated Woods metal bath and the temperature was maintained at 250–260 °C for 2 h while steam was passed through the condenser

and with maintenance of a slow flow of N_2. The cooled reaction mixture was diluted with benzene and filtered from the catalyst, which was washed with benzene. After removal of the benzene on a rotary evaporator, the 1-methylnapthalene, 1,1-diphenylethane, and unreacted 1,1-diphenylethene were removed under reduced pressure (0.025 Torr, 50–60 °C) on a Kugel-Rohr. The resultant orange oily residue was crystallized from 95% ethanol to afford 1.54–1.67 g (82–89% yield) of **10B** as beige colored needles, mp 107–109.5 °C. A sample recrystallized from 95% ethanol melted at 109–109.5 °C: IR (KBr) 1720 (C=O), 1250 (CO—O), 1192, 1097, 1024, 886, 770, 744 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.1 (3 H, t, J = 7 Hz), 4.1 (2 H, q, J = 7 Hz), 4.3 (2 H, s), 7.2–8.9 (11 H, m).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.24; H, 5.72.

Benzo[a]pyrene (1). A solution of 1.42 g (4.5 mmol) of ethyl 1-benz[a]anthraceneacetate (**10B**), mp 109–109.5 °C, in 45 mL of dry toluene was cooled to −75 °C under a N_2 atmosphere. To this solution was added 4.5 mL of 1 M diisobutylaluminum hydride (DIBAH) in hexane. The reaction mixture was stirred for 1 h at −75 °C, and the pale yellow complex was hydrolyzed by the addition of 1 mL of concentrated HCl in 9 mL of THF. After warming to room temperature, the reaction mixture was extracted with 5% aqueous NH_4Cl and the toluene layer was dried over $MgSO_4$. Removal of the toluene gave the aldehyde **11B** as a pale yellow oil which was directly dissolved in 65 mL of methanesulfonic acid and stirred under a N_2 atmosphere for 40 min while warming in a water bath. The deep red complex was hydrolyzed by pouring the reaction mixture into 100 mL of water and ice, which resulted in the precipitation of benzo[a]pyrene (**1**) as a yellow solid. This crude product was chromatographed on neutral alumina using benzene as the eluting solvent. The benzene eluate was concentrated and methanol was added to give 0.70 g of lemon yellow shiny platelets, mp 177.5–178 °C (reported[17] mp 176–177 °C). An additional 0.23 g (82% overall yield) of product, mp 176–177 °C, was obtained from the mother liquor.

1-Benz[a]anthraceneacetic Acid (12B). To a solution of 1.41 g (4.5 mmol) of ethyl 1-benz[a]anthraceneacetate (**10B**), mp 108.5–109.5 °C, in 50 mL of 95% ethanol was added 1.00 g (15.1 mmol) of 85% KOH, and the solution was refluxed for 3 h. The ethanol was removed and the residue was dissolved in water and acidified with concentrated HCl to give crude 1-benz[a]anthraceneacetic acid (**12B**) as an off-white solid. Recrystallization from benzene gave 1.22 g (95% yield) of off-white fibrous needles, mp 202–203 °C (reported mp 203.6–204.6 °C).[4a]

11,12-Dihydrobenzo[a]pyrene-11,12-dione (3). A solution of 286 mg (1.00 mmol) of 1-benz[a]anthraceneacetic acid (**12B**), mp 202.5–204 °C, in 10 mL of methanesulfonic acid under a N_2 atmosphere was stirred for 30 min. The deep red complex was hydrolyzed by pouring into 100 g of water and ice, and the green precipitate which was collected was directly dissolved in 50 mL of acetone and added to a solution of 1.07 g (4.0 mmol) of dipotassium nitrosodisulfonate (Fremy's salt) in 40 mL of water buffered with 10 mL of 0.167 M KH_2PO_4. The solution was shaken in a stoppered Pyrex hydrogenation bottle on a Parr shaker until it no longer exhibited fluroescence when illuminated with a short-wave UV lamp. The acetone was removed on a rotary evaporator; the red-brown precipitate was collected and dried under reduced pressure. This crude product was dissolved in CH_2Cl_2 and applied to a silica gel column, the quinone being eluted with 1:1 chloroform/ethyl acetate. After removal of the solvent, the dark red solid was dissolved in CH_2Cl_2 and reduced in volume, and ethyl acetate was added to facilitate crystallization to afford 230 mg (82% yield) of **3** as dark red needles, mp 253–254.5 °C. An analytical sample, mp 257.5–259 °C (evac), was prepared by recrystallization from CH_2Cl_2/ethyl acetate: IR (KBr) 1655 (COCO), 1283, 1177, 1115, 891, 820 cm^{-1}.

Anal. Calcd for $C_{20}H_{10}O_2$: C, 85.09; H, 3.57. Found: C, 84.73; H, 3.51.

Ethyl 4-Hydryoxy-1,2,3,4-tetrahydro-4-chryseneacetate (8). In like manner to that described above for the synthesis of **9**, 4.92 g (20.0 mmol) of 1,2-dihydrochrysen-4(3*H*)-one (**6**),[3] mp 124–125 °C, was allowed to react with the lithium enolate prepared from 1.78 g (20.0 mmol) of ethyl acetate. Workup provided a pale yellow oil which solidified on trituration with 95% ethanol. Crystallization of this oil from 95% ethanol gave 5.48 g (82%) of colorless **8**, mp 77–81 °C (reported[3] as an oil), which was shown by TLC to contain trace amounts of the ketone **6**. Further crystallization failed to improve the melting point or remove the traces of **6**: IR (KBr) 3470 (OH), 1710 (C=O), 1395, 1300, 1230, 1197, 1168, 1090, 1032, 753 cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.04; H, 6.59. Found: C, 78.95; H, 6.51.

Ethyl 4-Chryseneacetate (10A) and 4-Chryseneacetic Acid (12A). Dehydration and dehydrogenation of 2.5 g (7.5 mmol) of the hydroxy ester **8**, mp 77–81 °C, was carried out as described above for **9**. Workup afforded a brown oil which was crystallized from 95% ethanol to give 1.75 g (74%) of the ester **10A** as colorless prisms: mp 63.5–65 °C; IR (KBr) 1735 (C=O), 1380, 1257, 1095, 1030, 833 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.2 (3 H, t, J = 7 Hz), 4.1 (2 H, q, J = 7 Hz), 4.3 (2 H, s), 7.3–8.7 (11 H, m).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.20; H, 5.59.

The residue in the mother liquor from the crystallization of **10A** was heated with 0.1 g of KOH in 15 mL of 95% ethanol for 1.5 h. The ethanol was removed, the residue was dissolved in water, and the solution was filtered through filter-cel and acidified to give crude 4-chryseneacetic acid (**12A**). Recrystallization from toluene gave 0.17 g (8% yield) of **12A**, mp 203–205.5 °C (reported[3b] mp 206.5–207.5 °C). The total yield of dehydrogenated product thus amounted to 82%. Direct saponification of the crude oily ester in a similar run gave 1.59 g (74%) of the acid **12A**, mp 205.5–207 °C, after recrystallization from toluene: IR (KBr) 2700–3200 (br, COOH), 1700 (C=O), 1376, 1270, 1225, 1205, 836, 813 cm^{-1}.

Benzo[a]pyrene (1). Reduction of 0.94 g (3.0 mmol) of the ester **10A** was carried out as described above for **10B**. Workup provided the aldehyde **11A** as a pale yellow oil which solidified on standing: IR (KBr) 3050, 2830 (CHO), 2725 (CHO), 1715 (C=O), 1465, 1376, 1265, 1222, 1183, 1152, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.3 (2 H, d, J = 3 Hz), 7–8.8 (11 H, m), 9.8 (1 H, t, J = 3 Hz). Cyclization of the crude aldehyde as described for **11B** gave benzo[a]pyrene as a pale green solid. Chromatography over neutral alumina followed by crystallization from benzene/methanol afforded 0.64 g (85%) of **1**, mp 176.5–178 °C.

4,5-Dihydrobenzo[a]pyrene-4,5-dione (2). A solution of 0.576 g (2.00 mmol) of the acid **12A**, mp 205.5–207 °C, in 35 mL of methanesulfonic acid was stirred under N_2 for 30 min at 50 °C. Workup as described for **3** provided the phenol **13** as a yellow-green solid which was directly oxidized with Fremy's salt as above for 1 h. The red-brown precipitate formed during the reaction was collected and heated with 5% aqueous Na_2CO_3, releasing the bright orange-red quinone (**2**). Chromatography over silica gel followed by crystallization from $CHCl_3$/ethyl acetate gave 0.48 g (85% overall) of **2** as red-orange crystals; mp 256–257.5 °C (reported[11] mp 255–256 °C); IR (KBr) 1665 (COCO), 1440, 1380, 1286, 1275, 1168, 910, 850, 750 cm^{-1}.

Ethyl Acetate-*1*-^{13}C (17) and Ethyl Acetate-*2*-^{13}C (18). A two-neck 1-L round-bottom flask equipped with a sealed Teflon paddle stirrer and a 12 in. Vigreux column leading to a condenser for downward distillation, receiver, and dry ice trap was charged with 82.6 g (0.996 mol) of sodium acetate-*1*-^{13}C (dried at 110 °C (0.01 Torr) for 2 h) and 300 mL of triethyl phosphate (Aldrich, redistilled). The reaction mixture was heated to 176–180 °C in an oil bath with stirring, and in that range of temperature ethyl acetate-*1*-^{13}C distilled freely (bp 76–78 °C at the top of the Vigreux column). Care had to be taken to keep the reaction from getting out of control by lowering the oil bath when the reaction became too vigorous. As the reaction proceeded the slurry of sodium acetate in triethyl phosphate turned to a homogeneous solution. After 45 min the reaction was essentially complete. The distillate amounted to 78.3 g and was put aside while the reaction mixture was allowed to cool to 60 °C. The system was placed under reduced pressure (25 Torr) in order to obtain a further amount of product which was collected in the dry ice/2-propanol bath cooled trap. This was added to the initial distillate to give a total yield of 86.6 g of colorless product. This was shown to contain a small amount of phosphate ester by VPC, and was redistilled through a 12 in. Vigreux column to give 81.6 g (92% yield) of colorless ethyl acetate-*1*-^{13}C (**17**), bp 72 °C. This product is labeled at C_1 with 90% ^{13}C. In a similar experiment ethyl acetate-2-^{13}C (**18**) was prepared in comparable yield.

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Registry No.—**1**, 50-32-8; **1a**, 67194-47-2; **1b**, 67194-48-3; **1c**, 67194-49-4; **1d**, 67194-50-7; **2**, 42286-46-4; **3**, 60657-26-3; **6**, 66267-06-9; **7**, 57652-74-1; **8**, 67194-42-7; **9**, 57652-75-2; **10A**, 67194-43-8; **10B**, 67194-44-9; **11A**, 67194-45-0; **11B**, 67914-46-1; **12A**, 57652-73-0; **12B**, 57652-76-3; **13**, 24027-84-7; **17**, 3424-59-7; **18**, 58735-82-3; *N*-isopropylcyclohexylamine, 1195-42-2.

References and Notes

(1) Presented before the Division of Organic Chemistry at the 175th National Meeting of the American Chemical Society, Anaheim, California, March, 1978.
(2) Supported in part by Grant No. CA 16871 from the National Cancer Institute, DHEW.
(3) (a) L. F. Fieser and W. S. Johnson, *J. Am. Chem. Soc.*, **61**, 1647 (1939); (b) L. F. Fieser and W. S. Johnson, *ibid.*, **62**, 575 (1940).
(4) (a) L. F. Fieser and H. Heymann, *J. Am. Chem. Soc.*, **63**, 2333 (1941); (b) L. F. Fieser and M. A. Peters, *ibid.*, **54**, 4347 (1932).
(5) M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1970).
(6) R. D. Rieke and S. J. Uhm, *Synthesis*, **7**, 452 (1975).
(7) M. Bellassoued, R. Couffignal, and M. Gaudemar, *J. Organomet. Chem.*, **61**, 9 (1973).
(8) (a) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973); (b) M. W. Rathke, *ibid.*, **92**, 3222 (1970); (c) M. W. Rathke and A. Lindert, *ibid.*, **93**, 2318 (1971).
(9) P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973). It was originally intended to use methanesulfonic acid/P_2O_5 as described by Eaton et al., for these cyclizations; however, we have found that redistilled methanesulfonic acid without added P_2O_5 cyclized both the aldehydes and carboxylic acids in excellent yields under mild conditions.
(10) H.-J. Teuber and G. Steinmetz, *Chem. Ber.*, **98**, 666 (1965).
(11) R. G. Harvey, S. H. Goh, and C. Cortez, *J. Am. Chem. Soc.*, **97**, 3468 (1975).
(12) R. M. Moriarty, P. Dansette, and D. M. Jerina, *Tetrahedron Lett.*, **30**, 2557 (1975).
(13) D. J. McCaustland and J. F. Engel, *Tetrahedron Lett.*, **30**, 2549 (1975).
(14) G. A. Ropp, *J. Am. Chem. Soc.*, **72**, 2299 (1950).
(15) G. W. Buchanan and R. S. Ozubko, *Can. J. Chem.*, **53**, 1829 (1975).
(16) H. Yagi, G. M. Holder, P. J. Dansette, O. Hernandez, H. J. C. Yeh, R. A. LeMahieu, and D. M. Jerina, *J. Org. Chem.*, **41**, 977 (1976).
(17) L. F. Fieser and M. Fieser, *J. Am. Chem. Soc.*, **57**, 782 (1935).

Mechanism of Aryl Group Migration in the Formation of Stilbenes from 1,1-Bis(*p*-hydroxyaryl)ethane 2-*O*-Aryl Ethers

Josef Gierer and Charles R. Nelson*

Department of Chemistry, Swedish Forest Products Research Laboratory, S-114 86 Stockholm, Sweden

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The base-catalyzed displacement of the aryloxy substituent in 1,1-bis(*p*-hydroxyaryl)ethane 2-*O*-aryl ethers, via an aryl participation (A_1-3) reaction, and subsequent transformation to the corresponding stilbenes have been investigated. The relative migratory aptitudes of the phenolic nuclei were determined by rate studies and by the use of C-1 deuterium labeled substrates. The two methods gave similar results and showed that the A_1-3 reaction is enhanced when the migrating phenolic nucleus is substituted with electron-donating substituents. The rate-determining step in this reaction was found to be the intramolecular nucleophilic displacement of the aryloxy substituent by a cyclohexadienone carbanion.

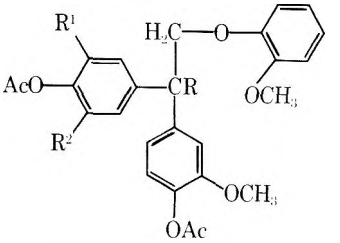
Recently, it was reported that the 1,1-bis(aryl)ethane 2-*O*-aryl ether **1** readily undergoes a base-catalyzed transformation to give, after reacetylation, stilbene **9**.[1] This transformation involves a [1,2] shift of an aryl group, and it was suggested that the mechanism may involve the displacement of the aryloxy substituent through an aryl participation (A_1-3) reaction (Scheme I). A priori, two possibilities for such a transformation can be formulated. As shown in Scheme I, the displacement can be brought about by an intramolecular nucleophilic attack by either carbanion **1b** or **1c** on the β-carbon atom, resulting in the formation of the spiro cyclohexadienone intermediate **8a** or **8b** which by rearrangement and elimination of a proton gives rise to stilbene **9a**.

This conversion of **1** → **9** by way of a spiro cyclohexadienone intermediate is based on well-established precedent, i.e., the alkaline solvolysis of 2-*p*-hydroxyphenylethyl bromide, which takes place by way of a spiro cyclohexadienone intermediate.[2,3] However, the transformation **1** → **9** involves a carbon skeleton rearrangement, and the mechanism of this rearrangement with regard to the identity of the migrating group remains a point of considerable uncertainty and interest. Accordingly, in order to obtain more information about the reaction step in which the aryloxy substituent is split off, and to elucidate more fully the mechanism of this reaction, we have studied the effect of substituents on the migratory aptitude of phenolic nuclei in 1,1-bis(aryl)ethane 2-*O*-aryl ether compounds and have tried to correlate the resulting rate data with parameters characteristic for the electronic effect of the substituent. Some results of this study are now reported.

Results and Discussion

The 1,1-bis(aryl)ethane 2-*O*-aryl ether compounds **1**–**7** were synthesized in an average overall yield of 80–90% by reacting **19** or its deuterated analogue **20** with either phenol or one of three different ortho-substituted phenols in the presence of a small amount of hydrogen chloride,[4] followed by column chromatographic isolation and purification. The condensation products were subsequently used in the form of their crystalline acetate derivatives. Structural proof of new compounds was based on analytical and spectral data (NMR and MS).

Alkaline treatment (1 M NaOH, 170 °C, 2 h) of the 1,1-bis(aryl)ethane 2-*O*-aryl ethers **1**–**4**, followed by acetylation of the resulting reaction mixtures and gas chromatographic



1, R = H; R¹, R² = CH_3
2, R, R¹, R² = H
3, R, R¹ = H; R² = CH_3
4, R, R¹ = H; R² = OCH_3
5, R = ^2H; R¹, R² = CH_3
6, R = ^2H; R¹ = H; R² = CH_3
7, R = ^2H; R¹, R² = H

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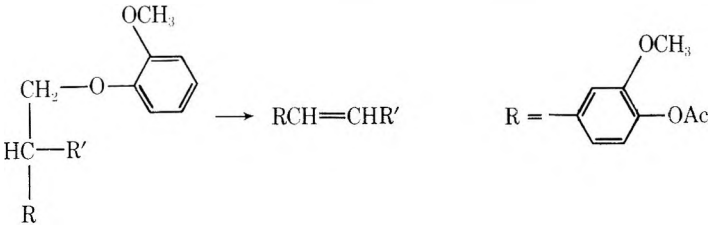
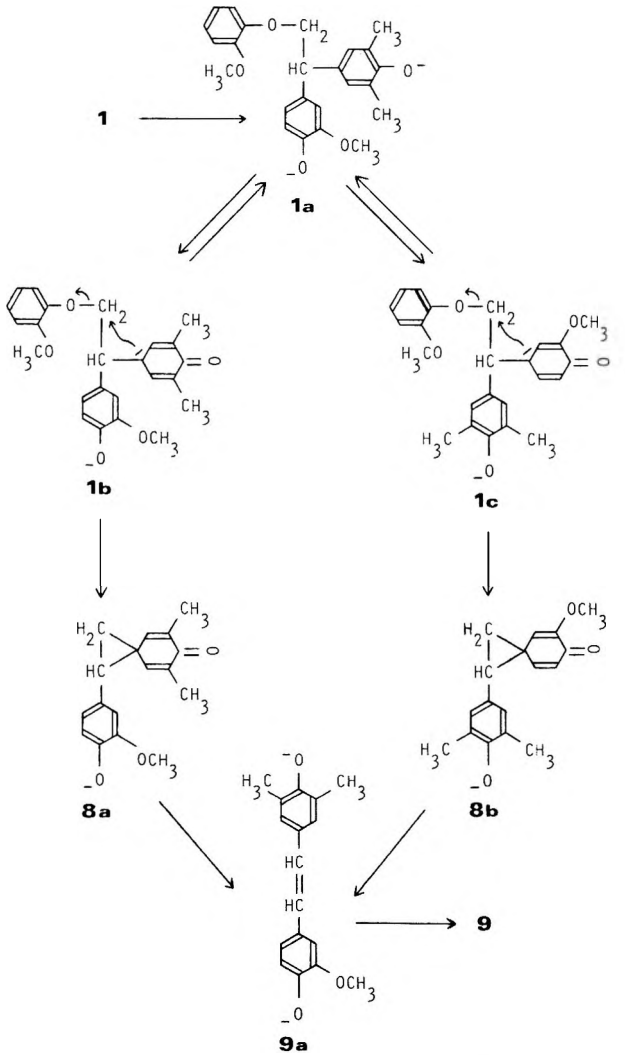
Table I. Stilbene Formation Data[a]



compd	registry no.	yields,[b] % starting material	yields,[b] % stilbene	registry no.	migrating group, extent of migration, % (% of total reaction) determined by rate studies R′	determined by rate studies R	determined by deuterium labeling[c] R′	determined by deuterium labeling[c] R	relative migration rate k_x/k_H	relative migration rate $\log k_x/k_H$
1	64702-05-2	31	69	67315-60-0	52 (75)	17 (25)			2.74	0.44
5	67315-54-2						50 (72)	19 (28)	2.50	
3	67315-55-3	51	49	67315-61-1	32 (65)	17 (35)			1.68	0.23
6	67315-56-4						32 (66)	17 (34)	1.60	
2	67315-57-5	64	36	67315-62-2	19 (53)	17 (47)			1.00	0.0
7	67315-58-6						20 (55)	16 (45)	1.00	
4	67315-59-7	66	34	54208-26-3	17 (50)	17 (50)			0.89	−0.05

[a] All reactions conducted in 1 M NaOH at 170 ± 1 °C for 2 h under atmosphere of N_2. [b] Determined by GLC. Accuracy ±1%. [c] Accuracy estimated to be ±3–5%.

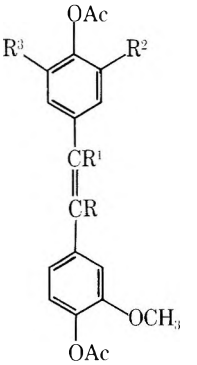
Scheme I



analysis, yielded the results summarized in Table I. For each compound, the yield of stilbene accounts for the total amount of starting compound consumed. Thus, no side reactions have taken place.

The rate study data listed in Table I were analyzed by the iterative dissection method, using the extent of reaction for the 1,1-bis(aryl)ethane compound containing two equivalent 4-hydroxy-3-methoxyphenyl moieties (**4**) to define the extent of migration of a single 4-hydroxy-3-methoxyphenyl nucleus, which was considered to be half (17%) that of the total amount (34%) of the symmetrical stilbene **12** formed under the reaction conditions. Assuming that this value is independent of the nature of the other phenolic moiety in the 1,1-bis(aryl)-ethane compound, the contribution of the latter moiety to the stilbene formation is obtained as the difference. The extents of migration of the two phenolic moieties are expressed as percent of the total reaction, and the migration rates of the substituted phenolic nuclei relative to that of the unsubstituted one, k_x/k_H, are obtained as the ratios of the corresponding extents of migration (Table I).

Identical treatment of the deuterated analogues **5**–**7** gave in each case a mixture of two deuterated stilbenes (**13**–**15**), the deuterium atom being located in the α position relative to the phenolic moiety which has not migrated. Catalytic hydrogenation of these stilbenes gave the corresponding deuterated 1,2-bis(aryl)ethanes **16**–**18**, the mass spectra of which revealed



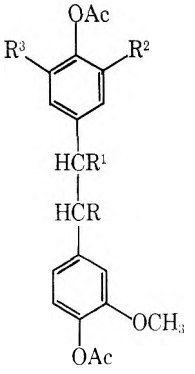
9, R, R^1 = H; R^2, R^3 = CH_3
10, R, R^1, R^2, R^3 = H
11, R, R^1, R^2 = H; R^3 = CH_3
12, R, R^1, R^2 = H; R^3 = OCH_3
13a, R = H; R^1 = ^2H; R^2, R^3 = CH_3
13b, R = ^2H; R^1 = H; R^2, R^3 = CH_3
14a, R, R^2, R^3 = H; R^1 = ^2H
14b, R^1, R^2, R^3 = H; R = ^2H
15a, R, R^2 = H; R^1 = ^2H; R^3 = CH_3
15b, R = ^2H; R^1, R^2 = H; R^3 = CH_3

Table II. Partial Mass Spectral Data for the Deuterated 1,2-Bis(aryl)ethanes[a]

mass, m/e	compound[b] 16	17	18
107		40	
108		36	
121			55
122			33
135	96		
136	47		
137	42	74	59
138	100	100	100

[a] Uncorrected for 1,2-bis(aryl)ethane-d_0, estimated at 2–3%. [b] Relative peak intensities uncorrected for C-13.

the deuterium atom location and content and, hence, the identity of the migrating phenolic moiety. Comparison of the relative intensities of the corresponding deuterated and undeuterated hydroxytropylium ion fragments[5] (Table II) gave the relative migration ratios shown in Table I.



16a, R = H; R¹ = ²H; R², R³ = CH_3
16b, R = ²H; R¹ = H; R², R³ = CH_3
17a, R = ²H; R¹, R², R³ = H
17b, R, R², R³ = H; R¹ = ²H
18a, R, R² = H; R¹ = ²H; R³ = CH_3
18b, R = ²H; R¹, R² = H; R³ = CH_3

As is evident from Table I, the two independent methods employed in this study for the elucidation of the identity of the migrating phenolic moiety gave essentially the same results. Evidently, other factors being equal, the rate of cleavage of the C–O bond (Scheme I) and subsequent formation of stilbene depend on the migratory aptitude of the phenolic nuclei, which the present study establishes is favored when the migrating phenolic nucleus is substituted with electron-donating substituents.

By treatment of the methyl and methoxyl groups as substituents on a phenolic nucleus, the empirical Hammett relationship was applied to the rate data. The Hammett plot of the log (k_x/k_H) values, calculated from the experimental results in Table I, vs. Brown's σ^+ substituent constants is shown in Figure 1. It can be seen that a straight line results with a slope of $\rho^+ = -3.3$. From the absolute value and the sign of the reaction constant it is evident that the reaction is facilitated by electron-donating substituents. The accelerating effect of electron-donating substituents X in the migrating aryl group as well as the magnitude of ρ^+ compare quite well to those observed in other anionotropic [1,2] aryl shifts.[6]

The overall effect of the electron-donating methyl substituents is to increase the basicity and nucleophilicity[7] of, for example, carbanion **1b** compared to that of the methoxyl-substituted carbanion **1c** (Scheme I), by increasing the electron density on the reaction center (inductive effect). Thus, the rates of formation of stilbene products are greater for compounds **1** and **3** than for compounds **2** and **4**. In harmony

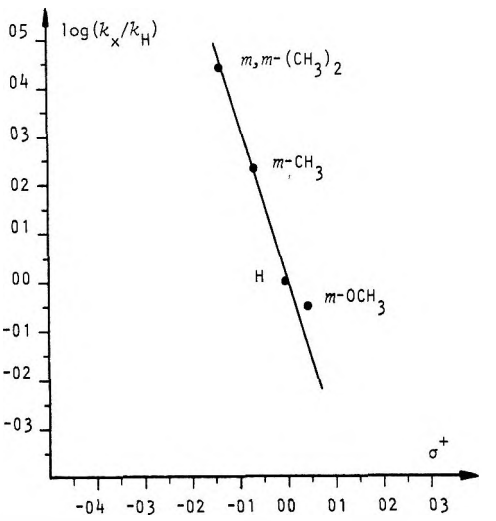
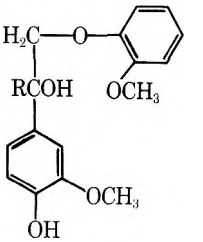


Figure 1. Hammett-Brown correlation of substituent effects on the migratory aptitude of phenolic nuclei.

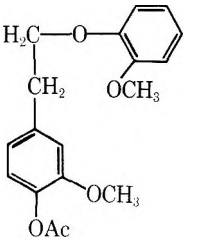
with this result and the general mechanism shown in Scheme I, the rates of migration of the methyl-substituted phenolic moieties are greater than that of the unsubstituted phenolic moiety (Table I). Conversely, a methoxyl substituent, due to its electron-withdrawing effect when situated meta to the reaction site, should retard the migration of a phenolic moiety. The data (Table I) indicate the expected migration retarding effect of a meta methoxyl substituent; however, the effect is considerably less than that which would be expected from the Hammett correlation (Figure 1). Probably, the electron-withdrawing effect of the methoxy substituent is more than compensated by the resonance effect of this substituent, an explanation which is compatible with the results of a wide variety of reactions involving a methoxyl group as a substituent on an aromatic nucleus.[8]

From a consideration of the overall reaction as depicted in Scheme I for the transformation **1** → **9**, it can be concluded that the key step of this reaction is the intramolecular nucleophilic displacement of the aryloxy substituent by the cyclohexadienone carbanion (**1b** or **1c**). This participation of the migrating group in the transition state of the rate-determining step explains the substantial effect of substituents X on the reaction rate. Owing to the facile electron redistribution, the unstable spiro cyclohexadienone intermediate[2,3] (**8a** or **8b**) is rapidly rearranged to the stilbene product **9a**. Overall then, this reaction is probably a concerted process with the [1,2] aryl shift occuring essentially simultaneously with the cleavage of the C–O ether bond.

When compound **21** was treated with alkali in a similar manner, no reaction was observed. This negative result shows that the aryl participation reaction is restricted to compounds containing at least two phenolic moieties linked to the β-carbon atom relative to the aryl ether linkage. The ability of a second aryl group β to a leaving group to facilitate the dissociation of the C_α–Z bond[9] is probably a major contributory factor to the substrate activation effect of a second aryl group



19, R = H
20, R = ²H



21

at C_β observed for the 1,1-bis(aryl)ethane 2-*O*-aryl ether compounds and lends support to our earlier conclusion that the rate-determining step in this reaction (Scheme I) involves cleavage of the C–O ether bond.

The unreactivity of compound **21** compared to 2-*p*-hydroxyphenylethyl bromide[2,3] can be accounted for by the fact that an aryloxy group is a considerably poorer leaving group than bromine, as much as two or three orders of magnitude poorer in reactions such as nucleophilic substitution at sp^3-hybridized carbon and alkene-forming eliminations.[10,11] In addition, the unreactivity of **21** indicates that the limited alkaline cleavage (about 30%) of the alkyl–O ether bond observed[12] with compound **19** is due to a neighboring group participation reaction involving the ionized benzylic hydroxyl group rather than the phenolic moiety as the nucleophilically attacking species. Hence, the alkaline cleavage of the C–O ether bond in **19** proceeds via an epoxide (cf. also the behavior of nonphenolic β-aryl ethers[12]) rather than via a spiro cyclohexadienone intermediate.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were obtained on a Perkin Elmer R-12 spectrometer (60 MHz) using $CDCl_3$ (internal Me_4Si) as the solvent. Chemical shifts are reported on the τ scale. Mass spectra were recorded on a Finnigan quadrupole instrument at 40 eV using the direct inlet system. Gas chromatographic analysis was performed on a Perkin Elmer F 17 instrument with a flame ionization detector. The column material was SE-30 (3%) on Chromosorb 750 (80/100 mesh). Peak areas were obtained with a Pye Unicam DP 88 computing integrator. Preparative separations were carried out by column chromatography using silica gel (Merck, 0.063–0.200 mm, 70–230 mesh, ASTM) as the adsorbent and light petroleum (60–71 °C)–ethyl acetate (4:1) as the solvent.

Materials. The following compounds were prepared as previously described: **19**[12] and **21**.[13] Compound **20** was prepared from the appropriate acetophenone as described for **19** by reduction with sodium tetradeuterioborate.

The NMR data along with the melting points of all new compounds are summarized in Table III.[14] Physical constants and spectral data for compounds **1**, **9**, and **12** were identical with those reported[1] previously for these compounds.

Preparation of 1,1-Bis(aryl)ethane 2-*O*-Aryl Ethers. General Procedure. The benzyl alcohol **19** or its deuterated analogue **20** (0.34 mmol), the appropriate phenol (5.0 mmol), and concentrated HCl (0.25 mL) were heated at 80 °C for 1 h with magnetic stirring.[4] The resulting condensation product was isolated by column chromatography on silica gel (125 g), acetylated with pyridine–acetic anhydride (1:1), and crystallized from diethyl ether. Recrystallization from diethyl ether yielded the 1,1-bis(aryl)ethane 2-*O*-aryl ethers **1–7** in 80–90% overall yield.

2. Anal. Calcd for $C_{26}H_{26}O_7$: C, 69.33; H, 5.78; O, 24.89. Found: C, 69.75; H, 5.65; O, 24.45. MS *m/e* (rel intensity) 450 (1, M^+), 327 (4), 313 (7), 285 (69), 271 (33), 243 (100), 229 (81), 199 (53), 137 (37).

3. Anal. Calcd for $C_{27}H_{28}O_7$: C, 69.83; H, 6.03; O, 24.14. Found: C, 69.84; H, 6.03; O, 23.98. MS *m/e* (rel intensity) 464 (3, M^+), 341 (5), 299 (63), 285 (15), 257 (100), 243 (48).

4. Anal. Calcd for $C_{27}H_{28}O_8$: C, 67.50; H, 5.83; O, 26.67. Found: C, 67.97; H, 6.07; O, 26.03. MS *m/e* (rel intensity) 480 (5, M^+), 396 (1), 357 (7), 343 (2), 315 (73), 301 (19), 273 (100), 259 (68).

5. MS *m/e* (rel intensity) 479 (1, M^+), 356 (3), 342 (1), 314 (47), 300 (13), 272 (100), 258 (50).

6. MS *m/e* (rel intensity) 465 (2, M^+), 342 (5), 328 (1), 300 (59), 286 (14), 258 (100), 244 (52), 137 (23).

7. MS *m/e* (rel intensity) 451 (3, M^+), 328 (5), 314 (7), 286 (80), 272 (34), 244 (100), 230 (73), 200 (25), 137 (24).

Rate Studies. Solutions of the 1,1-bis(aryl)ethane 2-*O*-aryl ethers **1–4** (0.07 mmol) in 1.0 M aqueous NaOH (10 mL) and ethylene glycol monomethyl ether (1 mL) were heated under N_2 atmosphere in a stainless steel bomb (25 mL capacity) at 170 ± 1 °C for 2 h. The reaction solution was then diluted with H_2O (15 mL), neutralized with 10% phosphoric acid, and extracted with $CHCl_3$ (4 × 10 mL), and the combined organic layers were concentrated under reduced pressure, and the residue was acetylated with pyridine–acetic anhydride (1:1). The resulting mixture of acetylated reaction products was analyzed by GLC.

Isolation of Reaction Products. The 1,1-bis(aryl)ethane 2-*O*-aryl ethers **1–7** (0.2 mmol) were reacted as described above. The acetylated reaction products were then separated by column chromatography on silica gel (125 g). The stilbene products were recrystallized from acetone.

10. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52; O, 24.54. Found: C, 69.99; H, 5.59; O, 24.54. MS *m/e* (rel intensity) 326 (1, M^+), 284 (21), 242 (100), 199 (19), 181 (75), 153 (38).

11. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.60; H, 5.88; O, 23.52. Found: C, 70.42; H, 5.97; O, 23.50. MS *m/e* (rel intensity) 340 (13, M^+), 298 (35), 256 (100), 195 (27), 181 (10), 152 (12).

13. MS *m/e* (rel intensity) 355 (1, M^+), 313 (9), 271 (100), 210 (19), 182 (18), 166 (23).

14. MS *m/e* (rel intensity) 327 (5, M^+), 285 (25), 243 (100), 210 (4), 200 (5), 182 (16), 154 (9).

15. MS *m/e* (rel intensity) 341 (5, M^+), 299 (21), 257 (100), 196 (14), 173 (33), 113 (25), 99 (59).

Reduction of the Deuterated Stilbenes 13–15. The deuterated stilbenes **13–15** (20 mg) were dissolved in ethyl acetate (25 mL) and hydrogenated over 5% palladium/charcoal (100 mg) at atmospheric pressure and ambient temperature for 24 h. The reaction solution was filtered through Celite and the filtrate was concentrated under reduced pressure. The 1,2-bis(aryl)ethane products **16–18** were crystallized from diethyl ether and recrystallized from acetone–light petroleum.

Method of Deuterium Analysis. The deuterated 1,2-bis(aryl)ethanes **16–18** were analyzed for deuterium content and location by mass spectrometric analysis of samples of the crystalline compounds. Consistent fragmentation patterns are produced which permit accurate localization and measurement of deuterium. The deuterium location and content were determined by monitoring the relative abundance of the deuterated and undeuterated hydroxytropylium ion fragments. Two sets of ions were monitored for each compound (Table II) corresponding to the hydroxytropylium ions originating from the two different aryl groups. The migration ratios of the aryl groups can be easily deduced from direct comparison of the relative peak intensities of the unlabeled and labeled ion fragments after correction due to the natural abundance (1.1%) of carbon-13.

Let P = the relative intensity of the unlabeled ion fragment, $P + 1$ = the relative intensity of the corresponding labeled ion fragment, and $(P + 1)_{corr}$ = the relative intensity of the labeled ion fragment corrected for the contribution of carbon-13. The P and $P + 1$ values are given in Table II.

$$\% \text{ aryl group migration} = \frac{P}{P + (P + 1)_{corr}} \times 100$$

The illustrative calculation for compound **17** is shown below:

$$m/e\ 107 \qquad P = 40$$

$$m/e\ 108 \qquad P + 1 = 36 \text{ and } (P + 1)_{corr} = 36 - (40 \times 0.077) = 32.92$$

$$\% \text{ } p\text{-hydroxyphenyl group migration} = \frac{40}{72.92} \times 100 = 55\%$$

Acknowledgments. Support for this research through grants from Cellulosaindustriens Stiftelse för Teknisk och Skoglig Forskning samt Utbildning is gratefully acknowledged.

Registry No.—**13a**, 67315-63-3; **13b**, 67315-64-4; **14a**, 67315-65-5; **14b**, 67315-66-6; **15a**, 67315-67-7; **15b**, 67315-68-8; **16a**, 67315-69-9; **16b**, 67315-70-2; **17a**, 67315-71-3; **17b**, 67315-72-4; **18a**, 67315-73-5; **18b**, 67315-74-6; **19**, 7382-68-5; **20**, 67315-75-7; **21**, 29340-52-1; phenol, 108-95-2; 2,6-dimethylphenol, 576-26-1; o-methylphenol, 95-48-7; *o*-methoxyphenol, 90-05-1.

Supplementary Material Available: Table III containing melting point and NMR data (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) J. Gierer and I. Pettersson, *Can. J. Chem.*, **55**, 593 (1977).
(2) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957).
(3) R. Baird and S. Winstein, *J. Am. Chem. Soc.*, **79**, 4238 (1957).
(4) H. Nimz, *Holzforschung*, **23**, 84 (1969).
(5) J. M. S. Talt, T. W. Shannon, and A. G. Harrison, *J. Am. Chem. Soc.*, **84**, 4 (1962).
(6) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1962, Chapter 15.
(7) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1962, p 354.
(8) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, Chapter 9.

(9) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1113 (1952).
(10) D. R. Marshall, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1898 (1977).
(11) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, Chapter 10.
(12) J. Gierer and I. Norén, *Acta. Chem. Scand.*, **16**, 1713 (1962).
(13) G. Gellerstedt and J. Gierer, *Acta. Chem. Scand.*, **24**, 1645 (1970).
(14) See paragraph at the end of the paper regarding supplementary material.

Mechanism and Catalysis for *o*-Hydroxyacetophenone Phenylhydrazone Formation[1]

Kaethy B. Alves, Marilene P. Bastos, and Luciano do Amaral*

Instituto de Química da Universidade de São Paulo, Caixa Postal 20.780, 01000 São Paulo, SP Brazil

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Acetophenone phenylhydrazone formation, like that of meta-/para-substituted benzaldehydes, occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamines from this substrate is subject to general acid–base catalysis by carboxylic acid–carboxylate buffers. 2′-Hydroxyacetophenone phenylhydrazone formation also occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamine from this substrate is subject to specific acid catalysis, but is not subject to detectable general acid–base catalysis by carboxylic acid–carboxylate buffers. It is proposed that this lack of general acid–base catalysis is due to internal hydrogen bond formation between the acidic hydrogen of the o-hydroxy substituent and the carbonyl group. The same was observed for carbinolamine formation from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones (substituent = nitro, cyano, chloro, and methyl). Rate constants for the hydrated proton catalysis and for the pH-independent reaction are well correlated by a dual Hammett substituent parameter treatment.

The rates of reaction of *o*-hydroxybenzaldehyde and the corresponding para isomer with a variety of nitrogen nucleophiles, including hydroxylamine, semicarbazide, *p*-toluidine, and phenylhydrazine, have been reported to exhibit ortho/para ratios considerably greater than unity.[2-5] This has been attributed to greater stabilization of the para- than the ortho-substituted benzaldehydes by substituents which donate electrons by resonance.[5]

A detailed study of the kinetics of phenylhydrazone formation from acetophenone and 2′-hydroxy-5′-substituted acetophenones was undertaken in order to examine the effect of ortho substituents capable of forming hydrogen bonds with the carbonyl oxygen of the acetophenone on reactivity toward nucleophiles.

Experimental Section

Materials. Acetophenone, 2′-hydroxyacetophenone, phenylhydrazine hydrochloride, and the carboxylic acids employed were obtained commercially and were either redistilled or recrystallized before use. *p*-Methyl-, *p*-chloro-, *p*-cyano-, and *p*-nitrophenyl acetates were prepared by the procedure of Bender and Nakamura.[6] 2′-Hydroxy-5′-methylacetophenone,[7] 2′-hydroxy-5′-chloroacetophenone,[8] 2′-hydroxy-5′-cyanoacetophenone,[8] and 2′-hydroxy-5′-nitroacetophenone[9] were prepared from the esters indicated above by procedures described in the literature. The acetophenone phenylhydrazones were prepared by the procedure of Vogel.[7]

p-Cyanophenyl acetate: mp 57–58 °C; NMR (60 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 7.47 (q, 4 H); IR (KBr) 2200, 1760, 1196, 840 cm^{-1}. Anal. Calcd: C, 67.08; H, 4.37; N, 8.65. Found: C, 66.40; H, 4.39; N, 8.58. 2′-Hydroxy-5′-cyanoacetophenone: mp 105–106 °C; NMR (60 MHz, $CDCl_3$) δ 2.68 (s, 3 H), 7.08 (d, 1 H), 7.75 (q, 1 H), 8.12 (d, 1 H), 12.7 (s, 1 H); IR (KBr) 2220, 1648, 1480, 1210, 840 cm^{-1}. Anal. Calcd: C, 67.08; H, 4.37; N, 8.70. Found: C, 66.77; H, 4.36; N, 8.75. 2′-Hydroxy-5′-chloroacetophenone phenylhydrazone: 174–175 °C; NMR (60 MHz, $(CD_3)_2SO$) δ 2.40 (s, 3 H), 6.60–7.80 (m, 8 H), 9.67 (s, 1 H), 12.8 (s, 1 H); IR (KBr) 3300, 1625 cm^{-1}. Anal. Calcd: C, 64.52; H, 4.99; N, 10.75. Found: C, 64.06; H, 5.28; N, 10.80. 2′-Hydroxy-5′-cyanoacetophenone phenylhydrazone: 192–193 °C; NMR (60 MHz, $(CD_3)_2SO$) δ 2.40 (s, 3 H), 6.60–7.80 (m, 8 H), 7.90 (d, 1 H), 9.60 (s, 1 H); IR 3325, 2225, 1615 cm^{-1}. Anal. Calcd: C, 71.87; H, 5.21; N, 16.72. Found: C, 71.08; H, 5.28; N, 16.53.

Kinetic measurements were carried out spectrophotometrically in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the phenylhydrazone of acetophenone at 332 nm, of 2′-hydroxyacetophenone at 337 nm, of 2′-hydroxy-5′-methylacetophenone at 340 nm, of 2′-hydroxy-5′-chloroacetophenone at 342 nm, and of 2′-hydroxy-5′-nitroacetophenone at 345 nm up to pH 8 and at 450 nm in basic solution. The initial concentration of the acetophenones was 3.3×10^{-5} M, and in all cases a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from slopes of plots of log $(OD_\infty - OD_t)$ against time in the usual manner.

As a result of the strong UV light absorption of phenylhydrazine, it was difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines. Similar difficulties have been noted in attempts to determine equilibrium constants for the formation of other phenylhydrazine carbinolamines.[10,11] With each of the acetophenones studied, the reaction is first-order in phenylhydrazine over the concentration range of 0.020 to 0.20 M, at pH 7. Consequently, all kinetic studies have been made employing phenylhydrazine concentrations lower than 0.20 M. Second-order rate constants could therefore be determined directly by dividing first-order rate constants by the concentration of phenylhydrazine free base. Catalytic third-order rate constants were evaluated from the slopes of plots of second-order rate constants against the concentration of catalyst.

Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculation of the concentration of phenylhydrazine free base and of undissociated carboxylic acid was made employing the Henderson–Hasselbalch equation and values of pK_a from ref 12.

pK_a Determination. The pK_a values of the 2′-hydroxy-5′-substituted acetophenones were measured in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 using a Zeiss PMQ II spectrophotometer. The effect of pH on the absorption of light was measured at the appropriate wavelength (Table I). The values of K_a were determined employing the equation $(E^- - E_t)/(E_t - E^0) = (H^+)/K_a$, where E^- is the absorption of the phenoxide, E^0 is the absorption of the phenol,

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Table I. Values of pK_a for Several 2′-Hydroxy-5′-substituted Acetophenones[a]

substituent	nm	slope	r	K_a	pK_a
NO_2	400	8.875×10^6	0.9991	1.127×10^{-7}	6.95
CN	350	5.447×10^7	0.9998	1.838×10^{-8}	7.74
Cl	370	3.503×10^9	0.9982	2.854×10^{-10}	9.55
H	364	2.544×10^{10}	0.9985	3.931×10^{-11}	10.40
CH_3	379	5.160×10^{10}	0.9989	1.937×10^{-11}	10.71

[a] In 20% aqueous ethanol at 25 °C and ionic strength 0.50.

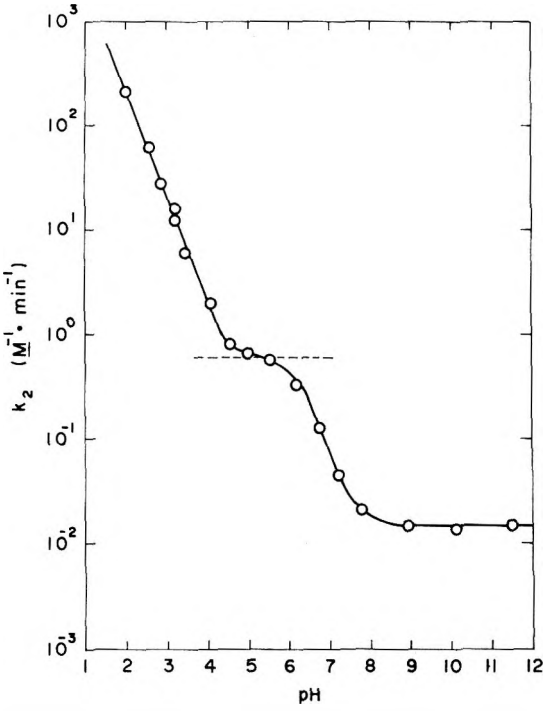


Figure 1. Logarithms of second-order rate constants for acetophenone phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH. Where necessary, the points were extrapolated to 0 buffer concentration. The broken line indicates the rate constant for the water-catalyzed process. Data have been taken from Table II.

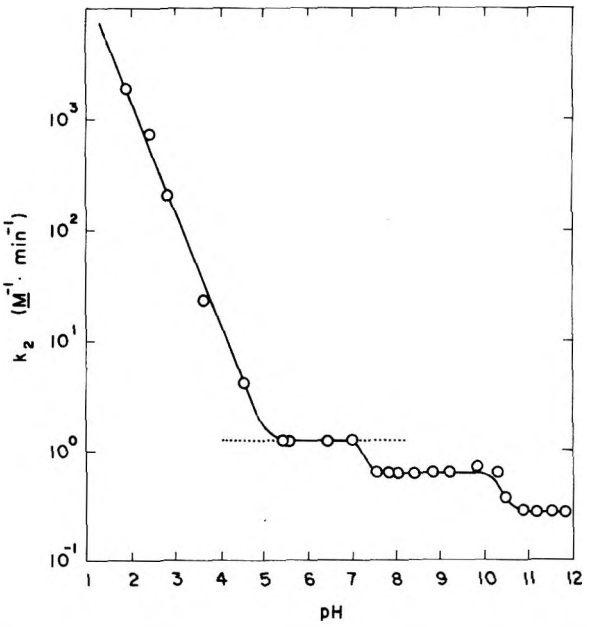


Figure 2. Logarithms of second-order rate constants for 2′-hydroxyacetophenone phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH. The dotted line indicates the rate constant for internal catalysis (see text). Data have been taken from Table II.

and E_t is the total absorption at the various pH values. Plots of $(E^- - E_t)/(E_t - E^0)$ vs. (H^+) yield the value of K_a (Table I).

Results

Acetophenone Phenylhydrazone Formation. Logarithms of second-order rate constants for the reaction of phenylhydrazine with acetophenone in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 are plotted as a function of pH in Figure 1. Where necessary, the second-order rate constants were extrapolated to 0 buffer concentration. The curve shows one break near pH 6 that must reflect the transition in rate-determining step from formation to dehydration of the carbinolamine intermediate.[10,12-16]

Second-order rate constants for acetophenone phenylhydrazone formation at pH 2.56 increased linear from 0.0113 to 0.0225 M^{-1} min^{-1} with an increase in cyanoacetate buffer concentration from 0.050 to 0.25 M. Buffer catalysis was also observed for chloroacetate, formate, and acetate. The nature of the catalysis, general acid or general base, was not defined.

2′-Hydroxyacetophenone Phenylhydrazone Formation. In Figure 2, logarithms of second-order rate constants for the reaction of phenylhydrazine with 2′-hydroxyacetophenone are plotted as a function of pH. The curve shows two breaks, one near pH 7 and the second near pH 10. The former must reflect the transition in rate-determining step, and the later, which occurs at the pK_a for the substrate, must reflect loss of the phenolic hydrogen of the substrate. Carbinolamine dehydration is presumably rate determining under quite basic conditions, although this point has not been carefully proved.

In the region of rate-determining carbinolamine formation (pH to 7), no catalysis by carboxylic acid–carboxylate buffers was observed, in contrast to the results for acetophenone itself.

2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation. In Figure 3, logarithms of second-order rate constants for the reaction of phenylhydrazine with 2′-hydroxy-5′-nitroacetophenone (I), 2′-hydroxy-5′-cyanoacetophenone (II), 2′-hydroxy-5′-chloroacetophenone (III), 2′-hydroxyacetophenone (V), and 2′-hydroxy-5′-methylacetophenone (VI) are plotted as a function of pH, in the pH range of 1 to 7. The curves show the pH-independent reaction and the acid-catalyzed carbinolamine formation as the rate-determining steps. For comparison, the curve obtained with acetophenone was included (IV).

In the region of rate-determining carbinolamine formation (pH 1 to 7), no catalysis by carboxylic acid–carboxylate buffers was observed for any of the 2′-hydroxy-5′-substituted acetophenones. Catalytic constants for the acid-catalyzed reaction (k_H) and the pH-independent one (k_O) have been evaluated from the data of Figure 3 and are collected in Table II.

Correlation Analysis of the log K_a Values of 2′-Hydroxy-5′-substituted Acetophenones. As is developed in detail below, the log K_a values of the 2′-hydroxy-5′-substituted acetophenones, as well as the rate constants for the hydrated proton catalysis and for the pH-independent reaction for

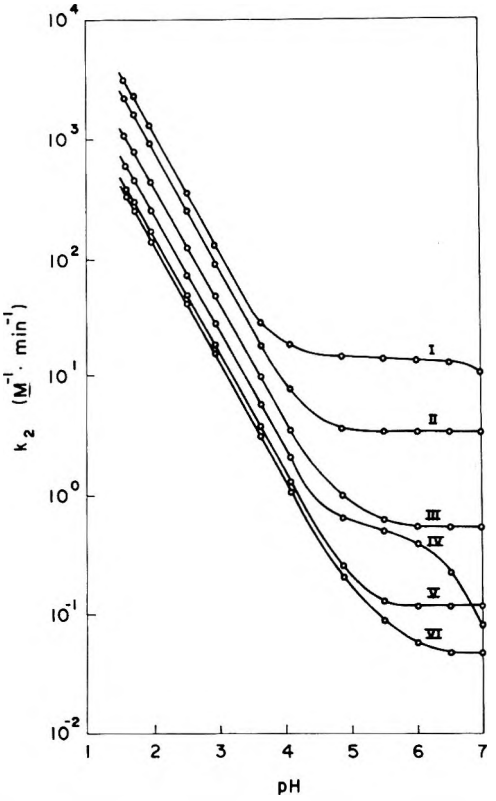


Figure 3. Logarithms of second-order rate constants for acetophenone and 2′-hydroxy-5′-substituted acetophenone phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH: (I) 2′-hydroxy-5′-nitroacetophenone; (II) 2′-hydroxy-5′-cyanoacetophenone; (III) 2′-hydroxy-5′-chloroacetophenone; (IV) acetopheone; (V) 2′-hydroxyacetophenone; and (VI) 2′-hydroxy-5′-methylacetophenone. The lines for the 2′-hydroxy-5′-substituted acetophenones are theoretical ones based on $k_2 = k_H(H_3O^+) + k_O$ and data from Table II.

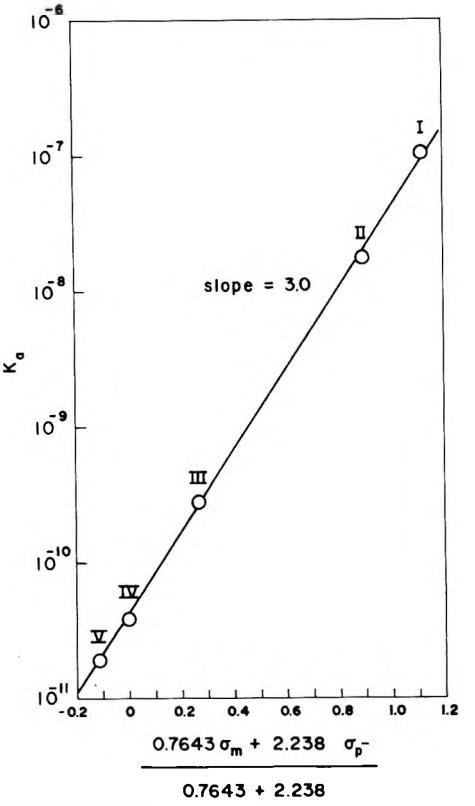
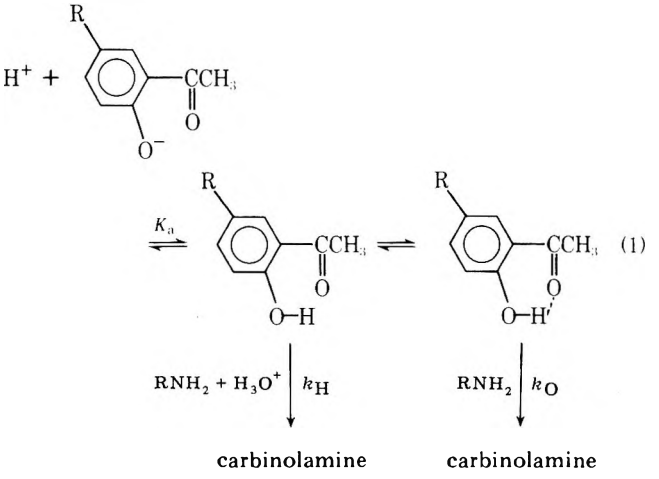


Figure 4. Logarithms of K_a of 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against $(0.7643\sigma_m + 2.2338\sigma_p^-)/(0.7643 + 2.2338)$: (I) 2′-hydroxy-5′-nitroacetophenone; (II) 2′-hydroxy-5′-cyanoacetophenone; (III) 2′-hydroxy-5′-chloroacetophenone; (IV) 2′-hydroxyacetophenone; and (V) 2′-hydroxy-5′-methylacetophenone. Data have been taken from Tables I and III.

phenylhydrazone formation from these compounds, are well correlated by dual Hammett substituent parameter treatment.

The K_a values of the 2′-hydroxy-5′-substituted acetophenones are influenced by the presence of the substituent R and by the presence of the acetyl group in the benzene ring (see eq 1 and Discussion).



The log K_a values were correlated by the modified Hammett equation 2. Multiple least-squares analysis with a computer program yielded eq 3. It was then possible to calculate the dual Hammett substituent parameters for the correlation analysis of the log K_a values of the 2′-hydroxy-5′-substituted acetophenones (Table III).

Table II. Catalytic Constants for the Hydronium Ion (k_H) and pH-Independent Reaction (k_O) for the Addition of Phenylhydrazine to Several Acetophenones[a]

compd	registry no.	k_H, M^{-2} min^{-1}	k_O, M^{-1} min^{-1}
2′-hydroxy-5′-nitroacetophenone	1450-76-6	1.1×10^5	1.3×10^1
2′-hydroxy-5′-cyanoacetophenone	35794-84-4	8.0×10^4	3.6×10^0
2′-hydroxy-5′-chloroacetophenone	1450-74-4	4.5×10^4	5.4×10^{-1}
acetophenone	98-86-2	2.3×10^4	6.2×10^{-1}
2′-hydroxyacetophenone	118-93-4	1.5×10^4	1.1×10^{-1}
2′-hydroxy-5′-methylacetophenone	1450-72-2	1.3×10^4	4.9×10^{-2}

[a] In 20% aqueous ethanol at 25 °C and ionic strength 0.50.

$$\log K_a = \log K_a^o + \sigma_m\rho_m + \sigma_p^-\rho_p^- \quad (2)$$

$$\log K_a = -10.383 + 0.7643\sigma_m + 2.238\sigma_p^- \quad (3)$$

In Figure 4, values of log K_a of the 2′-hydroxy-5′-substituted acetophenones (from Table I) are plotted as a function of the appropriate dual Hammett substituent parameters (from Table III). The points fall on a good straight line. By least-squares analysis, the value of the slope of the line is 3.0, the correlation coefficient $r = 0.9993$, and the standard deviation divided by the root mean square (SD/RMS) is 0.00509.

Correlation of log K_a values of 2′-hydroxy-5′-substituted acetophenones with any other set of substituent constants gives inferior correlation coefficients and/or higher SD/RMS ratios.

Table III. Values of σ for Some Substituents

group	σ_m[a]	σ_p[a]	σ_p^-[a]	$\frac{0.7643\sigma_m + 2.238\sigma_p^-}{0.7643 + 2.238}$	$\frac{1.401\sigma_m - 0.1850\sigma_p}{1.401 - 0.1850}$	$\frac{0.7419\sigma_m + 1.869\sigma_p}{0.7419 + 1.869}$
NO_2	0.71	0.78	1.27	1.12	0.70	0.76
CN	0.61	0.67	1.00	0.90	0.60	0.65
Cl	0.37	0.24	0.24	0.27	0.38	0.28
H	0	0	0	0	0	0
CH_3	−0.07	−0.13	−0.13	−0.11	−0.06	−0.11

[a] From ref 17.

Correlation Analysis of the log k_H Values for 2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation. The rate constants for the hydrated proton catalysis (k_H) for the formation of the carbinolamines from 2′-hydroxy-5′-substituted acetophenones and phenylhydrazine are influenced by the presence of the substituent R and by the presence of the hydroxy group in the benzene ring (see Discussion).

The logarithms of the k_H values were correlated by the modified Hammett equation 4. Multiple least-squares analysis with a computer program yielded eq 5. It was then possible to calculate the dual Hammett substituent parameters for the correlation analysis of the log k_H values for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (Table III).

$$\log k_H = \log k_H^o + \sigma_m\rho_m + \sigma_p\rho_p \quad (4)$$

$$\log k_H = 4.187 + 1.401\sigma_m - 0.1850\sigma_p \quad (5)$$

In Figure 5, values of log k_H for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted as a function of the appropriate dual Hammett substituent parameters (from Table III). The points fall in a good straight line. By least-squares analysis, the value of the slope of the line is 1.2, r = 0.9997, and SD/RMS = 0.00175.

Correlation of log k_H with any other set of substituent constants gives inferior correlation coefficients and higher SD/RMS ratios.

Correlation Analysis of the log k_O Values for 2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation. The rate constants for the pH-independent reaction (k_O) for the formation of the carbinolamines from 2′-hydroxy-5′-substituted acetophenones and phenylhydrazine are influenced by the presence of the substituents R and by the hydrogen bond between the phenolic group and the carbonyl group (see eq 1 and Discussion).

The logarithms of k_O values were correlated by the modified Hammett equation 6. Multiple least-squares analysis by a computer program yielded eq 7. It was then possible to calculate the dual Hammett substituent parameters for the correlation analysis of log k_O values for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (Table III).

$$\log k_O = \log k_O^o + \sigma_m\rho_m + \sigma_p\rho_p \quad (6)$$

$$\log k_O = -0.9968 + 0.7419\sigma_m + 1.869\sigma_p \quad (7)$$

In Figure 6, values of log k_O for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted as a function of the appropriate dual Hammett substituent parameters (from Table III). The points fall on a good straight line. By least-squares analysis, the value of the slope of the line is 2.6, r = 0.9906, and SD/RMS = 0.106.

Correlation of log k_O with any other set of substituent constants gives inferior correlation coefficients and higher values of SD/RMS.

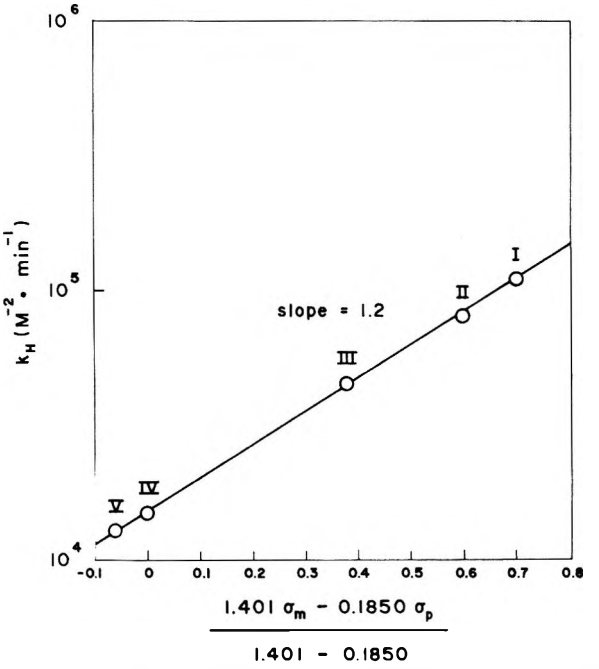


Figure 5. Logarithms of the catalytic constants for the hydrated proton (k_H) for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against $(1.401\sigma_m - 0.1850\sigma_p)/(1.401 - 0.1850)$. Data have been taken from Tables II and III.

Correlation Analysis of the log k_H Values for 2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation and the log K_a Values of 2′-Hydroxy-5′-substituted Acetophenones. In Figure 7, values of the logarithms of the catalytic constants for the hydrated proton (k_H) for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted against the pK_a values of the corresponding 2′-hydroxy-5′-substituted acetophenones (from Table I). The points fall on a single straight line, whose slope is 0.25 (r = 0.9766). Since the catalyst is the same (hydronium ion) for all of the reactions, this correlation is not a Brönsted plot. This plot correlates the simultaneous electronic effect of the substituent in the 5′ position of the benzene ring on the carbonyl group and on the phenolic hydroxy group.

In Figure 8, values of the logarithms of the pH-independent rate constants (k_O) for the formation of the carbinolamines from phenylhydrazine and the 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted against the pK_a values of the corresponding 2′-hydroxy-5′-substituted acetophenones (from Table I). The points fall on a single straight line, whose slope is 0.60 (r = 0.9923).

Discussion

The reaction of phenylhydrazine with acetophenone occurs with rate-determining carbinolamine formation under slightly acidic conditions. This step is subject to both specific catalysis

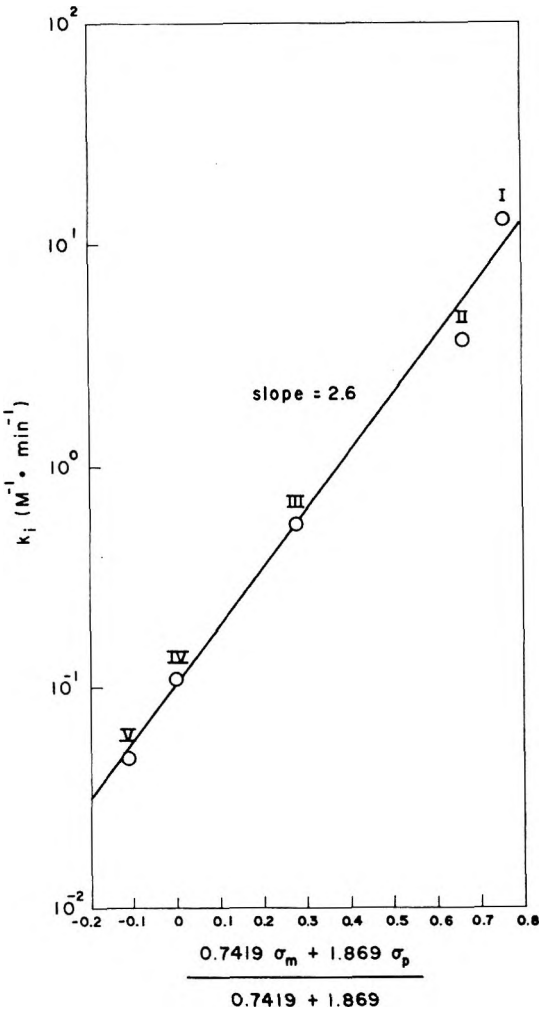


Figure 6. Logarithms of the internal catalytic constants (k_O) for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against $(0.7419\sigma_m + 1.869\sigma_p)/(0.7419 + 1.869)$: (I) 2′-hydroxy-5′-nitroacetophenone; (II) 2′-hydroxy-5′-cyanoacetophenone; (III) 2′-hydroxy-5′-chloroacetophenone; (IV) 2′-hydroxyacetophenone; and (V) 2′-hydroxy-5′-methylacetophenone. Data have been taken from Tables II and III.

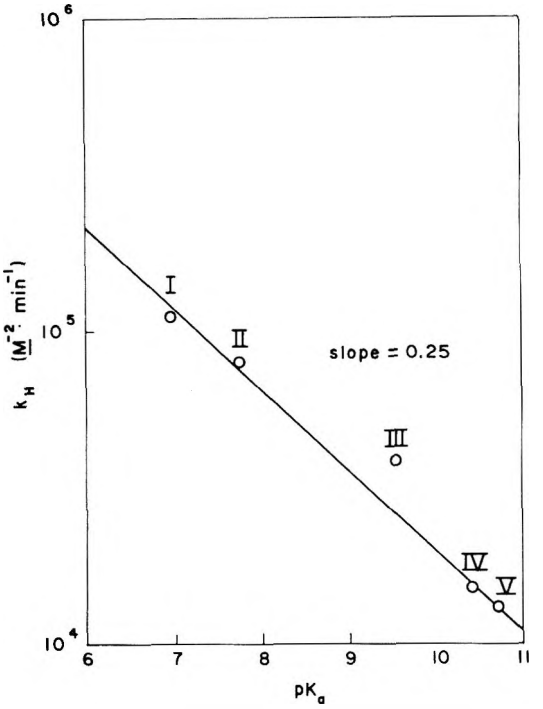
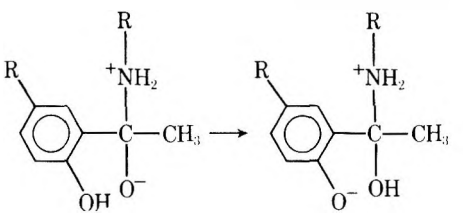


Figure 7. Logarithms of catalytic constants for the hydrated proton for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against their respective pK_a values: (I) nitro; (II) cyano; (III) chloro; (IV) unsubstituted; and (V) methyl. Data have been taken from Tables I and II.

(hydronium ion) and buffer catalysis by carboxylic acid–carboxylate buffers. Under basic conditions, dehydration of the carbinolamine becomes rate determining. The behavior is similar to that observed in the reaction of phenylhydrazine and meta-/para-substituted benzaldehydes.[10] As expected, acetophenone is less reactive than benzaldehyde.[10]

The reaction of phenylhydrazine with 2′-hydroxyacetophenone occurs with rate-determining carbinolamine formation below pH 7. This step shows specific acid catalysis and pH-independent reaction, but not detectable buffer catalysis by carboxylic acid–carboxylate buffers.

The pH-independent reaction for the 2′-hydroxy substrates could be (i) trapping of the zwitterionic intermediate by –OH (eq 8), (ii) concerted internal protonization by –OH (eq 9), or (iii) rate-determining proton switch (eq 10). Our data suggests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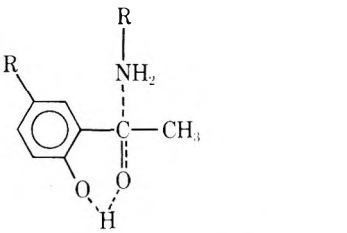
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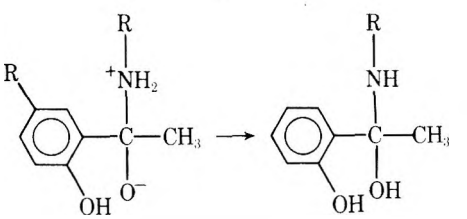

(10)

that the last mechanism is probably wrong, but it does not distinguish between the first two.

The plot of values of the logarithms of the pH-independent rate constants (k_O) for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (Figure 8) may reflect the simultaneous electronic effect of the substituents in the 5′ position of the benzene ring upon the carbonyl and phenolic groups, a true Brönsted-type free energy relationship between the logarithms of the internal catalytic constants and the pK_a's of the phenols, or a combination of these effects. We prefer the last explanation. The simultaneous effect gives rise to a slope of 0.25. The α Brönsted plot value measured for the formation of the carbinolamine from phenylhydrazine and several carbonyl compounds[10,12,15,16] is always 0.35. The slope of 0.60 in Figure 8 is the total of both effects (0.25 + 0.35 = 0.60). This would suggest that both reactions are concerted, not stepwise.[19]

It is well known that in 2′-hydroxyacetophenone there is an internal hydrogen bond between the hydrogen of the phenolic group and the oxygen of the carbonyl group.[18] The best explanation for the pH-independent reaction is that the

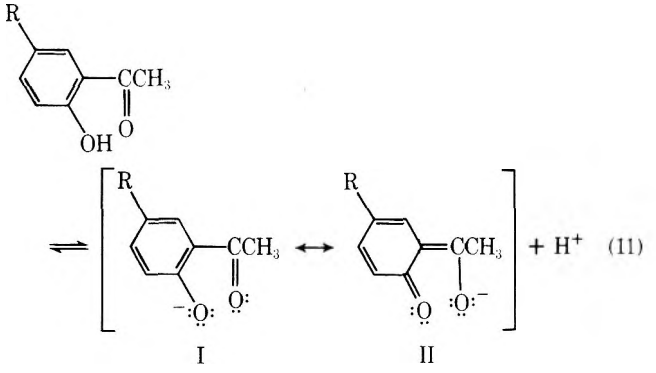
reaction is subject to a concerted internal protonization by the intramolecular hydrogen bond between the hydrogen of the hydroxylic group on the ortho position and the oxygen of the carbonyl group.[20-22] The rate law for this reaction is then $k_2 = k_H(H_3O^+) + k_O$. The internal hydrogen bond explains the observation that the formation of the carbinolamine from phenylhydrazine and 2′-hydroxyacetophenone occurs without detectable generated acid catalysis by carboxylic acids.

The specific acid catalysis is observed because there is an equilibrium between the hydrogen-bonded form of the 2′-hydroxyacetophenone (cyclic form) and the form without the hydrogen bond (open form), as shown in eq 1. The open form reacts with hydronium ion catalysis.

In comparison to the case of acetophenone, the mechanism of dehydration of the carbinolamine derived from the reaction of phenylhydrazine and 2′-hydroxyacetophenone, observed as rate determining in pH above 7, is less straightforward. Several forms of the carbinolamine with different kinds of internal hydrogen bonding may be involved.

We have limited, therefore, the study of the addition of phenylhydrazine to the 2′-hydroxy-5′-substituted acetophenones to pH 1–7, a region in which the formation of the carbinolamine is rate determining.

The R substituents in the 5′ position of the ring, meta to the carbonyl group and para to the hydroxy group, exert an electronic effect on both groups in a way that affects both the ionization of the phenolic group and the rate of the carbinolamine formation. The pK_a values of the 2′-hydroxy-5′-substituted acetophenones are influenced by the presence of the R substituents and by the presence of the acetyl group in the benzene ring. The ionization is given by eq 11, where it is



shown that the acetyl group contributes to the stabilization of the phenoxide ion.

Electron-withdrawing R substituents increase the K_a value of the hydroxylic group by decreasing its electronic density and by decreasing the electronic density of the carbonyl group, thus stabilizing form II. Electron-donating R substituents exert an opposite effect.

The log K_a values were then correlated by a modified Hammett equation (eq 2) that gives rise to the values in eq 3. The largest contribution is given by σ_p^- values, but a minor contribution is observed from the σ_m substituent constants.

The influence of the substituents R and the hydroxy group on the rate of formation of the carbinolamines will now be discussed.

The k_H values for the formation of the carbinolamines from phenylhydrazine and the 2′-hydroxy-5′-substituted acetophenones are influenced by the presence of the R substituents and by the presence of the hydroxy group in the benzene. The protonization of the carbonyl group is increased by the hydroxy group (eq 12).

If R is an electron-withdrawing substituent, the rate of the carbinolamine formation increases due to the decrease in electronic density of the carbonyl group. On the other hand, electron-withdrawing R substituents decrease the rate of

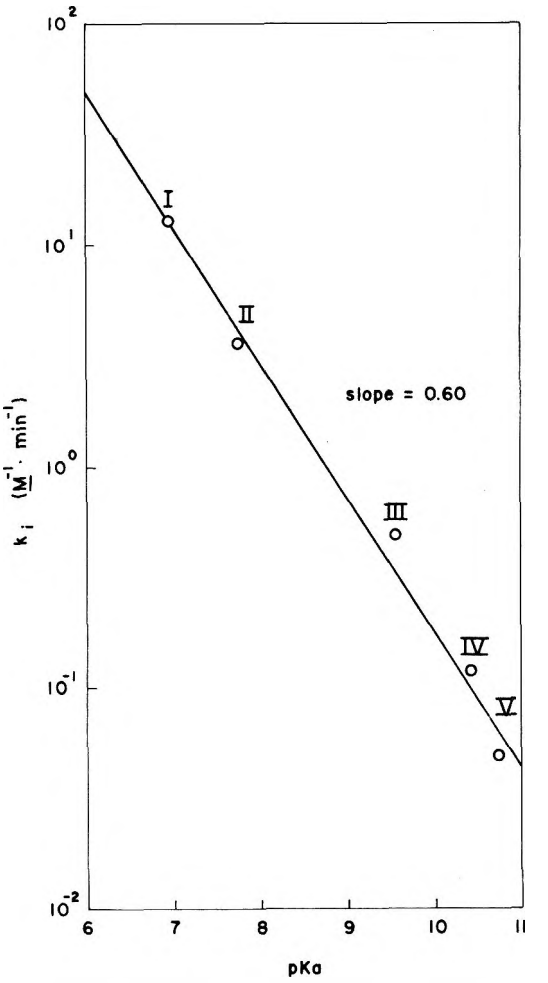
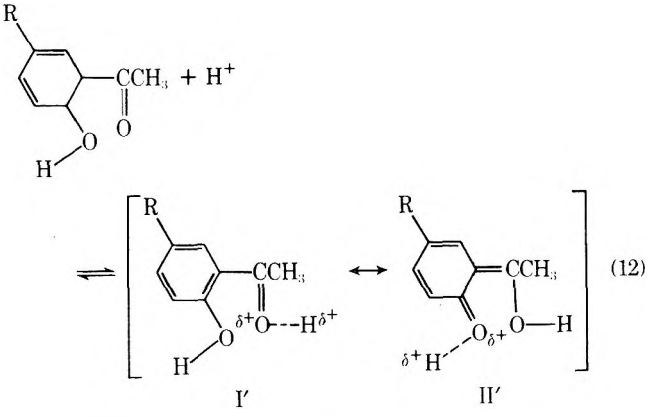


Figure 8. Logarithms of the internal catalytic constants for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against their respective pK_a values: (I) nitro; (II) cyano; (III) chloro; (IV) unsubstituted; and (V) methyl. Data have been taken from Tables I and II.



carbinolamine formation by decreasing the electronic density of the hydroxy group, thus destabilizing form II′. The electron-donating R substituents exert an opposite effect.

The log k_H values were then correlated by a modified Hammett equation (eq 4) that gives rise to the values of eq 5. As a consequence of the electronic effect of R on the carbonyl group in the meta position, the contribution of σ_m is positive; as a consequence of the electronic effect of R on the hydroxy group in the para position, the contribution of σ_p is negative. The largest contribution is given by σ_m values.

With respect to the internal catalysis, the electron-withdrawing R substituents increase the rate of the carbinolamine

formation by decreasing the electronic density of the carbonyl group and by decreasing the electronic density of the hydroxy group. This makes the phenolic group a stronger acid, and consequently leads to a strong hydrogen bond. The electron-donating R substituents exert an opposite effect.

The log k_O values were then correlated by a modified Hammett equation (eq 6) that gives rise to the values in eq 7. The values show a positive contribution of σ_m and a positive contribution of σ_p. The contribution of σ_p is higher than the contribution of σ_m.

Acknowledgment. The author is indebted to Dr. Luiz Juliano Neto for helpful comments concerning this work.

Registry No.—Phenylhydrazine, 100-63-0; *p*-cyanophenyl acetate, 13031-41-9; 2′-hydroxy-5′-chloroacetophenone phenylhydrazone, 67338-35-6; 2′-hydroxy-5′-cyanoacetophenone phenylhydrazone, 67338-36-7.

References and Notes

(1) Supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(2) G. Vavon and P. Montheard, *Bull. Soc. Chim. Fr.*, **7**, 551 (1940).
(3) D. G. Knorre and N. M. Emanuel, *Dokl. Akad. Nauk SSSR*, **91**, 1163 (1953).
(4) O. Bloch-Chaudé, *C. R. Hebd. Seances Acad. Sci.*, **239**, 804 (1954).
(5) R. Wolfenden and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 2763 (1961).
(6) M. L. Bender and K. Nakamura, *J. Am. Chem. Soc.*, **84**, 2577 (1962).
(7) A. I. Vogel, "A Text Book of Practical Organic Chemistry", 3rd ed, Longmans, London, 1967.
(8) N. M. Shah and S. R. Parikh, *J. Indian Chem. Soc.*, **36**, 11 (1959).
(9) T. Szell, *Ber.*, **91**, 2609 (1958).
(10) L. do Amaral and M. P. Bastos, *J. Org. Chem.*, **36**, 3412 (1971).
(11) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).
(12) R. Moscovici, J. P. Ferraz, E. A. Neves, J. O. Tognoli, M. I. El Seoud, and L. do Amaral, *J. Org. Chem.*, **41**, 4093 (1976).
(13) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 73 (1964).
(14) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969.
(15) L. do Amaral, W. A. Sandstron, and E. H. Cordes, *J. Am. Chem. Soc.*, **88**, 2225 (1966).
(16) L. do Amaral, *J. Org. Chem.*, **37**, 1433 (1972).
(17) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 821 (1959); H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(18) Z. Yoshida and M. Haruta, *Tetrahedron Lett.*, 2631 (1964).
(19) J. M. Sayer, B. Pinsky, A. Schobrunn, and W. Washtein, *J. Am. Chem. Soc.*, **96**, 7998 (1974).
(20) M. S. C. Flett, *Spectrochim. Acta*, **10**, 21 (1957).
(21) W. Gordy and S. C. Stanford, *J. Chem. Phys.*, **9**, 204 (1955).
(22) D. G. Knorre and N. M. Emanuel, *Usp. Khim.*, **24**, 275 (1955).

Catalysis in Aromatic Nucleophilic Substitution. 3.[1] Reactions of Piperidine with 2-Methoxy-3-nitrothiophene and 2-Methoxy-5-nitrothiophene in Methanol

D. Spinelli* and G. Consiglio

Cattedra di Chimica Organica, Faculty of Pharmacy, University of Bologna, Via Zanolini 3, Bologna 40126, Italy

R. Noto

Institute of Organic Chemistry, University of Palermo, Via Archirafi 20, Palermo 90123, Italy

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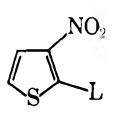
The kinetics of piperidino substitution of 2-methoxy-3-nitrothiophene (If) and of 2-methoxy-5-nitrothiophene (IIf) have been studied in methanol as a function of amine concentration. The reaction of IIf is second order overall, whereas that of If is base catalyzed. Kinetic data are presented which show that sodium methoxide (added or deriving from the reaction of piperidine with methanol) is the only effective catalyst. The complex kinetic system resulting from the competition, at high sodium methoxide concentrations, between the reactions of If respectively with piperidine and with sodium methoxide (Meisenheimer-type adduct formation) has been computer analyzed and the rate coefficients for the single reactions have been estimated. The whole of the data obtained shows that acid catalysis of leaving-group departure by the conjugated acid of piperidine does not occur or is insignificant. The special role of the activating nitro group is discussed.

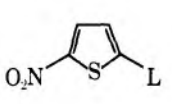
A recent study[1] of piperidino substitutions of some 2-L-3-nitro- (Ia–e) and 2-L-5-nitrothiophenes (IIa–e), in benzene and in methanol, has shown that only the reactions of compounds IId,e in benzene are piperidine catalyzed due to the poor nucleofugicity of *p*-nitrophenoxy and phenylsulfonyl groups in this solvent; while in compounds Ia–e the *o*-nitro group can assist the intermediate decomposition in both solvents.[2]

For piperidino substitutions in methanol, we now wish to report straightforward second-order kinetic behavior for 2-methoxy-5-nitrothiophene (IIf) but base catalysis for 2-methoxy-3-nitrothiophene (If). The role played by the position of activating nitro group (hyper-ortho or quasi-para) in determining the occurrence of base catalysis will be discussed.



I

a, L = Cl
b, L = Br
c, L = I



II

d, L = $OC_6H_4NO_2$-*p*
e, L = SO_2Ph
f, L = OMe

Results and Discussion

Products. Compounds If and IIf gave the corresponding substitution products with piperidine in high yields (>95%) as shown by TLC and/or UV–visible spectral analysis of the reaction mixtures at infinity.

Reaction of IIf with Piperidine. The apparent second-order kinetic constant, k_A, for the piperidino substitution of IIf in methanol at 20 °C (Table I) is independent of the initial piperidine concentration over a tenfold change.

There can be little doubt that this reaction is second order overall, first order both in substrate and in nucleophile, and that there is no measurable catalysis by the amine acting as a base. This corresponds to the situation where $k_A = k_1$ (see below).

Reaction of If with Piperidine. Items 1–6, 8–10, 12, 14, and 16 in Table II show that k_A increases in a curvilinear

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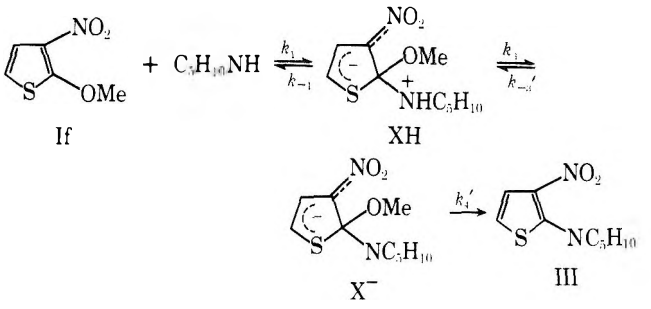
Table I. Kinetic and Activation Parameters[a] for the Reaction of 2-Methoxy-5-nitrothiophene (IIf) with Piperidine in Methanol

[pip], M	0.0203	0.0203	0.0203	0.102	0.203
10^3k, M^{-1} s^{-1}	1.12[b]	2.19[c]	4.02[d]	1.11[b]	1.11[b]

[a] $\Delta H^{\ddagger}$ = 11.1 kcal/mol at 20 °C (maximum error 0.5 kcal/mol); $\Delta S^{\ddagger}$ = −34 eu at 20 °C. [b] At 20.1 °C. [c] At 30.1 °C. [d] At 40.1 °C.

Scheme I



fashion with increasing piperidine concentration (Figure 1). On the other hand, k_A is much lower in the presence of piperidine hydrochloride (items 25–29).

Since a principal effect of this salt is to reduce the concentration of methoxide ion, the increase in k_A with piperidine concentration could be due mainly to catalysis by methoxide ion, a catalyst much more efficient than piperidine.

$$C_5H_{10}NH + MeOH \overset{K_b}{\rightleftharpoons} C_5H_{10}NH_2^+ + MeO^- \quad (1)$$

Kinetic runs performed in the presence of added sodium methoxide (items 7, 11, 13, 15, 17–24) show that, at constant piperidine concentration, k_A increases with increasing methoxide ion concentration. Moreover, items 7 and 8, 10 and 11, 12 and 13, and 20 and 21 point out that piperidine catalysis is unlikely to occur in any great extent. Finally, items 26 and 29–31 show that the reaction is influenced by the ionic strength.

With reference to Scheme I, the general expression for k_A, in terms of rate coefficients for specific steps, is[3]

$$k_A = k_1k_3'k_4'/(k_{-1}k_{-3}' + k_{-1}k_4' + k_3'k_4') \quad (2)$$

with

$$k_3' = k_3 + \sum_{i=1}^{n} k_3^{B_i}[B_i] \quad (3)$$

$$k_{-3}' = k_{-3} + \sum_{i=1}^{n} k_{-3}^{B_i}[BH_i] \quad (4)$$

where k_3 and $k_3^{B_i}$ refer to the deprotonation of XH by the solvent and by any general base, B_i, and k_{-3}, $k_{-3}^{B_i}$ refer to the protonation of X^- by the solvent and by any general acid, BH_i, respectively. Assuming $k_{-3}' \gg k_4'$ (SB-GA mechanism)[4] leads to the following simplification of eq 2

$$k_A = k_1K_3'k_4'/(k_{-1} + K_3'k_4') \quad (5)$$

where

$$K_3' = k_3'/k_{-3}' = k_3^{MeO}[MeO^-]/k_{-3}^{MeO} = k_3^{pip}[pip]/k_{-3}^{pip}[pipH^+] = k_3/k_{-3}[MeOH_2^+] = K_X/[MeOH_2^+] \quad (6)$$

If, on the contrary, one assumes $k_{-3} \ll k_4'$, eq 2 reduces to

$$k_A = k_1k_3'/(k_{-1} + k_3') = k_1(k_3 + k_3^{MeO}[MeO^-] + k_3^{pip}[pip])/(k_{-1} + k_3 + k_3^{MeO}[MeO^-] + k_3^{pip}[pip]) \quad (7)$$

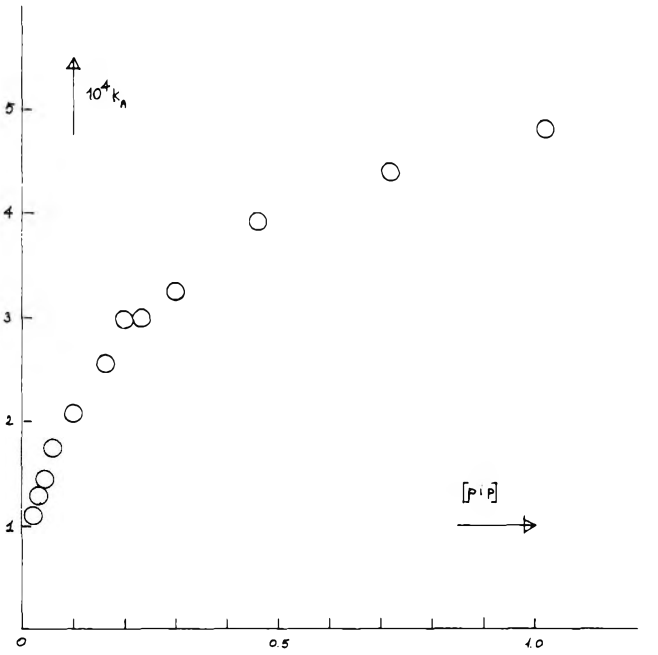
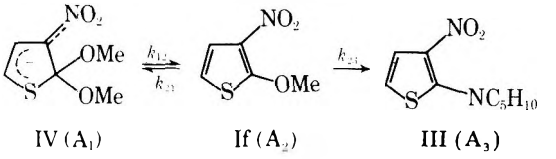


Figure 1. Plot of apparent second-order kinetic constants (k_A) for the piperidino substitution of If in methanol at 20 °C vs. piperidine concentration.

Scheme II



With respect to the dependence of k_A on $[B_i]$, eq 5 and 7 are formally identical. As a consequence, one can write

$$k_A = a(b + cx_1 + dx_2)/(1 + b + cx_1 + dx_2) \quad (8)$$

where x_1 = [pip] and x_2 = [MeO^-].

We have fitted our kinetic data to eq 8 using a least-squares method[5] and the results of the correlation are reported in Table III. It is evident that there is no significant contribution to k_A from the solvent- and/or the piperidine-catalyzed pathway. Thus, the reaction of If with piperidine is catalyzed by methoxide ion in methanol at 20 °C according to the catalysis law

$$k_A = k_1k^*[MeO^-]/(1 + k^*[MeO^-]) \quad (9)$$

with $k_1 = 8.15 \times 10^{-4}$ M^{-1} s^{-1} and $k^* = 489$ M^{-1} (Table III, line five).[6]

Kinetic Measurements at High Sodium Methoxide Concentrations. Recently[8] we have studied the kinetics and equilibrium for combination of sodium methoxide with If to form the Meisenheimer-type adduct IV.

At methoxide ion concentrations as high as 0.1 M, the piperidino substitution reaction of If has to be treated according to Scheme II.[9] Assuming that each step behaves as a first-order reaction, the differential eq 10–12 are obtained.

$$dA_1/dt = k_{21}A_2 - k_{12}A_1 \quad (10)$$

$$-dA_2/dt = k_{21}A_2 + k_{23}A_2 - k_{12}A_1 \quad (11)$$

$$dA_3/dt = k_{23}A_2 \quad (12)$$

Integration according to a general method[10] gives

$$A_1 = A_2^0k_{21}(e^{-\lambda_3 t} - e^{-\lambda_2 t})/(\lambda_2 - \lambda_3) \quad (13)$$

Table II. Kinetic and Apparent Activation Parameters for the Reaction of 2-Methoxy-3-nitrothiophene (If) with Piperidine in Methanol[a] at 20 °C

no.	[pip], M	10^3[MeONa],[b] M	10^3[MeO^-],[c] M	10^4k_A, $M^{-1}\,s^{-1}$	$(10^4k_A)_{calcd}$[d] $M^{-1}\,s^{-1}$	$\Delta H^{\ddagger}$,[e] kcal/mol	$-\Delta S^{\ddagger}$,[f] eu
1	0.0206		0.384	1.09			
2	0.0304		0.467	1.29		6.1	56
3	0.0450		0.569	1.45		6.9	53
4	0.0617		0.667	1.76		7.6	50
5	0.101		0.855	2.07		8.2	47
6	0.158		1.07	2.56	2.80	8.4	46
7	0.0298	1.00	1.18	2.83	2.98		
8	0.202		1.21	2.98	3.03		
9	0.234		1.30	2.99	3.17	9.0	44
10	0.298		1.47	3.26	3.41	9.1	43
11	0.102	0.940	1.45	3.39	3.38		
12	0.458		1.82	3.92	3.84	9.8	41
13	0.254	0.940	1.91	4.00	3.93		
14	0.717		2.28	4.40	4.29	10.1	39
15	0.508	0.940	2.45	4.57	4.44		
16	1.02		2.72	4.82	4.65	10.0	39
17	0.0298	3.00	3.07	5.02	4.89		
18	0.0298	4.00	4.05	5.51	5.41		
19	0.0298	5.00	5.04	5.83	5.79		
20	0.0298	5.64	5.70	6.01	6.00		
21	0.202	5.25	5.52	6.06	5.94	12.5	30
22	0.0508	7.52	7.57	6.34	6.41		
23	0.0508	9.40	9.44	6.61	6.70		
24	0.202	10.5	10.6	6.65	6.83	13.0	29
25	0.200[g]		0.0146	0.686			
26	0.200[h]		0.0292	0.750			
27	0.200[i]		0.0730	0.897			
28	0.200[j]		0.146	1.13			
29	0.400[g]		0.0292	1.25			
30	0.202[k]		1.21	5.05			
31	0.202[l]		1.21	5.22			

[a] The apparent activation parameters have been obtained from measurements at three temperatures in the range 20–40 °C. These further kinetic data are given in the microfilm edition of this volume of the journal. See the Supplementary Material available paragraph. [b] Added sodium methoxide. [c] Total methoxide ion; values calculated using $K_b = 7.3 \times 10^{-6}$ [J. R. Schaefgen, M. S. Newman, and F. H. Verhoek, *J. Am. Chem. Soc.*, **66**, 1847 (1944)]. [d] Values calculated by eq 9. [e] At 20 °C, the probable error is ±0.5 kcal/mol. [f] At 20 °C. [g] Piperidine hydrochloride (pipHCl) = 0.1 M. [h] [pipHCl] = 0.05 M. [i] [pipHCl] = 0.02 M. [j] [pipHCl] = 0.01 M. [k] Sodium acetate = 0.1 M. [l] Sodium perchlorate = 0.1 M.

Table III. Results of Least-Squares Fitting to Equation 8 of Apparent Second-Order Kinetic Constants, k_A, for the Piperidino Substitution of If in Methanol, at 20.0 °C[a]

constraints	$10^4\,(a \pm s_a)$, $M^{-1}\,s^{-1}$	$b \pm s_b$	$c \pm s_c$, M^{-1}	$d \pm s_d$, M^{-1}	items
none	7.95 ± 0.13	0.00 ± 0.02	0.05 ± 0.08	554 ± 40	1–24
$b = 0$	8.44 ± 0.17		0.14 ± 0.07	423 ± 25	1–24
$c = 0$	7.91 ± 0.11	0.00 ± 0.02		573 ± 30	1–24
$b = 0; c = 0$	8.32 ± 0.15			455 ± 20	1–24
$b = 0; c = 0$	8.15 ± 0.13			489 ± 20	6–24

[a] s_a, s_b, s_c, and s_d are the standard errors of a, b, c, and d, respectively.

$$A_2 = A_2^0\{[(k_{12} - \lambda_3)e^{-\lambda_3 t}/(\lambda_2 - \lambda_3)] - [(k_{12} - \lambda_2)e^{-\lambda_2 t}/(\lambda_2 - \lambda_3)]\} \quad (14)$$

$$A_3 = A_2^0\{1 + [k_{23}(k_{12} - \lambda_2)e^{-\lambda_2 t}/(\lambda_2 - \lambda_3)\lambda_2] - [k_{23}(k_{12} - \lambda_3)e^{-\lambda_3 t}/\lambda_3(\lambda_2 - \lambda_3)]\} \quad (15)$$

where $\lambda_2 = (p + q)/2$; $\lambda_3 = (p - q)/2$; $p = k_{12} + k_{21} + k_{23}$; $q = p^2 - [4k_{12}k_{23}]^{1/2}$. By measuring, at different intervals, the optical densities of the reaction mixtures at the wavelengths of the absorption maxima of III and IV, respectively, the concentrations of each compound can be easily determined according to eq 16 and 17

$$D_1 = \epsilon_{11}A_1 + \epsilon_{12}A_2 + \epsilon_{13}A_3 \quad (16)$$

$$D_2 = \epsilon_{21}A_1 + \epsilon_{22}A_2 + \epsilon_{23}A_3 \quad (17)$$

where ϵ_{1j} and ϵ_{2j} ($j = 1, 2, 3$) are the molar extinction coefficients of A_j, respectively, at 340 and 398 nm.[8,11]

Applying the above curve-fitting method to eq 15[12] gives the results set forth in Table IV. The k_{23} values in Table IV give second-order kinetic constants, k_A, in excellent agreement with k_1 (eq 9) obtained from kinetic measurements at low methoxide ion concentrations and provide a check of the internal consistency of our results. On the other hand, the k_{12} and k_{21} values in Table IV compare well with those previously obtained.[8]

Implications. Catalysis by methoxide ion in the reaction of If with piperidine in methanol is observable as long as k_{-1} is larger than or similar to $K_3'k_4'$ or k_3' (Scheme I). Since piperidino substitution reactions of compounds Ia–e in methanol are not catalyzed,[1] base assistance in the substitution of methoxy leaving group could be, in principle, needed because

Table IV. Results of Least-Squares Fitting to Equation 15 of Experimental A_3 Values[a] at 20 °C

[MeONa]	10^5k_{12}, s^{-1}	10^4k_{21}, s^{-1}	10^4k_{23}, s^{-1}	10^3k_f, M^{-1} s^{-1}	10^4k_A, M^{-1} s^{-1}	K_e[b], M^{-1}
0.102	9.99 (1.25)	1.55 (0.16)	1.73 (0.07)	1.52	8.40	15
0.205	6.69 (0.13)	3.28 (0.35)	1.66 (0.11)	1.60	8.06	24

[a] [pip] = 0.206 M; the values in parentheses are standard errors; number of data points, 20. [b] $K_e = k_f/k_{12}$.

of a larger k_{-1} and/or a lower $K_3'k_4'$ (or k_3') for methoxy than for the other leaving groups studied.

According to Bernasconi[4] k_{-1} should be little affected by leaving group variation. In our opinion, a particular situation occurs in *o*-nitro activated S_NAr of thiophene compounds. The hyper-ortho relation[13] between substituents linked to 2 and 3 carbon atoms of the thiophene ring makes the first transition state for piperidino substitution of If closely resemble the reaction intermediate.[14] As a consequence, the two transition states involved in the addition–elimination mechanism could be of similar importance in determining the overall reaction rate.

The quasi-para nitro substituted isomer IIf lacks this through-conjugation factor and the absence of catalysis is accordingly accounted for.

Assuming the SB-GA mechanism for base catalysis implies $k_{-1} \gg K_3'k_4'$, indeed, k_4' refers to a bond-breaking process and it is likely to be quite low with the poor methoxy leaving group.[16]

The piperidino substitution of If in methanol is not catalyzed by acetate ion. In fact, the rate-enhancing effect of sodium acetate is comparable with that produced by sodium perchlorate (items 30 and 31, Table II) and undoubtedly represents the medium effect of an "inert" salt. The absence of catalysis by piperidine and acetate ion could be explained on grounds of low $k_3^{B_i}$ values (Scheme I) for these bases.[19]

In view of recent discussions on this subject,[21] our results could imply, alternatively, the absence of general base catalysis and the operation of specific base catalysis (SB) by methoxide ion.

Conclusions. The piperidino substitution reaction of 2-methoxy-3-nitrothiophene in methanol constitutes the first exemplum of o-mononitro activated S_NAr for which base catalysis is needed. The hyper-ortho relation is the major factor implied. All of the data obtained agree with a SB (SB-GA) mechanism for base catalysis.

Experimental Section

Materials. Compounds If,[22] IIf,[23] piperidine,[11] and methanol[11] were prepared and/or purified according to the methods reported.

Kinetic Measurements. The kinetics were followed spectrophotometrically as previously described.[1,24] The concentrations used were 1×10^{-3} M for substrates and those indicated in the tables for piperidine, sodium methoxide, piperidine hydrochloride, sodium acetate, and sodium perchlorate. The rate constants are accurate to within ±3%.

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Registry No.—If, 30549-14-5; IIf, 30549-16-7; piperidine, 110-89-4.

Supplementary Material Available: Table of rate constants and apparent activation parameters for the reaction of 2-methoxy-3-nitrothiophene (If) with piperidine in methanol (1 page). Ordering information can be found on any current masthead page.

References and Notes

(1) Part 2. D. Spinelli, G. Consiglio, and R. Noto, *J. Heterocycl. Chem.*, **14**, 1325 (1977).
(2) F. Pietra and F. Del Cima, *Tetrahedron Lett.*, 4573 (1967).
(3) C. F. Bernasconi and F. Terrier, *J. Am. Chem. Soc.*, **97**, 7458 (1975).
(4) C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **3**, 33 (1973), and references therein.
(5) W. R. Busing and H. A. Levy, "A General Least Squares Program", Oak Ridge National Laboratory, Oak Ridge, Tenn.
(6) The agreement of experimental k_A values with those calculated by eq 9 was excellent for all but five (items 1–5) of the kinetic runs in Table II. At low piperidine concentrations, unavoidable traces of water and carbon dioxide could interfere with methoxide ion and introduce inaccuracies in the calculated values of its concentration. For this reason items 1–5 have been excluded from the calculation. Equation 9 applied to items 6–24 gives calculated k_A values (Table II) which do not differ from k_A within the experimental error. Since the term containing $[MeO^-]$ is the sole contributor to k_3', it is possible to apply the "inversion plot" treatment[7] to items 6–24. The results ($1/k_1 = 1140 \pm 40$, $1/k_1k^* = 2.67 \pm 0.07$, $r = 0.994$) nicely reproduce those obtained by the curve-fitting method.
(7) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3879 (1965).
(8) D. Spinelli, G. Consiglio, and R. Noto, *J. Chem. Res. (S)*, 242 (1978); *J. Chem. Res. (M)*, 2984 (1978).
(9) In Scheme II, $k_{23} = k_A[pip]$; $k_{21} = k_f[MeO^-]$; k_f = second-order kinetic constant for the adduct formation; k_{12} = kinetic constant for the adduct decomposition (under the experimental conditions used in the present work, both [pip] and $[MeO^-]$ are to be considered constant); A_1 = [IV]; A_2 = [If]; A_3 = [III]. We estimate that if $(k_{23} + k_{12})/k_{21} > 20$ there is no significant adduct formation; items 6–24 in Table II all meet this condition.
(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961, Chapter 8.
(11) D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim. (Rome)*, **55**, 1260 (1965).
(12) Although the A_1 values calculated as a function of time reaction, *t*, gave the expected trend (i.e., rapid increase, reaching of a maximum, and decrease to zero), the consistent contribution to absorption from If[8] prevented their use for the subsequent treatment.
(13) D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Chem. Soc., Perkin Trans. 2*, 441 (1972); D. Spinelli, R. Noto, and G. Consiglio, *ibid.*, 747 (1976).
(14) In the reaction of If with sodium methoxide in methanol, to form the Meisenheimer-type adduct, k_1 and k_{-1} are of the same order of magnitude.[8] The reaction of the same substrate with a neutral nucleophile should involve a somewhat more like-intermediate transition state.[15]
(15) L. R. Parks, G. S. Hammond, and M. F. Hawthorne, *J. Am. Chem. Soc.*, **77**, 2903 (1955).
(16) The reaction of 2-trifluoroethoxy-3-nitrothiophene with piperidine in methanol is second order overall[17] and has $\Delta H^{\ddagger} = 12.5$ kcal/mol and $\Delta S^{\ddagger} = -26$ eu. An estimate of the upper limits of the apparent activation parameters in Table II indicates a similar $\Delta S^{\ddagger}$ value and a higher $\Delta H^{\ddagger}$ value for methoxy leaving group. According to the Hammond postulate[18] this implies a lower k_{-1} value for the trifluoroethoxy leaving group; moreover, this is more nucleofugic than the methoxy group. Thus, the $K_3'k_4'/k_{-1}$ ratio is likely to be greater than unity and the overall reaction rate is controlled by the formation of intermediate.
(17) D. Spinelli, G. Consiglio, and R. Noto, unpublished results.
(18) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(19) The piperidino substitution reaction of 2,4-dinitroanisole in 10% dioxane–90% H_2O is catalyzed by both HO^- and piperidine.[20] If the SB-GA mechanism is assumed, the $K_3^{OH}k_4^{OH}/K_3^{pip}k_4^{pip}$ ratio observed is 170.[4] The corresponding $K_3^{MeO}k_4^{MeO}/K_3^{pip}k_4^{pip}$ ratio for the less activated thiophene system If is likely to be so high as to make catalysis by piperidine undetectable.
(20) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967), and references therein.
(21) C. F. Bernasconi, R. H. de Rossi, and P. Schmid, *J. Am. Chem. Soc.*, **99**, 4090 (1977).
(22) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74**, 2965 (1952).
(23) J. Sicé, *J. Am. Chem. Soc.*, **75**, 3697 (1953).
(24) D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim.* (Rome), **52**, 1156 (1962).

Studies on Decarboxylation Reactions. 3.[1a] Micellar Catalysis in the Decarboxylation of 5-Amino-1,3,4-thiadiazole-2-carboxylic Acid

Domenico Spinelli*

Cattedra di Chimica Organica, Faculty of Pharmacy, University of Bologna, Bologna 40126, Italy

Renato Noto, Giovanni Consiglio, Giuseppe Werber, and Francesco Buccheri

Institute of Organic Chemistry, University of Palermo, Palermo 90123, Italy

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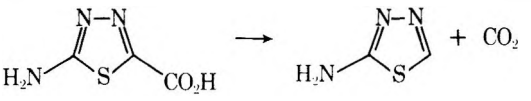
The rate constants of the decarboxylation of 5-amino-1,3,4-thiadiazole-2-carboxylic acid (I) have been measured in the presence of cationic (CTAB), anionic (LSNa), and nonionic (Triton X-100) micelles. The results obtained at constant and/or variable proton activity (an acceleration with cationic and nonionic micelles and almost no effect with anionic micelles), as well as salt addition effects, agree with a decarboxyprotonation mechanism of the zwitterion.

Continuing our researches[1] on the decarboxylation of heterocyclic amino acids we report in this paper data on the behavior of 5-amino-1,3,4-thiadiazole-2-carboxylic acid (I) in



I

water in the presence of cetyltrimethylammonium bromide (CTAB), sodium lauryl sulfate (NaLS), and polyoxyethylenediisobutylphenol(Triton X-100), i.e., surfactants able to give respectively cationic, anionic, and nonionic micelles.

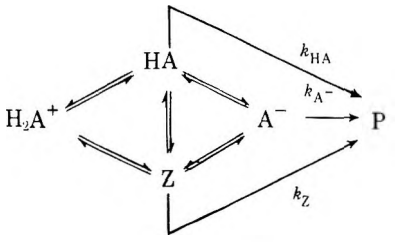
5-Amino-1,3,4-thiadiazole-2-carboxylic acid decarboxylates in water over the pH range 0.25–3.91 and the data obtained agree with two different mechanisms: unimolecular decomposition of the zwitterion (or of the undissociated acid) and/or protiodecarboxylation of the anionic species (Scheme I).

On the basis of chemical considerations[1] we have excluded the mechanism of protiodecarboxylation (carbon–hydrogen bond forming, often rate determining, followed by carbon–carbon bond breaking) and preferred a unimolecular decomposition of the zwitterion (rate-determining carbon–carbon bond breaking followed by carbon–hydrogen bond forming).

Surfactants influence rate and equilibrium constants of many chemical processes.[2] The behavior of micelles is especially interesting in what concerns the simulation of enzyme action.[3] Several studies have been reported on reactions carried out in the presence of micelles, including some unimolecular decarboxylation processes.[4] These have all been concerned with anions which decarboxylate through a transition state where the negative charge is delocalized more than in the initial state and therefore micellar catalysis is expected to be important.

The present study constitutes the first exemplum, in our knowledge, concerning micellar effects on the decarboxylation reaction of zwitterionic species and it seems to us of some interest in that micelles could simulate the enzyme-catalyzed decarboxylation of natural amino acids.

Scheme I



Kinetic Data. The apparent first-order kinetic constants and the thermodynamic parameters measured at variable surfactant concentration in the presence of 0.025 M HCl are collected in Tables I and II. Data at constant surfactant concentration and variable HCl concentration are in Table III. Moreover data related to salt effects are in Table IV.

Kinetic data in Table I (see also Figure 1) clearly indicate a positive catalytic effect by both Triton X-100 and CTAB and a slight effect by NaLS.[5]

One can observe that in spite of high surfactant concentrations (respectively, Triton X-100 0.16 and CTAB 0.17 M) the typical plateau of unimolecular[4a,b,7] reactions is not observed, thus indicating a low incorporation of substrate in micelles. A low binding constant is expected if the species to be decarboxylated is the zwitterion (see below): hence the apparently low k_m/k_w ratios.

Examination of data at constant surfactant concentration and variable proton activity confirms this hypothesis. In fact, we have observed (data in Table III, see also Figure 2) trends of kinetic constants vs. proton activities similar to those observed in the absence of surfactants,[8] thus indicating that the equilibria in Scheme I are only scarcely affected by the present

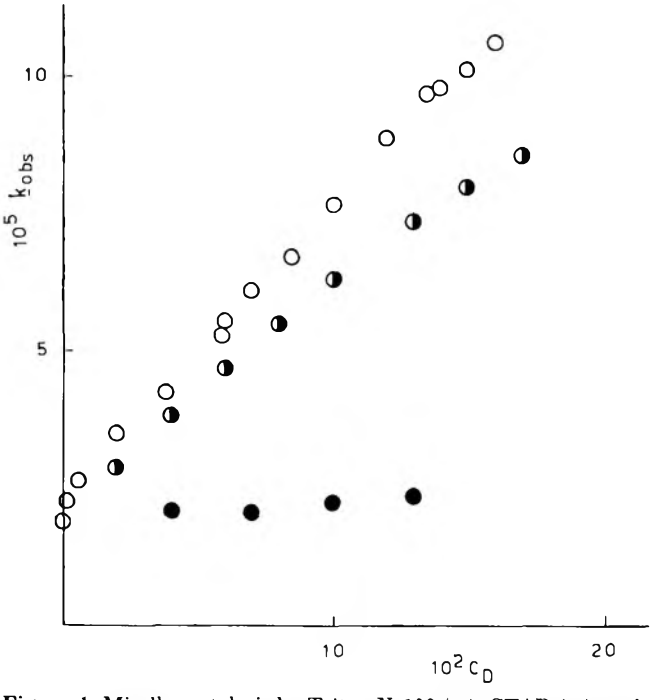


Figure 1. Micellar catalysis by Triton X-100 (○), CTAB (◑), and NaLS (●) for decarboxylation of I in the presence of 0.025 M hydrochloric acid at 40.0 ± 0.1 °C.

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Table I. Apparent Rate Constants for the Decarboxylation of I in the Presence of Surfactants and Hydrochloric Acid (0.025 M) at 40.0 ± 0.1 °C

Triton X-100		CTAB		NaLS	
$C_D \times 10^2$, mol L^{-1}	$k_{obsd} \times 10^5$,[a] s^{-1}	$C_D \times 10^2$ mol L^{-1}	$k_{obsd} \times 10^5$,[a] s^{-1}	$C_D \times 10^2$, mol L^{-1}	$k_{obsd} \times 10^5$,[a] s^{-1}
	1.86		1.86		1.86
	9.60 (50.6 °C)		9.60 (50.6 °C)		9.60 (50.6 °C)
	38.5 (60.3 °C)		38.5 (60.3 °C)		38.5 (60.3 °C)
0.16	2.22	2.0	2.85	4.0	2.08
0.60	2.58	4.0	3.80	7.0	2.07
2.0	3.46	6.0	4.67	10.0	2.22
3.8	4.21	8.0	5.47	13.0	2.35
5.9	5.25	8.0	22.4 (50.6 °C)	13.0	10.9 (50.6 °C)
5.9	22.2 (50.3 °C)	8.0	73.9 (60.2 °C)	13.0	43.8 (60.3 °C)
5.9	76.1 (59.9 °C)	10.0	6.28		
6.0	5.52	13.0	7.32		
7.0	6.08	15.0	7.96		
8.5	6.71	17.0	8.53		
10.0	7.64	17.0	31.9 (50.4 °C)		
12.0	8.84	17.0	106 (60.3 °C)		
13.5	9.65				
14.0	9.76				
15.0	10.1				
16.0	10.6				

[a] The rate constants are accurate to within ±3%.

Table II. Activation Parameters for the Decarboxylation of I in the Presence of Surfactants and Hydrochloric Acid (0.025 M)

surfactant	$C_D \times 10^2$, mol L^{-1}	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}$,[b] cal mol^{-1} K^{-1}
		30.6	17.3
Triton X-100	5.9	27.3	8.8
CTAB	8.0	26.3	5.7
CTAB	17.0	25.3	3.5
NaLS	13.0	29.1	13.2

[a] At 40 °C, the maximum error is 0.6 kcal mol^{-1}. [b] At 40 °C.

surfactants. On the other hand, the close resemblance between the curves in Figure 2 implies that the reaction mechanism in the presence of surfactants is of the same kind as that observed in pure water. Thus, the behavior of I in the presence of micelles can help to elucidate the decarboxylation mechanism.

We have suggested that the decarboxylating species should be the zwitterion. The structure of zwitterion with the positive charge delocalized on exo- and endocyclic nitrogen atoms accounts for the higher catalytic effect of nonionic and cationic micelles compared to anionic micelles, e.g., NaLS, which are likely to cause strong electrostatic repulsive interactions with the negative center of the zwitterion.

On the whole, nonionic and cationic micelles should give weak attractive or feebly repulsive interactions with the reactive species, which turns out destabilized[4b] going from water phase to micelles; of course the situation should be more favorable in the transition states. In fact, because of the higher dispersion of the negative charge, these interact with micelles to a greater extent.

The behavior observed in the decarboxylation of I recalls that observed by Fendler and co-workers[9] in the hydrolysis of potassium 2,4-dinitrophenylsulfate.

The results obtained allows the following conclusions to be drawn: (a) The protiodecarboxylation mechanism can be definitively excluded. In fact, if the species which is decarboxylated were the anion, the trend of apparent first-order kinetic constants vs. surfactant concentration should have been different; i.e., the reaction should have been *inhibited* by cationic micelles. (b) The unimolecular decarboxylation of the undissociated acid is unlikely to occur; in this case there should have been large attractive interactions between

Table III. Apparent Rate Constants for the Decarboxylation of I at Various Hydrochloric Acid Concentrations in the Presence of Surfactants at 40.0 ± 0.1 °C

Triton X-100[a]			CTAB[b]			NaLS[c]		
HCl, mol L^{-1}	pH	$k_{obsd} \times 10^5$,[d] s^{-1}	HCl, mol L^{-1}	pH	$k_{obsd} \times 10^5$,[d] s^{-1}	HCl, mol L^{-1}	pH	$k_{obsd} \times 10^5$,[d] s^{-1}
0.400	0.46	2.57	0.200	0.85	4.89	0.200	0.90	1.37
0.200	0.78	3.58	0.100	1.13	5.77	0.100	1.27	1.65
0.100	1.10	4.54	0.050	1.45	6.20	0.075	1.42	1.77
0.075	1.22	4.83	0.040	1.59	6.18	0.050	1.64	1.96
0.050	1.39	5.42	0.025	1.80	6.28	0.025	2.00	2.07
0.025	1.70	5.52	0.020	1.92	6.27	0.0125	2.46	1.96
0.0125	2.02	5.53	0.0100	2.29	5.51	0.0100	2.64	1.76
0.0100	2.16	5.32	0.0050	2.70	3.84	0.0080	2.75	1.56
0.0075	2.33	4.87						
0.0050	2.60	4.45						
0.0025	3.11	2.62						
0.0010	4.09	0.476						

[a] 6×10^{-2} mol L^{-1}. [b] 10×10^{-2} mol L^{-1}. [c] 7×10^{-2} mol L^{-1}. [d] The rate constants are accurate to within ±3%.

Table IV. Salt Effect on the Decarboxylation of I in the presence of CTAB (0.1 M) and Hydrochloric Acid (0.025 M) at 40.0 ± 0.1 °C

added salt,[a] mol L^{-1}	$k_{obsd} \times 10^5$,[b] s^{-1}
	6.28
A, 0.05	6.51
A, 0.10	6.52
A, 0.20	6.55
A, 0.40	6.52
B, 0.05	6.14
B, 0.10	6.38
B, 0.20	6.53

[a] Added salts: A, KCl; B, KBr. [b] The rate constants are accurate to within ±3%.

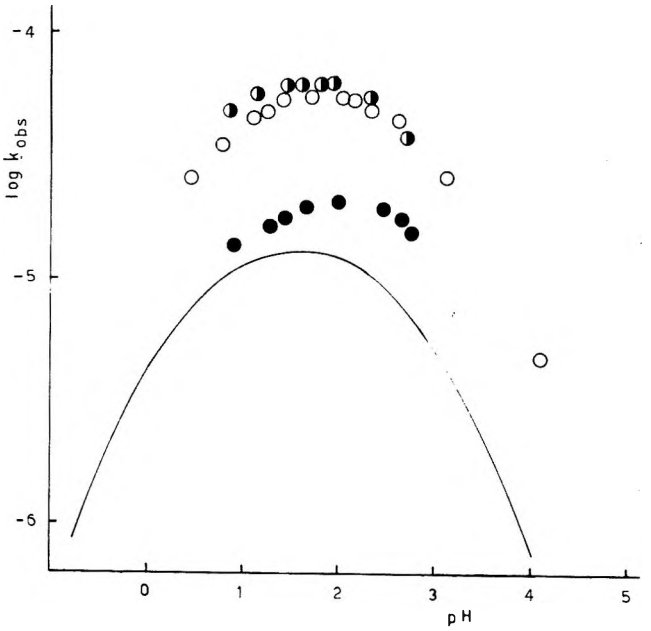

Figure 2. Plot of log k_{obsd} for decarboxylation of I at 40.0 ± 0.1 °C vs. acidity function: ○ Triton X-100 (6×10^{-2} M), ◑ CTAB (10^{-1} M), and ● NaLS (7×10^{-2} M). The curve is that calculated for reactions in the absence of surfactants.

starting material and micelles and low repulsive interactions between transition states (with incipient zwitterionic character) and micelles, especially for nonionic micelles. This prevision disagrees with experimental data. (c) The unimolecular decarboxylation of the zwitterion remains the most probable decarboxylation mechanism of I (see above).

Salt effects on micellar catalysis support the proposed mechanism. In fact, the decarboxylation of I in pure water is retarded by salt addition[10] at variance with what happens in the presence of cationic micelles (see Table IV). This is because salt addition lowers the ionic character of micelles favoring micelle–substrate interactions.

Also the activation parameters agree with the proposed mechanism (see Table II). The activation entropy values are more negative than in pure water, as expected with dependence on the higher order deriving from interactions with micelles; on the other hand the activation enthalpy values are lower than in pure water because interactions with micelles favor the charge dispersion in the transition states.

Experimental Section

Materials. The acid was prepared and purified as described.[11] Commercial CTAB and NaLS (Merck, pro analysis) and Triton X-100 (J. Baker) were used without further purification.

Kinetic Measurements. The kinetics of decarboxylation were followed spectrophotometrically as previously described[1a] by measuring the disappearance of I, respectively, at 290 nm for the runs in the presence of CTAB and NaLS and at 300 nm in the case of Triton X-100.

The pH measurements were made as previously described.[1a]

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References and Notes

(1) (a) Part 2: D. Spinelli, R. Noto, G. Consiglio, and F. Buccheri, *J. Heterocycl. Chem.*, **14**, 309 (1977); (b) D. Spinelli, R. Noto, G. Consiglio, G. Werber, and F. Buccheri, *J. Chem. Soc., Perkin Trans. 2*, 639 (1977), and references cited therein.
(2) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems," Academic Press, New York, N.Y., 1975.
(3) D. Piszkiewicz, *J. Am. Chem. Soc.*, **98**, 3053 (1976), and references cited therein.
(4) (a) C. A. Bunton and M. J. Minch, *Tetrahedron Lett.*, 3881 (1970); (b) C. A. Bunton, A. Kamego, and M. J. Minch, *J. Org. Chem.*, **37**, 1388 (1972); (c) L. Ka-Ming Lam and D. E. Schmidt, Jr., *Can. J. Chem.*, **51**, 1959 (1972); J. Suh, I. S. Scarpa, and I. M. Klotz, *J. Am. Chem. Soc.*, **98**, 7060 (1976); W. J. Spetnagel and I. M. Klotz, *ibid.*, **98**, 8199 (1976).
(5) The small size of this effect does not allow any mechanistic speculation to be made; in fact, many overlapping factors can operate (variation of proton activity in water in the presence of micelles, which should cause a negative catalytic effect in water phase;[6] influence of the relatively high oxonium ion concentration on micelle structure, etc.[6]).
(6) C. A. Bunton and B. Wolfe, *J. Am. Chem. Soc.*, **95**, 3742 (1973).
(7) G. J. Buist, C. A. Bunton, L. Robinson, L. Sepulveda, and M. F. Stam, *J. Am. Chem. Soc.*, **92**, 4072 (1970).
(8) The low shift observed can be explained taking into account that kinetic runs in the presence of surfactants have not been carried out at constant ionic strength and that micelles influence the proton activity of solutions.
(9) E. J. Fendler, R. R. Leichti, and J. H. Fendler, *J. Org. Chem.*, **35**, 1658 (1970).
(10) D. Spinelli, R. Noto, and G. Consiglio, unpublished results.
(11) G. Werber and F. Maggio, *Ann. Chim.*, **53**, 3 (1963).

Kinetics of the Thermolysis of 3,3-Bis(*p*-anisyl)-1,2-dioxetane

William H. Richardson,* James H. Anderegg, Mary E. Price, and Richard Crawford

Department of Chemistry, San Diego State University, San Diego, California 92182

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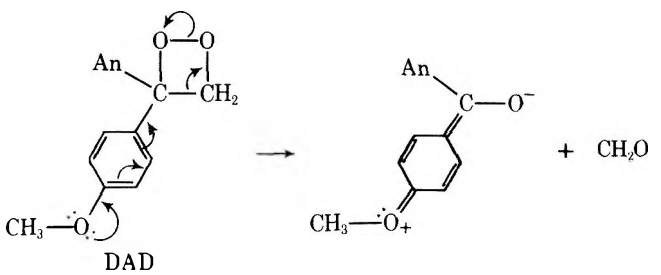
3,3-Bis(*p*-anisyl)-1,2-dioxetane (DAD) was prepared and the kinetics of thermolysis were studied in benzene and methanol solvents in order to probe the possibility of a concerted reaction. Activation parameters for DAD in benzene are E_a = 20.9 ± 0.3 kcal/mol, log A = 11.77 ± 0.18, $\Delta H^{\ddagger}$ = 20.2 ± 0.3 kcal/mol, $\Delta S^{\ddagger}$ = −6.8 ± 0.8 eu, $\Delta G^{\ddagger}$ = 22.5 ± 0.3 kcal/mol; and in methanol they are E_a = 21.0 ± 0.2 kcal/mol, log A = 11.99 ± 0.16, $\Delta H^{\ddagger}$ = 20.3 ± 0.2 kcal/mol, $\Delta S^{\ddagger}$ = −5.8 ± 0.7 eu, $\Delta G^{\ddagger}$ = 22.2 ± 0.2 kcal/mol. The unsubstituted model compound, 3,3-diphenyl-1,2-dioxetane (DPD), was previously found to have E_a values in both benzene (22.7 kcal/mol) and methanol (22.2 kcal/mol) which are somewhat larger than those for DAD. In terms of rate enhancement by the *p*-methoxy substituents k_{DAD}/k_{DPD} is 3.90 and 4.55 at 60 °C in benzene and methanol, respectively. These data are considered in terms of a concerted process and a stepwise biradical mechanism. The results appear to be most reasonably interpreted in terms of the biradical mechanism where the substituent effect is associated with homolysis of the O–O bond.

Thermolysis of several simply substituted 1,2-dioxetanes appears to be most readily accommodated by a biradical mechanism.[1] Several lines of evidence have led us to this conclusion. First, calculated activation parameters based on a biradical process are in good agreement with the experimental parameters. Second, substituents have little effect on the rates of dioxetane thermolyses. Third, the activation parameters for thermolysis show little sensitivity upon changing from an aprotic nonpolar solvent such as benzene to a protic polar solvent such as methanol. Finally, the biradical mechanism can accommodate the high efficiency of triplet carbonyl production[2] within the context of spin conservation.

Currently we have been searching for dioxetanes that would show the characteristics of a concerted thermolysis reaction.[1d] We have used two approaches in the design of the structure of dioxetanes in an attempt to realize this goal. First, the dioxetane ring has been progressively substituted with phenyl groups.[1d] Thermochemical kinetic calculations indicate that such substitution should progressively weaken the C–C bond of the dioxetane ring. At some point in the successive phenyl substitution, one might anticipate that the C–C and O–O bonds would become sufficiently comparable in energy so that a concerted decomposition would occur. With up to three phenyl substituents, it still appears that a stepwise decomposition occurs.[1d]

A second approach is to design dioxetanes with aryl groups bearing substituents that would facilitate a concerted process. This approach is reported here with 3,3-bis(*p*-anisyl)-1,2-dioxetane (DAD). One may envisage an unzipping of the



DAD

dioxetane ring in a concerted manner, which is facilitated by the *p*-methoxy substituents in DAD as indicated below, where An = *p*-$CH_3OC_6H_4$.

It may also be possible to encourage a concerted process by an appropriate choice of solvent. Previously, we have presented arguments to suggest that methanol solvent should facilitate a concerted reaction.[1c] A comparison of activation parameters obtained in benzene and in methanol is used here to assess the possibility of a concerted process for DAD.

Results

DAD was prepared by the closure of the corresponding bromohydroperoxide, 1-bromo-2-hydroperoxy-2,2-bis(*p*-anisyl)ethane (BHA). The latter hydroperoxide could be obtained as a white crystalline solid by recrystallization from carbon tetrachloride at low temperature. Recrystallization of DAD proved unsuccessful, so column chromatography on silica gel with and without impregnation with EDTA was attempted. After several attempts, we were unable to obtain any peroxidic fractions from either type of chromatography. For these reasons, DAD was used without further purification. The presence of DAD was detected by the characteristic dioxetane ring ^{1}H NMR absorption at δ 5.68, which disappeared upon heating the solution. A crude rate coefficient of 0.96 × 10^{-3} s^{-1} at 37.5 °C was obtained in carbon tetrachloride solution by following the disappearance of dioxetane ring protons by NMR. This value compares favorably with a rate coefficient of 1.15 × 10^{-3} s^{-1}, calculated from the activation parameters for DAD in benzene, as obtained by light emission data. Concentrations of DAD were determined by iodometric biamperometric analyses, which were corrected for contamination by BHA.

Kinetic measurements were obtained from light emission of DAD in the presence of 9,10-dibromoanthracene (DBA) by previously reported methods.[1c] Under these conditions, no light emission was observed from BHA. To avoid spurious transition metal ion catalysis, the methanol solvent was treated with EDTA and EDTA was added to the kinetic cells with either methanol or benzene solvent.[1c,3] In addition, anhydrous sodium sulfate was added to the kinetic cells to avoid contamination by water.

The rate coefficients as a function of temperature and concentration of the dioxetane in benzene solvent are given in Table I. Rate data for the thermolysis of DAD in methanol solvent are shown in Table II. Activation parameters calculated from these data are given in Table III along with the previously reported experimental and calculated activation parameters for 3,3-diphenyl-1,2-dioxetane (DPD).[1b,c] It is seen from Table I that a 50- to 100-fold variation in the initial DAD concentration causes only a small change in the rate coefficient. Thus, the thermolysis of DAD adheres to first-order behavior at low concentrations, as was previously observed with other dioxetanes.[1]

Discussion

In comparison to 3,3-diphenyl-1,2-dioxetane (DPD), activation energies (E_a) are lowered by the di-*p*-methoxy substitution in DAD by 1.8 and 1.2 kcal/mol respectively in benzene and methanol solvents. This does not appear to be

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Table I. Rate Coefficients for the Thermolysis of 3,3-Bis(*p*-anisyl)-1,2-dioxetane (DAD) in Benzene Solvent[a,b]

10^4[DAD], M	t, °C	10^3k,[c] s^{-1}
1.17	25.05	0.277 ± 0.002
1.60	25.05	0.298 ± 0.006
117	25.10	0.238 ± 0.002
2.03	35.15	0.767 ± 0.007
117	35.12	0.805 ± 0.007
1.17	45.10	2.52 ± 0.01
1.17	45.10	2.47 ± 0.03
1.60	55.10	6.57 ± 0.08
1.60	55.10	6.52 ± 0.07
1.17	70.05	27.2 ± 0.3
1.17	70.10	27.8 ± 0.3

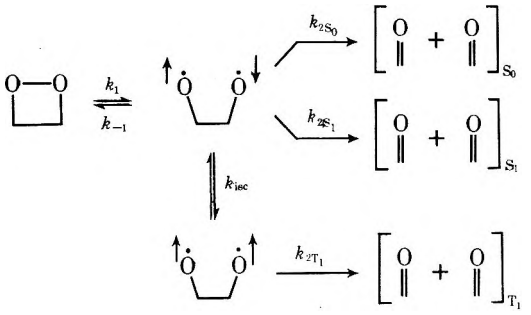
[a] With [DBA] = 2.44×10^{-4} M. [b] Solutions were saturated with Na_2EDTA and protected from moisture with anhydrous Na_2SO_4. [c] By least squares with standard error.

Table II. Rate Coefficients for the Thermolysis of 3,3-Bis(*p*-anisyl)-1,2-dioxetane (DAD) in Methanol Solvent[a-c]

t, °C	$10k$, s^{-1}	t, °C	$10\,k$,[d] s^{-1}
17.89	0.180 ± 0.002	35.08	1.22 ± 0.01
17.89	0.175 ± 0.001	35.08	1.46 ± 0.01
25.13	0.437 ± 0.003	35.08	1.32 ± 0.01
25.13	0.432 ± 0.005	45.03	3.90 ± 0.02
25.13	0.427 ± 0.012	45.03	3.90 ± 0.01
35.08	1.28 ± 0.01	55.22	10.9 ± 0.1
		55.22	11.2 ± 0.1

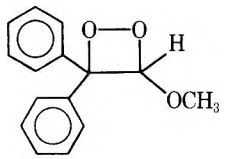
[a] Solutions were saturated with Ha_2EDTA and protected from moisture with anhydrous Na_2SO_4. [b] [DAD] = 1.40×10^{-4} M. [c] [DBA] = 5.50×10^{-4} M. [d] Least-squares analysis with standard error in individual measurements.

Scheme I



the result of compensating changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, since $\Delta G^{\ddagger}$ is about 1.0 kcal/mol lower for DAD compared to DPD in both solvents. In terms of relative rates (k_{DAD}/k_{DPD}) at 60 °C, the two *p*-methoxy substituents accelerate the rate by factors of 3.90 and 4.55 respectively in benzene and methanol solvents.

First of all, it should be noted that the substituent effect of the two *p*-methoxy groups in DAD is small compared to the unsubstituted model DPD. Previously, we had found that the biradical scheme shown below readily accommodated our data for other substituted dioxetanes, including DPD.[1a-d] It seems most likely then that DAD is undergoing thermolysis according to Scheme I with little or no progress toward a concerted decomposition. In one report,[4] where a change from a stepwise to a concerted process may be occurring, there is a considerably greater decrease in E_a than is observed between DAD and DPD. For example, the Arrhenius activation energy decreases from 26.1 kcal/mol for **1** to 21.0 kcal/mol for **2**,[4] where a stepwise mechanism is most likely for **1** while a concerted process may be associated with **2**. Based on a comparison of **1** and **2**, one might expect a greater decrease in E_a between DAD and DPD if a concerted process was operative with DAD.



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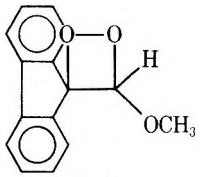

2

One test that we have used previously to probe the possibility of a concerted reaction is a comparison of kinetic data in benzene vs. methanol solvent.[1c] Here it is expected that the activation energy would be decreased and the rate increased upon changing from benzene to methanol solvent if a concerted process is operative. This expectation is based upon the development of the polar carbonyl bond in the activated complex of the concerted process, which should be stabilized by the polar-protic methanol solvent. This prediction finds support in the solvent effect associated with the β scission of the *tert*-butoxy radical.[5] As seen from Table III, the activation parameters for DAD in benzene and methanol are the same within experimental error. These data also suggest that a concerted process is not operative or at least little progress has been made in breaking the C–C bond of the dioxetane ring in the activated complex of the rate-determining step.

The small substituent effect observed with DAD as compared to DPD seems most reasonably assigned to the breaking of the O–O bond (i.e., k_1 in Scheme I). In support of this proposal, a comparison of the thermolysis kinetics of benzoyl peroxide (**3**) and its *p,p'*-dimethoxy derivative (**4**) may be considered.[6] At 80 °C the relative rates (k_4/k_3) in acetophenone and dioxane are 3.61[6a] and 2.81,[6b] respectively. These values are similar to those found for k_{DAD}/k_{DPD} (3.90 and 4.55 at 60 °C in benzene and methanol solvent, respectively). Furthermore, the activation energy is decreased in proceeding from **3** to **4** by 1.5 kcal/mol in acetophenone and by 1.0 kcal/mol in dioxane solvent. The decrease in activation energy with the di-*p*-methoxy substitution in the benzoyl peroxide series is then similar as well to that observed with the dioxetanes (1.8 and 1.2 kcal/mol in benzene and methanol solvent, respectively).

Enhanced light emission from DAD in the presence of DBA is indicative of triplet carbonyl formation.[7] This observation is also most readily explained in terms of Scheme I rather than a concerted process, since in the latter process a violation of spin conservation results. Since this rule has found such wide applicability,[8] considerable doubt is cast upon a concerted mode which involves triplet carbonyl production. One could argue that they are two competing reactions: a concerted decomposition of DAD to give singlet carbonyl products and a second reaction to give triplet carbonyl products. Although the first process avoids the problem of spin conservation violation, the second reaction introduces this problem once again. At least, at this point in our understanding of the thermolyses of simply substituted dioxetanes, the generalized Scheme I would appear to accommodate all of the observations with the greatest economy.

Recently, the volume of activation was determined for tetramethyl-1,2-dioxetane (TMD) to be 11 ± 3 cm^3/mol.[9] This value is considerably larger than the expected value of about 5 cm^3/mol for either homolysis of one bond in Scheme I with $k_{-1} \ll (k_{2S_0} + k_{2S_1} + k_{2T_1})$ or a concerted rupture of two bonds.[10] It appears that the only way to rationalize the ΔV^* value for TMD is to propose that k_{-1} and $(k_{2S_0} + k_{2S_1} + k_{2T_1})$ are more nearly comparable. This proposal has certain restrictions, considering our substituent studies, including the present results with DAD. Very small substituent changes

Table III. Activation Parameters for 3,3-Bis(*p*-anisyl)-1,2-dioxetane[e] (DAD) and 3,3-Diphenyl-1,2-dioxetane[f] (DPD).

dioxetane	solvent	E_a[a]	log A	$\Delta H^{\ddagger}$ [a,b]	$\Delta S^{\ddagger}$ [c]	$\Delta G^{\ddagger}$ [a,b]
DAD	benzene	20.9 ± 0.3	11.77 ± 0.18	20.2 ± 0.3	−6.8 ± 0.8	22.5 ± 0.3
DAD	methanol	21.0 ± 0.2	11.99 ± 0.16	20.3 ± 0.2	−5.8 ± 0.7	22.2 ± 0.2
DPD	benzene	22.7 ± 0.1	12.36 ± 0.06	22.0 ± 0.1	−4.1 ± 0.3	23.4 ± 0.1
DPD	methanol	22.2 ± 0.2	12.12 ± 0.08	21.6 ± 0.2	−5.1 ± 0.5	23.3 ± 0.2
DPD (calcd)		22.6	12.71	21.9	−2.5	22.7

[a] Kcal/mol. [b] Calculated at 60 °C. [c] eu. [d] Calculated on the basis of the stepwise biradical process. [e] Registry no. 67087-29-0. [f] Registry no. 53399-67-0.

were observed with a progressive replacement of methyl with phenyl groups on the dioxetane ring.[1a-d] With DAD compared to DPD, it appears that the small substituent effect can be attributed to step k_1 in Scheme I, by analogy to benzoyl peroxides. These substituent effects then require that k_{-1} must be less than $(k_{2S_0} + k_{2S_1} + k_{2T_1})$. It is possible that k_{-1} is only somewhat less than $(k_{2S_0} + k_{2S_1} + k_{2T_1})$. For cyclobutane pyrolysis, which appears to be best explained in terms of a biradical mechanism, the activation energies associated with the back reaction (k_{-1}) and the forward reaction (k_2) from the biradical are estimated to be 6.6 and 8.3 kcal/mol, respectively.[11] Since the π bond in carbonyls is of lower energy than the π bond in olefins,[12] it was initially thought that the comparable activation energies in the dioxy biradical process would be skewed so that $E_{-1} \gg E_2$. This reasoning is, of course, based on the ground state energies of the product carbonyls vs. olefins and the activation energies may not be proportional to the ground state energies. In fact, reactions of 1,4-biradicals (or zwitterions) have been suggested to be subject to orbital symmetry rules.[14] In effect, the orbital memory may not be lost in proceeding from the reactant to the intermediate biradical and on to the product. Since the $[2_S + 2_S]$ reaction of the dioxetane to carbonyl products is forbidden, this would mean that the biradical to carbonyl process is also forbidden. This could result in a more substantial activation energy for the biradical to carbonyl process than was previously anticipated. With this reasoning, one can rationalize the substituent effect data and the value of ΔV^* for TMD, where k_{-1} is less but more nearly comparable to $(k_{2S_0} + k_{2S_1} + k_{2T_1})$.[15]

Experimental Section[16]

1,1-Bis(*p*-anisyl)ethanol. This carbonyl was prepared in 94% yield, by a method which was similar to a previously reported procedure,[17] from *p,p'*-dimethoxybenzophenone (Aldrich) and methylmagnesium iodode. The resulting crude semisolid was not further purified, since the carbinol was found to undergo dehydration upon recrystallization from 95% ethanol which contained a few drops of 6 N sodium hydroxide. Spectral data were in accord with the expected product: IR 3610, 3500 (OH), 3050, 3010 (Ar–H), 2960, 2845 cm^{-1} (aliph C–H); NMR 3.70, (s, 6.0, CH_3O), 1.79 (s, 3.1, CH_3), 4.46 (s, 0.80, OH), 6.90 (AB, J = 9.0 Hz, 8.8, Ar–H).

1,1-Bis(*p*-anisyl)ethene. A 10.8 g (41.9 mmol) sample of the above carbinol was treated with 50 mL of 20% sulfuric acid in acetic acid for 10 min.[18] Water (50 mL) was added and the mixture was extracted with methylene chloride. After washing the methylene chloride extract with water and drying it over magnesium sulfate, rotoevaporation gave 10.75 g of a light tan solid. Recrystallization from 30 mL of benzene/16 mL of 95% ethanol gave 7.75 g (77% yield) of white plates, mp 140–141.5 °C (lit.[19] mp 142–144 °C). A second crop was obtained upon partial concentration of the filtrate, which upon recrystallization from cyclohexane gave 1.32 g (13% yield) of white plates, mp 126–128 °C. Spectral data of the first crop showed: IR 3100, 890 (=CH_2), 3050, 3010 (ArH), 2960, 1845 (aliph CH), 1620 cm^{-1} (C=C); NMR 3.70 (s, 5.9, CH_3O), 5.09 (s, 2.0, =CH_2), 6.83, (AB, J = 11.4 Hz, 8.0, ArH).

1-Bromo-2-hydroperoxy-2,2-bis(*p*-anisyl)ethane (BHA). The above olefin (3.0 g, 12.5 mmol) was dissolved in 40 mL of dry tetrahydrofuran (THF) and the solution was cooled to −10 °C under a nitrogen atmosphere. Hydrogen peroxide (45 mL of 1.37 M) in THF was added. The hydrogen peroxide solution was prepared from 98% hydrogen peroxide (FMC) and anhydrous THF and then dried for 24 h at 25 °C over anhydrous magnesium sulfate. To affect solution of the olefin, it was necessary to raise the temperature to 0 °C and then 1.72 g (6.00 mmol) of 1,3-dibromohydantoin (Matheson Coleman and Bell) was added in portions over a 30-min period with stirring.[20] The reaction flask was wrapped with aluminum foil during the reaction. After the addition of the brominating agent was completed, the mixture was allowed to stir at 0 °C for 45 min, gradually warmed to room temperature over about 30 min, and then stirred for an additional 1.5 h. The mixture was then transferred to a separatory funnel containing 50 mL of ether and 50 mL of 5% sodium bicarbonate solution. After shaking, the organic phase was separated and further washed with 5% sodium bicarbonate solution and then with water. The ether phase was dried over anhydrous sodium sulfate and then rotevaporated to give a light yellow semisolid, which gave a positive peroxide test to potassium iodide starch paper. A biamperometric titration of the product indicated that BHA was obtained in 65% yield. The crude product was recrystallized from carbon tetrachloride at about −20 °C to give a white solid, mp 91–92.5 °C dec, 97.7% pure by iodometric analysis: NMR 3.71 (s, 6.1, CH_3O), 4.10 (s, 2.0, CH_2), 7.33 (s, 0.77, OOH), 6.86, (AB, J = 10 Hz, 8.1, ArH).

3,3-Bis(*p*-anisyl)-1,2-dioxetane (DAD). This dioxetane was prepared by a previously reported method,[1b,20] whereby BHA was cyclized at 0 °C with sodium hydroxide in methanol containing 2 mol % Na_2EDTA. After quenching with cold water, the mixture was rapidly extracted with cold carbon tetrachloride. Attempts to crystallize DAD failed. When chromatographed on silica (with or without Na_2EDTA impregnation),[21] the dioxetane decomposed on the column. The NMR spectrum of the unpurified carbon tetrachloride solution showed, in addition to several other absorptions, the following absorptions: 5.68, (s, 2.0, CH_2), 3.77 (s, 6.0, CH_3O), 7.33 (AB, J = 9 Hz, Ar). The aromatic region contained other absorptions so that it was not possible to obtain a reliable integral.

The net amount of DAD in a carbon tetrachloride solution was determined by the difference between biamperometric iodometric peroxide analyses[22] before and after heating the sample at 42 °C for about 6 h. During the heating period DAD decomposed, while in an independent experiment, BHA was found to be stable. In one such analysis the initial and final peroxide concentrations were 8.04×10^{-3} M and 5.09×10^{-4} M, respectively. This corresponds to 6.3% BHA and 93.7% DAD in the peroxidic fraction.

Kinetic Methods. Rate measurements were made by the emission technique in the presence of DBA according to a previously reported method.[1bc,23] In one instance, the rate of disappearance of DAD was followed by monitoring the dioxetane ring protons in carbon tetrachloride solution at 37.5 °C by NMR.

Acknowledgment. We thank the U.S. Army Research Office for support of this research.

Registry No.—BHA, 67087-30-3; 1,1-bis(*p*-anisyl)ethanol, 31067-02-4; *p,p'*-dimethoxybenzophenone, 39193-85-6; 1,1-bis(*p*-anisyl)ethene, 4356-69-8; 1,3-dibromohydantoin, 3304-74-3.

References and Notes

(1) (a) W. H. Richardson, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, **94**, 1619 (1972); (b) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and H. E. O'Neal, *ibid.*, **96**, 7525 (1974); (c) W. H. Richardson, F. C. Montgomery, P. Slusser, and M. B. Yelvington, *ibid.*, **97**, 2819 (1975); (d) W. H. Richardson, J. H. Anderegg, M. E. Price, W. A. Tappen, and H. E. O'Neal, *J. Org. Chem.*, submitted for publication; (e) T. Wilson, D. E. Golan, M. S. Harris, and A. L. Baumstark, *J. Am. Chem. Soc.*, **98**, 1086 (1976); (f) J-Y. Koo and G. B. Schuster, *ibid.*, **99**, 5403 (1977).
(2) Cf. N. J. Turro, P. Lechtken, N. E. Shore, G. Schuster, H.-C. Steinmetzer, and A. Yekta, *Acc. Chem. Res.*, **7**, 97 (1974).
(3) T. Wilson, M. E. Landis, A. L. Baumstark, and P. D. Bartlett, *J. Am. Chem. Soc.*, **95**, 4765 (1973).
(4) A. L. Baumstark, T. Wilson, M. E. Landis, and P. D. Bartlett, *Tetrahedron Lett.*, 2397 (1976).
(5) (a) C. Walling and P. J. Wagner, *J. Am. Chem. Soc.*, **86**, 3368 (1964); (b) C. Walling, *Pure Appl. Chem.*, **15**, 69 (1967).
(6) (a) A. T. Bloomquist and A. J. Buselli, *J. Am. Chem. Soc.*, **73**, 3883 (1951);

(b) C. G. Swain, W. Stockmayer, and T. Clarke, *ibid.*, **72**, 5426 (1950); (c) W. H. Richardson and H. E. O'Neal, "Comprehensive Chemical Kinetics", Vol. 5, C. H. Bamford and C. F. H. Tipper, Ed., 1972, p 381.
(7) N. J. Turro, P. Lechtken, G. Schuster, J. Orell, and H.-C. Steinmetzer, *J. Am. Chem. Soc.*, **96**, 1627 (1974).
(8) Cf. D. M. Silver, *J. Am. Chem. Soc.*, **96**, 5659 (1974).
(9) R. Schmidt, H.-C. Steinmetzer, H.-D. Brauer, and H. Kelm, *J. Am. Chem. Soc.*, **98**, 8181 (1976).
(10) R. C. Neuman, Jr., *Acc. Chem. Res.*, **5**, 381 (1972).
(11) P. C. Beadle, D. M. Golden, K. D. King, and S. W. Benson, *J. Am. Chem. Soc.*, **94**, 2943 (1972).
(12) For example, the carbonyl π-bond energy in formaldehyde is estimated to be 71 kcal/mol, while the olefinic π-bond energy in ethylene is placed at 60 kcal/mol.[13]
(13) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).
(14) Cf. R. Huisgin, *Acc. Chem. Res.*, **10**, 199 (1977).
(15) In terms of the simplistic two-step process for TMD, $\Delta V^{\ddagger} \simeq 5$ cm^3/mol and $RT\delta \ln [1 + k_{-1}/k_2]/\delta P \simeq 11 \pm 3\text{–}5 = 6 \pm 3$ cm^3/mol under these conditions.
(16) Temperatures of kinetic measurements and melting points are corrected. The NMR spectra were measured in carbon tetrachloride with a Varian EM-390 spectrometer. The NMR data are reported on the δ scale in parts per million as (δ, coupling, area).
(17) O. Grummitt and D. Marsh, *J. Am. Chem. Soc.*, **70**, 1289 (1948).
(18) Cf. E. W. Garbisch, *J. Org. Chem.*, **26**, 4165 (1961).
(19) D. S. Tarbell and E. G. Lindstrom, *J. Am. Chem. Soc.*, **68**, 1930 (1946).
(20) Cf. K. R. Kopecky and C. Mumford, *Can. J. Chem.*, **47**, 709 (1969).
(21) Cf. M. A. Umbreit and E. H. White, *J. Org. Chem.*, **41**, 479 (1976).
(22) F. C. Montgomery, R. W. Larson, and W. H. Richardson, *Anal. Chem.*, **45**, 2258 (1973).
(23) W. H. Richardson, R. S. Smith, G. Snyder, B. Anderson, and G. L. Krantz, *J. Org. Chem.*, **37**, 3915 (1972).

Cyclic Peroxides by Intramolecular Peroxymercuration of Unsaturated Hydroperoxides

J. R. Nixon, M. A. Cudd, and N. A. Porter*[19]

P. M. Gross Chemical Laboratories, Duke University, Durham, North Carolina 27706

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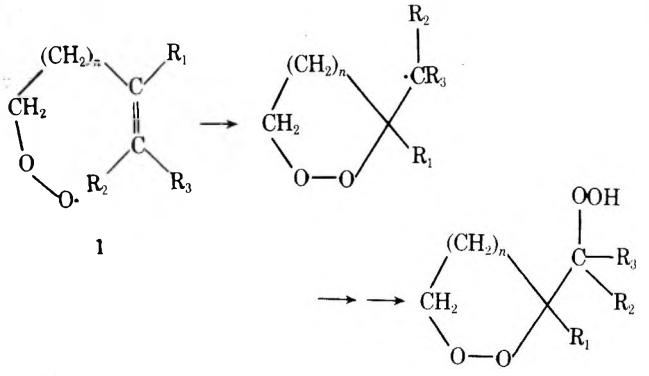
Unsaturated hydroperoxides undergo cyclization when treated with mercuric nitrate or trifluoroacetate. The β-mercurated cyclic peroxide products are isolated by high-pressure liquid chromatography as the alkyl mercuric bromides. Yields of analytically pure cyclic peroxides range from 60 to 90%. Treatment of the β-mercurated peroxides with molecular bromine gives the β-bromo cyclic peroxides in 80–90%, while reaction of the β-mercurated peroxides with borohydride leads to the parent cyclic peroxides in yields that range from 10 to 100%.

Cyclization reactions of unsaturated hydroperoxides have provided a synthetic approach for the preparation of a variety of cyclic peroxides. Thus, unsaturated hydroperoxides undergo cyclization,[1,2] presumably via a peroxy radical such as **1**, when subjected to autoxidation conditions. Cyclization of



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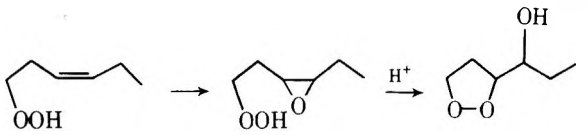
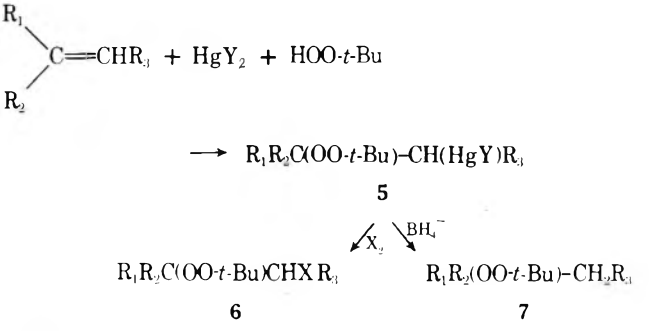
unsaturated hydroperoxides can also be induced by generating an electron deficient site from the olefin functionality. For example, the hydroperoxide **2** is converted[2] to a β-hydroxy cyclic peroxide **4** via the oxirane–hydroperoxide **3**. The dis-



2 **3** **4**

covery that compounds like **4** have interesting pharmacological properties[3] prompted us to explore other methods of generating cyclic peroxides from unsaturated hydroperoxides. In particular, we sought to extend the established method of intermolecular olefin peroxymercuration to our unsaturated hydroperoxides.

Peroxymercuration of olefins has been effectively employed as a method for the preparation of β-substituted peroxides.[4–6] A variety of substituted olefins react with mercuric salts such as the acetate, trifluoroacetate, or nitrate in the presence of hydroperoxides to yield the β-mercurated peroxide **5**. These

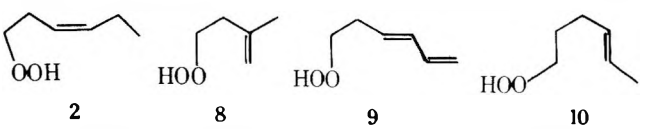


5 **6** **7**

compounds can be efficiently converted into the corresponding β-halogeno or β-hydrido peroxides by halogenodemercuration[4] or hydridodemercuration.[5] We report here that intramolecular peroxymercuration is affected by reacting hydroperoxides such as **2** with mercuric(II) compounds. The versatile β-mercurated cyclic peroxides so generated are a source of several new cyclic peroxide compounds.

Results and Discussion

The Synthesis of β-Mercuri Cyclic Peroxides. The unsaturated hydroperoxides **2**, **8**, **9**, and **10** react with 1 equiv of



2 **8** **9** **10**

$Hg(NO_3)_2 \cdot H_2O$ in dichloromethane at 22 °C. The products formed are isolated as the mercuric bromides, and the cyclic peroxides so generated are isolated and purified by high-

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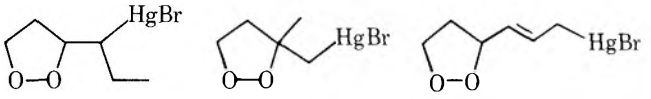
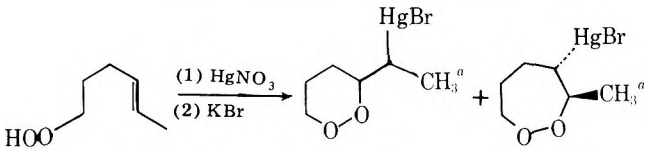
pressure liquid chromatography (LC). Yields of LC purified β-mercurated cyclic peroxides exceed 55% in all cases investigated. The structure assignment of the mercurated cyclic peroxides is supported by ^1H and ^{13}C NMR spectroscopy and elemental analysis.

2, **8**, and **9** are converted solely into the five-membered ring cyclic peroxides **11**, **12**, and **13** with none of the possible six-



11 **12** **13**

membered ring isomer being detected by LC or NMR. **10** yields a mixture of two cyclic peroxides, **14** and **15**, upon re-

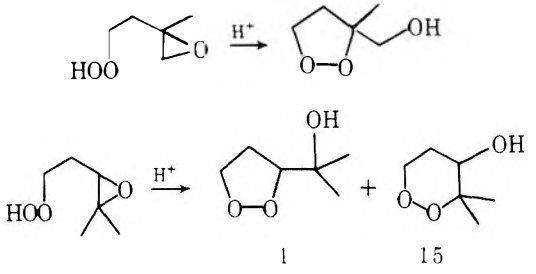


10 **14** **15**

action with $Hg(NO_3)_2 \cdot H_2O$. These isomers can be readily separated by LC, and the ratio of **14**/**15** as judged by NMR of the crude reaction mixture and by LC isolation is 3:1, the six-membered ring product being favored. The ^1H (and ^{13}C) NMR spectra of **14** and **15** are strikingly similar, each showing a 3 H multiplet from δ 3.8 to 4.6 (α to peroxide), a 1 H multiplet at δ 2.6 (α to HgBr), and a doublet at δ ~1.4 (α-CH_3^a). The structures of **14** and **15** can be unequivocally assigned, however, by double irradiation experiments. Thus, for **14** the CH_3^a methyl doublet (δ 1.42) is shown to be coupled with the hydrogen α to HgBr and for **15** the CH_3^a doublet (δ 1.30) is coupled to a proton α to the peroxide linkage.

Although there are two possible diastereomers of **14** and **15**, we find only one of the diastereomers for both **14** and **15** as products of the cyclization. Further evidence is presented in the discussion of bromodemercuration that also suggests that the initial cyclization led to only one diastereomer of **14** and **15** (presumably by trans addition).

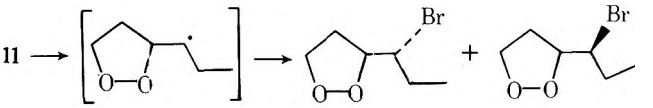
Comment should be made about the ring size preference for cyclization. The preferred formation of five-membered ring peroxides from **2**, **8**, and **9** is as expected from the rules of cyclization as described by Baldwin.[7,8] Baldwin suggests that the rules for opening three-membered rings to form cyclic structures seem to lie between those for tetrahedral and trigonal systems, generally exo modes being preferred. Thus, nucleophilic attack of the hydroperoxide on the mercurinium–olefin complex should lead to exo cyclization as is observed for **2**, **8**, and **9**. The rules for the Hg(II) cyclization of **10** are less definite, however, and our observation that both the 6-exo and 7-endo cyclization products are formed indicates that these cyclization modes are competitive. In this regard, we note that electronic effects may well modify any predictions for nucleophilic cyclization at electron deficient three-membered rings. As previously reported,[2] the 5-exo preference of acid-catalyzed oxirane–hydroperoxide cyclization may be altered by substituents on the oxirane. 6-Endo



product formation, in apparent violation of the rules, can dominate for suitably substituted oxiranes.

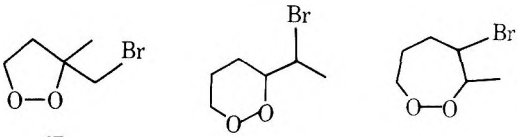
Bromo- and Hydridodemercuration. The four β-mercurated cyclic peroxides **11**, **12**, **14**, and **15** were subjected to reaction conditions for conversion to the β-bromo[4] cyclic peroxides. Thus, treatment of the β-mercurated cyclic peroxides with molecular bromine in methylene chloride leads to β-bromo cyclic peroxides (LC pure) in greater than 74% isolated yield. The β-bromo products derived from **11**, **14**, and **15** are mixtures of two diastereomers which can be separated in each case by LC. Whereas the peroxymercuration reaction leads, as expected, to only one diasteromer, the demercuration, which proceeds by a radical mechanism, leads to a 1:1 mixture of diastereomers.

The example of bromodemercuration of **11** is illustrative. **11** is assigned the threo structure since the peroxymercuration presumably occurs by trans addition.[9] Bromodemercuration of **11** in methylene chloride leads to **16**, a 1:1 mixture of the



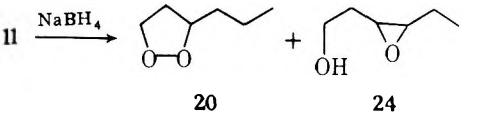
16a **16b**

threo and erythro β-bromo peroxides. These diastereomers can be separated by LC. When the bromodemercuration is carried out in pyridine, one stereoisomer is formed exclusively under our conditions. This is in accord with the earlier report[10] that bromodemercuration in pyridine proceeds by retention of configuration via a nonradical mechanism. The β-bromo peroxides **17**, **18**, and **19** could be prepared by bromodemercuration of **12**, **14**, and **15**, respectively.



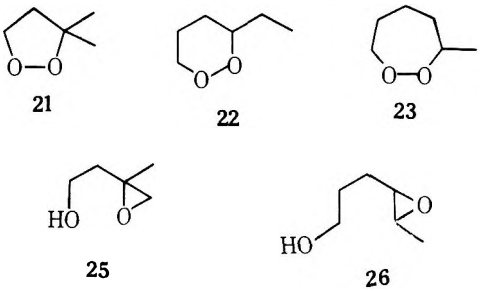
17 **18** **19**

Reaction of compounds **11**, **12**, **14**, and **15** with basic sodium borohydride leads to mixtures of cyclic peroxides and epoxy alcohols. When **11** is subjected to hydridodemercuration, for example, the peroxide **20** and the epoxy alcohol **24** are formed



20 **24**

in a 3:1 ratio. Similarly, the alkylmercuri bromides **12**, **14**, and **15** lead to the cyclic peroxides **21**–**23** and the epoxy alcohols **25** and **26**.



21 **22** **23**

25 **26**

The ratio of peroxide to epoxy alcohol formed is dramatically dependent on the structure of the starting β-mercurated peroxide, as is shown in Table I. The conditions of the hydridodemercuration are identical for every experiment, and the peroxide/epoxy alcohol ratio varies from 20:80 for **14** to 100:0 for **15**. Under the conditions of the reaction, **26**, the epoxy al-

Table I. Products Formed from Sodium Borohydride Reduction of β-Mercurated Cyclic Peroxides

reactant	peroxide (yield, %)	epoxy alcohol (yield, %)
11	**20** (75)	**24** (25)
12	**21** (90)	**25** (10)
14	**22** (<10)	**26** (90[a])
15	**23** (100)	**26** (0[a])

[a] Yield of epoxy alcohol plus tetrahydrofuran and tetrahydropyran derived from the epoxide under the hydridodemercuration conditions.

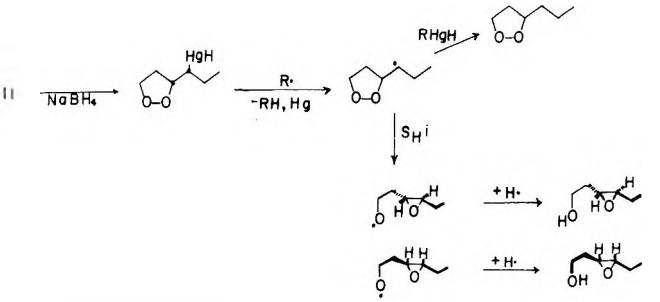
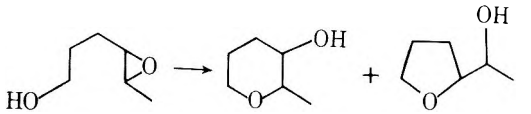


Figure 1. Reaction of **11**.

cohol derived from **14** and **15**, partially rearranges to tetrahydropyran and tetrahydrofuran products **27** and **28**. In fact, if one attempts to prepare **26** by *m*-chloroperbenzoic epoxidation of the olefin, only **27** and **28** are isolated. The



26 **27** **28**

epoxide **26** can be isolated, however, by neutral epoxidation of the olefin with H_2O_2/benzonitrile.[11,12]

The mechanism for sodium borohydride demercuration has been thoroughly investigated,[5,13,14] and alkyl radicals are established intermediates in the reaction. The intermediate alkyl radical can abstract hydrogen from a suitable donor (R–Hg–H has been suggested as an intermediate[14]) to yield the peroxide. In competition with hydrogen abstraction is intramolecular radical attack (S_Hi) on the peroxide linkage by the alkyl radical, a reaction that ultimately leads to epoxy alcohol products as shown for the reaction of **11** in Figure 1.

Two observations support the mechanism presented in Figure 1. The percentage yield of peroxide formed is dependent on the rate of addition of borohydride to the β-mercurated peroxide. Thus, rapid addition of the borohydride solution (see Experimental Section) leads reproducibly to the product mixtures shown in Table I. If borohydride is added slowly (10–15-min addition), the epoxy alcohol becomes a dominate product in all of the reactions. Thus, when borohydride is added slowly, the in situ concentration of R–Hg–H is low and the competing H atom transfer leading to peroxide product is slow compared to the S_Hi pathway leading to epoxy alcohol. Rapid addition of borohydride leads to a high in situ R–Hg–H concentration and favors the H atom transfer pathway that leads to peroxide products.

A second observation eliminates consideration of a mechanism involving nucleophilic attack of borohydride on the peroxide bond followed by alkoxide displacement of bromide. This mechanism requires that cis epoxide should be formed exclusively from **11**. In fact, both cis and trans epoxy alcohols **24** are formed with the trans product being the major product (an observation that is in accord with the radical mechanism). Finally, we should note that Bloodworth[5] has published a detailed description of the reaction of acyclic β-mercurated cyclic peroxides with borohydride, and he has presented strong evidence in support of the free-radical mechanism for this reaction.

The variation in peroxide product yield is striking. Borohydride reduction of **14** leads to under 10% of the peroxide under the best reaction conditions. **15**, on the other hand, leads only to cyclic peroxide under borohydride reaction. We suggest that the peroxide–epoxy alcohol yields shown in Table I may well reflect the ease of S_Hi radical attack on the cyclic peroxide bond. We shall defer a more detailed discussion of the implications of these observations vis-à-vis the stereochemistry of the S_Hi and S_H2 reactions until a more detailed kinetic investigation of this system is concluded.

Experimental Section

Proton NMR spectra were recorded using a Jeol JNM-MH-100 spectrometer. Carbon NMR spectra were recorded using a Jeol JNM-FX-60 Fourier transform spectrometer. A Waters Associates Model ALC-GPC-301 was used for high-performance liquid chromatographic separations. A Varian Aerograph Model 700 gas chromatograph was used for preparative gas chromatography.

Solvents. Burdick and Jackson Laboratories, Inc. (Muskegon, Mich.), "Distilled in Glass" chromatographic grade hexane, chloroform, and isopropyl alcohol were used for LC without further purification. Fisher Certified methylene chloride and pentane were also used without further purification for reactions and chromatography.

Syntheses. The unsaturated hydroperoxides **2**, **8**, and **10** were prepared as previously described by the method of Porter.[2] **2** and **8** were synthesized from commercially available alcohols,[15] while **10** was made from the alcohol prepared by the procedure of Crombie and Harper.[16] *trans*-Hexa-3,5-diene 1-hydroperoxide (**9**) was synthesized by the method of Mosher[17] from the precursor alcohol. *trans*-Hexa-3,5-dien-1-ol was prepared by $LiAlH_4$ reduction of methyl 3,5-hexadienoate. The procedure for conversion of the mesylate of *trans*-hexa-3,5-dien-1-ol to **9** is given below.

3,5-Hexadiene 1-Hydroperoxide (9). A 4.4-g (0.025-mol) amount of crude mesylate was combined with 3 mL of H_2O and 30 mL of methanol at ambient temperature with magnetic stirring. The stirred solution was cooled to 0–5 °C, followed by the slow dropwise addition of 163 g (0.10 mol) of 30% H_2O_2. Aqueous KOH (50%; 1.5 g, 0.013 mol) was slowly added. The system was flushed with N_2, brought to ambient temperature, and stirred for 16 h. After 16 h, the reaction vessel was immersed in an ice bath and taken to 0–5 °C. Aqueous KOH (50%; 9.89 g, 0.04 mol) was slowly added, after which time the solution was transferred to a separatory funnel and extracted with benzene. The aqueous phase was cooled to 0–5 °C, neutralized with concentrated HCl, and then extracted with benzene. The combined organic extractions were dried over Na_2SO_4, filtered, and stripped of solvent. The hydroperoxide product was purified by chromatography on a 1 × 35 cm silica gel column, 60–200 mesh, grade 950, at −10 °C. A hexane/ethyl ether eluent gradient was employed. Spectra of the purified product indicated the presence of a single hydroperoxide isomer (0.57 g, a 20% yield of chromatographed product from starting mesylate): ^1H NMR ($CDCl_3$) δ 2.2–2.4 (q, 2 H), 3.9–4.1 (t, 2 H), 4.9–5.1 (m, 2 H), 5.4–5.7 (m, 1 H), 5.9–6.4 (m, 2 H); J_{H_3,H_4} = 16 Hz (trans). The corresponding alcohol, 3,5-hexadienol, was submitted for C, H analysis. Anal. Calcd for $C_6H_{10}O_2$: C, 73.49; H, 10.29. Found: C, 73.34; H, 10.59.

Reaction of Unsaturated Hydroperoxides with Mercuric Nitrate. The synthesis of 3-(1-bromomercuripropyl)-1,2-dioxolane (**11**) from *cis*-hex-3-ene 1-hydroperoxide (**2**) is illustrative of the cyclization procedure and is described in detail below.

***threo*-3-(1-Bromomercuripropyl)-1,2-dioxolane (11).** Hydroperoxide **2** was purified by LC (8 ft × 3/8 in, Porasil A, 5% isopropyl alcohol in hexane, 6.0 mL min^{-1}) immediately prior to use.[2] The purified hydroperoxide (0.238 g, 2.05 mmol) was dissolved in methylene chloride (35 mL) and added dropwise under N_2 over a 15-min period to a stirred suspension of mercuric nitrate (0.738 g, 2.15 mmol) in methylene chloride (75 mL) at 22 °C. The suspension was stirred for 15 additional minutes after completion of the addition. H_2O (8 mL) was then added, followed by the addition of 0.256 g (2.25 mmol) of KBr. A white precipitate immediately appeared upon addition of the salt. This precipitate ultimately dissolved into the organic phase with continued stirring. The mixture was transferred to a separatory

Table II. Spectral Data for β-Mercuribromo Peroxides

compd	yield, % (LC pure)	^{1}H NMR, δ	^{13}C NMR, ppm
11[a]	65	1.0–1.3 (t, 3 H), 1.8–2.1 (p, 2 H), 2.2–3.1 (m, 3 H), 3.9–4.4 (m, 2 H), 4.6–4.9 (m, 1 H)	16.53, 27.00, 42.15, 65.66, 69.80, 83.49
12[a]	68	1.45 (s, 3 H), 2.2–2.5 (m, 4 H), 4.0–4.3 (m, 2 H)	27.61, 46.54, 48.49, 70.74, 85.52
14[a]	49	1.42 (d, 3 H), 1.5–2.1 (m, 4 H), 2.6–2.9 (q, H), 4.05–4.3 (m, 2 H), 4.4–4.7 (m, 1 H)	15.88, 23.92, 30.90, 52.75, 72.81, 85.03
15[a]	16	1.3 (d, 3 H), 1.9–2.4 (m, 4 H), 2.6–2.9 (m, 1 H), 3.9–4.8 (m, 4 H)	20.67, 29.20, 32.12, 64.81, 74.35, 83.04
13[a]	58	2.2–2.9 (m, 4 H), 4.05–4.2 (t, 2 H), 4.4–4.7 (q, 1 H), 5.2–6.1 (m, 2 H); vinyl–vinyl J = 16 Hz	36.79, 41.34, 70.17, 80.73, 126.70, 133.20

[a] Satisfactory combustion analytical data for C and H (±0.3%) were provided for these compounds (Ed.).

Table III. Spectral Data for β-Bromo Cyclic Peroxides

compd	yield, %	LC order of elution	^{1}H NMR, δ	^{13}C NMR, ppm
16b, (erythro)	40	first	1.1 (t, 3 H), 1.4–2.2 (m, 2 H), 2.5–2.8 (m, 2 H), 3.8–4.2 (m, 3 H), 4.4–4.6 (m, 1 H)	12.34, 27.13, 38.17, 57.83, 70.25, 81.79
16a (threo)[a]	40	last	1.05 (t, 3 H), 1.5–2.3 (m, 2 H), 2.5–2.9 (m, 2 H), 3.7–4.5 (m, 4 H)	11.53, 28.67, 40.64, 59.21, 70.01, 82.11
17[a]	67		1.5 (s, 3 H), 2.3–2.9 (m, 3 H), 3.5 (s, 2 H), 4.05–4.15 (m, 2 H)	22.09, 38.50, 44.35, 70.74, 83.90
18a (erythro)	37	first	1.65 (d, 3 H), 1.8–1.9 (m, 4 H), 3.8–4.1 (m, 4 H)	22.21, 22.94, 25.46, 47.96, 72.65, 84.59
18b (threo)	37	last	1.65 (d, 3 H), 1.7–1.95 (m, 4 H), 3.9–4.2 (m, 4 H)	21.60, 23.63, 25.42, 47.59, 72.69, 84.39
19a (trans)	38	first	1.3 (d, 3 H), 1.9 (m, 2 H), 2.2–2.3 (m, 2 H), 3.6–4.4 (m, 4 H)	19.13, 29.16, 35.86, 58.48, 75.17, 87.17
19b (cis)	38	last	1.2 (d, 3 H), 1.9 (m, 2 H), 2.2–2.3 (m, 2 H), 3.8–4.5 (m, 4 H)	17.91, 24.93, 32.04, 60.34, 74.15, 83.25

[a] See Table II, footnote *a*.

funnel. The organic phase was collected, washed once with water (10 mL), dried over anhydrous sodium sulfate, filtered, and stripped in vacuo to a clear and colorless oil.

The product was then purified by preparative LC (8 ft × 3/8 in, Porasil A, 9:9:2 hexane/chloroform/methylene chloride, 5.0 mL min^{-1}). The endoperoxide fraction was stripped to a clear and colorless liquid (65%).

The spectral and analytical data of the β-mercurated cyclic peroxides are presented in Table II.

Reaction of 3,5-Hexadiene 1-Hydroperoxide with Mercuric Nitrate. The procedure for cyclization of this diene was changed so that mercuric salt would never be in excess to the diene. **9** (114 mg, 1.00 mmol) was suspended in 30 mL of CH_2Cl_2 with magnetic stirring under positive N_2 pressure at ambient temperature. Solid $Hg(NO_3)\cdot H_2O$ (359 mg, 1.00 mequiv) was added with stirring as a fine powder under CH_2Cl_2. After some 30 min of stirring, 10 mL of H_2O was added followed at once by 119.0 mg (1.00 mmol) of KBr. After vigorous stirring, the mixture was filtered into a separatory funnel and the phases were separated. The water layer was washed with CH_2Cl_2 (5 mL × 2). All CH_2Cl_2 phases were combined over Na_2SO_4, dried, filtered, and stripped of solvent. The product, a white solid, was purified by column chromatography; a 1 × 35 cm silica gel column, 60–200 mesh, grade 950, at 10 °C was employed. Elution was affected with a hexane/CH_2Cl_2 solvent gradient. Spectra of the purified product revealed the presence of a single endoperoxide mercuric bromide, 228 mg (58%), from starting hydroperoxide.

Bromodemercuration. The typical procedure for bromodemercuration is presented below for 3-(1-bromomercuripropyl)-1,2-dioxolane (**11**).

3-(1-Bromopropyl)-1,2-dioxolane (16). The endoperoxide **11** (0.135 g, 0.34 mmol) was dissolved in 5 mL of methylene chloride and then added dropwise over a 15-min period to a magnetically stirred solution of Br_2 (0.164 g, 1.0 mmol) in methylene chloride (5 mL) under N_2 in subdued lighting. The solvent and excess bromine were removed in vacuo after 4 h of stirring. The resulting residue was extracted with petroleum ether (30 mL) and dried over anhydrous sodium sulfate. The solution was filtered and stripped to a pale-yellow oil. The product was purified by preparative LC (8 ft × 38 in, Porasil A, 3% isopropyl alcohol in hexane, 6.0 mL min^{-1}). Two stereoisomers (threo and erythro) of equal yield were collected. Anal. (for the mixture of threo and erythro isomers) Calcd for $C_6H_{11}O_2Br$: C, 36.96; H, 5.65. Found: C, 36.84; H, 5.71.

The assignment of the more polar diastereomer as the stereoisomer **16a** (threo configuration) was based on the results of bromodemercuration performed in pyridine as described later.

The spectral data for the β-bromo peroxides are presented in Table III.

Bromodemercuration in Pyridine. The preferential formation of the bromo endoperoxides with retained configuration was performed by the procedure described here in detail for endoperoxide **14**.

Reaction of *erythro*-3-(1-Bromomercuriethyl)-1,2-dioxane (14) with Bromine in Pyridine. 14 (0.163 g, 4.12 mmol) was dissolved in 12 mL of pyridine. Br_2 (0.098 g, 6.15 mmol) was added to pyridine (2.5 mL), which was then added dropwise over a 5-min period to the magnetically stirred endoperoxide solution. The mixture was stirred in subdued lighting for 20 h. Diethyl ether (150 mL) was then added to the reaction mixture. The resulting solution was washed twice with a total of 100 mL of 10% HCl. The acid washes were extracted once with 100 mL of diethyl ether. The ether fractions were combined and washed once more with 25 mL of 10% HCl followed by a 25-mL wash with a saturated sodium bicarbonate solution. The ether solution was then dried over anhydrous sodium sulfate. The dried ether was filtered and stripped to a clear, colorless viscous oil (0.07 g, 88% crude). The proton NMR spectrum of the product was identical without exception with that of the less polar diastereomer, the erythro isomer **18a**. The NMR spectrum did not indicate the presence of any of stereoisomeric threo compound **18b**.

Hydridodemercuration. The typical procedure for hydridodemercuration is presented below in detail for 3-(1-bromomercuripropyl)-1,2-dioxolane (**11**).

3-Propyl-1,2-dioxolane (20). The endoperoxide **11** (0.704 g, 1.78 mmol) was dissolved in 6 mL of methylene chloride and 15 mL of H_2O. Sodium borohydride (55 mg, 1.46 mmol) was dissolved in 5.5 mL of 2 N NaOH and transferred to a 10-mL syringe which was then cooled in an ice bath. The endoperoxide solution was cooled to −2 °C and stirred vigorously under a nitrogen atmosphere. The basic borohydride solution was added to the endoperoxide solution over a 15-s

Table IV. NMR Spectral Data for Cyclic Peroxides

compd	^{1}H, δ	^{13}C, ppm
20	0.95 (t, 3 H), 1.3–1.5 (m, 4 H), 2.0–2.3 (m, 1 H), 2.5–2.8 (m, 1 H), 4.0–4.2 (m, 3 H)	14.04, 19.70, 35.73, 40.77, 69.66, 80.36
21[a]	1.3 (s, 6 H), 2.3 (t, 2 H), 4.0 (5, 2 H)	25.83, 47.02, 70.09, 82.11
22	0.95 (t, 3 H), 1.4–2.0 (m, 4 H), 3.9–4.2 (m, 2 H)	
23[a]	1.1 (d, 3 H), 1.5–1.9 (m, 6 H), 3.8–4.2 (m, 3 H)	19.41, 22.50, 30.62, 37.52, 75.29, 80.57

[a] See Table II, footnote *a*.

period followed by stirring for an additional 4 min. Methylene chloride (75 mL) was then added, and the resulting mixture was immediately filtered into a separatory funnel. The organic layer was collected, washed once with H_2O (15 mL), and dried over anhydrous sodium sulfate. The dried solution was then filtered and the solvent removed on a rotary evaporator with a bath temperature of 0 °C. The recovered liquid, clear and colorless, was chromatographed in a jacketed column at −20 °C on 15 g of silica gel (pentane/methylene chloride), yield 0.111 g (55%).[18]

The spectral data for the cyclic peroxides are presented in Table IV.

Registry No.—**2,** 60653-71-6; **8,** 55175-91-2; **9,** 67393-81-1; **10,** 60653-70-5; **11,** 67393-65-1; **12,** 67393-66-2; **13,** 67393-82-2; **14,** 67393-67-3; **15,** 67393-68-4; **16a,** 67393-75-3; **16b,** 67393-74-2; **17,** 67393-76-4; **18a,** 67393-77-5; **18b,** 67393-78-6; **19a,** 67393-79-7; **19b,** 67393-80-0; **20,** 67393-69-5; **21,** 67393-70-8; **22,** 67393-71-9; **23,** 67393-72-0; *cis*-**24,** 67393-83-3; *trans*-**24,** 67393-84-4; **25,** 59954-67-5; **26,** 67393-73-1; *trans*-hexa-3,5-dien-1-ol mesylate, 67393-85-5.

References and Notes

(1) N. A. Porter and M. O. Funk, *J. Org. Chem.*, **40,** 3613 (1975).
(2) N. A. Porter, M. O. Funk, D. W. Gilmore, R. Isaac, and J. R. Nixon, *J. Am. Chem. Soc.*, **98,** 6000 (1976).
(3) D. B. Menzel, J. H. Roycroft, J. R. Nixon, S. R. Isaac, and N. A. Porter, *Res. Commun. Chem. Pathol. and Pharmacol.*, **15,** 767 (1976).
(4) A. J. Bloodworth and I. M. Griffin, *J. Chem. Soc., Perkin Trans. 1,* 688 (1974), and references cited therein.
(5) A. J. Bloodworth and G. S. Bylina, *J. Chem. Soc., Perkin Trans. 1,* 2433 (1972).
(6) A. J. Bloodworth and M. E. Loveitt, *J. Chem. Soc., Chem. Commun.*, 94 (1976).
(7) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
(8) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 738 (1976).
(9) M. C. Cabaleiro, A. D. Ayala, and M. D. Johnson, *J. Chem. Soc., Perkin Trans. 2,* 1207 (1973).
(10) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials", McGraw-Hill, New York, N.Y., 1968, p 92.
(11) We thank Dr. M. O. Funk for carrying out these experiments.
(12) G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, **26,** 659 (1961).
(13) R. P. Quirk and R. E. Lea, *J. Am. Chem. Soc.*, **98,** 5973 (1976).
(14) C. C. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, **96,** 870 (1974).
(15) Aldrich Chemical Co.
(16) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707 (1950).
(17) H. R. Williams and H. S. Mosher, *J. Am. Chem. Soc.*, **76,** 2984 (1954).
(18) Although the alkylmercuri peroxides gave good C, H analyses, some of the bromo peroxides and hydrido peroxides have repeatedly exploded upon attempted C, H analysis.
(19) NIH Career Development Awardee, 1977–1982.

Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction. 4. Experimental and Theoretical Examination of the Reaction of Acrylonitrile with 1-(Phenylthio)-2-methoxy-1,3-butadiene. Determination of the Conformations of the Four Cyclohexene Adducts by ^{1}H NMR Spectroscopy

Theodore Cohen,*[1a] Robert J. Ruffner,[1a] David W. Shull,[1a] Wlodzimierz M. Daniewski,[1a] Raphael M. Ottenbrite,[1b] and Peter V. Alston*[1c]

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284, and Chemicals, Dyes, and Pigments Department, Jackson Laboratory, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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The importance of secondary orbital interactions in controlling regiochemistry in the Diels–Alder reaction has been assessed by determining the composition of the adduct mixture formed by the reaction of (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene with acrylonitrile. All four possible regio- and stereoisomers were separated by high-pressure liquid chromatography and their structures and approximate conformational preferences were determined by 250-MHz proton magnetic resonance spectroscopy. It was also determined that the product composition remains invariant with time under the reaction conditions. As predicted by frontier molecular orbital theory, the ratio of ortho (phenylthio and cyano groups) to meta regioisomers is greater (three to four times) in the (cis) products of endo addition than in the (trans) products of exo addition, thus indicating that secondary orbital interactions, which can only occur in the transition states for endo addition, play a substantial role in controlling regiochemistry.

The origin of the regioselectivity, which is so crucial to the magnificent synthetic utility of the Diels–Alder reaction, has intrigued organic chemists since the discovery of the reaction by Diels and Alder.[2] Of the many theories which have been proposed to explain this regioselectivity, the frontier molecular orbital (FMO) approach has been the most successful. In the application of FMO theory, several investigators[3–6] have used just the primary orbital interactions to predict the preferred regioisomer; however, we have observed numerous cases in which this approach failed to predict the regioselectivity that was observed.[7] In these cases the preferred regioisomer can be predicted by including secondary orbital interactions[8] in the theory.

An obvious test of the influence of secondary orbital in-

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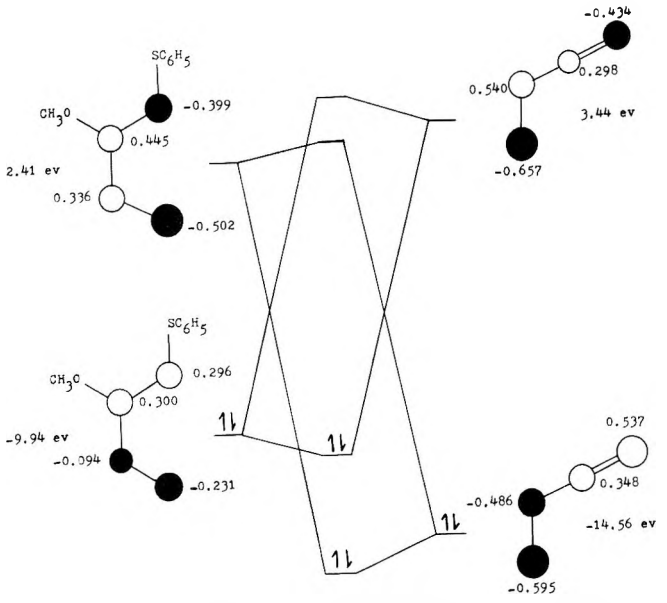


Figure 1. CNDO/2 frontier molecular orbital interaction diagram for the Diels–Alder reaction between 1-(phenylthio)-2-methoxy-1,3-butadiene and acrylonitrile.

teractions would involve determining the relationship of stereoselectivity to regioselectivity in a Diels–Alder reaction which produces all four possible isomers and in which a different regioselectivity is predicted for the exo and endo transition states. Before the advent of high-performance chromatographic techniques and nuclear magnetic resonance instruments utilizing superconducting magnets, this would have been a formidable if not an impossible task. Indeed, even reported yields for one or two major products frequently have been of questionable validity due to the extensive purification procedures that have been required or to the undetermined purities of these products.[9] In the words of Inukai and Kojima,[10] "many of the reported isomer ratios are suspect or at best only semiquantitative." Furthermore, experiments designed to determine whether the products decompose to unknown materials or revert to reactants (therefore resulting in products of thermodynamic rather than kinetic control) have only rarely been performed.

Because none of the published data of which we are aware are appropriate for such a test of secondary orbital interactions,[13] we initiated a study of the reaction of the readily obtainable (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene (**1**)[11,12] with acrylonitrile. We have previously shown[7c] that secondary orbital interactions are expected to have a significant effect on the regiochemistry of addition of this diene to methyl vinyl ketone, and as predicted the product is exclusively that of endo addition (cis) with the phenylthio group vicinally oriented with respect to the acetyl group.[11] In order to provide for weaker secondary orbital interactions in the transition state and thus to promote the formation of the other possible isomeric products, the weaker dienophile acrylonitrile was chosen.

Results and Discussion

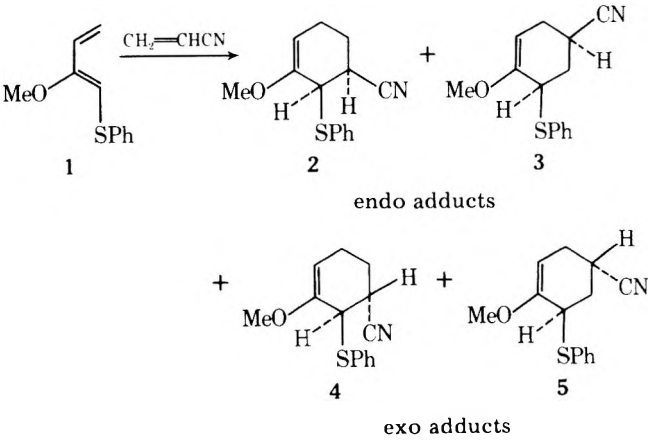
Theoretical Expectations. CNDO/2 calculations[14] predict that the energy separation between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile is considerably smaller than the energy separation between the LUMO of the diene and the HOMO of the dienophile. Thus, the principal stabilization of the transition state will result from the former MO interaction, and the latter is usually neglected in such cases.[3-7,15] However, because of the large difference in the magnitudes of the primary orbital coefficients of the diene LUMO, the latter MO interaction does significantly affect the regioselectivity and can not be neglected in this case (Figure 1).

Using CNDO/2 frontier molecular orbital energies and coefficients, the stabilization energies for the two regioisomeric transition states have been calculated from eq 1 in both the endo and the exo modes of addition of the dienophile to the diene.[16,17] In this equation the γ's are the atomic orbital

$$\Delta E = \frac{2\left(\sum_{rs} c_r c_s \gamma_{rs}\right)^2}{E_r^{\mathrm{HOMO}} - E_s^{\mathrm{LUMO}}} + \frac{2\left(\sum_{rs} c_r c_s \gamma_{rs}\right)^2}{E_s^{\mathrm{HOMO}} - E_r^{\mathrm{LUMO}}} \quad (1)$$

orbital transition state resonance integrals for the p_z carbon atomic orbitals. The c_r's and c_s's are the coefficients of the atomic orbitals which have a bonding interaction in the transition state. The E_r's and E_s's are the energies of the interacting molecular orbitals. The resonance integrals for the primary orbital interactions and the secondary orbital interactions were assigned values of 7 and 2.8 eV, respectively. The value of 7 eV for the resonance integral of the primary orbital interactions was derived from the concerted transition state that ab initio calculations[17] predicted for the cycloaddition of ethylene to butadiene along with consideration for the narrowing of the FMO energy separation in the transition state and a larger than experimental CNDO/2 energy separation between the interacting MO's. The resonance integral for the secondary orbital interactions was assigned a smaller value because the geometry of the transition state favors the overlap between the primary orbitals at the expense of the secondary orbital overlap. These values have been used with CNDO/2 FMO energies and coefficients to predict the preferred regioisomer in approximately 100 examples of the Diels–Alder reaction.[7c]

In the endo addition, which includes both the primary and secondary orbital interactions, the energy difference between the regioisomeric transition states was 5.4 kcal/mol in favor of the ortho regioisomer (**2**) (in which the phenylthio and nitrile groups are on adjacent carbon atoms). In the exo addition, which has no secondary orbital interactions, the ortho regioisomer (**4**) was favored again, but only by 0.6 kcal/mol. Consequently, our theory predicts less regioselectivity in the exo addition than in the endo addition.[18] If only the primary orbital interactions are considered, the same regioselectivity is predicted for both stereochemical modes of addition.



Experimental Findings. Early attempts to perform the reaction of 1-(phenylthio)-2-methoxy-1,3-butadiene (**1**) with acrylonitrile, either neat or in methanol at 125 °C, in the presence of 5 mol % of the free radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (to prevent polymerization of the reactants), resulted in yields in the vicinity of 25%. One reason for the low yields is that the *Z* diene

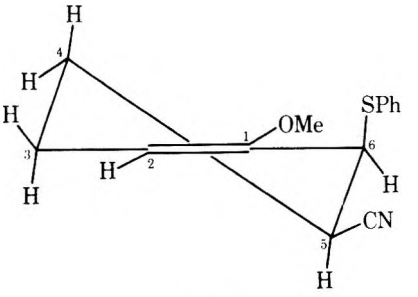
isomerizes fairly readily to the more stable *E* diene.[12] A sample of the latter was prepared by heating the *Z* isomer in methylene chloride and removing the small quantity of unisomerized *Z* diene as its Diels–Alder adduct with methyl vinyl ketone; as expected, the reaction of the *E* isomer with acrylonitrile was far slower than that of the *Z* isomer and the reaction yields a mixture which includes only a small proportion of Diels–Alder adducts. The rate of this isomerization was reduced and the yield of purified (see below) adducts thus increased to 39–45% by the inclusion of diisopropylethylamine in the reaction medium; the reaction was performed at 110 °C for 44 h. The rate of isomerization was further reduced and the yield of adducts increased to 69% when, in addition, a silanized reaction vessel was used.

The adducts could be separated from unreacted diene by gravity chromatography on silica gel using benzene as eluent. Gas chromatography of the adduct mixture was not capable of separating all four isomers, but it appeared to reveal two isomers in a ratio of ca. 2:1; lesser components were apparently present, but the areas of the minor peaks (and to some extent of the major ones as well) were found to depend on the GLC conditions due to a minor degree of decomposition in the injection port. It thus became evident that GLC could not be used to completely analyze the reaction mixture. The two major products (but not the minor ones) could be isolated in pure form by gravity chromatography on silica using 1:5 ethyl acetate–hexane as eluent. The spectroscopic analyses of these two isomers were performed on samples obtained by this procedure.

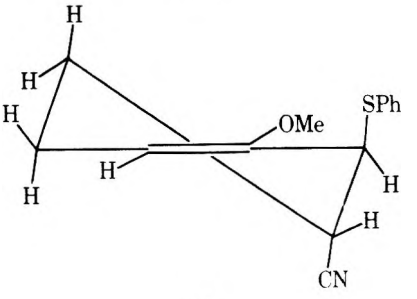
The quantitative determination of all four adducts and isolation of the two minor isomers required the use of high-pressure liquid chromatography. All four adducts exhibited correct elemental composition data,[19] and all had 15-eV mass spectra which exhibited a parent peak of *m/e* 245, a base peak in which the elements of thiophenol had been lost, and other expected fragments (see Experimental Section). Unequivocal structural assignments were made on the basis of the 250-mHz ^{1}H NMR spectra in deuteriochloroform.

The major isomer exhibited peaks at δ 1.934–2.259 (m, $H_{3a'}$, $H_{3e'}$, H_{4a}, and H_{4e}, 4 H), 2.971 (m, H_5, 1 H), 3.517 (d, $J_{5,6}$ = 4.6 Hz, H_6, 1 H), 3.551 (s, CH_3, 3 H), 4.621 (m, four peaks with shoulders, H_2, 1 H), and 7.23–7.77 (m, aromatic H, 5 H). Upon irradiation at the frequency of H_6, the peak for H_5 at δ 2.971 narrowed slightly and changed its splitting pattern to a doublet of doublets ($J_{4,5\ trans}$ = 9.6 Hz and $J_{4,5\ cis}$ = 3.9 Hz) and the peak for H_2 at δ 4.621 very slightly narrowed and changed shape, indicating slight allylic coupling between H_2 and H_6. The chemical shift and especially the coupling pattern of H_6 clearly establish that it is on a carbon atom adjacent to that bearing the methoxyl group, while the decoupling experiment establishes that the nitrile and phenylthio functions are on adjacent carbon atoms. The stereochemistry is defined as cis (structure **2**) by the coupling constants $J_{5,6}$ and $J_{4,5\ trans}$.[20,21] The spectrum is consistent with that[11] of the sole adduct (ortho, cis) of the same diene with methyl vinyl ketone; as expected, the acetyl group, being considerably bulkier than the nitrile function, assumes a more nearly completely, probably totally, equatorial conformation as indicated by the value of 13 Hz for $J_{4,5\ trans}$ and 2.5 Hz for $J_{4,5\ cis}$.[24,25] Assuming a value of 13.0[24] and 4.9 Hz,[21] respectively, for $J_{4a,5a}$ and $J_{4e,5e}$, the value of $J_{4,5\ trans}$ (9.6 Hz) for **2** indicates that this adduct exists to the extent of ca. 58% in conformation **2A**.

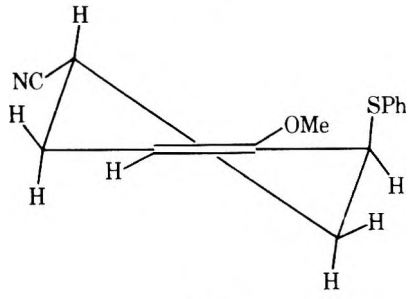
The second most prevalent adduct showed δ 1.828 (broad m, H_{4a}, 1 H), 2.120–2.235 (m, $H_{3e'}$ or $H_{3a'}$ and H_{4e}, 2 H), 2.373 (m, $\sum J$ = 33.5 Hz, $H_{3e'}$ or $H_{3a'}$, 1 H), 2.935 (m, H_5, 1 H), 3.565 (s, CH_3, 3 H), 3.750 (m, width at half-height = 5 Hz, H_6, 1 H), 4.792 (t, width at half-height = 10 Hz, H_2, 1 H), and 7.15–7.43 (m, aromatic H, 5 H). Upon irradiation of the sample at the frequency of H_6, the H_5 peak at δ 2.935 perceptibly narrowed



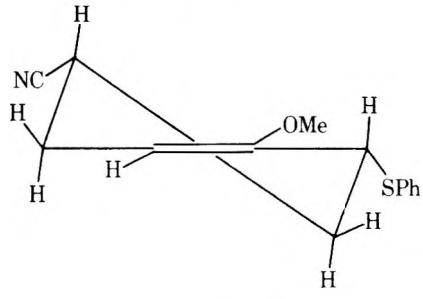
2A



4A



5A



3A

and appeared as a triplet ($J_{4,5\ cis} \simeq J_{4,5} \simeq$ 3.5 Hz). None of the other peaks changed shape noticeably during this decoupling experiment. Upon irradiation at the frequency of H_5, the peak at δ 3.750 narrowed somewhat and changed shape. The chemical shift of H_6 and the fact that irradiation at its frequency did not noticeably perturb the peak of the vinyl hydrogen place the phenylthio group on the allylic carbon atom (C_6) adjacent to that bearing the methoxy group. The decoupling experiments place the nitrile group on the other adjacent carbon atom (C_5). The narrow peak width due to H_6 and the small value of $J_{4,5}$ (3.5 Hz) clearly establish the conformation very predominantly as **4A** in which the substituents are axial and quasiaxial.

One of the two very minor products exhibited δ 2.074 (ddd, $J_{5,5}$ = 13.4 Hz, $J_{4,5\ trans}$ = 11.7 Hz, $J_{5,6\ cis}$ = 4.2 Hz, H_{5a}, 1 H), 2.185 (m, H_{5e}, 1 H), 2.350 (ddd, $J_{3,3}$ = 16.7 Hz, $J_{3,4\ trans}$ = 10.7 Hz, $J_{2,3a'}$ = 2.9 Hz, $H_{3a'}$, 1 H), 2.534 (d of t, $J_{3,3}$ = 16.7 Hz, $J_{3,4\ cis}$ = 5.4 Hz, $J_{2,3e'}$ = 5.4 Hz, $H_{3e'}$, 1 H), 3.112 (12 line m, $J_{4,5\ trans}$ = 11.7 Hz, $J_{3,4\ trans}$ = 10.7 Hz, $J_{3,4\ cis}$ = 5.4 Hz, $J_{4,5\ cis}$ = 3.4 Hz, H_4, 1 H), 3.533 (s, CH_3, 3 H), 3.655 (dd, $J_{5,6\ cis} \simeq J_{5,6\ trans} \simeq$ 4Hz, H_6, 1 H), 4.630 (dd, $J_{2,3e'}$ = 5.4 Hz, $J_{2,3a'}$ = 2.9

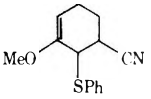
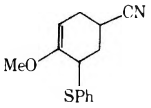
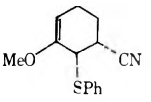
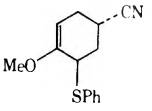
Hz, H_2, 1 H), 7.260 (m, meta and para aromatic H, 3 H), and 7.420 (dd, ortho aromatic, 2 H). The similarity of the chemical shift of H_6 to those of the corresponding protons of **2** and **4** makes it appear very likely that this proton is on an allylic carbon atom which is attached to both the phenylthio group and the vinyl carbon atom bearing the methoxyl group. The chemical shifts of the protons on C_3 and, particularly, the nature of their coupling to H_2, to H_4, and to each other clearly indicate that C_3 is the other, and unsubstituted, allylic carbon atom and that it is adjacent to the carbon atom bearing the nitrile function. The large magnitude of the two vicinal couplings of H_4 requires that the latter be predominantly axial. Finally, the coupling pattern of the protons on C_5 indicates that it is unsubstituted and flanked by one predominantly axial and one predominantly equatorial vicinal proton. Thus, the structure is clearly **5** and, using the assumptions discussed for **2** above, approximately 84% of this material is in conformation **5A.**

The second very minor product showed δ 1.963 (ddd, $J_{5,5}$ = 13.2 Hz, $J_{4,5\ \mathrm{trans}}$ = 12.1 Hz, $J_{5,6\ \mathrm{trans}}$ = 10.4 Hz, H_{5a}, 1 H), 2.233–2.459 (m, $H_{3a'}$, $H_{3e'}$, and H_{5e}, 3 H), 2.559 (15 line multiplet, $J_{4,5\ \mathrm{trans}}$ = 12.1 Hz, $J_{3,4\ \mathrm{trans}}$ = 10.5 Hz, $J_{3,4\ \mathrm{cis}}$ = 4.8 Hz, $J_{4,5\ \mathrm{cis}}$ = 3.1 Hz, H_4, 1 H), 3.550 (s, CH_3, 3 H), 3.664 (broad m, H_6, 1 H), 4.643 (dd, $J_{2,3e'}$ = 5.1 Hz, $J_{2,3a'}$ = 2.1 Hz, H_2, 1 H), 7.244 (m, meta and para aromatic H, 3 H), 7.400 (dd, ortho aromatic H, 2 H). Upon irradiation at the frequency of H_{5a}, the multiplet at δ 2.233–2.459 narrowed and exhibited less peaks, the 15 line multiplet at δ 2.559 for the proton α to the nitrile function narrowed and simplified to an 8 line multiplet, and the broad peak for the proton on the sulfur-bearing carbon atom at δ 3.664 narrowed considerably. The structure is thus clearly **3** and, according to the value (12.1 Hz) of $J_{4,5\ \mathrm{trans}}$, it is approximately 89% in conformation **3A.**

In order to ascertain the yields of the four adducts and to provide evidence concerning the stability of the products to the reaction conditions, a mixture of diene, excess acrylonitrile, diisopropylethylamine, and a small quantity of the radical inhibitor was divided into several silanized ampules which were sealed in an argon atmosphere and heated at 110 °C for lengths of time from 1 to 40 h. The percent conversion of diene to adducts in an ampule could be determined either by weighing the unreacted diene and the adducts after separation of the two fractions on preparative thin-layer chromatography (TLC) or by estimating the composition of the diene–adduct mixture by analytical LC using calibrated response factors. In this way, it was determined that at the end of 1 and 40 h, respectively, 36 and 68% of the diene had been converted to adducts. The incomplete conversion to adducts in the 40-h run was undoubtedly due to isomerization of the *Z* diene to the far less reactive *E* isomer, a process which is competitive with the addition. The recovered diene (32% of that charged) from the 40-h ampule was almost certainly (see above) of the *E* configuration. Since the 1-h reaction had already proceeded to a moderate extent, only the 1-h and 40-h samples were analyzed in the most rigorous fashion on the high-pressure analytical liquid chromatographic assembly in order to determine the relative yields of the four adducts both early and at the end of the reaction. In addition, the contents of each ampule were submitted to preparative thin-layer chromatography to separate the adducts, diene, and radical scavenger; the dienes and adduct mixtures were weighed, and the latter from each of the 2-, 4-, 8-, and 40-h ampules was separated into its four components in the preparative LC assembly. The percent compositions in the 1-h and 40-h runs, as determined by integration of the liquid chromatograms, and the compositions determined by isolation (upon separation by preparative LC) of the combined samples from the 2-, 4-, 8-, and 40-h experiments are compared in Table I.

The differences between the compositions at the end of 1 and 40 h are considered to be within experimental error, and the adducts therefore appear to be stable to the reaction conditions and almost certainly are the kinetic products. This conclusion is also consistent with the finding, made before the LC technique was developed, that the major product (**2**), when treated under the reaction conditions for 46 h, undergoes no isomerization to the next most prevalent adduct, **4**, its exo counterpart. Confidence in the reliability of the data is enhanced by the gratifying correspondence between the product compositions as determined by integration of the detector responses and those obtained upon isolation.

Table I. Adduct Composition

no.	adduct	% composition 1 h	40 h	isolated
2		61	64	62
3		5.6	5.7	5.4
4		27	22	25
5		6.8	8.1	6.8

The predictions made assuming a role for secondary orbital interactions in the control of regiochemistry are seen to be qualitatively valid. The ratio of ortho to meta product (**2/3**) generated in the endo transition state is three to four times greater than the same regioisomeric ratio (**4/5**) generated in the exo transition state. As indicated above, these ratios should be approximately equal in the absence of secondary orbital interactions: yield ratio of endo adducts **2/3** = 11; yield ratio of exo adducts **4/5** = 3.4.

With regard to the preferred conformations of these adducts, it should be recognized that the percentages given are only fairly crude approximations of the true values because coupling constants vary with changes in dihedral angles, which may be substitutent sensitive. Nevertheless, there can be little doubt that the equilibria lie far in favor of **3A, 4A,** and **5A** and that in the case of **2,** there is no great preference for **2A** or its ring inverted conformational isomer. Conformation **3A** is, of course, simple to rationalize since the substituents are oriented in an equatorial and quasiequatorial fashion. Although the A[29] value of phenylthio is presumably far larger than that of cyano[27] and the corresponding value (E_4)[29] for the latter group in the **4** position of a cyclohexene is about 0,[25c,26c,30] the phenylthio group assumes the quasiaxial orientation partially in **2** and substantially in **5;** however, it is clear that the preference of substituents for the quasiequatorial position on a cyclohexene ring is far less than that for the equatorial position on a cyclohexane ring,[20] and the interactions between the phenylthio group and the other substituents on the rings in all of the half-chair conformations are difficult to evaluate. Many of the same factors are probably responsible for the very predominant axial–quasiaxial conformation of **4A** with the added and probably decisive factor of a strong vicinal repulsion that must occur between the cyano and phenylthio groups when they are equatorial–quasiequatorial.

Experimental Section

Analytical Procedure. The analytical high-pressure liquid chromatography was performed on a Dupont Model 830 instrument

utilizing ultraviolet (254 nm) detection. Two 25 cm × 4 mm columns, in series, packed with Partisil 10 were used; the theoretical plate count was about 9000. All four adducts could be estimated quantitatively on a very small drop of the crude concentrated reaction mixture when a solution of 15% ethyl acetate–85% hexane was used as eluent at a flow rate of 1.5 mL/min at 600 psi.

The preparative LC was performed on a Waters apparatus using refractive index detection and four 30 cm × 8 mm columns, in series, packed with Lichrosorb 10; the theoretical plate count was ca. 15 000. Preparative TLC using benzene for development was used to separate the adducts from other components (as above). Individual injections were 60–70 mg of adduct, and the eluent was the same as above; the flow rate was 6 mL/min at 1850 psi.

^{1}H NMR spectra were measured on a custom built 250-mHz instrument maintained by NIH Grant R.R.00292-6 to the Mellon-Pitt-Carnegie (M.P.C.) Corp. The spectrometer utilizes a supercooled solanoid and is interfaced with a Sigma 5 computer, which allows printouts of the peak positions accurate to at least ±0.16 Hz. A number (usually between 10 and 50) of fast scans (0.6–0.8 s sweep time) were accumulated for each spectrum, and the signal to noise ratio was enhanced by the correlation technique.[31] On this high-field instrument, most of the coupling constants of interest (all of those reported) could be obtained by first-order analyses.

Diels–Alder Reactions. The inside surfaces of glass reaction vessels were soaked overnight with aqueous ammonia and rinsed consecutively with water, acetone, and hexane, and the containers were allowed to remain filled with chlorotrimethylsilane containing a little Silyl-8 (a GLC column conditioner sold by Pierce Chemical Co.) for 3 days. The vessel was then rinsed with aqueous ammonia, triethylamine, and hexane and dried in an oven.

(A) A solution containing 0.466 g (2.43 mmol) of (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene,[11,12] 0.8 g (15 mmol) of acrylonitrile, 44 mg (0.12 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (Aldrich Chemical Co.), and 940 mg (7.3 mmol) of diisopropylethylamine was heated in a glass pressure reactor (Fisher-Porter tube) immersed in a bath maintained at 110 °C for 44 h. The product mixture was concentrated and chromatographed on silica gel using benzene as eluent, whereby a 69% yield of an adduct mixture was isolated. This mixture, according to its NMR spectrum (see Results and Discussion), consisted approximately of a 2:1 mixture of isomers. The mixture was separated into two components by chromatography on silica gel using 1:5 ethyl acetate–hexane as eluent. Major adduct (**2**): R_f 0.3; IR ($CHCl_3$) 2245 (w), 1665 (m), 1360 (m) cm^{-1}; MS (15 eV) *m/e* (relative intensity, assignment) 247 (8.6), 246 (45), 245 (64, P), 192 (24, P − CH_2CHCN), 136 (71, P − PhS), 135 (100, P − PhSH). Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.53; H, 6.16; N, 5.70. Found: C, 68.41; H, 6.06; N, 5.77.

Minor adduct (**4**): R_f 0.4; IR ($CHCl_3$) 2240 (w), 1663 (m), 1365 (m) cm^{-1}; MS (15 eV) *m/e* 247 (18), 246 (47), 245 (53, P), 192 (19, P − CH_2CHCN), 137 (45), 136 (61, P − PhS), 135 (100, P − PhSH). Anal. Found: C, 68.38; H, 6.16.

The ^{1}H NMR spectra are reported in the Results and Discussion. When the major isomer was heated under the reaction conditions for 46 h, none of the minor isomer was produced as judged by GLC analysis.

(B) A solution of 454 mg (2.36 mmol) of the diene, 0.8 g (15 mmol) of acrylonitrile, 0.8 g (6 mmol) of diisopropylethylamine, and 45 mg (0.12 mmol) of the radical trap was divided into four portions of approximately 100 mg each and a fifth portion containing the remainder (ca. 1.6 g). Each portion was sealed in an ampule under argon and heated at a bath temperature of 110 °C. The small ampules were heated respectively for 1, 2, 4, and 8 h, and the large one was heated for 40 h. Each ampule was broken, and the pale yellow contents were concentrated. All of the adduct samples were analyzed by analytical LC, and all but the 1-h sample were separated into the four components using preparative LC. Compound **5**: MS (15 eV) *m/e* 247 (2.9), 246 (10), 245 (48, P), 194 (21), 136 (30, P − PhS), 135 (100, P − PhSH), 110 (22, $PhSH^+$). High-resolution mol wt, 245.0863; calcd for $C_{14}H_{15}NOS$, 245.0874.

Compound **3**: MS (15 eV) m/e 247 (2.4), 246 (7.4), 245 (39, P), 136 (30, P − PhS), 135 (100, P − PhSH), 110 (15, $PhSH^+$); high-resolution mol wt, 245.0846.

As an example of the determination of the approximate extent of reaction, evaporation of the contents of the 1-h ampule yielded 24.2 mg, which was separated by preparative TLC into 10 mg (0.041 mmol) of adduct and 13.9 mg (0.072 mmol) of diene; since only a trace of polymer (which may or may not have incorporated diene) and no other diene-containing products were in the sample, the extent of conversion was estimated as 0.041/(0.041 + 0.072) = 0.36. In the case of the 40-h sample, the detector response for recovered diene in one injection was 2629, and the combined responses of the four adducts was 2957; when these numbers were corrected for the molar response factors of the two types of compound, it was evident that 68% conversion of diene to adducts had occurred and diene was still present.

Isomerization of *Z* Diene to *E* Diene and Reaction of the Latter with Acrylonitrile. A solution of *Z* diene in methylene chloride was heated at reflux for 4 h. Upon TLC analysis (silica, 3:2 benzene–hexane), it was evident that most, but not all, of the *Z* diene had been converted to a slightly faster moving material. The mixture was stirred for 1 day at ambient temperature with an excess of methyl vinyl ketone containing a trace of radical inhibitor, and the extremely slow reacting *E* diene was isolated as a colorless oil by chromatography on silica gel using 3:2 benzene–hexane as eluent: IR (CCl_4) 1635 (w), 1585 (m), 1555 (s), 1480 (s), 1440 (m), 1215 (s), 1095 (s) cm^{-1}; ^{1}H NMR (60 mHz) δ 3.72 (s, CH_3, 3 H), 5.13–5.84 (m, CH_2 and CHSPh, 3 H), 6.80 (higher field half of dd; the other half is apparently in the aromatic region; J_{cis} = 10 Hz, =CHC(OMe)=, 0.5 H), 7.13 (broad s, aromatic plus one-half of vinyl absorption, 5.5 H).

The latter spectrum resembles that[13] of the *Z* isomer. A Diels–Alder reaction between this diene and acrylonitrile was extremely slow, and according to a crude GLC analysis the product was a complex mixture which probably contained small amounts of **2** and **4**.

Acknowledgment. We thank Messrs. Vance Bell, Glen Herman, and George Majetich for recording the mass spectra, Mr. Robert Bittner for recording the 250-mHz ^{1}H NMR spectra, Professor Patrick McCurry for help in interpreting the latter, the National Institutes of Health for support of the work at the University of Pittsburgh (Grant GM 22760), and the Chemistry Department of the University of North Carolina for its hospitality to T.C. while he was on leave there during the writing of part of this paper.

Registry No.—(*Z*)-**1**, 60466-66-2; (*E*)-**1**, 67315-81-5; **2**, 67315-82-6; **3**, 67315-83-7; **4**, 67315-84-8; **5**, 67315-85-9; acrylonitrile, 107-13-1.

References and Notes

(1) (a) University of Pittsburgh; (b) Virginia Commonwealth University; (c) E. I. du Pont de Nemours and Co.
(2) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).
(3) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975), and references cited therein.
(4) O. Eisenstein, J. M. Lefour, N. T. Anh, and R. F. Hudson, *Tetrahedron*, **33**, 523 (1977), and references cited therein.
(5) N. D. Epiotis, *J. Am. Chem. Soc.*, **95**, 5624 (1973).
(6) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, N.Y., 1976.
(7) (a) P. V. Alston, R. M. Ottenbrite, and D. D. Shillady, *J. Org. Chem.*, **38**, 4075 (1973); (b) P. V. Alston and R. M. Ottenbrite, *ibid.*, **40**, 1111 (1975); (c) P. V. Alston, R. M. Ottenbrite, and T. Cohen, *ibid.*, **43**, 1864 (1978).
(8) This term refers to the interaction of the π orbitals of C_2 and C_3 of the 1,3-diene with those of the unsaturated activating group of the dienophile.
(9) (a) Reviews of the Diels–Alder reaction: Y. A. Titov, *Russ. Chem. Rev.* (*Engl. Transl.*), **31**, 267 (1962); J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966); *ibid.*, **6**, 16 (1967); A. S. Onishchenko, "Diene Synthesis", Israel Program of Scientific Translation, Jerusalem, 1964; H. Wollweber, *Methoden Org. Chem.* (*Houben-Weyl*), *4th Ed., 1970*, **5**, Part 3, 977 (1970). (b) For a fairly typical example of the difficulties in determining quantitative yields in earlier work, see G. A. Ropp and E. C. Coyner, *J. Am. Chem. Soc.*, **72**, 3960 (1950). Even in much recent work, methods of yield determination and criteria for purity are not stated.
(10) T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971).
(11) (a) T. Cohen, A. J. Mura, Jr., D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Falck, *J. Org. Chem.*, **41**, 3218 (1976). (b) For other recent work on the directive effects of SR groups attached to dienes, see B. M. Trost, J. Ippen, and W. C. Vladuchick, *J. Am. Chem. Soc.*, **99**, 8116 (1977), and B. M. Trost and A. J. Bridges, *ibid.*, **98**, 5017 (1976).
(12) T. Cohen, R. J. Ruffner, D. W. Shull, E. R. Fogel, and J. R. Falck, *Org. Synth.*, in press.
(13) (a) The best previous study along these lines that we have been able to find reports the quantitative analysis, isolation, and structural evidence for all four regio- and stereoisomers from the reaction of methyl sorbate with styrene. Although the study appears to be the most complete and probably reliable reported up to that time, one cannot have complete confidence in either the quantitative results, which appear to have been determined by distillation followed by several preparative gas chromatographic separations, with all the losses that such procedures entail, or the structural assignments, which depend on a number of assumptions (albeit not unreasonable ones) concerning expected similarities and differences in the mass spectra of structural and stereochemical isomers and also the conformations of very mobile structures. Furthermore, a number of other products were also formed, and it is not clear how the stability of the adducts to the reaction conditions was established: O. Korver, T. L. Kwa, and C. Boelhouwer, *Tetrahedron*, **22**, 3305 (1966). (b) A recent communication reports the use of LC to detect all four adducts (after esterification) of the reaction of 2,4-pentadienoic acid with methyl acrylate: L. E. Overman, G.

F. Taylor, and P. J. Jessup, *Tetrahedron Lett.*, 3089 (1976).
(14) CNDO/2 MO method: J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(15) R. Sustmann and R. Schubert, *Angew. Chem., Int. Ed. Engl.*, **11**, 840 (1972), and references cited therein.
(16) A molecular orbital explanation of the endo/exo stereoselectivity in the Diels–Alder reaction has been given by R. B. Woodward and R. Hoffman [*Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969)].
(17) (a) R. E. Townsend, G. Ramunni, G. Segal, W. J. Hehre, and L. Salem, *J. Am. Chem. Soc.*, **98**, 2190 (1976); (b) L. A. Burke, G. Leroy, and M. Sana, *Theor. Chim. Acta.*, **40**, 313 (1975).
(18) In a previous study of Diels–Alder regioselectivity,[4] an asymmetrical transition state was assumed, that is, $\gamma_{rs} \neq \gamma_{r's'}$ for the primary orbital interactions. If such a transition state is assumed in this case, the predictions of the theory would be unchanged.
(19) Combustion analyses were obtained for the two major isomers and high-resolution mass spectra for the two minor isomers.
(20) For a review of the conformational analysis of cyclohexenes, see H. Gunther and G. Jikeli, *Chem. Rev.*, **77**, 599 (1977).
(21) Typical values of coupling constants (in hertz) to be expected for pure conformers are the following: $J_{5a,6e'} = 5$–6;[22] $J_{5a,6a'} = 10$–12;[22,23] $J_{4a,5a} = 12$–13.2;[11a,22,23,26b] $J_{4e,5a} = J_{4a,5e} = 2.5$–$4.0$;[11a,20,23] $J_{4e,5e} = 4.7$–4.9 [These values are derived by substituting 12 and 13.2,[24a] respectively, for $J_{a,a}$ in the expression[20] $(J_{a,a} + J_{e,e})/2 = 8.94$, which was determined for $J_{4,5\ trans}$ of 1,2,3,3,6,6-hexadeuteriocyclohexene.]. Equatorial, axial, quasiequatorial, and quasiaxial are designated by e, a, e', and a', respectively.
(22) P. C. Jain, Y. N. Mukergee, and N. Anand, *J. Am. Chem. Soc.*, **96**, 2996 (1974).
(23) J.-P. Aycard and H. Bodot, *Org. Magn. Reson.*, **7**, 226 (1975).
(24) (a) The highest value of $J_{4,5\ trans}$ which we have been able to locate is 13.2 Hz,[23] and a number of compounds in which the trans 4,5 protons would be expected to be essentially purely diaxial have values in the range 12.0–13.2 Hz.[11,22,23,26b] The value of 13.0 Hz is thus chosen for a typical value of $J_{4a,5a}$; the value of 4.9 Hz for $J_{4e,5e}$ is then found as described above.[21] (b) Zefirov[25] as well as Aycard and Bodot[23,26] have analyzed the conformations of a number of deuterated cyclohexenes on the basis of $J_{4,5}$.
(25) (a) N. S. Zefirov, N. M. Victorova, S. P. Knyazev, and N. M. Sergeyev, *Tetrahedron Lett.*, 1091 (1972); (b) N. S. Zefirov and N. M. Viktorova, *J. Org. Chem. USSR (Engl. Transl.)* **6**, 1350 (1970); (c) N. S. Zefirov, V. N. Chekulaeva, and A. I. Belozerov, *ibid.*, **5**, 619 (1969); (d) N. S. Zefirov, V. N. Chekulaeva, and A. I. Belozerov, *Tetrahedron*, **25**, 1997 (1969).
(26) (a) R. Lafrance, J.-P. Aycard, and H. Bodot, *Org. Magn. Reson.*, **9**, 253 (1977); (b) J.-P. Aycard, R. Geuss, J. Berger, and H. Bodot, *ibid.*, **5**, 473 (1973); (c) J.-P. Aycard, H. Bodot, R. Garnier, R. Lauricella, and G. Pouzard, *ibid.*, **2**, 7 (1970).
(27) A good model, the methylthio group, has an *A* value of about 1.0,[28] while that for cyano is 0.24.[28b]
(28) (a) E. L. Eliel and D. Kandasamy, *J. Org. Chem.*, **41**, 3899 (1976); (b) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.*, **91**, 344 (1969).
(29) F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 139 (1971).
(30) A. N. Vereshchagin and A. P. Anastas'eva, *Vopr. Stereokhim.*, **1**, 97 (1971); *Chem. Abstr.*, **77**, 139338z (1972).
(31) J. Dadok and R. F. Sprecher, *J. Magn. Reson.*, **13**, 243 (1974).

Scope of the Homo-Diels–Alder Reaction

Garry N. Fickes* and Thomas E. Metz

Department of Chemistry, University of Nevada, Reno, Nevada 89557

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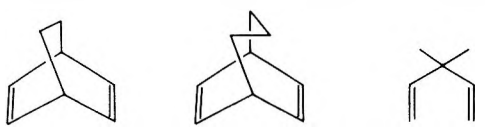
The reactivity of bicyclo[2.2.2]octa-2,5-diene, bicyclo[3.2.2]nona-6,8-diene, and 3,3-dimethyl-1,4-pentadiene in the homo-Diels–Alder reaction has been investigated to aid in an assessment of the scope of this reaction. The scope is seen to be rather limited, with the efficiency of the diene in the reaction generally being related to the distance between the double bonds.

The 1,5-addition of dienophiles to 1,4-dienes (the homo-Diels–Alder reaction) is a useful synthetic reaction for the preparation of certain tetracyclic compounds (Scheme I). Most studies of this reaction have involved norbornadiene with a variety of dienophiles.[1] Recent studies with norbornadiene have been concerned with the stereochemistry of the reaction,[2] a competing ionic reaction,[3] and the effects of Ni(0) catalyst on the reaction.[4] Other diene systems studied include the Dewar benzene,[5] barrelene,[6] and 1,4-cyclohexadiene systems.[7]

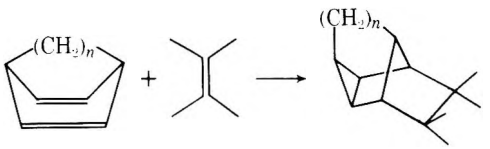
We were interested in the scope of the homo-Diels–Alder reaction with regard to the diene to see what the limitations are on the ring systems that can be synthesized by this reaction. Since the ease of the reaction must depend critically on the alignment and distance between the double bonds, we have investigated the behavior in this reaction of several dienes in which the double bonds are at increasingly greater distances than in norbornadiene. The dienes studied were bicyclo[2.2.2]octa-2,5-diene (**1**), bicyclo[3.2.2]nona-6,8-diene (**2**), and 3,3-dimethyl-1,4-pentadiene (**3**). The results of these



1 2 3

studies along with previous information in the literature can be used to assess the scope of the homo-Diels–Alder reaction.

Scheme I



Discussion

Bicyclo[2.2.2]octa-2,5-diene (**1**) was prepared by the method of Grob et al.,[8,9] which ultimately involves a Cope elimination from the *N*-oxide of 5-(dimethylamino)bicyclo[2.2.2 oct-2-ene. In order to avoid contamination of the diene with tricyclo[3.2.1.$0^{2,7}$]oct-3-ene, which apparently results from elimination from the exo amine oxide,[10] an attempt was made to prepare the starting material for the synthesis, *endo*-5-carbethoxybicyclo[2.2.2]oct-2-ene, with a high degree of configurational purity. It was found that the procedure of Inukai et al. for the aluminum chloride catalyzed Diels–Alder reaction[11] gave this ester in yields comparable to the uncatalyzed reaction[12] but the bicyclic ester was 98% endo isomer compared to 76% for the uncatalyzed reaction.

The same procedure was used to prepare bicyclo[3.2.2]-nona-6,8-diene (**2**).[13] In this case, the aluminum chloride catalyzed reaction of ethyl acrylate with 1,3-cycloheptadiene gave the bicyclic ester in 54% yield. Analysis showed that it was 98.5% exo isomer (this relates to the endo isomer in the bicyclooctyl case). 3,3-Dimethyl-1,4-pentadiene (**3**) was prepared by a modification of the procedure of Ciola and Burwell.[14]

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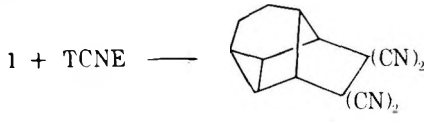
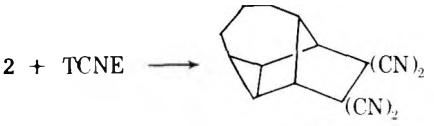
The homo-Diels–Alder reaction of bicyclooctadiene 1 was first tried with the highly reactive dienophile tetracyanoethylene (TCNE). A solution of these two in benzene produces an orange-amber color, presumably due to the formation of a charge-transfer complex. Refluxing for 30 h gives a crystalline product in yields as high as 85%. Spectral and elemental analyses of the compound were consistent with the expected 1:1 adduct 9,9,10,10-tetracyanotetracyclo[5.3.0.$0^{2,4}$.$0^{3,8}$]decane (4). Attempts to shorten the reaction time by carrying the reaction out at a higher temperature (100 °C, 11 h, benzene solvent) led to a lower yield of product (53%); this is apparently due to a competing retro-Diels–Alder reaction of the diene to benzene and ethylene.[8] The reaction of 1 with a less reactive dienophile, dimethyl acetylenedicarboxylate, was also attempted. In this case, no adduct was obtained after heating the reactants at reflux in benzene for 4 days (some polymer is formed). Heating at 100 °C for 36 h still did not produce the desired product, but led instead to thermal decomposition of the diene. Attempts to catalyze the reaction with aluminum chloride also failed (polymeric material is formed). In contrast, reaction of this dienophile with norbornadiene produces the adduct in 50% yield when a mixture of the two is heated at reflux for 12 h.[1i]



4

Bicyclononadiene 2 was found to be considerably less reactive than the bicyclooctadiene in the homo-Diels–Alder reaction, but because of its greater thermal stability and lesser tendency to polymerize than 1 (no change after heating at 150 °C for 24 h) more forcing conditions can be used. Addition of 2 to a benzene solution of TCNE again produced an orange-amber color, but no reaction was observed when the mixture was heated at reflux. However, heating the benzene solution to 145 °C for 15 h gave the desired product in yields to 24%. At this temperature the TCNE undergoes considerable decomposition to give a black carbon-like residue. The crystalline adduct was assigned the structure 10,10,11,11-tetracyanotetracyclo[6.3.0.$0^{2,4}$.$0^{3,9}$]undecane (5) on the basis of its IR and NMR spectra. As with the octadiene 1, none of the tetracyclic adduct was observed for the reaction of 2 and dimethyl acetylenedicarboxylate (150 °C, 24 h).

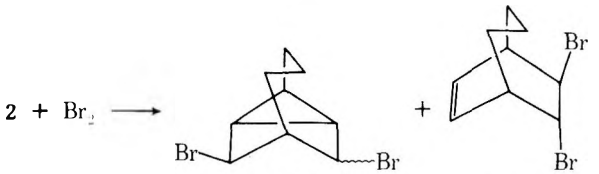


5

The reactivity of 3,3-dimethyl-1,4-pentadiene (3) in the homo-Diels–Alder reaction was examined with a variety of dienophiles. Although the addition of TCNE to a benzene solution of 3 produces a light amber color, heating of this solution, even at 145 °C for 52 h, does not lead to any detectable reaction. Attempted reaction also with dimethyl acetylenedicarboxylate, maleic anhydride, and *N*-phenylmaleimide (the latter two reactions at elevated temperatures) failed to produce the 1,5-adduct.

The above results, taken with others reported in the literature, indicate that the scope of the homo-Diels–Alder reaction is indeed rather limited. The reaction works well with norbornadiene, giving a quantitative yield of adduct with TCNE after 30 min at reflux in benzene,[1b] and with numerous other less reactive dienophiles.[1] Hexamethyl Dewar benzene has been reported to give an 85% yield of mono adduct when refluxed with TCNE in chlorobenzene. The product is 90% homo-Diels–Alder adduct and 10% rearranged product. In this case, the reaction is considered to be an ionic one.[5] Barrelene also gives a good yield of the homo-Diels–Alder product (95% with dicyanoacetylene at room temperature[6b]). In the present study bicyclooctadiene 1 was found to give an 85% yield of adduct with TCNE after 30 h at reflux in benzene, but it did not react with the less reactive dienophile dimethyl acetylenedicarboxylate.

The efficiency of the reaction decreases markedly with bicyclo[3.2.2]nona-6,8-diene (2); a 25% yield of adduct was obtained on heating with TCNE at 145 °C for 15 h. This decreased reactivity parallels a decreased tendency for homoconjugate addition of bromine to this diene compared to some of the compounds mentioned above. We find that the addition of bromine to 2 gives only 11% of the tricyclic dibromide 6 and 89% of the bicyclic dibromide 7. The tricyclic dibromide appears to be a mixture of epimers. In contrast, norbornadiene gives 80% of tricyclic dibromide,[15] barrelene 83%,[16] and bicyclooctadiene 1 about 30%.[17] Both 1,4-cyclohexadiene and 3,3,6,6-tetramethyl-1,4-cyclohexadiene fail to undergo the homo-Diels–Alder reaction at all.[7] This parallels their failure to undergo homoconjugate addition with, for example, bromine or the Prevost reagents (iodine and silver benzoate).



6, 11% 7, 89%

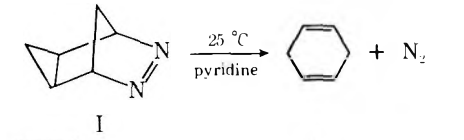
Only 1,2-addition products are formed in these reactions. The more flexible but less hindered 3,3-dimethyl-1,4-pentadiene (3) also gives no homo-Diels–Alder product, and it gives an inseparable mass of tarry products in the Prevost reaction.

It is apparent in considering the series of dienes mentioned above that there is a good correlation between the ease of homo-Diels–Alder reaction and the distance between the double bonds in the diene. These distances as determined from Dreiding models are as follows: norbornadiene, 2.40 Å (a more flexible Framework Molecular Model, Prentice Hall, Inc., was used for this diene); barrelene, 2.46 Å; bicyclooctadiene 1, 2.47 Å; bicyclononadiene 2, 2.51 Å; 3,3,6,6-tetramethyl-1,4-cyclohexadiene, 2.54 Å; and 3,3-dimethyl-1,4-pentadiene (3), 2.51 Å (for the more flexible systems, the distance is for the conformation giving the closest approach and parallel orientation of the double bonds).

The ease of the reaction can in turn be correlated with other effects dependent upon the distance between double bonds, for example, electronic interaction of the double bonds. The homo-Diels–Alder reaction is considered to be a concerted [$2_\pi + 2_\pi + 2_\pi$] cycloaddition reaction since it leads to the stereospecific formation of products,[2] although, as mentioned, the reaction of hexamethyl Dewar benzene with TCNE is apparently an ionic reaction[5] and a competing ionic reaction has been found in the case of norbornadiene and chlorocyanoacetylene.[3] Interaction of the double bonds in nonconjugated dienes can be classified into two types: through-space and through-bond interaction.[18] It is the through-space interaction which is thought to be important for the homo-Diels–Alder reaction.[2b] Norbornadiene is considered to be a model compound for through-space interaction, while 1,4-cyclohexadiene is a good model for through-bond interaction.[18] The interaction energy of the double bonds in these two systems has been measured by photoelectron spectroscopy.[19] This technique shows that through-space interaction is also important for barrelene[20] and bicyclooctadiene 1,[19] while bicyclononadiene 2 has a near cancellation of through-space and through-bond

interactions and seems to be the transition point for dienes with regard to the relative importance of these two types of interactions.[13b] It is clear that there is a good correlation between the ease of homo-Diels–Alder reaction and the amount of through-space interaction in these dienes.

The relative reactivities of the dienes can also be correlated with the ease of approach to the transition state for formation of the homo-Diels–Alder product. Generally speaking, the closer together the double bonds are the closer the diene would be to the transition state for the reaction. The superiority of norbornadiene to the other dienes from this point of view can be seen by looking at the ease of the reverse reaction, the retro homo-Diels–Alder reaction, of the azo compounds I[21] and II.[1e] As can be seen, I is much more reactive than II due to the greater relief of strain associated with the formation of 1,4-cyclohexadiene than the formation of norbornadiene. Apparently, the strain associated with formation of the three-membered ring as well as a lack of through-space interaction of the double bonds is sufficient to limit the homo-Diels–Alder reaction to dienes with double bonds no farther apart than they are in the bicyclononadiene **2**. For acyclic dienes such as **3**, entropy effects would also be important.



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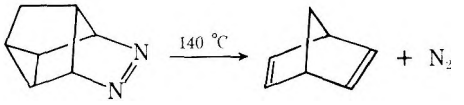
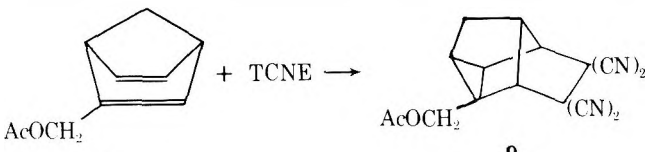


II

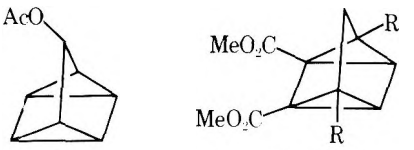
In an attempt to look at the effects of substituents in the diene on the homo-Diels–Alder reaction, the reaction of TCNE with 2-(acetoxymethyl)norbornadiene (**8**) was investigated. Mixing of the two in benzene produces an orange-red solution, and heating to reflux causes the formation of a 1:1 adduct in yields to 41%. The adduct was assigned structure **9** on the basis of its NMR spectrum, which showed a broad singlet at δ 1.80 (4 H), assigned to the two cyclopropyl hydrogens and the hydrogens of the methylene bridge, a broad multiplet at δ 2.55 (1 H), assigned to the bridgehead hydrogen facing the cyano groups, a broad singlet at δ 3.41 (2 H), assigned to the two remaining bridgehead hydrogens, and a quartet at δ 4.42 (2 H), assigned to the methylene adjacent to the acetate group. The acetate methyl appears as a sharp singlet at δ 2.05. The methylene adjacent to the acetate group is also adjacent to an asymmetric center, which causes it to appear as an AB quartet (J_{AB} = 12.5 Hz and $\Delta\nu_{AB}$ = 43 Hz). Compound **8** is apparently less reactive in the homo-Diels–



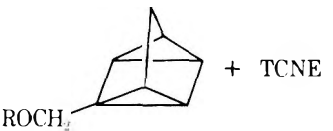
8 **9**

Alder reaction than norbornadiene itself since we were unable to isolate any adduct from **8** and dimethyl acetylenedicarboxylate after heating the two for 24 h at 120 °C in benzene.

The product from **8** is formed by addition of the dienophile at the least hindered side of the diene. This regiospecificity may be explained by both steric and electronic factors. It is interesting to note that the same regiospecificity is seen in 1,2-cycloaddition reactions of quadricyclanes. The quadricyclanes **10** and **11** have both been reported to give the 1,2-addition product resulting from reaction at the side away from



10 **11**, R = H or C_6H_5



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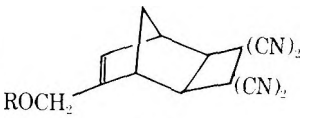

13

a, R = H; b, R = $-\overset{O}{\overset{\|}{C}}CH_3$

the substituent.[22,23] We have found analogous results with 1-(hydroxymethyl)quadricyclane (**12a**) and 1-(acetoxymethyl)quadricyclane (**12b**). These quadricyclanes with TCNE produce **13** as shown by NMR analysis. Thus, it appears that the substituent effect may be general for both of these 1,2- and 1,5-cycloaddition reactions and steric in origin.

Experimental Section[24]

Bicyclo[2.2.2]octa-2,5-diene (1). 5-Carbethoxybicyclo[2.2.2]-oct-2-ene was prepared by a procedure similar to that reported for aluminum chloride catalyzed Diels–Alder reactions.[11] A benzene solution of 1,3-cyclohexadiene[8] was added dropwise to a stirred solution of a 5:1 mixture of ethyl acrylate and aluminum chloride in benzene at 50–55 °C over a 3-h period. The reaction mixture was stirred for an additional 8 h after the addition was complete. Workup and fractional distillation gave the ester in 80% yield, bp 106 °C (15 mm) [lit.[8] bp 98–100 °C (12 mm)]. GC analysis showed the ester to be 98% endo isomer. The ester was converted to **1** using the method of Grob et al.,[8] along with some modifications of Wilcox et al.,[25] mp 58–60 °C (after sublimation at 50 °C (10 mm); lit.[8] mp 57 °C).

Bicyclo[3.2.2]nona-6,8-diene (2) was prepared in the same manner as **1**. The procedure of Grob et al.[8] for the preparation of 1,3-cyclohexadiene was used to prepare 1,3-cycloheptadiene from 3-chlorocycloheptene (bp 88 °C (45 mm); 68% yield from cycloheptene) in 62% yield, bp 112–114 °C (650 mm) [lit.[26] bp 120–121.5 °C (758 mm)]. 8-Carbethoxybicyclo[3.2.2]non-6-ene was obtained in 53% yield using the aluminum chloride catalyzed Diels–Alder reaction described above and stirring the reaction for 62 h, bp 110–113 °C (6 mm). GC showed that the ester was 98.5% exo isomer.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.17; H, 9.34. Found: C, 74.57; H, 9.32.

The bicyclic ester was converted to **2** using the same seven-step procedure used to prepare **1**. The hydrazide was obtained as a white solid [mp 90–91 °C (from benzene)]. The carbamate was obtained as a thick oil and was reduced without purification to the monomethylamine, bp 77–78 °C (14 mm). The dimethylamine, a colorless oil, bp 80 °C (4.5 mm), was converted to the *N*-oxide, a white waxy solid. The *N*-oxide was decomposed to the diene, without purification or drying, at 90–115 °C in 74% yield. **2** was obtained as a white waxy solid that sublimed readily at 75 °C (20 mm), mp 89–91 °C (st) (lit. mp 83–84[13a] and 84 °C[13b]). The NMR spectrum was in agreement with that reported for **2**.[13b] **2** showed UV absorption (ethanol) at 205 nm (ϵ 4040) and 245 (41).

Bromine Addition to 2. A solution of 320 mg (2.0 mmole) of freshly distilled bromine in 10 mL of carbon tetrachloride was added dropwise to an ice-cold solution of 240 mg (2.0 mmol) of **2** in 10 mL of carbon tetrachloride, and the reaction mixture was stirred for an additional 24 h after addition was complete. Removal of solvent on a rotary evaporator left 560 mg (100%) of dibromide as a light orange oil. TLC indicated the presence of two components. The mixture was separated on a slurry-packed Florisil column using hexane as the eluting solvent. The major component (89% by NMR) was a colorless oil, and it was

assigned the structure of the 1,2-addition product, *trans*-8,9-dibromobicyclo[3.2.2]non-6-ene (**7**), by analogy to the reaction of bromine with I[10,17] and on the basis of the following spectral data: IR (neat) 3055 (m, vinyl hydrogens), 1640 (m, double bond), 710 (s, cis disubstituted double bond) cm^{-1}; NMR (CCl_4) δ 1.15–1.95 (m, 5 H, propyl bridge), 2.42 (m, 2 H, bridgehead), 2.72 (m, 1 H, hydrogen of the propyl bridge over the endo bromine), 4.47 (poorly resolved quintet, 1 H, exo CHBr), 5.25 (broad d, 1 H, endo CHBr), 5.35–5.74 (m, 1 H, vinyl), 6.09 (q, 1 H, vinyl hydrogen across from exo bromine).

Anal. Calcd for $C_9H_{12}Br_2$: C, 38.61; H, 4.32. Found: C, 38.44; H, 4.31.

The minor component (11% by NMR) appeared to be pure by TLC, but NMR spectroscopy indicated it to be a mixture of *syn*- and *anti*-6,9-dibromotricyclo[3.2.2.$0^{7,8}$]nonane (**6**), although the exact ratio of the two isomers could not be determined. The structural assignment was based on the following spectral data: IR (neat) 3030 cm^{-1} (w, cyclopropyl hydrogens), no double-bond absorption; the NMR spectrum (CCl_4) was weak but indicated absorptions at δ 1.25 (m, cyclopropyl), 1.59 (m, propyl bridge), 2.42 (m, bridgehead), 2.82 (m, hydrogen over endo bromine) 4.30 (m, CHBr of syn isomer), 4.42 and 5.21 (m, CHBr of anti isomer). Due to the small amount of tricyclic dibromide isolated, no elemental analysis was obtained.

3,3-Dimethyl-1,4-pentadiene (3) was prepared by the method of Ciola and Burwell,[14] bp 65–66 °C (650 mm) [lit.[14] bp 70.2 °C (750.5 mm)].

2-(Acetoxymethyl)norbornadiene (8). 2-(Hydroxymethyl)-norbornadiene was prepared according to the procedure of Graham et al.,[27] bp 96–97 °C (8 mm) [lit.[27] bp 100–103 °C (9–11 mm)], and acetylated using acetic anhydride and sodium acetate,[28] bp 103–105 °C (25 mm) [lit.[27] bp 80–82 °C (4 mm)].

1-(Hydroxymethyl)quadricyclane (12a) and 1-(acetoxymethyl)quadricyclane (12b) were obtained by irradiating a 2% ether solution of 2-(hydroxymethyl)- or 2-(acetoxymethyl)norbornadiene (**8**) for 20 h in a Rayonet photochemical reactor.[29] IR and NMR spectroscopy showed the loss of double bond and the appearance of cyclopropyl hydrogens. GC analysis showed the alcohol to be 90% pure and the acetate 95% pure. Due to the instability of these quadricyclanes, no elemental analyses were obtained; the ether solutions from photolysis were used directly for the cycloaddition reactions.

Cycloaddition Reactions with TCNE.[30] A. 9,9,10,10-Tetracyanotetracyclo[5.3.0.$0^{2,4}$.$0^{3,8}$]decane (4). To a yellow solution of 0.35 g (2.7 mmol) of TCNE in 3 mL of benzene was added 0.50 g (4.7 mmol) of bicyclo[2.2.2]octa-2,5-diene (**1**). The resulting orange-amber colored solution was refluxed with stirring for 30 h (after 6 h, the solution had become noticeably darker and a precipitate had formed) and then cooled in an ice bath. The crystals were suction filtered to give 0.48 g (75%) of a grayish-brown amorphous solid, which gave white needles on recrystallization from benzene, mp 244–245 °C. The overall yield of adduct was about 85% based on workup of material from the mother liquors. Assignment of structure **4** to the adduct was based on the following spectral data: NMR δ 1.25 (broad m, 1 H, cyclopropyl), 1.45 (broad s, 2 H, cyclopropyl), 1.70 (broad s, 4 H, ethano bridge), 2.05 (m, 1 H, bridgehead), 3.50 (broad s, 2 H, bridgehead); IR (KBr) 3040 (w, cyclopropyl hydrogens), 2250 (w, unconjugated nitrile) cm^{-1}, no double-bond absorption.

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.79; H, 4.30. Found: C, 71.53; H, 4.22.

B. 10,10,11,11-Tetracyanotetracyclo[6.3.0.$0^{2,4}$.$0^{3,9}$]undecane (5). To a heavy-walled tube containing 200 mg (1.6 mmol) of TCNE and a few crystals of hydroquinone was added a solution of 100 mg (0.84 mmol) of bicyclo[3.2.2]nona-6,8-diene (**2**) in 0.7 mL of benzene. The tube was flushed with nitrogen, cooled, sealed, and heated in an oil bath at 140–145 °C for 15 h. After cooling, the tube was opened and the dark contents were dissolved in excess benzene and filtered hot to remove the insoluble residue. After concentration and cooling, the benzene solution yielded 50 mg (24%) of light brown platelets. Decolorization with activated carbon and two recrystallizations from benzene gave 10 mg of white platelets, mp 235–236 °C. Structure **5** was assigned to the adduct on the basis of the following spectral data: NMR δ 1.00 (m, 1 H, cyclopropyl), 1.48 (broad s, 2 H, cyclopropyl), 1.75 (m, overlapped with cyclopropyl hydrogens, 6 H, propyl bridge), 2.10 (m, 1 H, bridgehead), 3.71 (broad s, 2 H, bridgehead); IR (KBr) 3025 (w, cyclopropyl hydrogens), 2250 (w, unconjugated nitrile) cm^{-1}, no double-bond absorption.

Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87. Found: C, 72.57; H, 5.01.

C. 2-Acetoxymethyl-8,8,9,9-tetracyanotetracyclo-[4.3.0.$0^{2,4}$.$0^{3,7}$]nonane (9). To a solution of 130 mg (1.0 mmol) of TCNE in 3 mL of benzene was added 170 mg (1.0 mmol) of 2-(acetoxymethyl)norbornadiene (**8**) and a few crystals of hydroquinone. No apparent reaction had taken place on standing for 2 days at room temperature. Refluxing for 1 h caused the initial red color to fade to an orange-amber color. Evaporation of solvent left an orange crystalline mass which was recrystallized from 3 mL of benzene to give 120 mg (41%) of tan platelets. After decolorization with activated carbon and two recrystallizations from benzene, the product was obtained as white platelets: mp 147.5–148.5 °C; IR (KBr) 3070 (w, cyclopropyl hydrogens), 2250 (w, unconjugated nitrile) cm^{-1}, no double-bond absorption; NMR data is given in the text.

Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.74; H, 4.15; N, 19.17. Found: C: 65.55; H, 4.23; N, 19.60.

D. 8-Hydroxymethyl-3,3,4,4-tetracyanotricyclo[4.2.1.$0^{2,5}$]-non-7-ene (13a). A solution of 800 mg (6.5 mmol) of 1-(hydroxymethyl)quadricyclane (**12a**) in 10 mL of benzene was added all at once to a yellow solution of 210 mg (1.6 mmol) of TCNE in 10 mL of benzene. The yellow color disappeared instantaneously, and after a few minutes a colorless precipitate began to form. The solution was cooled and filtered to give 410 mg (100%) of a white powder, mp 171.5–173.5 °C dec. After two recrystallizations from ethylene dichloride and decolorization with activated carbon (material turned pink on heating), the product was a white powder, mp 175–176 °C. Repeated recrystallizations from ethylene dichloride failed to raise the melting point, but the elemental analysis remained slightly off for the compound named. The IR, NMR and mass spectra, however, were all consistent with the assigned structure **13a:** IR (KBr) 3540 (s, hydroxyl), 3020 (w, vinyl hydrogens), 2250 (w, unconjugated nitrile), 1620 (w, double bond), 1030 (s, C–O bond) cm^{-1}; NMR δ 1.82 (q, 2 H, methylene bridge), 3.05 (s, 2 H, cyclobutyl), 3.22 (broad s, 2 H, bridgehead), 3.75 (s, 1 H, OH), 4.02 (d, 2 H, CH_2OH), 5.88 (m, 1 H, vinyl); mass spectrum (70 eV), *m/e* (relative intensity) 250 (3, M^+), 232 (36, $M^+ - H_2O$).

Anal. Calcd for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.40. Found: C, 66.52; H, 4.31; N, 22.01.

E. 8-Acetoxymethyl-3,3,4,4-tetracyanotricyclo[4.2.1.$0^{2,5}$]-non-7-ene (13b). To a solution of 82 mg (0.64 mmol) of TCNE in 25 mL of ether was added all at once a solution of 100 mg (0.61 mmol) of 1-(acetoxymethyl)quadricyclane (**12b**) in 10 mL of ether. The light orange color of the TCNE-ether complex disappeared in about 10 s, and after about 30 s a white precipitate began to form. The solution was allowed to stand at room temperature for 2 h and then was cooled and filtered with suction to give 150 mg (79%) of a white powder, mp 163–165 °C. The product was recrystallized twice from a 1:1 mixture of ethylene dichloride–hexane (benzene was not suitable for recrystallization since it seemed to complex with the product) to give white needles, mp 167–168 °C. Structure **13b** was assigned to the product on the basis of its spectral data: IR (KBr) 3005 (w, vinyl hydrogens), 2250 (w, unconjugated nitrile), 1720 (s, acetate carbonyl), 1640 (w, double bond), 1035 (m, C–O bond) cm^{-1}; NMR δ 1.84 (q, 2 H, methylene bridge), 2.07 (s, 3 H, acetate methyl), 3.07 (poorly resolved d, 2 H, cyclobutyl), 3.25 (broad s, 2 H, bridgehead), 4.62 (broad s, 2 H, CH_2 adjacent to acetate), 6.02 (m, 1 H, vinyl).

Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.74; H, 4.14; N, 19.18. Found: C, 65.55; H, 4.33; N, 19.41.

Attempted Cycloaddition Reactions. A. Bicyclo[2.2.2]octa-2,5-diene (1) with Dimethyl Acetylenedicarboxylate. To a solution of 670 mg (4.7 mmol) of dimethyl acetylenedicarboxylate in 3 mL of benzene was added 500 mg (4.7 mmol) of **1**. After stirring at reflux for 4 days, a small amount of waxy precipitate was observed. Solvent and unreacted starting materials were removed on a rotary evaporator to leave about 50 mg of an orange waxy material. Attempts to isolate the adduct from this material by chromatography on alumina were unsuccessful. The same reaction was carried out in a heavy-walled tube (sealed under nitrogen) at 100 °C for 36 h. Distillation of the contents of the tube yielded only benzene and dienophile.

Catalysis of the reaction with aluminum chloride was attempted. To a stirred solution of 125 mg (0.94 mol) of aluminum chloride in 4 mL of benzene heated at 50 °C was added dropwise 670 mg (4.7 mmol) of dimethyl acetylenedicarboxylate in 2.0 mL of benzene. After addition was complete, a solution of 500 mg (4.7 mmol) of **1** in 2.0 mL of benzene was added slowly over a 30-min period while the reaction mixture was maintained at 50–55 °C. The mixture was stirred at 50–55 °C for an additional 8 h and then cooled in an ice bath while 2 mL of 5% hydrochloric acid was added. The layers were separated, and the benzene layer was washed once with water and dried over sodium sulfate. Chromatography on alumina gave only starting material and a trace of yellow amorphous material. The experiment was repeated using a 2:1 molar excess of aluminum chloride to dienophile and the reaction mixture was stirred at 50–55 °C for 25 h after addition of the diene. Workup and removal of solvent left 1 g of a viscous orange oil which yielded no adduct on chromatography on alumina.

B. Bicyclo[3.2.2]nona-6,8-diene (2) with Dimethyl Acetylenedicarboxylate. To a solution of 120 mg (1 mmol) of **2** in 1 mL of benzene was added 142 mg (1 mmol) of dimethyl acetylenedicarboxylate and a few crystals of hydroquinone. The mixture was sealed in a heavy-walled tube under nitrogen and heated at 150 °C for 24 h. Removal of solvent left a red tarry residue. Attempts to purify this residue by chromatography on silica gel failed to yield any cycloaddition product.

C. Reactions of 3,3-Dimethyl-1,4-pentadiene (3). With TCNE. To a solution of 2.5 g (0.026 mol) of **3** in 20 mL of benzene was added 2.0 g (0.016 mol) of TCNE, and the resulting light amber solution was refluxed for 9 h. Workup gave only recovered TCNE. Heating the solution in a sealed tube at 140–145 °C for up to 52 h also produced no adduct.

With Dimethyl Acetylenedicarboxylate. A solution of 3.0 g (0.031 mol) of **3**, 3.0 g (0.021 mol) of dimethyl acetylenedicarboxylate, and a few crystals of hydroquinone was refluxed for 6 h. Distillation of unreacted diene and dienophile from the reaction mixture left a trace of a viscous oil in which none of the adduct could be detected.

With Maleic Anhydride and *N*-Phenylmaleimide. A mixture of 0.5 g (5.2 mmol) of **3**, 1 mmol of maleic anhydride or *N*-phenylmaleimide, and 0.25 mL of chloroform was heated at 50 °C for 1 week. NMR analysis showed that no reaction had occurred. The experiments were repeated at a higher temperature by heating 0.7 g (7.3 mmol) of **3**, 5 mmol of maleic anhydride or *N*-phenylmaleimide, and 1 mL of dry diglyme at 125–130 °C for 2 days in a tube sealed under nitrogen. Workup gave no detectable amounts of cycloadduct. The experiment was repeated at 190 °C for 3 days in the absence of solvent. No reaction occurred with the *N*-phenylmaleimide, but some brown oil was produced in the maleic anhydride case. Attempts to purify this material by column chromatography failed. Although the IR spectrum of the material showed some aliphatic absorption, the NMR spectrum was very complex and no definite structure could be assigned.

Registry No.—1, 500-23-2; **2**, 7164-08-1; **3**, 1112-35-2; **4**, 61822-60-4; **5**, 67271-14-1; **6** (isomer 1), 67271-15-2; **6** (isomer 2), 67335-53-9; **7**, 67271-16-3; **8**, 56682-74-7; **9**, 67271-17-4; **12a**, 56682-76-9; **12b**, 56682-75-8; **13a**, 67271-18-5; **13b**, 67271-19-6; *endo*-5-carbethoxybicyclo[2.2.2]oct-2-ene, 67335-54-0; *exo*-8-carbethoxybicyclo[3.2.2]non-6-ene, 23217-51-8; *exo*-8-carbethoxybicyclo[3.2.2]non-6-ene hydrazide, 23217-54-1; 8-(methylamino)bicyclo[3.2.2]non-6-ene, 67271-20-9; 8-(dimethylamino)bicyclo[3.2.2]non-6-ene, 67271-21-0; 8-(dimethylamino)bicyclo[3.2.2]non-6-ene *N*-oxide, 67271-22-1; 1,3-cyclohexadiene, 592-57-4; ethyl acrylate, 140-88-5; 1,3-cycloheptadiene, 4054-38-0; 3-chlorocycloheptene, 35021-99-9; bromine, 7726-95-6; TCNE, 670-54-2; dimethyl acetylenedicarboxylate, 762-42-5; maleic anhydride, 108-31-6; *N*-phenylmaleimide, 941-69-5.

References and Notes

(1) (a) E. F. Ullman, *Chem. Ind. (London)*, 1173 (1958); (b) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **81**, 667 (1959); (c) H. K. Hall, *J. Org. Chem.*, **25**, 42 (1960); (d) S. J. Cristol, E. L. Allred, and D. L. Wetzel, *ibid.*, **27**, 4058 (1962); (e) R. M. Moriarity, *ibid.*, **28**, 2385 (1963); (f) R. C. Cookson, and J. Dance, *Tetrahedron Lett.*, 879 (1962); (g) R. C. Cookson, J. Dance, and J. Hudec, *ibid.*, 5416 (1964); (h) G. N. Schrauzer and P. Glockner, *Chem. Ber.*, **97**, 2451 (1964); (i) C. F. Huebner, E. Donoghue, L. Dorfman, E. A. Stuber, N. Danieli, and E. Wenkert, *Tetrahedron Lett.*, 1185 (1966); (j) J. J. Tufariello, T. F. Mich, and P. S. Miller, *ibid.*, 2293 (1966).

(2) (a) Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Tueno, *J. Am. Chem. Soc.*, **94**, 3633 (1972); (b) I. Tabushi, K. Yamamura, Z. Yoshida, and A. Togashi, *Bull. Chem. Soc. Jpn.*, **48**, 2922 (1975).

(3) T. Sasaki, S. Eguchi, M. Sugimoto, and F. Hibi, *J. Org. Chem.*, **37**, 2317 (1972).

(4) (a) R. Noyori, I. Umeda, H. Kawauchi, and H. Takaya, *J. Am. Chem. Soc.*, **97**, 812 (1975); (b) S. Yoshikawa, K. Aoki, J. Kiji, and J. Furukawa, *Bull. Chem. Soc. Jpn.*, **48**, 3239 (1975).

(5) H. Iwamura, Y. Tanabe, and H. Kobayashi, *Tetrahedron Lett.*, 1987 (1976), and references contained therein.

(6) (a) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.*, **83**, 3428 (1961); (b) H. E. Zimmerman and G. L. Grunewald, *ibid.*, 86, 1434 (1964).

(7) F. W. Grant, R. W. Gleason, and C. H. Bushweller, *J. Org. Chem.*, **30**, 290 (1965), and references contained therein.

(8) C. A. Grob, H. Kny, and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957).

(9) An alternative procedure for the synthesis of **1** using 1,4-cyclohexadiene in an alkylation reaction has been reported by S. W. Staley, G. W. Cramer, and W. G. Kingsley, *J. Am. Chem. Soc.*, **95**, 5052 (1973).

(10) C. A. Grob and J. Hostynek, *Helv. Chim. Acta*, **46**, 1676 (1963).

(11) (a) T. Inukai and M. Kasai, *J. Org. Chem.*, **30**, 3567 (1965); (b) T. Inukai and T. Kajima, *ibid.*, **31**, 2032 (1966).

(12) R. Seka and O. Tramposch, *Ber.*, **75**, 1379 (1942).

(13) Synthesis of this diene by the electrolytic and chemical decarboxylation of bicyclo[3.2.2]non-6-ene-8,9-dicarboxylic acid anhydride has been reported: (a) A. J. Baker, A. M. Chalmers, W. W. Flood, D. D. MacNicol, A. B. Penrose, and R. A. Raphael, *Chem. Commun.*, 166 (1970); (b) J. Goldstein, S. Natowsky, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta*, **56**, 294 (1973).

(14) R. Ciola and R. L. Burwell, Jr., *J. Org. Chem.*, **23**, 1063 (1958).

(15) (a) S. Winstein and M. Shatavsky, *Chem. Ind. (London)*, 56 (1956); (b) L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Am. Chem. Soc.*, **78**, 2819 (1956).

(16) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *J. Am. Chem. Soc.*, **91**, 2330 (1969).

(17) C. A. Grob and A. Gagneux, *Helv. Chim. Acta*, **42**, 1753 (1959).

(18) R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971).

(19) P. Bischof, J. A. Hashmall, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta*, **52**, 1745 (1969).

(20) E. Haselbach, E. Heilbronner, and G. Schröder, *Helv. Chim. Acta*, **54**, 153 (1971).

(21) E. L. Allred, J. C. Hinshaw, and A. L. Johnson, *J. Am. Chem. Soc.*, **91**, 3382 (1969).

(22) C. D. Smith, *J. Am. Chem. Soc.*, **88**, 4273 (1966).

(23) H. Prinzbach and M. Thyes, *Chem. Ber.*, **104**, 2489 (1971), and references contained therein.

(24) Nuclear magnetic resonance spectra were determined in deuterated dimethyl sulfoxide, unless otherwise noted, with a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Beckman Model IR-8 spectrophotometer and were calibrated with a polystyrene film. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Gas chromatographic analyses were carried out on a 150 ft × 0.01 in stainless steel capillary column coated with tris(β-cyanoethoxy)propane. Microanalyses were carried out by Chemalytics, Inc., Tempe, Ariz.

(25) C. F. Wilcox, Jr., and C. Whitney, *J. Org. Chem.*, 32, 3348 (1967).

(26) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).

(27) P. J. Graham, E. L. Buhle, and N. Pappas, *J. Org. Chem.*, **26**, 4658 (1961).

(28) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964.

(29) For the photolytic conversion of norbornadienes to quadricyclanes, see, for example, ref 23.

(30) TCNE was sublimed prior to use (140 °C, 1 mm) mp 199–200 °C (st). Benzene solvent was dried over sodium.

Rearrangement Approaches to Polycyclic Skeletons. 1. Bridgehead-Substituted Bicyclo[3.2.1]octene Derivatives from Bicyclo[2.2.2]octene Precursors[1]

Stephen A. Monti,* Shen-Chu Chen, Yuh-Lin Yang,
Sun-Shine Yuan, and Oliver P. Bourgeois

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

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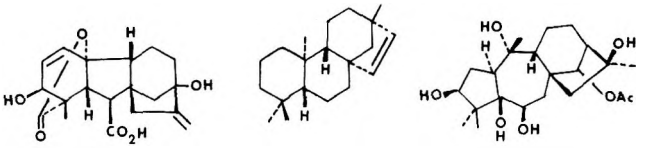
Preparation of a variety of 1-substituted bicyclo[3.2.1]oct-3- (and -6-) en-2-yl derivatives by acid-catalyzed rearrangement of 1-H and 1-methoxy-2-alkylbicyclo[2.2.2]oct-5-en-2-ols and of 1-methoxybicyclo[2.2.2]oct-5-en-2-alkylidene derivatives is described. In the 1-H series, both the exo and the endo tertiary alcohol precursors yield the more stable bicyclo[3.2.1]oct-3-en-2-yl product; in the 1-methoxy series, the exo tertiary alcohols and the α,β-unsaturated ester precursors furnish the nonconjugated bicyclo[3.2.1]oct-6-en-2-one products, while the endo tertiary alcohols and the unsaturated ketone starting materials give the conjugated bicyclo[3.2.1]oct-3-en-2-one products predominantly. A facile rearrangement of 1-ketoalkylbicyclo[3.2.1]oct-6-en-2-ones to 1-ketoalkylbicyclo[3.2.1]oct-3-en-2-ones is described. The observed regioselectivity of these rearrangements is discussed.

The structural complexities and diverse biological activities of several classes of tetracyclic natural products, such as the gibberellins (**1**), the beyeranes (**2**), and the grayanotoxins (**3**), among others,[2] make them important and challenging

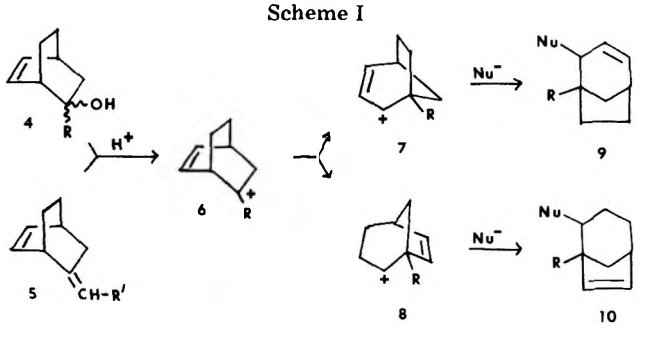


1, Gibberellic Acid 2, Stachene 3, Grayanotoxin I

synthetic targets.[3] Structurally, each of these families contain a 1,2-disubstituted bicyclo[3.2.1]octane nucleus, and the presence of this common element provides the basis for an attractive convergent synthetic approach to these related materials. The synthetic strategy envisioned involves initial preparation of suitably functionalized, bridgehead-substituted bicyclo[3.2.1]octane derivatives, followed by subsequent elaboration of the fused-ring skeleton: a formal C/D → A-B-C/D route to these tetracyclic substances. The successful completion of the initial synthetic goal of this general approach, the development of an efficient procedure to prepare a variety of C/D ring synthons which contain functionality suitable for further conversion into the target natural products, is described herein.

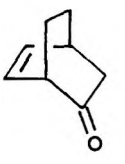
The overall route to the desired bridgehead-substituted bicyclo[3.2.1]octane derivatives is depicted in Scheme I. The key step involves the rearrangement of the bicyclo[2.2.2]octenyl cation **6** into the bicyclo[3.2.1]octenyl cations **7** and/or **8**.[4] Nucleophilic trapping of these cations then furnishes 1-alkylbicyclo[3.2.1]octene derivatives containing either functionality only in the three-carbon bridge (**9**) or differentiated functionality in the two- and the three-carbon bridges (**10**). As described below, the bicyclo[2.2.2]octene derivatives, the exo and/or endo tertiary alcohols **4**, as well as the dienes **5**, can serve as formal precursors to cation **6**; these bicyclo[2.2.2]-octene substrates are readily prepared by a convergent sequence which allows structural variation in both the bicyclic skeleton and in the R substituent; and the rearrangement regioselectivity exhibited by these substrates is such that controlled synthetic entry into either bicyclo[3.2.1]octene series, **9** or **10**, can be achieved.

Scheme I

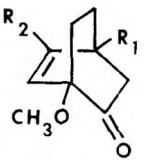


Results

The starting materials for the preparation of the bicyclo[2.2.2]octene precursors **4** and **5** were the Diels–Alder derived bicyclo[2.2.2]octenones **11**,[5] **12**,[6] and **13**. Both the known



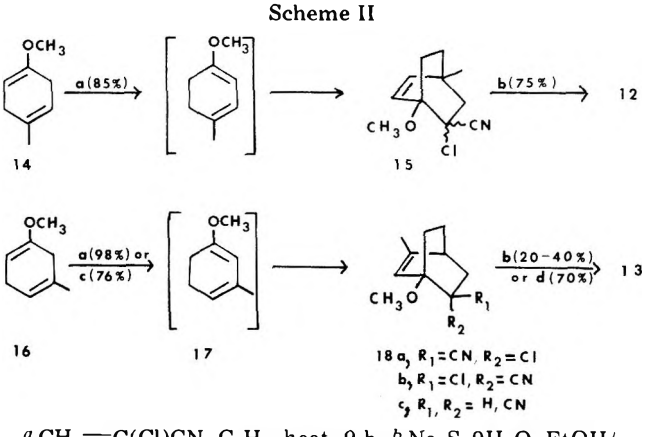
11



12, R_1=CH_3, R_2=H
13, R_1=H, R_2=CH_3

1-methoxy-4-methyl ketone **12** and the previously unreported 5-methyl derivative **13** were prepared from the Birch reduction products **14** and **16** as shown in Scheme II. Cycloaddition[6,7] of α-chloroacrylonitrile with the conjugated diene **17**, generated in situ from **16**, yielded a separable mixture of chloronitriles **18a,b** (2:1) in 90% yield in which the exo-nitrile **18a** predominated.[8] A third product was isolated in ca. 10%

Scheme II



[a] CH_2=C(Cl)CN, C_6H_6, heat, 9 h. [b] $Na_2S\cdot 9H_2O$, EtOH/H_2O, heat, 15 h. [c] CH_2=CHCN, 120 °C, 16 h. [d] (i) LDA/THF, −78 °C; (ii) O_2, −78 °C; (iii) Na_2SO_3, 0–25 °C.

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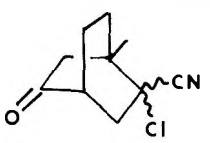
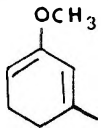
yield from this reaction, and after aqueous acid hydrolysis it was tentatively identified as the keto chloronitrile **19** on the basis of spectral properties. Presumably, this minor product results from cycloaddition of the alternative conjugated endocyclic diene **20**. The conversion of chloronitriles **18a,b** to 5-methyl ketone **13** under a variety of conditions[5,6] gave reproducibly poor yields[9] (20–40%) and led to an examination of an alternative route to **13**. In practice, a more satisfactory preparation of ketone **13** was achieved by cycloaddition of acrylonitrile and diene **16** to give nitrile **18c**, which when treated sequentially with lithium diisopropylamide in THF, dry oxygen, and then sodium sulfite[10] yielded 5-methyl ketone **13** in 53% overall yield from diene **16**.

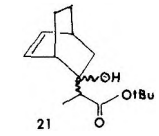


19

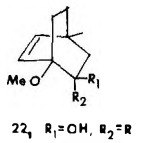


20

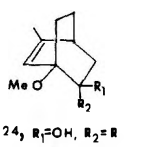
The exo and endo tertiary alcohols **4** and the dienes **5**, which serve as precursors of the bicyclo[3.2.1]octenes **9** and **10** containing substituted acetic acid substituents at C-1 (see Table I), were prepared as follows. Reformatsky reaction[11] of ketones **11**, **12**, and **13** with the appropriate α-bromo ester furnished nonseparable mixtures of the β-hydroxy esters **21**, **22a** and **23a**, and **24a** and **25a** in ca. 80% isolated yield. Reaction of



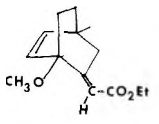
21



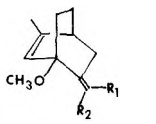
22, R_1=OH, R_2=R
23, R_1=R, R_2=OH



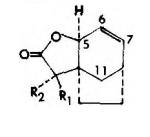
24, R_1=OH, R_2=R
25, R_1=R, R_2=OH



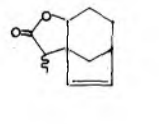
26



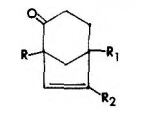
27, R_1=CO_2Et, R_2=H
28, R_1=H, R_2=CO_2Et



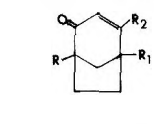
29, R_1=CH_3, R_2=H
30, R_1=H, R_2=CH_3



31



32, R_1=CH_3, R_2=H
33, R_1=H, R_2=CH_3



34, R_1=CH_3, R_2=H
35, R_1=H, R_2=CH_3

a, R=CH_2CO_2Et
b, R=CH_2CO_2H
c, R=$CH(CH_3)CO_2H$
d, R=$CH(C_6H_5)COOH$
e, R=$CH(C_6H_4(m\text{-}OMe))COOH$
f, R=$CH_2CH_2C(=O)CH_3$
g, R=$CH_2CH_2C(=O)CH_3$
h, R=$CH_2CH_2CH_2S\text{-}Ph$
i, R=$CH_2C(=O)CH_2CO_2Me$
j, R=$CH_2C(=O)CH_3$

ketone **13** with the appropriate carboxylic acid dianion[12] gave mixtures of the β-hydroxy acids **24,25** (**b–e**) in 60–80% yield in which the exo alcohol **24** usually predominated. Crystallization of these mixtures normally furnished the pure exo alcohols, e.g., **24c,d,e**, although in one case the pure endo alcohol **25b** was obtained. The exo/endo structure assignments were based on the observation that the NMR chemical shift of the substituent methylene or methine group proton(s) in the exo alcohol **24** was shifted upfield due to the shielding effect of the adjacent C_5–C_6 double bond[13] (see Experimental Section for details). In addition, formation of the exo alcohols **24** as the major products is consistent with addition to the less hindered face of the bicyclo[2.2.2]octenone substrates.[4,14] When the 5-methyl ketone **13** was allowed to react with the lithium enolate of ethyl trimethylsilylacetate,[15] a mixture of α,β-unsaturated esters **27,28** was obtained which showed bridgehead methoxy group signals at δ 3.35 and 3.46 (1:2 ratio). The minor component (δ 3.35) is assigned as the *Z* isomer **28** on the basis of the expected shielding effect of the carbethoxy group on the methoxy substituent.[16] Dehydration of the β-hydroxy esters **22a,23a** and **24a,25a** with thionyl chloride/pyridine yielded *only* the 5-methylbicyclo[2.2.2]octene *E* isomer **27** and a single α,β-unsaturated ester **26** in the 4-methyl series, which by analogy is tentatively assigned the *E* configuration (i.e., formation of the more stable isomer).

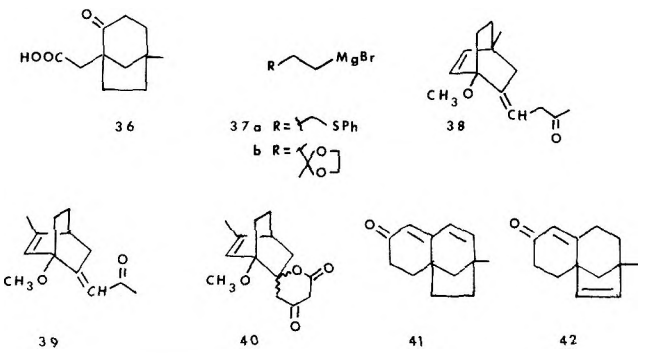
Table I. Rearrangement of Bicyclo[2.2.2]octenes to Bicyclo[3.2.1]octene-1-acetic Acid Derivatives

substrate	conditions	products (yield, %)
alcohols		
21	*a*	**29,30** (70)
22a,23a (1:1)	*a*	**32b** (59), **34b** (35)[c]
24c	*a*	**33c** (90)
24d	*a*	**33d** (93)
24e	*a*	**33e** (100)
25b	*a*	**33b** (33), **35b** (67)
dienes		
26	*b*	**32b** (80), **34b** (10)[c]
27,28	*b*	**33b** (80)[c]

[a] Catalytic amount of TsOH in acetic acid, Δ, 4h. [b] TsOH (1 equiv) in acetic acid, Δ, 4h. [c] Isolated initially as a mixture of ethyl esters and carboxylic acids.

As summarized in Table I, exposure of the 1-H and 1-methoxy series β-hydroxy acid and ester substrates to a catalytic amount of *p*-toluenesulfonic acid in acetic acid at reflux for ca. 4 h resulted in smooth rearrangement to give bridgehead-substituted bicyclo[3.2.1]octene derivatives in good to excellent yield. Under similar conditions, the 1-methoxy series diene precursers **26**, **27**, and **28** were recovered unchanged; however, when these dienes were treated at reflux with 1 equiv of TsOH in acetic acid, rearrangement to the 1-substituted bicyclo[3.2.1]octenone nucleus did occur in excellent yield. In each case, the isolated bicyclo[3.2.1]octenone-1-acetic acid products [**32–35** (**a–e**)] were shown to be stable to the reaction conditions.

Rearrangement of the epimeric 1-H series β-hydroxy esters **21** yielded a mixture of two crystalline products which was assigned as the isomeric lactones **29,30**. The contiguous nature of the C-5 oxygen-substituted carbon atom of the lactone group and the C_6–C_7 double bond was established by the observed coupling, $J_{5,6}$ = 4 Hz, in both isomers. The cis fusion of the γ-lactone moiety on the six-membered ring is consistent with the mode of formation (vide infra) and was confirmed in both lactones by an observed long-range (W) coupling of the C-5 hydrogen and the anti C-11 hydrogen in the one-carbon bridge of J = 1 Hz.[17] No evidence for the alternative rearrangement product, lactone **31**, was observed. In the rearrangement of the 1-methoxy series substrates, the exo alcohols **22,24** and the 5-methyl dienes **27,28** gave the *nonconjugated* bicyclo[3.2.1]octenones **32,33** as the exclusive products, while the endo alcohols **23,25** and the 4-methyl diene **26** yielded a mixture of both possible structural isomers, the nonconjugated enones **32,33** and the conjugated bicyclo[3.2.1]octenones **34,35**. The structures assigned to the two series of products are fully consistent with the observed spectral data. In the case of enones **34,35**, the presence of the bicyclo[3.2.1]octenone nucleus is established unambiguously since this carbon skeleton is required to accommodate the observed (IR) α,β-unsaturated carbonyl moiety in these materials. The nonconjugated enones **32,33** are also assigned as bicyclo[3.2.1]octenone derivatives, and in the case of acid **32b** this assignment was confirmed since catalytic hydrogenation of **32b** and the conjugated isomer **34b** yielded the same saturated bicyclic acid **36**.



Attention was next directed toward the preparation of tertiary alcohol **4** and diene **5** precursors containing other functional groups. Treatment of the 4-methyl ketone **12** with Grignard reagents[18] **37** yielded separable mixtures of *exo*-/*endo*-γ-phenylthio alcohols **22h,23h** (94%, 3.5:1) and *exo*-/*endo*-γ-hydroxy ketals **22f,23f** (95%, 2.5:1). Dehydration of the hydroxy ketal mixture **22f,23f** with thionyl chloride/pyridine yielded, after aqueous workup, a crude mixture of two isomers of the β,γ-unsaturated ketone **38** (80%). In the 5-methyl series, addition of the dianion[19] of methyl acetoacetate to ketone **13** gave an exo/endo mixture of γ-hydroxy-β-keto esters **24i,25i** (2:1) in 65% yield. When this mixture is heated (~200 °C), a facile dehydration–decarbethoxylation occurs to give the α,β-unsaturated ketone **39** as the only observed product (83%). This interesting transformation, which may involve the intermediary of lactone **40** and a Stobbe-like elimination, constitutes an attractive alternative to the Wittig–Emmons-type routes to α,β-unsaturated ketones.

Rearrangement of the isomerically pure exo and endo tertiary alcohols **22f** and **23f** and the exo/endo mixture **24i,25i** using a catalytic amount of TsOH in acetic acid, as well as the pure exo and endo alcohols **22h,23h** using 0.5 equiv of TsOH in acetic acid, proceeded analogously to that described above for the β-hydroxy acid/esters to give the bicyclo[3.2.1]octenes shown in Table II. In marked contrast to the α,β-unsaturated esters **26** and **27,28**, the conjugated dienone **39** underwent facile rearrangement when treated with catalytic TsOH in acetic acid to give a mixture of the nonconjugated and conjugated bicyclo[3.2.1]octenones **33j** and **35j** (Table II). When dienones **38** and **39** were treated with 1 equiv of TsOH in acetic acid, the *exclusive* products observed were the conjugated derivatives **41** and **35j**. Presumably, the conjugated tricyclic ketone **41** is formed by acid-catalyzed aldol cyclization of the corresponding conjugated bicyclic enone **34g**. Appropriate control experiments revealed that while the nonconjugated ketones **32g** and **33j** were moderately stable to catalytic TsOH in acetic acid, exposure of these substances to 1 equiv of TsOH in acetic acid resulted in rapid and essentially quantitative rearrangement to the conjugated species **41** and **35j**. Although no detailed kinetic studies were conducted, a qualitative estimate of the relative rates of initial rearrangement of dienone **39** and the nonconjugated product **33j** suggests that both **33j** and the conjugated product **35j** are primary rearrangement products. In separate experiments it was shown that the alternative aldol product **42**, prepared readily from **32g** by base treatment, was stable to exposure to 1 equiv of TsOH in acetic acid at reflux, as was the nonconjugated γ-phenylthiopropyl bridgehead-substituted derivative **32h**.

Discussion

The experimental results summarized in Tables I and II show that both tertiary alcohols **4** and dienes **5** function as efficient precursors of bridgehead-substituted bicyclo[3.2.1]-octene derivatives **9** and **10**. The qualitative differences in the rearrangement conditions required for these two substrates, catalytic TsOH for the tertiary alcohols **4** and, in general, 1

Table II. Rearrangement of Bicyclo[2.2.2]octenes to 1-Propyl and 1-Butylbicyclo[3.2.1]octene Derivatives

substrate	conditions	products (yield, %)
alcohols		
22f	*a*	**32g** (96)
23f	*a*	**32g** (28), **34g** (56)
22h	*c*	**32h** (90)
23h	*c*	**32h** (24), **34h** (64)
24i,25i (2:1)	*a*	**33j** (36), **35j** (36)
dienes		
38	*b*	**41** (96)
39	*a*	**33j** (19), **35j** (57)
39	*b*	**35j** (85)

[a,b] See footnotes *a* and *b* in Table I. [c] TsOH (0.5 equiv) in acetic acid, Δ, 20 h.

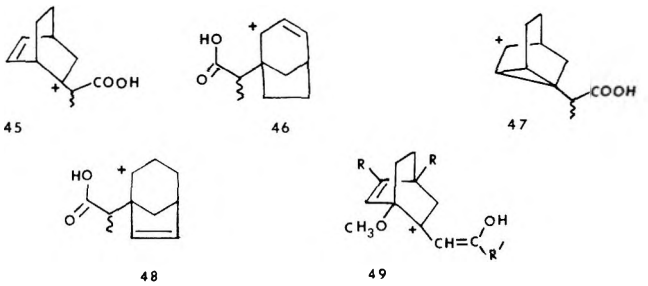
prepared as the major or exclusive products from the 1-methoxy series exo alcohols **22** and **24** as well as from the α,β-unsaturated esters **26** and **27,28**. Alternatively, the preparation of bicyclo[3.2.1]octene derivatives containing functionality only in the three-carbon bridge, e.g., **29, 30, 34,** and **35,** can be realized from the 1-H series exo/endo alcohols **21**, the 1-methoxy series endo alcohols **23** and **25,** and the diene precursors containing a ketone group substituent, e.g., **38** and **39.**

The regioselectivity observed in the rearrangement of the 1-methoxy series exo alcohols **22** and **24** can be rationalized satisfactorily by postulating solvolysis of the tertiary hydroxyl group with concomitant participation of the double bond to furnish a cyclopropylcarbinyl intermediate, e.g., structure **43.** equiv of TsOH for the dienes **5,** suggest that the dienes **5** are not intermediates in the rearrangement of the tertiary alcohols **4.** In terms of the actual synthetic goals, the nonconjugated bicyclo[3.2.1]octenone derivatives containing differentiated functionality in two bridges, e.g., **32** and **33,** can be readily

Assisted fragmentation of **43** (see arrows) yields intermediate **44,** which after hydrolysis gives the nonconjugated bicyclo[3.2.1]octenones **32,33.** The facile fragmentation of cation **43** thus accounts for the exclusive migration of the trans antiparallel vinyl carbon atom observed in the rearrangement of these exo-bicyclo[2.2.2]octenols.

The predominant formation of the conjugated bicyclo[3.2.1]octenones **34** and **35** from rearrangement of the 1-methoxy series endo alcohols **23** and **25** suggests that these products are formed via a concerted trans antiparallel migration (pinacol-type) in which some crossover occurs to give products formally derived from the cyclopropylcarbinyl intermediate **43.**

In contrast to the 1-methoxy series substrates, the regioselectivity observed in the 1-H series exo/endo alcohols **21** appears to involve acid-catalyzed solvolysis of **21** to give cation **45** with concomitant hydrolysis of the *tert*-butyl ester, rearrangement of **45** to the thermodynamically more stable allylic carbonium ion **46,** and finally intramolecular trapping of cation **46** by the carboxyl group via the less strained transition state to give the cis-fused cyclohexene γ-lactone moiety. Delocalization of the cation **45** by π-bond participation to give the cyclopropylcarbinyl species **47** may occur, but in the absence of the bridgehead methoxy group (e.g., **43**), formation



of the isolated secondary carbonium ion **48** (and/or lactone **31**) is apparently not competitive with the formation of the resonance-stabilized cation **46**.

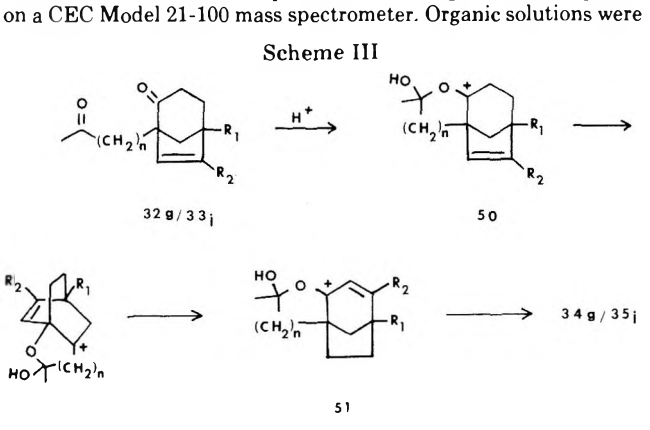
The rearrangement of the 1-methoxy series α,β-unsaturated diene precursors presumably is initiated by initial protonation on the oxygen atom of the carbonyl moiety to generate cation **49**.[20] The preferential formation of the nonconjugated products **32,33** from the α,β-unsaturated ester substrates **26** and **27,28** suggests the intermediacy of the cyclopropylcarbinyl cation **43** followed by fragmentation as described above. The greater regioselectivity shown by the 5-methyl precursors **27,28** as compared to the 4-methyl derivative **26** may be a reflection of the relative stabilities of the cyclopropylcarbinyl cations **43** ($R_2 = CH_3$ vs. $R_2 = H$). The decreased rearrangement regioselectivity exhibited by the α,β-unsaturated ketone **39**, as well as the relative ease with which enone **39** undergoes rearrangement as compared to the α,β-unsaturated esters **27,28**, apparently reflects the relative stability of the initial protonation species **49** ($R' = CH_3$ or $R' = OH$).

Lastly, the rearrangement of the nonconjugated 1-ketoalkylbicyclo[3.2.1]oct-6-en-2-ones **32g** and **33j** to furnish the conjugated derivatives **34g** and **35j** is a mechanistically interesting and a synthetically useful observation. Of the various bridgehead substituent functional groups examined, e.g., aryl, carboxyl, thioether, and keto, only those bicyclo[3.2.1]octenone substrates containing a C-1 keto alkyl substituent undergo further rearrangement when exposed to 1 equiv of TsOH in acetic acid. As shown in Scheme III, this rearrangement is postulated to involve intramolecular participation of the C-1 substituent ketone group to give the oxonium ion **50**, which then rearranges to the *more stable* allyl oxonium ion **51**. Thus, both structural series, **9** and **10**, can be conveniently obtained when a C-1 keto alkyl substituent is present.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer; nuclear magnetic resonance spectra were measured on Varian Associates Model A-60 and HA-100 or Perkin-Elmer Model R-12 spectrometers, and chemical shifts are reported in parts per million downfield (δ) from internal Me_4Si; and ultraviolet spectra were recorded on a Cary Model 14 spectrometer. Low-resolution mass spectra were obtained on a DuPont Model 21-491 mass spectrometer and high-resolution spectra on a CEC Model 21-100 mass spectrometer. Organic solutions were routinely dried over anhydrous $MgSO_4$. Combustion analyses were performed by Chemalytics Inc., Tempe, Ariz.

Scheme III



1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-one (12). Crude chloronitriles **15** (42.3 g, 0.2 mol) and $Na_2S{\cdot}9H_2O$ (144 g, 0.6 mol) were dissolved in 95% ethanol (400 mL) and water (200 mL). The mixture was heated at reflux under N_2 for 15 h, cooled, and extracted with benzene/ether (1:3). The combined organic extracts were washed with brine, the solvent was evaporated, and the residue was distilled to give 25 g (75%) of the known[6] 4-methyl ketone **12**: bp 79–81 °C (0.6 mm); IR ($CHCl_3$) 1730 cm^{-1}; NMR (CCl_4) δ 1.27 (s, 3), 1.35 (2.20 (m, 6), 3.45 (s, 3), 6.05 (d, 1, J = 8.6 Hz), and 6.22 (d, 1, J = 8.6 Hz); mass spectrum, m/e (relative intensity) 166 (5, M^+), 151 (5), 138 (10), 124 (100), 109 (60), 91 (20), and 67 (20).

1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one (13). A. Using the procedure described above for the 4-methyl ketone **12**, reaction of chloronitrile mixture **18a,b** with $Na_2S{\cdot}9H_2O$ (0.1-mol scale) yielded pure 5-methyl ketone **13** in 20–40% yield: bp 68–72 °C (0.2 mm); IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.1 (m, 4), 1.87 (d, 3, J = 1.5 Hz), 2.0 (d, 2, J = 2.5 Hz), 2.67 (m, 1), 3.43 (s, 3), and 5.77 (m, 1); mass spectrum, m/e (relative intensity) 166 (6), 138 (38), 124 (50), 123 (100), 110 (54), 109 (53), and 91 (36).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.95; H, 8.49.

B. Nitrile **18c** (56.5 g, 0.32 mol) in THF (100 mL) was added dropwise at −78 °C to a stirred solution of lithium diisopropylamide (0.33 mol), prepared by the dropwise addition of *n*-butyllithium (2.23 M, 148 mL, 0.33 mol) to diisopropylamine (33.3 g, 0.33 mol) in THF (250 mL) at −78 °C under N_2. After stirring for 1 h, oxygen (dried by passing through a KOH tower) was bubbled into the lithionitrile solution at −78 °C for 5 h. The reaction was quenched with 1 *M* sodium sulfite (300 mL) and allowed to stir for 30 min at 0 °C and then for 12 h at 25 °C. The reaction mixture was extracted with ether, and the combined organic extracts were washed with 2 N sodium hydroxide and saturated brine solution and then dried. The solvent was evaporated and the residue distilled to give 37.7 g (70%) of ketone **73**, bp 80–85 °C (0.6 mm). This material was identical by NMR and IR with that prepared by method A.

1-Methoxy-4-methyl-1,4-cyclohexadiene (14). Lithium wire (11.2 g, 1.6 g-atom) was added in small pieces to a stirred solution of *p*-methylanisole (48.8 g, 0.4 mol), *tert*-butyl alcohol (200 mL), and THF (200 mL) in liquid ammonia (1000 mL). After stirring for 1 h, methanol (80 mL) was added dropwise and the ammonia was allowed to evaporate. Water and ether were added, the organic phase was separated, the aqueous phase was extracted with fresh ether, and the combined organic phases were washed with a saturated brine solution and then dried (K_2CO_3). The organic solvent was evaporated and the residue distilled to give 38.9 g (78%) of pure diene **14**: bp 71–73 °C (23 mm) [lit.[21] bp 74 °C (17 mm)]; NMR (CCl_4) δ 1.67 (broad s, 3), 2.63 (broad s, 4), 3.46 (s, 3), 4.46 (m, 1), and 5.28 (m, 1).

1-Methoxy-2-chloro-2-cyano-4-methylbicyclo[2.2.2]oct-5-ene (15). Diene **14** (6.2 g, 0.05 mol) was added dropwise to a solution of freshly distilled 2-chloroacrylonitrile (8.8 g, 0.1 mol) and phenothiazine (50 mg) in benzene (45 mL). The resulting mixture was treated at reflux for 9 h under N_2. The benzene and excess 2-chloroacrylonitrile were removed by distillation, and the residue solidified on standing at 0 °C to give 9.9 g (85%) of a mixture of known[6] bicyclic chloronitriles **15**; crystallization from hexane yielded a single epimer of **15**: mp 64–65 °C; IR ($CHCl_3$) 2240 cm^{-1}; NMR (CCl_4) δ 1.18 (s, 3), 1.35, 2.50 (m, 6), 3.48 (s, 3), 6.04 (d, 1, J = 8.6 Hz), and 6.23 (d, 1, J = 8.6 Hz); mass spectrum, m/e (relative intensity) 211 (very weak) 183 (5), 175 (2), 160 (2), 148 (30), 124 (100), 109 (35), 91 (6), and 77 (8).

1-Methoxy-5-methyl-1,4-cyclohexadiene (16) was prepared from *m*-methylanisole using the procedure described above in 80% yield: bp 77–79 °C (25–28 mm) [lit.[22] bp 75–77 °C (aspirator pressure)]; IR ($CHCl_3$) 1700 and 1670 cm^{-1}; NMR (CCl_4) δ 1.68 (s, 3), 2.59 (m, 4), 3.46 (s, 3), 4.50 (m, 1), and 5.31 (m, 1); mass spectrum, m/e (relative intensity) 124 (100), 123 (31), 122 (31), 109 (76), and 91 (28).

1-Methoxy-2-chloro-2-cyano-5-methylbicyclo[2.2.2]oct-5-ene (18a,b). Using the general procedure described above for **15** with the *crucial* modification that the benzene solvent was distilled from $LiAlH_4$ prior to use, diene **16** and 2-chloroacrylonitrile furnished a quantitative yield of crude cycloaddition products. VPC analysis (QF-1, 180 °C) revealed a 9:1 mixture of **18a,b** and the enol ether of **19**. This mixture was separated by chromatography on Al_2O_3 using hexane/ethyl acetate to give a 2:1 mixture of chloronitriles **18a,b** (90%): NMR (CCl_4) δ 1.33–2.75 (m, 7), 1.83 (d, 3, J = 1.5 Hz), 3.44 (s, 3), 5.8 (m, 0.67), and 5.95 (m, 0.33).

Crystallization of this mixture from hexane yield the pure exo nitrile–endo chloro derivative **18a**: mp 85–87 °C; IR (CCl_3) 2250 and

1650 cm^{-1}; NMR ($CDCl_3$) δ 1.33–2.75 (m, 7), 1.83 (d, 3, J = 1.5 Hz), 3.44 (s, 3), and 5.75 (m, 1); mass spectrum, m/e (relative intensity) 211 (1), 148 (33), 124 (100), and 109 (78).

Anal. Calcd for $C_{11}H_{14}ClNO$; C, 62.40; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.44; H, 6.67; Cl, 16.92; N, 6.56.

Treatment of the minor chromatography fraction with dilute hydrochloric acid furnished, after crystallization from ether/hexane, a material tentatively assigned structure **19:** mp 160–162 °C; IR (CCl_4) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (s, 3) and 1.7–3.15 (m, 9); mass spectrum, m/e (relative intensity) 199 (5), 197 (14), 124 (80), 118 (57), 110 (100), 109 (47), 95 (75), 77 (50), 55 (80), 41 (62), 39 (67), and 27 (43).

Anal. ($C_{10}H_{12}NOCl$): calcd mol wt, 197.0607; found, 197.0615.

1-Methoxy-2-cyano-5-methylbicyclo[2.2.2]oct-5-ene (18c). A mixture of diene **16** (44.0 g, 0.36 mol), acrylonitrile (37.6 g, 0.71 mol), and hydroquinone (10 mg) was placed in a stainless steel bomb and heated at 120 °C for 16 h. After cooling, the reaction mixture was dissolved in ether and filtered through Al_2O_3. Distillation gave 49.1 g (76%) of a 1:1 mixture of nitriles **18c:** bp 107–110 °C (0.5 mm); IR ($CHCl_3$) 2225 cm^{-1}; NMR (CCl_4) δ 1.26–2.9 (m, 8), 1.80 (d, 1.5, J = 1.5 Hz), 1.85 (d, 1.5, J = 1.5 Hz), 3.35 (s, 3), and 5.9 (m, 1); mass spectrum, m/e (relative intensity) 177 (5), 130 (27), 124 (100), 123 (57), 109 (75), and 91 (22). VPC analysis (5% SE 30, 180 °C) indicated a 1:1 mixture of isomers.

Alternatively, reduction of chloronitrile **18a** with lithium in liquid ammonia furnished nitrile **18c** in 72% yield.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.28; H, 8.34; N, 8.19.

***tert*-Butyl 2-(2-Hydroxybicyclo[2.2.2]oct-5-en-2-yl)propionate (21).** A solution of ketone **11**[5] (48.9 g, 0.44 mol) and *tert*-butyl 2-bromopropionate[23] (109.0 g, 0.52 mol) in THF (300 mL) was added gradually to a mixture of magnesium[24] (18.3 g, 0.8 g-atom), iodine (one crystal), and methyl iodide (3 drops) in THF (300 mL) heated at reflux under N_2. After the vigorous reaction subsided, the mixture was heated at reflux for an additional 12 h and then cooled and added to ice-cold 1 M sulfuric acid (1 L). This resulting mixture was extracted with ether. After drying, the ether was evaporated and the residue was distilled to give 90.8 g (81%) of product **21,** which contained two major components by TLC: bp 91–92 °C (0.1 mm); IR (CCl_4) 3479 and 1700 cm^{-1}; NMR (CCl_4) δ 1.0–2.7 (m, 12), 1.45 (d, 9, J = 3 Hz), 3.3–3.7 (m, 1), and 6.18 (m, 2).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 70.99; H, 9.59.

Ethyl (1-Methoxy-2-hydroxy-4-methylbicyclo[2.2.2]oct-5-en-2-yl)acetate (22a,23a). Using the general procedure of Rathke,[11b] 4-methyl ketone **12** (13.3 g, 0.08 mol), activated[25] zinc (8.8 g, 0.12 g-atom), and ethyl bromoacetate (13.3 g, 0.12 mol) in THF (25 mL) and trimethyl borate (25 mL) yielded, after 48 h at room temperature, 4.0 g of recovered 4-methyl ketone 12 and 11.0 g (80%) of a 1:1 mixture (by NMR) of hydroxy esters **22a** and **23a,** bp 117–125 °C (0.4 mm), which could not be separated by crystallization or chromatography: IR ($CHCl_3$) 3530, 1715, and 1600 cm^{-1}; NMR (CCl_4) δ 1.10 (s, 1.5), 1.13 (s, 1.5), 1.25 (t, 3, J = 7.0 Hz), 3.32 (s, 1.5), 3.37 (s, 1.5), 4.0 (q, 2, J = 7.0 Hz), and 6.0 (m, 2); mass spectrum, m/e (relative intensity) 254 (very weak, M^+), 237 (5), 209 (10), and 124 (100).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.85; H, 8.86.

2-(2-[1-Methoxy-2-hydroxy-4-methylbicyclo[2.2.2]oct-5-en-2-yl]ethyl)-2-methyl-1,3-dioxolane (22f,23f). A solution of the Grignard reagent **37b** prepared from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (1.95 g, 10 mmol) using the procedure of Ponaras[18b] was added at 0 °C to a stirred solution of 4-methyl ketone **12** (1.40 g, 8.4 mmol) in THF (10 mL). After stirring for 5 h at room temperature, the reaction mixture was added to ammonium chloride (20%, 40 mL) and extracted with ether. The combined extracts were washed with water and then brine, dried, and evaporated to yield 2.1 g (87.5%) of crude product. Chromatography of a portion of this crude product (1.0 g) on silica gel using ether/pentane (1:1) yielded recovered 4-methyl ketone **12** (150 mg), pure liquid *endo*-hydroxy ketal **23f** (240 mg, 27% overall yield), and crystalline *exo*-hydroxy ketal **22f** (600 mg, 68% overall yield). Pure **22f** could also be obtained by crystallization of the crude product from ether/pentane. Pure **23f:** NMR (CCl_4) δ 1.12 (s, 3), 1.25 (s, 3), 1.30–2.00 (m, 10), 3.40 (s, 3), 3.86 (s, 4), 5.94 (d, 1, J = 9.0 Hz), and 6.26 (d, 1, J = 9.0 Hz); mass spectrum, m/e (relative intensity) 282 (very weak), 267 (1), 221 (3), 167 (1), 135 (5), 124 (100), 109 (20), and 87 (15).

Anal. ($C_{16}H_{26}O_4$); calcd mol wt, 282.1834; found, 282.1843.

Pure **22f:** mp 68.5–~69.5 °C; NMR (CCl_4) δ 1.10 (s, 3), 1.20 (s, 3), 1.25–2.00 (m, 10), 3.32 (s, 3), 3.81 (s, 4), 5.82 (d, 1, J = 9.0 Hz), and 6.20 (d, 1, J = 9.0 Hz); mass spectrum, m/e (relative intensity) 282 (very weak), 267 (1), 221 (1), 162 (1), 138 (9), 124 (100), 109 (22), and 87 (30).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.08; H, 9.22. Found: C, 68.02; H, 9.54.

1-Methoxy-2-hydroxy-2-(γ-phenylthiopropyl)-4-methylbicyclo[2.2.2]oct-5-ene (22h,23h). The Grignard reagent[18a] generated from 3-bromopropyl phenyl sulfide (1.62 g, 7 mmol) and magnesium (170 mg, 7 mmol) in ether (10 mL) was added dropwise to the 4-methyl ketone **12** (500 mg, 3 mmol) in ether (10 mL) in an ice–water bath. After stirring for 6 h at room temperature, the reaction mixture was added to ammonium chloride (30 mL) and extracted with ether. The combined extracts were washed with water and then brine, dried, and evaporated to yield 950 mg (≈100%) of crude product. Chromatography of this crude product on silica gel using ether/pentane (2:1) yielded pure liquid *endo*-γ-phenylthio alcohol **23h** (200 mg, 21% overall yield) and crystalline *exo*-γ-phenylthio alcohol **22h** (700 mg, 74% overall yield). Pure **22h** could also be obtained by crystallization of the crude product from ether/pentane. Pure **23h:** NMR (CCl_4) δ 1.09 (s, 3), 1.20–~2.00 (m, 10), 2.93 (t, 2, J = 6.0 Hz), 3.37 (s, 3), 5.91 (d, 1, J = 8 Hz), 6.21 (d, 1, J = 8 Hz), and 7.23 (broad s, 5). Pure **22h:** mp 72–~73 °C; NMR (CCl_4) δ 1.07 (s, 3), 1.15–~2.0 (m, 10), 2.83 (t, 2, J = 6 Hz), 3.31 (s, 3), 5.80 (d, 1, J = 9 Hz), 6.17 (d, 1, J = 9 Hz), 7.22 (broad s, 5); mass spectrum (low temperature), m/e (relative intensity) 318 (30, M^+), 286 (5), 261 (3), 205 (10), 191 (12), 152 (10), 136 (10), 124 (100), and 109 (50).

Anal. Calcd for $C_{19}H_{26}O_2S$: C, 71.70; H, 8.18; S, 10.06. Found: C, 71.88; H, 8.05; S, 9.97.

(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)acetic Acid (24b,25b). To a stirred solution of lithium diisopropylamide at −20 °C, prepared by the dropwise addition of *n*-butyllithium in ether (2.23 M, 60 mL, 0.14 mol) to diisopropylamine (14.2 g, 0.14 mol) in THF (100 mL) at −20 °C, was added a solution of acetic acid (4.2 g, 0.07 mol) in THF (10 mL) dropwise. The reaction mixture was stirred for 30 min at −20 °C and then at 40–50 °C for 1 h. This mixture was cooled to 0 °C, the 5-methyl ketone **13** (10.0 g, 0.06 mol) in THF (20 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 1 h and then at 25 °C for 12 h. After acidification with dilute HCl, the reaction mixture was extracted with ether. The combined organic extracts were extracted with 0.3 N NaOH, and the basic aqueous phase was acidified with cold 10% HCl and then extracted with ether to yield 5.5 g (81% based on 48% conversion) of a 1:1 mixture (by NMR) of hydroxy acids **24b** and **25b:** IR ($CHCl_3$) 3350–2850, 1700, and 1645 cm^{-1}. Crystallization of this mixture from ether yielded pure endo isomer **25b:** mp 105–107 °C; NMR ($CDCl_3$) δ 1.37–1.90 (m, 6), 1.85 (d, 3, J = 1.5 Hz), 2.35 (m, 1), 2.49 (d, 1, J = 15 Hz), 2.92 (d, 1, J = 15 Hz), 3.39 (s, 3), and 5.9 (m, 1); mass spectrum, m/e (relative intensity) 180 (13), 138 (29), 124 (100), 123 (67), 109 (52), and 91 (41). The mother liquors contained a 2:1 mixture of **24b** and **25b.** The characteristic NMR signals of **24b** were ($CDCl_3$) δ 2.44 (d, 1, J = 15 Hz) and 2.77 (d, 1, J = 15 Hz).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.78; H, 7.75.

2-(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)propionic Acid (24c,25c). Using the general procedure described above, 5-methyl ketone **13** (4.5 g, 27 mmol) and propionic acid (2.0 g, 27 mmol) furnished 2.3 g (64% based on 56% conversion) of a 2:1 mixture (by NMR) of **24c** and **25c.** The major component was obtained by crystallization from acetonitrile and was assigned structure **24c:** mp 134–135 °C; IR ($CHCl_3$) 3500–2500 and 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.05–2.6 (m, 8), 1.18 (d, 3, J = 7 Hz), 1.77 (d, 3, J = 1.5 Hz), 3.29 (s, 3), and 5.92 (m, 1); mass spectrum, m/e (relative intensity) 194 (2), 124 (100), and 109 (41). The mother liquors contained a 1:1 mixture of **24c** and **25c.** The characteristic NMR methyl signal for **25c** was ($CDCl_3$) δ 1.22 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.26; H, 8.39.

(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)phenylacetic Acid (24d,25d). Using the general procedure described above, 5-methyl ketone **13** (2.0 g, 12 mmol) and phenylacetic acid (1.63 g, 12 mmol) furnished 1.7 g (60% based on 78% conversion) of a 2:1 mixture (by NMR) of **24d** and **25d.** The major component was obtained by crystallization from acetonitrile and was assigned structure **24d:** mp 189–191 °C; IR ($CHCl_3$) 3450, 3300–2800, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.14–2.34 (m, 7), 1.77 (d, 3, J = 1.5 Hz), 3.20 (s, 3), 3.48 (s, 1), 5.95 (m, 1), and 7.18–7.62 (m, 5); mass spectrum, m/e (relative intensity) 256 (4), 138 (78), 136 (48), 124 (100), 123 (95), 118 (50), 110 (85), 109 (73), 91 (71), and 65 (60). The mother liquors contained a 1:1 mixture of **24d** and **25d.** The characteristic NMR methine signal for **25d** was ($CDCl_3$) δ 3.50 (s, 1).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.63; H, 7.32.

(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-

yl)-*m*-methoxyphenylacetic Acid (24e,25e). Using the general procedure described above, 5-methyl ketone **13** (4.0 g, 24 mmol) and *m*-methoxy phenylacetic acid (4.32 g, 26 mmol) furnished 4.97 g (83% based on 75% conversion) of a 4:1 mixture (by NMR) of **24e** and **25e.** The major component was obtained by crystallization from acetonitrile and was assigned structure **24e:** mp 186–187 °C; IR ($CHCl_3$) 3400, 3300–2800, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.17–2.33 (m, 7), 1.75 (d, 3, J = 1.5 Hz), 3.22 (s, 3), 3.45 (s, 1), 3.77 (s, 3), 5.95 (m, 1), and 6.7–7.3 (m, 4); mass spectrum, *m/e* (relative intensity) 286 (5), 166 (75), 148 (76), 138 (52), 124 (100), 123 (87), 121 (78), 110 (36), 109 (30), and 91 (52). The mother liquors contained a 1:1 mixture of **24e** and **25e.** The characteristic NMR methine signal for **25e** was ($CDCl_3$) δ 3.49 (s, 1).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.67; H, 7.48.

Methyl 4-(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)-3-oxobutanoate (24i,25i). Methyl acetoacetate (0.70 g, 6 mmol) was added dropwise to the cooled slurry of sodium hydride (0.30 g, 7 mmol) in THF (25 mL) at 0 °C. After stirring for 10 min at 0 °C, *n*-butyllithium (4.5 mL, 1.6 M, 7 mmol) was added dropwise, and the reaction was allowed to stir at 0 °C for 10 min. The 5-methyl ketone **13** (1.00 g, 6 mmol) was added in one portion, and the reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 2 h. Concentrated hydrochloric acid (2 mL), water (100 mL), and ether (35 mL) were added, the reaction mixture was extracted with ether, and the combined organic extracts were washed with brine, dried, and then evaporated to give a residue which was purified by chromatography on Al_2O_3 with hexane/ethyl acetate to give 1.12 g (65%) of a 2:1 mixture (by NMR) of **24i** and **25i** which was not separated: IR (CCl_4) 3500, 1750, 1705, and 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.3–3.05 (m, 10), 1.75 (d, 2, J = 1.5 Hz), 1.81 (d, 1, J = 1.5 Hz), 3.34 (s, 2), 3.39 (s, 1), 3.54 (s, 1.33), 3.64 (s, 0.67), 3.73 (s, 3), and 5.7–5.93 (m, 1); mass spectrum, *m/e* (relative intensity) 264 (2), 124 (100), 123 (50), 109 (45), and 91 (23).

Anal. ($C_{15}H_{22}O_5$): calcd mol wt for $M^+ - 18$, *m/e* 264.1362; found, *m/e* 264.1361.

Ethyl (1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-ylidine)acetate (26). Thionyl chloride (0.57 g, 4.8 mmol) was added dropwise to a stirred solution of β-hydroxy esters **22a/23a** (1.00 g, 4 mmol) in pyridine (10 mL) at 0 °C. After the addition was completed, the mixture was allowed to warm to 25 °C. It was stirred for 1 h, poured into ice water, and, after acidification with 20% HCl, extracted with ether. After drying, evaporation of the ether yielded 700 mg (74%) of crude liquid diene **26,** which could be purified by chromatography on alumina with pentane/ether (2:1). Diene 26: IR ($CHCl_3$) 1705 and 1650 cm^{-1}; NMR (CCl_4) δ 1.23 (t, 3, J = 8 Hz), 1.25 (s, 3), 1.40–~3.00 (m, 6), 3.41 (s, 3), 4.07 (q, 2, J = 8.0 Hz), 5.81 (t, 1, J = 2.0 Hz), 6.00 (d, 1, J = 8.0 Hz), 6.21 (d, 1, J = 8.0 Hz); mass spectrum, *m/e* (relative intensity) 236 (5, M^+), 208 (100), 179 (18), 162 (50), 147 (25), 135 (20), 121 (15), and 91 (14).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47. Found: C, 70.27; H, 8.19.

Ethyl (1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-ylidene)acetate (27,28). Method A. Thionyl chloride was added dropwise to a solution of β-hydroxy esters **24a/25a** (5.1 g, 0.02 mol) in pyridine (25 mL) at 0 °C. The reaction mixture was stirred for 8 h as it warmed to room temperature and then poured into ice. The mixture was acidified with 10% HCl and extracted with ether. The ether solution was washed with H_2O and dried. The solvent was evaporated at reduced pressure, and the residue was distilled to give 1.7 g (36%) of diene **27:** bp 125–130 °C (0.7 mm); IR (CCl_4) 1710 and 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, 3, J = 7 Hz), 1.83 (d, 3, J = 1.5 Hz), 1.43–2.75 (m, 7), 3.46 (s, 3), 4.06 (q, 2, J = 7 Hz), and 5.82 (m, 2); mass spectrum, *m/e* (relative intensity) 236 (17, M^+), 208 (100), 179 (53), 135 (40), 124 (33), and 91 (28).

Method B. *n*-Butyllithium (1.33 M, 15 mL, 20 mmol) was added dropwise to a solution of diisopropylamine (2.02 g, 20 mmol) in tetrahydrofuran (100 mL) at −70 °C. After 15 min, ethyl trimethylsilylacetate (3.2 g, 20 mmol) was added dropwise over a 10-min period and the mixture was stirred for 10 min at −70 °C. Ketone **13** (1.66 g, 10 mmol) in tetrahydrofuran (20 mL) was added dropwise, and the resulting solution was stirred at −70 °C for 1 h, at −25 °C for 1 h, and at 25 °C for 6 h. The mixture was acidified with 10% HCl and extracted with ether. The ether solution was washed with H_2O and dried. The solvent was evaporated in vacuo, and the residue was chromatographed (Al_2O_3, hexane/ethyl acetate) to give 1.40 g (60%) of a 2:1 mixture (NMR) of dienes **27** and **28.** The distinguishing NMR signals ($CDCl_3$) for **28** were δ 1.31 (t, 3, J = 7 Hz), 3.35 (s, 3), 4.20 (q, 2, J = 7 Hz), 5.56 (t, 1, J = 2 Hz), and 5.89 (m, 1).

Anal. ($C_{14}H_{20}O_3$): calcd mol wt, 236.1421; found, 236.1419.

Rearrangement of 2-Hydroxybicyclo[2.2.2]oct-5-en-2-yl Derivatives: General Procedures. A. A mixture in the approximate ratio of bicyclic alcohol or diene (1 mmol), acetic acid (10 mL), and *p*-toluenesulfonic acid (ca. 10 mg) was heated at reflux for 4 h, and then the acetic acid was evaporated at reduced pressure and the product was isolated by normal workup.

B. This was identical with procedure A, except that 1 mmol of *p*-toluenesulfonic acid was used per 1 mmol of bicyclic substrate.

Rearrangement of hydroxy esters 21 (90.8 g, 0.38 mol) using procedure A yielded 48.2 g (70%) of 2-methyl-4-oxatricyclo[6.2.1.$0^{1,5}$]undec-6-en-3-one (**29/30**). Fractional crystallization from ethyl acetate/ether yielded one pure epimer: mp 105–105.5 °C; IR (CCl_4) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3, J = 8 Hz), 1.3–2.0 (m, 6), 2.42 (q, 1, J = 7 Hz), 2.6 (m, 1), 4.45 (dd, 1, J = 4 and 1 Hz), 5.7 (dd, 1, J = 10 and 4 Hz), and 6.4 (dd, 1, J = 10 and 6 Hz). Fractional crystallization from *n*-hexane yielded the other epimer: mp 57–58 °C; IR (CCl_4) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.1 (d, 3, J = 8 Hz), 1.2–2.0 (m, 6), 2.6 (m, 1), 2.75 (q, 1, J = 7 Hz), 4.25 (dd, 1, J = 4 and 1 Hz), 5.7 (dd, 1, J = 10 and 4 Hz), and 6.4 (dd, 1, J = 10 and 6 Hz). When treated with sodium methoxide, the two epimers were interconverted and the mp 105 °C epimer predominated at apparent equilibrium. Mass spectrum, *m/e* (relative intensity) 178 (9), 176 (49), 161 (36), 148 (70), 123 (43), 106 (47), 105 (100), 91 (73), 79 (51), and 69 (45).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.01; H, 7.56.

Rearrangement of hydroxy esters 22a,23a (1:1, 2.0 g, 8.0 mmol) using procedure A yielded 1.30 g (73%) of a 2:1 mixture (by NMR) of esters **32a** and **34a** and 325 mg (21%) of a 1:1 mixture (by NMR) of acids **32b** and **34b.** Hydrolysis of esters **32a,34a** with aqueous methanolic KOH gave, in 80% yield, acids **32b** and **34b.** This mixture of acids was separated by fractional crystallization from ether/pentane to give (5-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)acetic acid (**32b**) [mp 60–61 °C; IR ($CHCl_3$) 3600, 3400–2800, and ≈1710 (broad) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 3), 1.3–2.0 (m, 4), 2.05 (m, 2), 2.60 (s, 2), and 5.95 (s, 2); mass spectrum, *m/e* (relative intensity) 194 (10, M^+), 176 (20), and 93 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.73; H, 7.44.] and (5-methylbicyclo[3.2.1]oct-3-en-2-on-1-yl)acetic acid (**34b**) [mp 121–123 °C; IR ($CHCl_3$) 3400–2800, 1710, and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 3), 1.5–2.3 (m, 6), 2.50 (d, 1, J = 17 Hz), 2.95 (d, 1, J = 17 Hz), 5.93 (d, 1, J = 9.0 Hz), and 7.07 (dd, 1, J = 9 and 2 Hz); mass spectrum, *m/e* (relative intensity) 194 (60, M^+), 176 (60), 166 (30), 148 (50), 138 (40), 134 (20), 120 (15), 105 (30), and 95 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.87; H, 7.52.].

Rearrangement of *exo*-hydroxy acid 24c (0.24 g, 1 mmol) using procedure A yielded 0.18 g (90%) of 2-(6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)propionic acid (**33c**): mp 123–125 °C; IR ($CHCl_3$) 3400–2800 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (d, 3, J = 7 Hz), 1.83 (d, 3, J = 1.5 Hz), 1.75–2.8 (m, 7), 3.03 (q, 1, J = 7 Hz), 5.3 (m, 1), and 10.83 (s, 1); mass spectrum, *m/e* (relative intensity) 208 (23), 152 (57), 107 (100), and 91 (20).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.03; H, 8.00.

Rearrangement of *exo*-hydroxy acid 24d (296 mg, 1 mmol) using procedure A gave 247 mg (93%) of (6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)phenylacetic acid (**33d**): mp 196–198 °C; IR ($CHCl_3$) 3300–2800 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.7 (m, 7), 1.68 (d, 3, J = 1.5 Hz), 4.30 (s, 1), 5.24 (m, 1), and 7.28 (s, 5); mass spectrum, *m/e* (relative intensity) 270 (6), 214 (21), 170 (30), 169 (100), 118 (38), and 91 (60).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.41; H, 6.80.

Rearrangement of *exo*-hydroxy acid 24e (420 mg, 1.3 mmol) using procedure A furnished 380 mg (100%) of (6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)-*m*-methoxyphenylacetic acid (**33e**): mp 194–195 °C; IR ($CHCl_3$) 3500–2800 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.8 (m, 7), 1.68 (d, 3, J = 1.5 Hz), 3.75 (s, 3), 4.25 (m, 1), 6.7–7.25 (m, 4), and 8.4–8.75 (m, 1); mass spectrum, *m/e* (relative intensity) 300 (27), 244 (33), 199 (64), 166 (92), 148 (31), 124 (45), 121 (100), and 91 (37).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.90.

Rearrangement of *endo*-hydroxy acid 25b (440 mg, 1.9 mmol) using procedure A gave 370 mg (100%) of a 2:1 mixture (by NMR) of keto acids **35b** and **33b.** Crystallization of this mixture from ether gave the major isomer, (4-methylbicyclo[3.2.1]oct-3-en-2-on-1-yl)acetic acid (**35b**): mp 145–146.5 °C; IR ($CHCl_3$) 3500–2600, 1710, 1670, and 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.9 (m, 6), 2.04 (d, 3, J = 1.5 Hz), 2.50 (d, 1, J = 16 Hz), 2.86 (d, 1, J = 16 Hz), 2.79 (m, 1), 5.69 (m, 1), and 8.58–9.16 (m, 1); mass spectrum, *m/e* (relative intensity) 194 (57), 148 (28), 138 (39), 95 (100), 93 (50), and 67 (37).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.73; H,

7.08.

The minor isomer was assigned as (6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)acetic acid (**33b**) on the basis of the following data for the methyl ester (CH_2N_2) of **33b**: IR (CCl_4) 1740 and 1710 cm^{-1}; NMR (CCl_4) δ 1.6–2.7 (m, 9), 1.82 (d, 3, J = 1.5 Hz), 3.55 (s, 3), and 5.47 (m, 1).

Anal. ($C_{12}H_{16}O_3$): calcd mol wt, 208.1099; found, 208.1099.

Rearrangement of α,β-Unsaturated Ester 26. Using procedure B, ester **26** (260 g, 11 mmol) gave 730 mg (30%) of neutral products, which were shown by NMR to be a 2:1 mixture of esters **32a** and **34a**, and 1.28 g (60%) of acid **32b**. The ester mixture was hydrolyzed with 5% methanolic KOH (70% yield), and after separation of the mixture by crystallization the individual acids from the product ester, as well as the initial acid product, were identified by spectral comparison (IR and NMR) with authentic material.

Rearrangement of α,β-Unsaturated Esters 27,28. Using procedure B, ester **27**, a mixture of esters **27,28**, and a sample of α,β-unsaturated acids obtained by base hydrolysis of **27,28** gave an ca. 80% yield of product. In the case of the ester substrates, the initial product contained 50% neutral material, assigned as ester **33a** on the basis of spectral data [IR (CCl_4) 1730 and 1710 cm^{-1}; NMR (CCl_4) δ 1.22 (t, 3, J = 7 Hz), 1.85 (d, 3, J = 1.5 Hz), 1.50–2.75 (m, 9), 4.03 (q, 2, J = 7 Hz), and 5.50 (m, 1)], and 30% of an acidic material, identified as acid **33b** by a comparison of IR and NMR data with authentic material. Rearrangement of the precursor unsaturated acids gave acid **33b** as the only observed product.

(5-Methylbicyclo[3.2.1]octan-2-on-1-yl)acetic Acid (36). A stirred ca. 2:1 mixture of unsaturated keto acids **32b** and **34b** (120 mg, 0.62 mmol) and a catalytic amount of PtO_2 in glacial acetic acid (10 mL) was allowed to react with hydrogen gas at 25 °C and atmospheric pressure until the uptake of hydrogen ceased (30 min). The reaction mixture was filtered, concentrated, dissolved in ether, and extracted with sodium bicarbonate. The aqueous extracts were acidified with 10% HCl and extracted with ether, and after drying the organic phase was evaporated to give 120 mg (100%) of crude acid **36** [NMR ($CDCl_3$) δ 1.15 (s, 3), 1.50–2.10 (m, 8), and 2.30–2.70 (m, 4)], which was characterized as its methyl ester (CH_2N_2, 100%): IR ($CHCl_3$) 1735 and 1705 cm^{-1}; NMR (CCl_4) δ 1.16 (s, 3), 1.50–2.0 (m, 8), 2.2–2.5 (m, 4), and 3.59 (s, 3); mass spectrum, m/e (relative intensity) 210 (25, M^+), 195 (10), 179 (30), 153 (100), 135 (8), 121 (30), 107 (15), 93 (100), and 81 (65). VPC analysis (10% SE 30) of this ester showed a single component; the sharp quaternary methyl group signal in the NMR spectrum of both the acid **36** and its methyl ester confirms the presence of a single hydrogenation product from both unsaturated keto acids.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.66; H, 8.59.

1-(1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-ylidene)-3-butanone (38). A 1:2 mixture of hydroxy ketal **22f,23f** (1.00 g, 3.5 mmol) was dissolved in pyridine (20 mL). The solution was cooled in an ice bath, and thionyl chloride (520 mg, 4.3 mmol) was added dropwise to the stirred solution. The mixture was then stirred at room temperature for an additional hour. The resulting suspension was poured onto cracked ice, and the mixture was acidified with cold 20% hydrochloric acid and then extracted with ether. The organic phase was dried and evaporated to give 620 mg (80%) of crude dienone **38** which by NMR was a 1:1 mixture of the two geometrical isomers. The crude product **38**, which was used without further purification, showed the following: IR ($CHCl_3$) 1715 and 1710 cm^{-1}; NMR (CCl_4) δ 1.22 (s, 1.5), 1.25 (s, 5), 2.06 (s, 1.5), 2.08 (s, 1.5), 3.42 (s, 1.5), 3.51 (s, 1.5), and 5.30–≈6.50 (m, 1). All attempts to prepare an analytical sample were unsuccessful.

1-(1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-ylidene)-2-propanone (39). The γ-hydroxy-β-keto esters **24i,25i** (2:1 mixture) (4.42 g, 15.6 mmol) were distilled (pot temperature, 190–220 °C) to furnish 2.70 g (83%) of **39**: bp 130–137 °C (1 mm); IR (CCl_4) 1680 and 1610 cm^{-1}; NMR (CCl_4) δ 1.30–1.70 (m, 4), 1.84 (d, 3, J = 1.5 Hz), 2.11 (s, 3), 2.45–2.70 (m, 3), 3.40 (s, 3), 5.83 (m, 1), and 6.62 (t, 1, J = 2 Hz); mass spectrum, m/e (relative intensity) 206 (11, M^+), 178 (68), 135 (100), 124 (85), 109 (60), and 91 (35).

Anal. ($C_{13}H_{18}O_2$): calcd mol wt, 206.1307; found, 206.1300.

Conjugated Tricyclic Dienone 41. A mixture of bicyclic dione **32g** (103 mg, 0.5 mmol) and TsOH (95 mg, 0.5 mmol) in acetic acid (5 mL) was heated at reflux for 10 h, the acetic acid was then evaporated at reduced pressure, and, after normal workup, 90 mg (95%) of a 9:1 (by NMR) mixture of products was isolated. After separation by chromatography on silica gel, the minor component was identified as the nonconjugated tricyclic dienone **42** by spectral comparison (IR and NMR) with authentic material. The major component was assigned as the conjugated tricyclic dienone **41** on the basis of the following data: UV (MeOH) λ_{max} 290 nm (log ϵ 4.38); IR ($CHCl_3$) 1650 and 1610 cm^{-1}; NMR (CCl_4) δ 1.24 (s, 3), 1.40–≈2.50 (m, 10), 5.46 (s, 1), 6.02 (d, 1, J = 9 Hz), and 6.25 (d, 1, J = 9 Hz); mass spectrum, m/e (relative intensity) 188 (66, M^+), 160 (40), 146 (21), 132 (60), 118 (100), 104 (26), and 91 (35).

Anal. ($C_{13}H_{16}O$): calcd mol wt, 188.1201; found, 188.1208.

Conjugated Tricyclic Dienone 42. Bicyclic dione **32g** (688 mg, 3.34 mmol) in benzene (10 mL) was added to a suspension of potassium *tert*-butoxide (561 mg, 5 mmol) in benzene (90 mL). The dark colored solution was heated at reflux for 5 h and then acidified with 5% hydrochloric acid until the color turned yellow. The organic layer was separated, and the aqueous layer was then extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate, water, and then brine. After drying, evaporation yielded 600 mg (95%) of crude product. Chromatography of this crude product on silica gel with ether/pentane (1:1) yielded 490 mg (78%) of pure liquid tricyclic dienone **42**: UV (MeOH) λ_{max} 242 nm (log ϵ 4.3); IR ($CHCl_3$) 1670 and 1615 cm^{-1}; NMR (CCl_4) δ 1.17 (s, 3), 1.30–≈2.70 (m, 10), 5.64 (m, 1), and 5.73 (s, 2); mass spectrum, m/e (relative intensity) 188 (54, M^+), 160 (100), 145 (30), 132 (70), 118 (80), 105 (20), 91 (40), and 77 (30).

Anal. ($C_{13}H_{16}O$): calcd mol wt, 188.1201; found, 188.1207.

Rearrangement of *exo*-hydroxy ketal 22f (980 mg, 3.5 mmol) using procedure A yielded a mixture of ethylene glycol diacetal and a bicyclo[3.2.1]octenone product which was separated by treatment with excess sodium methoxide in methanol (25 °C, 1 h) followed by chromatography on silica gel using ether/pentane to give 688 mg (96%) of liquid 4-(5-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)butan-2-one (**32g**): IR ($CHCl_3$) 1705 cm^{-1}; NMR (CCl_4) δ 1.24 (s, 3), 1.5–2.0 (m, 6), 2.08 (s, 3), 2.2–2.7 (m, 4), 5.66 (d, 1, J = 6.0 Hz), and 5.89 (d, 1, J = 6.0 Hz); mass spectrum, m/e (relative intensity) 206 (25, M^+), 163 (12), 150 (18), 107 (100), 92 (78), and 77 (25).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74. Found: C, 75.44; H, 9.00.

Rearrangement of *endo*-hydroxy ketal 23f (120 mg, 0.4 mmol) using procedure A yielded, after treatment with sodium methoxide in methanol, 100 mg (84%) of a 2:1 mixture of **34g** and **32g** as judged by NMR. No attempt was made to separate this mixture. The major product, **34g**, showed the following spectral properties: IR ($CHCl_3$) 1670 cm^{-1}; NMR (CCl_4) δ 1.31 (s, 3), 1.5–≈2.0 (m, 8), 2.08 (s, 3), 2.2–≈2.5 (m, 2), 5.90 (d, 1, J = 6 Hz), and 6.90 (m, 1).

Rearrangement of *exo*-Phenylthio Alcohol 22h. A mixture of *exo*-phenylthio alcohol **22h** (1.0 g, 3.14 mmol) and TsOH (300 mg, 1.57 mmol) in acetic acid (100 mL) was heated at reflux for 20 h, the acetic acid was evaporated at reduced pressure, and 850 mg (94%) of crude product was isolated by normal workup. Chromatography of this crude product on silica gel using pentane/ether (2:1) yielded 810 mg (90%) of pure liquid bicyclic [3.2.1] phenylthioenone **32h**: IR (CCl_4) 1705, 1580, 1455, and 685 cm^{-1}; NMR (CCl_4) δ 1.20 (s, 3), 1.40–≈2.00 (m, 8), 2.00–≈2.50 (m, 2), 2.88 (m, 2), 5.61 (d, 1, J = 5 Hz), 5.84 (d, 1, J = 5 Hz), and 7.22 (broad s, 5); mass spectrum, m/e (relative intensity) 286 (90, M^+), 230 (30), 177 (40), 149 (22), 136 (100), 120 (90), 105 (44), and 91 (33).

Anal. Calcd for $C_{18}H_{22}OS$: C, 75.52; H, 7.69; S, 11.19. Found: C, 75.77; H, 7.89; S, 11.00.

Rearrangement of *endo*-Phenylthio Alcohol 23h. Following the procedure described for the rearrangement of **22h**, *endo*-phenylthio alcohol **23h** (160 mg, 0.5 mmol) yield 34 mg (24%) of a liquid product, which was assigned as **32h** by comparison of the spectral data (IR and NMR) with authentic material, and 91 mg (64%) of a second liquid product, which was assigned as **34h** on the basis of the following data: IR (CCl_4) 1675, 1580, 1450, and 690 cm^{-1}; NMR (CCl_4) δ 1.26 (s, 3), 1.40–≈2.20 (m, 10), 2.88 (m, 2), 5.72 (d, 1, J = 10 Hz), 6.81 (dd, 1, J = 11 and 2 Hz), and 7.22 (broad s, 5); mass spectrum, m/e (relative intensity) 286 (25, M^+), 210 (4), 177 (100), 149 (67), 135 (15), 121 (18), 110 (14), and 91 (15).

Anal. ($C_{18}H_{22}OS$): calcd mol wt, 286.1391; found, 286.1397.

Rearrangement of hydroxy keto esters 24i,25i (2:1, 1.0 g, 3.5 mmol) using procedure A gave 500 mg (73%) of a 1:1 mixture (by NMR) of diketones **33j** and **35j**, which was separated by chromatography on Al_2O_3 using pentane/$CHCl_3$. Liquid 1-(6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)propan-2-one (**33j**): IR ($CHCl_3$) 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.95 (m, 9), 1.84 (d, 3, J = 1.5 Hz), 2.10 (s, 3), and 5.50 (m, 1); mass spectrum, m/e (relative intensity) 192 (17), 149 (23), 136 (30), 124 (23), 107 (22), 93 (100), 91 (30), 77 (26), and 43 (67).

Anal. ($C_{12}H_{16}O_2$): calcd mol wt, 192.1150; found, 192.1151.

1-(4-Methylbicyclo[3.2.1]oct-3-en-2-on-1-yl)propan-2-one (**35j**): mp 62–63.5 °C (from hexane); IR ($CHCl_3$) 1715 and 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.47–2.79 (m, 7), 2.01 (d, 3, J = 1.5 Hz), 2.21 (s, 3), 2.45 (d, 1, J = 17 Hz), 3.22 (d, 1, J = 17 Hz), and 5.7 (m, 1); mass spectrum, m/e (relative intensity) 192 (11), 177 (17), 149 (39), 134 (21), 122 (65),

121 (23), 95 (100), 67 (36), and 43 (66).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.15.

Rearrangement of Dienone 38. Using procedure B, crude dienone **38** (220 mg, 1.0 mmol) furnished 180 mg (96%) of conjugated tricyclic dienone **41**, which was identified by comparison of spectral data (IR and NMR) with authentic material.

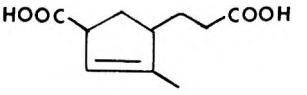
Rearrangement of α,β-Unsaturated Ketone 39. Using the general conditions described in procedure A and a reaction time of 2 h, ketone **39** (200 mg, 1.0 mmol) yielded 150 mg (78%) of a mixture which was shown by VPC (10% SE 30) to contain nonconjugated enone **33j** and conjugated enone **35j** in a ratio of 1:3. Exposure of product **33j** to identical conditions and reaction time resulted in a 1:1 mixture of **33j** and **35j**, thus suggesting that **33j** is a primary rearrangement product of **39**. Using procedure B, ketone **39** (1.1 g, 5.3 mmol) yielded 850 mg (85%) of conjugated enone **35j**.

Stability of Bicyclo[3.2.1]octene Products. Exposure of the nonconjugated enones **32g** and **33j** to procedure B conditions resulted in complete rearrangement to the conjugated products **41** and **35j**, respectively, as judged by IR and NMR. The nonconjugated bicyclo[3.2.1]octenones **32b, 32h, 33c–e,** and **42** did not rearrange to the corresponding conjugated analogues under these conditions.

Registry No.—**11,** 2220-40-8; **12,** 38258-84-3; **13,** 67316-12-5; **14,** 20023-36-3; **15** (isomer 1), 67337-34-2; **15** (isomer 2), 67337-35-3; **16,** 13697-84-2; **18a,** 64918-89-4; **18b,** 67337-36-4; **18c** (isomer 1), 67316-13-6; **18c** (isomer 2), 67337-37-5; **19,** 67316-14-7; **21,** 67316-15-8; **22a,** 67315-86-0; **22f,** 67316-02-3; **22h,** 67316-03-4; **23a,** 67337-29-5; **23f,** 67337-31-9; **23h,** 67337-32-0; **24a,** 67375-28-4; **24b,** 67337-38-6; **24c,** 67315-87-1; **24d,** 67315-88-2; **24e,** 67315-89-3; **24i,** 67316-04-5; **25a,** 67316-16-9; **25b,** 67315-90-6; **25i,** 67337-33-1; **26,** 67315-91-7; **27,** 67315-92-8; **28,** 67315-93-9; **29,** 67315-94-0; **30,** 67337-30-8; **32a,** 67316-17-0; **32b,** 67315-95-1; **32g,** 67316-07-8; **32h,** 67316-08-9; **33a,** 67316-18-1; **33b,** 67315-99-5; **33c,** 67315-96-2; **33d,** 67315-97-3; **33e,** 67315-98-4; **33j,** 67316-09-0; **34a,** 67316-19-2; **34b,** 67316-01-2; **34g,** 67316-20-5; **34h,** 67316-21-6; **35b,** 67316-00-1; **35j,** 67316-11-4; **36,** 67316-22-7; **36,** methyl ester, 67316-24-9; **38,** 67316-05-6; **39,** 67316-06-7; **41,** 67316-10-3; **42,** 67316-23-8; *p*-methylanisole, 104-93-8; 2-chloroacrylonitrile, 920-37-6; *m*-methylanisole, 100-84-5; acrylonitrile, 107-13-1; *tert*-butyl 2-bromopropionate, 39149-80-9; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; 3-bromopropyl phenyl sulfide, 3238-98-0; acetic acid, 64-19-7; propionic acid, 79-09-4; phenylacetic acid, 103-82-2; *m*-methoxyphenylacetic acid, 1798-09-0; methyl acetoacetate, 105-45-3.

References and Notes

(1) Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.
(2) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol. 2, Academic Press, New York and London, 1972.
(3) M. Koreeda in "Natural Products Chemistry", Vol. 1, K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Ed., Kodansha, Ltd., Tokyo, Academic Press, New York, N.Y., 1974, Chapter 4.
(4) Cf. I. Alfaro, W. Ashton, K. L. Rabone, and N. A. J. Rogers, *Tetrahedron*, **30,** 559 (1974).
(5) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, **33,** 2211 (1968).
(6) D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 121 (1972).
(7) A. J. Birch and K. P. Dastur, *Tetrahedron Lett.*, 4195 (1972); *J. Chem. Soc., Perkin Trans 1,* 1650 (1973).
(8) This structure was established by X-ray crystallography: R. E. Davis, personal communication; also see J. M. Mellor and C. F. Webl, *J. Chem. Soc., Perkin Trans 1,* 17 (1974).
(9) The major product isolated under these conditions is tentatively assigned as diacid A. R. Chen, unpublished observation.



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(10) D. S. Watt and S. J. Selikson, *J. Org. Chem.*, **40,** 267 (1975).
(11) (a) T. Moriwake, *J. Org. Chem.*, **31,** 983 (1966); (b) M. W. Rathke and A. Lindert, *ibid.*, **35,** 3967 (1970).
(12) G. W. Moersch and A. R. Burkett, *J. org. Chem.*, **36,** 1149 (1971).
(13) J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86,** 5019 (1964).
(14) D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97,** 4765 (1975); D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 137 (1972).
(15) K. Shimoyi, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96,** 1620 (1974).
(16) B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, **97,** 4018 (1975).
(17) C. W. Jefford, B. Waegell, and K. Ramey, *J. Am. Chem. Soc.*, **87,** 2191 (1965); C. W. Jefford, J. Gunsher, and K. Ramey, *ibid.*, **87,** 4384 (1965).
(18) (a) P. Bakuzis, M. L. F. Bakuzis, C. C. Fortes, and R. Santos, *J. Org. Chem.*, **41,** 2769 (1976); P. Bakuzis and M. L. F. Bakuzis, *ibid.*, **42,** 2362 (1977); (b) A. A. Pcnaras, *Tetrahedron Lett.*, 3105 (1976).
(19) S. N. Huckius and L. Weiler, *Can. J. Chem.*, **52,** 2157 (1974).
(20) Cf. W. R. Vaughan and R. Caple, *J. Am. Chem. Soc.*, **86,** 4928 (1964); R. C. Fahey and H. J. Schneider, *ibid.*, 92, 6885 (1970); C. Armstrong, J. A. Blair, and J. Homer, *Chem. Commun.*, 103 (1969).
(21) A. J. Birch, *J. Chem. Soc.*, 596 (1946).
(22) R. E. Ireland, G. G. Brown, Jr., R. H. Stanford, Jr., and T. C. McKenzie, *J. Org. Chem.*, **39,** 51 (1974).
(23) J. Cason, K. L. Rinehart, and S. O. Thornton, *J. Org. Chem.*, **18,** 1598 (1953).
(24) Cf. T. Moriwake, *J. Org. Chem.*, **31,** 983 (1966).
(25) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 1285 and 1286.

Association Phenomena. 5. Synthesis and Properties of 1,4-Dipolar Substituted Cyclohexenes

Te C. Kung and C. David Gutsche*

Department of Chemistry, Washington University, St. Louis, Missouri 63130

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To study the intramolecular association between oppositely charged centers, several cyclohexenes substituted at the 1 and 4 positions with groups capable of carrying positive and negative charges have been synthesized. Included among these are the cis and trans isomers of 3-(methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic acid (**7** and **9**), 6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (**8** and **10**), 2,3-dimethyl-6-(methylamino)cyclohexenecarboxylic acid (**17a** and **19**), and 3-carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (**18a** and **20**) and the cis isomers of 3-methyl-6-(methylamino)cyclohexenecarboxylic acid (**17b**) and 3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (**18b**). However, the expectation that the zwitterions of these compounds should, to a greater extent than the anionic or cationic species, exist in the boat conformation failed to be clearly demonstrable by ^1H and ^{13}C NMR measurements. It is postulated that the apparent lack of conformational response to changing pH is due to the rather large nonbonded interactions arising from the groups at C-2 (i.e., CH_2 in **7–10**, CH_3 in **17a–20**, and H in **17b** and **18b**) and at C-4 (i.e., $NHCH_3$ or $N(CH_3)_3^+$), which favor the half-chair conformation, and the rather small coulombic interaction of the carboxylate and ammonium centers in the zwitterion (calculated to be 3–5 kcal/mol), which favors the boat conformation.

Papers 1–4 of this series[1] deal with intermolecular association phenomena involving interactions between positively and negatively charged moieties. The present paper represents an intramolecular counterpart of these systems and involves an attempt to measure the extent of intramolecular association in cyclohexenes substituted at the 1 and 4 positions with

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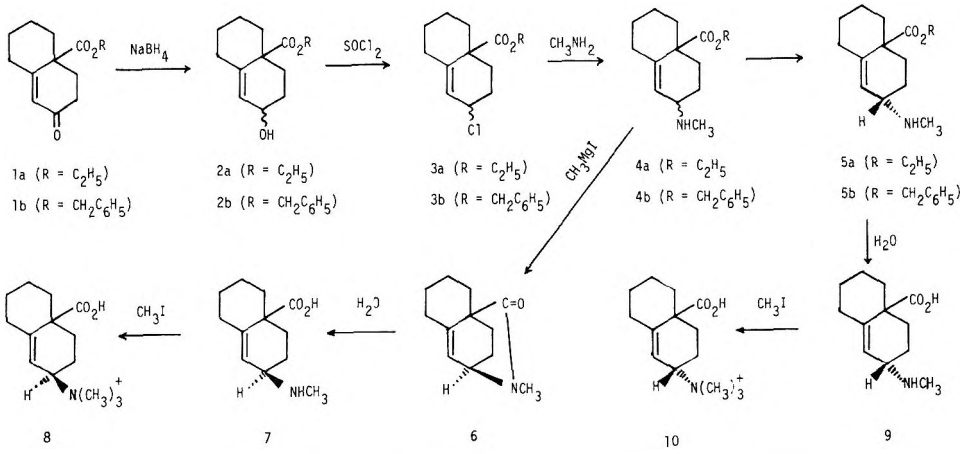


Figure 1. Synthesis of *cis*- and *trans*-6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (8 and **10**).

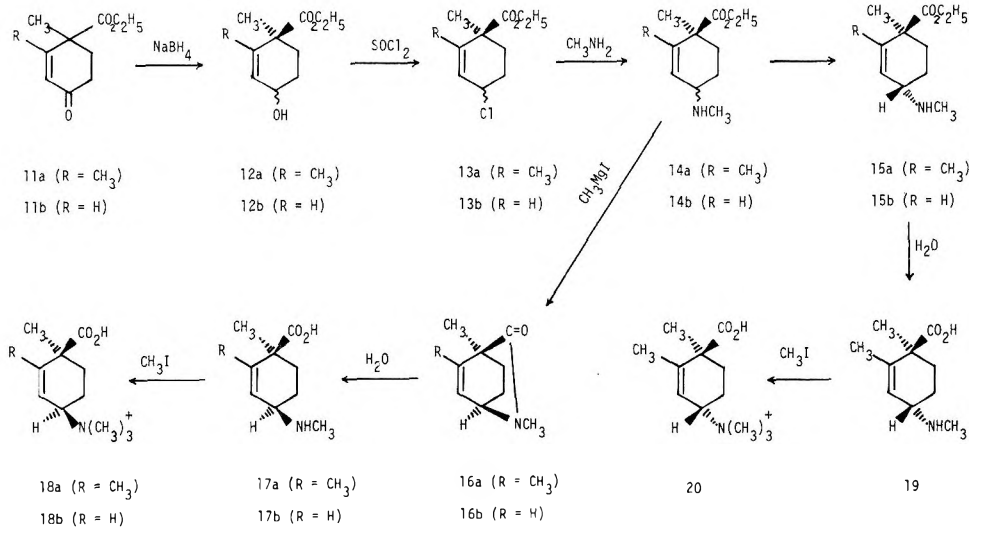
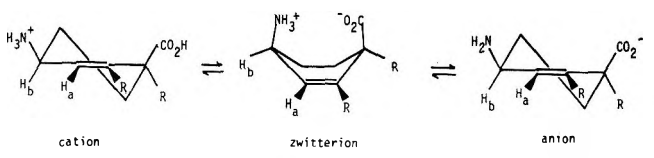


Figure 2. Synthesis of *cis*- and *trans*-3-carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (**18a** and **20**) and *cis*-3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (**18b**).

groups capable of carrying positive and negative charges, respectively. To this end, several *cis*-4-amino-2-cyclohexene-1-carboxylic acids have been synthesized to test whether the conformation of the cyclohexene ring is a function of the extent of protonation of the amino and carboxyl groups. At high and low pH the aminocarboxycyclohexenes are singly charged (i.e., negatively and positively, respectively), and the ring might be expected to exist predominately in the half-chair conformation; at intermediate pH regions, however, the compounds are zwitterions and, as a result, should be more likely to assume the boat conformation because of electrostatic attraction between the oppositely charged groups, viz., Scheme I. It was hoped that the conformation of the cyclohexene ring could be discerned from the line shape of the NMR resonances arising from the vinyl hydrogen (H_a) that is coupled with the hydrogen α to the amino function (H_b). Although the results fell short of expectation, some observations requiring explanation have been obtained and some useful syntheses have been achieved.

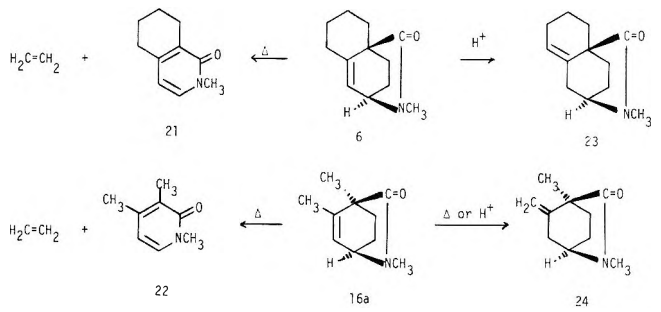
Synthesis of Compounds Containing the 4-Amino-2-cyclohexene-1-carboxylic Acid Moiety. Three series of compounds containing the 4-amino-2-cyclohexene-1-carboxylic acid moiety were synthesized. The first of these, the cis and trans isomers of 6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (**8** and **10**), involved the sequence of reactions outlined in Figure 1. The second, the cis and trans isomers of 3-carboxy-2,3-dimethyl-6-(trimethylammonio)-cyclohexene chloride (**18a** and **20**), and the third, the cis isomer of 3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (**18b**), involved the equivalent sequence of reactions, as outlined in Figure 2. A key step in all cases is the separation of the cis and trans isomers of the amino esters (compounds **4** in Figure 1 and compounds **14** in Figure 2) via methylmagnesium iodide induced conversion[2] to the lactams **6** and **16**, the trans isomers of the amino esters remaining unchanged in the process. Separation of the lactams from the *trans*-amino esters, hydrolysis to the corresponding *cis*- and *trans*-amino acids, and methylation yielded the desired trimethylammonium compounds **8**, **10**, **18a**, **18b**, **and 20**.

Scheme I



The major difficulty in the syntheses involved the formation of the lactams **6** and **16** and their subsequent conversion to the *cis*-amino acids. Attempts to form lactam **6** by heating **4a** resulted in the formation of the pyridone **21**, presumably the result of a $\pi 4_s + \pi 2_s$ cycloreversion reaction of the initially formed lactam. In similar fashion **14a** yields the pyridone when heated. Hydrolysis of lactam **6** proved to be particularly difficult, and prolonged treatment with 4 N sodium hydroxide

Scheme II



in ethanol was necessary to achieve optimum, although low, yields of **7**. Acid-catalyzed hydrolysis of the lactams was precluded, for **6** and **16a** were both shown to isomerize to **23** and **24**, respectively, in the presence of acid (Scheme II).

In an attempt to achieve a stereoselective synthesis of **7**, the benzyl ester (**1b**) was used as the starting material and was converted to *cis*-**2b** with lithium tri-*tert*-butoxyaluminum hydride. Treatment of *cis*-**2b** with thionyl chloride in pyridine yielded a mixture of *cis*- and *trans*-**3b**, however, thereby negating the stereoselective character of the sequence. Amination of this mixture with methylamine in benzene solution gave a mixture of *cis*- and *trans*-**4b**; amination in the absence of a solvent produced *trans*-**4b** in 95% yield.

Conformations of the Anionic, Cationic, and Zwitterionic Forms of the 4-Amino-2-cyclohexene-1-carboxylic Acids. Examination of the Dreiding models of the cis isomers of the monocyclic and bicyclic compounds containing the 4-amino-2-cyclohexene-1-carboxylic acid moiety indicates that there are four limiting conformations, viz., two boat forms (B_{aa} and B_{ee}) and two half-chair forms ($C_{a'e'}$ and $C_{e'a'}$), as illustrated in Figure 3. Measurement of the distance between the center of the amino function and a point extending 1.45 Å beyond the carbon atom of the carboxyl group along an axis midway between the oxygen atoms[3] shows that the amino and carboxyl functions can be as close as 2.7 Å (in B_{aa}) and as far apart as 7.2 Å (in B_{ee}), as indicated in Figure 3. Also shown in Figure 3 are the dihedral angles between the H_a and H_b hydrogens in the four conformations and the magnitude of the NMR coupling constant between these hydrogens that might be expected for the various dihedral angles.

The magnitude of the coupling constant between the vinyl hydrogen and the adjacent allylic hydrogens in cycloalkenes is a function of the dihedral angle between the hydrogens,[4] and it changes, for example, from 1.8 Hz for cyclobutene (dihedral angle 66°) to 5.7 Hz for cycloheptene (dihedral angle 11°).[5] The relation between the coupling constant and the dihedral angle has been used to assign a conformation to 3,4,5-trihydroxy-1-cyclohexenecarboxylic acid (shikimic acid),[6] and it was expected that it could be used in similar fashion in the present case. When the resonances arising from H_a in compounds **7**, **8**, **9**, **10**, **17a**, **18a**, **19**, and **20** were measured, however, essentially unresolved envelopes were obtained. That this can be attributed, at least in part, to long-range coupling with the homoallylic hydrogens is indicated by the ^1H NMR spectra of the lactams **6** and **16a** (constrained in the boat conformation), which show multiplet rather than doublet patterns for H_a. Compound **6**, for example, shows a doublet of triplets for which coupling constants of 5.5 (for J_{ab}) and 1.5 Hz (long-range coupling) can be determined. To gain a rough estimate of the coupling constants, therefore, the widths of the envelopes at half-height were measured; the differences in these widths with and without spin decoupling with the adjacent hydrogen (i.e., H_a or H_b) were taken as measures of the coupling constants J_{ab}, as shown in Table I. Although the uncertainties in this procedure are large and the significance of small differences is questionable, it does turn out that the widths at half-height for H_a, corrected in this fashion, are

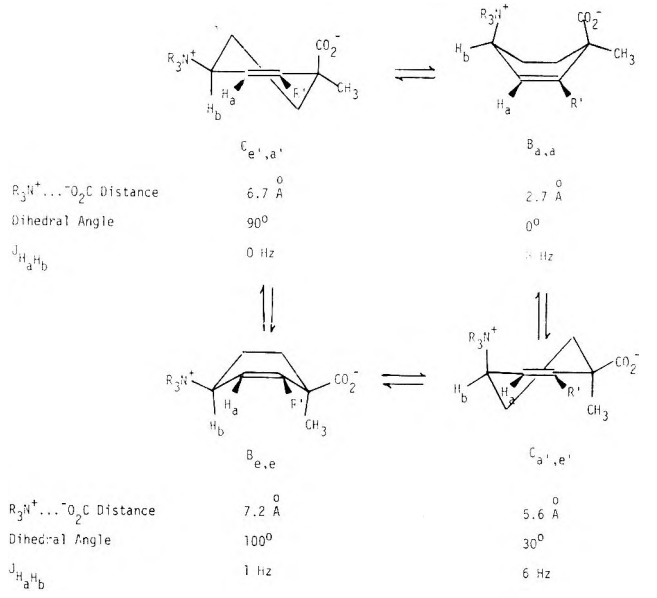


Figure 3. The four limiting conformations of the 4-amino-2-cyclohexene-1-carboxylic acids.

greater for the zwitterionic form than for either the anionic or cationic form for the cis isomers of the NCH_3 compounds (i.e., **7** and **17a**). Since this is not true for any of the other compounds shown in Figure 4, it suggests that the cis compounds **7** and **17a** may, at least to some small extent, exist in a boat conformation. A similar circumstance is observed when the "corrected" widths at half-height for the H_b hydrogens are considered; here, also, the widths for the cis isomers of the NCH_3 compounds are greater for the zwitterions than for the anionic and cationic species, although the uncertainties in the measurements are even more apparent in these cases.

The widths at half-height for H_b hydrogens are somewhat greater for the cis isomers of the $N(CH_3)_3^+$ compounds (14.0–18.5 Hz) than for the cis isomers of the NCH_3 compounds (9.5–12.5 Hz), suggesting that the two series assume different conformations. It is known that hydrogens in the axial alignment on a cyclohexane ring have broader resonances than those in the equatorial alignment,[7] and Garbisch[8] has shown this to be true for the allylic hydrogens in 1-methylcyclohexene as well. Thus, the greater width of the H_b resonances in the trimethylammonium compounds **8** and **18a** as compared with the methylamino compounds **7** and **17a** suggests that the former are in the $C_{e'a'}$ conformation and the latter in the $C_{a'e'}$ conformation (or, possibly, the B_{aa} conformation). That the larger trimethylammonium group should show a greater preference than the smaller methylamino group for a pseudoequatorial alignment is reasonable.

The relative energies of the half-chair and boat conformations for the compounds represented in Figure 3 depend, among other things, on the size of the R′ group. In the half-chair conformations $C_{e'a'}$ and $C_{a'e}$, the R′ group is approximately staggered with the CH_3 and CO_2H groups at C-1, whereas in the boat conformations B_{aa} and B_{ee} it is eclipsed with the CH_3 or the CO_2H group at C-1. Thus, the energy difference between the half-chair and boat forms might be expected to be lower when R′ is hydrogen than when it is methyl (as in **17a–20**) or methylene (as in **7–10**). However, the compounds in which R′ is hydrogen (i.e., **17b** and **18b**) give no clearer ^1H NMR evidence for conformational differences between the neutral zwitterion species and the charged anionic or cationic species than do the members of the other two series of compounds. They do, though, show well-resolved ^1H NMR envelopes for the vinyl hydrogens at C-3 (i.e., H_b) and C-2, from which the following coupling constants were measured:

Table I. ^{1}H NMR Data for 4-Amino-2-cyclohexene-1-carboxylic Acids

registry no.	compd	nitrogen function	config-uration	charge species	widths at half height, Hz: vinyl proton (H_a) *a*	*b*	diff	allyl proton (H_b) *a*	*c*	diff
67394-09-6	**9**	$NHCH_3$	trans	0,+	7.0	3.0	4.0	10.5	9.5	1.0
				−,+	6.5	3.0	3.5	9.0	7.5	1.5
				−,0	6.0	3.0	3.0	10.0	7.0	3.0
67394-10-9	**10**	$^+N(CH_3)_3$	trans	0,+	5.5	4.0	1.5	12.5	13.0	0.5
				−,+	6.0	4.5	1.5	13.0	12.0	1.0
67394-11-0	**7**	$NHCH_3$	cis	0,+	4.5	4.0	0.5	12.0	11.0	1.0
				−,+	4.0	2.5	1.5	13.0	9.5	3.5
				−,0	3.5	3.0	0.5	12.5	10.0	2.5
67394-12-1	**8**	$^+N(CH_3)_3$	cis	0,+	5.0	4.5	0.5	18.5	17.5	1.0
				−,+	5.0	4.5	0.5	17.5	17.0	0.5
67394-13-2	**19a**	$NHCH_3$	trans	0,+	6.0	4.0	2.0	13.0	14.0	−1.0
				−,+	6.0	4.0	2.0	14.0	15.5	−1.5
				−,0	5.5	4.0	1.5	14.0	17.0	−3.0
67394-14-3	**20a**	$^+N(CH_3)_3$	trans	0,+	5.5	5.0	0.5	15.5	15.5	0
				−,+	5.5	4.5	1.0	14.0	15.0	−1.0
67394-15-4	**17a**	$NHCH_3$	cis	0,+	5.5	4.0	1.5	13.0	12.0	1.0
				−,+	6.0	4.0	2.0	13.5	11.0	2.5
				−,0	5.5	4.5	1.0	13.0	12.5	0.5
67394-16-5	**18a**	$^+N(CH_3)_3$	cis	0,+	5.5	5.0	0.5	16.0	17.0	−1.0
				−,+	6.0	5.0	1.0	17.0	17.0	0

[a] Without decoupling. [b] With decoupling with H_b. [c] With decoupling with H_a.

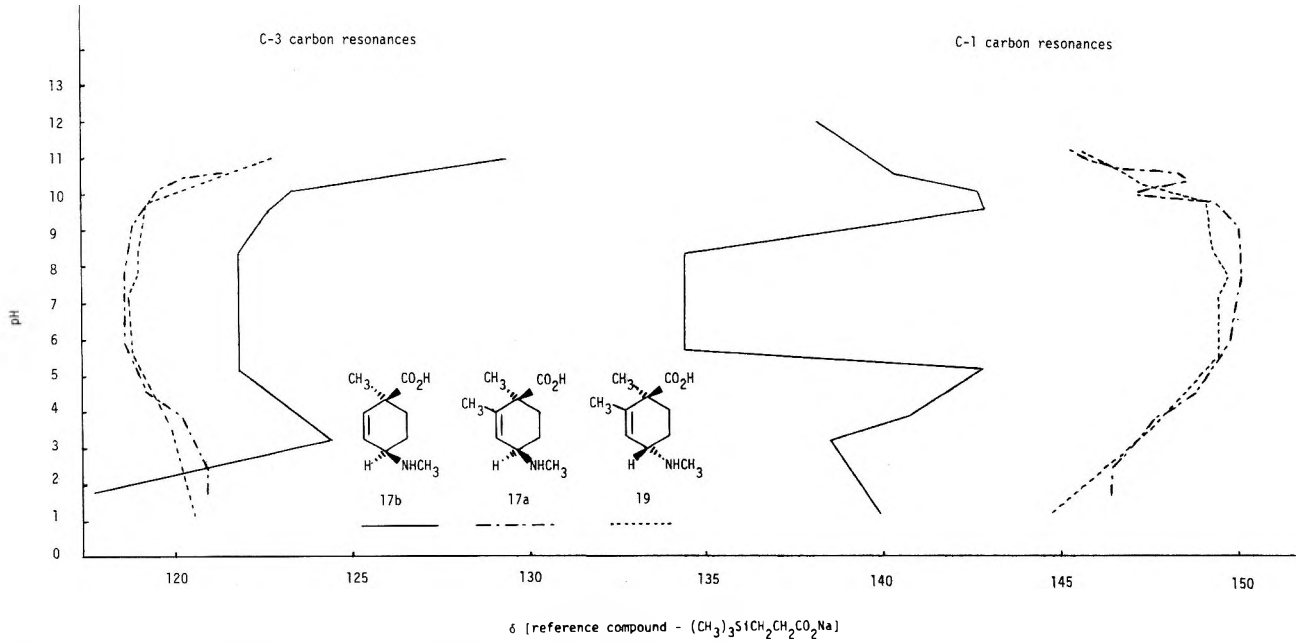


Figure 4. ^{13}C NMR–pH profiles for 4-amino-2-cyclohexene-1-carboxylic acids.

J_{ab} for **17b**, (0,+) form = 2.0 Hz, (−,+) form = 2.0 Hz, (−,0) form = 1.5 Hz; J_{ab} for **18b**, (0,+) form = 1.0 Hz, (−, +) form = 1.0 Hz. The ^{13}C NMR spectra, on the other hand, provide a modicum of evidence for special behavior of the zwitterion of **17b**. As shown in Figure 4, the chemical shift pH profile for **17b** is different from that of **17a** and **19a**, particularly in the pH region 5–8 where the zwitterion is present as the major species.

The difference in energy between the boat and half-chair conformations of cyclohexene is estimated, both on the basis of experiment[9a] and theory,[9b] to be approximately 5 kcal/mol. Substitution of a pair of geminal allylic hydrogens by a methyl or methylene group and a carboxyl group (the common feature at C-1 in all of the cyclohexenes in the present study) should probably not change this value significantly because of the similarity in size of these two groups (e.g., ΔG value of CH_3 is 1.70 and that of CO_2^- is 1.92[10]). On the basis of ΔG values for substituents in cyclohexane systems,[10] however, the substituent at C-4 is estimated to increase the nonbonded interaction by 1–2 kcal/mol for the $NHCH_3$ and $NH_2CH_3^+$ groups and 4 kcal/mol for the $N(CH_3)_3^+$ group; the nonbonded interaction between the groups at C-1 and the substituent at C-2 will also increase the relative stability of the half-chair form. Thus, the difference in energy between the boat and half-chair conformations for **7**, **9**, **17a**, and **19a** is predicted to be at least 7 kcal/mol, that for **8**, **10**, **18a**, and **20** to be at least 10 kcal/mol, that for **17b** to be ~6 kcal/mol, and that for **18b** to be ~9 kcal/mol.

By means of the Kirkwood–Westheimer method for estimating the magnitude of electrostatic interactions[11] it was calculated that the stabilization from the coulombic interaction between the carboxylate and ammonium centers should be 3–5 kcal/mol in the boat conformation. Thus, it is not surprising that most of the compounds tested failed to show

significant conformational responses to changes in pH, although it might have been expected that **17b** should show more dramatic behavior than was observed.

Experimental Section[12]

Synthesis of *cis*- and *trans*-6-Carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene Iodide (8 and 10). Ethyl 3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylate (4a). A 222-g (1.0 mol) sample of ethyl 3-ketobicyclo[4.4.0]dec-1-ene-6-carboxylate (**1a**)[13,14] was reduced to **2a** by treatment at 0 °C for 2 h with 18.9 g (0.50 mol) of sodium borohydride in 1 L of absolute ethanol. A 203-g sample of the crude product, obtained in 96% yield, was dissolved in 200 mL of dry benzene, cooled to 0 °C and treated with a solution of 77 mL (1.07 mol) of purified[15] thionyl chloride in 200 mL of benzene, added over a period of 1.5 h. The reaction mixture was stirred an additional 5 h at 0 °C, and the solvent and excess reagent were removed under reduced pressure at 35–45 °C to leave 234 g (100%) of a brown oil consisting of a mixture of *cis*- and *trans*-ethyl 3-chlorobicyclo[4.4.0]dec-1-ene-6-carboxylate (**3a**): IR (neat) ν 1735 (C=O), 1675 (C=C), 680 cm^{-1} (CCl); NMR (CCl_4) δ 5.59 (m, 1, CCH), 4.54 (m, 1, HCCl), 4.15 (2 q, 2, J = 7.5 and 7.0 Hz, ester CH_2), 2.54–0.83 (m, 12, ring CH_2), 1.25 (2 t, 3, J = 7.5 and 7.0 Hz, ester CH_3). Attempted purification of **3a** at 80 °C resulted in dehydrochlorination, yielding **ethyl bicyclo[4.4.0]deca-1,9-diene-6-carboxylate:** bp 63–65 °C (0.26 mm); IR (neat) ν 1725 (C=O), 1600 (C=C), 690 cm^{-1} (=CH); NMR (CCl_4) δ 6.14–5.33 (m, 3, =CH), 4.06 (q, 1, J = 7 Hz, ester CH_2), 2.95–1.00 (m, 10, ring CH_2), 1.2. (t, 3, J = 7 Hz, ester CH_3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.84; H, 9.01.

A 216-g sample of **3a** was dissolved in 430 mL of dry benzene, and gaseous methylamine was bubbled through the solution until it was saturated. The flask was tightly stoppered, and the reaction mixture was stirred at room temperature for 10 days. The crude product was distilled through a 12-in. Vigreux column to give 144 g (65%) of a mixture of *cis*- and *trans*-**4a**: bp 93–94 °C (0.10 mm); IR (neat) ν 3400 (NH), 1740 cm^{-1} (C=O); NMR (CCl_4) δ 5.45 (m, 1, =CH), 4.10 (q, 2, J = 7 Hz, ester CH_2), 2.94 (m, 1, HCN), 2.33 (s, 3, NCH_3), 2.23–1.00 (m, 12, ring CH_2), 1.24 (t, 3, J = 7 Hz, ester CH_3), 0.87 (s, 1, NH).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.96; H, 9.71; N, 5.95.

From the acid-insoluble fraction, 42 g (19%) of **3a** was recovered; no trace of the diene was discerned. An alternative procedure involving a 12-h reaction at 45 °C in a high-pressure bomb resulted in a 51% yield of **4a** and the production of a significant amount of diene.

10-Methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-2-en-9-one (6). Using a procedure analogous to that of Bassett and Thomas,[16] a 26.5-g (0.167 mol) sample of a mixture of *cis*- and *trans*-**4a** in 150 mL of ether was added over a period of 1 h to a solution containing 26 g (0.182 mol) of methyl iodide in 225 mL of ether. The mixture was refluxed for 12 h, cooled, treated with 100 mL of water followed by 100 mL of 2 N hydrochloric acid added slowly, and stirred until all of the solid had dissolved. The solution was then extracted with ether and the ether was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate, and saturated sodium chloride solution, dried over magnesium sulfate, and removed under vacuum to yield 23 g (63%) of **6** as a colorless oil: bp 95 °C (0.13 mm); IR (neat) ν 1665 cm^{-1} (C=O); NMR (CCl_4) δ 6.00 (t of d, 1, J = 5.5 and 1.5 Hz, =CH), 4.02 (m, 1, HCN), 2.78 (s, 3, NCH_3), 2.48–1.11 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.23; H, 8.82; N, 7.52.

10-Methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-3-en-9-one, a double bond position isomer of **6**, was produced by the action of anhydrous hydrogen chloride on **6** and was obtained as a colorless oil: IR (neat) ν 1690 cm^{-1} (C=O); NMR (CCl_4) δ 5.49 (m, 1, =CH), 3.56 (m, 1, HCN), 3.11 (s, 3, NCH_3), 2.54–0.88 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.20; H, 9.05; N, 7.28.

***cis*-3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic Acid (7).** A mixture of 31 g (0.162 mol) of **6** in 180 mL of ethanol and 180 mL of 4 N sodium hydroxide was refluxed for 156 h in an atmosphere of nitrogen. Most of the ethanol was then removed by evaporation, the aqueous solution was filtered, and the filtrate was washed four times with ether and made acidic with concentrated hydrochloric acid. The gelatinous substance that formed was removed by dissolving the acidified filtrate in hot ethanol, filtering the cooled solution, and concentrating the filtrate. The thick oil that remained after the fourth of these treatments solidified and was recrystallized from ethanol–acetone to give 9.8 g of the hydrochloride salt of **7**: mp 245 °C dec; IR (KBr) ν 2490 (N^+H), 1730 (C=O), 1680 (C=C), 718 cm^{-1} (CN^+); NMR (D_2O) δ 5.88 (s, 1, =CH), 4.12 (m, 1, HCN), 2.91 (s, 3, NCH_3), 2.66–1.00 (m, 12, ring CH_2). A solution containing 9.8 g of the hydrochloride salt of **7** in 35 mL of water was adjusted to pH 8 with 8 N sodium hydroxide solution and cooled in an ice bath for 1 h. The precipitate was removed by filtration, washed with ice water and cold ethanol, and dried to yield 8.89 g (99%) of the monohydrate of **7**: mp 214 °C dec; IR (KBr) ν 1670 (C=C), 1630 cm^{-1} (CO_2^-); NMR (D_2O) δ 5.46 (s, 1, =CH), 3.83 (m, 1, HCN), 2.70 (s, 3, NCH_3), 2.40–0.90 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{19}NO_2 \cdot H_2O$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.27; H, 9.33; N, 6.06.

The combined ether extracts of the basic solution yielded 22 g (71% recovery) of unchanged **6**.

***trans*-3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic Acid (9).** The combined acid extract from the preparation of 10-methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-2-en-9-one (see above) was made basic (pH 11) with 5 N sodium hydroxide solution, and most of the magnesium hydroxide was removed by centrifugation. The supernatant solution was extracted with four 50-mL portions of ether, and the ether extract was then dried and saturated with anhydrous hydrogen chloride. The hydrochloride salt of **5a** precipitated and was removed by filtration. This material was treated with 25 mL of 5 N sodium hydroxide solution and extracted with ether, and the ether was dried and evaporated to give 7.8 g (19%) of **5a**: bp 87–89 °C (0.15 mm); IR (neat) ν 3400 (NH), 1735 (C=O), 1680 cm^{-1} (C=C); NMR (CCl_4) δ 5.52 (d, 1, J = 3.8 Hz, =CH), 4.13 (q, 2, J = 7 Hz, ester CH_2), 2.89 (m, 1, HCN), 2.35 (s, 3, NCH_3), 2.23–1.03 (m, 12, ring CH_2), 1.22 (t, 3, J = 7 Hz, ester CH_2), 0.68 (s, 1, NH).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.91; H, 9.65; N, 5.97.

A solution of 10.4 g of **5a** in 104 mL of 2 N hydrochloric acid was refluxed for 120 h in an atmosphere of nitrogen. The acidic solution was made basic (to pH 11) with 5 N sodium hydroxide, extracted four times with ether, made acidic (to pH 2) with concentrated hydrochloric acid, and extracted four more times with ether. The water was evaporated under reduced pressure, and the sodium chloride was removed by dissolving the slurry in hot absolute ethanol, filtering the chilled solution, and concentrating the filtrate, this process being repeated several times. The remaining oil solidified upon contact with acetone to give 7.27 g (69%) of the hydrochloride of the desired acid, mp 225 °C dec. Treatment of a solution of this material with 5.07 g of silver oxide for 5 h at room temperature yielded 6.02 g (98%) of **9** as colorless needles after recrystallization from ethanol–acetone–water: mp 168 °C dec; IR (KBr) ν 1680 (C=C), 1640 cm^{-1} (CO_2^-); NMR (D_2O) δ 5.73 (d, 1, J = 4 Hz, =CH), 3.82 (m, 1, HCN), 2.87 (s, 3, NCH_3), 2.62–1.08 (m, 12, ring CH_2).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.75; H, 9.14; N, 6.53.

***cis*-6-Carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene Chloride (8).** Using a procedure modeled after that of Patchett and Witkop,[17] a slurry of 0.84 g (4 mmol) of **7** and 1.11 g (5 mmol) of silver oxide in 20 mL of water was stirred at room temperature for 3 h. A solution of 0.51 mL (12 mmol) of methyl iodide in 100 mL of methanol was then added, the mixture was stirred for 3 h, a second solution of 0.34 mL of methanol was added, and stirring was continued another 4 h. The methanol and excess methyl iodide were removed by evaporation, the remaining aqueous solution was treated with 1.11 g (5 mmol) of silver oxide, and the mixture was stirred for 0.5 h. Filtration, acidification with concentrated hydrochloric acid followed by another filtration, and concentration of the filtrate produced a thick oil which, after trituration with acetone, yielded 0.74 g (67%) of **8**. Recrystallization from ethanol–acetone yielded a colorless solid: mp 226 °C dec; IR (KBr) ν 1700 (C=O), 720 cm^{-1} (CN^+); NMR (D_2O) δ 5.95 (m, 1, =CH), 4.30 (m, 1, HCN), 3.24 (s, 9, NCH_3), 2.64–1.16 (m, 12, ring CH_2).

Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.43; H, 8.84; N, 5.12. Found: C, 61.26; H, 9.01; N, 4.99.

***trans*-6-Carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene Chloride (10).** Using the procedure described above, **10** was obtained as a colorless solid: mp 211 °C dec; IR (KBr) ν 1720 (C=O), 1680 (C=C), 720 cm^{-1} (CN^+); NMR (D_2O) δ 6.03 (m, 1, =CH), 4.20 (m, 1, HCN), 3.28 (s, 9, NCH_3), 2.62–1.20 (m, 12, ring CH_2).

Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.43; H, 8.84; N, 5.12. Found: C, 61.28; H, 8.79; N, 4.98.

Benzyl 3-(Methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylate (4b). Benzyl 2-ketocyclohexanecarboxylate, prepared by ester interchange from the ethyl 2-ketocyclohexanecarboxylate and benzyl alcohol, was subjected to the Robinson annelation procedure[18] to yield **benzyl 3-ketobicyclo[4.4.0]dec-1-ene-6-carboxylate (1b)**

as a colorless oil: bp 170 °C (0.43 mm); IR (neat) ν 1740 (ester C=O), 1680 (ketone C=O), 1500 (Ar), 788, 756, 699 cm^{-1} (Ar); NMR (CCl_4) δ 7.25 (s, 5, ArH), 5.78 (s, 1, =CH), 5.13 (s, 2, ester CH_2), 2.74–0.94 (m, 12, ring CH_2).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.89; H, 7.22.

Reduction of a 33.4-g (0.12 mol) sample of this material with lithium tri-*tert*-butoxyaluminum hydride, prepared from 5.2 g (0.13 mol) of lithium aluminum hydride, yielded 32.2 g (96%) of the alcohol **2b**. Treatment of 10 g (35 mmole) of crude **2b** with 2.78 mL (38 mmole) of thionyl chloride in 30 mL of dry pyridine at 0 °C yielded 7.81 g (74%) of the chloro compound **3b**. A 10.3-g (34 mmole) sample of **3b** was allowed to react with an equal volume of methylamine in a pressure bomb for 18 h at 60 °C. The crude hydrochloride of **4b** was recrystallized from ethanol–ether to give 3.9 g of material, mp 172–174 °C, which was converted to 2.9 g (29%) of **4b** by treatment with sodium hydroxide: bp 142 °C (0.09 mm); IR (neat) ν 3450 (NH), 1740 (C=O), 1640 (C=C), 1620 (Ar); 752, 736, 698 cm^{-1} (Ar); NMR (CCl_4) δ 7.25 (s, 5, ArH), 5.50 (d, 1, J = 4 Hz, =CH), 5.06 (s, 2, ester CH_2), 2.89 (m, 1, HCN), 2.30 (s, 3, NCH_3), 2.27–0.98 (m, 12, ring CH_2), 0.82 (s, 1, NH).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.09; H, 8.61; N, 4.57.

When a 6.95-g (23 mmol) sample of **4b** was refluxed for 24 h with 100 mL of 20% hydrochloric acid, 4.7 g (82%) of *trans*-3-(methylamino)-6-carboxybicyclo[4.4.0]dec-1-ene chloride, mp 225 °C dec, was obtained that had spectral properties identical with those of the product obtained from the ethyl ester, **4a**, as described above.

Synthesis of *cis*- and *trans*-3-Carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexane Chloride (18a and 20a). Ethyl 2,3-Dimethyl-6-(methylamino)cyclohexene-3-carboxylate (14a). Ethyl 2,3-dimethyl-6-ketocyclohexene-3-carboxylate (**11a**) was prepared by condensation of ethyl methylacetoacetate with methyl vinyl ketone to ethyl 2-acetyl-2-methyl-5-ketohexanoate followed by piperidine acetate catalyzed cyclization.[19] Following the procedure of Plieninger, Arnold, and Hoffmann,[20] a 42-g (0.215 mol) sample of this material was converted in 100% yield to the alcohol **12a** by treatment with 4.1 g (0.107 mol) of sodium borohydride in 300 mL of absolute ethanol at 0 °C. By the action of thionyl chloride in benzene **12a** was converted in 100% yield to the chloride **13a**, obtained as a pale yellow oil which was used without purification. Treatment of **13a** in benzene solution with methylamine for 12 days at room temperature yielded, after distillation of the crude product through a 12-in. Vigreux column, 79 g (79%) of **14a** as a colorless oil: bp 80–81 °C (0.35 mm); IR (neat) ν 3380 (NH), 1735 (C=O), 1675 cm^{-1} (C=C); NMR (CCl_4) δ 5.47 (q, 1, J = 1.5 Hz, =CH), 4.10 (q, 2, J = 7 Hz, ester CH_2), 2.98 (m, 1, HCN), 2.36 (s, 1, NCH_3), 2.24–1.41 (m, 7, ring CH_2, $=CCH_3$), 1.26 (s, 3, CCH_3), 1.22 (t, 3, J = 7 Hz, ester CH_3), 1.02 (s, 1, NH).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.38; H, 9.98; N, 6.79.

1,6,8-Trimethyl-8-azabicyclo[2.2.2]oct-5-en-7-one (16a). Employing the procedure described above for the conversion of **4a** to 6, 79 g (0.37 mol) of **14a** was treated with methylmagnesium iodide to yield, after distillation of the crude product through a 6-in. Vigreux column, 19 g (31%) of **16a**, obtained as a colorless oil: bp 69–70 °C (0.20 mm); IR (neat) ν 1675 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 6.08 (t of t, 1, J = 1.5 and 5.5 Hz, =CH), 4.02 (m, 1, HCN), 2.75 (s, 3, NCH_3), 2.21–1.11 (m, 4, ring CH_2), 1.72 (d, 3, J = 1.5 Hz, $=CCH_3$), 1.27 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.54; H, 8.97; N, 8.61.

***cis*-2,3-Dimethyl-6-(methylamino)cyclohexenecarboxylic Acid (17a).** A two-phase system containing 27 g of **16a** and 270 mL of 2 N sodium hydroxide was refluxed for 42 h in an atmosphere of nitrogen. The cooled solution was filtered, and the filtrate was washed three times with ether and acidified to pH 2 with concentrated hydrochloric acid. The acidified solution was filtered, washed with three portions of ether, and evaporated under reduced pressure. The residue was triturated three times with ethanol to leave 22 g (61%) of the chloride of **17a**, mp 211 °C dec. A slurry of 7.2 g (33 mmol) of the chloride was stirred for 5 h at room temperature with 5.1 g (22 mmol) of silver oxide in 150 mL of water to yield 6.0 g (100%) of a solid which was recrystallized from acetone–ethanol to give **17a** as colorless rhombs: mp 220 °C dec; IR (KBr) ν 1635 cm^{-1} (CO_2^-); NMR (D_2O) δ 5.66 (m, 1, =CH), 3.87 (m, 1 HCN), 2.86 (s, 3, NCH_3), 2.42–1.50 (m, 7, ring CH_2 and $=CCH_3$), 1.33 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.42; H, 9.40; N, 7.50.

***trans*-2,3-Dimethyl-6-(methylamino)cyclohexenecarboxylic Acid (19a).** The combined acid extract from the preparation of 1,6,8-trimethyl-8-azabicyclo[2.2.2]oct-5-en-7-one (**16a**) was treated as described above for the corresponding tricyclic lactam 6 to yield 19% of **ethyl *trans*-2,3-dimethyl-6-(methylamino)cyclohexenecarboxylate (15a)** as a colorless oil: bp 78 °C (0.20 mm); IR (neat) ν 3380 (NH), 1735 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 5.44 (q, 1, J = 1.4 Hz, =CH), 4.09 (q, 2, J = 7.5 Hz, ester CH_2), 2.99 (m, 1, HCN), 2.35 (s, 3, NCH_3), 2.22–1.42 (m, 7, ring CH_2 and $=CCH_3$), 1.24 (s, 3, CCH_3), 1.22 (t, 3, J = 7.5 Hz, ester CH_3), 0.72 (s, 1, NH).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.05; H, 10.13; N, 6.67.

A 15-g sample of **15a** was refluxed for 24 h with 150 mL of 2 N hydrochloric acid in an atmosphere of nitrogen to yield 13 g (87%) of the chloride of **19a**, obtained as colorless rhombs after recrystallization from ethanol–acetone, mp 178 °C dec. Treatment of this material with silver oxide in the manner described above for the cis isomer yielded **19a** as colorless rhombs after recrystallization from ethanol–acetone: mp 239 °C dec; IR (KBr) ν 1635 cm^{-1} (CO_2^-); NMR (CCl_4) δ 5.64 (m, 1, =CH), 3.92 (m, 1, HCN), 2.85 (s, 3, NCH_3), 2.50–1.60 (m, 7, ring CH_2 and $=CCH_3$), 1.39 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.63; H, 9.36; N, 7.54.

***cis*-3-Carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene Chloride (18a).** A slurry of 4.5 g (25 mmol) of **17a** and 6.9 g (29 mmol) of silver oxide in 90 mL of water was treated with an excess of methyl iodide in the manner described above for the bicyclic analogue 7 to yield 4.6 (77%) of crude product which was recrystallized from ethanol–acetone to yield **18a** as colorless rhombs: mp 229 °C dec; IR (KBr) ν 1730 (C=O), 1670 (C=C), 730 cm^{-1} (CN^+); NMR (D_2O) δ 5.94 (m, 1, HCN), 3.32 (s, 9, NCH_3), 2.56–1.67 (m, 7, ring CH_2 and $=CCH_3$), 1.45 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{22}ClNO_2$: C, 58.15; H, 8.90; N, 5.65. Found: C, 58.01; H, 8.98; N, 5.58.

***trans*-3-Carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (20)** was obtained in a comparable fashion as colorless rhombs after recrystallization from ethanol–acetone: mp 225 °C dec; IR (KBr) ν 1725 (C=O), 1665 (C=C), 720 cm^{-1} (CN^+); NMR (D_2O) δ 5.83 (m, 1, =CH), 4.25 (m, 1, HCN), 3.25 (s, 9, NCH_3), 2.60–1.72 (m, 7, ring CH_2 and $=CCH_3$), 1.49 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{22}ClNO_2$: C, 58.15; H, 8.90; N, 5.65. Found: C, 58.02; H, 9.06; N, 5.48.

Synthesis of *cis*-3-Carboxy-3-methyl-6-(trimethylammonio)cyclohexene Chloride (18b). Ethyl 3-Methyl-6-(methylamino)cyclohexene-3-carboxylate (14b). Following the general procedures described above for the preparation of **14a**, ethyl 2-formylpropanoate[21] was condensed with methyl vinyl ketone[22] to yield ethyl 2-formyl-2-methyl-5-ketohexanoate, which was cyclized in the presence of piperidine acetate to ethyl 3-methyl-6-(methylamino)cyclohexene-3-carboxylate (**11b**), obtained as a colorless oil, bp 87–88 °C (2 mm). Reduction of 239 g (1.31 mol) of **11b** in 650 mL of absolute ethanol by treatment at −5 °C with a solution of 24.8 g (0.66 mol) of sodium borohydride in 1500 mL of absolute ethanol yielded 240 g (100%) of the alcohol **12b** as a slightly greenish oil which was converted, without purification, to the chloride **13b** by treatment with thionyl chloride in benzene at 0–5 °C. This product, isolated in 100% yield, was also used without purification for conversion to the methylamino compound **14b** by treatment with methylamine in the manner described above for the analogues **3a** and **13a**. The product **14b** was obtained in 37% yield as a colorless oil: bp 65–68 °C (0.36–0.27 mm); IR (neat) ν 3400 (NH), 1740 (C=O), 1660 cm^{-1} (C=C); NMR (CCl_4) δ 5.68 (s, 3, NCH_3), 2.27–1.10 (m, 4, ring CH_2), 1.23 (s, 3, CCH_3), 1.20 (t, 3, J = 7 Hz, ester CH_3), 0.82 (s, 1, NH).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.01; H, 9.67; N, 7.09.

6,8-Dimethyl-8-azabicyclo[2.2.2]oct-2-en-7-one (16b). A 20-g sample of **14b** was heated for 20 h at 170 °C in an atmosphere of nitrogen. The reaction mixture was dissolved in 100 mL of ether, and the ether solution was saturated with anhydrous hydrogen chloride. The precipitate that formed was removed by filtration, the filtrate was again saturated with hydrogen chloride, and a second crop of crystals was collected. The filtrate was concentrated, and the residue was distilled through a 6-in. Vigreux column to yield 3.1 g (31%) of **16b** as a colorless oil: bp 60 °C (0.21 mm); IR (neat) ν 1675 (C=O), 1635 cm^{-1} (C=C); NMR (CCl_4) δ 6.41 (d of d, 1, J = 7.5 and 6 Hz, =CHCN), 6.00 (d of d, J = 7.5 and 1 Hz, HC=CCN), 4.24–4.00 (m, 1, HCN), 2.80 (s, 3, NCH_3), 2.20–1.00 (m, 4, ring CH_2), 1.32 (s, 3, CCH_3).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.36; H, 8.70; N, 9.63.

The precipitate described above consisted of the hydrochloride of the starting material **14b**, from which **14b** could be recovered by basification.

***cis*-3-Methyl-6-(methylamino)cyclohexenecarboxylic Acid**

Table II. pK Values of Compounds 7–10 and 17–20

compd	pK_1	pK_2
7	3.79 ± 0.04	11.10 ± 0.03
8	3.97 ± 0.02	
9	3.75 ± 0.02	10.92 ± 0.02
10	3.79 ± 0.04	
17a	3.82 ± 0.04	11.08 ± 0.04
18a	3.95 ± 0.03	
19a	3.79 ± 0.02	10.81 ± 0.01
20	3.83 ± 0.02	

(17b). A mixture of 9.37 g of **16b** in 93 mL of 2 N sodium hydroxide was refluxed for 24 h in an atmosphere of nitrogen. The product was worked up as described above for **17a** to give the chloride of **17b** as colorless rhombs, mp 182 °C dec. A slurry of 3 g of the chloride and 2.55 g of silver oxide in 60 mL of water was stirred at room temperature for 4 h to yield 2.24 g (91%) of material from which pure **17b** was obtained as colorless rhombs by recrystallization from absolute ethanol: mp 256 °C dec; IR (KBr) ν 2500 (N^+H), 1640 cm^{-1} (CO_2^-); NMR (D_2O) δ 6.11 (d of d, 1, J = 10 and 1 Hz, HC=CCN), 5.65 (d of d, J = 10 and 3 Hz, =CHCH), 3.91–3.58 (m, 1, HCN), 2.67 (s, 3, NCH_3), 2.30–1.04 (m, 4, ring CH_2), 1.18 (s, 1, CCH_3).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.56; H, 9.04; N, 8.12.

***cis*-3-Carboxy-3-methyl-6-(trimethylammonio)cyclohexene Chloride (18b).** A slurry of 4 g (19.4 mmol) of **17b** and 7.86 g (34 mmol) of silver oxide in 80 mL of water was treated with an excess of methyl iodide in the manner described above for the bicyclic analogue **7** to yield 3.18 g (70%) of crude product which was recrystallized from ethanol–acetone to yield **18b** as colorless rhombs: mp 250 °C dec; IR (KBr) ν 1730 (C=O), 1670 (C=C), 740 cm^{-1} (CN^+); NMR (D_2O) δ 6.29 (d of d, 1, J = 10 and 1 Hz, =CHCH), 6.00 (br d, 1, J = 10 Hz, HC=CCN), 4.39–4.03 (m, 1, HCCN), 3.11 (s, 9, NCH_3), 2.55–1.50 (m, 4, ring CH_2), 1.30 (s, 3, CCH_3).

Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.46; H, 5.55; N, 5.99. Found: C, 56.02; H, 5.49; N, 6.08.

Other Syntheses. Ethyl 3-oximinobicyclo[4.4.0]dec-1-ene-6-carboxylate (oxime of 1a) was obtained as colorless rhombs, mp 104–106 °C.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.79; H, 7.95; N, 6.01.

3-Methyl-2-oxo-3-azabicyclo[4.4.0]deca-1(6),4-diene (21). A 4-g sample of **6** was heated for 30 min at 265–270 °C in an atmosphere of nitrogen. The gas evolved during this treatment decolorized a solution of bromine in carbon tetrachloride. The reaction mixture was distilled, and the distillate was recrystallized from petroleum ether (bp 60–68 °C) to yield **21** as colorless rhombs: mp 81–82 °C; IR (KBr) ν 1660 (C=O), 684 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 7.12 (d, 1, J = 7 Hz, =CHCN), 5.92 (d, 1, J = 7 Hz, =CH), 3.50 (s, 3, NCH_3), 2.76–2.18 (m, 4, allylic CH_2), 1.99–1.42 (m, 4, ring CH_2); UV (95% EtOH) λ_{max} (ϵ) 295 (6760), 236 (3980) nm.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.09; N, 8.58. Found: C, 73.44; H, 8.00; N, 8.61.

1,4,5-Trimethyl-6-oxo-1-azacyclohexa-2,4-diene (22). A 6-g sample of **16a** was heated for 30 min at 265–270 °C in an atmosphere of nitrogen. The gas evolved during this treatment decolorized a solution of bromine in carbon tetrachloride. The reaction mixture, shown by NMR analysis to consist of 65% of **22** and 35% of 1,8-dimethyl-2-methylene-8-azabicyclo[2.2.0]octan-7-one (**24**), was purified by crystallization from petroleum ether (bp 28–30 °C) to yield **22** as colorless rhombs: mp 63–64 °C IR (KBr) ν 1665 (C=O), 682 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 7.20 (d, 1, J = 7 Hz, =CHCN), 6.00 (d, 1, J = 7 Hz, =CHCN), 3.51 (s, 3, NCH_3), 2.12 (s, 3, CH_3), 2.08 (s, 3, CH_3).

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.17; H, 7.92; N, 10.23.

The **lactam 24** was isolated from the reaction mixture by chromatography on alumina and was obtained, after distillation, as a colorless oil: IR (neat) ν 1665 (C=O), 890 cm^{-1} (C=C); NMR (CCl_4) δ 4.84 (m, 2, allylic CH_2), 2.08–1.47 (m, 4, ring CH_2), 1.19 (s, 3, CCH_3).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.48; H, 9.37; N, 8.20.

Physical Measurements. Ionization Constant Measurements. Using the method described by Albert and Serjeant,[23] the pK values shown in Table II were obtained. The pH measurements were made with a Beckman Model G meter equipped with a Beckman 41252 general purpose glass electrode and a Beckman 41239 fiber junction calomel reference electrode. All measurements were made under a slow stream of nitrogen at 25 ± 0.2 °C after the electrodes had been immersed in the solutions for 30 min.

^{1}H NMR Measurements. A 0.5-mL quantity of a 0.5 M deuterium oxide solution of the compound was placed in an NMR tube and treated with a measured quantity of 5 N trifluoroacetic acid-d_1 or sodium deuterioxide (0, 0.25, 0.5, 0.75, 1, and 2 molar equiv amounts used). The spectral characteristics of the H_a and H_b hydrogens are shown in Table I.

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Registry No.—**1a**, 7478-39-9; 1a oxime, 67394-17-6; **1b**, 67394-04-1; **2a**, 67394-18-7; **2b**, 67394-19-8; *cis*-**3a**, 67394-20-1; *trans*-**3a**, 67394-21-2; **3b**, 67394-22-3; *cis*-**4a**, 67394-23-4; *trans*-**4a**, 67394-24-5; **4b**, 67394-25-6; **5a** HCl, 67394,26-7; **6**, 67394-27-8; **7** HCl, 67394-28-9; **8** chloride analogue, 67394-07-4; **10** chloride analogue, 67394-08-5; **11a**, 28790-87-6; **11b**, 1489-55-0; **12a**, 67394-29-0; **12b**, 67394-30-3; **13a**, 67393-88-8; **13b**, 67393-89-9; **14a**, 67393-90-2; **14b**, 67393-91-3; **15a**, 67393-92-4; **16a**, 67393-93-5; **16b**, 67393-94-6; **17a** HCl, 67393-95-7; **17b**, 67393-96-8; **17b** HCl, 67393-97-9; **19a** HCl, 67393-98-0; **21**, 67393-98-0; **22**, 67394-00-7; **24**, 67394-01-8; ethyl bicyclo[4.4.0]deca-1,9-diene-6-carboxylate, 67394-02-9; 10-methyl-10-azatricyclo[6.2.2.0^{3,8}]dodec-3-en-9-one, 67394-03-0; *trans*-3-(methylamino)-6-carboxybicyclo[4.4.0]dec-1-one hydrochloride, 67394-05-2; ethyl methylacetoacetate, 609-14-3; methyl vinyl ketone, 78-94-4; ethyl 2-acetyl-2-methyl-5-ketohexanoate, 28793-08-0; ethyl 2-formylpropanoate, 2772-62-9; ethyl 2-formyl-2-methyl-5-ketohexanoate, 1523-87-1.

References and Notes

(1) J. L. Kurz and C. D. Gutsche, *J. Am. Chem. Soc.*, **82**, 2175 (1960); L. L. Melhado and C. D. Gutsche, *ibid.*, **100**, 1850 (1978); H-P. Lau and C. D. Gutsche, *ibid.*, **100**, 1857 (1978); G. A. Gettys and C. D. Gutsche, *Bioorg. Chem.*, **7**, 141 (1978).
(2) F. Bodroux, *Bull. Soc. Chim. Fr.*, **33**, 831 (1905); H. L. Bassett and C. R. Thomas, *J. Chem. Soc.*, 1188 (1954).
(3) E. J. King, "Acid-Base Equilibria", Macmillan, New York, N.Y., 1965, p 164.
(4) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(5) G. V. Smith and H. Kriloff, *J. Am. Chem. Soc.*, **85**, 2016 (1963).
(6) L. D. Hall, *J. Org. Chem.*, **29**, 297 (1964).
(7) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).
(8) E. W. Garbisch, *J. Org. Chem.*, **27**, 4249 (1962).
(9) (a) F. A. L. Anet and M. Z. Haq, *J. Am. Chem. Soc.*, **87**, 3147 (1965); (b) N. L. Allinger and J. T. Sprague, *ibid.*, **94**, 5734 (1972).
(10) J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
(11) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938). For details of the calculation see T. C. Kung, Ph.D. Thesis, Washington University, 1971.
(12) All melting and boiling points are uncorrected. The infrared spectra were measured on a Perkin-Elmer Infracord instrument. The ultraviolet spectra were measured on Cary Models 11 and 14 spectrometers. The ^{1}H NMR spectra were recorded on Varian A-60A and AH-100 spectrometers, using tetramethylsilane as an internal reference compound. The ^{13}C NMR spectra were obtained on a Bruker HFX-90 spectrometer by Mr. Duane Bude, working under the auspices of Dr. J. A. Schaefer of the Monsanto Co. and to whom we are indebted for making the instrument available for our use. Microanalyses were performed by Dr. Josej Zak, Mikroanalytisches Laboratorium, Vienna, Austria.
(13) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).
(14) A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Am. Chem. Soc.* **75**, 4727 (1953).
(15) L. Friedman and W. P. Wetter described in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 1158.
(16) H. L. Bassett and C. R. Thomas, *J. Chem. Soc.*, 1188 (1954).
(17) A. A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, 79, 185 (1957).
(18) See H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 606, for references and discussion.
(19) H. Plieninger and T. Suehiro, *Chem. Ber.*, **89**, 2789 (1956).
(20) H. Plieninger, L. Arnold, and W. Hoffmann, *Chem. Ber.*, **98**, 1399 (1965).
(21) H. H. Harkins and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1237 (1929).
(22) S. Ramanchandran and M. S. Newman, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 486.
(23) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Wiley, New York, N.Y., 1962.

Efficient Intramolecular Monophenol Oxidative Coupling

S. Morris Kupchan,[1] Om P. Dhingra,*[2] and Chang-Kyu Kim

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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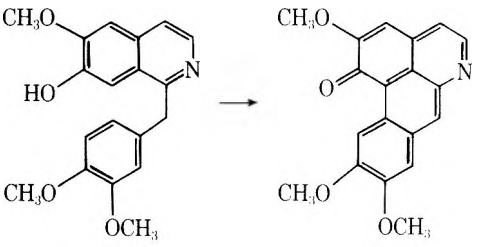
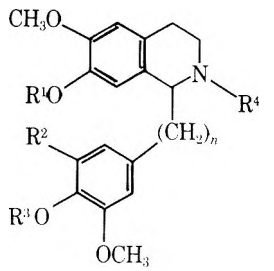
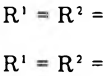
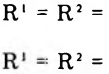
Intramolecular oxidative coupling of monophenolic benzyl- and phenethyltetrahydroisoquinolines using VOF_3–TFA/TFAA as the coupling reagent has resulted in remarkably efficient syntheses of several aporphines, homoaporphines, homoproaporphines, and a homoproerythrinadienone. Treatment of 7-hydroxy-1-benzyltetrahydroisoquinolines **3c, 3f,** and **3h** with VOF_3–TFA/TFAA gave aporphines **4a, 4b,** and **4d** (70–80%). Oxidations of 7-hydroxy-1-phenethyltetrahydroisoquinolines **3i, 3k, 3n,** and **3p** yielded, depending upon the reaction time, homoproaporphines **8a, 8b, 9a,** and **9b** (4–54%) and homoaporphines **7a, 7e, 7f,** and **7g** (54–77%). Oxidation of 6-hydroxy-1-phenethyltetrahydroisoquinoline **11** proceeded smoothly to give homoproerythrinadienone **12** in 98% yield. When the VOF_3–TFA/TFAA oxidation was extended to a monophenolic *N*-benzylphenethylamine (**16**), a dienone (**18**), the precursor of the Amaryllidaceae alkaloid (±)-oxocrinine, was obtained in 88% yield.

Although diphenolic oxidative coupling reactions play an important role in the biosynthesis of alkaloids,[3] the synthetic utility of intramolecular oxidative coupling of diphenols has been limited by low yields. Recently, attention has been directed toward the utilization of monophenolic substrates in an attempt to develop effective intramolecular coupling methods for use in alkaloid synthesis.[4,5] Schwartz et al. synthesized homomorphinandienones via monophenolic oxidative coupling using thallium tris(trifluoroacetate) in dichloromethane as the reagent.[4a] In 1973, we reported the conversion of the monophenolic benzylisoquinoline (**1**) to the quinonoid oxoaporphine (**2**) using a variety of oxidizing agents.[6] One of the most effective agents was vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) yielding **2** in 59% yield. Since then we have demonstrated that VOF_3 is a useful reagent for intramolecular oxidative coupling of nonphenolic benzyl-[7] and phenethyltetrahydroisoquinolines.[8] We now report the VOF_3-induced intramolecular oxidative coupling of monophenolic tetrahydroisoquinoline derivatives and *N*-benzylphenethylamines resulting in remarkably efficient syntheses of several aporphines, homoaporphines, homoproaporphines, a homoproerythrinadienone, and the Amaryllidaceae alkaloid (±)-oxocrinine precursor (**18**).[9]



1 **2**



3a, $R^1 = CH_2Ph$; $R^2 = R^4 = H$; $R^3 = CH_3$; $n = 1$
b, $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 1$
c, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 1$
d, $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = R^4 = CH_3$; $n = 1$
e, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$; $n = 1$
f, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 =$  ; $n = 1$
g, $R^1 = R^2 = H$; $R^3 = CH_2Ph$; $R^4 = CH_3$; $n = 1$
h, $R^1 = R^2 = H$; $R^3 = CH_2Ph$; $R^4 =$  ; $n = 1$
i, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 2$
j, $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = R^4 = CH_3$; $n = 2$
k, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$; $n = 2$
l, $R^1 = CH_2Ph$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = H$; $n = 2$
m, $R^1 = CH_2Ph$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 2$
n, $R^1 = H$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 2$
o, $R^1 = CH_2Ph$; $R^2 = OCH_3$; $R^3 = R^4 = CH_3$; $n = 2$
p, $R^1 = H$; $R^2 = OCH_3$; $R^3 = R^4 = CH_3$; $n = 2$

(±)-Codamine (**3e**) and (±)-*N*-trifluoroacetylnorcodamine (**3c**), typical monophenolic benzyltetrahydroisoquinoline derivatives, were prepared by the conventional method[8] and subjected to VOF_3–TFA/TFAA oxidation. Treatment of a solution of (±)-*N*-trifluoroacetylnorcodamine (**3c**) in dichloromethane and trifluoroacetic acid:trifluoroacetic anhydride (TFA/TFAA; 20:1 by wt.)[14] at −10 °C with a solution of VOF_3 in ethyl acetate and TFA/TFAA (20:1 by wt) for 10 min, followed by aqueous workup, gave (±)-*N*-trifluoroacetylwilsonirine (**4a,** 70%) along with morphinandienone (**5a,** 8%). The structure of aporphine **4a** was confirmed by transforming it to the naturally occurring aporphine (±)-thalicimidine[11] (**4b**) via hydrolysis of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation with formaldehyde–sodium borohydride. The structure of morphinandienone **5a** was confirmed by alkaline hydrolysis to the secondary amine (**5b**), conversion of the secondary amine to the *N*-methyl dienols (**6**) by treatment with formaldehyde–sodium borohydride, and subsequent oxidations of the dienols with manganese dioxide to (±)-*O*-methylflavinantine (**5c**).[12]

Oxidation of codamine (**3e**) by the above procedure gave a complex mixture of products from which only (±)-thalicmidine[11] (**4b,** 38%) was isolable. Interestingly, when codamine (**3e**) was treated with diborane in tetrahydrofuran–dichloromethane, and the resulting protected amine (**3f**) oxidized with VOF_3, thalicmidine (**4b**) was obtained in 80% yield after removal of the blocking group by heating with anhydrous sodium carbonate in methanol under reflux. Morphinandienone **5c** could not be detected by thin layer chromatography in either of the latter experiments. The facile and high yield conversions of the monophenolic benzyltetrahydroisoqunolines **3c** and **3e** to aporphines **4a** and **4b** constitute an efficient route to 1,2,9,10-tetrasubstituted aporphines.

In order to test the general applicability of the VOF_3–TFA/TFAA coupling method for the synthesis of 1,2,9,10-tetrasubstituted aporphines, the total synthesis of (±)-bracteoline (**4d**) was undertaken. The monophenolic benzyltetrahydroisoquinoline **3g** required for the synthesis was prepared by the method of Hara et al.[13] Treatment of **3g** with diborane in THF–CH_2Cl_2 gave the desired protected amine **3h.**

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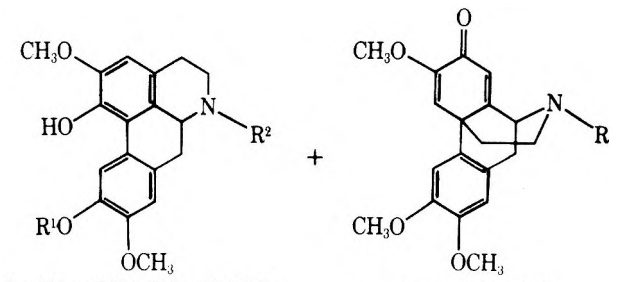
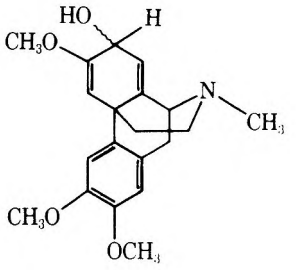
3c, e, f, h →



4a, $R^1 = CH_3$; $R^2 = COCF_3$
b, $R^1 = R^2 = CH_3$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$
d, $R^1 = H$; $R = CH_3$

5a, $R = COCF_3$
b, $R = H$
c, $R = CH_3$



6

Oxidation of **3h** with VOF_3, according to the procedure described earlier, gave (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine (**4c**) in 75% yield after removal of the blocking group by heating with sodium carbonate in methanol under reflux. Catalytic debenzylation of **4c** afforded (±)-bracteoline[13] (**4d**) in 78% yield.

To evaluate the potential of the monophenolic oxidative coupling procedure using VOF_3–TFA/TFAA for the synthesis of homoaporphines, and homomorphinandienones, 7-hydroxy-1-phenethyltetrahydroisoquinolines **3i, 3k, 3n,** and **3p** were prepared by the conventional method[8] and subjected to VOF_3 oxidation.

Oxidative coupling of the phenethyltetrahydroisoquinoline **3i** with VOF_3 at −15 °C for 10 min according to the procedure described earlier yielded the homoaporphine **7a**[8] (40%) along with the homoproaporphine **8a** (18%). The structure of the homoproaporphine **8a** was assigned on the basis of the following evidence. Treatment of **8a** with boron trifluoride etherate in dichloromethane at room temperature for 2 h gave homoaporphine **7d,** which on hydrolytic cleavage of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation with formaldehyde–sodium borohydride treatment gave a diphenolic homoaporphine (**7c**), identical with the product obtained from the dienone–phenol rearrangement of **8b.**[21]

Oxidation of phenethyltetrahydroisoquinoline **3k** with VOF_3 at −10 °C for 6 min gave the homoproaporphine **8b**[17,18,21] (42%) in addition to homoaporphine **7e**[19] (14%).

Interestingly, only one isomer of the homoproaporphine, **8a** or **8b,** was obtained in the oxidation of **3i** or **3k** in contrast to the diastereoisomeric mixtures obtained by oxidation of the diphenolic precursor.[8]

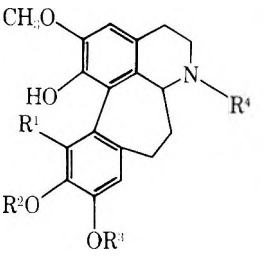
Oxidation of the phenethyltetrahydroisoquinoline **3n** with VOF_3 at −10 °C for 10 min yielded homoaporphine **7f** and homoproaporphine **9a** in 46 and 4% yield, respectively. The structure of homoaporphine **7f** was confirmed by transformation into the naturally occurring homoaporphine (±)-kreysigine (**7g**) via hydrolysis of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation with formaldehyde–sodium borohydride. The structure of homoproaporphine **9a** was assigned on the basis of its physical and spectral data (see Experimental Section).

Oxidation of phenethyltetrahydroisoquinoline **3p** with VOF_3 at −10 °C for 10 min gave homoproaporphine **9b**[20] (54%) in addition to (±)-kreysigine[20] (**7g,** 16%).

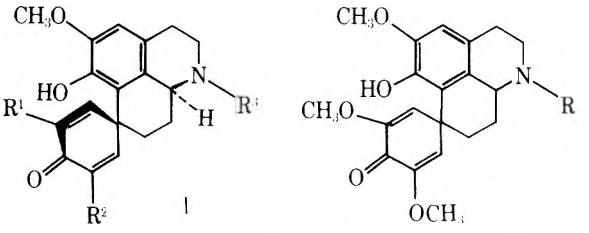
Homoproaporphines **8a, 8b, 9a,** and **9b** underwent smooth dienone–phenol rearrangement upon treatment with boron trifluoride etherate in dichloromethane at room temperature. Thus, homoproaporphine **8a** afforded homoaporphine **7d** in 93% yield. The structure of **7d** was confirmed by transforming it to homoaporphine **7c,** as described above. Homoproaporphine **8b** afforded homoaporphine **7c**[21] in 70% yield. Homoproaporphine **9a** gave homoaporphine **7h** in 87% yield. The structure of homoaporphine **7h** was assigned on the basis of its physical and spectral data (see Experimental Section). Homoproaporphine **9b** afforded homoaporphine (±)-multifloramine (**7i**)[20] in 72% yield.

The formation of homoproaporphines **8a, 8b, 9a,** and **9b** and of homoaporphines **7a, 7e, 7f,** and **7g** in the oxidation of **3i, 3k, 3n,** and **3p,** and the demonstrated facile acid-catalyzed rearrangment of homoproaporphines **8a, 8b, 9a,** and **9b** to homoaporphines **7d, 7c, 7h,** and **7i,** suggested that the formation of homoaporphines **7a, 7c, 7f,** and **7g** from **3i, 3k, 3n,** and **3p** may proceed via homoproaporphine-type intermediates (e.g., **10**) and, in part, via direct coupling. Thus, homoaporphines **7a, 7e, 7f,** and **7g** might be obtained in high yields if enough time were allowed for rearrangement of the corresponding homoproaporphine-type intermediates (e.g., **10**) Indeed, the phenethyltetrahydroisoquinolines **3i, 3k,** and **3n** gave homoaporphines **7a** (77%), **7e** (60%), and **7f** (54%), respectively, upon treatment with VOF_3–TFA/TFAA for 30–60 min. The phenethyltetrahydroisoquinoline **3p** failed to give homoaporphine **7g** in high yield even after longer reaction

3i, k, n, p →



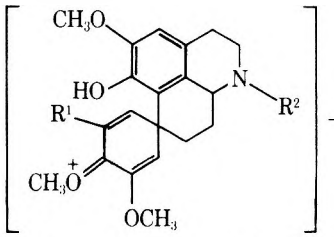
7a, $R^1 = H$; $R^2 = R^3 = CH_3$; $R^4 = COCF_3$
b, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$
c, $R^1 = R^3 = H$; $R^2 = R^4 = CH_3$
d, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = COCF_3$
e, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$
f, $R^1 = OCH_3$; $R^2 = R^3 = CH_3$; $R^4 = COCF_3$
g, $R^1 = OCH_3$; $R^2 = R^3 = R^4 = CH_3$
h, $R^1 = OCH_3$; $R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$
i, $R^1 = OCH_3$; $R^2 = H$; $R^3 = R^4 = CH_3$



8a, $R^1 = H$; $R^2 = OCH_3$; $R^3 = COCF_3$
b, $R^1 = H$; $R^2 = OCH_3$; $R^3 = CH_3$

9a, $R = COCF_3$
b, $R = CH_3$

3i, k, n, p →



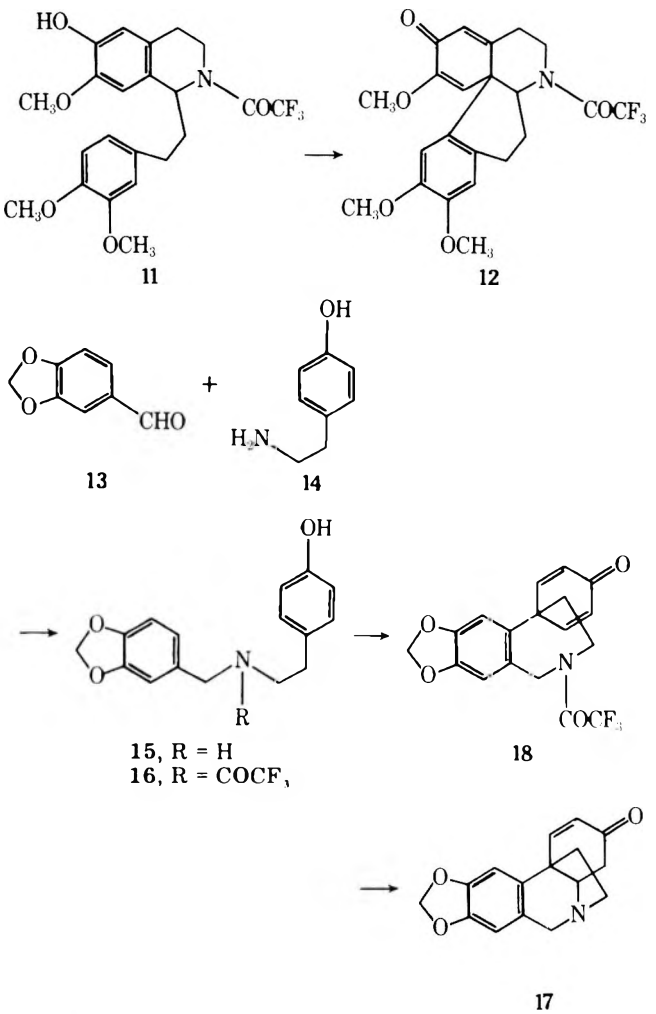
→ 7a, e, f, g

10, $R^1 = H$ or OCH_3; $R^2 = CH_3$ or $COCF_3$

time, probably owing to slow rearrangement of homoproaporphine-type intermediate (**10**).

To evaluate the potential of the monophenol oxidative coupling procedure for the synthesis of homoproerythrinadienones, 6-hydroxyl-1-phenethyltetrahydroisoquinoline **11**, prepared by catalytic debenzylation of 1-(3,4-dimethoxyphenethyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline,[8] was subjected to VOF_3 oxidation (10 min at −10 °C) and homoproerythrinadienone **12** was obtained in 98% yield. This result contrasts remarkably with those of prior studies of oxidative cyclization of diphenolic precursors using $VOCl_3$ in dichloromethane[22] (35%) and VOF_3–TFA/TFAA[8] (78%).

The remarkable success achieved in the synthesis of various isoquinoline alkaloids using VOF_3–TFA/TFAA as the coupling reagent prompted us to evaluate the potential of this coupling method for the synthesis of dienone **18**, the precursor of the amaryllidaceae alkaloid (±)-oxocrinine (**17**), from monophenolic *N*-benzylphenethylamine **16**. The phenethylamine **15** was prepared by condensation of piperonal (**13**) and tyramine (**14**) to the corresponding imine followed by borohydride reduction.[4a,23] Treatment of the amine **15** with trifluoroacetic anhydride and pyridine yielded the *N*-trifluoroacetylnorbelladine derivative **16**. When a solution of **16** in CH_2Cl_2 and TFA/TFAA was treated with a solution of VOF_3 in EtOAc and TFA/TFAA (at −10 °C for 10 min), the dienone **18** was obtained in 88% yield, as compared to the 19% yield obtained by Schwartz using thallium tris(trifluoroacetate)[4a] as the coupling reagent.



Experimental Section

General. Melting points were determined on a Mettler FP2 melting point apparatus and are uncorrected. UV and IR spectra were determined on Beckman DK-2A and Perkin-Elmer 337 spectrophotometers, respectively. NMR spectra were recorded on a JEOL PS-100p FT NMR spectrometer interfaced to a Texas Instruments JEOL 980A computer with Me_4Si as the internal standard. Mass spectra were obtained on Hitachi Perkin-Elmer RMU-6E and AEI MS-902 spectrometers. All thin layer chromatography was carried out on commercially prepared plates (E. M. Laboratories); Silica Gel 60 F-254 plates (2, 0.5, or 0.25 mm, thickness 20 × 20 cm) were used for preparative TLC. Visualization of the alkaloids was performed by means of ultraviolet light and/or by spraying the entire analytical plate, or the edges of the preparative plate, with an aqueous solution of iodoplatinic acid reagent (1.0 g in 250 mL of water containing 15 g of potassium iodide). Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Ga. Column chromatography was carried out on Silica Gel 60 (70–230 mesh ASTM) obtained from E. M. Laboratories. Anhydrous sodium sulfate was used as the drying agent, exclusively. Benzyl- and phenethyltetrahydroisoquinolines **3a–p** were prepared by a standard method,[8] *i.e.*, condensation of benzyloxyphenethylamines and acids to corresponding amides followed by Bischler-Napieralski cyclization, $NaBH_4$ reduction, N-acetylation or N-methylation, and subsequent debenzylation by hydrogenolysis.

VOF_3 Oxidation. General Procedure. In a typical oxidation 0.25–1.0 mmol of the substrate [0.05 M solution in CH_2Cl_2 containing 20% TFA/TFAA (20:1 by wt)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of 1:1 solution of ethyl acetate and TFA/TFAA (20:1 by wt)] at −10 °C (ice-salt bath) and the resulting dark blue solution was stirred for various lengths of time (see Table I). The reaction was quenched with 10% citric acid solution and the pH adjusted to ~7.5 with 58% NH_4OH. The solution was extracted with CH_2Cl_2 and the extract washed with brine, dried, and evaporated under reduced pressure to give the crude product.

1-(3,4-Dimethoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (3a). From 9.8 g (21.6 mmol) of 1-(3,4-dimethoxybenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[10] by $NaBH_4$ reduction in methanol there was obtained 8.84 g (90%) of **3a** as the hydrochloride salt: mp 214.5–215 °C (methanol–ether); NMR ($CDCl_3/CD_3OD$) δ 7.32 (s, 5 H, $PhCH_2$), 6.77 (m, 4 H, ArH), 6.31 (s, 1 H, ArH), 4.87 (d, 2 H, OCH_2, J = 3 Hz), 3.87 (s, 6 H, OCH_3), 3.82 (s, 3 H, OCH_3).

Anal. Calcd for $C_{26}H_{29}NO_4$·HCl: C, 68.48; H, 6.63; N, 3.07. Found: C, 68.21; H, 6.65; N, 3.12.

1-(3,4-Dimethoxybenzyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3b). From 2.03 g (4.83 mmol) of **3a**, 3 mL of TFAA, and 0.4 mL of pyridine in 25 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and ususal workup, 2.5 g of a white solid. Crystallization from methanol afforded 2.368 g (95%) of **3b**: mp 159.5–160 °C; IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.34 (s, 5 H, $PhCH_2O$), 6.50 (m, 5H, ArH), 5.47 (t, 1 H, CH, J = 6.0 Hz), 4.96 (s, 2 H, OCH_2), 3.86, 3.84, and 3.74 (all s, 9 H, OCH_3).

Anal. Calcd for $C_{28}H_{28}O_5NF_3$: C, 65.23; H, 5.47; N, 2.72. Found: C, 65.08; H, 5.49; N, 2.74.

(±)-*N*-Trifluoroacetylnorcodamine (3c). From 1.3 g (2.5 mmol) of **3b** in 50 mL of ethanol containing 200 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 1.012 g (94%) of **3c** as colorless cyrstals: mp 149–150 °C (ether); NMR ($CDCl_3$) δ 6.60 (m, 5 H, ArH), 5.57 (s, 1 H, OH), 3.87, 3.84, and 3.75 (all s, 9 H, OCH_3); mass spectrum m/e 425 (M^+).

Anal. Calcd for $C_{21}H_{22}O_5NF_3$: C, 59.29; H, 5.21; N, 3.29. Found: C, 59.13; H, 5.26; N, 3.24.

VOF_3 Oxidation of (±)-*N*-Trifluoroacetylnorcodamine (3c). Oxidation of 213 mg (0.5 mmol) of **3c** gave 230 mg of a dark solid. Preparative TLC ($CHCl_3$, four elutions) afforded the following two products: **5a** and **4a**.

5a (16.8 mg; 8%): mp 179.5–181.5 °C (ether); UV λ_{max} (EtOH) (log ε) 236 (4.32), 284 (3.82); IR ($CHCl_3$) 1670 (C=O); 1650 and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.85, 6.63, 6.42, and 6.36 (each s, 4 H, olefinic and aromatic protons), 3.91, 3.87, and 3.82 (each s, 9 H, OCH_3); mass spectrum m/e 423 (M^+), 297.

Anal. Calcd for $C_{21}H_{20}NO_5F_3$: C, 59.27; H, 4.76; N, 3.31. Found: C, 59.29; H, 4.80; N, 3.33.

4a (159 mg; 70%): mp 196.5–197 °C ($CHCl_3$–methanol); UV λ_{max} (EtOH) (log ε) 222 (4.56), 282 (4.03), 306 (4.11); IR ($CHCl_3$) 3540 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.12 (s, 1 H, C-11H), 6.78 and 6.58 (both s, 2 H, ArH), 6.23 (s, 1 H, OH), 3.93 (s, 6 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.49 (s, 3 H, CH_3OH of crystallization); mass spectrum m/e 423 (M^+), 297.

Anal. Calcd for $C_{21}H_{20}NO_5F_3$·CH_3OH: C, 58.01; H, 5.31; N, 3.07. Found: C, 57.80; H, 5.29; N, 3.10.

Conversion of (±)-*N*-Trifluoroacetylwilsonirine (4a) to

Table I. Oxidation of Monophenolic Benzyl- and Phenethyltetrahydroisoquinolines with VOF_3 in CH_2Cl_2–TFA/TFAA

substrate	registry no.	temp, °C	time, min	products	registry no.	yield, %
3c	61659-86-7	−10	10	**4a**	61659-87-8	70
				5a	61659-88-9	8
3f	61659-89-0	−10	10	**4b**	2755-00-2	80
3h	67393-30-0	−10	10	**4c**	60888-76-8	74.5
3i	61659-90-3	−10	10	**7a**	61659-92-5	40
				8a	67393-31-1	18
		−10–30[a]	60	**7a**		77
3k	38726-24-0	−10	6	**8b**	51744-25-3	42
				7e	31735-21-4	14
		−10–30[a]	60	**7e**		60
3n	61659-91-4	−10	10	**7f**	61659-98-1	46
				9a	61659-94-7	4
		−10–30[a]	30	**7f**		54
3p	38726-41-9	−10	10	**9b**	36217-47-7	54
				7g	31735-22-5	16
11	61659-97-0	−10	10	**12**	67393-32-2	98
16	40135-88-4	−10	10	**18**	67393-33-3	88

[a] The reaction mixture was slowly allowed to attain room temperature (30 °C). However, the same results are obtained if the reaction is run at −10 °C.

(±)-Thalicmidine (4b). A solution of 30 mg of **4a** in 5 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 6 h. The solution was evaporated to dryness and the residue suspended in water and extracted with ether. The ether solution was washed with brine, dried, and evaporated to give 25 mg of a colorless glass. The glass was dissolved in 1 mL of methanol and treated with 0.1 mL of 37% formaldehyde solution and the mixture was stirred at room temperature for 3 h. The reaction was diluted with 10 mL of methanol, 20 mg of sodium borohydride was added, and the reaction was stirred for 0.5 h. The methanol was evaporated and the residue suspended in water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to give 25 mg of a light brown gum. Preparative TLC ($CHCl_3$–5% methanol) gave 19.2 mg (80%) of **4b** as colorless crystals: mp 191–193 °C (methanol–ether). The melting point, mixture melting point, UV, IR, TLC, NMR and mass spectrum were identical with those of the product obtained by VOF_3 oxidation of **3e**.

Conversion of Morphinandienone 5a to (±)-*O*-Methylflavinantine (5c). A solution of 10.0 mg of **5a** in 1 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 3 h. The reaction mixture was evaporated and the residue suspended in water, and extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to give 8 mg of **5b** as a colorless oil. The oil was taken up in 3 mL of methanol and treated with 3 drops of 37% formaldehyde solution. The reaction was stirred at room temperature for 15 min, treated with 20 mg of sodium borohydride, and stirred for an additional 1 h. The reaction mixture was evaporated and the residue suspended in water and extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to leave 8 mg of an oil (**6**). The oil was taken up in 1 mL of chloroform and stirred with 8 mg of active manganese dioxide at room temperature for 16 h. The oxide was filtered and washed with chloroform. The filtrate and the washings were evaporated to leave 8 mg of a colorless oil. Preparative TLC ($CHCl_3$–5% methanol) afforded 5.2 mg (65% from **5a**) of (±)-*O*-methylflavinantine (**5c**) as colorless needles: mp 161–162 °C (methanol); NMR ($CDCl_3$) δ 6.81, 6.63, 6.36, and 6.33 (each s, 4 H, aromatic and olefinic protons); 3.89, 3.86, and 3.81 (each s, 9 H, OCH_3), 2.47 (s, 3 H, NCH_3). The melting point, mixture melting point, IR, NMR, and mass spectrum were identical with those of authentic sample of (±)-*O*-methylflavinantine.[25]

Preparation of Borane Complex of (±)-Codamine, 3e (3f). A solution of 190 mg (0.55 mmol) of (±)-codamine[10] (**3e**) in 5 mL of chloroform was treated with 0.64 mL of a 1 M solution of diborane in THF (Aldrich) and the reaction was stirred at room temperature for 15 min. The chloroform was evaporated and the residue was chromatographed on a 2 mm preparative silica gel plate using 5% methanol in chloroform. The major band was collected to leave 150 mg of the borane complex as colorless amorphous solid (**3f**): mass spectrum *m/e* 357 (M^+), 341 ($M^+ - BH_3$).

VOF_3 Oxidation of 3f. Oxidation of 111 mg (0.31 mmol) of **3f** gave 120 mg of a light brown glass which was taken up in 15 mL of methanol and heated under reflux with 130 mg of anhydrous sodium carbonate for 2 h. The solution was filtered and evaporated to give a brown residue. Preparative TLC ($CHCl_3$–10% methanol) afforded 90 mg of a light brown gum which was crystallized from methanol–ether to give 85.5 mg (80%) of (±)-thalicmidine (**4b**): mp 191–193 °C dec (lit.[11] mp 190–192 °C). The melting point, mixture melting point, and NMR spectrum were identical with those of an authentic sample of (±)-thalicmidine.[8]

Preparation of a Borane Complex of 3g (3h). A solution of 2.0 g (4.77 mmol) of **3g**[13] in 30 mL of anhydrous chloroform was treated with 12.5 mL of a 1 M solution of diborane in THF according to the procedure given for the preparation of **3f** to give 2.05 g (99%) of **3h** as colorless foam: IR ($CHCl_3$) 2380 cm^{-1} (B–H); mass spectrum *m/e* 433 (M^+, very weak), 419 (100).

VOF_3 Oxidation of 3h. Oxidation of 130.0 mg (0.3 mmol) of **3h** afforded, after removal of the blocking group with anhydrous sodium carbonate in refluxing methanol, 82.5 mg (74.5%) of (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine as the ether solvate (**4c**): mp 73–75 °C (lit.[13] mp 74–76 °C).

(±)-Bracteoline (4d). A solution of 40 mg of **4c** in 10 mL of methanol containing 20 mg of 10% Pd/C was hydrogenated at atmospheric pressure and temperature until uptake of hydrogen ceased. The catalyst was filtered and the filtrate evaporated to a yellow residue which was crystallized from ether–methanol yielding 24.0 mg (78%) of (±)-bracteoline (**4d**): mp 207–210 °C dec (lit.[13] mp 208–210 °C dec).

1-(3,4-Dimethoxyphenethyl)-7-hydroxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3i). From 3.575 g (6.4 mmol) of 1-(3,4-dimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline[8] in 75 mL of ethanol containing 500 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 2.830 g (93%) of **3i** as colorless crystals: mp 138.7–139.6 °C (ether); NMR ($CDCl_3$) δ 6.75 (s, 3 H, ArH), 6.66 and 6.57 (each s, 2 H, ArH), 5.54 (s, 1 H, OH), 3.86 (s, 9 H, OCH_3), 3.6–2.24 (m, 8 H, CH_2); mass spectrum *m/e* 439 (M^+), 274 (100).

Anal. Calcd for $C_{22}H_{24}NO_5F_3$: C, 60.13; H, 5.51; N, 3.19. Found: C, 60.26; H, 5.51; N, 3.22.

1-(3,4,5-Trimethoxyphenethyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (3l). From 8.1 g (16.2 mmol) of 1-(3,4,5-trimethoxyphenethyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[19] by $NaBH_4$ reduction in methanol there was obtained 7.4 g (91%) of **3l** as the hydrochloride salt: mp 195.7–196 °C (CH_3OH–ether); NMR ($CDCl_3$) δ 10.37 (mound, 1 H, HCl), 9.73 (mound, 1 H, NH), 7.40 (m, 5 H, $PhCH_2O$), 6.62 (s, 1 H, ArH), 6.55 (s, 3 H, ArH), 5.08 (s, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 3.82 (s, 9 H, OCH_3), 3.68–2.5 (m, 8 H, CH_2).

Anal. Calcd for $C_{28}H_{34}O_5NCl$: C, 67.25; H, 6.85; N, 2.80. Found: C, 67.13; H, 6.76; N, 2.89.

1-(3,4,5-Trimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3m). From 2.315 g (5 mmol) of **3l**, 2.6 mL of TFAA, and 0.5 mL of pyridine in 40 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and the usual workup, 2.9 g of a yellow oil which was crystallized from methanol yielding 2.69 g (96%) of **3**: mp 127.3–128 °C; IR ($CHCl_3$) 1685 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.37 (m, 5 H, $PhCH_2O$), 6.62, 6.57 (each s, 2 H, ArH), 6.38 (s, 2 H, ArH), 5.47 (t, 1 H, C-1H, J = 7.0 Hz), 5.09 (s, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3),

3.82 (s, 3 H, OCH_3), 3.8–2.05 (m, 8 H, CH_2).

Anal. Calcd for $C_{30}H_{32}O_6NH_3$: C, 64.39; H, 5.76; N, 2.50. Found: C, 64.46; H, 5.78; N, 2.49.

1-(3,4,5-Trimethoxyphenethyl)-7-hydroxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3n). From 2.54 g (4.57 mmol) of **3m** in 75 mL of ethanol containing 500 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 2.082 g (97%) of **3n:** mp 145–146 °C (methanol); NMR ($CDCl_3$) δ 6.67, 6.58 (both s, 2 H, ArH), 6.41 (s, 2 H, ArH), 5.57 (s, 1 H, OH), 3.86 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.5–2.1 (m, 8 H, CH_2).

Anal. Calcd for $C_{23}H_{26}O_6NF_3$: C, 58.84; H, 5.58; N, 2.98. Found: C, 58.82; H, 5.60; N, 2.96.

VOF_3 Oxidation of 3i. Oxidation of 110 mg (0.25 mmol) of **3i** gave 140 mg of a dark brown residue. Preparative TLC ($CHCl_3$–4% methanol) afforded the following two products: **7a** (44 mg; 40%); mp 200–201 °C (transition at 110 °C). The melting point, mixture melting point, TLC, UV, NMR, and mass spectrum were identical with those of an authentic sample.[8]

8a (19 mg; 18%): mp 192.5–193.5 °C (ether); NMR ($CDCl_3$) δ 6.92 (dd, 1 H, H_B, J_{AB} = 2.5 Hz, J_{BX} = 10 Hz), 6.60 (s, 1 H, ArH), 6.24 (d, 1 H, H_X, J_{BX} = 10 Hz), 5.82 (d, 1 H, H_A, J_{BA} = 2.5 Hz), 5.64 (s, 1 H, OH), 3.85 (s, 3 H, aromatic OCH_3), 3.67 (s, 3 H, olefinic OCH_3), 3.5–1.7 (m, 8 H, CH_2); UV λ_{max} (EtOH) (log ε) 290 (3.78), 243 (sh); IR ($CHCl_3$) 1690 (C=O), 1665, and 1635 (C=C), 3530 cm^{-1} (OH); mass spectrum *m/e* 423 (M^+), 395, 380.

Anal. Calcd for $C_{21}H_{20}NO_5F_3$: C, 59.55; H, 4.76; N, 3.30. Found: C, 59.62; H, 4.76; N, 3.38.

Rearrangement of Homoproaporphine 8a with Boron Trifluoride Etherate. A mixture of 30 mg of **8a,** 5 mL of CH_2Cl_2, and 3 drops of boron trifluoride etherate was stirred at room temperature for 2 h. After the solution had been diluted with CH_2Cl_2 to 25 mL, the solution was washed with water, dried, and evaporated to an oil which was crystallized from ether giving 26 mg (93%) of diphenolic homoaporphine **7d:** mp 167–168 °C; IR ($CHCl_3$) 3540 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.04 (s, 1 H, C-12H), 6.84 (s, 1 H, C-3H), 6.61 (s, 1 H, C-9H), 5.72 (s, 2 H, OH), 3.92, 3.87 (both s, 6 H, OCH_3), 5.08 (t, 1 H, CH, *J* = 7 Hz), 3.8–2.2 (m, 8 H, CH_2); mass spectrum *m/e* 423 (M^+).

Anal. Calcd for $C_{21}H_{20}NO_5F_3$: C, 59.57; H, 4.76; N, 3.31. Found: C, 59.34; H, 4.84; N, 3.25.

Conversion of *N*-Trifluoroacetylhomoaporphine (7d) to *N*-Methylhomoaporphine (7c). A 25-mg sample of **7d** was treated with 1 N methanolic sodium hydroxide and then subjected to reductive methylation according to the procedure described for the conversion of **4a** to **4b,** to give 11 mg of a yellow glass. Preparative TLC ($CHCl_3$–10% methanol) gives, after crystallization from methanol–ether, 5 mg of **7c:** mp 238–240 °C dec (lit.[21] mp 241–242 °C).

VOF_3 Oxidation of Homocodamine (3k). Oxidation of 95 mg (0.266 mmol) of **3k**[15] gave 95 mg of a yellow glass. Preparative TLC ($CHCl_3$–10% methanol; two elutions) afforded the following two products: **7e** and **8b.**

7e (13 mg; 14%): mp 190–192 °C (CH_2Cl_2–ether; lit.[15] mp 195–196 °C).

8b (38 mg; 42%): mp 200–201 °C (benzene–hexane; lit.[26] mp 200–202 °C). The melting point, mixture melting point, TLC, UV, IR, NMR, and mass spectrum were identical with those of an authentic sample.[8]

VOF_3 Oxidation of 3n. Oxidation of 235 mg (0.5 mmol) of **3n** gave 250 mg of a brown residue. Preparative TLC ($CHCl_3$–4% methanol) afforded the following two products: **7f** and **9a.**

7f (107 mg; 46%): mp 161–162 °C (ether); UV λ_{max} (EtOH) (log ε) 258 (4.11), 296 (3.72) nm; IR ($CHCl_3$) 3540 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.65, 6.63 (both s, 2 H, ArH), 6.24 (s, 1 H, OH), 3.91 (s, 9 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.6–2.3 (m, 8 H, CH_2); mass spectrum *m/e* 467 (M^+), 450, 436, 341.

9a (9.5 mg; 4%): mp 213–215 °C dec (ether); UV λ_{max} (EtOH) (log ε) 276 (4.09), 235 (sh); IR ($CHCl_3$) 3540 (OH), 1690 (C=O), 1650 and 1615 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.60 (s, 1 H, ArH), 5.87 (d, 2 H, olefinic protons, *J* = 3.5 Hz), 5.62 (s, 1 H, OH), 3.85 (s, 3 H, aromatic OCH_3), 3.68 and 3.60 (both s, 6 H, OCH_3), 3.5–2.2 (m, 8 H, CH_2); mass spectrum *m/e* 453 (M^+), 436, 421.

Anal. Calcd for $C_{22}H_{22}O_6NF_3$: C, 58.28; H, 4.89; N, 3.09. Found: C, 58.06; H, 4.98; N, 3.07.

Conversion of *N*-Trifluoroacetylhomoaporphine (7f) to *N*-Methylhomoaporphine (7g). A 50-mg sample of **7f** was treated with 1 N methanolic sodium hydroxide and then subjected to reductive methylation according to the procedure described for the conversion of **4a** to **4b** to give 45 mg of a colorless glass which was crystallized from ether yielding 36 mg of (±)-kreysigine (**7g**): mp 186–187 °C (lit.[20] mp 187–189 °C). The melting point, mixture melting point, TLC, UV, IR, NMR, and mass spectrum were identical with those of (±)-kreysigine obtained by VOF_3 oxidation of **3p.**

VOF_3 Oxidation of 3p. Oxidation of 96 mg (0.25 mmol) of **3p** gave a yellow residue. Preparative TLC ($CHCl_3$–5% methanol) afforded the following two products: **7g** and **9b.**

7g (15 mg; 16%); mp 185–187 °C (ether: lit.[20] mp 187–189 °C).

9b (50.5 mg; 54%); mp 174–176 °C (ether; lit.[20] 176–178 °C).

Rearrangement of 8b with Boron Trifluoride Etherate. A mixture of 20 mg of **8b,** 5 mL of CH_2Cl_2, and 0.4 mL of boron trifluoride etherate was stirred at room temperature for 2 h. After the usual workup and crystallization from methanol–ether there was obtained 14 mg (70%) of homoaporphine **7c:** mp 240–241 °C dec (lit.[21] mp 241–242 °C).

Rearrangement of 9a with Boron Trifluoride Etherate. A mixture of 50 mg of **9a,** 5 mL of CH_2Cl_2, and 1 mL of boron trifluoride etherate was stirred at room temperature for 2 h. After the usual workup and crystallization from ether there was obtained 35.0 mg (87%) of homoaporphine **7h:** mp 208–208.5 °C; UV λ_{max} (EtOH) (log ε) 260 (3.95), 296 (3.77) nm: IR ($CHCl_3$) 3545 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.66 and 6.62 (both s, 2 H, ArH), 3.95, 3.92, and 3.62 (each s, 9 H, OCH_3); mass spectrum *m/e* 453 (M^+), 436, 327.

Anal. Calcd for $C_{22}H_{22}O_6NF_3$: C, 58.28; H, 4.89; N, 3.09. Found: C, 58.27; H, 4.98; N, 3.12.

Rearrangement of 9b with Boron Trifluoride Etherate. A mixture of 25 mg of **9b,** 5 mL of CH_2Cl_2, and 0.5 mL of boron trifluoride etherate was stirred at room temperature for 15 h. The usual workup and preparative TLC ($CHCl_3$–12% methanol) afforded 20 mg (80%) of **7i:** mp 189–191 °C (lit.[20] 190–192 °C dec).

1-(3,4-Dimethoxyphenethyl)-6-hydroxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (11). From 500 mg (0.94 mmol) of 1-(3,4-dimethoxyphenethyl)-6-benzyloxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline[8] in 40 mL of ethyl alcohol containing 100 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 363 mg (87%) of **11** as colorless crystals: mp 109–111 °C (ether); NMR ($CDCl_3$) δ 6.76 (s, 3 H, ArH), 6.66, 6.50 (both s, 2 H, ArH), 5.56 (s, 1 H, OH), 3.87 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3).

Anal. Calcd for $C_{22}H_{24}NO_5F_3$: C, 60.13; H, 5.51; N, 3.19. Found: C, 59.97; H, 5.40; N, 3.23.

VOF_3 Oxidation of 11. Oxidation of 110 mg (0.25 mmol) of **11** gave 120 mg of a colorless glass which after chromatography on silica gel ($CHCl_3$) and crystallization from ether afforded 109 mg (98%) of **16** as colorless crystals: mp 125 °C, solidifies and remelts at 160–162 °C. The melting point, mixture melting point, TLC, UV, and NMR were identical with those of an authentic sample.[8]

***N*-(3,4-Methylenedioxybenzyl)-4-hydroxyphenethylamine (15).** A solution of 1.5 g (10 mmol) of piperonal and 1.37 g (10 mmol) of tyramine in 130 mL of methanol was stirred for 2 h. Sodium borohydride (2.5 g) was added portionwise over 45 min and the reaction mixture stirred for an additional hour. The methanol was evaporated and the residue suspended in water and extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to a colorless glass which was converted into the hydrochloride salt and crystallized from methanol–ether yielding 2.65 g (89%) of the amine (**15**) as the hydrochloride salt: mp 215–217.2 °C; NMR ($CDCl_3/CD_3OD$) δ 7.09–6.72 (m, 7 H, ArH), 6.01 (s, 2 H, OCH_2O), 4.04 (s, 2 H, $ArCH_2N$).

Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.90; N, 4.53. Found: C, 62.41; H, 5.95; N, 4.53.

***N*-Trifluoroacetyl-*N*-(3,4-methylenedioxybenzyl)-4-hydroxyphenethylamine (16).** The hydrochloride salt of **15** (2.553 g; 8.3 mmol) was converted into the free amine and treated with 5.5 mL of trifluoroacetic anhydride and 0.5 mL of pyridine according to the procedure described for the preparation of **3b** to give 3.21 g of an orange-brown oil. The oil was chromatographed on silica gel eluting with chloroform to give a colorless oil which was crystallized from ether–hexane yielding 2.711 g of **16** as white crystals: mp 118.4–118.9 °C; NMR ($CDCl_3$) δ 7.04–6.55 (m, 7 H, ArH), 5.95 (d, 2H, OCH_2O, *J* = 1.5 Hz), 5.20 (s, 1 H, OH), 4.41 (d, 2 H, $ArCH_2N$, *J* = 25.9 Hz), 3.37 (m, 2 H, $ArCH_2CH_2N$), 2.78 (m, 2 H, $ArCH_2CH_2N$).

Anal. Calcd for $C_{18}H_{16}O_4NF_3$: C, 58.85; H, 4.39; N, 3.81. Found: C, 58.71; H, 4.45; N, 3.75.

VOF_3 Oxidation of 16. Oxidation of 184 mg (0.5 mmol) of **16** gave 202.5 mg of an amorphous solid. Preparative TLC (ether–10% acetone) afforded, after crystallization from ether–hexane–methanol, 160 mg (88%) of **18** as slightly yellow crystals: mp 179.5–181.2 °C (transition at 138.8 °C; lit.[4a] mp 138–142 °C; 181–182 °C); NMR ($CDCl_3$) δ 7.06–6.25 (eight peaks, 6 H, aromatic and olefinic protons), 5.94 (d, 2 H, OCH_2O, *J* = 2.0 Hz), 4.76 (s, 2 H, $ArCH_2N$), 3.93 (m, 2 H, $ArCH_2CH_2$), 2.40 (m, 2 H, NCH_2CH_2).

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Registry No.—**3a**·HCl, 23843-20-1; **3b**, 67393-34-4; **3e**, 5977-85-5; **3g**, 60888-73-5; **3l**, 67393-35-5; **3m**, 67393-36-6; **4d**, 28230-74-2; **5c**, 22169-18-2; **7c**, 59168-20-6; **7d**, 61659-95-8; **7h**, 61659-96-9; **7i**, 16845-28-6; **15**, 56114-14-8; 1-(3,4-dimethoxybenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 41183-10-2; 1-(3,4-dimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline, 61660-08-0; 1-(3,4,5-trimethoxyphenethyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 67393-37-7; 1-(3,4-dimethoxyphenethyl)-6-benzyloxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline, 61660-07-9; piperonal, 120-57-0; tyramine, 51-67-2.

References and Notes

(1) Deceased October 19, 1976.
(2) To whom correspondence should be addressed at the Department of Chemistry, Oregon State University, Corvallis, Oregon 97331.
(3) (a) W. I. Taylor and A. R. Battersby, Ed., "Oxidative Coupling of Phenols", Marcel Dekker, New York, N.Y., 1967; (b) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology", Academic Press, New York, N.Y., 1972; (c) T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972).
(4) (a) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973); (b) M. A. Schwartz, B. F. Rose, R. A. Molten, S. W. Scott, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **99**, 2571 (1977).
(5) U. Palmquist, A. Nilsson, V. D. Parker, and A. Rolan, *J. Am. Chem. Soc.*, **98**, 2571 (1976).
(6) S. M. Kupchan and A. J. Liepa, *J. Am. Chem. Soc.*, **95**, 4062 (1973).
(7) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973); S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *J. Am. Chem. Soc.*, **97**, 5622 (1975).
(8) S. M. Kupchan, O. P. Dhingra, C.-K. Kim, and V. Kameswaran, *J. Org. Chem.*, **43**, 2521 (1978), and references cited therein.
(9) A portion of this work was reported in preliminary form; S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, *J. Org. Chem.*, **41**, 4049 (1976).
(10) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).
(11) S. M. Kupchan, V. Kameswaran, and J. W. Findlay, *J. Org. Chem.*, **38**, 405 (1973).
(12) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **93**, 5941 (1971).
(13) H. Hara, O. Hoshino, and B. Umezawa, *Chem. Parm. Bull.*, **24**, 1921 (1976).
(14) A mixture of TFA–TFAA (20:1 by weight) was used to make sure that the medium was anhydrous. Absence of TFAA results in a lower yield of products.
(15) O. Hoshino, T. Toshioka, K. Ohyama, and B. Umezawa, *Chem. Pharm. Bull.*, **22**, 1307 (1976).
(16) A. Brossi, J. Van Burik, and S. Teitel, *Helv. Chim. Acta*, **51**, 1965 (1968).
(17) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).
(18) H. Hara, O. Hoshino, B. Umezawa, and Y. Iitaka, *Heterocycles*, **7** (1), 307–314 (1977).
(19) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **36**, 3733 (1971).
(20) A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *J. Chem. Soc., Perkin Trans. 1*, 1394 (1974).
(21) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc. C*, 1003 (1968).
(22) J. P. Marino and J. M. Samanen, *Tetrahedron Lett.*, 4553 (1973).
(23) M. A. Schwartz and R. A. Holten, *J. Am. Chem. Soc.*, **92**, 1090 (1970).
(24) R. E. Herman and B. L. Jensen, *J. Heterocycl. Chem.*, **7**, 1077 (1970).
(25) S. M. Kupchan and C.-K. Kim, *J. Am. Chem. Soc.*, **97**, 5623 (1975).
(26) A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 934 (1967).

1,4-Diketones from Skipped Acetylenes

Walter J. Gensler,* Jean-Claude Petitpierre, and John W. Dean

Department of Chemistry, Boston University, Boston, Massachusetts 02215

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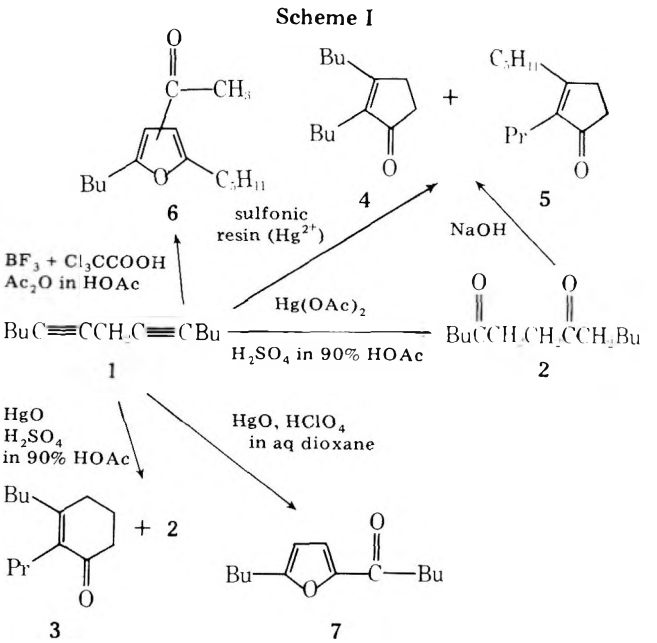
Under various acidic hydrating conditions, 5,8-tridecadiyne gives rise to 5,8-tridecanedione, 2-propyl-3-butyl-2-cyclohexenone, 2-propyl-3-pentyl-2-cyclopentenone, 2,3-dibutyl-2-cyclopentenone, 2-pentanoyl-5-butylfuran, and acetylated 2-butyl-5-pentylfuran. 1,4-Nonadiyne yields 2,5-nonanedione and also can give 5-butylfurfural; 1,4,7-dodecatriyne yields 2,5,8-dodecanetrione. Reaction pathways are proposed that rely on neighboring group effects to direct the course of the several processes.

1,4-Dicarbonyl compounds[1-5] are recognized as useful precursors for preparing five-membered heterocycles as well as cyclopentenones. We wish to report a new general synthesis of this kind of carbonyl compound by the hydration of 1,4- (or skipped) acetylenes, which can be obtained readily by coupling acetylenic Grignard reagents with propargyl bromides. This paper describes the results with 5,8-tridecadiyne (**1**)[6] and 1,4-nonadiyne (**8**),[7] which furnish, respectively, 5,8-tridecanedione (**2**) and 2,4-nonanedione (**9**), as well as other products. Skipped triyne, 1,4,7-dodecatriyne (**12**),[7] also has been investigated, and shown to give 2,5,8-dodecanetrione (**13**).

Results

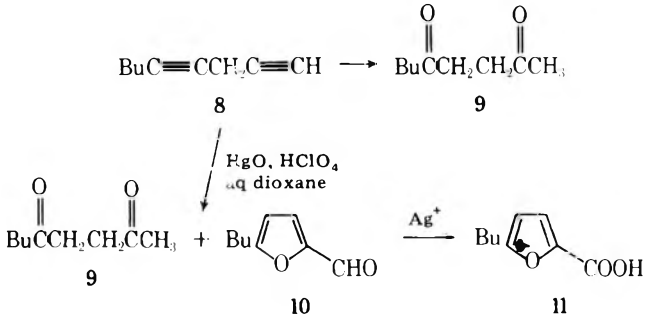
Hydration[8] of 5,8-tridecadiyne (**1**) in aqueous acetic acid in the presence of mercuric acetate and sulfuric acid produced 5,8-tridecanedione (**2**) in 70% yield. Substitution of mercuric oxide for the mercuric acetate gave the same diketone, although now it was accompanied by small amounts of 2-propyl-3-butyl-2-cyclohexenone (**3**). When a sulfonated resin loaded with mercuric ion[9] was used as a solid catalyst, none of the diketone **2** was obtained; instead the product was a mixture of cyclopentenones **4** and **5** together with a little cyclohexenone **3**. The same cyclopentenones **4** and **5** free of cyclohexenone were obtained more conveniently by cyclizing 5,8-tridecanedione (**2**) with base.[10]

Scheme I

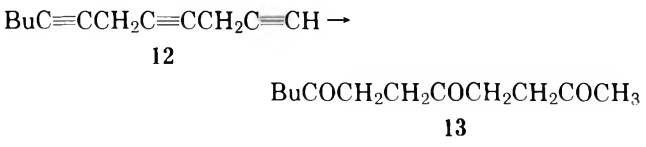


Stirred at room temperature in acetic acid–acetic anhydride containing trichloroacetic acid, mercuric oxide, and boron

trifluoride,[11] diyne 1 cyclized to an acetylated furan, to which we have assigned the structure of ring acetyl-2-butyl-5-pentylfuran (6). Finally, with aqueous dioxane in the presence of perchloric acid and mercuric ion,[12] an oxidative process occurred giving 2-pentanoyl-5-butylfuran (7) in 65% yield.



Trials with terminally unsaturated skipped acetylenes showed that these compounds also lead to 1,4-diketones. Thus, 1,4-nonadiyne (8) with the mercuric acetate catalyst gave 2,5-nonanedione (9)[3] in 67% yield. Application of the mercuric oxide–perchloric acid conditions led to the same 2,5-nonadione (9) now accompanied by 5-butylfurfural (10). The nature of the aldehyde product was established by relating it to 5-butylfuroic acid (11), which was obtained from methyl furoate. The triply unsaturated compound, 1,4,7-dodecatriyne (12), afforded 2,5,8-dodecanetrione (13) in good yield. On the reasonable assumption that no carbonyl group can develop past the dodecane 8 position, formulation 13 is fully consistent with the spectroscopic properties of the product.

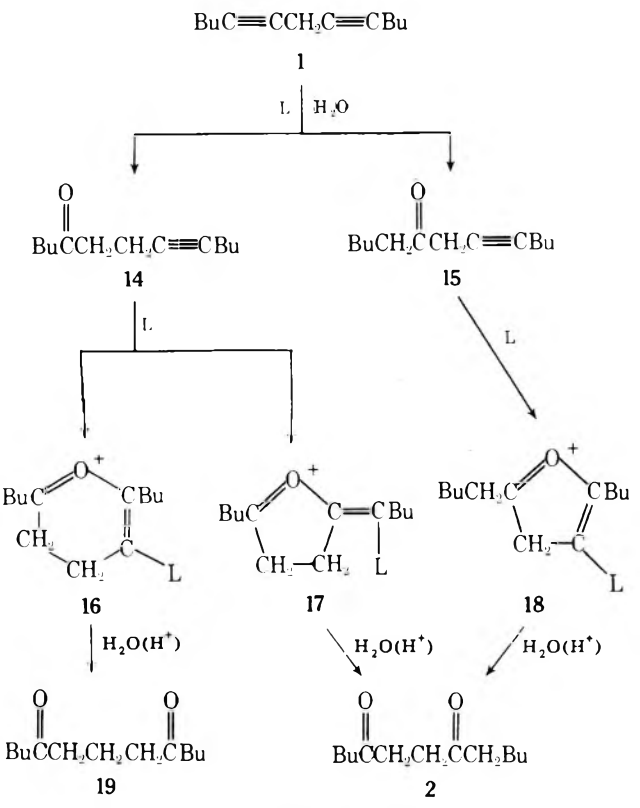


Reaction Sequence. Hydration of skipped acetylene can lead, a priori, to more than one ketonic product. For example, diyne 1 could give the diketones 6,8-nonanedione, 5,8-nonanedione (2), or 5,9-nonanedione. Significantly, none of the 1,3- or the 1,5-diketones were observed, the only diketonic product detected being the 1,4-diketone **2.** Interpretations based on internally directed processes account for this selectively.

Thus starting with 5,8-tridecadiyne (5), the yne–ones **14** and **15** are taken to form in an unexceptional way. In the second stage of the hydration, possible intermediates would include the five-membered heterocycles **17** and **18** and (or) the six-membered heterocycle **16.** Hydrolysis of **17** or **18** would give the observed 1,4-diketone **2,** whereas **16** would give the 1,5-diketone **19.** The preferred formation of the 1,4-diketone can be understood if five-membered rings as in **17** and **18** form and react faster than the six-membered ring, as in **16,** and for that matter faster than *any* cyclic or acyclic intermediate that could lead to the 1,5- (or the 1,3) diketone. Since no intermediate yne–ones were detected at any stage in any of the reactions, the second part of the process starting from **14** and **15** must be appreciably faster than the first. The enhanced rates may be attributed to anchimeric assistance. In its outlines, this argument is analogous to that advanced before[4] to account for the preferred appearance of 1,4-diones in the hydration of γ,δ-unsaturated acetylenic ketones related to **14.**

The terminally unsaturated skipped acetylenes 8 and 12 also gave 1,4-spaced carbonyls. Since there is a recognized kinetic preference for hydration of terminal acetylenes over internal acetylenes,[13] we may accept the initial formation of 2-keto-4-nonyne and 2-keto-4,7-dodecatriyne from 1,4-nonadiyne (8) and 1,4,7-dodecatriyne (12), respectively. Once these intermediates are involved, the same kind of reasoning as before, involving neighboring group effects, predicts that only carbonyls spaced at intervals of four carbon atoms will emerge.

Scheme II

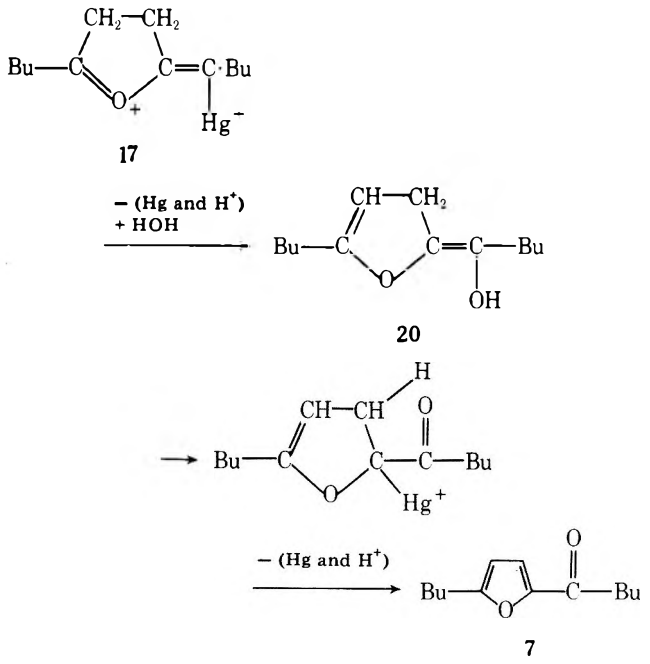


L = electrophile catalyst

Turning to the cyclic products, and considering first the cyclopentenones **4** and **5,** we have no basis for not accepting formation, and then, under the same conditions, cyclization, of 5,8-tridecanedione (2). In the resin-catalyzed process, cyclopentenones **4** and **5** are obtained with 5,8-tridecadiyne or with 5,8-tridecanedione as starting material. Also relevant is the observation that the mercuric ion–sulfuric acid procedure, which after a 5-h reflux period forms 5,8-tridecanedione from 5,8-tridecadiyne, after a 3-day reflux period gives the cyclopentenone mixture **4** plus **5.**[17]

In contrast, similar experimental tests show that the 1,4-diketones **2** or **9** cannot serve as intermediates in the oxidative formation of acylfurans **7** and **10.** Under conditions that give furans **7** and **10,** replacing the diyne starting materials **1** and **8** with diketones **2** and **9** leaves the diketones unchanged. The possibility that 2-butyl-5-pentylfuran and 2-butyl-5-methylfuran are intermediates may also be rejected. If this kind of molecule were oxidized, it is likely that the 2-pentanoyl-5-butylfuran (7), for example, would emerge as a 50:50 mixture with 2-butanoyl-5-pentylfuran. Yet no sign of twin peaks appeared in any of our routine gas-liquid chromatographic analyses. In one run, analysis with a high-efficiency (75 000–150 000 plate) capillary gas-liquid chromatographic column still showed only a single, sharp, symmetrical peak. Finally, the mass fragmentation pattern, in being consistent with 2-pentanoyl-5-butylfuran (7) but not with 2-butanoyl-5-pentylfuran, confirmed both the homogeneity and the assigned structure.

Rationalization of this oxidation process makes use of intermediate **17** as the starting point. In the pathway leading to diketone **2,** the mercury group in **17** leaves as mercuric ion and is replaced with hydrogen; in the oxidative process, however, mercury leaves with its pair of electrons as metallic mercury,[15] and is replaced with hydroxyl (as in **20**). A second



mercuration again followed by loss of mercury gives rise to the observed product **7**. Although other sequences can be written, this one is short, direct, and reasonable. Why oxidation occurs here but not in the other mercury-catalyzed hydrations may be related to the relatively large amounts of mercuric ion as well as to the enhanced solvolytic properties of 25% aqueous dioxane over the other solvents. A similar mechanism can be formulated for formation of 5-butylfurfural (**10**) from 1,4-nonadiyne (**8**).

To reach cyclohexenone **3**, we assume as intermediate the 1,5-dicarbonyl compound **19** which undergoes acid catalyzed aldol cyclization to give **3**.[16,17] The fact that the cyclohexenone **3** was invariably obtained in poor yield as a minor product agrees with the postulated slow rate of formation of intermediate **16**.

The boron trifluoride process converting 5,8-tridecadiyne (**1**) to acetylated furan **6** is run under anhydrous conditions. Here, a straightforward reaction pathway calls for cyclization to 2-butyl-5-pentylfuran, which then undergoes ring acetylation.[18] Whether 5,8-tridecanedione (**2**) would give the acetylated furan **6** under the conditions used was not investigated.

Summary. Skippd diynes and triynes have been shown to be useful and convenient precursors in the preparation of polyketones and various hetero- and homocyclic derivatives. Under appropriate conditions, the following compounds were prepared in practical though still not optimized yield: from 5,8-tridecadiyne (**1**), 5,8-tridecanedione (**2**, 71%), 2,3-dialkylcyclopentenones (**4** and **5**, 62%), acetylated 2-butyl-5-pentylfuran (**6**, 55%), and 2-pentanoyl-5-butylfuran (**7**, 65%); from 1,4-nonadiyne (**8**), 2,5-nonanedione (**9**, 67%); and from 1,4,7-dodecatriyne (**12**), 2,5,8-dodecanetrione (**13**, 63%). Other compounds were also obtained in lower yield. Reaction sequences accounting for these products have been proposed.

Experimental Section

General. Analyses for elements' content were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn., Scandinavian Microanalytical laboratory, Herlev, Denmark, and Carol K. Fitz, Carlisle, Mass. Temperatures are uncorrected. Melting points were taken in open capillary tubes.

5,8-Tridecanedione (2) from 5,8-Tridecadiyne (1). After allene-free 5,8-tridecadiyne (**1**) (4.4 g or 25 mmol) was added to mercuric acetate (0.6 g, 2 mmol) in 30 mL of 90% acetic acid–10% water plus 0.25 mL (4 mmol) of concentrated sulfuric acid, the solution under nitrogen was stirred and refluxed for 5 h.[19] Turbidity developed gradually, and occasionally mercury was deposited. Sodium hydroxide (18 g) in water (100 mL) was added (cooling), and product was extracted with several portions of carbon tetrachloride. The combined extracts, after rinsing with water, were dried and stripped of volatiles. Two crystallizations of the residue (5.0 g) from aqueous ethanol furnished 3.7 g (71%) of white crystalline plates of 5,8-tridecanedione (**2**): mp 40.5–41.5 °C; bp 123–125 °C (0.4 mm); IR (CCl_4 or isooctane) 1715 cm^{-1}; UV (6×10^{-3} M) in methanol, λ_{max} 274 nm (log ϵ 1.72) and in cyclohexane, 268.5 nm (1.72);[20] NMR (CCl_4) δ 2.55 (s, 6,7-di-CH_2), 2.38 (t, J = 6.5 Hz, 4,9-di-CH_2), 1.35 (m, five CH_2's), and 0.90 (t, J = 5.5 Hz, 2 CH_3). The integration ratio above and below δ 2 was 8:16 as required.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.7; H, 11.4.

When a reaction mixture consisting of 5,8-tridecadiyne (8.1 mmol), 95% alcohol (15 mL), water (4 mL), mercuric sulfate (0.6 g), and concentrated sulfuric acid (0.05 mL)[21] was refluxed for 24 h, the major product was again 5,8-tridecanedione (55%); trace amounts of cyclohexenone **3** and furan **7** were also formed under these conditions.

To confirm the assigned structure of 5,8-tridecadione (**2**) it was converted to a pyrrole derivative by heating with *p*-bromaniline in the presence of a trace of hydrochloric acid. 1-(*p*-Bromophenyl)-2-butyl-5-pentylpyrrole, bp 130–145 °C (0.05 mm), was obtained in 68% yield.

Anal. Calcd for $C_{19}H_{26}BrN$: C, 65.51; H, 7.52; Br, 22.94; N, 4.02. Found: C, 65.67; H, 7.50; Br, 22.65; N, 4.03.

The IR and NMR absorption spectra for this pyrrole were entirely consistent with the spectra determined for 1-(*p*-bromophenyl)-2,5-dimethylpyrrole, mp 73–73.5 °C (lit.[22] 74 °C), prepared for comparison.

The bis(2,4-dinitrophenylhydrazone) from 5,8-tridecanedione crystallized from aqueous dioxane as an orange solid, mp 185–186 °C.

Anal. Calcd for $C_{25}H_{32}N_8O_8$: N, 19.6. Found: N, 19.3.

2-Propyl-3-butyl-2-cyclohexenone (3) from 5,8-Tridecadiyne (1). Diyne **1** (1.3 g, 7.6 mmol) in 13 mL of 90% acetic acid and 0.13 mL of concentrated sulfuric acid containing 0.2 g (0.9 mmol) of yellow mercuric oxide was refluxed in an atmosphere of nitrogen for 4 h. Ether extraction, etc., furnished 1.5 g of a brown, solvent-free product, containing 15% of 2-propyl-3-butyl-2-cyclohexenone (**3**) and 70% of 5,8-tridecanedione (**2**). Distillation through a spinning band column led to fractions richer in the cyclohexenone but still not free of diketone. Preparative gas-liquid chromatography (Chromosorb at 178 °C) afforded the desired cyclohexenone **3** (6%) as the faster moving fraction.

Homogeneous 2-propyl-3-butyl-2-cyclohexenone (**3**) was obtained as a faintly yellow oil: IR (CCl_4) 1710, 1660, 1620 cm^{-1}; UV (4.5×10^{-5} M in methanol) λ_{max} 247 nm (log ϵ 3.95) or (5.5×10^{-5} M in cyclohexane) 238 (4.08); NMR (CCl_4) δ 2.15 (m, 10, ring CH_2's plus CH_2's attached to positions 2 and 3), 1.40 (m, 6, other CH_2's), 0.95 (m, 5, CH_3's).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41 Found: C, 80.12; H, 11.37.

Various other appropriate spectroscopic data are available in the literature for comparison.[4,17,23]

In a similar mixture, where 5,8-tridecanedione (**2**) was taken as reactant in place of 5,8-tridecadiyne (**1**), after a 10-h reflux period, no cyclic ketone was present; unchanged dione was the only material isolated (92% crude; 68% pure).

2-Propyl-3-pentyl-2-cyclopentenone (5) and 2,3-Dibutyl-2-cyclopentenone (4) A. From 5,8-Tridecanedione (2). A mixture of 5,8-tridecanedione (0.28 g or 1.3 mmol), 7 mL of methanol, 7 mL of water, and sodium hydroxide (1.4 g) was refluxed under nitrogen for 5 h. Standard processing afforded an oil (0.23 g), which according to gas-liquid chromatography consisted of a single material different from cyclohexenone **3**. Distillation gave 0.17 g (64%) of the desired mixture of 2-propyl-3-pentyl- and 2,3-dibutyl-2-cyclopentenone (**5** and **4**): bp 110–120 °C (0.62 mm); IR (CCl_4) 1705, 1645 cm^{-1}; UV (ethanol, 6.4×10^{-5} M) λ_{max} 237 nm (log ϵ 4.19); NMR (CCl_4) δ 2.2 (m, 8, ring CH_2's plus CH_2's attached to ring), 1.4 (m, all other CH_2's), 0.9 (m, CH_3 groups). The last two signals corresponded to 14 protons. Ultraviolet, IR, and NMR data for many similarly constituted cyclopentenones are available and are consistent with our values.[24]

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.56; H, 11.38.

The action of dione **2** with 1% sodium ethoxide in absolute alcohol for 15 min led to complete recovery of unchanged dione.

B. From 5,8-Tridecadiyne (1). A solid catalyst was prepared from 10 g of a finely ground commercial sulfonated polystyrene resin (Dowex 50X-4) by first treating the powder with 2 N sulfuric acid and then stirring it overnight in a solution of 0.1 g of mercuric oxide in 200 mL of 2 N sulfuric acid. The resin was washed repeatedly with water

and then stored in vacuo over calcium sulfate for 1 day.

A refluxing mixture of 5,8-tridecadiyne (**1**, 0.96 g, 5.4 mmol) in 10 mL of glacial acetic acid and 1 mL of water containing 2 g of the prepared resin was stirred for 3 days under nitrogen. Addition of water, extraction with ether, and the appropriate aqueous rinses afforded 1.11 g of a yellow solvent-free oil, which by gas-liquid chromatographic analysis contained 0.66 g (62%) of 2-propyl-3-pentyl-2-cyclopentenone (**5**) plus 2,3-dibutyl-2-cyclopentenone (**4**) as well as 0.21 g (20%) of 2-propyl-3-butyl-2-cyclohexenone (**3**).

The same products were obtained in about the same amounts when the reactant mixture (tridecadiyne **1** with Hg^{2+}, aqueous acetic acid, and H_2SO_4) used to prepare 5,8-tridecanedione (**2**) from tridecadiyne **1** was refluxed for 3 days instead of 5 h.

In the resin-catalyzed reaction, when 5,8-tridecanedione (2) was taken as starting material in place of 5,8-tridecadiyne (**1**), no cyclohexenone **3** was formed and no dione was recovered. The single product was the cyclopentenone mixture **4** and **5**.

2-Pentanoyl-5-butylfuran (7) from 5,8-Tridecadiyne (1). The reaction mixture contained diyne **1** (2.0 g, 0.011 mol) in a solution of yellow mercuric oxide (12 g; 0.055 mol) in 32 g of 70% perchloric acid plus 15 mL of water and enough dioxane to bring the final volume to 80 mL. After the mixture was stirred under nitrogen at room temperature for 45 min, 80 mL of water was added, and ether was used to extract product. Some metallic mercury was noted. The ether solution was washed with water, dried, and then warmed to remove all volatiles. Distillation of the residual oil gave 1.5 g (65%) of very faintly yellow 2-pentanoyl-5-butylfuran (**7**), bp 82–96 °C (0.04 mm), which according to gas-liquid chromatography was 99% pure. The product showed the following spectral properties: IR (neat) 1675, 1585, 1520 cm^{-1}; UV (2×10^{-5} M in methanol) λ_{max} 286 nm (log ϵ 4.2), 221 (3.48); NMR (CCl_4) δ 6.99 (d, J = 3.5 Hz, 1, furan H), 6.11 (d, J = 3.5 Hz, 1, furan H), 2.71 (t, J = 6.5 Hz, 4, furyl CH_2 plus CCH_2), 1.5 (m, remaining CH_2), 0.94 (distorted t, J = 6 Hz, methyl groups). Combined integration of the δ 1.5 and 0.94 signals showed 14 protons as required. In the mass spectrum, the molecular peak was observed at m/e 208; the base peak at 166 was assigned to the McLafferty cleavage fragment, $C_{10}H_{14}O_2^{+\cdot}$; intense peaks at 151 and 123 were attributed respectively to the 2-furoyl-5-butyl and the 5-butylfuryl ion radicals.[25]

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.94; H, 9.68. Found: C, 74.76; H, 9.91.

When 5,8-tridecanedione (2) was used in this reaction instead of 5,8-tridecadiyne (**1**), the only product was unchanged dione (82%), mp 38.5–40 °C; no infrared absorption peak appeared at 1675 cm^{-1}.

3(or 4)-Acetyl-2-butyl-5-pentylfuran (6) from 5,8-Tridecadiyne (1). 5,8-Tridecadiyne (1.0 g, 5.8 mmol) was added to a solution of yellow mercuric oxide (0.50 g, 2.3 mmol) in trichloracetic acid (0.1 g, 0.6 mmol), acetic anhydride (10 mL), acetic acid (40 mL), and freshly distilled boron trifluoride etherate (1 mL), and the reaction mixture was stirred under nitrogen for 24 h. The mixture was processed by adding water (ice cooling), extracting with ether, and appropriately washing, etc., to get 1.3 g of a yellow, viscous liquid. Quantitative gas-liquid chromatography (hexadecyl bromide internal standard) showed that this liquid contained a major component, the acetylated butylpentylfuran (**6**, 0.76 g, 55%), as well as a minor component recognized as 2-propyl-3-butyl-2-cyclohexenone (**3**, 0.14 g or 10%).

Preparative gas-liquid chromatography (Chromosorb with neopentyl glycol succinate at 186 °C) afforded homogeneous 3(or 4)-acetyl-2-butyl-5-pentylfuran (**6**): IR (CCl_4) 1675, 1600, 1560, 1510 cm^{-1}; UV (6×10^{-5} in methanol) λ_{max} 280 nm (log ϵ 3.74) and in cyclohexane solvent at 5.5×10^{-5} M, 273 (3.76); NMR (CCl_4) δ 6.10 (s, 1, furan H), 2.90 (t, J = 7 Hz, 2, CH_2 furan next to acetyl), 2.55 (t, J = 7 Hz, 2, CH_2 furan opposite to acetyl), 2.25 (s, 3, CH_3CO), 1.43 (m, other CH_2's), 0.88 (distorted t, J = 6 Hz, alkyl CH_3's). Integration of the two high-field signals together showed 16 protons. The spectral properties (IR, UV, and NMR) of 3-acetyl-2,5-dimethylfuran, prepared for comparison according to Hurd and Wilkinson,[26] were in good agreement with those of **6**. The semicarbazone of 3(or 4)-acetyl-2-butyl-5-pentylfuran (**6**) melted at 97–99 °C.

Anal. Calcd for $C_{15}H_{27}N_3O_2$: C, 65.50; H, 9.28; N, 14.32. Found: C, 65.23; H, 9.26; N, 14.06.

2,5-Nonanedione (9) from 1,4-Nonadiyne (8). A mixture of 10.0 g (83 mmol) of 1,4-nonadiyne, mercuric acetate (1.0 g, 3.1 mmol), and concentrated sulfuric acid (0.5 mL) in 100 mL of 90% acetate acid was refluxed for 2 h. The dark reaction mixture containing some mercury was poured into cold water (200 mL) and extracted with ether. The ether extracts were washed with bicarbonate and with water, dried, and distilled to give faintly yellow 2,5-nonanedione (9.2 g, 67%): bp 76–78 °C (0.2 mm); n^{25}_D 1.4327; IR (CCl_4 or isooctane) 1725 cm^{-1}; UV (10^{-3} M in methanol) λ_{max} 274 nm (log ϵ 2.47); NMR (neat) δ 2.63 (s, 3,4-di-CH_2), 2.42 (t, J = 6.5 Hz, 2, CH_2 at 6), 2.07 (s, 3, CH_3CO), 1.4 (s, 7,8-di-CH_2), 0.88 (distorted t, J = 6 Hz, CH_3 at 9). Integration of the last two signals showed a total of 7 protons. No signals appeared at δ 9.2–10.3 even in the crude product.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.31. Found: C, 69.4; H, 10.3.

The product before (85% yield) and after distillation gave the same gas-liquid chromatograms.

The bis(2,4-dinitrophenylhydrazone) of 2,5-nonanedione (**9**), after crystallization from ethyl alcohol–ethyl acetate (7:4), showed mp 180.5–181.5 °C.

Anal. Calcd for $C_{21}H_{24}N_8O_8$: C, 48.83; H, 4.68; N, 21.70. Found: C, 48.9; H, 4.7; N, 21.5.

Hydration of 1,4-nonadiyne (**8**) with mercuric sulfate (0.82 g) in 87% formic acid (8.2 mL) for 20 min at 0 °C afforded appreciable 2,5-dione as well as unchanged diyne (40%).

5-Butylfurfural (10). Hydration of 1,4-nonadiyne (**8**) with mercuric oxide (18.4 g, 0.085 mol) dissolved in 70% perchloric acid (24.6 g, 0.17 mol, or 55 g, 0.38 mol) containing water (20.4 mL) and enough dioxane to bring the total volume to 120 mL was effected by stirring the mixture under nitrogen at room temperature for 45 min. 2,5-Nonanedione (**9**) as well as a new product, taken as 5-butylfurfural (**10**), were obtained, both in low yield. An NMR absorption curve for the mixture included signals at δ 9.50 (CHO) as well as two doublets at δ 6.99 and 6.11 (aromatic furan H's), which integrated to a proton ratio of 1:1:1. When 2,5-nonanedione was used as starting material here instead of 1,4-nonadiyne, no furfural product was detected; the homogeneous dione was recovered to an extent of 94%.

5-Butylfuroic Acid (11). A. From the 5-Butylfurfuraldehyde Hydration Product. The crude mixture containing the two products from the mercuric oxide–perchloric acid reaction was suspended in a mixture of silver nitrate (6.7 g), sodium hydroxide (3.2 g), and water (70 mL) and was stirred at reflux temperature for 40 min. After neutralization with 2 *N* hydrochloric acid, the mixture was filtered and both the solids and the filtrate were extracted with ether. Acidic material was brought into concentrated bicarbonate solution and was recovered by adjusting the pH to 2, saturating the mixture with sodium chloride, and extracting with ether. 5-Butylfuroic acid (**11**), mp 66.5–69 °C, was obtained from the extracted solids after several low-temperature crystallizations from aqueous ethanol. Mixed with authentic 5-butylfuroic acid (mp 69–70 °C), this product showed mp 67–69.5 °C. Both materials gave single peaks on gas-liquid chromatography appearing at the same retention time.

B. From Methyl Furoate.[27] Stannic chloride (78 g, 0.30 mol) was dropped into a nitrogen-blanketed, ice-cold mixture of methyl furoate (13 g, 0.10 mol) and butyric anhydride (16 g, 0.10 mol) over a period of 1 h. The mixture was stirred for 3 days at room temperature and then for 1 day at 45–50 °C. Addition of ice-cold water (300 mL), followed by standard proceedings, afforded 4.3 g of methyl 5-butanoylfuroate, mp 66–67 °C, after two crystallizations from 95% alcohol (lit.[27] mp 67–68 °C).

Saponification led to the corresponding acid, 5-butanoylfuroic acid, mp 179. 5–180.5 °C (lit.[28] 176 °C), which was reduced as follows to remove the carbonyl oxygen. Hydrazine hydrate (0.6 mL, 12 mmol) was added dropwise to 5-butanoylfuroic acid (0.60 g, 3.3 mmol) in 10 mL of absolute alcohol. After a 15-min reflux, the mixture was cooled, treated with potassium *tert*-butoxide (3.0 g, 27 mmol) in 20 mL of absolute alcohol, and then over a period of 1.5 h gradually warmed to 200 °C, during which time solvent was escaping. The reaction mixture was then held at 200 °C for 25 min. The cooled alkaline system was diluted with 10 mL of cold water, acidified to pH 3 with hydrochloric acid, saturated with sodium chloride and the acid mixture extracted with ether. Recrystallization of the crude product from aqueous alcohol gave 0.38 g (68%) of 5-butylfuroic acid: mp 69–70 °C; IR (mineral oil mull) 3550, 3000, 1695 cm^{-1}; UV (10^{-4} M in 95% EtOH) λ_{max} 257 nm (log ϵ 4.03); NMR (CCl_4) δ 11.55 (broad s, 1, COOH), 7.10 (d, J = 3.5 Hz, 1, 2-furyl-H), 6.05 (d, J = 3.5 Hz, 1, 3-furyl-H), 2.65 (t, J = 7.2 Hz, CH_2 attached to furan), 1.5 (m), and 0.90 (t, 7, all other protons).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.11.

2,5,8-Dodecanetrione (13) from 1,4,7-Dodecatriyne (12). A mixture of 1,4,7-dodecatriyne (2.4 g, 15 mmol) and mercuric acetate (0.7 g, 2 mmol) in 25 mL of 90% acetic acid containing 0.25 mL of concentrated sulfuric acid was stirred and refluxed under nitrogen for 2.5 h. The cooled mixture was made basic with aqueous sodium hydroxide before extraction with carbon tetrachloride. The extract was rinsed, dried, and distilled to give 2.0 g (63%) of faintly yellow trione **13**, bp 106.5–108 °C (0.57 mm), which solidified in the receiver. After charcoal decolorization (ether solution), the product was re-

crystallized from aqueous ethanol. The white, crystalline, 2,5,8-dodecanetrione (**13**, 38%) had mp 57.5–58 °C: IR (CCl_4) 1715 cm^{-1}; UV (10^{-2} M in methanol) λ_{max} 217 nm (log ϵ 1.91); NMR (CCl_4) δ 2.61 (s, 8, CH_2's at positions 3, 4, 6, 7), 2.35 (t, J = 6.5 Hz, 2, CH_2 at position 9), 2.11 (s, 3, $COCH_3$), 1.55 and 0.90 (7, remaining H's).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.00; H, 9.43.

No infrared absorption maximum appeared at 1625 cm^{-1} (α,γ-dione), and no NMR signal appeared in the δ 10 region (aldehyde H).

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Registry No.—**1**, 67238-15-7; **2**, 67238-16-8; **2** bis(2,4-DNP), 67238-17-9; **3**, 67238-18-0; **4**, 67238-19-1; **5**, 67238-20-4; **6**, 67238-52-2; **6** semicarbazone, 67238-53-3; **7**, 67238-21-5; **8**, 6088-94-4; **9**, 25234-82-6; **9** bis(2,4-DNP), 67238-22-6; **10**, 23074-13-7; **11**, 67238-23-7; **12**, 67238-24-8; **13**, 67238-25-9; 1-(*p*-bromophenyl)-2-butyl-5-pentylpyrrole, 67238-26-0; methyl 5-butanoylfuroate, 67238-27-1; 5-butanoylfuroic acid, 67238-28-2; *p*-bromoaniline, 106-40-1; butyric anhydride, 106-31-0.

References and Notes

(1) G. Rio and A. Lecas-Nawrocka, *Bull. Soc. Chim. Fr.*, 317 (1976).
(2) T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973); Th. Cuvigny, M. Larchevêque, and H. Normant, *Tetrahedron Lett.*, 1237 (1974).
(3) R. A. Ellison and W. D. Woessner, *J. Chem. Soc., Chem. Commun.*, 529 (1972).
(4) G. Stork and R. Borch, *J. Am. Chem. Soc.*, **86**, 935, 936 (1964).
(5) Y. Ito, T. Konoike, T. Harada, and T. Saegusa, *J. Am. Chem. Soc.*, **99**, 1487 (1977).
(6) W. J. Gensler and A. P. Mahadevan, *J. Am. Chem. Soc.*, **77**, 3076 (1955).
(7) W. J. Gensler, A. P. Mahadevan, and J. Casella, Jr., *J. Am. Chem. Soc.*, **78**, 163 (1956).
(8) See reviews in E. Müller, Ed., "Methoden der Organischen Chemie": H. Stetter, Vol. VII/2a, Part 1, 1973, pp 816–842; V. Jäger and H. G. Viehe, Vol. V/2a, 1977, pp 726–743. Also cf. M. Miocque, N. M. Hung, and Y. Q. Yen, *Ann. Chim. (Paris)*, **8**, 157 (1963).
(9) See M. S. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1953); S. A. Vartanyan, S. K. Pirenyan, and N. G. Manasyan, *Chem. Abstr.*, **55**, 23336 (1961); *Zh. Obschei. Khim.*, **31**, 1269 (1961).
(10) Many examples are known. Inter alia, see ref 3 and 4 as well as A. Takada, S. Wada, M. Fujii, I. Nakasima, and S. Hirata, *Bull. Soc. Chem. Jpn.*, **44**, 1342 (1971); H. Hunsdiecker, *Chem. Ber.*, **75**, 447 (1942).
(11) The method combines features from the procedures of A. M. Islam and R. A. Raphael, *J. Chem. Soc. (London)*, 4086 (1952), and from E. Hardegger and C. Scholz, *Helv. Chim. Acta*, **28**, 1355 (1945).
(12) W. L. Budde and R. E. Dessy, *Tetrahedron Lett.*, 651 (1963); *J. Am. Chem. Soc.*, **85**, 3964 (1963).
(13) For example, I. D. Campbell, N. A. Dobson, and G. Eglinton, *J. Chem. Soc. (London)*, 1092 (1964), find that 1,7-undecadiyne forms 2-keto-7-undecyne; D. S. Noyce, M. A. Matesich, M. D. Schiavelli, and P. E. Peterson, *J. Am. Chem. Soc.*, **87**, 2295 (1965), show that phenylacetylene hydrates faster than 1-phenyl-1-propyne.
(14) Interestingly, the conclusion has been reached that 1,4-diketones under acid catalysis cyclize to cyclopentenones with difficulty, if at all. Base catalysis is preferred. See H. Hunsdiecker, *Chem. Ber.*, **75**, 455 (1942).
(15) This could involve a carbonium ion, as suggested by F. R. Jensen and R. J. Ouellette, *J. Am. Chem. Soc.*, **83**, 4477 (1961), in their study of oxidation by mercuric ion.
(16) Similar processes are known. For example, C. E. Harding and M. Hanack, *Tetrahedron*, **17**, 1253 (1971), report formation of 2,3-dimethyl-2-cyclohexenone on treating 2-keto-6-octyne with acid.
(17) M. S. F. Lie Ken Jie and C. H. Lam, *Chem. Phys. Lipids*, **19**, 275 (1977).
(18) Cyclization of 1,4-dicarbonyl compounds to furans is a standard method of preparation. Also Friedel–Crafts acetylation of furans is well known. Cf. A. P. Dunlop and F. N. Peters, "The Furans", Reinhold Publishing Corporation, New York, N.Y., 1953, pp 35, 442, and 443. Also see Lie Ken Jie and Lam in ref 17.
(19) The procedure is an adaption of one described by M. M. Fraser and R. A. Raphael, *J. Chem. Soc. (London)*, 226 (1952).
(20) Compare with the observed λ_{max} 270–271 (log ϵ 2.1) for 2,5-hexanedione. See E. Schauenstein, *Monatsh. Chem.*, **80**, 70 (1949); A. Seher, *Arch. Pharm. (Weinheim, Ger.)*, **292**, 519 (1959).
(21) Modeled after I. D. Campbell, N. A. Dobson, and G. Eglinton, *Arch. Pharm. (Weinheim, Ger.)*, 1092 (1964).
(22) H. Gilman and G. J. O'Donnell, *J. Am. Chem. Soc.*, **66**, 840 (1944).
(23) R. Mecke and K. Noack, *Spectrochim. Acta*, **12**, 391 (1958); J.-M. Conia and A. LeCraz, *Bull. Soc. Chim. Fr.*, 1929 (1960); R. Mecke and K. Noack, *Chem. Ber.*, **93**, 210 (1960).
(24) See, For example, ref 4 and 17, as well as Hunsdiecker in ref 10: also W. Keller-Schierlin, M. L. Mihailović, and V. Perlog, *Helv. Chim. Acta*, **41**, 220 (1958); R. L. Frank, R. Armstrong, J. Kwiatek, and H. A. Price, *J. Am. Chem. Soc.*, **70**, 1379 (1948).
(25) For comparison data on 2-alkanoyl-5-alkylfurans, cf. A. R. Katritzky and A. P. Ambler, "Physical Methods in Heterocyclic Chemistry", Vol. II, Academic Press, New York, N.Y., 1963, p 165; M. K. Kal'ful and D. V. Sokal'skii, *Chem. Abstr.*, **52**, 2510 (1958); *Vestn. Akad. Nauk Kaz. SSR*, **13**, 74 (1957); R. Andrisana and R. Passerini, *Chem. Abstr.*, **46**, 3995 (1952); *Gazz. Chim. Ital.*, **80**, 730 (1950); N. S. Bhacca, L. F. Jonson, and J. N. Shoolery, "NMR Spectra Catalog", Vol. I, Varian Associates, Palo Alto, Calif., 1962, p 165.
(26) C. D. Hurd and K. Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948). Also see M. Fétizon and P. Baranger, *Bull. Soc. Chim. Fr.*, 1311 (1957); B. Gestblom, S. Gronowitz, R. A. Hoffman, and B. Mathiasson, *Ark. Kemi*, **23**, 517 (1965).
(27) This Friedel–Crafts acylation uses an improved version of the procedure of H. Gilman and H. O. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
(28) T. Ueda, T. Hirano, Y. Kawabe, and T. Suzui, *Chem. Abstr.*, **56**, 12856 (1962); Japanese Patent 2 817 (1961).

Base-Catalyzed Reactions of α,β-Unsaturated Esters and Nitriles. 3. Alkali Metal Catalyzed Di- and Trimerization of Acrylates[1]

Joseph Shabtai* and Eva Ney-Igner

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Herman Pines*

The Ipatieff Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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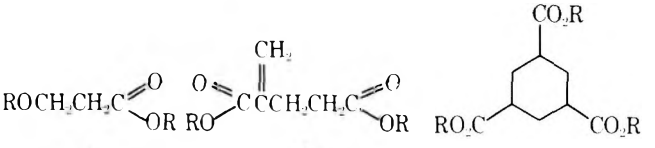
Potassium- or sodium-catalyzed reaction of acrylic acid esters (1) having appropriate alcoholic groups (R = C_4–C_{12} alkyl or cycloalkyl) produces three low molecular weight compounds, i.e., a 3-alkoxypropionate (2), an open-chain dimer, 2-methyleneglutarate (3), and a cyclic trimer, 1,3,5-cyclohexanetricarboxylate (4). 2 is favored (yields up to 66%) only at low temperature (20–70 °C) and low catalyst/1 molar ratios (r_{mol} = 0.12–0.23), whereas dimer 3 is predominant (yields up to 79%) at higher temperatures (100–216 °C) and/or higher r_{mol} levels (0.36–0.40). Trimer 4 is formed only at r_{mol} = 0.7–1.0. Dimerization selectivity, i.e., the dimer 3/polymer ratio, increases markedly with increase in the size of the R group in the acrylate. The catalytic activity of potassium–benzylpotassium is about 2.4 times higher than that of sodium–benzylsodium, but the latter is more selective since it does not catalyze formation of 2. It is proposed that formation of dimer 3 is initiated by metalation of the acrylate at the α-vinylic position, while formation of trimer 4 proceeds through a cyclic carbanion precursor, stabilized by charge delocalization. Alkoxy ester 2 is derived by concerted elimination–transfer of an alkoxy anion from the metalated 1 to a second acrylate molecule.

High molecular weight polymerization of acrylates in the presence of base catalysts or initiators, e.g., organolithium and organomagnesium compounds, is usually accompanied by limited formation (<10% by weight) of lower products.[2–4] For instance, small amounts of a cyclic β-keto ester, i.e., 5-(9-fluorenyl)-4-oxocyclohexane 1,3-dicarboxylate, were found in the product of 9-fluorenyllithium-initiated polymerization of acrylates.[5]

The patent literature cites the anionic polymerization of acrylates in aliphatic or aromatic solvents, using dispersed sodium or potassium metals in admixture with an alkali or alkaline-earth salt as catalysts.[6] This process yields products with molecular weights in the range of 90 000 to 1 000 000, depending on the monomer/catalyst molar ratio. Oligomerization of acrylates leading to dimers and/or trimers as main products has not been previously reported. It was recently found, on the other hand, that by applying promoted alkali metal catalysts under appropriate conditions it is possible to attain selective di- and/or trimerization of α,β-unsaturated esters and nitriles possessing a β-methyl substituent. For instance, in the presence of a potassium–benzylpotassium catalyst, ethyl crotonate is dimerized to diethyl 2-ethylidene-3-methylglutarate with 90% selectivity,[7] while 2-butenonitrile yields 20–23% of 2-ethylidene-3-methylglutaronitrile and 67–75% of a cyclic trimer, i.e., 1,3,5-tricyano-2,4,6-trimethylcyclohexane.[1]

The purpose of the present study was to explore catalyst systems and experimental conditions which could lead to oligomerization of acrylates with suppression of high molecular weight polymerization. Several series of comparative experiments were performed in order to determine the change in product composition as a function of monomer structure (type of alcoholic R group), concentration and type of base catalyst, and reaction temperature. The experimental procedure was similar to that used previously.[1,7] Products were identified and quantitatively analyzed by a combination of gas chromatography, NMR, and mass-spectral methods (see Experimental Section).

It is found that by using promoted alkali metal catalysts, e.g., potassium–benzylpotassium, and acrylate monomers having alcoholic R groups of appropriate size, e.g., 2-ethyl-1-hexyl acrylate (1), the formation of high molecular weight polymers is greatly suppressed, and three low molecular weight compounds are obtained as main products, i.e., a 3-alkoxypropionate (2), an open-chain dimer, 2-methyleneglutarate (3), and a cyclic trimer, the triester of 1,3,5-cyclohexanetricarboxylic acid (4).



2 3 4

Results and Discussion

Effect of Catalyst Concentration. Using 2-ethyl-1-hexyl acrylate (1) as starting monomer, ethylcyclohexane as solvent, and potassium–benzylpotassium as catalyst, a series of experiments were performed in which the catalyst/monomer molar ratio (r_{mol}) was changed from 0.12 to 1.00 (gram-atom of K/moles of monomer).

Results obtained are summarized in Table I. As seen, the product distribution obtained is very sensitive to the change in the concentration of the catalyst. In experiments with low catalyst/1 ratios (r_{mol} = 0.12–0.32) the alkoxy ester 2 is formed as the principal nonpolymeric product, while at higher ratios (r_{mol} = 0.36–0.44) the predominant reaction is formation of dimer 3. At the highest ratios employed (r_{mol} = 0.71–1.00) compounds 2 and 3 are absent from the product, while significant amounts of the cyclic trimer 4 are produced. The main products under these conditions are 2-ethyl-1-hexanol (5) and high molecular weight polymeric compounds. It is also noted that the overall conversion of monomer 1 increases with increase in r_{mol} from 0.12 to 0.32, but then remains essentially constant at r_{mol} = 0.36–1.00.

The formation of 3-alkoxypropionate (2) can be interpreted as occurring through elimination of an alkoxy anion (RO^-) from the metalated monomer 1a, and transfer of this anion to a second monomer molecule in a subsequent step, or more likely by a concerted mechanism. Removal of the alkoxy group should produce an equimolar amount of 1-oxo-1,2-propadiene (methylene ketene) (1b), which could be expected to undergo fast polymerization.

A closely similar type of elimination, leading to formation of a ketene, has been recently reported to result from tri-

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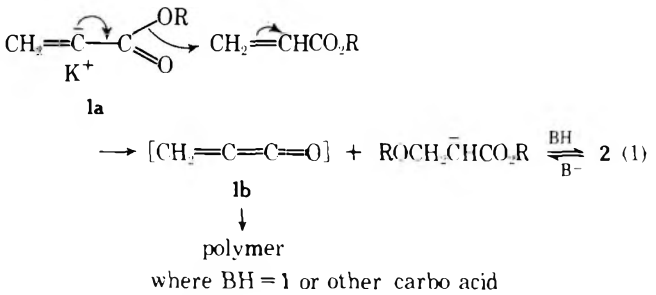
Table I. Composition of Products from $K/C_6H_5CH_2K$ Catalyzed Reaction of 2-Ethyl-1-hexyl Acrylate (1) as a Function of Catalyst Concentration[a,b]

expt no.	1	2	3	4	5	6	7	8
catalyst/1 molar ratio (r_{mol})	0.12	0.23	0.32	0.36	0.40	0.44	0.71	1.0
conversion of 1, mol %	30.4	60.5	71.1	80.4	80.4	80.1	80.2	80.5
product distribution,[c] % by wt								
2	65.2	59.6	50.4	25.4	20.1	9.6	trace	
3	15.0	20.7	33.0	57.0	63.5	42.1	0.5	
4						trace	16.1	19.4
other products[d]				5.6	6.4	24.1	43.4	45.0
polymer[e]	19.8	19.7	16.6	12.0	10.0	20.2	30.0	34.6
mol % 1 converted to:								
3-alkoxy ester (2)	37.2	33.7	28.9	14.3	11.7	5.8		
dimer (3)	17.1	23.4	35.6	54.9	62.9	43.3	0.6	
trimer (4)						trace	17.9	19.5
$(CH_2{=}C{=}CO)$[f]	37.3	33.7	28.4	23.8	20.6	42.7	68.2	64.4
"polymer"[g]	8.4	9.2	7.6	7.0	4.8	8.2	13.3	16.0

[a] In each experiment were used 0.05 mol of **1**, 0.5 mol of solvent, and the calculated amount of $K/C_6H_5CH_2K$ catalyst. [b] Reaction temperature, 132 °C; total reaction time, 120 min. [c] R = 2-ethyl-1-hexyl. [d] Consisting mostly (>95%) of 2-ethyl-1-hexanol (**5**). [e] High boiling components. [f] In the form of high boiling products (number of moles of methylene ketene calculated as equal to the number of moles of **2** plus **5**; see text). [g] Products of direct polymerization of **1** (calculated by difference).

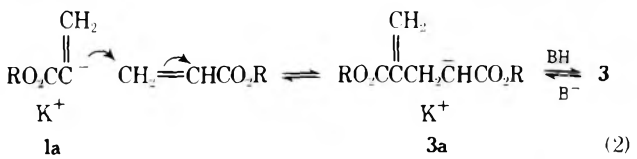


methylamine-initiated dehydrochlorination of 2-butenoyl chloride.[8]

The amounts of polymer formed at low catalyst/monomer ratios (r_{mol} 0.12–0.40) are in approximate agreement with reaction 1, since for each mole of 3-alkoxypropionate (**2**) formed there is at least 1 mol of the suggested methylene ketene (**1b**) found in the polymeric form (Table I). Further, the amount of polymer in the above range of r_{mol} values decreases with decrease in the concentration of **2**. On the other hand, the marked increase in polymeric products at r_{mol} = 0.4–1.0 is apparently connected with the formation of 2-ethyl-1-hexanol (**5**) by decomposition of the metalated acrylate (vide infra).

The addition of an alkoxide anion at the C-3 position of an α,β-unsaturated ester seems to be limited to acrylates having no substituents at this position. No such reaction was observed with ethyl crotonate,[7] indicating that a β-alkyl substituent hinders this type of addition. Addition of alcohols to acrylates in the presence of base catalysts has been reported.[9]

By analogy with the mechanism proposed for dimerization of ethyl crotonate,[7] the formation of dimer **3** could proceed

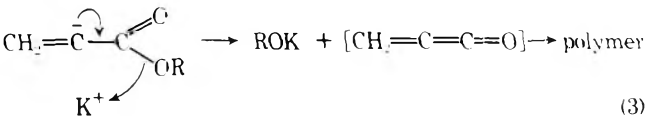


by metalation of the acrylate at the α-vinylic position, followed by addition of the resulting carbanion to a second monomer molecule.

Trimer **4** is most likely formed by addition of the dimeric anion **3a** to another monomer molecule to form a resonance-stabilized cylic precursor, which on protonation yields **4**. A similar mechanism was previously proposed for the high-yield trimerization of 2-butenonitrile to 1,3,5-tricyano-2,4,6-trimethylcyclohexane.[1]

The inversion in the relative importance of sequences 1 and 2, accompanying the increase in conversion from 30 to 80% (Table I), may be partially related to changes in the extent of ionic dissociation of the metalated monomer with the progress of the reaction. It should be noted that, while alkoxide elimination from the ion pair **1a** (reaction 1) may proceed without steric interference by the alkali counterion, the rate of addition of the monomeric carbanion to a second acrylate molecule (reaction 2) may considerably depend on the steric effect of this cation. In the initial low-polar reaction medium, consisting mainly of ethylcyclohexane, the extent of ionization of **1a** is very low and, therefore, reaction 1 is apparently faster than reaction 2. However, with increase in conversion, i.e., with gradual accumulation of the alkoxy ester **2**, the polarity of the reaction medium is expected to be augmented, with consequent increase in the ionization of **1a**. This could facilitate addition of the monomeric carbanion and increase the relative rate of reaction 2.

The absence of compounds **2** and **3**, and the preferential formation of 2-ethyl-1-hexanol (**5**) and high-boiling polymers at high catalyst/monomer ratios (r_{mol} = 0.71–1.00) can be explained in terms of the anticipated high extent of metalation of the starting acrylate under these conditions. In the absence of sufficient concentration of nonmetalated monomer, serving as a free carbanion acceptor, the metalated monomer **1a** could



gradually decompose to yield polymeric products and alkoxide **5a**, which upon acidification at the end of the reaction gives the free alcohol **5** (R = 2-ethyl-1-hexyl).

It is not excluded, however, that part of the alkoxide anion is derived by retrogressive reaction of the alkoxy ester **2**, which might have been formed in the initial stage of the reaction.

Since the concentration of protonating agent available in the reaction system at r_{mol} = 0.7–1.0 should be low, any dimeric anion produced under such conditions may tend to add to another monomer molecule, yielding a cyclic trimeric carbanion prior to the terminating protonation step. This could explain the preferred formation of trimer **4** rather than

Table II. Composition of Products from $K/C_6H_5CH_2K$ Catalyzed Reaction of 2-Ethyl-1-hexyl Acrylate (1) as a Function of Reaction Temperature[a,b]

expt no	9	10	11	12	13	14	15
reaction temp, °C	20	70	100	132	150	174	216
conversion of 1, mol %	84.8	86.4	84.6	80.4	71.1	70.8	65.3
product distribution,[c] % by wt							
2	65.6	56.5	42.2	25.4	10.2	9.7	9.1
3	13.2	25.5	43.5	57.0	65.9	71.9	75.8
other products[d]	21.2	18.0	14.3	17.6	23.9	18.4	15.1

[a] In each experiment were used 0.05 mol of **1**, 0.5 mol of solvent, and the calculated amount of $K/C_6H_5CH_2K$ catalyst (0.018 g-atom of K metal and 0.005 mol of *o*-chlorotoluene). [b] Total reaction time, 120 min. [c] R = 2-ethyl-1-hexyl. [d] Compounds **4** and **5**, plus polymeric products.

Table III. Dependence of Product Composition from $K/C_6H_5CH_2K$-Catalyzed Reaction of Acrylates upon the Type of Alcoholic (R) Group[a,b]

expt no.	16	17	18	19	20	21	22
starting acrylate (CH_2=$CHCO_2R$), R =	CH_3 (**1a**)	C_2H_5 (**1b**)	isobutyl (**1c**)	2-ethyl-1-hexyl (**1d**)	cyclohexyl (**1e**)	*n*-$C_{12}H_{25}$) (**1f**)	1-bornyl (**1g**)
registry no.	96-33-3	140-88-5	106-63-8	103-11-7	3066-71-5	2156-97-0	67253-41-2
monomer conversion, mol %	~100	~100	80.2	80.4	79.8	3.2	5.1
product distribution,[c] % by wt							
2		3.0	20.1	21.3	22.3	22.1	18.0
registry no.		763-69-9	67208-80-4	38940-91-9	67208-81-5	67208-82-6	67208-83-7
3		6.0	46.0	58.5	60.2	75.9	79.0
registry no.		5621-43-2	67208-84-8	67208-85-9	23720-24-3	67208-86-0	67208-87-1
polymer	~100	91.0	33.9	20.2	17.5	2.0	2.0
$r_{\text{dimer 3/polymer}}$		0.06	1.35	2.9	3.5	37.9	39.5
mol % 1 converted to:							
3-Alkoxypropionate (**2**)		3	12.8	12.7	14.3	12.8	10.7
Dimer (**3**)		6	46.0	58.4	59.0	74.5	78.6
(CH_2=C=CO)[d]		3	12.8	12.7	14.3	12.8	10.7
"polymer"[e]	100	88	28.4	16.2	12.4		
registry no.	9003-21-8	9003-32-1	26335-74-0	9003-77-4	27458-65-7		

[a,b] As in Table I; catalyst/monomer ratio = 0.36. [c] No significant amounts of trimer **4** could be detected under the experimental conditions. [d,e] See footnotes f and g (Table I), respectively.

dimer **3** in experiments 7 and 8.

Effect of Reaction Temperature. The change in product distribution as a function of reaction temperature was investigated in the range of 20–216 °C, using **1** as starting monomer and keeping a constant potassium–benzylpotassium/**1** ratio (r_{mol} = 0.36) in all experiments. Methyl- or ethylcyclohexane was used as solvent for temperatures up to 132 °C, and *n*-decane or *n*-dodecane was used for temperatures in the range of 150–216 °C.

Results obtained are summarized in Table II. As seen, alkoxy ester **2** is the main product at 20 and 70 °C, even at the high conversion levels reached (84.8 and 86.4%, respectively). This seems to indicate that at these relatively low temperatures the alkoxide transfer sequence (eq 1) remains kinetically favored even if the polarity of the solvent is somewhat changed with the progress of the reaction. However, with increase in reaction temperature above 100 °C there is a gradual increase in the relative rate of the competing dimerization reaction (eq 2), and the range of 174–216 °C is adaptable for preparation of dimer **3** in good yields (72–76% by weight). It is also observed that, while dimerization selectivity increases with increase in temperature from 100 to 216 °C, the total monomer conversion somewhat decreases. This can be explained by increased retrogressive reaction of dimer **3**, leading to the monomer (reaction 2).

Influence of the Alcoholic (R) Group. The dependence of product composition upon the type of alcoholic (R) group in the acrylate monomer was investigated by a series of comparative experiments with different acrylates (R = CH_3, C_2H_5, isobutyl, 2-ethyl-1-hexyl, cyclohexyl, *n*-dodecyl, and 1-bornyl), using potassium–benzylpotassium as catalyst.

Results obtained are summarized in Table III. As seen, both monomer conversion and product distribution change considerably with variation in the type of R group. Under the experimental conditions, conversion is quantitative for methyl and ethyl acrylates (**1a** and **1b**, respectively), decreases for monomers with medium size R groups, e.g., compounds **1c**, **1d**, and **1e**, and drops sharply for acrylates with long-chain or bulky R groups, e.g., compounds **1f** and **1g**. In the latter case the deactivation effect seems to be mainly steric, although it is uncertain whether hindrance by a bulky R group affects the first reaction step, i.e., the metalation of the acrylate, or the subsequent addition steps of the process. A deactivating effect of bulky R groups has been also observed in radical type polymerization of acrylates.[11]

The effect of the R group is particularly pronounced in controlling the relative extent of dimerization vs. that of polymerization. Whereas methyl acrylate is exceptional in yielding exclusively high molecular weight polymers, it is found (Table III) that the dimer **3**/polymer ratio increases markedly with increase in the size of the R group. Polymer formation is low with cyclohexyl acrylate and is fully sup-

Table IV. Dependence of Product Composition from the Reaction of 2-Ethyl-1-hexyl Acrylate (1) upon Catalyst Type[a,b]

expt no.	23	24	25	26
catalyst system	K/KCH_2-C_6H_5	Na/Na-CH_2-C_6H_5	$Li/Li\ CH_2$-C_6H_5[c]	Na/Al_2O_3[d]
conversion of **1**, mol %	70.8	30.2	<1.0	12.2
product distribution, % by wt				
2	9.7	<0.1		10.7
3	71.9	76.4		24.1
other products	18.4	23.6		65.2

[a] In experiments 23, 24, and 25 were used 0.05 mol of monomer, 0.018 g atom of metal, 0.5 mol of solvent, and 0.005 mol of promoter (o-chlorotoluene). [b] Reaction temperature, 174 °C, except in expt 26 (132 °C); reaction time, 120 min. [c] In the preparation of this catalyst, the Li metal (0.18 g atom) was dispersed at 216 °C, instead of 170 °C, as used for the other alkali metals. [d] 0.5 g (0.22 g atom) of sodium and 3 g of alumina were used for preparation of this catalyst.

pressed with *n*-dodecyl and 1-bornyl acrylates. The increase in dimerization selectivity for such compounds indicates that a bulky R group may prevent the growth of a polymeric chain beyond the dimeric stage, i.e., the rate of protonation of a dimeric anion in such cases may be faster than propagation.

Effect of Catalyst Type. The dependence of relative reaction rate and of product composition upon the type of alkali metal catalyst was examined by a series of experiments with **1** in the presence of promoted potassium, sodium, and lithium metal dispersions, as well as sodium supported on alumina. A sufficiently high temperature (174 °C) was used in experiments with the nonsupported catalysts in order to increase dimerization selectivity. The supported sodium–alumina catalyst was employed at 132 °C.

Results obtained are summarized in Table IV. As seen, the relative activity of the nonsupported alkali metal catalysts increases with increase in the electropositivity of the alkali metal, the order being K > Na > Li. Although potassium–benzylpotassium is about 2.4 times more active than sodium–benzylsodium (expt 23 vs. 24), the latter is a more selective dimerization catalyst since it does not catalyze the formation of the alkoxy ester **2**. Lithium–benzyllithium is essentially inactive for this reaction. These results are in agreement with the sharp decrease in ionic character of metal–carbon bonds in passing from potassium to sodium to lithium. It is known that the extent of separation between the counterion and the carbanion end group of an oligomer is the primary factor which determines the rate of reaction propagation.[12,13]

The main reaction in the presence of the supported sodium–alumina catalyst is polymerization, 63.5%, and only 24.1% of dimer **3** is produced, based on reacted monomer.

Experimental Section

Apparatus, Catalysts, and Experimental Procedure. The apparatus consisted of a 250-mL three-neck flask, provided with a high-speed stirrer (10 000 rpm), a reflux condenser, an inlet for dry nitrogen, a thermometer, and a calibrated Sage syringe pump. Heat was provided by means of a thermo-regulated heating mantle. Typical experiments with promoted alkali metal catalysts were performed, using the following procedure.

About 20 mL of solvent, e.g., methylcyclohexane, was introduced in the reaction flask and the desired amount of freshly cut alkali metal was added to it under a stream, ~30 mL/min, of nitrogen. The mixture was heated at the reflux temperature of the solvent for a period of 20 min, and the melted metal was subsequently dispersed into a fine powder form by stirring for a period of at least 1 h. The calculated amount of promoter, usually o-chlorotoluene, was then added to the mixture to generate the benzylalkali salt,[6,7] and the stirring was contined for another 2 h. After bringing the mixture to the desired reaction temperature, the monomer solution (monomer/solvent molar ratio 1:10) was added dropwise to the flask at a constant feed rate. At the end of the selected reaction period, the mixture was cooled to −10 °C, and the alkali metal catalyst was decomposed by adding absolute ethanol. This was followed by consecutive washing of the mixture with 10% aqueous hydrochloric acid, 10% aqueous sodium bicarbonate, and, finally, with water. The product obtained was dried on anhydrous magnesium sulfate, filtered, and examined by gas chromatography, usually without removal of the solvent. In some cases, gas chromatography was preceded by flash distillation of the product at 0.1 Torr.

The supported sodium–alumina catalyst was prepared and used in situ according to a general procedure described previously.[14]

Quantitative gas chromatographic analysis of product components was performed with the following types of columns: (a) a 6 ft × 1/8 in. tube packed with 10% silicone gum rubber on 80–100 mesh Diatoport S; (b) a 6 ft × 1/8 in. tube packed with 10% of diethylene glycol succinate on 80–90 mesh Anakrom A; and (c) a 300 ft × 0.01 in. Golay column coated with trifluoropropylmethylsilicone. Preparative 6 ft 3/8 in. columns packed as in a and b were also employed.

Individual product components were isolated by fractional distillation and/or preparative gas chromatography, and subsequently identified by a combination of NMR, infrared, and mass spectral methods.

Preparation of Starting Materials. Acrylic acid esters (purity >98%) were prepared by sulfuric acid catalyzed alcoholysis of methyl acrylate[15,16] with an excess of the desired alcohol (isobutyl alcohol, cyclohexanol, 2-ethyl-1-hexanol, 1-borneol, or 1-dodecanol) followed by distillation at 15 Torr.

Isolation and Identification of Products. Alkyl 3-Alkoxypropionate (2). The isolation and identification of 3-alkoxypropionates obtained from different acrylates is illustrated by the following example.

Isobutyl 3-isobutoxypropionate (2c) was isolated by fractional distillation of the combined product from several experiments. Repurification by preparative gas chromatography gave a sample of 98% purity: bp 74–75 °C (0.5 mm); IR (CS_2) 2945–2860 (CH_3 stretching), 1735 (C=O stretching), 1374–1360 (CH deformation in $(CH_3)_2C$),[17] 1105 and 1065 (C–O–C strecthing) cm^{-1}; NMR (CCl_4) δ 3.80 (d, 2 H, J = 6.5 Hz, $CO_2CH_2CH(CH_3)_2$, 3.63 (t, 2 H, J = 6.5 Hz, $OCH_2CH_2CO_2R$), 3.16 (d, 2 H, J = 6.5 Hz, $(CH_3)_2CHCH_2OCH_2$), 2.47 (t, 2 H, J = 6.0 Hz, $OCH_2CH_2CO_2R$), 2.15–1.44 (m, 2 H, two $CH(CH_3)_2$), 0.95 (d, 12 H, J = 3 Hz, two $(CH_3)_2CH$); *m/e* 202 (M^+). Complete separation of all NMR absorption bands was achieved by using tris[1,1,1,2,2,3,3-heptafluoro-7,7,-dimethyl-4,6-octanedionato]europium [Eu(fod)$_3$] as a shift reagent. This included separation of the two closely spaced doublets (δ 3.80 and 3.63), and resolution of the multiplet (δ 2.15–1.44) into two simpler multiplets, corresponding to the two different types of methine groups.

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.70; H, 11.04. Found: C, 65.60; H, 11.07.

The other 3-alkoxypropionates (**2b–g**, Table III) were analyzed by the same methods, and their identity was confirmed by mass spectrometry.

Dialkyl α-Methyleneglutarate (3). The isolation and identification of the series of dimers **3** produced from different acrylates is illustrated by the following example.

Diisobutyl α-methyleneglutarate (3c) was obtained in 93% purity by fractional distillation. Further purification by preparative gas chromatography gave a sample of 99% purity: bp 118–120 °C (0.5 mm); IR (CS_2) 2940–2860 (CH_3 stretching), 1744 (C=O stretching in CH_2CO_2R),[17] 1720 (C=O stretching in $C{=}CCO_2R$),[17] 1632 (conjugated C=C) cm^{-1}; NMR (CCl_4) δ 6.15 (s, 1 H, *trans*-HCH=C(CO_2R)$CH_2CH_2CO_2R$),[7] 5.60 (s, 1 H, *cis*-HCH=C(CO_2R)-$CH_2CH_2CO_2R$),[7] 3.90 (d, 2H, J = 6.5 Hz, $C{=}CCO_2CH_2CH$), 3.80 (d, 2 H, J = 6.5 Hz, OCH_2CH), 2.53 (t, 4 H, J = 3.5 Hz, $CH_2CH_2CO_2R$), 1.00 (d, 6 H, J = 2.5 Hz, $(CH_3)_2CH$), 0.93 (d, 6 H, J = 2.5 Hz, $(CH_3)_2CH$); *m/e* 256 (M^+).

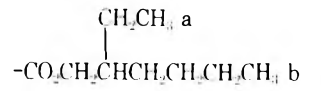
Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.52; H, 9.50.

The identity of the other α-methyleneglutarates (**3b, 3d–g**, Table III) was determined by the same methods and confirmed by mass spectrometry.

Tris(2-ethyl-1-hexyl) 1,3,5-Cyclohexanetricarboxylate (4d). Liquid chromatography of the product from experiments 7 and 8 gave a 0.4-g sample of compound **4d** in 98% purity. The chromatographic column, 40 in. × 1/4 in., was packed with 200 g of kieselgel 60, 70–230 mesh ASTM. Compound **4d** shows R_f 0.5 (hexane/ethyl acetate 9:1,

silica gel precoated aluminum plates; UV lamp development); NMR (CCl_4) δ 3.98 (m, 6 H, superposition of three doublets of OCH_2 groups), 2.5–2.0 (m, 6 H, CH of the 2-ethyl-1-hexyl group and CH of the ring), 1.67–1.10 (br signals, 30 H, ring CH_2, and esteric CH_2 groups), 0.83 (m, 18 H, superimposed triplets of the CH_2CH_3 groups); IR ($CHCl_3$) 2980 (CH_3 stretching), 2915 (CH_2 stretching), 2890–2880 (CH stretching), 1735 (C=O stretching, saturated CO_2R),[17] 1265–1000 (cyclohexane ring deformation bands);[17] *m/e* 552 (M^+).

The ^{13}C NMR spectrum of compound **4d** is composed of nine major signals corresponding to the different types of carbons, as the anticipated tenth carbon is apparently not sufficiently resolved. A definite broadening of certain signals, e.g., those centered at 30.35, 23.86, and 10.98 ppm, may be due to dynamic equilibrium between different conformations of **4d** under the conditions of measurement (25 °C). For chair–chair interconversion compound **4d** should be preferably in an axial–equatorial–equatorial (a,e,e) conformation, whereas for the energetically less likely chair–boat interconversion, all the ester groups should be equatorially disposed (e,e,e conformation). Examination of the spectrum indeed shows the presence of several narrow signals at 63.94, 31.95, 29.30, 23.40, 22.70, 19.76, and 14.47 ppm, which may be due to the presence of small amounts of the e,e,e conformer. Assignment of the major signals in the ^{13}C NMR spectrum of **4**, based on assignments in the spectrum of the starting monomer **1d**, is as follows: 10.97 (CH_3 b), 14.01 (CH_3 a), 23.86 ($CH_2CH_2CH_3$), 28.96 (CH_2CH_3 a), 30.35 (CH_2CH), 38.74 (–CH–), 67.11 (OCH_2), the designation of the a and b positions of CH_3 in the ester group being



1,3,5-Cyclohexanetricarboxylates obtained from other acrylates were analyzed by the same methods.

Registry No.—**4d**, 67208-88-2; benzylpotassium, 2785-29-7; potassium, 7440-09-7; isobutyl alcohol, 78-83-1; cyclohexanol, 108-93-0; 2-ethyl-1-hexanol, 104-76-7; 1-borneol, 507-70—; 1-dodecanol, 112-53-8.

References and Notes

(1) Paper 2: J.Shabtai, E. Ney-Igner, and H. Pines, *J. Org. Chem.*, **40**, 1158 (1975).
(2) W. E. Goode, F. H. Owens and W. L. Myers, *J. Polym. Sci.*, **47**, 75 (1960).
(3) T. C. Fox, B. S. Garrett, W. E. Goode, S. Gratch, J. F. Kincaid, A. Spell, and J. D.Stroupe, *J. Am. Chem. Soc.*, **80**, 1768 (1958).
(4) W. E. Goode, F. H. Owens, R. P. Fellmann, W. H. Snyder, and J. E. Moore, *J. Polym. Sci.*, **46**, 317 (1960).
(5) D. L. Glusker, L. Lysloff, and E. Stiles, *J. Polym. Sci.*, **49**, 315 (1961).
(6) R. C. Fettes (to Rohm and Haas Co.), U.S. Patent 2,956,990 (1960); *Chem. Abstr.* **55**, 6922h (1961).
(7) J. Shabtai and H. Pines, *J. Org. Chem.*, **30**, 3854 (1965).
(8) R. W. Holder, H. S. Freiman, and M. F. Stefanchik, *J. Org. Chem.*, **41**, 3303 (1976).
(9) C. E. Rehberg, M. B. Dixon, and C. H. Fischer, *J. Am. Chem. Soc.*, **68**, 544 (1946).
(10) N. E. Sartoris and H. Pines, *J. Org. Chem.*, **34**, 2119 (1969).
(11) K. Sanvi, T. Asahara and N. Ogata, *J. Polym. Sci., Part A-1*, **6**, 1195 (1968).
(12) R. Lenz, "Organic Chemistry of Synthetic High Polymers", Wiley Interscience, New York, N.Y., 1968.
(13) M. Szwarc, "Carbanion Living Polymers and Electron Transfer Processes", Wiley-Interscience, New York, N.Y., 1968.
(14) (a) W. O. Haag and H. Pines, *J. Am. Chem. Soc.*, **82**, 387 (1960); (b) J. Shabtai and E. Gil-Av, *J. Org. Chem.*, **28**, 2893 (1963).
(15) C. E. Rehberg and C. H. Fisher, *J. Am. Chem. Soc.*, **66**, 1203 (1944).
(16) C. E. Rehberg, W. A. Faucette, and C. H. Fisher, *J. Am. Chem. Soc.*, **66**, 1723 (1944).
(17) L. J. Bellami, "The Infrared Spectra of Complex Molecules", Methuen, London, 1962.

Base-Catalyzed Alkylation of Cyclopentadiene Rings with Alcohols and Amines

Stephen S. Hirsch[1,2] and William J. Bailey*

Department of Chemistry, University of Maryland, College Park, Maryland 20742

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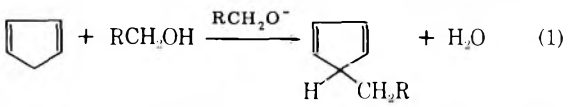
Multiple alkylations of several compounds possessing cyclopentadiene rings were accomplished by the action of alcohols in the presence of their corresponding alkoxides. Several new 1,3-dialkylindenes and 3,5-dialkyl-1,2,4-triphenylcyclopenta-1,3-dienes were synthesized. 1,2,3,4,5-Pentabenzylcyclopenta-1,3-diene was prepared for the first time. It was also demonstrated that 9-benzylfluorene resulted from the action of benzylamine and sodium amide on fluorene.

Since active methylene groups of cyclopentadienes were shown to be alkylated by alcohols and base,[3,4] a research program was undertaken to expand the scope of this reaction. In general form the reaction may be depicted as shown in eq 1, a simplified formulation which disguises informative aspects



(1)

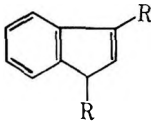
of the mechanism.[3] However, an examination of this mechanism suggested that more than one, but not necessarily all, of the unsubstituted ring carbon atoms of variously constituted cyclopentadiene moieties should be capable of substitution.

It has already been demonstrated that each hydroxyl group of certain glycols will alkylate a fluorene molecule to afford bis(9-fluorenyl)alkanes[5,6] and that benzyl alcohol will benzylate indene at both the 1 and 3 positions.[4] Douris and Mathieu,[7] however, isolated only a mixture of 1,3-dibenzylindene and 1-benzyl-3-benzalindene from treatment of indene with benzyl alcohol in the presence of sodium alkoxide or potassium hydroxide, although methanol, ethanol, and 2-propanol gave only the corresponding monoalkylated derivatives under the same conditions. Fritz et al.,[6] using less than molar equivalents of potassium hydroxide, were able to obtain a 74% yield of the dialkylated product with 2-ethylhexanol and indene and 26% yield of dialkylated product with cyclohexanol; however, only a monoalkylate derivative was obtained with 2-propanol.

It was desirable, therefore, to increase the applicability of the reaction to "multifunctional" cyclopentadienes (i.e., cyclopentadienes possessing more than one potentially active methylene group) to provide groundwork for the possible synthesis of a new class of all-hydrocarbon condensation polymers, some of which would be expected to possess a high order of thermal stability. It was further of interest to determine whether amines (which are considerably more basic than alcohols) could be similarly employed. Such a reaction would make possible alkylation by a similar route of methylene or methyl groups much less acidic than those present in cyclopentadienes.

Results and Discussion

1,3-Dialkylindenes. In contrast to the work just cited[6,7] the reaction of indene with a large excess of alcohol (ethanol, 1-propanol, 2-propanol, and benzyl alcohol in separate experiments) in the presence of the corresponding sodium alkoxide in a heated pressure vessel afforded good yields of 1,3-dialkylindenes. What had previously been an isolated

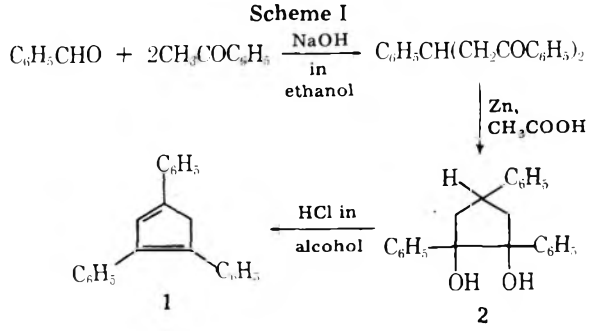


example of hydrocarbon difunctionality in this reaction[4] has now been shown to be quite general. Since in earlier work[4] care was taken to prove conclusively that indene was benzylated in the 1 and 3 positions but not elsewhere, it was only necessary at this time to consider the elemental analyses, boiling temperatures in relation to indene and the reported[8] 1,3-dimethylindene, and the boiling point order (diethyl < diisopropyl < di-*n*-propyl) to be reasonably certain of the structures.

An interesting exception to the dialkylation of indene was the attempt made with methanol. Although 1,3-dimethylindene is a known stable compound,[8] bp 212 °C, none whatever could be isolated by the present method; in fact, no material boiling above 208 °C was present in the reaction product from indene, methanol, and sodium methoxide. Two fractions boiling in the range 202–208 °C were collected, however. Gas chromatographic analysis revealed the presence of two partially resolved peaks. Elemental analyses of these products afforded values corresponding to $C_{11}H_{14}$, identified as a mixture of *cis*- and *trans*-1,3-dimethylindane. Since the basic alcoholic mixture is known to reduce carbon–carbon double bonds,[3] it appears that under the conditions used methanol is capable of reducing any 1,3-dimethylindene formed to a mixture of *cis*- and *trans*-1,3-dimethylindane [reported[9] bp 202.3 °C (740.5 mm)], which would account for the two partially resolved peaks upon gas chromatography.

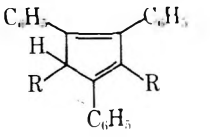
1,2,4-Triphenylcyclopenta-1,3-diene and the 3,5-Dialkyl-1,2,4-triphenylcyclopenta-1,3-dienes. The dialkyltriphenylcyclopentadienes were prepared by reaction of 1,2,4-triphenylcyclopenta-1,3-diene with appropriate alcohols and corresponding sodium alkoxides. The chemistry of the starting material contains much that is of interest. 1,2,4-Triphenylcyclopenta-1,3-diene (1) was prepared by the series of reported reactions[10–12] depicted in Scheme I. The first two steps are straightforward, but the conversion of the pinacol **2** to the hydrocarbon merits some discussion. Dehydration is preferred over a pinacol rearrangement, a fact contrary to many typical cases. Although the 1,2 migration would not be favored because of the attendant formation of a cyclobutane ring from a cyclopentane moiety, phenyl migration could be expected to give a stable triphenylcyclopentanone. Two possible explanations for the direction of the reaction may be proposed. First, dehydration gives the resonance-stabilized conjugated diene,[13] which would provide a driving force for

Scheme I



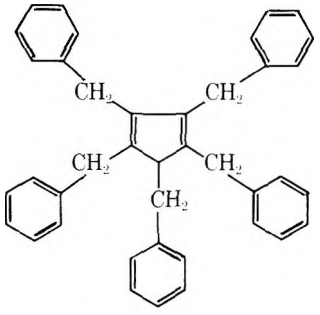
this manner of reaction. A second explanation is on steric grounds. It is known that the pinacol rearrangement on ring systems is favorable only if the migrating and leaving groups lie trans to each other.[12,13] Thus, if the glycol is principally the trans isomer (that is, if the phenyl migrating group is *not* opposite the OH group), rearrangement would not be favored. It is possible that there is some 2,2,4-triphenylcyclopentan-1-one resulting from a pinacol–pinacolone rearrangement in the small amount of byproduct having a wide melting range.

The 3,5-dimethyl and 3,5-di-*n*-propyl derivatives were prepared in 35 and 63% yields, respectively, from the corresponding alcohols and their alkoxides by heating with the trisubstituted cyclopentadiene 1 in a steel reaction vessel as described for the preparation of the dialkylindenes. That the compounds possess the claimed structure is indicated by the presence in the UV spectra of the longer wavelength band demonstrated in the starting material. In the alkylated



products, the band suffers a slight hypsochromic shift and is decreased somewhat in intensity, presumably due to steric interference with planarity. It should be noted that in this more highly conjugated system, methanol is a suitable alkylating alcohol, in contrast to the reaction with indene.

1,2,3,4,5-Pentabenzylcyclopenta-1,3-diene. The reaction of cyclopentadiene dimer with a large excess of benzyl alcohol and sodium benzyloxide in diisopropylbenzene solvent under reflux afforded a 19% yield of pentabenzylcyclopentadiene (**4**).



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The structure of this hitherto unreported hydrocarbon was established by ultimate analysis, molecular weight determination, and NMR spectroscopy. The NMR spectrum obtained in deuteriochloroform was consistent with the pentabenzylcyclopentadiene structure. Peaks at τ 2.80 (relative area = 20) and τ 3.21 (relative area = 5) were assigned to aromatic protons. The unique aromatic ring is almost assuredly the one linked ultimately to the 5-carbon atom of the five-membered ring. Its relatively high-field position suggests that it is held essentially above (or below) the planes of the nearby aromatic rings. Moreover, peaks in the range τ 5.91–6.82 had a total relative area of approximately 11, consistent with the nature and number of the nonaromatic protons in the molecule. In connection with the nonplanarity of the structure, Pauson has determined that in the related multiphenylcyclopentadienes, the aromatic rings are twisted out of plane.[16]

When similar reactions with ethanol or 1-propanol as the alkylating alcohol were attempted, only mixtures of products could be obtained. Evidence points to varying degrees of reaction, with termination prior to pentaalkylation likely due to reduction of the double bonds of the cyclopentadiene ring (see the above discussion of the attempted preparation of 1,3-dimethylindene). Such an occurrence would account for

the low yield of the pentabenzyl compound as well. It should be noted that reduction of the double bonds in cyclopentadiene itself due to diminished opportunity for resonance stabilization would be favored over such a process in the other compounds of this class which have been subjected to the reaction.

9-Benzylfluorene from Fluorene and Benzylamine. During the course of this work it became of interest to determine whether amines could split out ammonia when heated with one of the acidic hydrocarbons and base, just as the alcohols lose a molecule of water. Such a process would result in similar alkylations, but since an amine plus sodium amide is much more basic a mixture than is an alcohol and its alkoxide, the former mixture should be able to alkylate much more weakly acidic molecules. It was felt that the first step in testing such a hypothesis should be alkylation by this method of one of the hydrocarbons known to be alkylated by alcohols. Accordingly, when fluorene was heated with an excess of benzylamine and some sodium amide in diisopropylbenzene solvent, ammonia was evolved and a 67% yield of 9-benzylfluorene was obtained. Although there is no conclusive evidence, it is very probable that the mechanism of this reaction is similar to that with alcohols.

Experimental Section[17,18]

1,3-Diethylindene. To a solution of 7.7 g (0.33 g-atom) of sodium metal in 150 mL of absolute ethanol[19] in a 300-mL steel reaction vessel was added 13.2 g (0.114 mol) of indene (Neville Chemical Co., 97.5% minimum purity). After the mixture was heated and rocked at 205 °C for 8 h, the reaction product was removed with the aid of 400 mL of water and 150 mL of benzene added alternately in small portions. The resulting mixture was acidified with a small amount of hydrochloric acid, and the layers were separated. After the aqueous layer was shaken with 50 mL of benzene, the extract was combined with the original organic layer. The combined organic solutions were washed with two 400-mL portions of water and then dried over potassium carbonate. After the benzene had been removed by distillation through a 6-in. Vigreux column, the residue was vacuum distilled through a ⅓ × 12-in., helix-packed column to give 12.5 g (65%) of 1,3-diethylindene: bp 136 (26 mm), 140 °C (28.5 mm); n^{26}_D 1.5385. A purity of at least 95% was indicated by gas chromatography.

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.80; H, 9.54.

1,3-Di-*n*-propylindene. A mixture of 11 g (0.095 mol) of indene and a solution of 6 g (0.026 g-atom) of sodium metal reacted with 150 mL of 1-propanol[19] was treated as described for the preparation of diethylindene to give 13.5 g (72%) of 1,3-di-*n*-propylindene, bp 159.8–161.7 °C (20.5 mm), n^{26}_D 1.5270, which showed a single peak when examined by gas chromatography.

Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 90.03; H, 9.89.

1,3-Diisopropylindene. This reaction was a duplicate of that for di-*n*-propylindene with the same quantities of reagents, but with 2-propanol replacing 1-propanol. Because the solubility of sodium isopropoxide in 2-propanol is fairly low, the hot alcoholic solution solidified when an attempt was made to pour it into the reaction vessel. For this reason the sodium metal was allowed to react with the alcohol in the vessel under reflux and the indene was then added. Fractionation gave 14.0 g (74%) of 1,3-diisopropylindene, bp 144.9–148.8 °C (20 mm), n^{26}_D 1.5234, which likewise gave a single peak when examined by gas chromatography.

Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 90.20; H, 10.10.

1,3-Dibenzylindene. A mixture of 7.0 g (0.06 mol) of indene and a solution of 4.0 g (0.17 g-atom) of sodium metal reacted with 150 mL of benzyl alcohol[19] was treated exactly as for the diethylation of indene, except that during the workup, after acidification, the organic layer was extracted with three portions of a sodium bicarbonate solution to remove precipitated benzoic acid. Fractionation gave 7.6 g (43%) of 1,3-dibenzylindene, bp 166–173 °C (0.05–0.08 mm) [reported[4] bp 240–247 °C (5 mm)].

Reaction of Indene with Sodium Methoxide and Methanol. A mixture of 13.2 g (0.114 mol) of indene and a solution of 7.7 g (0.33 g-atom) of metallic sodium reacted with 150 mL of methanol[19] contained in a 300-mL reaction vessel was heated and rocked for 16 h at 220 °C. The workup to the distillation was exactly as described for diethylindene. Distillation without a column was carried out at atmospheric pressure to give one fraction, bp 200–205 °C, and a second fraction, bp 205–208 °C. No material was collected that distilled above 208 °C, even though the bath temperature was taken as high as 280 °C and a small amount of liquid remained in the flask (reported[6] for 1,3-dimethylindene, bp 212–214 °C). The fractions were combined and redistilled through a ⅓ × 12-in., helix-packed column at atmospheric pressure to give 2.5 g of a mixture of *cis*- and *trans*-1,3-dimethylindane, bp 202–203 °C [reported[9] bp 202.3 °C (740.5 mm)], and 1 g of residue that was collected by flash distillation. On examination by gas chromatography on a 1:6 silicone grease on Chromosorb P column at 220 °C, cut 1 gave a partially resolved doublet while cut 2 corresponded mainly to the second peak found for cut 1.

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.57; H, 9.80.

1,3,5-Triphenyl-1,5-pentanedione (Benzaldiacetophenone). To a mixture of 60.0 g (0.57 mol) of benzaldehyde and 180 g (1.50 mol) of acetophenone dissolved in 600 g of ethanol was added 150 g of 40% aqueous sodium hydroxide. After the mixture was heated under reflux for 15 min, the solution was cooled to room temperature and 600 mL of water was added, whereupon a deep orange oil settled to the bottom of the vessel. To a solution of this oil in hot ethanol was added just enough water to approach but not reach the precipitation point. When the mixture was allowed to stand, oil but not solid was deposited. The mixture was then poured with stirring into 1.5 L of water and allowed to stand overnight to produce a mass of light yellow crystals. These crystals were collected, crushed, and stirred with 250 mL of cold methanol to obtain 122 g of white product, mp 82–84 °C (reported[11] mp 85 °C). The mother liquor was evaporated to 25% of its volume, cooled, and allowed to crystallize to provide an additional 15 g (for a total 73% yield) of 1,3,5-triphenyl-1,5-pentanedione, mp 81.5–83.5 °C.

1,2,4-Triphenyl-1,2-cyclopentanediol. To a solution of 80.0 g (0.24 mol) of 1,3,5-triphenyl-1,5-pentanedione in 4000 mL of glacial acetic acid at 95 °C contained in a 5-L, three-neck flask equipped with a mercury sealed stirrer, a reflux condenser, and a thermometer dipping into the liquid, a fivefold excess of zinc dust was added periodically with stirring during 5 h. Considerable unreacted zinc remained at the end of this time. The hot mixture was filtered and the filtrate was poured into 4 gal of cold water to give a voluminous light yellow precipitate. After the solid was collected on a filter with suction and air dried, the material was dissolved in hot ethanol and reprecipitated by pouring the solution into 4 gal of cold water. The precipitate was recrystallized from 90–100 °C petroleum ether to afford 42 g (53%) of white solid 1,2,4-triphenyl-1,2-cyclopentanediol, mp 140.5–144.5 °C (reported[11] mp 142 °C).

1,2,4-Triphenylcyclopenta-1,3-diene. When a mixture of 75 mL of concentrated hydrochloric acid, 400 mL of ethanol, and 42 g (0.13 mol) of 1,2,4-triphenyl-1,2-cyclopentanediol was heated under reflux for 3 h, the precipitate (which formed after the first few minutes of boiling) was separated by filtration from the cooled mixture to give a yellow solid, mp 147.8–150.2 °C. One crystallization from the minimum quantity of boiling ethanol afforded 26.6 g (70%) of yellow crystals, mp 151.6–152.9 °C (reported[11] mp 149 °C).

Anal. Calcd for $C_{23}H_{18}$: C, 93.84; H, 6.16. Found: C, 93.88; H, 6.24.

The ultraviolet spectrum taken on a solution of 1.236 ± 0.004 mg of the diene in 100 mL of isooctane gave the following results.

λ, nm	absorbance	log ε
229	0.817	4.290
244	0.746	4.250
256	0.778	4.267
338	0.723	4.236

An NMR spectrum on a saturated solution of the compound in carbon tetrachloride showed that the ratio vinyl/allylic hydrogen atoms was 2:1. A second portion of impure crystals (6.5 g, 100 °C melting range) was deposited from the mother liquor of the recrystallization step after being allowed to stand at −20 °.

3,5-Dimethyl-1,2,4-triphenylcyclopenta-1,3-diene. A mixture of 2.94 g (0.01 mol) of 1,2,4-triphenylcyclopentadiene and a solution of 4.5 g (0.20 g-atom) of metallic sodium reacted with 80 mL of methanol was heated and rocked in a steel reaction vessel at 215 °C for 17 h. After the vessel was allowed to cool and the mixture was removed with the aid of several alternate portions of benzene and water, the resulting mixture was neutralized with dilute hydrochloric acid. After the aqueous layer was extracted with three small portions of benzene, the combined extracts and benzene layer were washed with three portions of a dilute calcium chloride solution and then dried over

potassium carbonate. Most of the solvent was gradually removed with a rotary evaporator (the solution became quite cold) until an appreciable amount of solid was deposited. Rapid filtering and drying gave 1.26 g of light yellow powder. (Only tar was deposited upon removal of additional solvent from the mother liquor in the same manner.) The powder was recrystallized in 83% recovery from methanol to give 1.05 g (35%) of 3,5-dimethyl-1,2,4-triphenylcyclopenta-1,3-diene, mp 122–124 °C. Recrystallization from ethanol plus a few drops of chloroform gave an analytical sample, mp 125.7–126.7 °C.

Anal. Calcd for $C_{25}H_{22}$: C, 93.12; H, 6.88. Found: C, 93.28; H, 7.05.

An ultraviolet spectrum on a solution of 1.025 ± 0.004 mg of the methylated diene in 100 mL of isooctane gave λ_{max} 230 (log ϵ 4.253) and 322 nm (log ϵ 4.220) with a slight shoulder at 253 nm.

3,5-Di-*n*-propyl-1,2,4-triphenylcyclopenta-1,3-diene. The same method described for the dimethyl derivative was followed, with an equal volume of 1-propanol instead of the methanol and heating and rocking at 210 °C for 17 h. After the solvent was removed in a rotary evaporator, 2.38 g (63%) of the light yellow powder was obtained. This material was recrystallized first from methanol, then from 1:1 methanol–ethanol and finally from methanol plus 10% ethanol to give an analytical sample of 3,5-di-*n*-propyl-1,2,4-triphenylcyclopenta-1,3-diene, mp 93.7–94.7 °C.

Anal. Calcd for $C_{29}H_{30}$: C, 92.01; H, 7.99. Found: C, 91.74; H, 7.79.

An ultraviolet spectrum on a solution of 1.015 ± 0.004 mg of the dipropyl derivative in 100 mL of isooctane gave λ_{max} 257 (log ϵ 4.230) and 315 nm (log ϵ 4.152).

1,2,3,4,5-Pentabenzylcyclopenta-1,3-diene. After 324 g (3 mol) of benzyl alcohol and 23 g (1 g-atom) of metallic sodium cut into small pieces had been reacted under a flow of prepurified nitrogen, the mixture was allowed to cool and 300 mL of diisopropylbenzene (mixed isomers) plus 6.6 g (0.05 mol) of cyclopentadiene dimer (Carbide and Carbon Chemicals Co.) was added. While the mixture was stirred under reflux for 16 h in an atmosphere of nitrogen, the liquid temperature increased from 182 °C at the commencement of boiling to a maximum of 203 °C 6 h later, during which time 8 mL of aqueous layer had collected in a Dean Stark trap filled with benzyl alcohol. The temperature did not change with further reflux. As the reaction mixture was allowed to cool, a gel of sodium benzoate deposited. The semisolid mixture was dissolved in a mixture of benzene and water. After the organic layer was washed with three portions of water and dried with sodium sulfate, the solvent was removed by distillation at atmospheric pressure until 90 mL of liquid remained in the flask. After the liquid was cooled, the pressure was lowered to 16 mm with a water aspirator and solvent was removed until no more would come over at a bath temperature of 165 °C. The residue was distilled from a Claisen flask (no column) in an oil bath at a pressure of 0.8 mm to give a forerun, fraction A, bp 250–255 °C, and fraction B, bp 255–275 °C. These two fractions could not be poured when cool. Each of these two fractions was dissolved separately in hot methanol and allowed to stand for 4 days at 2 °C. From fraction A was obtained 4 g of white solid, mp 64–71 °C, while fraction B gave 6 g of yellowish crystals, mp 67.5–74.0 °C. The total amount represented 19% of the theoretical yield based on cyclopentadiene dimer. Each sample was recrystallized from methanol to give from solid A a material with mp 69.2–75.7 °C, and from solid B a material with mp 68.5–75.7 °C. These two samples were recrystallized again from the methanol to give crystals, mp 73.5–75.5 and mp 73.2–76.0 °C, respectively. A mixture melting point of the two samples gave a value of 72.8–75.5 °C. The combined samples were recrystallized three times from methanol plus a small amount of chloroform to obtain an analytical sample, mp 74.0–74.7 °C.

Anal. Calcd for $C_{40}H_{36}$: C, 92.97; H, 7.02, mol wt, 517. Found: C, 92.96; H, 6.80; mol wt, 494.

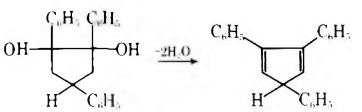
Molecular weight determination was cryoscopic in benzene. The ultraviolet spectrum in isooctane gave a single peak with λ_{max} 276 nm (log ϵ 3.92), while the infrared spectrum confirmed that the material was a hydrocarbon.

9-Benzylfluorene from Fluorene and Benzylamine. Into a 250-mL, three-neck flask equipped with a mercury sealed stirrer, a reflux condenser, a tube for admitting prepurified nitrogen, and a thermometer extending through the condenser far enough to dip into the liquid were placed 4.15 g (0.025 mol) of fluorene (Eastman Organic Chemicals, recrystallized from acetone), 10 g (0.093 mol) of benzylamine, 1.4 g (0.035 mol) of sodium amide, and 100 mL of diisopropylbenzene. Heat was gradually applied until boiling commenced at 199 °C (flask temperature). As the reflux was continued, the color became progressively darker and the temperature attained a maximum of 204 °C 8 h later, but refluxing was continued for an additional 2 h. The copious flow of ammonia which first was liberated gradually dwindled until after 10 h only a trace was evident as indicated by moist red litmus paper held at the exit tube. After the mixture was allowed to cool overnight under the nitrogen stream, the solution was decanted and the remaining solid was dissolved by rinsing alternately with benzene and ethanol. After the combined extracts and main solution were washed with three portions of water, the brown organic layer was dried with sodium sulfate and calcium chloride. When the solvent was removed by distillation until the residue amounted to 10 mL, green crystals were deposited from the cold solution. Removal of additional solvent by distillation afforded a second crop of brown crystals. The combined samples (4.31 g, 67%) were recrystallized from hexane with the aid of decolorizing carbon to give 3.5 g of cream-colored crystals, mp 133.7–135.0 ° C. The crystallization was repeated from a small amount of toluene together with the hexane to give 3.12 g of almost white crystals, mp 134.5–136.0 °C. A mixture melting point with authentic sample of 9-benzylfluorene, mp 135.7–136.0 °C, prepared by the method of Sprinzak,[20] melted at 135.5–136.4 °C.

Registry No.—**1**, 5074-28-2; **2**, 67209-28-3; **4**, 67209-29-4; 1,3-diethylindene, 67209-30-7; ethanol, 64-17-5; sodium ethoxide, 141-52-6; indene, 95-13-6; 1,3-di-*n*-propylindene, 67209-31-8; 1-propanol, 71-23-8; sodium propoxide, 6819-41-6; 1,3-diisopropylindene, 67209-32-9; 2-propanol, 67-63-0; sodium isopropoxide, 683-60-3; 1,3-dibenzylindene, 40241-58-5; benzyl alcohol, 100-51-6; sodium benzyloxide, 20194-18-7; methanol, 67-56-1; sodium methoxide, 124-41-4; *cis*-1,3-dimethylindane, 26561-33-1; *trans*-1,3-dimethylindane, 40324-83-2; benzaldiacetophenone, 6263-84-9; benzaldehyde, 100-52-7; acetophenone, 98-86-2; 3,5-dimethyl-1,2,4-triphenylcyclopenta-1,3-diene, 67209-33-0; 3,5-di-*n*-propyl-1,2,4-triphenylcyclopenta-1,3-diene, 67209-34-1; cyclopentadiene dimer, 7313-32-8; 9-benzylfluorene, 1572-46-9; fluorene, 86-73-7; benzylamine, 100-46-9.

References and Notes

(1) American Chemical Society Petroleum Research Fund Fellow, 1959–1961; Celanese Fellow, 1961–1962; Goodyear Tire and Rubber Co. Fellow, 1962.
(2) Research Laboratories, Hooker Chemicals, Grand Island, New York 14072.
(3) E. I. Becker, *J. Chem. Educ.*, **36**, 119 (1959).
(4) S. S. Hirsch, D. H. Lorenz, and E. I. Becker, *J. Org. Chem.*, **23**, 1829 (1958).
(5) I. D. Rubin and E. I. Becker, *J. Org. Chem.*, **22**, 1623 (1957).
(6) H. E. Fritz, D. W. Peck, M. A. Eccles, and K. E. Atkins, *J. Org. Chem.*, **30**, 2540 (1965).
(7) J. Douris and A. Mathieu, *Bull. Soc. Chim. Fr.*, 709 (1973).
(8) J. von Braun and G. Kirschbaum, *Ber. Dtsch. Chem. Ges.*, **46**, 3041 (1913).
(9) J. Entel, C. H. Ruof, and H. C. Howard, *Anal. Chem.*, **25**, 1303 (1953).
(10) S. V. Kostanecki and C. Rossbach, *Ber. Dtsch. Chem. Ges.*, **29**, 1488 (1896).
(11) S. V. Kostanecki and G. Rossbach, *Ber. Dtsch. Chem. Ges.*, **29**, 1493 (1896).
(12) F. H. Newmann, *Justus Liebigs Ann. Chem.*, **302**, 236 (1898).
(13) Granted that dehydration occurs, there is still an unanswered question concerning the structure of the product. Newmann[12] clearly pictures (without proof) that water is split out from the diol in the "conventional" manner to give 2,3,5-triphenylcyclopenta-1,3-diene (**3**). (The original article used a different numbering system for the ring to obfuscate the situation



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even further.) Two sets of later workers [ref 14 and W. Dilthey and W. Schommer, *J. Prakt. Chem.*, **136**, 293 (1933)] repeated this preparation and *without comment* pictured the product as 1,2,4-triphenylcyclopenta-1,3-diene (**1**). It seemed logical to the present authors that the structure **1**, possessing both the conjugated stilbene and 1,4-diphenylbutadiene systems, would be *favored over* **3**, which *merely can* claim styrene contributions. To prove this contention, ultraviolet and NMR spectra were obtained. In the ultraviolet the compound showed, in addition to several other bands, a strong absorption maximum at 338 nm (log ϵ 4.236). This can be rationalized only in terms of the more highly conjugated structure **1**. Nuclear magnetic resonance, however, was the ideal tool for distinguishing between *structures* **1** and **3**. *Formula* **3** possesses (in addition to aromatic protons) two vinyl protons and one nonvinyl type. The reverse is true of structure **1**. The spectrum clearly showed that the vinyl peak was half the size of the allylic one. Thus, water is split out from the glycol to give as the final product the thermodynamically favored isomer, not the most "straightforward" one.
(14) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Henry Holt and Co., New York, N.Y., 1959, p 603.
(15) (a) P. D. Bartlett and I. Pöchel, *J. Am. Chem. Soc.*, **59**, 820 (1937); (b) P. D. Bartlett and A. Bavley, *ibid.*, **60**, 2416 (1938); (c) P. D. Bartlett and R. F. Brown, *ibid.*, **62**, 2927 (1940).

(16) P. L. Pauson, *J. Am. Chem. Soc.*, **76**, 2187 (1954).
(17) The authors are grateful to Drs. Leon Petrakis and Byron Arison for obtaining and interpreting NMR spectra and to Dr. Franz Kasler for obtaining the microanalyses.
(18) All melting points, boiling points, and refractive indices are corrected. The melting points were determined with a micro Kofler hot stage and a polarizing microscope. Ultraviolet spectra were taken on a model 14 Cary spectrometer at 25 °C and NMR spectra were obtained with a Varian Associates Model DP-60 nuclear magnetic resonance spectrometer.
(19) After sodium metal was dissolved in the appropriate alcohols, the resulting solutions were deliberately exposed to the atmosphere for about 1 min before further use. The reason for this step is that the mechanism (see ref 3) requires that a trace of aldehyde be present for reaction to occur.
(20) Y. Sprinzak, *Bull. Res. Counc. Isr.*, **3**, 104 (1953).

Stereoselective Alkylation of Cyclic Ketones by Dialkylamino- and Aryloxy(methyl)magnesium Compounds

E. C. Ashby* and G. Fred Willard

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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Reactions of dialkylamino(methyl)magnesium compounds, CH_3MgNR_2 (where NR_2 = N-*i*-Pr_2, NPh_2, and $NC_5H_8Me_2$), and aryloxy(methyl)magnesium compounds, CH_3MgOR (where OR = O-2,6-*i*-$Pr_2C_6H_3$ and O-2,6-*t*-Bu_2-4-MeC_6H_2), with cyclic ketones such as 4-*tert*-butylcyclohexanone and 2,2,6,6-tetramethyl-4-*tert*-butylcyclohexanone have been studied. These reagents exhibit excellent stereoselectivity in the alkylation of these model compounds. The selectivity of the amide or aryloxy reagent has been shown to depend on the steric requirement of the aryloxy group, the steric requirement of the ketone, and the nature of the solvent.

A recent review[1] concerning the stereochemistry of organometallic compound addition to ketones points out the paucity of stereoselective alkylating agents, especially for the case of methylation of unhindered ketones. The reaction of methyllithium, in the presence of a lithium salt such as $LiClO_4$, with 4-*tert*-butylcyclohexanone to give a 94:6 axial/equatorial alcohol ratio is probably the best example of stereoselective methylation hitherto reported.[2]

Our success with the stereoselective reduction of cyclic and bicyclic ketones with dialkylaminomagnesium hydrides[3] prompted us to apply similar reasoning to the problem of stereoselective alkylation. Namely, if such hydrides are good stereoselective reducing agents by virtue of their bulky dialkylamino groups, then similar bulkiness in an alkylating agent should produce a similar effect.

We would now like to report on the reactions of dialkylamino- and aryloxy(methyl)magnesium compounds with cyclic ketones, showing their unusual stereoselective behavior as alkylating reagents.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[4] GLC analyses were performed on an F and M Model 720 gas chromatograph. NMR spectra were recorded on a Jeol 100 MHz Fourier transform NMR spectrometer.

Analyses. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid or methanol on a standard vacuum line equipped with a Toepler pump. Magnesium was determined by EDTA titration at pH 10 using Eriochrome Black T as an indicator.

Materials. Diisopropylamine (Aldrich), 2,6-dimethylpiperidine (Aldrich), and 2,6-diisopropylphenol (Ethyl Corp.) were dried over NaOH and fractionally distilled prior to use. Diphenylamine (Fisher), *tert*-amyl alcohol (Mallinckrodt), 2,6-di-*tert*-butyl-*p*-cresol (Eastman), and triphenylphosphine (Fisher) were used without further purification. 4-*tert*-Butylcyclohexanone (Frinton) was sublimed under vacuum prior to use.

Diethyl ether and benzene were distilled from $LiAlH_4$ and $NaAlH_4$, respectively. Diphenyl ether was fractionally distilled under vacuum. Dimethylmagnesium was prepared by the reaction of dimethylmercury with excess magnesium metal (Ventron chips) at 25 °C.[5] A solution in diethyl ether was standardized by magnesium and methane analyses (Mg/CH_4 ratio was 1.00:1.98).

Preparation of 2,2,6,6-Tetramethyl-4-*tert*-butylcyclohexanone. To a 1-L three-neck flask equipped with a reflux condenser and nitrogen bubbler was added 34.5 g of sodium (1.50 mol) and 178 mL of *tert*-amyl alcohol (excess). The mixture was stirred for 24 h under reflux until no sodium remained. Then 38.8 g of 4-*tert*-butylcyclohexanone (0.252 mol) in 158.4 g of methyl iodide (excess) was added dropwise, and the refluxing was continued for 1 week. The reaction mixture was then quenched with water and extracted with diethyl ether. The ether extract was dried over $MgSO_4$ and reduced under vacuum to give 49.6 g of an oil (93.7% crude yield). The material was crystallized twice from pentane to give 8.2 g (15.5% yield), mp 77.0–78.0 °C. The solid was sublimed at 65–85 °C at 2 mmHg. The yield was 7.1 g (mp 92.0–93.0 °C). The 2,2,6,6-tetramethyl-4-*tert*-butylcyclohexanone thus prepared was hygroscopic and was handled in a glovebox: NMR ($CDCl_3$) δ 0.95 (s, 9 H), 1.10 (s, 6 H), 1.18 (s, 6 H), 1.62 (m, 5 H); IR (Nujol) 1715 cm^{-1} (C=O); MS *m/e* 210 (M^+), 153 ($M^+ - C_4H_9$). Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.69; H, 12.40.

Characterization of *cis*- and *trans*-1,2,2,6,6-Pentamethyl-4-*tert*-butylcyclohexanol (Axial and Equatorial). The methylation products from the reaction of 2,2,6,6-tetramethyl-4-*tert*-butylcyclohexanone and methylmagnesium bromide were collected via GLC on a 4 ft × 0.5 in 5% Carbowax 20M on Chromosorb W column. The equatorial alcohol eluted first, as will be shown later.

***trans*-1,2,2,6,6-Pentamethyl-4-*tert*-butycyclohexanol (Equatorial).** The first material collected by GLC gave the following data: mp 44.0–45.0 °C; NMR ($CDCl_3$) δ 0.85 (s, 9 H), 0.98 (s, 3 H), 1.05 (s, 6 H), 1.13 (s, 6 H), 1.26 (m, 4 H), 1.61 (m, 1 H); IR (as melt) 3620, 3500 cm^{-1} (OH); MS *m/e* 226 (M^+), 169 ($M^+ - C_4H_9$). Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.35. Found: C, 79.39; H, 13.39.

***cis*-1,2,2,6,6-Pentamethyl-4-*tert*-butylcyclohexan-1-ol (Axial).** The second material collected by glc gave the following data: mp 35.5–36.0 °C; NMR ($CDCl_3$) δ 0.85 (s, 9 H), 0.95 (s, 3 H), 1.10 (s, 6 H), 1.15 (s, 6 H), 1.20 (m, 4 H), 1.32 (m, 1 H); IR (as melt) 3620, 3500 cm^{-1} (OH); MS *m/e* 169 ($M^+ - C_4H_9$). Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.35. Found: C, 79.40; H, 13.34.

Assignment of Stereochemistry. Preliminary assignment of stereochemistry for the isomeric alcohols was based on melting point and NMR data. The axial alcohol is expected to have a lower melting point because of less steric hindrance from association due to hydrogen bonding. Also, the α-methyl group of the axial alcohol (δ 0.95) was found at a higher field in the NMR spectrum than the corresponding signal of the α-methyl group in the equatorial alcohol (δ 0.98) since the α-methyl group is shielded more by the β-methyl groups in the axial alcohol.

In order to verify the assignment of stereochemistry, a shift reagent study was conducted. NMR samples were prepared from standard solutions of pure axial and equatorial alcohols in $CDCl_3$. Small aliquots of a standard solution of $Eu(fod)_3$ (Bio-Rad) in $CDCl_3$ were added using a microliter syringe. The NMR spectra were recorded for various shift reagent/alcohol ratios, and chemical shifts due to the

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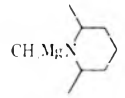
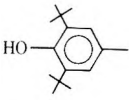
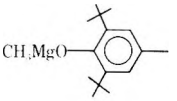
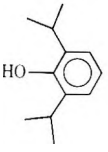
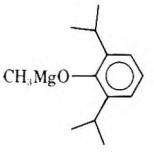
Table I. Preparation of Dialkylamino(methyl)magnesium and Methylmagnesium Aryloxide Reagents [a]

reactants					
$(CH_3)_2Mg$,[b] mmol	R_2NH or ROH, mmol	registry no.	product	registry no.	analysis (ratio) Mg/CH_3
49.9	HN-*i*-Pr_2 50.0	108-18-9	CH_3MgN-*i*-Pr_2	67209-22-7	1.00:0.99
42.9	$HNPh_2$ 42.8	122-39-4	CH_3MgNPh_2	67209-23-8	1.00:1.02
47.2	 16.1	504-03-0		67254-40-4	1.00:0.98
15.8	 47.5	2078-54-8	 (A)	67209-25-0	1.00:0.98
16.0	 15.9	128-37-0	 (B)	67209-24-9	1.00:0.99

[a] All reactions were carried out at room temperature in diethyl ether for 1 h. [b] Registry no.: $(CH_3)_2Mg$, 2999-74-8.

tert-butyl group were followed for each alcohol. The data are plotted in Figure 1. The effect of addition of the shift reagent would be expected to be larger on the axial alcohol where the *tert*-butyl and hydroxyl groups are cis; thus, the compound with the larger slope (0.854 compared to 0.283) is assigned to the axial alcohol.[6] These data are compatible with the preliminary stereochemical assignment.

Attempts to obtain a single crystal of the axial alcohol for X-ray analysis failed to yield a suitable crystal. The *p*-bromobenzoyl ester derivative was prepared but was also unsuitable.

Results and Discussion

The dialkylamino(methyl)magnesium compounds,[7] CH_3MgNR_2 (where NR_2 = N-*i*-Pr_2, NPh_2, and $NC_5H_8Me_2$), used in these studies were prepared conveniently and quantitatively by the reaction of dimethylmagnesium with an equal molar amount of the corresponding secondary amine at room temperature (eq 1). Preparation and analytical data are summarized in Table I.

$$CH_3MgCH_3 + HN\text{-}i\text{-}Pr_2 \xrightarrow{Et_2O} CH_3MgN\text{-}i\text{-}Pr_2 + CH_4 \quad (1)$$

The CH_3MgNR_2 compounds prepared by the method of eq 1 were allowed to react with two representative ketones, i.e., 4-*tert*-butylcyclohexanone (I), representing a nonsterically hindered ketone, and 2,2,6,6-tetramethyl-4-*tert*-butylcyclohexanone (II), representing a sterically hindered ketone. The results of these reactions are summarized in Tables II and III.

The least hindered methylating agents among magnesium compounds of the type CH_3MgX are methyl Grignard and dimethylmagnesium. These compounds give 60 and 64% equatorial attack, respectively, with ketone I[8] and 71 and 85% equatorial attack, respectively, with ketone II in diethyl ether. It was reasoned that increasing the steric bulk of the alkylating agent, CH_3MgX, would cause a corresponding increase in attack from the less hindered side of the ketone, namely, from the equatorial side. Hence, the effect of replacing X with the bulkier dialkylamino group $R_2'N$ was studied. In the case of ketone I, it was found that dialkyamino(methyl)magnesium compounds give essentially the same results as methyl Grignard and dimethylmagnesium in diethyl ether (expt 1–3) and benzene (expt 13 and 14). It is apparent that the bulkiness of the dialkylamino group is too far removed from the reaction center to be effective. However, the discovery was made that addition of triphenylphosphine to the reagent in a 2:1 ratio increased the steric bulk of the reagent by forming a complex between the phosphine and the magnesium. For the reagents diisopropylamino(methyl)magnesium (expt 4) and diphenylamino(methyl)magnesium (expt 5), excellent stereochemical results were obtained (95 and 100% equatorial attack, respectively). For the 2,6-dimethylpiperidine reagent (expt 6), there was only a small increase in the amount of equatorial attack with the addition of triphenylphosphine, indicating

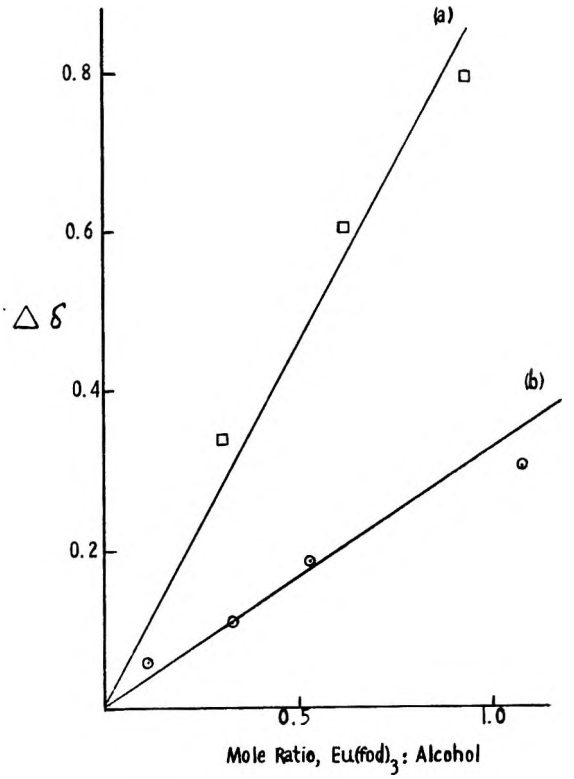
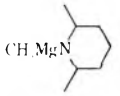
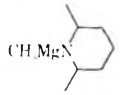
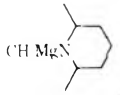
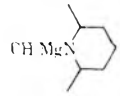
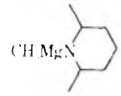


Figure 1. $Eu(fod)_3$ shift reagent study on *cis*- and *trans*-1,2,2,6,6-pentamethyl-4-*tert*-butylcyclohexanol: (a) axial alcohol and (b) equatorial alcohol.

Table II. Reactions of 4-*tert*-Butylcyclohexanone with Dialkylamino(methyl)magnesium Compounds [a]

expt.	reagent	solvent	additive	relative yield,[b] % axial OH	relative yield,[b] % equatorial OH	yield of alcohols, %	mass balance,[c] %
1	CH_3MgN-*i*-Pr_2	Et_2O		73	27	26	98
2	CH_3MgNPh_2	Et_2O		72	28	33	97
3		Et_2O		71	29	10	57
4	CH_3MgN-*i*-Pr_2	Et_2O	$2Ph_3P$	95	5	8	43
5	CH_3MgNPh_2	Et_2O	$2Ph_3P$	100	0	4	34
6		Et_2O	$2Ph_3P$	78	22	12	64
7	CH_3MgN-*i*-Pr_2	Et_2O	Ph_3P	73	27	22	12
8	CH_3MgBr	Et_2O	$2Ph_3P$	64	36	93	93
9	CH_3MgCH_3	Et_2O	$2Ph_3P$	70	31	25	52
10	CH_3MgN-*i*-Pr_2	Et_2O	$LiClO_4$	79	21	10	56
11	CH_3MgNPh_2	Et_2O	$LiClO_4$	100	0	9	87
12		Et_2O	$LiClO_4$	0	0	0	13
13	CH_3MgN-*i*-Pr_2	PhH		63	37	44	99
14	CH_3MgNPh_2	PhH		71	29	30	100
15	CH_3MgN-*i*-Pr_2	PhH	$2Ph_3P$	84	16	16	62
16	CH_3MgBr	Ph_2O		100	0	24	35
17	CH_3MgBr	Ph_2O	$2Ph_3P$	100	0	34	55
18	CH_3MgCH_3	Ph_2O		84	16	12	27
19	CH_3MgCH_3	Ph_2O	$2Ph_3P$	91	9	15.3	31.2
20	CH_3MgN-*i*-Pr_2	Ph_2O		76	24	8.6	49.3
21	CH_3MgN-*i*-Pr_2	Ph_2O	$2Ph_3P$	88	12	6.0	35.7
22	CH_3MgNPh_2	Ph_2O		100	0	3.2	50.3
23	CH_3MgNPh_2	Ph_2O	$2Ph_3P$	100	0	3.1	57.8
24		Ph_2O		0	0	0	10.3
25		Ph_2O	$2Ph_3P$	0	0	0	11.2

[a] The molar ratio of reagent to ketone was 1.0:1.0. Reactions were performed at room temperature. [b] Yields were determined by GLC using an internal standard. [c] The mass balance includes the yield of alcohols and recovered ketone.

that the steric bulk of the reagent was only slightly affected. The 2,6-dimethyl groups probably decrease the degree of bonding between magnesium and triphenylphosphine due to steric interference. When triphenylphosphine was added to the reagent in a 1:1 ratio (expt 7), there was no increase in equatorial attack. Also, the addition of triphenylphosphine to Grignard reagent in a 2:1 ratio (expt 8) or dimethylmagnesium (expt 9) had no effect on the sterochemical course of reaction. Excellent stereochemistry, however, was obtained for diphenylamino(methyl)magnesium when $LiClO_4$ was added (expt 11). The mechanism here, however, probably involves complexation of the ketone by the lithium salt.[2]

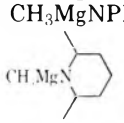
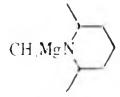
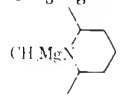
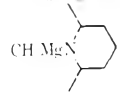
Changing solvents from diethyl ether to benzene gives no increase in equatorial attack, but a change to diphenyl ether, a less basic and more sterically hindered ether than diethyl ether, does give more equatorial attack. For example, diphenylamino(methyl)magnesium gives 100% equatorial attack in diphenyl ether (expt 22) compared to 72% in diethyl ether (expt 2). The effect is less for diisopropylamino(methyl)-magnesium (expt 20), and apparently the diphenyl ether even interferes with the ability of triphenylphosphine to complex the reagents (compare expt 21 and 4). The low yields and low mass balances obtained in all of the reactions with ketone I are due to enolization followed by Aldol condensation reactions in many cases.

Clearly then, CH_3MgNPh_2 is the most stereoselective of the CH_3MgNR_2 compounds, giving 100% equatorial attack when the solvent system is Et_2O–$2Ph_3P$ (expt 5), Et_2O–$LiClO_4$ (expt 11), or Ph_2O (expt 22); however, the yields are low (3.1–9.4%). On the other hand, CH_3MgBr in Ph_2O (expt 16) and Ph_2O–$2Ph_3P$ (expt 17) not only resulted in 100% equatorial attack, but also produced much higher yields (23.6–34.0%) than the CH_3MgNR_2 compounds. Of course, less enolization is expected with the CH_3MgBr compound than for the more basic CH_3MgNR_2 reagents.

In order to study the reagents further and circumvent the problem of enolization, alkylation studies were conducted on ketone II, a nonenolizable ketone. The results are summarized in Table III. The diisopropylamino(methyl)magnesium compound in ether gives the best stereochemical results (expt 26–28, 100% axial alcohol), even without added triphenylphosphine. The addition of triphenylphosphine increases the amount of axial alcohol for the other reagents (expt 33–35 in ether and expt 43–45 in Ph_2O), including methyl Grignard and dimethylmagnesium (expt 31 and 32 and 41 and 42), as expected. In addition, changing solvent from diethyl ether to diphenyl ether also gave increased yields of axial alcohol with all reagents (expt 36–40).

The aryloxy(methyl)magnesium compounds,[9] CH_3MgOR (where OR = O-2,6-*i*-$Pr_2C_6H_3$ and O-2,6-*t*-Bu_2-4-MeC_6H_2),

Table III. Reactions of 2,2,6,6-Tetramethyl-4-*tert*-butylcyclohexanone with Dialkylamino(methyl)magnesium Compounds [a]

expt	reagent	solvent	additive	relative yield,[b] % axial OH	relative yield,[b] % equatorial OH	yield of alcohols, %	mass balance,[c] %
26	CH_3MgBr	Et_2O		71	29	81	104
27	CH_3MgCH_3	Et_2O		86	14	109	109
28	CH_3MgN-*i*-Pr_2	Et_2O		100	0	103	106
29	CH_3MgNPh_2	Et_2O		87	13	118	118
30		Et_2O		97	3	96	103
31	CH_3MgBr	Et_2O	$2Ph_3P$	81	19	94	94
32	CH_3MgCH_3	Et_2O	$2Ph_3P$	95	5	92	92
33	CH_3MgN-*i*-Pr_2	Et_2O	$2Ph_3P$	100	0	80	89
34	CH_3MgNPh_2	Et_2O	$2Ph_3P$	88	12	108	108
35		Et_2O	$2Ph_3P$	100	0	82	83
36	CH_3MgBr	Ph_2O		79	21	106	106
37	CH_3MgCH_3	Ph_2O		89	11	92	92
38	CH_3MgN-*i*-Pr_2	Ph_2O		100	0	99	99
39	CH_3MgNPh_2	Ph_2O		79	21	80	80
40		Ph_2O		100	0	95	103
41	CH_3MgBr	Ph_2O	$2Ph_3P$	90	10	104	104
42	CH_3MgCH_3	Ph_2O	$2Ph_3P$	80	20	104	104
43	CH_3MgN-*i*-Pr_2	Ph_2O	$2Ph_3P$	100	0	91	91
44	CH_3MgNPh_2	Ph_2O	$2Ph_3P$	100	0	28	100
45		Ph_2O	$2Ph_3P$	100	0	89	96

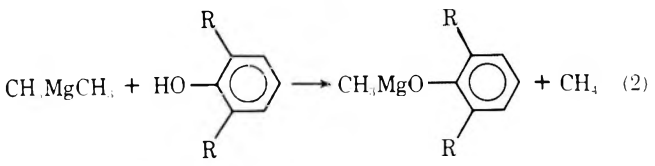
[a] The molar ratio of reagent to ketone was 2.0:1.0. Reactions were performed at room temperature. [b] Yields were determined by GLC using an internal standard. [c] The mass balance includes the yield of alcohols and recovered ketone.

Table IV. Reactions of 4-*tert*-Butylcyclohexanone with Methylmagnesium Aryloxides [a]

expt	reagent	solvent	additive	relative yield,[d] axial OH	relative yield,[d] equatorial OH	yield of alcohols, %	mass balance,[e] %
46	A[b]	Et_2O		56	44	15	68
47	B[c]	Et_2O		87	13	33	74
48	A	Et_2O	$2Ph_3P$	57	43	14	67
49	B	Et_2O	$2Ph_3P$	77	23	39	73
50	A	Ph_2O		0	0	0	0
51	B	Ph_2O		0	0	0	39
52	A	Ph_2O	$2Ph_3P$	0	0	0	0
53	B	Ph_2O	$2Ph_3P$	0	0	0	77

[a] The molar ratio of reagent to ketone was 1.0:1.0. Reactions were performed at room temperature. [b] Reagent A is CH_3MgO-2,6-*t*-Bu_2-4-MeC_6H_2; analysis is provided in Table I. [c] Reagent B is CH_3MgO-2,6-*i*-$Pr_2C_6H_3$; analysis is provided in Table II. [d] Yields were determined by GLC using an internal standard. [e] The mass balance includes the yield of alcohols and recovered ketone.

used in these studies were prepared conveniently and quantitatively by the reaction of dimethylmagnesium with an equal molar amount of the corresponding phenol at room temperature (eq 2, where R = *i*-Pr and *t*-Bu). Preparation and analytical data are summarized in Table I.



(2)

The CH_3MgOR compounds prepared from eq 2 were allowed to react with the two representative ketones, 4-*tert*-butylcyclohexanone (I) and 2,2,6,6-tetramethyl-4-*tert*-butylcyclohexanone (II). The results of these reactions are summarized in Tables IV and V.

The effect of replacing X in the general formula CH_3MgX with the bulkier aryloxy group (OPh) was studied. In the case of ketone I, it was found that reagent A (CH_3MgO-2,6-*t*-Bu_2-4-MeC_6H_2) gave similar results to the methyl Grignard and reagent B (CH_3MgO-2,6-*i*-$Pr_2C_6H_3$) gave a modest increase in the amount of equatorial attack (expt 46 and 47). For both reagents the addition of triphenylphosphine to the reagent in a 2:1 ratio produced little change in the results. Previously, the addition of triphenylphosphine to dialkylamino(methyl)magnesium compounds led to a substantial increase in the amount of equatorial attack, presumably because the steric bulk of the reagent was increased by complexation of the magnesium by Ph_3P (expt 48 and 49). Changing solvent

Table V. Reactions of 2,2,6,6-Tetramethyl-4-*tert*-butylcyclohexanone with Methylmagnesium Alkoxides [a]

expt	reagent	solvent	additive	relative yield,[d] % axial OH	relative yield,[d] % equatorial OH	yield of alcohols, %	mass balance,[e] %
54	A[b]	Et_2O		94	6	95	95
55	B[c]	Et_2O		100	0	89	96
56	A	Et_2O	$2Ph_3P$	89	11	107	107
57	B	Et_2O	$2Ph_3P$	100	0	99	99
58	A	Ph_2O		100	0	89	111
59	B	Ph_2O		100	0	71	89
60	A	Ph_2O	$2Ph_3P$	100	0	32	91
61	B	Ph_2O	$2Ph_3P$	100	0	19	72

[a] The molar ratio of reagent to ketone was 2.0:1.0. Reactions were performed at room temperature. [b] Same as footnote *b* in Table IV. [c] Same as footnote *c* in Table IV. [d] Yields were determined by GLC using an internal standard. [e] The mass balance includes the yield of alcohols and recovered ketone.

from diethyl ether to diphenyl ether (expt 50 and 51) resulted in the loss of all alcohol products, unlike the advantageous effect found with the CH_3MgNR_2 compounds. Enolization, followed by Aldol condensation reactions, was responsible for the low yields and low mass balances.

The problem of enolization was removed by employing a nonenolizable substrate, ketone II. Excellent stereochemical results (100% axial alcohol) were obtained for reagent B in diethyl ether even without added triphenylphosphine (expt 55). Changing solvents from diethyl ether to diphenyl ether gave an increase in equatorial attack for reagent A (from 94 to 100% axial alcohol), and so both reagents A and B give 100% equatorial attack in Ph_2O. As in the case of alkylation with CH_3MgNR_2 compounds, the addition of Ph_3P (expt 60 and 61) to ketones I and II in Ph_2O has a detrimental effect on the yield.

It is evident from the data that the stereoselectivity of dialkylamino- and aryloxy(methyl)magnesium compounds as alkylating agents depends on several factors. However, the steric requirement of the reagent seems to be the most important factor. Of course, the effectiveness of a reagent can be increased if the ketone contains a group close enough to the carbonyl group to supply some steric hindrance at the carbonyl site. Presumably, for steric reasons the choice of solvent also has an influence. Diphenyl ether is a more effective solvent than diethyl ether, perhaps because the association of the reagent changes, being more associated in diphenyl ether than in diethyl ether. If indeed the degree of association of the reagent is nearly the same in both solvents or if only the monomer reacts regardless of the concentration of associated species, Ph_2O solvated to the magnesium compounds would be expected to provide significantly greater steric hindrance than the reagent solvated to diethyl ether if the degree of solvation is the same. Past experience would indicate that it is the monomer that is reacting, and these results indicate that the degree of solvation of the magnesium compounds with Ph_2O and Et_2O is approximately the same.

The ease of preparation of these alkylating reagents in addition to the excellent stereochemistry observed indicates that these dialkylamino- and aryloxy(methyl)magnesium reagents may have considerable potential as stereoselective alkylating agents, especially for nonenolizable substrates.

Acknowledgment. We wish to thank the National Science Foundation (Grant No. MPS 7504127) for partial support of this work.

Registry No.—CH_3Br, 74-83-9; 4-*tert*-butylcyclohexanone, 98-53-3; 2,2,6,6-tetramethyl-4-*tert*-butylcyclohexanone, 49714-25-2; *cis*-1,2,2,6,6-pentamethyl-4-*tert*-butylcyclohexan-1-ol, 67209-26-1; *trans*-1,2,2,6,6-pentamethyl-4-*tert*-butylcyclohexan-1-ol, 67209-27-2.

References and Notes

(1) E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975).
(2) E. C. Ashby, J. J. Lin, and J. J. Watkins, *Tetrahedron Lett.*, 1709 (1977).
(3) E. C. Ashby, J. J. Lin, and A. B. Goel, *J. Org. Chem.*, in press.
(4) D. R. Shriver, "The Manipulation of Air Sensitive Compounds", McGraw-Hill, New York. N.Y., 1969.
(5) E. C. Ashby and R. Arnott, *J. Organomet. Chem.*, **14**, 1 (1968).
(6) (a) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Am. Chem. Soc.*, **92**, 5734 (1970); (b) P. Belanger, C. Freppel, D. Tizane, and J. C. Richer, *Can. J. Chem.*, **49**, 1985 (1971).
(7) (a) G. E. Coates, M. L. H. Green, and K. Wade, "Organometallic Compounds", Vol. 1, Meuthen and Co., London, 1967; (b) J. Nackashi, Ph.D. Thesis, Georgia Institute of Technology, 1974.
(8) H. O. House and W. L. Respess, *J. Org. Chem.*, **30**, 201 (1965).
(9) (a) See ref 7a. (b) J. P. Oliver, Ph.D. Thesis, Georgia Institute of Technology, in progress. (c) E. C. Ashby, J. Nackashi, and G. E. Parris, *J. Am.Chem. Soc.*, **97**, 3162 (1975).

Reactions of Cyclometalated Palladium Complexes with Organolithium Compounds or Grignard Reagents. Selective Ortho Alkylation and Arylation of Benzaldehydes, Azobenzenes, and Tertiary Benzylic Amines

Shun-Ichi Murahashi,* Yoshihiro Tamba, Masaaki Yamamura, and Noriaki Yoshimura

Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka, Japan, 560

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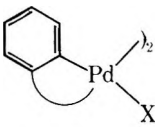
Cyclometalated complexes, di-μ-chloro-bis[2-(phenylazo)phenyl]dipalladium (**2**), di-μ-chloro-bis[2-(*N*,*N*-dimethylaminomethyl)phenyl]dipalladium (**3**), and di-μ-chloro-bis[2-(*N*-phenylformimidolyl)phenyl]dipalladium (**4**), can undergo coupling reactions with either organolithium compounds or Grignard reagents in the presence of triphenylphosphine, giving the corresponding ortho-substituted aromatic compounds highly efficiently. 2-Substituted complexes of **4** (**11**–**13**) were prepared from the corresponding 2-substituted benzaldehyde in over 94% yield. Similar methylation reactions of **11**–**13**, followed by hydrolysis, gave 2,6-disubstituted benzaldehydes **15**, **21**, and **22** in high yields. Secondary alkyllithium compounds undergo the cross-coupling reaction accompanied by alkyl group isomerization from secondary to primary. The products are assumed to be formed via a nucleophilic attack of the carbon nucleophile on the phosphine-coordinated palladium monomer of **1**, giving arylalkylpalladium intermediates, which form products by reductive coupling.

Numerous compounds containing a transition metal σ bonded to an aromatic ring derived by cyclometalation have been reported in recent years. These compounds encompass a variety of transition metals and also different types of substitution on the benzene ring.[1-4] Structural studies of the complexes have received widespread attention.[1-5] On the other hand, few studies have been carried out aiming at using these complexes for organic synthesis. Ortho deuteriation can be performed by reductive cleavage of metalated compounds with $LiAlD_4$[6] or the specific ortho hydrogen/deuterium exchange on treatment of complexes such as $RhCl[P(OPh_3)]_3$ or $RuHCl(PPh_3)_3$ with D_2.[4,7] The ortho positions of azobenzene are chlorinated upon reaction with chlorine in the presence of catalytic quantities of $PdCl_2$.[8] Carbonylation[9-12] or reaction with isocyanides[13] of ortho palladation products from α-arylnitrogen derivatives and palladium salts provides a convenient process for synthesis of various heterocyclic compounds. Cyclopalladation complexes react with α olefins,[14] acrylic esters,[15] and vinyl ketones[16] to give ortho-substituted arylalkenes. Further, a method for the regiospecific attachment of carbon nucleophiles to the β carbon of allylic sulfides and amines using palladium complexes recently has been developed.[17]

In this paper we describe reactions of cyclometalation products (**1**) of azobenzene,[6] tertiary benzylic amines,[18,19] and



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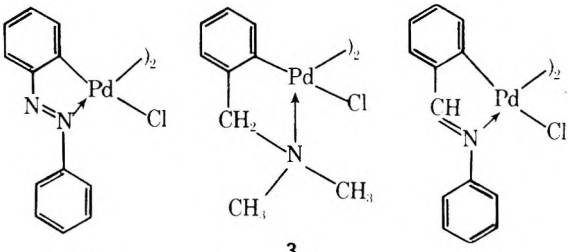
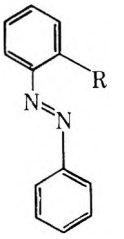
Schiff bases[20,21] with either organolithium compounds or Grignard reagents, which provide a convenient method for synthesis of ortho-substituted aromatic compounds and give important mechanistic insight into the carbon–carbon bond formation via palladium complexes.[22]

Results and Discussion

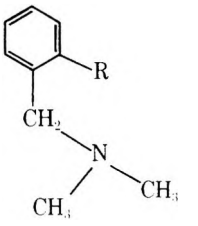
The Reaction of the Complex 1 with Alkyllithium Compounds or Grignard Reagents. The reactions of cyclometallation products **1**, such as di-μ-chloro-bis[2-(phenylazo)phenyl]dipalladium (**2**), di-μ-chloro-bis[2-(*N*,*N*-dimethylaminomethyl)phenyl]dipalladium (**3**), and di-μ-chloro-bis[2-(*N*-phenylformimidolyl)phenyl]dipalladium (**4**), with alkyllithium compounds were carried out in ether at 0–5 °C under heterogeneous conditions. Treatment of **2** with methyllithium produced 2-methylazobenzene (**5b**) and azobenzene (**5a**) in 55 and 45% yields, respectively. The similar reaction of **2** with phenyllithium gave **5c** (42%) and **5a** (58%).



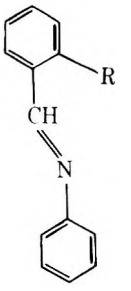
2 **3** **4**



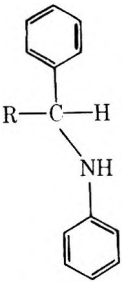
5a, R = H
b, R = CH_3
c, R = C_6H_5
d, R = C_4H_9



6a, R = H
b, R = CH_3
c, R = $CH{=}CH_2$
d, R = C_2H_5
e, R = C_4H_9



7a, R = H
b, R = CH_3
c, R = t-C_4H_9
d, R = C_6H_5
e, R = C_4H_9



8a, R = t-C_4H_9
b, R = C_6H_5
c, R = C_4H_9

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Table I. Reaction of the Complexes 2–4 with Alkyllithium Compounds and Grignard Reagents[a]

complexes	RLi or RMgBr	product yield,[b] % ortho-substituted products	reductive products	addition products
2	CH_3Li	**5b** (55)	**5a** (44)	
2	C_6H_5Li	**5c** (42)	**5a** (58)	
2	n-C_4H_9Li	**5d** (5)	**5a** (89)	
3	CH_3Li	**6b** (49)	**6a** (47)	
3	CH_2=$CHMgBr$	**6c** (44)	**6a** (31)[c]	
3	C_2H_5MgBr	**6d** (2)	**6a** (80)	
3	n-C_4H_9Li	**6e** (5)	**6a** (80)	
4	CH_3Li	**7b** (76)	**7a** (21)	
4	t-C_4H_9Li	**7c** (28)	**7a** (34)	**8a** (14)
4	C_6H_5Li	**7d** (22)		**8b** (48)
4	C_6H_5MgBr	**7d** (28)		**8b** (28)
4	n-C_4H_9Li	**7e** (1)		**8c** (64)

[a] Palladium complex (5.5 mmol) was reacted with organolithium compounds (13 mmol) in ether at room temperature for 3–4 h. [b] VPC yield using internal standard. [c] Additional product was 6d (13%).

Table III. Effect of Ligands for the Reaction of 2 with Methyllithium[a]

ligand (L)	product yield, % compd **5b**	compd **5a**
none	55	45
PPh_3	91	0
$P(OPh)_3$	2	0
$P(n$-$Bu)_3$	56	11
$(Ph_2PCH_2)_2$	18	0

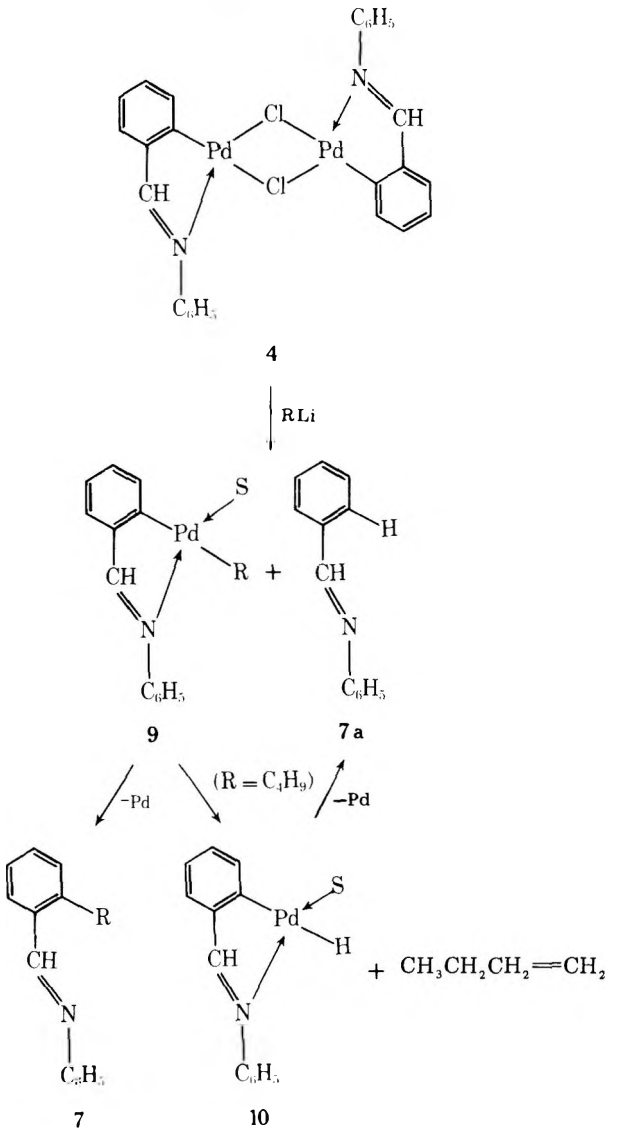
[a] To the suspension of **2** (0.5 mmol) and PPh_3 (2.0 mmol) in benzene was added an ethereal solution of methyllithium (1.0 mmol).

The structures of the products were established either by comparison of spectral data with those of authentic samples or by elemental analyses and spectral data as summarized in Table II (see supplementary material). The ortho-substituted products **5b** or **5c** and reductive product **5a** were each obtained in approximately 50% yield. On the contrary, **5a** was obtained almost exclusively (89%) along with a small amount of **5d** (5%) upon treatment with n-butyllithium.

Similar reactions of complexes **3** and **4** with alkyllithium compounds also gave the corresponding 1-alkyl-substituted benzylamines (**6**) and Schiff bases (**7**), respectively, as shown in Table I. o-(*tert*-Butyl)benzaldehyde was prepared upon treatment of **4** with *tert*-butyllithium followed by acid hydrolysis in 25% yield. The previous method for synthesis of this aldehyde required six steps, and the yield was poor.[23] The ortho alkylation products of **4** are sometimes contaminated with N-(α-substituted)benzylaniline (**8**), derived from the addition of alkyllithium compounds into the carbon–nitrogen double bond of the Schiff bases. Grignard reagents also react with these complexes. Thus, treatment of **3** with vinylmagnesium bromide gave **6a** (31%), **6c** (31%), and **6d** (13%).

The reaction of complex **4** with alkyllithiums can be envisioned to occur by Scheme I. The first step would be nucleophilic substitution of the chloride group by the alkyllithium, giving intermediate **9** accompanied by splitting of the bridge structure to liberate **7a**.[24] Subsequent reductive coupling of **9** would produce **7**. The predominant formation of **7a** upon treatment with n-butyllithium is consistent with this scheme. Butylpalladium complex **9** (R = C_4H_9) undergoes facile β elimination of a palladium hydride species[26] to give the hydride complex **10**, which is the precursor of **7a**.

Scheme I



The Reaction of Complex 1 with Organolithium Compounds or Grignard Reagents in the Presence of Triphenylphosphine. In view of selective syntheses of ortho-substituted **5** from **2**, the loss of the one part of azobenzene upon treatment with alkyllithium must be avoided. Should the reaction proceed as depicted in Scheme I, the preliminary splitting of **2** into two phosphine-coordinated monomer complexes[21,27] is necessary.

For this reason, chloro[2-(phenylazo)phenyl]bis(triphenylphosphine)palladium (**23**) was prepared by treatment of **2** with excess triphenylphosphine in methanol (86% yield). The methylation reaction of **23** with methyllithium in benzene/ether gave **5b** in 98% yield. Moreover, the reaction of **2** with methyllithium in the presence of 4 molar equiv of triphenylphosphine gave **5b** in 91% yield, indicating that the isolation of **23** is unnecessary. A similar reaction of **3** with methyllithium in the presence of 4 equiv of triphenylphosphine afforded 2-methyl-*N*,*N*-dimethylbenzylamine in 99% yield. Further, the reaction of **4** with methyllithium followed by acid hydrolysis gave o-methylbenzaldehyde (**14**) in 95% yield. A study of the ligand effect on the reaction of **2** with methyllithium showed that triphenylphosphine gave the best result among the ligands examined, as shown in Table III.

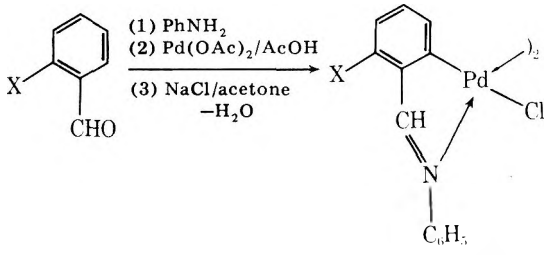
If the reaction is performed twice on the cyclometallation products, 2,6-dialkyl-substituted aromatic compounds, which are difficultly accessible, can be prepared readily. In anticipation of this double treatment, Schiff base–palladium complexes of ortho-substituted benzaldehydes, **11–13**, were

Table IV. Reaction of Palladium Complexes of Schiff Bases with Organolithium Compounds or Grignard Reagents in the Presence of Triphenylphosphine[a]

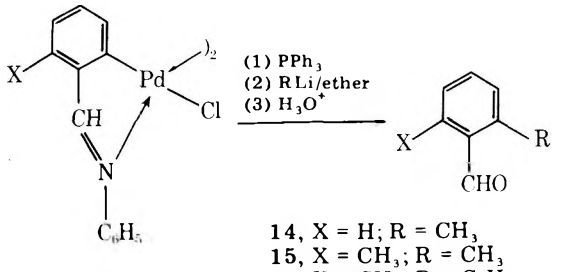
complexes[b]	RLi (RMgX)	ratio of PPh_3/Pd	products[c]	yield,[d] %
2	CH_3Li	4	**5b**	91
3	CH_3Li	4	**6b**	99
4	CH_3Li	2	**14**	90
4	CH_3Li	4	**14**	95
11	CH_3Li	4	**15**	86
11	CH_3MgX[e]	4	**15**	70
11	C_3H_7Li	4	**19**	90
11	C_4H_9Li	4	**16**	75
11	C_6H_5Li	4	**17**	60
12	CH_3Li	4	**21**	85
13	CH_3Li	4	**22**	60

[a] A mixture of palladium complex (0.5 mmol) and PPh_3 (2.0 mmol) was used with organolithium compounds (1.0 mmol) in ether at room temperature. [b] Complexes can be prepared in over 95% yield. [c] Obtained by acid hydrolysis. [d] Based upon the palladium complexes of Schiff bases. [e] A 4 molar equiv amount of CH_3MgX was reacted.

synthesized since the expected products, 2,6-disubstituted benzaldehydes, are difficultly accessible, useful compounds. The reaction of Schiff bases, derived from the corresponding aldehydes and aniline quantitatively, with equimolar quantities of palladium acetate in acetic acid at reflux followed by treatment with sodium chloride gave the expected palladium complexes in 95–96% yields. The methylation of di-μ-chloro-bis[o-(*N*-phenylformimidoyl)-2-methylphenyl]dipalladium (**11**) with methyllithium in the presence of 4 molar equiv of triphenylphosphine followed by hydrolysis gave 2,6-dimethylbenzaldehyde (**15**)[28] in 86% yield. The yield of **15** is dependent upon the added ligand in the order of P(*n*-$C_4H_9)_3$ (3%) < none (12%) < $P(OC_6H_5)_3$ (26%) < $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$ (75%) < $P(C_6H_5)_3$ (86%), indicating that triphenylphosphine is best. Other examples of the synthesis of 2,6-disubstituted benzaldehydes are summarized in Table IV. The structural assignment of these products was established by mass, IR, and NMR spectral data as shown in Table II. Unexpectedly, 2,6-disubstituted benzaldehydes **16–22** are unknown compounds, indicating the difficulty of their synthesis.[29] Grignard reagents are also applicable to this reaction; however, in this case the presence of 4 molar equiv of triphenylphosphine and the Grignard reagents is required because of the lower nucleophilicity of Grignard reagents in comparison with alkyllithiums. Actually, the yield of **15** from **11** decreased to 70% when methylmagnesium bromide was used instead of methyllithium. Acetate ligands can be replaced as well as chloride ligand. Thus, the reaction of di-μ-acetato-bis[2-(*N*-phenylimidoyl)-6-methylphenyl]dipalladium with methyllithium in the presence of PPh_3 followed by hydrolysis afforded **15** in 90% yield.



4, X = H (yellow)
11, X = CH_3 (yellow)
12, X = OCH_3 (yellow)
13, X = Cl (green)



14, X = H; R = CH_3
15, X = CH_3; R = CH_3
16, X = CH_3; R = C_4H_9
17, X = CH_3; R = C_6H_5
18, X = CH_3; R = $CH(CH_3)_2$
19, X = CH_3; R = C_3H_7
20, X = CH_3; R = $CH(CH_3)CH_2CH_3$
21, X = OCH_3; R = CH_3
22, X = Cl; R = CH_3

Table V. Ligand Effect of Triphenylphosphine in the Reaction of Palladium Complex 11 with *n*-Propyllithium or *n*-Butyllithium

alkyllithium	relative ratio of PPh_3/Pd	products,[a] (yield, %)
n-C_3H_7Li	0	**19** (10), **14** (73)
	2	**19** (37), **14** (45)
	4	**19** (90), **14** (9)
	8	**19** (68), **14** (1)
n-C_4H_9Li	0	**16** (5), **14** (91)
	4	**16** (75), **14** (4)

[a] Products were analyzed after acid hydrolysis.

Selective ortho alkylation of **11** can be depicted as shown in Scheme II. Dimeric palladium complex **11** can be converted into 2 mol of the phosphine-coordinated palladium complex **24** upon treatment with 4 equiv of PPh_3. The reaction with alkyllithium would lead to the σ-alkylarylpalladium complex **26** by nucleophilic substitution with the carbon nucleophile at the palladium of **24**. Actually, Parshall has isolated $FC_6H_4PdR(PEt_3)_2$, in which there are two C-bonded ligands, by the reaction of phenyl or methyl Grignard reagents with $FC_6H_5PdBr(PEt_3)_2$.[30] An alternative process leading to complex **26** may be substitution via palladium ate complex **25**.[31,32] Facile reductive coupling[30,33,34] of **26** would lead to **28**, which is the precursor of **14**.

In the case of the reaction of alkyllithiums bearing β hydrogens, the β elimination of **26** accompanied by loss of an alkene would lead to palladium hydrido complex **27**, which would readily undergo reductive coupling to give **29**. Indeed, when butyllithium was reacted with complex **11** in the presence of 4 equiv of triphenylphosphine, the desired 2-methyl-6-butylbenzaldehyde (**16**) was obtained in 75% yield along with the reductive coupling product, 2-methylbenzaldehyde (**14**; 9%). In the absence of PPh_3, however, **16** and **14** were obtained in 10 and 90% yields, respectively. The addition of PPh_3 retards the β elimination of the palladium hydride species in **26** drastically. The best yield of **19**, for example, was obtained when the relative ratio of triphenylphosphine to palladium was 4, as indicated in Table V. This is presumably due to an increase of stability of the σ-alkylpalladium intermediate **26** by coordination with PPh_3.[35] It is well known that phosphine ligand facilitates the π–σ conversion of π-allylpalladium chloride complexes.[36]

Secondary alkyllithium compounds also undergo the cross-coupling reaction, accompanied by alkyl group isomerization from secondary to primary.[37] The reaction of **11** with isopropyllithium in the presence of 2 molar triphenylphosphine followed by hydrolysis gave 2-methyl-6-isopropylbenzaldehyde (**18**; 6%), 2-methyl-6-propylbenzaldehyde (**19**; 5%), and 2-methylbenzaldehyde (**14**; 85%). Likewise, the reaction

of 11 with 1-methylpropyllithium afforded 2-methyl-6-(1-methylpropyl)benzaldehyde (**20**; 10%), 2-methyl-6-butylbenzaldehyde (**16**; 6%), and **14** (70%). The yields of alkylation products **16** and **18–20** depend upon the amount of phosphine ligand present. Reactions of primary alkyllithium compounds (Table V) are more strongly influenced than those of secondary alkyllithiums (Table VI). It is noteworthy that bidentated 1,2-bis(diphenylphosphino)ethane gave a relatively good result.

The initially formed complex **32**, bearing the Pd–$CH(CH_3)R$ bond, undergoes reductive coupling to give **30** (Scheme III). The rapid isomerization from secondary to primary alkylpalladium (**34**) proceeds via a hydride–olefin intermediate (**33**), a precursor of **14** as shown in Scheme IV. For the formation of **14** from **11**, an alternative process involving protonolysis[30] or homolytic cleavage of the Pd–C bond,[38] leading to a phenyl radical which abstracts hydrogen, was excluded by the following results. Although protonolysis of 11 with DCl[39] in benzene/D_2O gave 2-deuterio-6-methylbenzaldehyde, an NMR study showed that the H^2 proton of **14**, obtained from the reaction of 11 with isopropyllithium in the presence of PPh_3 followed by quenching with DCl, contained 0.10 *d*, indicating that only 10% of **14** was formed by protonolysis. The pyrolysis of **11** in benzene-d_6 gave **14**, whose H^2 proton contained only 0.04 *d*.

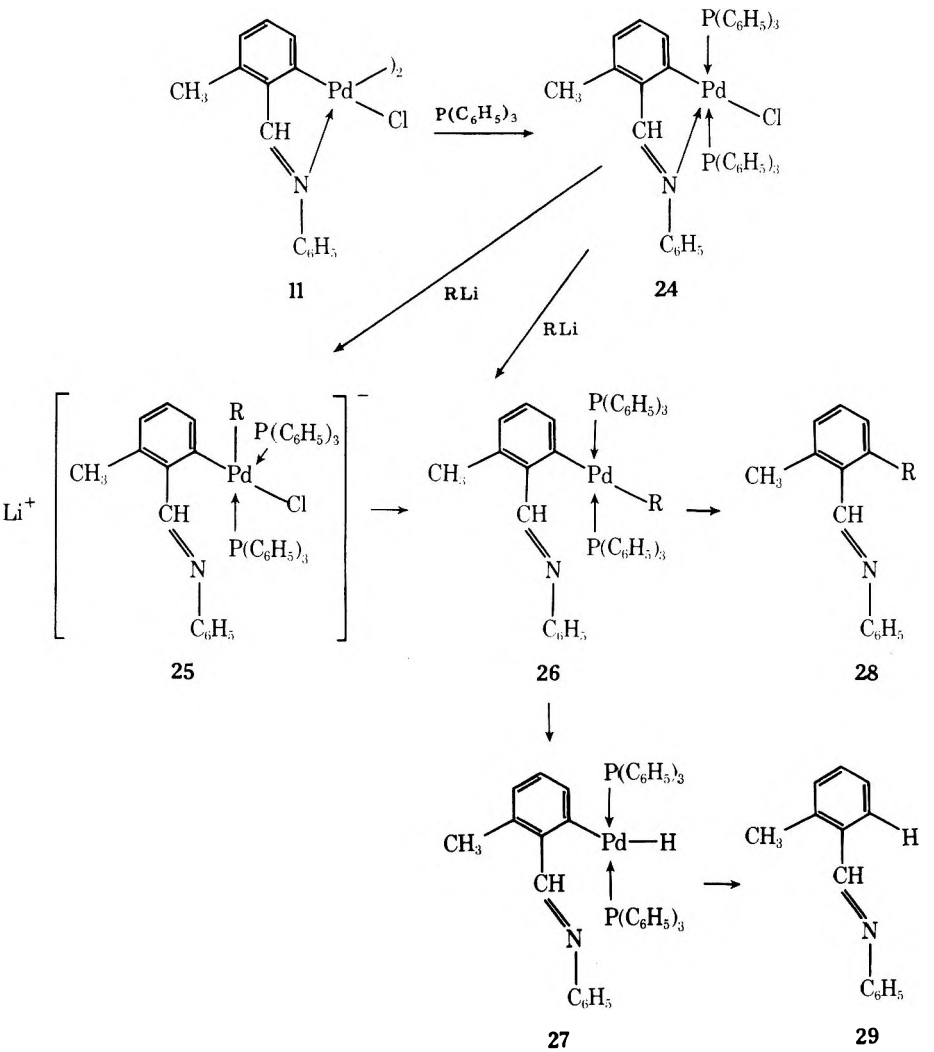
The reaction of 11 with propyllithium in the presence of PPh_3 gave **19** and **14** in 37 and 45% yields, respectively; however, none of the isomerized product **18** could be detected among the products. This may be due to the release of steric strain between the branched alkyl chain and the phenyl rings of the triphenylphosphine ligands rather than an electronic effect. An increase in the electron density on palladium owing to the electron-donating ligand seems not to facilitate the σ–π conversion.[35,36] The extent of the isomerization in the reaction of 11 with isopropyllithium was independent of the ligands used as seen from the results shown in Table VI. The present

Table VI. Reaction of Palladium Complex 11 with *sec*-Alkyllithiums[a]

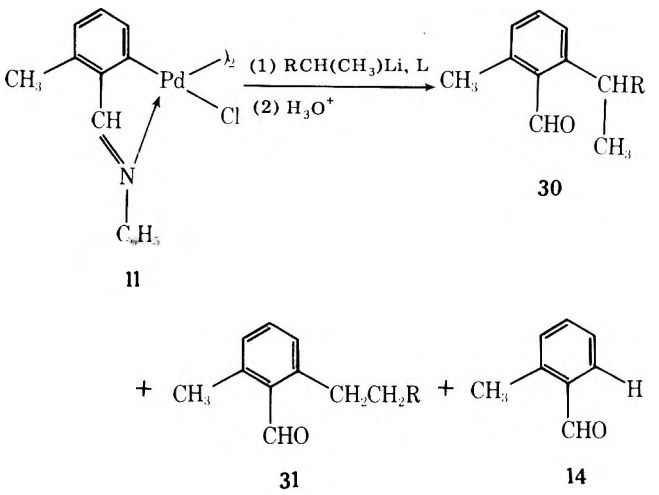
$R(CH_3)CHLi$, R	ligand (L)	relative ratio L/Pd	product,[b] (yield, %)[c]
CH_3	none		**18** (0), **19** (0), **14** (96)
CH_3	PPh_3	1	**18** (5), **19** (6), **14** (68)
CH_3	PPh_3	2	**18** (6), **19** (5), **14** (85)
CH_3	PPh_3	4	**18** (15), **19** (8), **14** (14)
CH_3	PPh_3	8	**18** (24), **19** (7), **14** (20)
CH_3	PPh_3	16	**18** (30), **19** (8), **14** (5)
CH_3	PBu_3	1	**18** (4), **19** (2), **14** (90)
CH_3	PBu_3	2	**18** (7), **19** (4), **14** (59)
CH_3	PBu_3	4	**18** (11), **19** (4), **14** (22)
CH_3	$Ph_2CH_2CH_2PPh_2$	2	**18** (18), **19** (8), **14** (15)
CH_3	$P(OPh)_3$	2	**18** (9), **19** (8), **14** (80)
CH_2CH_3	none		**20** (1), **16** (0), **14** (65)
CH_2CH_3	PPh_3	2	**20** (10), **16** (6), **14** (70)

[a] *sec*-Alkyllithiums were added to an equimolar amount of complex 11 in the presence of a ligand in benzene/hexane at room temperature. [b] Obtained by acid hydrolysis. [c] VPC yield.

Scheme II

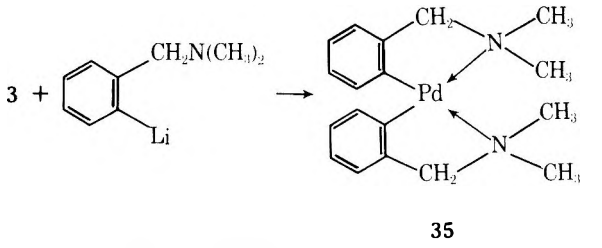


Scheme III

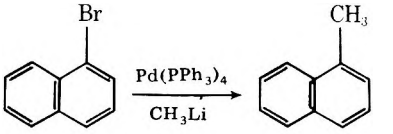


work is the first example of isomerism in palladium alkyls which are in thermal equilibrium. Generally, β elimination of palladium hydride species from alkylpalladium compounds proceeds readily to give alkenes.[26] Similar alkyl group isomerizations have been reported in alkyliridium,[40] -nickel,[41,42] -gold,[43] and -titanium[44] complexes. It is noteworthy that the isomerization of secondary alkylnickel complexes to primary alkyls is strongly dependent upon the electronic nature of the phosphine ligand.[41]

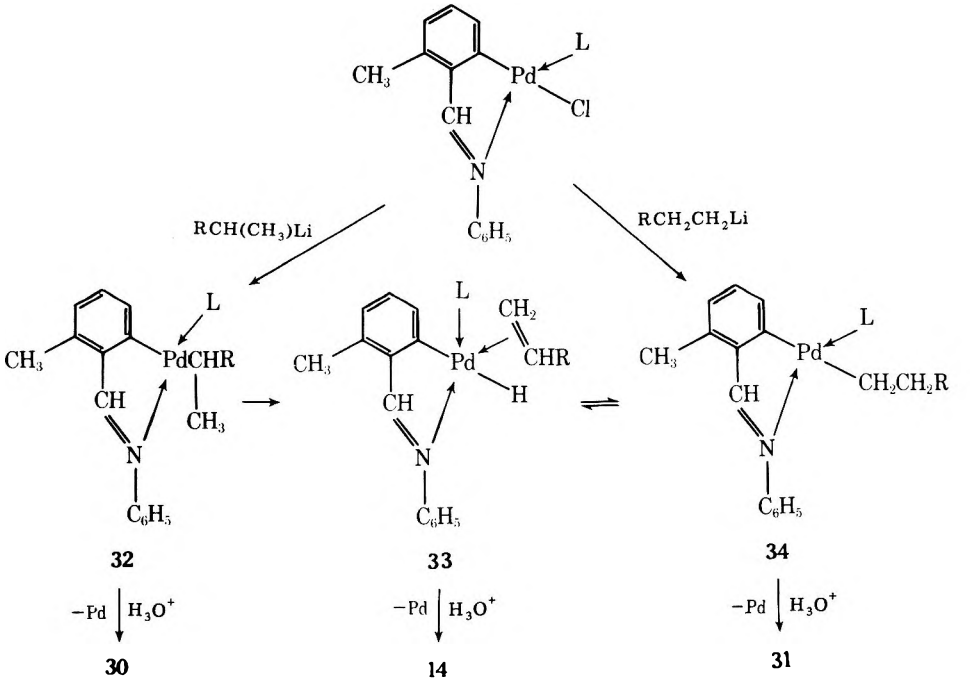
To determine the effect of a carbon ligand toward the cross-coupling reaction, *cis*-bis[2-(*N*,*N*-dimethylaminomethyl)phenyl]palladium (**35**) was prepared by the reaction of **3** with *o*-lithio-*N*,*N*-dimethylbenzylamine in 33% yield. This complex is identical with the cis complex previously formed from bis(dimethyl sulfide)palladium dichloride and 2 mol of *o*-lithio-*N*,*N*-dimethylamine.[45] The methylation of **35** with methyllithium gave **6b** in only 8% yield along with **6a** (90%). The addition of PPh_3 increases the yield of **6b** by the coordination of phosphine to palladium rather than the chelating of nitrogen of **35**, which stabilizes the $ArPdCH_3L_n$ intermediate. Thus, in the presence of 2 mol of PPh_3, the same reaction gave **6b** in 35% yield in addition to **6a** (60%). In comparison with the methylation of **3**, where **6b** was obtained in 49 or 99% yield, in the absence or presence of PPh_3, respectively, the yield of the methylation products of **35** is rather low. This may be attributed to the replacement of the methyl moiety of methyllithium with one of the aryl groups of **35** via an unstable palladium ate complex, yielding *o*-lithio-*N*,*N*-dimethylbenzylamine[32] or 2-(*N*,*N*-dimethylmethyl)phenyl radical,[46] both of which are precursors of **6a** if the reaction proceeds by Scheme II. Arylpalladium complexes generally have about the same stability as the methyl analogues.[35,38]



The reaction involves intermediacy of arylalkylpalladium species formed by nucleophilic attack of a carbon nucleophile on palladium in the arylpalladium complex. In support of this mechanism, alkyl isomerization from secondary to primary occurs under the reaction conditions. Furthermore, this alkylation proceeds only in the case of the harder carbon nucleophiles, such as alkyllithium or Grignard reagents, but not in the case of softer carbanions, which have been shown to attack carbon directly on the face of the olefin[47] and π-allyl units[48] opposite to that of palladium. Actually, arylpalladium species derived from oxidative addition[30,49] of aryl halides to zerovalent palladium complexes react with alkyllithium compounds, producing the corresponding coupling products, although for simple alkylations the nickel-catalyzed cross coupling with Grignard reagents[50,51] seems more practical. Treatment of α-bromonaphthalene with 1 equiv of tetrakis(triphenylphosphine)palladium in benzene at reflux followed

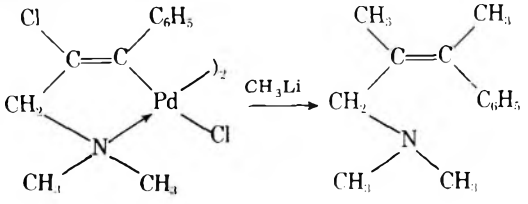


Scheme IV



by addition of methyllithium gave α-methylnaphthalene in 90% yield. Similarly, β-bromonaphthalene was converted into β-methylnaphthalene in 88% yield.

Finally, for comparison with the σ-aryl metalocyclic palladium complexes, σ-vinyl metalocyclic palladium complexes were subjected to the alkylation reaction, aiming at the stereoselective synthesis of allylamines. However, preliminary results with the methylation of di-μ-chloro-bis(2-chloro-3-*N*,*N*-dimethylamino-1-phenylpropenyl)dipalladium (**36**)[52] showed that it proceeded nonstereoselectively. Thus, treatment of **36** with 4 equiv of methyllithium gave *N*,*N*-dimethyl-*cis*-α,β-cinnamylamine (*cis*-**37**), the trans isomer (*trans*-**37**), and 3-(*N*,*N*-dimethylamino)-3-methylbut-1-yne in a relative ratio of 81:11:8, indicating that complicated processes are involved.



36 **37**

In summary, the reaction of ortho palladation products with organolithium compounds in the presence of triphenylphosphine provides direct access to 2- and 2,6-substituted azobenzenes, *N*,*N*-(dimethylaminomethyl)benzenes, and benzaldehydes, which are difficultly accessible. In most instances, these new methods are a marked improvement over existing methods[53] and should find application in the synthesis of complex molecules.

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer. The NMR spectra were obtained on a JNM-4H spectrometer, and chemical shifts are reported in δ values downfield from the internal standard tetramethylsilane. Mass spectra were taken on a Hitachi RSM-4 mass spectrometer. Vapor-phase chromatography was carried out with a Jeol-20K by using a 1 m analytical column packed with Carbowax 20M on Chromosorb or a 1 m column packed with Apieason L.

Di-μ-chloro-bis[2-(phenylazo)phenyl]dipalladium (2). This material was prepared by the method of Cope.[5]

Di-μ-chloro-bis[2-(*N*,*N*-dimethylaminomethyl)phenyl]dipalladium (3). The preparation of this compound has also been described by Cope.[6]

Di-μ-chloro-bis[2-(*N*-phenylformimidoyl)phenyl]dipalladium (4). This complex was prepared by the procedure of Onoue and Moritani.[20]

Reactions of Complex 2 with Organolithium Compounds. The following procedures are typical of those used to obtain the data in Table I.

(a) To a suspension of **2** (3.5 g, 5.5 mmol) in ether (30 mL) was added a solution of methyllithium (16.5 mmol) in ether (100 mL) with stirring. After continuous stirring for 4 h, the precipitated palladium black was filtered and the ether solution was treated with water and dried over $MgSO_4$. Distillation [bp 110–113 °C (1.5 mmHg)] gave red crystalline material (1.95 g) which was shown to contain azobenzene (**5a**; 44%) and 2-methylazobenzene (**5b**; 55%) by VPC analysis.

(b) Complex **2** (3.5 g, 5.5 mmol) was reacted with phenyllithium (13.5 mmol) in ether (50 mL). The products were subjected to chromatography on alumina. Elution with a mixture of petroleum ether/benzene gave biphenyl (0.6 g, 42 mmol), azobenzene (1.1 g, 58%), and 2-phenylazobenzene (**5c**; 1.2 g, 42%).

(c) To a suspension of **3** (3.0 g, 5.4 mmol) in ether was added a solution of vinylmagnesium bromide (16.0 mmol) in THF (15 mL) with stirring. After additional stirring for 1 h, the reaction mixture was heated at reflux for 30 min. Palladium black was filtered and washed with ether. The filtrate was extracted with ether. The ether extract was washed with water and dried over $MgSO_4$. Removal of the solvent followed by distillation gave 1.29 g of an oil [bp 80–100 °C (67 mmHg)] which contained **6a** (43%),[25] **6b** (13%), and **6c** (31%).

(d) To a suspension of **4** (3.3 g, 5.1 mmol) in ether (50 mL) was added a solution of phenyllithium (10.8 mmol) in ether (30 mL) with stirring. After additional stirring for 5 h, the reaction mixture was treated similarly as described in c. Distillation [140–165 °C (2 mmHg)] gave the products (2.28 g). Preparative VPC gave **7d** (22%) and *N*-phenyl-α-phenylbenzylamine (**8d**; 48%): mass spectrum, *m/e* 250 (M^+); IR ν (N–H) 3400 cm^{-1}.

Chloro[2-(phenylazo)phenyl]bis(triphenylphosphine)palladium (23). A suspension of di-μ-chloro-bis[2-(phenylazo)phenyl]-dipalladium (**2**) (0.64 g, 1 mmol) and triphenylphosphine (1.05 g, 4 mmol) in methanol (20 mL) was stirred for 8 h. Filtration followed by washing with a small amount of methanol gave 0.64 g of **23** (86%), mp 176–178 °C dec. Anal. Calcd for $C_{48}H_{39}N_2ClP_2Pd$: C, 68.02; H, 4.61; N, 3.39; Cl, 4.19. Found: C, 68.67; H, 4.46; N, 3.33; Cl, 4.43.

Reaction of Complex 23 with Methyllithium. To a suspension of **23** (0.74 g, 1.0 mmol) in dry benzene (14 mL) was added methyllithium (0.8 mL, 1.0 mmol) in ether under nitrogen. After additional stirring for 1 h, water was added. The ethereal extract was dried over $MgSO_4$ and subjected to VPC analysis (Carbowax 20M) using naphthalene as an internal standard, which showed that 2-methylazobenzene[54] was obtained in 98% yield.

Reaction of Di-μ-chloro-bis[2-(phenylazo)phenyl]dipalladium (2) with Methyllithium in the Presence of a Phosphine Ligand. A mixture of **2** (0.32 g, 0.5 mmol) and PPh_3 (0.52 g, 2.0 mmol) in benzene (15 mL) was stirred under nitrogen for 30 min at room temperature. To the resulting suspension was added an ethereal solution of methyllithium (0.8 mL, 1.0 mmol) with stirring, and the mixture was stirred for 1 h. The reaction mixture was poured into water and filtered off. The ethereal extract of the filtrate was washed with water and dried over $MgSO_4$. Filtration followed by evaporation gave 2-methylazobenzene (**5b**). The yield was determined to be 91% by VPC analysis (Carbowax 20M) using naphthalene as an internal standard. A similar reaction in the presence of other ligands was carried out, and the results are summarized in Table III.

Reaction of Di-μ-chloro-bis[2-(*N*,*N*-dimethylaminomethyl)phenyl]dipalladium (3) with Methyllithium in the Presence of Triphenylphosphine. A mixture of **3** (0.28 g, 0.5 mmol) and PPh_3 (0.52 g, 2.0 mmol) in benzene (15 mL) was stirred under nitrogen at room temperature for 30 min. A solution of methyllithium in ether (1.0 mmol, 0.8 mL) was added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and filtered. The ethereal extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 2-methyl-*N*,*N*-dimethylbenzylamine. The yield was determined to be 99% by VPC analysis: mass spectrum, *m/e* 149; NMR (CCl_4) δ 2.20 (s, 6 H), 2.33 (s, 3 H), 3.33 (s, 2 H), 7.04 (m, 4 H).

Reaction of Di-μ-chloro-bis[2-(*N*-phenylformimidoyl)phenyl]dipalladium (4) with Methyllithium in the Presence of Triphenylphosphine. A mixture of **4** (0.33 g, 0.50 mmol) and PPh_3 (0.52 g, 20 mmol) in benzene was stirred under nitrogen at room temperature for 30 min. To the resulting suspension was added ethereal methyllithium (1.0 mmol, 1 mL). After additional stirring for 1 h, water (20 mL) was added with stirring. The mixture was filtered off. The ethereal extract was washed with water, dried over $MgSO_4$, and distilled. VPC analysis showed that the yield of *N*-(2-methylbenzylidene)aniline was 95%: mass spectrum, *m/e* 195; NMR ($CDCl_3$) δ 2.52 (s, 3 H), 6.92–7.50 (m, 9 H), 8.65 (s, 1 H).

Di-μ-chloro-bis[2-(*N*-phenylimidoyl)-3-methylphenyl]dipalladium (11). A mixture of *N*-(2-methylbenzylidene)aniline (1.95 g, 10 mmol) and palladium acetate (2.24 g, 10 mmol) in acetic acid (50 mL) was heated at reflux for 1 h with stirring. The color of the reaction mixture changed from brown to green-yellow. After cooling to room temperature, addition of water followed by filtration gave di-μ-acetato-bis[2-(*N*-phenylimidoyl)-6-methylphenyl]dipalladium quantitatively: mp 220–224 °C dec; IR (Nujol mull) 1600, 1582 (C=N), 1568, 1418, 790, 766, 759, 720 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (s, 3 H), 2.37 (s, 3 H), 6.53–7.43 (m, 4 H), 7.88 (s, 1 H). Anal. Calcd for $C_{32}H_{30}N_2O_4Pd_2$: C, 53.43; H, 4.20; N, 3.89. Found: C, 53.25; H, 4.21; N, 3.75.

The complex was dissolved in methylene chloride (20 mL), and the solution was vigorously shaked with a saturated sodium chloride solution in a mixture of water (30 mL) and acetone (20 mL). Filtration of the precipitated green-yellow crystalline compound and washing with ethanol, benzene, and methylene chloride gave **11** (3.41 g) in 95% yield: mp 260–270 °C dec; IR (Nujol mull) 1570 cm^{-1} (C=N). Anal. Calcd for $C_{28}H_{24}Cl_2N_2Pd_2$: C, 50.00; H, 3.57; N, 4.17. Found: C, 50.36; H, 3.34; N, 4.11.

Di-μ-chloro-bis[2-(*N*-phenylimidoyl)-3-methoxyphenyl]dipalladium (12). This complex (yellow) was prepared from *N*-(2-methoxybenzylidene)aniline in 94% yield as described in the synthesis of **11**: mp 230–235 °C dec; IR (Nujol mull) 1580 cm^{-1} (C=N). Anal. Calcd for $C_{28}H_{24}Cl_2N_2O_2Pd_2$: C, 47.70; H, 3.44; N, 3.98. Found: C, 47.94; H, 3.48; N, 3.79.

Di-μ-chloro-bis[2-(*N*-phenylimidoyl)-3-chlorophenyl]dipalladium (13). This green complex was prepared from *N*-(2-chlorobenzylidene)aniline in 96% yield as described in the synthesis of **11**: mp 278–280 °C dec; IR (Nujol mull) 1580 cm^{-1} (C=N). Anal. Calcd for: $C_{26}H_{18}Cl_4N_2Pd_2$: C, 43.80; H, 2.54; N, 3.93. Found: C, 43.68; H, 2.44; N, 3.87.

Reaction of Organolithium Compounds with Complex 11 in the Presence of a Ligand. In a typical case, a mixture of **11** (0.335 g, 0.5 mmol) and triphenylphosphine (0.520 g, 2.0 mmol) in benzene (15 mL) was stirred for 30 min at room temperature. To the resulting suspension was added an ethereal solution of methyllithium (0.8 mL, 1.0 mmol) with stirring for 1 h, during which time the color of the reaction mixture changed from yellow to green-yellow. After addition of hydrochloric acid (1 N, 15 mL) with stirring for 1 h, the mixture was filtered off. The ethereal extract was dried over $MgSO_4$ and distilled. VPC analysis (SE 20) of the distillate using an internal standard of dibenzyl showed that the product consisted of 2,6-dimethylbenzaldehyde (**15**; 86%) and 2-methylbenzaldehyde (**14**; 10%). The ligand effect concerning in this methylation was also investigated under the same reaction conditions. The results are summarized in Table V. The structural assignment of the products was made by the spectral data shown in Table II and by elemental analyses.

The reactions of **11** with *sec*-alkyllithiums were carried out similarly. The results are summarized in Table VI. The ligand effect toward the reaction of **11** with isopropyllithium is also shown in Table VI.

2-Deuterio-6-methylbenzaldehyde. A mixture of complex **11** (0.180 g, 0.25 mmol) and PPh_3 (0.260 g, 1.0 mmol) in benzene (8 mL) was stirred for 30 min. To the resulting suspension, DCl/D_2O, prepared by the treatment of acetyl chloride (2 mL) with D_2O (10 mL), was added with stirring at room temperature for 1 h. Filtration, ether extraction, and distillation gave 2-deuterio-6-methylbenzaldehyde. A pure sample was collected by preparative VPC (SE 30, 120 °C): NMR (CCl_4) δ 2.63 (s, 3 H), 7.03–7.43 (m, 3 H), 10.12 (s, 1 H). The absorption corresponding to the ortho H (δ 7.60–7.87) disappeared.

Quenching the Product from 11 and Isopropyllithium with DCl/D_2O. The complex **11** was reacted with isopropyllithium under the reaction conditions described above. The reaction mixture was quenched with DCl/D_2O, and 2-methylbenzaldehyde (**14**) was collected by VPC (SE 30, 120 °C). The NMR spectrum of **14** indicated that the content of 2-deuterio-6-methylbenzaldehyde was 10%.

The Reaction of 11 with Isopropyllithium in Benzene-d_6. The complex **11** (0.18 g, 0.025 mmol) was allowed to react with isopropyllithium (0.025 mmol) in benzene-d_6 (7 mL) in the presence of PPh_3 (0.26 g, 1.0 mmol). The NMR analysis of 2-methylbenzaldehyde, collected by VPC as described above, showed that the number of protons of the ortho position was 0.96, indicating that the deuterium abstraction from benzene-d_6 under the reaction conditions is neglectable.

Bis[2-*N*,*N*-dimethylaminomethyl)phenyl]palladium (35). A solution of *o*-lithio-*N*,*N*-dimethylbenzylamine, prepared by treatment of *N*,*N*-dimethylbenzylamine (0.135 g, 1 mmol) with *n*-butyllithium (1 mmol) in ether under nitrogen, was added to a suspension of di-μ-chloro-bis[2-(*N*,*N*-dimethylaminomethyl)phenyl]dipalladium (**3**; 0.275 g, 0.5 mmol) in ether with stirring at room temperature. After additional stirring for 1 h, addition of water (2 mL), filtration, and washing with water gave the complex **35**. Recrystallization from THF gave analytically pure white needles of **35** (0.124 g, 33%): mp 221 °C dec (lit.[45] mp 180–210 °C); IR (Nujol mull) 1589, 738 cm^{-1}; NMR ($CDCl_3$) δ 2.63 (s, 6 H), 3.88 (s, 2 H), 6.93–7.77 (m, 4 H). Anal. Calcd for $C_{18}H_{24}N_2Pd$: C, 57.68; H, 6.43; N, 7.47. Found: C, 57.53; H, 6.47; N, 7.46.

Reaction of Complex 35 with Methyllithium. To a mixture of complex **35** (0.0187 g, 0.05 mmol) and PPh_3 (0.0524 g, 0.2 mmol) in ether was added an ethereal solution of methyllithium (0.08 mL, 0.10 mmol). After the standard treatment as mentioned above, the products were subjected to VPC analysis, indicating that **6b** (0.035 mmol, 35%) and **6a** (0.060 mmol, 60%) were obtained. When the same reaction was carried out in the absence of PPh_3, **6b** and **6a** were obtained in 8 and 90% yields, respectively.

Reaction of Bromonaphthalene with Methyllithium in the Presence of Tetrakis(triphenylphosphine)palladium. A mixture of α-bromonaphthalene (0.208 g, 1.0 mmol) and tetrakis(triphenylphosphine)palladium[55] (1.155 g, 1.0 mmol) in benzene (10 mL) was heated at reflux under an argon atmosphere for 5 h. After cooling to room temperature, an ethereal solution of methyllithium (0.8 mL, 1.0 mmol) was added to the resulting yellow solution, and the mixture was stirred for 1 h. The reaction mixture was poured into water and filtered off. The filtrate was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, and concentrated. VPC analysis using an internal standard (biphenyl) showed that α-methylnaphthalene was obtained in 90% yield. A similar reaction with β-bromonaphthalene gave β-methylnaphthalene in 88% yield.

Reaction of Di-μ-chloro-bis(2-chloro-3-*N*,*N*-dimethylamino-1-phenylpropenyl)dipalladium (36) with Methyllithium. The complex **36** was prepared from 3-(*N*,*N*-dimethylamino)-3-methylbut-1-yne with lithium chloride and palladium chloride by the method of Yukawa and Tsutsumi.[52] To a suspension of **36** (3.4 g, 5 mmol) in ether (25 mL) was added methyllithium (20 mmol) in ether (23 mL) with stirring at ambient temperature for 3 h. After heating at reflux for 1 h, the reaction mixture was poured into water and filtered off. The ethereal extract was washed with water and dried over $MgSO_4$. After removal of the solvent, distillation of the residual material gave 1.6 g of the products [bp 55–60 °C (12 $mmHg$)]. VPC analysis showed that three compounds were obtained. The first product was *N*,*N*-dimethyl-*cis*-α,β-dimethylcinnamylamine (**37**; 81%): mass spectrum, *m/e* 189 (M^+); NMR ($CDCl_3$) δ 1.88 (s, 3 H), 1.98 (s, 3 H), 2.04 (s, 6 H), 2.73 (s, 2 H), 7.00–7.40 (m, 5 H). Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.26; H, 10.09; N, 7.35. The assignment of the stereochemistry of **37** was made by comparison with an authentic sample. The second compound was the trans isomer of **37** (11%): mass spectrum, *m/e* 189 (M^+); NMR ($CDCl_3$) δ 1.63 (s, 3 H), 2.01 (s, 3 H), 2.28 (s, 6 H), 3.03 (s, 2 H), 7.10–7.50 (m, 5 H). Anal. Found: C, 82.27; H, 10.15; N, 7.27. The last compound was 3-(*N*,*N*-dimethylamino)-3-methylbut-1-yne[56] (8%).

***N*,*N*-Dimethyl-*cis*-α,β-dimethylcinnamylamine (37).** The usual reduction of *cis*-α,β-dimethylcinnamic acid[57] (3.0 g, 17 mmol) with $LiAlH_4$ (0.60 g, 12 mmol) gave *cis*-α,β-dimethylcinnamic alcohol (2.50 g, 88%): NMR ($CDCl_3$) δ 1.83 (s, 3 H), 1.93 (s, 3 H), 2.50 (s, 1 H), 3.85 (s, 2 H), 7.2 (m, 5 H). To a mixture of the alcohol (0.30 g, 4.8 mmol), pyridine (10 mL), and ether (30 mL) was added tribromophosphine (0.45 g, 1.6 mmol) with stirring for 2 h at 0–5 °C. After additional stirring for 2 h at room temperature, ice water (20 mL) and ether (20 mL) were added. The ethereal extract was washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated. Short-path distillation gave *cis*-α,β-dimethylcinnamyl bromide (0.88 g, 81%): NMR (CCl_4) δ 1.90 (s, 3 H), 1.95 (s, 3 H), 3.80 (s, 2 H), 7.20 (s, 5 H). The bromide (0.80 g, 3.6 mmol) was treated with dimethylamine (3.0 g, 67 mmol) in ether at 0–5 °C followed by preparative VPC (Carbowax 20 M, 150 °C) to give **37**.

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Registry No.—**2**, 14873-53-1; **3**, 18987-59-2; **4**, 20523-73-3; **5d**, 103-33-3; **5b**, 6676-90-0; **5c**, 14336-17-5; **5d**, 67292-49-3; **6a**, 103-83-3; **6b**, 4525-48-8; **6c**, 22826-55-7; **6d**, 52728-16-2; **6e**, 67292-50-6; **7a**, 538-51-2; **7b**, 10228-77-0; **7c**, 54884-52-5; **7d**, 67292-51-7; **7e**, 54884-53-6; **8a**, 67292-52-8; **8b**, 1865-12-9; **8c**, 62740-72-1; **11**, 54865-91-7; **12**, 54865-92-8; **13**, 67316-57-8; **14**, 529-20-4; **15**, 1123-56-4; **16**, 54876-93-6; **17**, 54884-54-7; 54876-90-3; **19**, 54876-91-4; **20**, 54876-92-5; **21**, 54884-55-8; **22**, 1194-64-5; **23**, 67337-39-7; **35**, 38437-97-7; **36**, 20492-75-5; *cis*-**37**, 67292-53-9; *trans*-**37**, 67292-54-0; triphenylphosphine, 603-35-0; di-μ-acetato-bis[2-(*N*-phenylimidoyl)-6-methylphenyl]dipalladium, 67316-56-7; *N*-(2-methoxybenzylidene)aniline, 3369-37-7; α-bromonaphthalene, 90-11-9; α-methylnaphthalene, 90-12-0; β-bromonaphthalene, 580-13-2; β-methylnaphthalene, 91-57-6; 3-(*N*,*N*-dimethylamino)-3-methylbut-1-yne, 19788-24-0; *cis*-α,β-dimethylcinnamic acid, 4540-79-8; *cis*-α,β-dimethylcinnamic alcohol, 21017-11-8; *cis*-α,β-dimethylcinnamyl bromide, 67292-55-1.

Supplementary Material Available: Spectral data of compounds **5b–d, 6b–e, 7b–e, 10,** and **14–22** (Table II) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) A. J. Carty, *Organomet. Chem. Rev., Sect. A*, **7**, 191 (1971).
(2) J. Dehand and M. Pfeffer, *Coord. Chem. Rev.*, **18**, 327 (1976).
(3) M. I. Bruce, *Angew. Chem., Int. Ed. Engl.* **16**, 73 (1977).
(4) G. W. Parshall, *Acc. Chem. Res.*, **3**, 139 (1970); **8**, 113 (1975).
(5) S. Trofimenko, *Inorg. Chem.*, **12**, 1215 (1973).
(6) A. C. Cope and R. W. Siekman, *J. Am. Chem. Soc.*, **87**, 3272 (1965).
(7) G. W. Parshall, W. H. Knoth, and R. A. Schunn, *J. Am. Chem. Soc.*, **91**, 4990 (1969).
(8) D. R. Fahey, *J. Organomet. Chem.*, **27**, 283 (1971).
(9) H. Takahashi and J. Tsuji, *J. Organomet. Chem.*, **10**, 511 (1967).
(10) D. Medema, R. van Helden, and C. F. Kobll, *Inorg. Chim. Acta*, **3**, 255 (1969).
(11) Y. Mori and J. Tsuji, *Tetrahedron*, **27**, 3811 (1971).
(12) J. M. Thompson and R. F. Heck, *J. Org. Chem.*, **40**, 2667 (1975).

(13) Y. Yamamoto and H. Yamazaki, *Synthesis*, 750 (1976).
(14) J. Tsuji, *Acc. Chem. Res.*, **2**, 144 (1969).
(15) M. Julia, M. Duteil, and J. Y. Lallemand, *J. Organomet. Chem.*, **102**, 239 (1975).
(16) R. A. Holton, *Tetrahedron Lett.*, 355 (1977).
(17) R. A. Holton and R. G. Davis, *J. Am. Chem. Soc.*, **99**, 4175 (1977); R. A. Holton and R. A. Kjonaas, *ibid.*, **99**, 4177 (1977).
(18) A. C. Cope and E. C. Friedrich, *J. Am. Chem. Soc.*, **90**, 909 (1968).
(19) M. G. Clerici, B. L. Shaw, and B. Weeks, *J. Chem. Soc., Chem. Commun.*, 516 (1973), and references therein.
(20) H. Onoue and I. Moritani, *J. Organomet. Chem.*, **43**, 431 (1972).
(21) R. L. Bennett, M. I. Bruce, B. L. Goodall, M. Z. Iqbal, and F. G. A. Stone, *J. Chem. Soc., Dalton Trans.*, 1787 (1972).
(22) The preliminary results were communicated: S.-I. Murahashi, Y. Tamba, M. Yamamura, and I. Moritani, *Tetrahedron Lett.*, 3749 (1974).
(23) M. H. Klouwen and H. Bodens, *Recl. Trav. Chim. Pays-Bas*, **79**, 1029 (1960).
(24) The formation of 7a is rationalized by assuming the splitting to a solvent-coordinating monomer aryl palladium complex followed by thermal decomposition to the aryl radical,[43] which abstracts hydrogen from the solvent easily.[25]
(25) W. A. Pryor, "Free Radicals", McGraw-Hill, New York, N.Y., 1966, p 167.
(26) N. Dieck and R. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974); P. M. Henry and G. A. Ward, *ibid.*, **93**, 1494 (1971).
(27) S. Otsuka, A. Nakamura, T. Kano, and K. Tani, *J. Am. Chem. Soc.*, **93**, 4301 (1971); K. Tani, L. D. Brown, J. Ahmed, J. A. Ibers, M. Yokota, A. Nakamura, and S. Otsuka, *ibid.*, **99**, 7876 (1977).
(28) J. C. Leffingwell and H. J. Bluhm, *J. Chem. Soc., Chem. Commun.*, 1151 (1969).
(29) V. Boekelheide and T. A. Hylton, *J. Am. Chem. Soc.*, **92**, 3669 (1970); K. L. Servis and K.-N. Fang, *ibid.*, **90**, 6712 (1968); M. Ryang, I. Rhee and S. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **37**, 341 (1964); W. J. Pale, L. Starr, and C. W. Strobel, *J. Org. Chem.*, **26**, 2225 (1961).
(30) G. W. Parshall, *J. Am. Chem. Soc.*, **96**, 2360 (1974).
(31) L. Cassar, *J. Organomet. Chem.*, **93**, 253 (1975).
(32) D. G. Morrell and J. K. Kochi, *J. Am. Chem. Soc.*, **97**, 7262 (1975).
(33) G. Calvin and G. E. Coates, *J. Chem. Soc.*, 2008 (1960).
(34) M. Tamura and J. K. Kochi, *Bull. Chem. Soc. Jpn.*, **44**, 3063 (1971).
(35) F. R. Hartley, "The Chemistry of Platinum and Palladium", Applied Science Publishers Ltd., London, 1973, p 331.
(36) M. L. Bullpitt and W. Kitching, *J. Organomet. Chem.*, **46**, 21 (1972), and references therein; K. Vrieze, A. P. Praat, and P. Cossee, *ibid.*, **12**, 533 (1968).
(37) M. Yamamura, I. Moritani, and S.-I. Murahashi, *Chem. Lett.*, 1423 (1974).
(38) M. C. Baird, *J. Organomet. Chem.*, **64**, 289 (1974).
(39) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967).
(40) M. A. Bennett and R. Carles, *J. Am. Chem. Soc.*, **94**, 666 (1972).
(41) K. Tamao, Y. Kiso, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972).
(42) Y. Kiso, K. Tamao, and M. Kumada, *J. Organomet. Chem.*, **50**, C12 (1973).
(43) A. Tamaki, S. A. Magennis, and J. K. Kochi, *J. Am. Chem. Soc.*, **96**, 6140 (1974).
(44) G. D. Cooper and H. L. Finkbeiner, *J. Org. Chem.*, **27**, 1493, 3795 (1962).
(45) G. Longoni and F. Canziani, *J. Organomet. Chem.*, **39**, 413 (1972). Cf. the trans isomer; see A. Kasahara and T. Izumi, *Bull. Chem. Soc. Jpn.*, **42**, 1765 (1969).
(46) P. S. Baterman and R. J. Cross, *Chem. Soc. Rev.*, **2**, 271 (1973), and references cited therein.
(47) S.-I. Murahashi, M. Yamamura, and N. Mita, *J. Org. Chem.*, **42**, 2870 (1977).
(48) B. M. Trost and L. Weber, *J. Am. Chem. Soc.*, **97**, 1611 (1975).
(49) H. A. Dieck and R. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974), and references cited therein; A. Sekiya and N. Ishikawa, *J. Organomet. Chem.*, **118**, 349 (1976).
(50) K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972); K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, **49**, 1958 (1976).
(51) R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 144 (1972).
(52) T. Yukawa and S. Tsutsumi, *Inorg. Chem.*, **7**, 1458 (1968).
(53) Ortho lithiations and related processes have recently been explored. Lithium compounds: D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976); L. Barsky, H. W. Gschwend, J. Mckenna, and H. R. Rodriguez, *ibid.*, **41**, 3651 (1976); P. Beak and R. A. Brown, *ibid.*, **42**, 1823 (1977). Copper compounds: G. van Koten, J. T. B. H. Jastrzebski, and J. G. Noltes, *J. Org. Chem.*, **42**, 2047 (1977); F. E. Ziegler, K. W. Fowler, and S. Kanfer, *J. Am. Chem. Soc.*, **98**, 8282 (1976).
(54) A. Bayer, *Chem. Ber.*, **7**, 1638 (1874).
(55) D. R. Coulson, *Inorg. Synth.*, **13**, 121 (1972).
(56) C. Mannich and F. T. Chang, *Chem. Ber.*, **66**, 418 (1933).
(57) L. M. Jackman and J. W. Lowns, *J. Chem. Soc.*, 3776 (1962).

The 1-Hetera-3-cyclohexanone System. Carbon-13 Magnetic Resonance, Transannular Effects, and Conformational Analysis[1a]

Jerry A. Hirsch*[1b] and Alvydas A. Jarmas

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079

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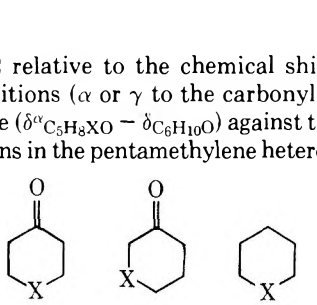
Carbon-13 (^{13}C NMR) magnetic resonance has been applied to the title compounds. Earlier suggestions[2,3] that the effects α to the heteroatom group reflect electrostatic effects and that the effects at a methylene carbon β to the heteroatom group indicate similar (chair) conformations are reinforced. The title compounds are therefore indicated to have chair conformations. Unusual heteroatom effects at the γ carbon are encountered. The groups appended to the heteroatoms are shown to have similar conformations in **1**, **2**, and **3** (under conditions of fast amide rotation). Transannular electron transfer is detected in the carbonyl chemical shifts of the thia analogue here and, to a lesser extent, in the 1-thia-4-cyclohexanone, modifying our earlier interpretation.[3] Other evidence for this transannular component is presented along with possible interpretations.

The use of carbon-13 nuclear magnetic resonance spectroscopy[2] (^{13}C NMR) as a probe[3] for conformational analysis[2-5] and transannular interactions[3] in six-membered heterocycles was evaluated in the 1-hetera-4-cyclohexanone system (**1**) in prior work. We wish herein to report an extension of this approach to the 1-hetera-3-cyclohexanone system (**2**), producing conclusions which reinforce earlier suggestions but which also require slight modification of our analysis of transannular interactions.

It has become fairly well-documented[2-6] that the effects of heteroatom groups on the α carbon reflect the heteroatom group electrostatic effects, and the 1-hetera-3-cyclohexanones (**2**) are no exception at either C-2 or C-6 (Figure 1). Plots of the chemical shifts (Table I) of the carbon resonances at C-2 and C-6 in **2** relative to the chemical shifts of the corresponding positions (α or γ to the carbonyl, respectively) in cyclohexanone ($\delta^{\alpha}_{C_5H_8XO} - \delta_{C_6H_{10}O}$) against the chemical shifts of the α carbons in the pentamethylene heterocycles[3] **3** relative



1 **2** **3**

a, X = S
b, X = N–CO–CH_3
c, X = N–CO–OR'
d, X = SO_2
e, X = N–CH_2Ph
f, X = N–CH_3
g, X = O
h, X = N–CO–C_6H_5

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Table I. ^{13}C NMR Data[a] for 1-Hetera-3-cyclohexanones

compd	X	registry no.	solvent	C-2	C=O	C-4	C-5	C-6	other
2a	S	19090-03-0	$CDCl_3$	41.8	203.6	38.5	28.5	33.6	
2b	$NC(=O)CH_3$	34456-78-5	$CDCl_3$	*b*	205.0	38.2	*b*	*b*	*c*
2c	$NC(=O)OCH_3$	61995-18-4	$CDCl_3$	54.0	205.1	38.4	22.5	42.4	*d*
2c	$NC(=O)OCH_2CH_3$	61995-19-5	$CDCl_3$	54.0	204.9	38.4	22.6	42.4	*e*
2c	$NC(=O)OCH_2C_6H_5$	61995-20-8	$CDCl_3$	53.8	204.9	38.2	22.2	42.2	*f*
2d	SO_2	29431-37-6	$(CD_3)_2SO$	65.8	197.6	39.3	18.1	49.7	
2e	$NCH_2C_6H_5$	40114-49-6	$CDCl_3$	64.3	205.8	38.5	23.9	51.4	*g*
2f	NCH_3	5519-50-6	$CDCl_3$	66.4	205.9	38.0	24.1	53.9	*h*
2g	O	23462-75-1	$CDCl_3$	74.9	207.1	37.5	25.2	65.9	
2h	$NCOC_6H_5$	67452-85-1	$CDCl_3$	53.6	204.1	38.2	22.8	43.7	*i*

[a]Chemical shifts are in parts per million relative to internal Me_4Si. [b]Not available above coalescence temperature. [c]CH_3 not available above T_c; amide C=O, 169.4 ppm. [d]OCH_3, 52.8 ppm; amide C=O, 155.7 ppm. [e]OCH_2, 61.5 ppm; CH_3, 14.7 ppm; amide C=O, 155.2 ppm. [f]OCH_2, 67.2 ppm; amide C=O, 154.9; Ar, 136.4, 128.4, 128.0, and 127.8 ppm. [g]NCH_2, 62.3 ppm; Ar, 137.3, 128.7, 128.1, and 127.1 ppm. [h]NCH_3, 40.4 ppm. [i]Amide C=O, 170.0 ppm; Ar, 135.2, 129.7, 128.3, and 126.7 ppm.

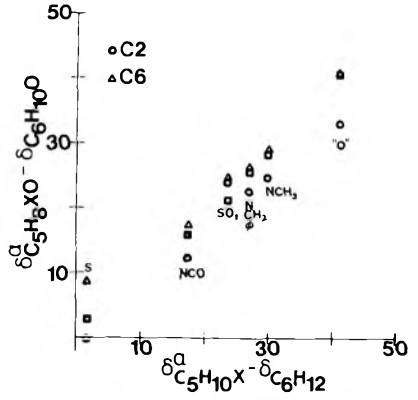

Figure 1. Comparison of the chemical shifts of the carbons α to the heteroatom in **3** (relative to cyclohexane) with the chemical shifts α to the heteroatom (relative to the appropriate position in cyclohexanone) (a) at C-2 in **2** (○), (b) at C-6 in **2** (△), and (c) in **1** (□).

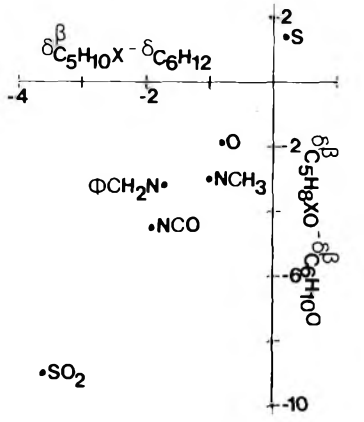

Figure 2. Comparison of the chemical shifts of the carbons β to the heteroatom in **3** (relative to cyclohexane) with the chemical shifts of the methylene carbons β to the heteroatom in **2** (relative to the position β to the carbonyl in cyclohexanone).

to cyclohexane ($\delta^{\alpha}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) give good linear relationships for each carbon set: C-2, $Y = 0.855X - 0.604$ ($r = 0.985$); C-6, $Y = 0.810X + 5.525$ ($r = 0.989$). The correlations for C-2, for C-6, and for the α carbon in the 1-hetera-4-cyclohexanones[3] (**1**) ($Y = 0.980X - 0.916$ ($r = 0.988$)) are all roughly parallel, supporting the idea of a common origin for the α effect in heterogroup electronegativities. As before,[3,5] the α-substituent effects are in the order O ≫ NCH_3 > $NCH_2C_6H_5$ > SO_2 > NCO ≫ S, consistent with the relative electron-withdrawing abilities O > N > S. As may be noted in Table I, all of the amides and urethanes (**2b**, **2c**, and **2h**) exhibit similar chemical shifts at all ring methylene carbons under conditions of rapid amide rotation.

When the chemical shifts of the carbons at C-5 in **2**, which are β to the heteroatom, relative to the corresponding position β to the carbonyl in cyclohexanone ($\delta^{\beta}_{C_5H_8XO} - \delta^{\beta}_{C_6H_{10}O}$), are plotted against the chemical shifts of the β carbons in the pentamethylene heterocycles[3] relative to cyclohexane ($\delta^{\beta}_{C_5H_{10}X} - \delta_{C_5H_{10}}$), another linear relationship is apparent (Figure 2): $Y = 2.619X + 0.475$ ($r = 0.986$). Following our earlier[3] suggestion that these β shifts may be the most useful quick probe of ring conformational preference, this linear relationship suggests that all of the 1-hetera-3-cyclohexanones (**2**) studied herein have similar (and presumably chair) ring conformations. The advantage of our "double difference" plot is again apparent. The linear relationships here and in Figure 1 indicate similar conformations of the mobile heteroatom appendages in **1**, **2**, and **3**.

The situation at carbon 4, the carbon γ to the heteroatom group in **2**, is less clear. Comparison of these chemical shifts relative to the carbon α to the carbonyl in cyclohexanone ($\delta^{\gamma}_{C_5H_8XO} - \delta^{\alpha}_{C_6H_{10}O}$) with the chemical shifts γ to the heteroatom group in the pentamethylene heterocycles (**3**) relative to cyclohexane ($\delta^{\gamma}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) produces a roughly horizontal correlation with high scatter. Such a line of roughly 0 slope would suggest that the heteroatom group has a constant influence at C-4 in **2** which is independent of the nature of the heteroatom group. This result would be unprecedented.[3,5-9] The high degree of scatter suggests the operation of several opposing factors, but the nature of the factors here (other than the traditional steric and electrostatic ones, which should not have resulted in high scatter) is unclear.

The remaining carbon to consider in **2** is the carbonyl carbon, which is β to the heteroatom group. When the chemical shift of the carbonyl carbons in **2** relative to the cyclohexanone carbonyl ($\delta^{C=O}_{C_5H_8XO} - \delta^{C=O}_{C_6H_{10}O}$) is plotted against the heteroatom β effect in the pentamethylene heterocycles (**3**) relative to cyclohexane ($\delta^{\beta}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) (Figure 3), clustering occurs about a possible linear relationship ($Y = 2.04X - 3.99$ ($r = 0.769$)) in a manner reminiscent of the graph obtained for the carbonyl carbon in **1** (Figure 5 of ref 3 with $Y = 1.238X - 0.450$ ($r = 0.834$)). However, in the 1-hetera-3-cyclohexanone series, Figure 3 clearly indicates that the thia analogue **2a** does not fall on any reasonable line ($Y = 3.312X - 1.078$ ($r = 0.964$) when **2a** is omitted).

Comparison of the carbonyl chemical shifts in **2** with those in the 1-hetera-4-cyclohexanones (**1**) is shown in Figure 4. Here a reasonable linear relationship is observed for all of the heteroatom groups except the sulfone group ($Y = 1.491X -$

Table II. Infrared and Ultraviolet Absorptions of 1-Hetera-3-cyclohexanones (2)

compd	X	IR (CO),[a] cm^{-1}	λ_{max},[b] nm
cyclohexanone	CH_2	1710	285 (ε 14) (in hexane)
2a	S	1710 [lit. 1710, 1721 (hexane)]	251 (log ε 2.44), 308 (2.36) [lit. 247 (log ε 2.47), 305 (2.38)]
2b	$NC(=O)CH_3$	lit. 1726	
2c	$NC(=O)OCH_3$	lit. 1722, 1710	
	$NC(=O)OCH_2CH_3$	lit. 1730, 1705	
	$NC(=O)OCH_2C_6H_5$	lit. 1720, 1703	
2d	SO_2	1725	289 (log ε 1.37)
2e	$NCH_2C_6H_5$	1723 (lit. 1720)	280 (sh)
2f	NCH_3	1725 (lit. 1720)	288 (log ε 1.27)
2g	O	1725	298 (log ε 1.21) [lit. 298 (ε 6) (in MeOH)]
2h	$NC(=O)C_6H_5$	1730	

[a] As a film unless otherwise indicated. [b] In 95% ethanol unless otherwise indicated.

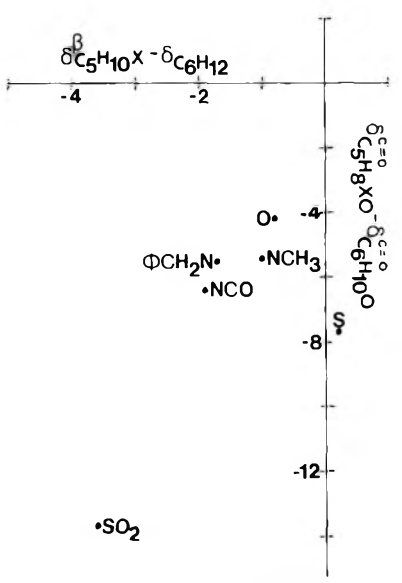

Figure 3. Comparison of the chemical shifts of the carbons β to the heteroatom in **3** (relative to cyclohexane) with the chemical shifts of the carbonyl carbons in **2** (relative to the carbonyl in cyclohexanone).

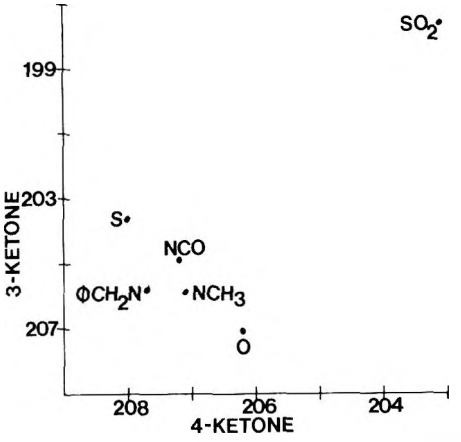

Figure 4. Comparison of the carbonyl carbon chemical shifts in **1** and **2**.

103.8 (r = 0.786) for all, but $Y = -1.587X + 534.28$ (r = −0.838) without the sulfone). While neither of these correlation coefficients are satisfactory, there is some justification for considering the sulfone to be anomalous in Figure 4. In the 1-hetera-3-cyclohexanones, the sulfone (**2d**) is the only compound containing two substituents on the heteroatom. This produces a γ effect in **2d**, but a quite different δ effect in **1d**. This γ effect cancels in Figure 3, but not in Figure 4. Other than the sulfones (**1d** and **2d**), the heteroatom group with the highest carbonyl δ value in **1** has the lowest carbonyl δ value in **2**, an inverse relationship. Bearing in mind that heteroatom groups are considered (and not isolated heteroatoms), the order of the carbonyl δs (other than for the sulfone group) reflects group electronegativities, as observed for the α carbons. The most electronegative group, the oxygen, has the least effect on the β carbonyl (in **2**), in the order and direction suggested by Lambert.[5] However, the most electronegative group has the greatest effect on the γ carbonyl (in **1**), which is opposite to Lambert's analysis.[5]

The observation that the thia compound is anomalous in Figure 3 but fits the trend in Figure 4 promoted reexamination of our analysis of the behavior of 1-thia-4-cyclohexanone (**1a**) in the γ plot, Figure 5 of ref 3. Indeed this thia system deviates significantly from a linear relationship derived by omitting this point from our previous analysis ($Y = 1.524X + 0.8688$ (r = 0.870)). Without doubt, the sulfur group interacts differently with a carbonyl group from the way that any other heteroatom group[28] interacts with the carbonyl group in both systems **1** and **2**.

While increased interaction between chromophores arranged as in **2** has been suggested based on mass spectral behavior[10] and from photoelectron, ultraviolet, infrared, and proton magnetic resonance spectroscopic measurements[11-14] on selected representatives, none of these results has provided information as easily quantifiable as our ^{13}C NMR method. The unique role of sulfur in series **2** is apparent in the infrared and ultraviolet spectra (Table II) as well as in Figure 3. The ultraviolet absorptions found for **2a** were also found recently in 7-thiabicyclo[2.2.1]heptan-2-one,[29] where the 300-nm band was assigned as n,π^* and the 260-nm band with enhanced absorption was assigned as intramolecular charge transfer, as suggested herein. Photoelectron spectroscopy results using acyclic analogues[12] clearly indicate that the presence of both a sulfur and a carbonyl oxygen lone pair leads to significant stabilization of both lone pairs with respect to the monofunctional components, while the oxygen analogues show only slight stabilization of the carbonyl oxygen lone pair along with significant stabilization of the ether lone pair. In line with these stabilization arguments[15] is the fact that replacement of the β-methylene in cyclopentanone[12] by oxygen affects the basicity much less than replacement by sulfur. Whether this "sulfur effect" is unique to sulfur or typical of a second-row heteroatom requires further experimentation. Epiotis' analysis[16] of heteroatom π-donating ability may be relevant. His group[16] suggests that the π-donating ability of second-row heteroatoms is greater than that of first-row heteroatoms if the acceptor contains a low-lying LUMO and the reverse if the acceptor contains a high-lying LUMO. If the carbonyl group

Table III. Infrared and Ultraviolet Absorptions of 1-Hetera-4-cyclohexanones (1)

compd	X	registry no.	IR (C=O),[a] cm^{-1}	λ_{max},[b] nm
cyclohexanone	CH_2	108-94-1	1710 [lit. 1717 (CCl_4)]	285 (ε 14) (in hexane)
1a	S	1072-72-6	1715 (CCl_4) [lit. 1715 (CCl_4)]	lit. 236 (ε 285), 298 (33)
1b	$NC(=O)CH_3$	32161-06-1	lit. 1712 ($CHCl_3$)	
1c	$NC(=O)OCH_3$	29976-54-3	lit. broad 1700 ($CHCl_3$)	
1d	SO_2	17396-35-9	1710 (Nujol)	
1f	NCH_3	1445-73-4	1724 (CCl_4)[c] (lit. 1710)	250 (ε 57) [lit. 285 (ε 15), 293 (15) (in hexane)]
1g	O	29943-42-8	1725 (CCl_4)[c] (lit. 1718)	230 (ε 334)
1h	$NC(=O)C_6H_5$	24686-78-0	lit. 1722 ($CHCl_3$)	

[a] As a film unless otherwise indicated. [b] In 95% ethanol unless otherwise indicated. [c] J. Reisse, private communication.

is placed in the first category, our data[28] support Epiotis' suggestions.

Since we are now suggesting that the sulfur and carbonyl groups do interact significantly in the 1-hetera-4-cyclohexanone series (1) and that this interaction is apparent in the 1-hetera-3-cyclohexanone series (2) from infrared, ultraviolet, and ^{13}C NMR data, it behooves us to tabulate infrared and ultraviolet data for representatives of series **1**. As shown in Table III, the sulfur analogue **1a** does show a slight bathochromic shift of the longest wavelength adsorption, but solvent changes must also be recognized. The infrared absorption data do not show any pattern here.

Experimental Section

All ^{13}C NMR spectra were recorded on a JEOL PS-100 NMR spectrometer equipped with a JEOL-JNM-PFT-100 pulse unit and a JEOL-JEC-6 computer. Field frequency stabilization was established by the deuterium signal of the solvent utilized ($CDCl_3$ or $(CD_3)_2SO$). The chemical shifts are expressed in parts per million relative to internal Me_4Si at 26 ± 2 °C (unless otherwise indicated) and are believed to be accurate to 0.2 ppm. All solutions are 10–15%, so dilution effects should be minor. The spectra were obtained under conditions of proton noise decoupling, with off-resonance decoupling used to verify peak assignments where needed.

All infrared spectra were obtained with a Perkin-Elmer Model 567 grating infrared spectrometer and were run as neat liquids unless otherwise stated. Ultraviolet spectra were determined on a Beckman Acta CIII UV–vis spectrophotometer in 95% ethanol unless otherwise stated. Proton NMR spectra (^1H NMR) were recorded on a Varian Associates Model T-60A spectrometer, and chemical shifts are reported in parts per million (ppm) downfield from internal Me_4Si at ambient temperatures. Elemental analyses were performed by Alfred Bernhardt Microanalytisches Laboratorium, Elbach, W. Ger. Gas chromatographic analyses were performed on a Varian Model 3700 chromatograph fitted with a thermal conductivity detector utilizing helium flow through a 6 ft × 0.25 in 20% DEGS column on 60–80 mesh Chromosorb W.

Samples of amide **2b** and urethanes **2c** (R′ = CH_3, CH_2CH_3, and $CH_2C_6H_5$) were kindly provided by Dr. Krogsgaard-Larsen.[17]

Thian-3-one (2a). Various reported routes[18–21] using Dieckmann condensations were utilized without developing a preference for a given procedure. Literature yields and physical properties were reproduced. Product **2a** exhibited the following: bp 79–80 °C (4mm); IR 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (2 H, s), 3.00–2.65 (2 H, m), 2.65–2.25 (4 H, m). Anal. Calcd for C_5H_8OS: C, 51.68; H, 6.94; S, 27.60. Found: C, 51.57; H, 6.94; S, 27.80. Attempts to oxidize commercially available thian-3-ol (Aldrich Chemical Co.) using a variety of oxidants failed.

Thian-3-one 1,1-Dioxide (2d). Peroxide oxidation[19] of **2a** was performed, but yields were improved using a slightly different procedure.[22] To a solution of 1.00 g (8.62 mmol) of **2a** in 20 mL of glacial acetic acid was added 4.0 mL (40 mmol) of 30% hydrogen peroxide dropwise while maintaining the temperature at 5–10 °C. After the mixture was stirred for an additional 24 h at room temperature, the solvent was evaporated under a slow stream of nitrogen to give a white solid. Recrystallization twice from absolute ethanol afforded 0.74g (58%) of colorless flakes: mp 142–143 °C (lit.[19] mp 136–139 °C); IR (Me_2SO) 1920 and 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.33 (2 H, s), 3.80–3.25 (2 H, m), 2.80–2.35 (2 H, m), 2.35–1.80 (2 H, m). Anal. Calcd for $C_5H_8O_3S$: C, 40.53, H, 5.45; S, 21.64. Found: C, 40.41; H, 5.46; S, 21.60.

1-Benzylazan-3-one (2e). Sodium bicarbonate treatment of the commercially available (Aldrich Chemical Co.) hydrated hydrochloride salt by the procedure of Krogsgaard-Larsen[17] smoothly provided the desired *N*-benzyl ketone in 79% yield with spectral properties as reported:[17] bp 139–140 °C (3.5 mm); IR 3030 and 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (5 H, s), 3.58 (2 H, s), 3.00 (2 H, s), 2.61 (2 H, t), 2.50–2.13 (2 H, m), 2.13–1.64 (2 H, m). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.14; H, 8.00; N, 7.40. Found: C, 76.10; H, 7.92; N, 7.28.

1-Methylazan-3-one (2f). Jones oxidation[10] gave poor yields of product which could not be purified other than by preparative vapor-phase chromatography. Use of Jones reagent in glacial acetic acid[23] was more successful. To a solution of 3.34 g (29 mmol) of 1-methylazan-3-ol in 58 mL of glacial acetic acid was added 1.6 mL of concentrated H_2SO_4 (in one portion) followed by 11 mL of Jones reagent over a period of 20 min. After stirring for 1 additional hour, 10 mL of 2-propanol was added. Dilution with 150 mL of water was followed by addition of 25.3 g (86 mmol) of trisodium citrate and 400 mg of amalgamated zinc. The flask was flushed with N_2 for 20 min, at which time the solution was made strongly basic with 25% aqueous NaOH and extracted with methylene chloride. The organic extracts were diluted with hexane, washed with saturated aqueous NaCl, and dried (Na_2SO_4). Solvents were removed on a rotary evaporator, and the orange-brown residue was distilled under N_2 to give 1.6 g (49%) of a colorless oil which rapidly turned yellow on exposure to air: bp 68–69 °C (12.5 mm) [lit.[26] bp 63–64 °C (13 mm)]; IR 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (2 H, s), 2.83–2.45 (2 H, m), 2.40 (3 H, s), 2.40–1.60 (4 H, m). Anal. Calcd for $C_6H_{11}NO$: C, 63.67; H, 9.82; N, 12.38. Found: 63.42; H, 9.72; N, 12.21.

Oxan-3-one (2g). Difficulties were encountered in preparation and purification by literature methods,[10,24,25] so the following sequence was developed. Hydroboration of 2,3-dihydropyran was performed using the procedure of Monson[27] with external borane generation, but with only a 5% excess of diborane. Alkaline peroxide oxidation[27] converted 8.41 g (100 mmol) of 2,3-dihydropyran into 7.52 g (74% yield) of oxan-3-ol as a colorless oil, bp 44–45 °C (0.9 mm). Jones oxidation[24] of this alcohol produced the ketone, bp 57–58 °C (9 mm), which required further purification. Column chromatography (Woelm neutral alumina I, 5:1 methylene chloride–ethyl acetate) and subsequent bulb-to-bulb distillation (Kugelrohr apparatus) produced 1.5 g (75% yield) of a colorless oil: IR 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (2 H, s), 3.90 (2 H, t), 2.72–2.40 (2 H, m), 2.32–1.82 (2 H, m). Anal. Calcd for $C_5H_8O_2$: C, 60.05; H, 7.99. Found: C, 59.84; H, 7.91.

1-Benzoylazan-3-one (2h). Jones oxidation[30] of 1-benzoyl-3-hydroxypiperidine[30] followed by column chromatography (Woelm neutral alumina I, 3:1 chloroform–ethyl acetate) produced a 56% yield of a viscous yellow oil: IR 1730 and 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (5 H, s), 4.15 (2 H, s), 3.70 (2 H, t), 2.23–1.65 (2 H, m).

Acknowledgment. We wish to thank Mr. C. Erkelens of the Department of Organic Chemistry, University of Leiden, The Netherlands, for operating the JEOL spectrometer and Professor E. Havinga and Dr. H. J. C. Jacobs for continuing cooperation in permitting the use of the spectrometer.

Registry No.—1-Methlyazan-3-ol, 3554-74-3; 2,3-dihydropyran, 110-87-2; oxan-3-ol, 19752-84-2; 1-benzoyl-3-hydroxypiperidine, 67452-86-2.

References and Notes

(1) (a) Presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, Calif. March 16, 1976, No. ORGN 158. (b) Dedicated to Professor Egbert Havinga of the University of Leiden on the occasion of his retirement.

(2) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Interscience, New York, N.Y., 1972; E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", Verlag Chemie, Weinheim/Bergstr., 1974.
(3) J. A. Hirsch and E. Havinga, *J. Org. Chem.*, **41**, 455 (1976).
(4) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8**, 1 (1974).
(5) J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975); J. B. Lambert, D. A. Netzel, H. Sun, and K. K. Lilianstrom, *J. Am. Chem. Soc.*, **98**, 3778 (1976).
(6) H.-J. Schneider and W. Freitag, *J. Am. Chem. Soc.*, **99**, 8363 (1977).
(7) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Wilier, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(8) W. A. Ayer, L. M. Browne, S. Fung, and J. B. Stothers, *Can. J. Chem.*, **54**, 3272 (1976).
(9) H. Beierbeck and J. K. Saunders, *Can. J. Chem.*, **54**, 632, 2985 (1976).
(10) J. H. Block, D. H. Smith, and C. Djerassi, *J. Org. Chem.*, **39**, 279 (1974).
(11) M. M. Cook and C. Djerassi, *J. Am. Chem. Soc.*, **95**, 3678 (1973).
(12) B. T. Buzzi, P. R. Olivato, R. Rittner, C. Trufen, H. Viertler, and B. Wladislaw, *J. Chem. Soc., Perkin Trans. 2*, 1294 (1975); P. R. Olivato, H. Viertler, B. Wladislaw, K. C. Cole, and C. Sandorfy, *Can. J. Chem.*, **54**, 3026 (1976), and references therein.
(13) C. C. Levin, R. Hoffmann, W. J. Hehre, and J. Hudec, *J. Chem. Soc., Perkin Trans. 2*, 210 (1973).
(14) P. Pasman, J. W. Verhoeven, and Th. J. deBoer, *Tetrahedron*, **32**, 2827 (1976); *Tetrahedron Lett.*, 207 (1977).
(15) Heat of combustion data [G. Geiseler and J. Sawistowsky, *Z. Phys. Chem. (Leipzig)*, **250**, 43 (1972)] suggest that destabilizing interactions in **1a** and **2a** result in strain energies of 14 and 36 kJ/mol, respectively, which somewhat contradicts the photoelectron analysis.
(16) F. Bernardi, A. Mangini, N. D. Epiotis, J. R. Larson, and S. Shaik, *J. Am. Chem. Soc.*, **99**, 7465 (1977).
(17) P. Krogsgaard-Larsen, and H. Hjeds, *Acta Chem. Scand., Ser. B.*, **30**, 884 (1976).
(18) N. J. Leonard and J. Figueras, *J. Am. Chem. Soc.*, **74**, 917 (1952).
(19) E. A. Fehnel, *J. Am. Chem. Soc.*, **74**, 1569 (1952).
(20) T. E. Young and L. J. Heitz, *J. Org. Chem.*, **38**, 1562 (1973).
(21) C. A. Grob and Y. Ide, *Helv. Chim. Acta*, **57**, 2562 (1974).
(22) R. Lesser and A. Mehrlander, *Ber.*, **56**, 1642 (1923).
(23) C. H. Mueller and P. M. DiPerdo, *J. Org. Chem.*, **42**, 3210 (1977).
(24) J. Gore and F. Guiges, *Bull. Soc. Chim. Fr.*, 3521 (1970).
(25) A. Groviller and H. Pacheco, *J. Heterocycl. Chem.*, **13**, 853 (1976), and references therein.
(26) E. A. Prill and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933).
(27) R. S. Monson, "Advanced Organic Synthesis: Methods and Techniques", Academic Press, New York, N.Y., 1971.
(28) The deviation observed for sulfur (**1a**) in the γ plot of ref 3 is also apparently observed for a variety of 4-phosphorinanones (X = P-CH_3, P(O)CH_3, P(S)CH_3, P-C_6H_5, P(O)C_6H_5, and P(S)C_6H_5): J. A. Hirsch, work in progress.
(29) I. Tabushi, Y. Tamaru, and Z. Yoshida, *Bull. Chem. Soc. Jpn.*, **51**, 1178 (1978).
(30) The procedure and sample of starting alcohol were kindly provided by Dr. R. L. Augustine, Seton Hall University.

Three Isomeric 1,3-Dimethyl-5-(dihydropyran-2′-yl)-2,4-pyrimidinediones. Palladium-Catalyzed Synthesis and Spectrometric Properties[1]

Isamu Arai and G. Doyle Daves, Jr.*

Department of Chemistry and Biochemical Sciences, Oregon Graduate Center, Beaverton, Oregon

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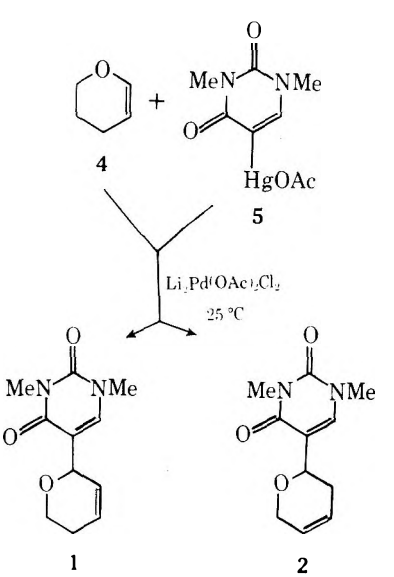
Reaction of 3,4-dihydro-2*H*-pyran with (1,3-dimethyl-2,4-pyrimidinedion-5-yl)mercury(II) acetate in the presence of 1 equiv of $Li_2Pd(OAc)_2Cl_2$ at 25 °C produced in high yield a mixture of two isomers, 1,3-dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**1**) and 1,3-dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-6′-yl)-2,4-pyrimidinedione (**2**). Palladium-catalyzed [$(Ph_3P)_2Pd(OAc)_2$] reaction with 3,4-dihydro-2*H*-pyran with 1,3-dimethyl-5-iodo-2,4-pyrimidinedione at 100 °C yielded a third isomer, 1,3-dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**3**). The relationship between the three isomers was established by reduction of each to the same product, 1,3-dimethyl-5-(tetrahydropyran-2′-yl)-2,4-pyrimidinedione (**7**). Structure assignments of the three isomers based on mass and ^1H nuclear magnetic resonance spectra are discussed.

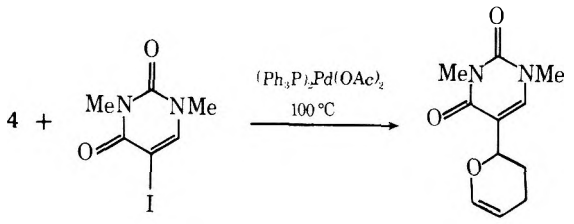
Reactions of cyclic enol ethers with palladium derivatives of nitrogen heterocycles[1] provide a potentially attractive synthetic route to C-nucleosides.[2,3] In preliminary investigations,[1] we have studied several reactions of enol ethers, including 3,4-dihydro-2*H*-pyran (**4**), with organopalladium reagents. In this report, we describe the preparation by this method and spectrometric properties of three isomeric 1, 3-dimethyl-5-(dihydropyran-2′-yl)-2, 4-pyrimidinediones (uracils) (**1–3**).

Two of the isomers, 1,3-dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**1**) and 1,3-dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-6′-yl)-2,4-pyrimidinedione (**2**), result from reaction of 3,4-dihydro-2*H*-pyran (**4**) with an organopalladium reagent generated in situ by treatment of (1,3-dimethyl-2,4-pyrimidinedion-5-yl)mercury(II) acetate (**5**) with the palladium(II) salt $Li_2Pd(OAc)_2Cl_2$ in acetonitrile at room temperature during 1 day.[1] The reaction apparently involves regiospecific addition of an intermediate pyrimidinylpalladium species derived from **5** to the double bond of 3,4-dihydro-2*H*-pyran (**4**) followed by elimination of a hydridopalladium salt to yield the initial (major) product **1**. Readdition of the hydridopalladium salt to the double bond of the dihydropyranyl moiety of **1** and subsequent reelimination produced the double bond shifted minor product **2**.[1]

The third isomer, 1,3-dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**3**), was produced as the sole isolable product of reaction of 3,4-dihydro-2*H*-pyran (**4**) with



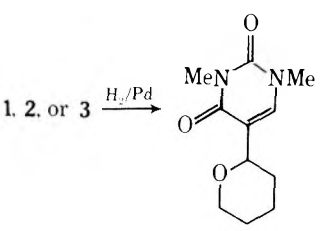
4 **5** **1** **2**



6 3

a similar pyrimidinylpalladium reagent formed from 1,3-dimethyl-5-iodouracil[4] (**6**) and a catalytic amount of diacetatobis(triphenylphosphine)palladium(II).[5] Presumably, the differing results of the two reactions are caused by the difference in reaction temperatures.[6] In the first reaction, the organopalladium species forms easily from the corresponding mercury derivative (**5**), and the reaction proceeds at room temperature.[1,6] In the second reaction, in which the organopalladium intermediate was generated from the 5-iodopyrimidine **6**, a temperature of 100 °C was required, resulting in the formation of **3** in which the double bond is stabilized by conjugation with the ring oxygen. It is not immediately clear why the fourth possible isomer, that in which the dihydropyranyl double bond is in conjugation with the pyrimidine rings, is not formed. Under similar conditions, palladium-catalyzed reaction of **6** with vinyl acetate readily yields the conjugated product, 1,3-dimethyl-5-vinyluracil.[7]

Isomers **1**–**3** were assigned structures after consideration of their chemical and spectrometric properties. Their isomeric nature was established by mass spectrometry. Further, reduction of isomers **1**–**3** produced a single compound, 1,3-dimethyl-5-(tetrahydropyran-2′-yl)-2,4-pyrimidinedione (**7**),



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establishing that the points of attachment of the pyrimidine and dihydropyranyl rings are the same for each isomer. The fact that isomers **1**–**3** exhibit identical ultraviolet spectra with absorption maxima at 270 nm (methanol) establishes that, in each compound, the dihydropyranyl double bond is not conjugated with the pyrimidine chromophore.[8]

The two structural features of each isomer remaining to be established, the point of attachment of the dihydropyranyl ring to the pyrimidine and the position of the dihydropyranyl double bond, were assigned from consideration of the respective ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra (see Experimental Section).[9] Structure assignments are particularly straightforward upon comparison of the three spectra. Thus, in the spectra of **1** and **2**, dihydropyranyl resonances assignable to olefinic hydrogens (two) and hydrogens on oxygen-bearing carbon (three) are apparent, establishing the 2′ position for linkage of the dihydropyranyl moiety to the pyrimidine ring. The downfield position of the 2′-H resonance in **1** (δ 5.25) as compared with that in **2** (δ 4.59) is indicative of its allylic relationship to the dihydropyranyl double bond of **1**. These and other obvious resonance assignments permit unique structures to be designated for **1** and **2**. Similarly, assignment of a unique structure to compound **3** is facile from examination of its ^{1}H NMR spectra in deuteriochloroform and deuteriobenzene (Experimental Section).[9] In these spectra the olefinic resonances are essentially those of dihydropyran itself,[10] and the single proton assignable to oxygen-bearing carbon is consistent only with structure **3**.

The mass spectra[9] reveal that the three isomers exhibit interesting differences in fragmentation modes. The mass spectrum of each isomer exhibits a different base ion. In the spectrum of **1** the base ion (*m/e* 167) corresponds to the pyrimidine moiety (B) plus a CO fragment derived from the dihydropyranyl ring. The mass spectrum of **2** exhibits a prominent B + 28 ion at *m/e* 167; however, in this case the B + H ion at *m/e* 140 is the base ion. An abundant B + H ion is characteristic of N- rather than C-nucleosides[11–13] and apparently arises in the spectrum of **2** because for this isomer transfer of a 5′-H of the dihydropyranyl ring to the pyrimidine moiety with rupture of the C_5–$C_{6'}$ bond and formation of 2*H*-pyran is particularly favored. The favored fragmentation mode for isomer **3** is still different. In this case the base ion at *m/e* 166 arises by retro-Diels–Alder reaction of the dihydropyranyl moiety, yielding acrolein and the 5-vinylpyrimidine. In the spectrum of each isomer an ion at *m/e* 81 corresponding to the heteroaromatic $(C_5H_5O)^+$ ion is observed.

Experimental Section

General Comments. Melting points were determined with a hot stage microscope and are uncorrected. Ultraviolet spectra were recorded with a Cary-15 spectrophotometer, and ^{1}H NMR spectra were obtained on deuteriochloroform and deuteriobenzene solutions using a Varian Associates HA-100 spectrometer. Mass spectra were obtained using a CEC 21-110B mass spectrometer (direct insertion probe, high-resolution data) and a DuPont 21-491 mass spectrometer (gas chromatography–mass spectrometry). Elemental analyses were provided by Dr. R. Wielesek, University of Oregon.

(1,3-Dimethyl-2,4-pyrimidinedion-5-yl)mercury(II) Acetate (5). A mixture of 14 g (0.1 mol) of 1,3-dimethyluracil[8] and 31.8 g (0.1 mol) of mercury(II) acetate in 200 mL of methanol containing several drops of 70% perchloric acid was stirred at room temperature for 12 h. The resulting precipitate was collected and washed with cold methanol to yield 36.4 g (93%) of (1,3-dimethyl-2,4-pyrimidinedion-5-yl)mercury(II) acetate (**5**), which was suitable for use without further purification.

1,3-Dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (1) and 1,3-Dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-6′-yl)-2,4-pyrimidinedione (2). A mixture consisting of 4.0 g (0.01 mol) of (1,3-dimethyl-2,4-pyrimidinedione-5-yl)mercury(II) acetate (**5**), 2.3 g (0.01 mol) of palladium acetate, 0.8 g (0.02 mol) of lithium chloride, and 1.6 g (0.02 mol) of 3,4-dihydro-2*H*-pyran (**4**) in 100 mL of anhydrous acetonitrile was stirred for 12 h at room temperature. During this time a black precipitate (presumably palladium) formed. Hydrogen sulfide was passed through the reaction mixture, and the resulting precipitated metal salts were removed by filtration. Evaporation of the filtrate left a residue (2.0 g, 91%) consisting of a mixture of **1** and **2** (3:1). The mixture of **1** and **2** was difficult to separate; silica gel chromatography with dichloromethane elution yielded in early fractions, 1,3-dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-6′-yl)-2,4-pyrimidinedione (**2**) as colorless crystals from hexane: mp 134–135 °C UV λ_{max} (MeOH) 270 nm (ϵ 7900); MS *m/e* 222.1029 (M^+·; calcd for $C_{11}H_{14}N_2O_3$, 222.1004), 167.0470 (calcd for $C_7H_7N_2O_3$, 167.0457); ^{1}H NMR ($CDCl_3$) δ 1.8–2.8 (m, 2 H, 5′-H), 3.38 and 3.43 (s and s, N-Me), 4.35 (brd, 2′-H), 4.59 (d of d, J = 5 and 10 Hz, 6′-H), 5.6–6.1 (m, 2 H, 3′- and 4′-H), 7.29 (s, 6-H).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.31; N, 12.6. Found: C, 59.1; H, 6.09; N, 12.6.

Further elution yielded middle fractions containing both **1** and **2** and finally late fractions containing pure 1,3-dimethyl-5-(5′,6′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**1**): mp 123–124 °C (from hexane); UV λ_{max} (MeOH) 270 nm (ϵ 8100); MS *m/e* 222.1000 (M^+·; calcd for $C_{11}H_{14}N_2O_3$, 222.1004); ^{1}H NMR ($CDCl_3$) δ 1.8–2.5 (m, 2 H, 5′-H), 3.37 and 3.42 (s and s, N-Me), 3.7–4.2 (m, 2 H, 6′-H), 5.25 (brd, 1 H, 2′-H), 5.7–6.1 (m, 2 H, 3′- and 4′-H), 7.27 (s, 1 H, 6-H).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.31; N, 12.6. Found: C, 59.4; H, 6.15; N, 12.6.

1,3-Dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (3). A mixture consisting of 0.27 g (1 mmol) of 1,3-dimethyl-5-iodouracil (**6**), 0.2 g (2 mmol) of triethylamine, 0.7 mg (0.01 mmol) of diacetatobis(triphenylphosphine)palladium(II)[5] and 10 mL of 3,4-dihydro-2*H*-pyran (**4**) contained in a sealed tube was heated at 100 °C for 5 h. The cooled reaction mixture was poured into water and extracted with chloroform. The chloroform extract was chromatographed on silica gel using dichloromethane–ether (9:1) for

elution to yield 0.14 g (64%) of 1,3-dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**3**) which exhibited λ_{max} (MeOH) 270 nm (ϵ 8000) and MS *m/e* 222.1008 (M^+·; calcd for $C_{11}H_{14}N_2O_3$, 222.1004) and 166.0737 (calcd for $C_8H_{10}N_2O_2$, 166.0742); ^{1}H NMR ($CDCl_3$) δ 1.5–2.5 (m, 4 H, 3′- and 4′-H), 3.37 and 3.45 (s and s, NMe), 5.7–5.95 (m, 2 H, 2′- and 5′-H), 6.45 (d, J = 6 Hz, 1 H, 6′-H), 7.27 (s, 1 H, 6-H). In deuteriobenzene solution, the resonances for 2′-H and 5′-H are separated,[9] permitting facile assignment.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.31; N, 12.6. Found: C, 59.3; H, 6.22; N, 12.5.

1,3-Dimethyl-5-(2′-tetrahydropyranyl)-2,4-pyrimidinedione (7). To a solution of 0.14 g of 1,3-dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**3**) in 50 mL of tetrahydrofuran was added 14 mg of 5% palladium on carbon. The resulting mixture was shaken under 2 atm of hydrogen pressure for 2 h. The catalyst was removed, and the solvent was evaporated to yield 0.10 g (71%) of 1,3-dimethyl-5-(2′-tetrahydropyranyl)-2,4-pyrimidinedione (**7**): mp 105–106 °C; UV λ_{max} (MeOH) 270 nm (ϵ 7900); MS *m/e* 224.1224 (M^+·; calcd for $C_{11}H_{16}N_2O_3$, 224.1191); ^{1}H NMR ($CDCl_3$) δ 3.35 and 3.40 (NMe), 4.35 (d, J = 11 Hz, 2′-H), 7.24 (6-H).

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.9; H, 7.14; N, 12.5. Found: C, 58.9; H, 7.16; N, 12.4.

Similar reductions of both **1** and **2** in methanol yielded **7**. Prolonged (>5 h) contact with the reducing conditions resulted in reduction of the pyrimidinedione ring, producing a tetrahydro product of M_r 226.

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Registry No.—**1**, 67464-93-1; **2**, 67464-94-2; **3**, 67464-95-3; **4**, 110-87-2; **5**, 65904-27-0; **6**, 40738-83-8; **7**, 67464-96-4; 1,3-dimethyluracil, 874-14-6; mercury(II) acetate, 1600-27-7.

Supplementary Material Available: Complete ^{1}H NMR and electron ionization mass spectra for compounds 1–3 (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For a preliminary account of a portion of this work, see I. Arai and G. D. Daves, Jr., *J. Am. Chem. Soc.*, **100**, 287 (1978).
(2) G. D. Daves, Jr., and C. C. Cheng, *Prog. Med. Chem.*, **13**, 303 (1976).
(3) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111 (1976).
(4) C. H. Evans, A. S. Jones, and R. T. Walker, *Tetrahedron*, **29**, 1611 (1973).
(5) T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, and G. Wilkinson, *J. Chem. Soc.*, **3632** (1965).
(6) R. F. Heck, *Ann. N.Y. Acad. Sci.*, **295**, 201 (1977).
(7) I. Arai and G. D. Daves, Jr., *J. Heterocycl. Chem.*, **15**, 351 (1978).
(8) 1,3-Dimethyl-2,4-pyrimidinedione exhibits λ_{max} (MeOH) 270 nm. See K. Yamauchi and M. Kinoshita, *J. Chem. Soc., Chem. Commun.*, 391 (1973).
(9) See paragraph on Supplementary Material Available at end of article.
(10) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Variann Associates, Palo Alto, Calif., 1962.
(11) D. C. DeJongh, *Synth. Proced. Nucleic Acid Chem. 1973*, **2**, 145–176 (1973).
(12) C. Hignite in "Biochemical Applications of Mass Spectrometry," G. R. Waller, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 429–447.
(13) L. B. Townsend and R. K. Robins, *J. Heterocycl. Chem.*, **6**, 459 (1969).

Reactions of Heteroaromatic Cations with Nucleophilic Reagents. Addition of Methoxide Ion to 2,6-Diphenyl- and 4-Methoxy-2,6-diphenylpyrylium Cations

Sergio Bersani, Giancarlo Doddi,* Simonetta Fornarini, and Franco Stegel*

Centro C.N.R. dei Meccanismi di Reazione, c/o Istituto di Chimica Organica, Università di Roma, 00185 Roma, Italy

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The title reactions have been studied mainly in methanol and 9:1 acetonitrile–methanol. 2,6-Diphenylpyrylium cation yields a 4*H*-pyran as the kinetically favored product and diphenylpentadienone **7**. The latter, which forms upon ring cleavage of a 2*H*-pyran, is the product of a thermodynamically favored pathway. In methanol the reaction of the methoxy-substituted cation yields comparable amounts of the isomeric 2*H*- and 4*H*-pyranic adducts; in this case the 2*H*-pyran apparently does not undergo ring cleavage. In 9:1 acetonitrile–methanol the only primary product is the 4*H*-pyran. The proticity of the medium seems to have an important role in promoting the interconversion of 4*H*-pyrans to other reaction products.

The pyrylium cation, one of the fundamental heteroaromatic systems, reacts easily with nucleophilic reagents. The nucleophilic attack occurs preferentially at the α or γ position;[1] in the absence of a good leaving group the reaction yields nonaromatic adducts (2*H*- or 4*H*-pyrans). The formation of a 2*H*-pyran is often followed by a ring-opening reaction, yielding a dienonic valence tautomer of the 2*H*-pyran.[2] If, on the other hand, the attacked position is bound to a good leaving group, the formation of the pyran is followed by the loss of this group and formation of a substituted pyrylium cation. Owing to the high reactivity of the pyrylium ring, substitution occurs easily, even with such poor leaving groups as alkoxy groups.[3,4]

Nucleophilic substitutions of pyrylium cations are similar to nucleophilic substitutions of pyridinium cations[5] and of activated benzenoid substrates,[6] where the intermediacy of σ adducts seems a general common feature.

While the equilibrium reactions of formation of Meisenheimer adducts from nitro-activated substrates[7] and of dihydropyridines from pyridinium cations[8] have been intensively investigated, reversible reactions of formation of pyrans from pyrylium cations have received limited attention so far.[9]

In view of the interest in the nucleophilic substitutions of pyrylium and related cations,[4,10,11] and in connection with our studies on the formation of adducts from heteroaromatic substrates,[12] we present the results concerning the course of the reaction of methoxide ion with 2,6-diphenylpyrylium (**1**) and 4-methoxy-2,6-diphenylpyrylium (**2**) cations and the structure assignment of the reaction products. Hydrogen and methoxyl groups are known to affect, in a different way, the structure and stability of Meisenheimer adducts.[13] The phenyl groups at the α positions were expected to have some hindering effect[14] toward attack at such positions and to decrease therein the reactivity, leaving virtually unaffected the reactivity of the γ position.

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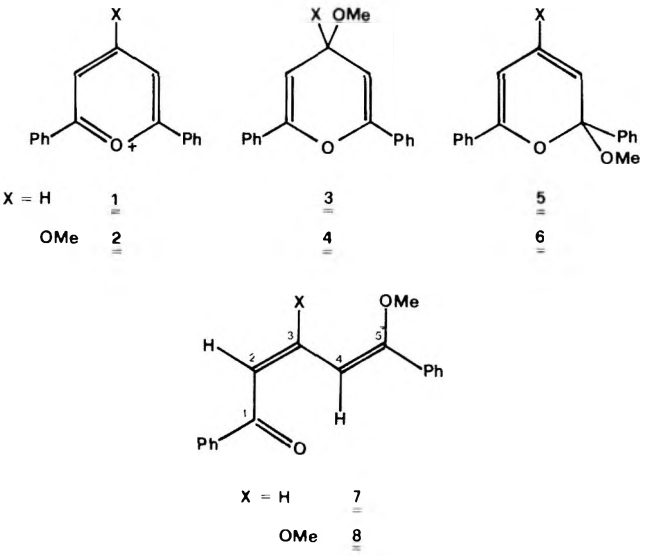
Table I. Chemical Shifts (δ) and Coupling Constants (Hz) for Compounds 1–4 and 6

Compd	Solvent	H-3,5	H-4	C_6H_5	OCH_3	$J_{3,4}$	$J_{3,5}$
1	CD_3CN	8.51	8.95	7.5–8.4		8.6	
3	CD_3CN[a]	5.80	4.80	7.3–7.9	*b*	4.5	
	CH_3OD	5.85	4.9	7.1–8.1	*b*	4.5	
	CCl_4	5.60	4.88	7.2–7.9	3.16	4.5	
2	CD_3CN	7.90		7.6–8.3	4.40		
	$(CD_3)_2SO$	8.40		7.5–7.9, 8.3–8.6	4.45		
4	CD_3CN[a]	5.77		7.2–7.9	*b*		
	CH_3OD	5.80		7.3–8.1	*b*		
	$(CD_3)_2SO$[a]	6.02		7.3–8.1	*b*		
	CCl_4	5.65		7.1–7.9	3.22		
6	CH_3OD	4.55, 6.00		7.3–8.1	*b*		2
	CD_3CN[a]	4.6, 5.9		7.3–8.1	*b*		2
	CCl_4	4.34, 5.82		7.1–7.9	3.19, 3.57		2

[a] In the presence of methanol. [b] Concealed by the solvent.



Results and Discussion

Originally, we planned to study these reactions in methanol for a direct comparison with the formation of Meisenheimer adducts from nitro-activated benzenes. Spectrophotometric (UV) studies were carried out conveniently in this solvent. However, owing to the low solubilities of the salts of **1** and **2** in MeOH, NMR studies were at first carried out by recording the spectra of the salts in acetonitrile-d_3 and by adding subsequently the appropriate amount of a 4–5 M solution of sodium methoxide in MeOH. The medium was thus a mixture of acetonitrile-d_3 and methanol, approximately 9:1 (v/v).

NMR Studies in Acetonitrile-d_3–Methanol (9:1). The addition of an equivalent amount of methoxide ion to **1** and **2** brings about a general upfield shift of the NMR signals. Thus, the AB_2 system of **1** is replaced immediately after the addition of methoxide by the AX_2 system of **3** (Table I). The strong upfield shift of the hydrogen at position 4 indicates that the carbon atom in 3 has undergone change from sp^2 to sp^3 hybridization. The coupling constant between the adjacent positions of **3** is similar to the $J_{3,4}$ value in 1,4-dihydropyridines.[15] The NMR spectrum shows also weak signals at δ 6.5–7.0, whose intensities increase with time to become comparable with the signals of **3** after several hours.

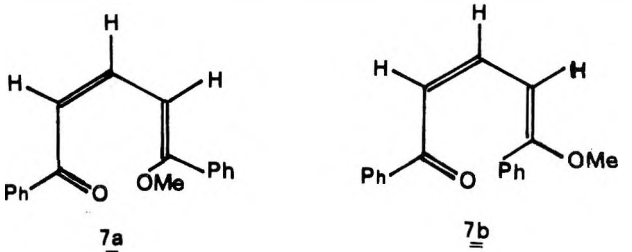
As to the reaction of **2**, the addition of the nucleophile leads immediately to the conversion of **2** to **4**. It can be excluded that the observed spectrum corresponds to that of a demethylation product because 2,6-diphenyl-4-pyranone shows a signal at δ 6.73. The signals of the methoxyls of **4** are concealed by the methanol introduced with the nucleophile. Besides the above described signals, the NMR spectrum shows very weak signals at δ 5.9 and 4.6, whose intensities increase very slowly to become in a few days comparable with the signal at δ 5.77. The nature of the slower reaction will be evident below.

NMR Studies in Methanol. (a) At Room Temperature. In the reaction of **1** the signals of adduct **3** are detected immediately after the addition of methoxide ion together with weak signals at δ 6.4–7.1. In a few minutes the signals of **3** decrease, with a corresponding increase of the signals at δ 6.4–7.1, and disappear completely in less than 1 h.

The final product was characterized as the dienone **7** by a 90 MHz spectrum in methanol: at δ 6.88 (H-3, triplet, J = 10.9 Hz); at nearly δ 6.6 (H-2, doublet of the same intensity, J = 10.9 Hz); intense multiplet in the range of the phenyl groups. Another proton, coupled only to H-3, was localized at δ 7.4 under the phenyl groups by a spin-tickling experiment; irradiation at δ 7.36 or 7.48 split each signal of the triplet into two doublets, leaving unchanged the doublet at δ 6.6. The signal at δ 7.4 corresponds to the proton at position 4, strongly deshielded by the adjacent carbonyl group, as already reported in dienones obtained upon ring opening of 2*H*-pyrans.[16] The methoxy group of **7** was detected at δ 3.90 in a CCl_4 solution, which otherwise showed the same pattern as in methanol. The difference between the chemical shift of H-4 in **7** (δ 7.4) and that reported for the dienone derived from 2,4,6-trimethyl-2*H*-pyran (δ 7.63)[16] is in better accordance with a *Z* configuration around the C_4–C_5 bond (δ_{calcd} 6.98)[17] than with an *E* configuration (δ_{calcd} 6.73).[17]

The value of $J_{2,3}$ (10.9 Hz), similar to that reported for ring-cleaved compounds formed after nucleophilic addition to pyridinium cations,[8c] shows the *Z* configuration of the double bond at C_2–C_3. The $J_{3,4}$ value (10.9 Hz) and the absence of coupling between positions 2 and 4, as previously reported for the dienone derived from 2,4,6-trimethyl-2*H*-pyran,[16] show that the more stable conformer of **7** is *s*-trans around the C_3–C_4 bond. Dienone **7** is presumably formed by the electrocyclic ring-opening reaction of 2*H*-pyran **5**. However, **5** is not detected as such by NMR spectroscopy. Weak signals in the alkene and methoxyl regions are in fact recorded, but their assignment to **5** is not straightforward. The absence of **5** shows that **7** is more stable and that, at the same time, a low energy barrier divides **7** from **5**.

2*H*-Pyran **5** could yield both **7a** and **7b**; the preferential formation of **7** as a stable conformer of **7a** shows that the



smaller methoxy group rotates inward during the ring-opening reaction because of a sterically favored transition state and finally turns out to be situated trans at H-4.

As to the reaction of **2**, this yields immediately a deep yellow solution of both 4*H*-pyran **4** and 2*H*-pyran **6**. The characterizing feature of the latter is given by two coupled signals of the same intensity. The $J_{3,5}$ value of **6** is in the range observed in 1,2-dihydropyridines[8c] and α-pyrones[18] (J = 1.5–3 Hz). The intensity ratio between each of the doublets and the singlet is nearly 0.5. At variance with the reaction of **1**, both 2*H*- and 4*H*-pyrans are observed separately in the reaction of **2**. Moreover, the electrocyclic ring opening of **6** is not observed. This spectrum changes slowly with time; after one day a signal is detected at δ 6.85, owing to the formation of a small amount of the demethylation product (2,6-diphenyl-4-pyranone).

(b) At Low Temperature. The disappearance of the signals of both substrates is complete within the time necessary to add the nucleophile and record the spectra.

The reaction of **1** at −30 °C yields only adduct **3**, which is converted to the open-chain dienone **7** on raising the temperature.

The reaction of **2** was performed at −50 °C. Even at this temperature, **2** yields both adducts **4** and **6** in a ratio not too different from that observed at room temperature.

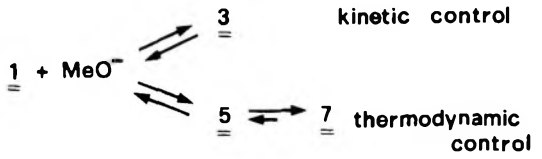
NMR Studies in Me_2SO-d_6–MeOH (9:1 v/v). Only the reaction of **2** was studied in Me_2SO because of the fast decomposition of **1** in this solvent. Upon addition of an equivalent amount of MeO^-, **2** yields adduct **4**. After one week at room temperature, this adduct is still almost unchanged, even if weak broad signals are detected at δ 7.1–7.2, probably owing to some decomposition. The demethylation product, 2,6-diphenyl-4-pyranone, is not detected.

Spectrophotometric Studies. 2,6-Diphenylpyrylium cation (**1**) in methanol has two absorption maxima at 277 nm (ϵ 1.62×10^4 M^{-1} cm^{-1}) and 400 (2.51×10^4). Upon addition of a slight excess of sodium methoxide to a 4.5×10^{-5} M solution of **1**, these maxima disappear immediately to be replaced by new maxima at 243 and 353 nm. With time the absorbance at 243 nm decreases, whereas that at 353 nm increases further. This conversion is characterized by the presence of an isosbestic point at 270 nm. After 15 min the reaction is practically finished, and a residual absorbance is observed in the range 230–260 nm together with the maximum at 353 nm. Upon addition of HCl in methanol the reaction products are converted back to pyrylium cation **1**. On the basis of the NMR data we attribute the absorbance maximum at 243 nm to 4*H*-pyran **3**. This hypothesis is in accordance with literature data[19] reporting that nonconjugated 4*H*-pyrans have maxima in the region of 225 and 250 nm. The absorbance maximum at 353 nm, again on the basis of the NMR and literature data[19] concerning the electronic spectra of 2*H*-2-benzyl- and 4*H*-4-benzyl-2,4,6-triphenylpyrans, is assigned to the open-chain dienone **7**. A clear distinction between 2*H*-pyrans and their open-chain valence tautomers does not seem feasible on the basis of the UV spectral data alone.[20]

In methanol, 4-methoxy-2,6-diphenylpyrylium cation (**2**) shows two absorption maxima at 274 nm (ϵ 2.45×10^4 M^{-1} cm^{-1}) and 355 (2.57×10^4). Upon addition of a slight excess of sodium methoxide, the spectrum of **2** disappears immediately and the formation of two maxima at 237 and 320 nm is observed (of intensity nearly 1:2). The disappearance of **2** is complete even with a methoxide ion concentration as low as 10^{-4} M. Upon acidification, the reaction products are converted back to cation **2**. On the basis of NMR and literature data[19] we assign the shorter wavelength maximum to 4*H*-pyran **4** and the longer wavelength one to 2*H*-pyran **6**. At variance with the reaction of **1**, small changes of the spectrum are observed only after several hours.

Course of the Reaction. The reaction of 2,6-diphenylpyrylium cation **1** yields 4*H*-pyran **3** as the kinetically controlled product. Nucleophilic addition occurs more easily at the γ position probably because of the lower steric requirement with respect to the α positions. This reaction is the only one observed in methanol at low temperature and in the 9:1 acetonitrile–methanol mixture.

Scheme I



When the reaction is run in methanol at room temperature, the initial formation of **3** is followed by the appearance of the ring-cleaved dienone **7**. Subsequently, **3** is completely transformed into the latter. The same behavior is observed when the reaction mixture is initially kept at low temperature and then warmed to room temperature.

Compound **7** is the result of a thermodynamically controlled pathway; the formation of a strongly conjugated dienone may then be considered a driving force. The reaction goes probably according to Scheme I. This involves the interaction of small amounts of the starting reactants, which are in equilibrium with **3** and may alternatively react to yield 2*H*-pyran **5**, the immediate precursor of **7**. So far it has not been possible to detect by NMR spectroscopy the presence of **5**. However, owing to the relatively low sensitivity of the NMR method and the expected complexity of the spectrum of **5**, we cannot exclude the presence of a small amount at equilibrium. In Scheme I methanol, as a hydrogen bond donor, is likely to act as a promoter of the departure of the methoxyl from **3** and of the return to pyrylium cation **1**; the use of a solvent with a low content of methanol slows down the conversion of the 4*H*-pyran to dienone **7** and allows even the isolation, upon removal of the solvent, of a mixture containing substantial amounts of adduct **3**.

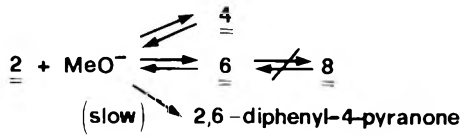
In the reaction of 4-methoxy-2,6-diphenylpyrylium cation **2**, the behavior is again strongly dependent upon the nature of the solvent. In methanol **4** is detected along with its isomeric 2*H*-pyran **6**; the ratio **4**/**6**, as measured by NMR spectroscopy, is independent of the temperature and does not change dramatically with time. The observed ratio seems thus to be a measure of the relative stability of **4** and **6**. On the other hand, in the acetonitrile-rich medium the observed product is only the 4*H*-pyran adduct **4**. On standing at room temperature, this adduct is slowly converted into a mixture of the isomeric adducts **4** and **6**. The conversion **4** → **6** is even slower in a Me_2SO-rich medium, where the hydrogen bond donor ability of methanol is presumably lower than in the acetonitrile-rich medium.

At variance with the behavior of the undetected 2*H*-pyran **5**, 2*H*-pyran **6** apparently does not undergo the ring-opening reaction to dienone **8**. This difference in behavior is related to the presence at position 4 of a substituent; while it seems difficult to estimate the role of electronic effects in the ring-opening reaction, the stability of 2*H*-pyran **6** may be connected to the fact that an increase of steric hindrance generally shifts the equilibrium 2*H*-pyran ⇌ dienone toward the left, probably because bulky groups decrease the conjugation degree in the dienone system.[20]

An assessment of the tendency of **6** to undergo the ring-opening reaction (**6** → **8**) is complicated by the fact that **2** is finally demethylated to 2,6-diphenyl-4-pyranone. This irreversible reaction, which can occur on small amounts of **2** and methoxide (Scheme II), could effectively compete with a possible slow ring-opening reaction.

The equilibria for the reactions of **1** and **2** with CH_3O^- are largely shifted to the pyrans, even in methanol solutions

Scheme II



containing very dilute methoxide ion. Under this aspect, the tendency of pyrylium cations to undergo nucleophilic addition seems qualitatively higher than that of pyridinium cations under similar conditions.[21] Further work will be necessary in order to assess quantitatively this tendency.

The possibility of rapid interconversions between the reaction products (isomeric pyrans and/or dienones) has some implication on the chemistry of pyrylium and related heteroaromatic cations in the sense that the relative reactivities of different positions in these cations cannot be immediately related to the yield of the respective addition product. Under this view, an important role is also played by the nature of the medium, which can strongly affect the rate of return of the adducts to the starting reagents, allowing the easy detection of the less stable reaction products in the media containing minor amounts of the hydroxylic solvent.

Experimental Section

Published procedures were followed for the synthesis of the perchlorates of 1[22] and 2.[23] We found it convenient to purify these salts by dissolving them in the least amount of dry acetonitrile and precipitating with dry ethyl ether.

Electronic spectra were recorded on a Perkin-Elmer 402 instrument; molar absorption coefficients of 1 and 2 in methanol were recorded in the presence of $HClO_4$ in order to avoid the methanolysis reaction. NMR experiments at 60 MHz were done on a Jeol C60-HL instrument; the spin-tickling experiment at 90 MHz was done on an HX90 Bruker apparatus. Since the perchlorates of 1 and 2 are poorly soluble in methanol, the NMR spectra of the reaction products can be conveniently recorded upon addition of an equivalent amount of sodium methoxide to a suspension of the perchlorates in this solvent (20–30 mg in 0.5 mL of CD_3OD). This operation brings about the complete solubilization of the substrates. In order to avoid any interference of the signals of the products with those of any residual light methanol, the reagent was freed from CH_3OH by alternating several times vacuum pumping and addition of CD_3OD.

Isolation of Adducts. General Procedure. To a solution of the perchlorate of 1 or 2 in acetonitrile (ca. 5×10^{-2} M) was added an equivalent amount of potassium methoxide as a 2.8 M solution in methanol. The solvents were rapidly removed under reduced pressure at room temperature, and the organic materials were dissolved in CCl_4 or ethyl ether. The oily residue of evaporation was induced to crystallize by scratching or prolonged cooling. Attempted purification of these solids by recrystallization or chromatography led to decomposition.

Adduct from 1: mp 54–66 °C dec; MS, weak peak at *m/e* 264 corresponding to the molecular peak from a 1:1 adduct between 1 and CH_3O^-, intense peak (base peak) at *m/e* 233 $(M - OCH_3)^+$, and absence of peaks beyond *m/e* 264. The NMR spectrum (CCl_4) is in accordance with the formation of 4*H*-pyran 3 (Table I), except for the somewhat higher intensity of the phenyl region, presumably related to the overlapping with phenyl groups of otherwise undetected side products.

Adduct from 2: mp 65–75 °C dec; MS, weak peak at *m/e* 294 (M^+ of 1:1 adduct), intense peak at *m/e* 263 $(M - OCH_3)^+$, and absence of peaks beyond *m/e* 294. The NMR spectrum (CCl_4) shows the presence of 4*H*-pyran adduct 4 and a minor amount of 2,6-diphenyl-4-pyranone.

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Registry No.—1, 41044-52-4; 1 perchlorate, 3558-68-7; **2**, 47075-64-9; **2** perchlorate, 17539-77-4; **3**, 53856-27-2; **4**, 67069-64-1; **6**, 67069-65-2; **7**, 67069-66-3.

References and Notes

(1) R. Livingstone in "Rodd's Chemistry of Carbon Compounds", Vol. 4, Part E, S. Coffey, Ed., 2nd ed., Elsevier, Amsterdam, 1977, p 1.
(2) E. N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, *J. Org. Chem.*, **37**, 2992 (1972), and references therein.
(3) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 117 (1946).
(4) J. A. Van Allan, G. A. Reynolds, and C. C. Petropoulos, *J. Heterocycl. Chem.*, **9**, 783 (1972).
(5) M. H. O'Leary and R. W. Stach, *J. Org. Chem.*, **37**, 1491 (1972).
(6) For a recent review, see C. F. Bernasconi, *Org. Chem., Ser. One, 1973*, **3**, 33 (1973).
(7) For a review, see M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(8) (a) U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972); (b) J. Schnekenburger, D. Heber, and E. Heber-Brunschweiger, *Justus Liebigs Ann. Chem.*, 1799 (1976); (c) J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.*, **41**, 1303 (1976); (d) J. W. Bunting and D. J. Norris, *J. Am. Chem. Soc.*, **99**, 1189 (1977).
(9) E. T. Østensen and M. M. Mishrikey, *Acta Chem. Scand.*, **30**, 635 (1976).
(10) S. Sib, *Tetrahedron*, **31**, 2229 (1975).
(11) S. Yoneda, T. Sugimoto, O. Tanaka, Y. Moriya, and Z. Yoshida, *Tetrahedron*, **31**, 2669 (1975).
(12) G. Baldini, G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.*, **41**, 2153 (1976).
(13) C. F. Bernasconi, *J. Am. Chem. Soc.*, **93**, 6975 (1971).
(14) A. T. Balaban, W. Schroth, and G. Fischer, *Adv. Heterocycl. Chem.*, **10**, 263 (1969).
(15) M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).
(16) E. N. Marvell and T. Gosink, *J. Org. Chem.*, **37**, 3036 (1972).
(17) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).
(18) J. L. Bloomer, S. M. H. Zaidi, J. T. Strupczewiski, C. S. Brosz, and L. A. Gudzyk, *J. Org. Chem.*, **39**, 3615 (1974).
(19) K. Dimroth, K. Wolf, and H. Kroke, *Justus Liebigs Ann. Chem.*, **678**, 183 (1964).
(20) T. A. Gosink, *J. Org. Chem.*, **39**, 1942 (1974).
(21) J. Kaválek, A. Lyčka, V. Macháček, and V. Štěrba, *Coll. Czech. Chem. Commun.*, **40**, 1166 (1975).
(22) K. Dimroth and K. H. Wolf in "Newer Methods of Preparative Organic Chemistry", Vol. 3, W. Foerst, Ed., Academic Press, New York, N.Y., 1964, p 409.
(23) G. A. Van Allan, G. A. Reynolds, and D. P. Maier, *J. Org. Chem.*, **33**, 4418 (1968).

Synthesis of 3-Aryl-5-bromo-2(5*H*)-furanones[1]

Mark T. Edgar, George R. Pettit,* and Thomas H. Smith

Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

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A synthetic route to 3-aryl-5-bromo-2(5*H*)-furanones (7) based on treating a methyl 2-aryl-4-oxobutyrate (5) with bromine in acetic acid has been developed. The methyl 2-aryl-4-oxobutyrates were prepared in high yield by the following sequence: alkylation of an arylacetic acid using lithium diisopropylamide and allyl bromide, esterification with diazomethane to yield a methyl 2-aryl-4-pentenoate (4), and ozonolysis (4 → 5).

Continued interest in the synthesis of cardenolides[2] and isocardenolides[3] for biological evaluation led us to consider simpler 2(5*H*)-furanones[4,5] for antineoplastic and/or cytotoxicity studies. Semonsky and co-workers[6] have examined

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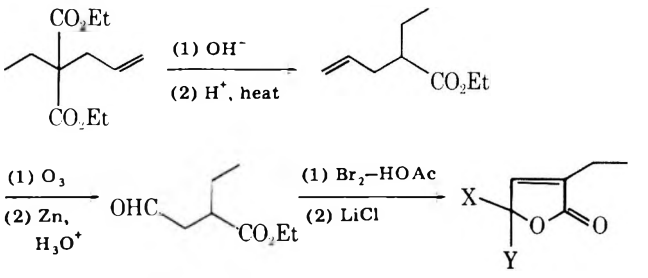
Scheme I



1a, X = Y = Cl
b, X = Cl; Y = Br
c, X = Y = Br
d, X = Br; Y = OEt
e, X = Br; Y = OAc

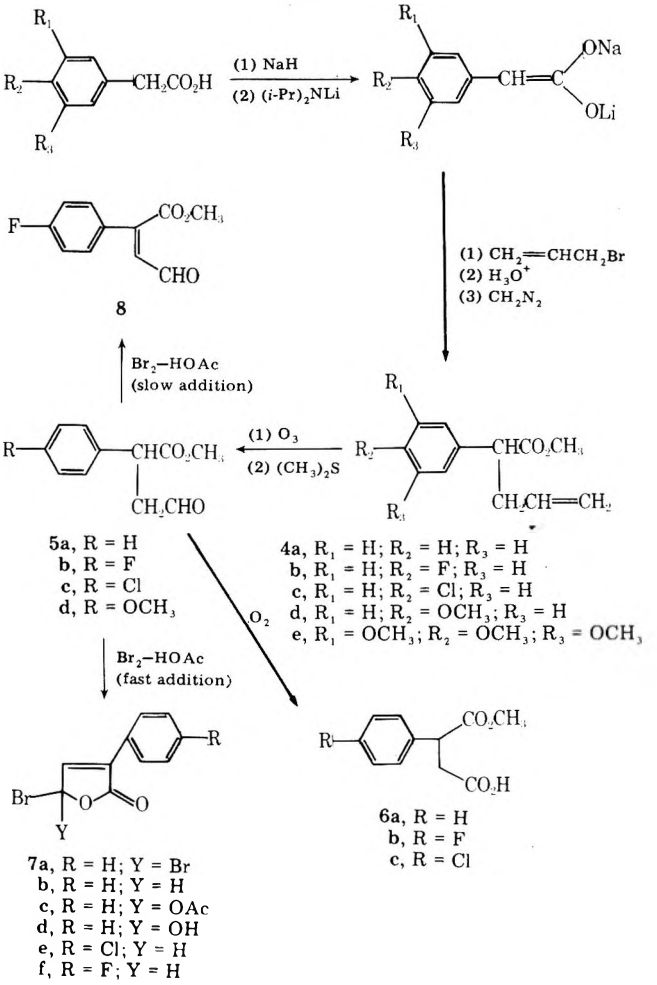
a series of 2(5*H*)-furanones of the 5-substituted mucohalic acid type for anticancer activity. Generally, the 5 substituent consisted of an aryl group or a side chain containing an aryl group. Among such lactones 3,4-dichloro-5-(*p*-methoxyphenyl)-2(5*H*)-furanone was found to display significant antineoplastic activity.

In the present study we explored the synthesis of the hitherto unknown 3-aryl-5-halo-2(5*H*)-furanones. A workable synthetic route was discovered[7] during an attempt to prepare ethyl 2-ethyl-4-oxo-2-butenoate by allowing bromine to react with ethyl 2-ethyl-4-oxobutyrate followed by addition of lithium chloride. Instead of the expected butenoate, a series (Scheme I) of 3-ethyl-5-halo-2(5*H*)-furanones (**1**) was isolated. Furanone **1c** was isolated from a reaction sequence where lithium chloride was not used. The furanones were obtained (silica gel chromatography) as oils and were only moderately stable at 0 °C. Consequently, the structures of these furanones were not confirmed by elemental analyses and biological evaluation was not pursued. Efforts to improve the yields of the 3-ethylfuranones by conducting the reactions at high dilution or in chloroform containing *p*-toluenesulfonic acid were not successful, and attention was focused on obtaining the presumably more stable 3-arylfuranones.

While ethyl 2-ethyl-4-pentenoate was readily available via a malonic ester synthesis,[8] the necessary alkyl 2-aryl-4-pentenoates required development of a convenient route.[9] The main step involved (Scheme II) alkylation of an arylacetic acid with allyl bromide based on a procedure outlined by Creger[10] for alkylating alkylacetic acids. The resulting acid was easily converted to the methyl ester 4 using diazomethane.[11]

Conversion of the methyl 2-aryl-4-pentenoates (**4**) to an aldehyde derivative (**5**) was originally accomplished employing ozone in an aprotic solvent followed by reduction of the ozonide with zinc and acetic acid. Reduction of the ozonide was found slow and somewhat unpredictable. Application of the Pappas[12] procedure by performing the ozonization in methanol and reduction of the resulting hydroperoxide with methyl sulfide afforded reasonable yields of the aldehyde. The methyl 2-aryl-4-oxobutyrates (see supplementary material) were stable at −11 °C for several months, but if exposed to air at 25 °C for several weeks they oxidized[13] to methyl esters of phenylsuccinic acids (**6**). Since the aldehydes were somewhat unstable, the 2,4-dinitrophenylhydrazone[14] derivatives were used to determine elemental composition. When bromine was rapidly added to methyl 2-phenyl-4-oxobutyrate in acetic acid, the deep red solution became yellow in about 1 h and the furanones were isolated as oils by silica gel chromatography to afford, in order of elution, 3-phenyl-5,5-dibromo-2(5*H*)-furanone (**7a**), 3-phenyl-5-bromo-2(5*H*)-furanone (**7b**), and 3-phenyl-5-acetoxy-5-bromo-2(5*H*)-furanone (**7c**). Rechromatography of a more polar fraction gave 3-phenyl-5-bromo-5-hydroxy-2(5*H*)-furanone (**7d**).[15]

Scheme II



5a, R = H
b, R = F
c, R = Cl
d, R = OCH_3

4a, R_1 = H; R_2 = H; R_3 = H
b, R_1 = H; R_2 = F; R_3 = H
c, R_1 = H; R_2 = Cl; R_3 = H
d, R_1 = H; R_2 = OCH_3; R_3 = H
e, R_1 = OCH_3; R_2 = OCH_3; R_3 = OCH_3

7a, R = H; Y = Br
b, R = H; Y = H
c, R = H; Y = OAc
d, R = H; Y = OH
e, R = Cl; Y = H
f, R = F; Y = H

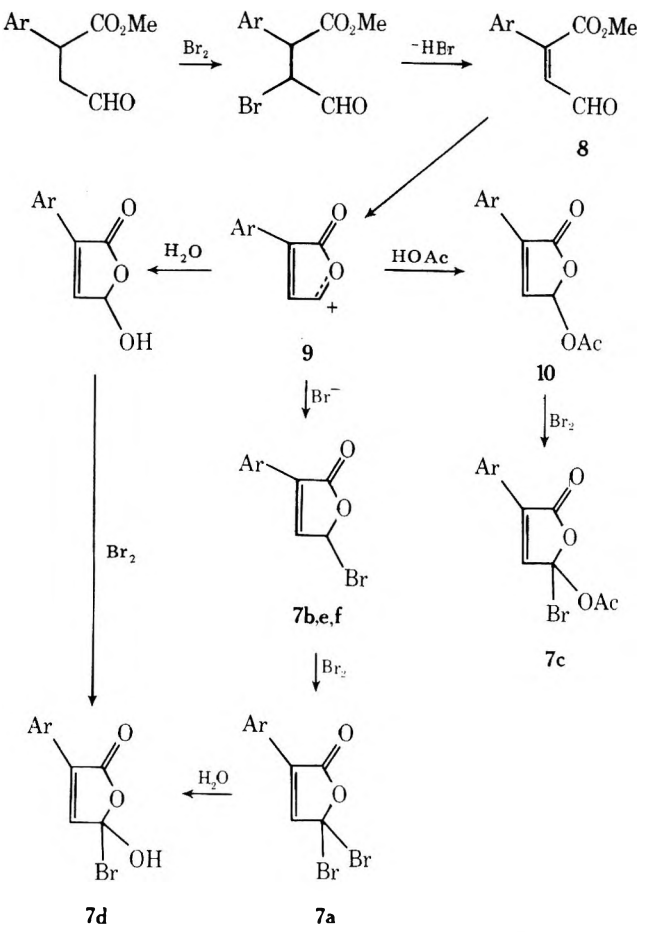
6a, R = H
b, R = F
c, R = Cl

In a similar manner (Scheme II), methyl 2-(*p*-chlorophenyl)-4-oxobutyrate led to 3-(*p*-chlorophenyl)-5-bromo-2(5*H*)-furanone (**7e**) and methyl 2-(*p*-fluorophenyl)-4-oxobutyrate afforded methyl 3-(*p*-fluorophenyl)-5-bromo-2(5*H*)-furanone (**7f**).[16] Here lactones **7e** and **7f** were the major products isolated. In both reaction sequences other products were formed, but isolation proved to be too difficult for practical purposes. With the methyl 2-(*p*-fluorophenyl)-4-oxobutyrate bromination products, at least two or three additional compounds were produced during silica gel chromatography. However, once the 3-arylfuranone was isolated, decomposition was not observed. In fact, sublimation at 80 °C (under vacuum) was used to purify furanones **7a** and **7e.** A mechanism has been suggested (Scheme III) to account for the products observed from the bromination sequence.[17]

Slow addition of small aliquots of bromine to a solution of methyl 2-(*p*-fluorophenyl)-4-oxobutyrate in glacial acetic acid resulted in the formation of methyl 2-(*p*-fluorophenyl)-3-formylacrylate (**8**). The formylacrylate, isolated as long yellow needles, was of sufficient stability to allow full characterization but underwent slow decomposition. The bromination of methyl 2-(*p*-methoxyphenyl)-4-oxobutyrate (**5d**) was suspended when only complex mixtures were obtained, probably a result of phenyl ring bromination. Similarly, reactions with methyl 2-(3′,4′,5′-trimethoxyphenyl)-4-pentenoate were not pursued further.

The ^1H NMR spectra of the 5-disubstituted and 5-monosubstituted 3-arylfuranones showed the aromatic protons as complex multiplets. The 5-disubstituted furanones displayed one vinyl proton (C-4) at δ 6.81, 6.92, and 6.12 for lactones **7a, 7c,** and **7d,** respectively. These values compared well with those noted for 3-ethyl-5,5-dibromo-2(5*H*)-furanone (**1c,** δ 6.72), 3-ethyl-5-acetoxy-5-bromo-2(5*H*)-furanone (**1e,** δ 6.81),

Scheme III



and 3-ethyl-5-bromo-5-ethoxy-2(5*H*)-furanone (**1d**, δ 5.91). The apparent shielding effects of the 5-ethoxy and 5-hydroxy groups (**1d** and **7d**) on the C-4 hydrogen may be caused by a shift of the double bond π cloud toward C-4 due to the oxygen electronegativity. On the other hand, the 5-acetoxy derivative **7c** could deshield the C-4 hydrogen by an anisotropic effect. Interestingly, replacement of the 3-ethyl substituent with an aryl group only deshielded the C-4 hydrogen by about 0.1 ppm.

For the 5-monosubstituted furanones, 5-bromo-2(5*H*)-furanone[18] proved to be a good model system. The C-4 and C-5 hydrogens of 5-bromo-2(5*H*)-furanone have been reported to resonate at δ 7.80 and 7.08 with a coupling constant of 1.3 Hz. The δ 7.08 signal for the C-5 hydrogen of 5-bromo-2(5*H*)-furanone compared well with the values of δ 6.94, 7.08, and 7.08 observed for 3-phenyl-5-bromo-2(5*H*)-furanone (**7b**), 3-(*p*-chlorophenyl)-5-bromo-2(5*H*)-furanone (**7e**), and 3-(*p*-fluorophenyl)-5-bromo-2(5*H*)-furanone (**7f**), respectively. As observed earlier, the phenyl ring has only a minor effect on the vinyl hydrogen, and the more distant C-5 hydrogen should exhibit an even smaller shift. The vinyl hydrogen signals of furanones **7b, 7e,** and **7f** were located at δ 7.62, 7.69, and 7.64, respectively, and they relate fairly well to the vinyl hydrogen signal (δ 7.80) of 5-bromo-2(5*H*)-furanone. The vinyl protons for the 5-disubstituted furanones were decidely upfield from those of the 5-monosubstituted lactones. Again this would appear to be the consequence of π-cloud polarization. The two electronegative C-5 substituents should shift the π cloud more toward C-4, thereby further shielding the C-4 proton.

The 5-disubstituted furanone mass spectra were characterized by the initial loss of either C-5 substituent; however, elimination of a bromine radical was preferred. Following the loss of bromine, carbon monoxide was twice expelled and the remaining C-5 substituent was lost, producing an arylacetylene. The order of these steps differed for each type of compound. Arylacetylene formation was evident for each furanone and methyl 2-(*p*-fluorophenyl)-3-formylacrylate (**8**). With 3-phenyl-5-acetoxy-5-bromo-2(5*H*)-furanone (**7c**) the major fragmentation pathway encompassed initial loss of ketene followed by cleavage of a bromine radical, CO_2H, and carbon monoxide to produce phenylacetylene.

The monosubstituted furanones invariably lost the 5-bromo group from the molecular ion followed by two successive losses of carbon monoxide. Alternatively, the second carbon monoxide elimination can be superseded by loss of CHO. In addition, the molecular ion for the 5-monosubstituted furanones can expel carbon dioxide. The intensity of this very weak ion decreased in the order 3-phenyl > 3-(*p*-chlorophenyl) > 3-(*p*-fluorophenyl). These fragmentation pathways were comparable to those deduced for the 3-ethylfuranones.

Preliminary screening of the 3-arylfuranones (**7**) and their precursors for cytotoxicity was carried out by the National Cancer Institute using the P388 murine lymphocytic leukemia and KB (human nasopharynx carcinoma) in vitro cell lines, but no significant activity was found. Before any conclusion can be reached about antineoplastic activity, further evaluation of furanones **7** against several in vivo tumor lines will be necessary.

Experimental Section

Reagents and solvents (ligroin refers to a fraction boiling at approximately 60 °C) used in this study were obtained from J. T. Baker Chemical Co., Mallinckrodt, Inc., Aldrich Chemical Co., and MC/B Manufacturing Chemists, with the exception of *N*-methyl-*N*-nitrosourea and *n*-butyllithium which were provided by Fairfield Chemical Co. and Thiokol Corp. (Ventron Division), respectively. All solvents were redistilled, and solvent extracts were dried over magnesium sulfate. Tetrahydrofuran was distilled from sodium hydride or lithium aluminum hydride. Silica gel F-254 (0.25 mm E. Merck, Darmstadt) plates were used for thin-layer chromatography, and the plates were visualized with UV light or an anisaldehyde–sulfuric acid–glacial acetic acid (1:2:97) spray. Column chromatography employed silica gel (70–230 mesh) supplied by E. Merck. In each case the silica gel/substrate ratio was 50:1. Deuteriochloroform was used as solvent and tetramethylsilane as an internal standard for nuclear magnetic resonance measurements (by Dr. J. Witschel, Varian XL-100 and T-60A instruments). The mass spectra (70 eV) were recorded by Mr. E. Kelley employing Atlas CH-4B and SM-1B instruments. Melting points (uncorrected) were taken on a Kofler melting point apparatus. Elemental analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Ethyl 2-Ethyl-4-oxobutyrate. Ethyl 2-ethyl-4-pentenoate[8] (9.0 g, 0.058 mol) was placed in chloroform (100 mL) and treated with ozone (3%) at −40 °C for 1.5 h until a blue color appeared. Zinc (5 g) in glacial acetic acid (20 mL) was added, and the mixture was stirred at 0 °C for 1 h. The solution was filtered and poured into water (100 mL). The organic layer was separated, washed with 5% sodium bicarbonate, and dried. The solvent was removed to yield 8.4 g (93%) of ethyl 2-ethyl-4-oxobutyrate. The product was converted[14] to the 2,4-dinitrophenylhydrazone, mp 79–81 °C.

Anal. Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.32; N, 16.57. Found: C, 49.86; H, 5.42; N, 16.67.

Bromination–Dehydrobromination of Ethyl 2-Ethyl-4-oxobutyrate. Ethyl 2-ethyl-4-oxobutyrate (8.4 g, 0.053 mol) was dissolved in glacial acetic acid (30 mL). Bromine (8.5 g, 0.053 mol) was added over 30 min, and the solution was stirred at 24 °C for one day. The reaction mixture was poured into water (100 mL) and extracted with chloroform. The combined extract was washed with 10% sodium thiosulfate, water, and 5% sodium bicarbonate and dried. Solvent was removed, and the 12.3 g of pale yellow oil was placed in dimethylformamide (50 mL). Lithium chloride (10 g) was added, and the mixture was stirred under nitrogen at 100 °C for 1 h. The reaction mixture was poured into water (150 mL) and then extracted with ligroin. The extracts were combined and dried, and the solvent was removed to yield 2.30 g of a yellow liquid. Purification by silica gel chromatography (70 g; benzene) afforded the following products in order of their elution: 1.19 g of **3-ethyl-5-bromo-5-chloro-2(5*H*)-furanone** (**1b**) and **3-ethyl-5,5-dichloro-2(5*H*)-furanone**

(**1a**) as a 4:1 mixture [IR (neat) 1790, 1650, 1010, 940, 910, 800 cm^{-1}; ^1H NMR δ 1.14 (t, 3 H), 2.42 (q, 2 H), 6.41 (s, 1 H); mass spectrum, *m/e* (relative intensity) 228 (1), 226 (6), 224 (4), 195 (6), 189 (34), 180 (6), 161 (2), 151 (20), 145 (100), 117 (8), 109 (10), 81 (25), 65 (46)]; **3-ethyl-5-bromo-5-ethoxy-2(5*H*)-furanone (1d)** (0.313 g) [IR (neat) 1770, 1660, 1180, 960, 940, 860 cm^{-1}; ^1H NMR δ 1.0–1.5 (two sets of overlapping triplets, 6 H), 2.40 (q, 2 H), 3.86 (q, 2 H), 5.91 (s, 1 H); mass spectrum, *m/e* (relative intensity) 236 (59), 234 (56), 207 (91), 205 (81), 191 (100), 189 (90), 162 (35), 160 (39), 155 (81), 111 (81), 109 (38), 83 (60), 81 (64), 65 (55), 53 (66)]; and **3-ethyl-5-acetoxy-5-bromo-2(5*H*)-furanone (1e)** (0.246 g) [IR (neat) 1765, 1740 sh, 1660, 1210, 1000, 945, 875 cm^{-1}; ^1H NMR δ 1.18 (t, 3 H), 2.1–2.5 (m, 5 H), 2.20, 6.81 (s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 247 (M − 1,1), 206 (6), 205 (6), 189 (29), 188 (28), 169 (37), 161 (3), 160 (10), 127 (59), 109 (16), 99 (13), 81 (56), 65 (50), 43 (100), 29 (78)].

Bromination of Ethyl 2-Ethyl-4-oxobutyrate. Ethyl 2-ethyl-4-oxobutyrate (5 g, 0.032 mol) was placed in glacial acetic acid (25 mL). Bromine (5.5 g, 0.35 mol) was added over 20 min, and the solution was stirred at 24 °C for 6 h. The reaction mixture was poured into water (75 mL) and extracted with chloroform. The combined extract was washed with 5% sodium bicarbonate, water, 10% sodium thiosulfate, and water and dried. The solvent was removed to yield 6.5 g of pale yellow liquid. Isolation by silica gel chromatography (180 g; benzene) afforded the following: **3-ethyl-5,5-dibromo-2(5*H*)-furanone** ([C((49.2 mg) [IR (neat) 1780, 1640, 1000, 940, 880 cm^{-1}; ^1H NMR δ 1.14 (t, 3 H), 2.42 (q, 2 H), 6.72 (s, 1 H); mass spectrum, *m/e* (relative intensity) 192 (18), 191 (100), 190 (17), 189 (77), 123 (29), 121 (26), 111 (15), 82 (22), 81 (24), 66 (42), 65 (51), 53 (55)]; and **ethyl 2-ethyl-3,3-dibromo-4-oxobutyrate** (1.45 g) [^1H NMR δ 1.00 (t, 3 H), 1.24 (t, 3 H), 1.90 (2 H), 3.18 (t, 1 H), 4.22 (q, 2 H), 9.18 (s, 1 H)].

General Procedure 1. Synthesis of Methyl 2-Aryl-4-pentenoates. A four-neck round-bottom flask (1000 mL) was equipped with a reflux condenser, mechanical stirrer, thermometer (held in contact with the flask contents by a ground glass joint), addition funnel, and nitrogen source. To the flask was added tetrahydrofuran (350 mL), diisopropylamine (11.0 mL, 0.15 mol), and sodium hydride (9.6 g of a 50% oil dispersion, 0.20 mol). The arylacetic acid (0.15 mol) in tetrahydrofuran (50 mL) was added with stirring over a 20-min period. The resulting gelatinous slurry was heated at reflux for 20 min to complete metalation of the arylacetic acid. At this time the addition funnel was replaced by a septum and the white slurry was cooled, under a brisk nitrogen flow, to 10 °C. Injection of *n*-butyllithium (2 M in heptane, 75 mL, 0.15 mol) into the flask was done at a rate that maintained the temperature at 10 °C or less. After stirring for 10 min at 10 °C, allyl bromide (25.4 mL, 0.15 mol) was added while maintaining the temperature at or below 10 °C. The reaction mixture was stirred at 10 °C for 15 min and then at 25 °C for 1 h. Water (200 mL) was slowly added to the reaction flask. The organic layer was removed, and the remaining aqueous layer was washed with ether, acidified to pH 2 with 6 N HCl, and extracted with ether. The combined ether extract was washed with a saturated sodium chloride solution, dried, and concentrated to leave the 2-aryl-4-pentenoic acid as an oil. Diazomethane[11] was slowly added to a solution of the crude 2-aryl-4-pentenoic acid in 1,2-dimethoxyethane (50 mL) at 10 °C until an excess of diazomethane was present. The solvent was removed in vacuo, leaving an oily residue which was purified by vacuum distillation.

Methyl 2-Phenyl-4-pentenoate (4a). Application of general procedure 1 to phenylacetic acid (20.4 g, 0.15 mol) provided an oil which distilled at 98–104 °C (0.5 mm) to provide 24.7 g (86.6%) of ester **4a** as a colorless liquid.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.46. Found: C, 75.41; H, 7.30.

Methyl 2-(*p*-Fluorophenyl)-4-pentenoate (4b). Extension of general procedure 1 to *p*-fluorophenylacetic acid (95% pure; 25.0 g, 0.15 mol) furnished a dark brown oil. Distillation at 76–79 °C (0.3 mm) gave 29.7 g (95%) of ester **4b** as a colorless oil.

Anal. Calcd for $C_{12}H_{13}FO_2$: C, 69.25; H, 6.25; F, 9.13. Found: C, 69.24; H, 6.30; F, 9.28.

Methyl 2-(*p*-Chlorophenyl)-4-pentenoate (4c). Use of general procedure 1 with *p*-chlorophenylacetic acid (26.4 g, 0.15 mol) produced a clear brown oil. Distillation at 84–86 °C (0.20 mm) gave 23.9 g (70.9%) of ester **4c** as a slightly yellow oil.

Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.09; H, 5.86; Cl, 15.67.

Methyl 2-(*p*-Methoxyphenyl)-4-pentenoate (4d). Using procedure 1, *p*-methoxyphenylacetic acid (24.9 g, 0.15 mol) afforded, after distillation at 90–92 °C (0.1 mm), 24.6 g (74.4%) of ester **4d** as a colorless oil.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 69.85; H, 6.97.[19]

Methyl 2-(3′,4′,5′-Trimethoxyphenyl)-4-pentenoate (4e). By means of general procedure 1, 3,4,5-trimethoxyphenylacetic acid (8.20 g, 0.034 mol) was alkylated and esterified to give a yellow oil. Distillation at 174–176 °C (3 mm) gave 5.8 g (61%) of ester **4e** as a pale yellow oil.

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.24; H, 7.25.

General Procedure 2. Synthesis of Methyl 2-Aryl-4-oxobutyrates. An excess of ozone was bubbled through a solution of the methyl 2-aryl-4-pentenoate in methanol at −78 °C. After excess ozone was removed by passing nitrogen through the solution, methyl sulfide (30% excess) was introduced and the cold solution was allowed to warm to 25 °C. After stirring for 3–5 h at 25 °C, the solvent was removed to give an oil. Vacuum distillation of this oil afforded dimethyl sulfoxide and the methyl 2-aryl-4-oxobutyrate.

Methyl 2-Phenyl-4-oxobutyrate (5a). Application of general procedure 2 to methyl 2-phenyl-4-pentenoate (28.1 g, 0.15 mol) in methanol (500 mL) furnished a colorless oil which was distilled to give dimethyl sulfoxide at 50–60 °C (0.7 mm) and aldehyde **5a** (22.6 g, 78.5%) at 104–105 °C (0.7 mm) as a colorless oil.

The 2,4-dinitrophenylhydrazone derivative of aldehyde **5a** was synthesized in the usual manner to yield, upon recrystallization from ethanol (100%), orange needles, mp 135–136 °C.

Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 54.83; H, 4.26; N, 15.03.

Methyl 2-(*p*-Fluorophenyl)-4-oxobutyrate (5b). Adoption of general procedure 2 to methyl 2-(*p*-fluorophenyl)-4-pentenoate (10.0 g, 0.048 mol) in methanol (275 mL) resulted in a colorless oil. Distillation of this oil afforded dimethyl sulfoxide at 50 °C (0.17 mm) and aldehyde **5b** (7.30 g, 72.4%) at 100–103 °C (0.17 mm) as a colorless oil.

Elemental microanalysis was performed on the 2,4-dinitrophenylhydrazone derivative of aldehyde **5b**, which was recrystallized (5 times) from ethanol (100%), resulting in orange needles, mp 158–159 °C.

Anal. Calcd for $C_{17}H_{15}FN_4O_6$: C, 52.31; H, 3.87; F, 4.87; N, 14.35. Found: C, 52.36; H, 3.85; F, 4.92; N, 14.37.

Methyl 2-(*p*-Chlorophenyl)-4-oxobutyrate (5c). Utilization of general procedure 2 with methyl 2-(*p*-chlorophenyl)-4-pentenoate (20.0 g, 0.089 mol) in methanol (200 mL) gave a brown oil which was distilled to yield dimethyl sulfoxide (42 °C, 0.3 mm) and aldehyde **5c** (15.9 g, 78.7%) at 108–110 °C (0.06 mm) as a colorless oil.

The 2,4-dinitrophenylhydrazone derivative of aldehyde **5c** was synthesized and recrystallized several times from ethanol (100%) to produce orange needles, mp 164.5–165.5 °C.

Anal. Calcd for $C_{17}H_{15}ClN_4O_6$: C, 50.20; H, 3.72; Cl, 8.72; N, 13.77. Found: C, 50.38; H, 3.51; Cl, 8.71; N, 13.79.

Methyl 2-(*p*-Methoxyphenyl)-4-oxobutyrate (5d). Employing general procedure 2 with methyl 2-(*p*-methoxyphenyl)-4-pentenoate (22.0 g, 0.10 mol) in methanol (500 mL) gave a light yellow oil which slowly darkened at 25 °C. Distillation of this oil gave dimethyl sulfoxide (50 °C at 1.4 mm) and aldehyde **5d** (16.2 g, 73%) at 159–163 °C (1.3 mm) as a colorless oil.

Elemental analytical data was obtained for the 2,4-dinitrophenylhydrazone derivative of aldehyde **5d**. Three recrystallizations from ethanol (100%) gave orange needles, mp 159–160 °C.

Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51; N, 13.93. Found: C, 53.74; H, 4.58; N, 14.04.

Methyl Ester of Phenylsuccinic Acid (6a). Carboxylic acid **6a** was produced by exposing methyl 2-phenyl-4-oxobutyrate to air for about 3 weeks. During this time the liquid aldehyde began to solidify, yielding a colorless solid. Recrystallization (several times) from chloroform–ligroin yielded colorless prisms of acid **6a** (yield ca. 50%), mp 100–101 °C.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.80. Found: C, 63.40; H, 5.75.

Methyl Ester of *p*-Fluorophenylsuccinic Acid (6b). When methyl 2-(*p*-fluorophenyl)-4-oxobutyrate (2.2 g) was exposed to air at 25 °C for more than 2 months, only an oil resulted (in contrast to aldehyde **5a**). However, the oil solidified upon seeding with a few small crystals of acid **6b** from a previous experiment. A solution of the solid in hot chloroform was mixed with hexane until turbidity was observed. Slow cooling to 25 °C produced colorless crystals. The process was repeated three times to afford needles (0.81 g), mp 103–105 °C.

Anal. Calcd for $C_{11}H_{11}FO_4$: C, 58.40; H, 4.91; F, 8.40. Found: C, 58.42; H, 4.87; F, 8.42.

Methyl Ester of *p*-Chlorophenylsuccinic Acid (6c). As noted for aldehyde **5a**, methyl 2-(*p*-chlorophenyl)-4-oxobutyrate solidified

after exposure to air (25 °C) for several weeks. The solid recrystallized from chloroform–ligroin, furnishing acid **6c** as colorless crystals, mp 129–130 °C.

Anal. Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57; Cl, 14.61. Found: C, 54.25; H, 4.54; Cl, 14.77.

Bromination of Methyl 2-Phenyl-4-oxobutyrate (5a). Bromine (1.3 g, 8.4 mmol) was quickly added to a stirred solution of aldehyde **5a** (1.6 g, 8.4 mmol) in glacial acetic acid (13 mL). In approximately 1 h the deep red solution turned light yellow. Stirring was continued for 20 h at 25 °C. The reaction mixture was diluted with water (20 mL) and extracted with chloroform, and the combined extract was washed with 10% sodium bicarbonate, water, and 10% sodium thiosulfate. Removal of solvent led to 1.21 g of a yellow oil. Silica gel chromatography (chloroform) afforded the following products in order of elution. The first product, **3-phenyl-5,5-dibromo-2(5*H*)-furanone (7a;** 0.233 g), was purified by a single sublimation (72 °C at 0.15 mm) that resulted in colorless crystals: mp 65–65.5 °C; IR (KBr) 3000, 1765, 1620, 1485, 1435, 1290, 1265, 1178, 1080, 1020, 1000, 990, 943, 878, 775, 748, 734, 690, 680 cm^{-1}; ^1H NMR δ 6.81 (s, 1 H, vinyl CH), 7.40–7.86 (m, 5 H, aromatic); mass spectrum, *m/e* (relative intensity) 320 (6), 318 (13), 316 (6), 240 (19), 239 (100), 238 (19), 237 (99), 211 (16), 209 (17), 183 (16), 181 (17), 129 (8), 102 (53); UV λ_{max} (EtOH, 100%) 264 nm (ϵ 10 200).

Anal. Calcd for $C_{10}H_6Br_2O_2$: C, 37.77; H, 1.90; Br, 50.26. Found: C, 37.78; H, 1.87; Br, 50.22.

The second product, **3-phenyl-5-bromo-2(5*H*)-furanone (7b;** 0.103 g), was crystallized from hexane to give colorless crystals: mp 82.5–83.5 °C; IR (KBr) 3000, 1775, 1620, 1495, 1440, 1315, 1255, 1182, 1090, 1062, 980, 930, 858, 785, 743 cm^{-1}; ^1H NMR δ 6.94 (d, 1 H, J = 2 Hz, CH), 7.38–7.49 (m, 3 H, aromatic), 7.62 (d, 1 H, J = 2 Hz, vinyl CH), 7.79–7.89 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 240 (3), 238 (3), 196 (2), 194 (11), 160 (36), 159 (100), 139 (2), 137 (9), 131 (29), 103 (66), 102 (44); UV λ_{max} (EtOH, 100%) 273 nm (ϵ 9900). High-resolution mass spectrum: calcd for $C_{10}H_7{}^{79}BrO_2$, 237.9630; found, 237.9628; calcd for $C_{10}H_7{}^{81}BrO_2$, 239.9610; found, 239.9642.

The third product, **3-phenyl-5-acetoxy-5-bromo-2(5*H*)-furanone (7c;** 0.081 g), was recrystallized from pentane and resulted in colorless plates: mp 80.5–81.0 °C; IR (KBr) 3100, 3000, 1770 br, 1660, 1600, 1495, 1440, 1420, 1378, 1340, 1298, 1198, 1165, 1118, 1047, 984, 952, 915, 870, 785, 765, 752, 697 cm^{-1}; ^1H NMR δ 2.18 (s, 3 H, CH_3CO_2), 6.92 (s, 1 H, vinyl CH), 7.40–7.52 (m, 3 H aromatic), 7.74–7.88 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 298 (15), 296 (15), 256 (29), 254 (31), 239 (12), 237 (12), 217 (<1), 183 (14), 181 (14), 176 (14), 175 (59), 174 (100), 145 (77), 131 (22), 130 (27), 129 (42), 102 (65); UV λ_{max} (EtOH, 100%) 272 nm (ϵ 10 500).

Anal. Calcd for $C_{12}H_9BrO_4$: C, 48.52; H, 3.05; Br, 26.89. Found: C, 48.64; H, 3.05; Br, 26.91.

Finally, the column was washed with chloroform–methanol (10:1), furnishing a fraction (ca. 0.330 g) composed of two components. Silica gel chromatography (ethyl acetate) of this mixture led to a tan tar (0.215 g) and a minor compound (0.013 g) not further identified. The major product, **3-phenyl-5-bromo-5-hydroxy-2(5*H*)-furanone (7d)**, crystallized from chloroform–hexane as colorless crystals: mp 100–101 °C; IR (KBr) 3400 br, 1760, 1640, 1600, 1490, 1440, 1325, 1295, 1125, 1000, 975, 863, 770, 743, 688 cm^{-1}; ^1H NMR δ 5.50 (broad s, 1 H, exchanges with D_2O, OH), 6.12 (s, 1 H, vinyl CH), 7.20–7.91 (m, 5 H, aromatic); mass spectrum, *m/e* (relative intensity) 256 (9), 254 (11), 240 (5), 238 (5), 175 (21), 159 (9), 148 (14), 147 (20), 131 (43), 130 (100), 129 (96), 102 (86); UV λ_{max} (EtOH, 100%) 286 nm (ϵ 15 000).

Anal. Calcd for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77; Br, 31.32. Found: C, 46.86; H, 3.13; Br, 31.24.

Bromination of Methyl 2-(*p*-Chlorophenyl)-4-oxobutyrate (5c). To a solution of methyl 2-(*p*-chlorophenyl)-4-oxobutyrate (8.0 g, 0.035 mol) in glacial acetic acid (100 mL) was added bromine (5.6 g, 0.035 mol) in glacial acetic acid (80 mL). The deep red solution turned light yellow in 30 min. After stirring for 7 h, the reaction mixture was diluted with water (500 mL) and extracted with chloroform. The combined chloroform extract was washed with water, 10% sodium bicarbonate, and 10% sodium thiosulfate. Subsequent drying and solvent removal led to a yellow oil (9.6 g) comprised of four compounds (TLC; ligroin–acetone, 4:1). The oil was dry-loaded on a column of silica gel. Elution with ligroin–acetone (4:1) yielded a yellow oil (2.2 g) as the major component (also highest R_f). This compound was found to be **3-(*p*-chlorophenyl)-5-bromo-2(5*H*)-furanone (7e)** and was further purified by crystallization from ether–pentane followed by sublimation of the resulting yellow solid at 80 °C (0.01 mm). Finally, recrystallization of the colorless powder from ether–pentane resulted in colorless plates: mp 115–116 °C; IR (KBr) 3078, 2973, 1761, 1608, 1580, 1488, 1405, 1307, 1295, 1243, 1170, 1087, 1060, 1010, 970, 918, 880, 830, 756, 665 cm^{-1}; ^1H NMR δ 7.08 (d, 1 H, J = 2 Hz, CH), 7.38–7.56 (m, 2 H, aromatic), 7.69 (d, 1 H, J = 2 Hz, vinyl CH), 7.82–7.99 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 276 (4), 274 (2), 272 (2), 230 (1), 228 (2), 222 (3), 221 (17), 220 (16), 215 (5), 214 (6), 206 (5), 196 (7), 195 (40), 194 (22), 193 (100), 180 (18), 165 (12), 139 (19), 138 (14), 137 (49), 136 (27); UV λ_{max} (EtOH, 100%) 283 nm (ϵ 12 300).

Anal. Calcd for $C_{10}H_6BrClO_2$: C, 43.91; H, 2.21; Br, 29.22; Cl, 12.96. Found: C, 43.85; H, 2.16; Br, 29.20; Cl, 12.96.

Bromination of Methyl 2-(*p*-Fluorophenyl)-4-oxobutyrate (5b). Bromine (4.00 g, 0.025 mol) in glacial acetic acid (10 mL) was rapidly introduced into a solution of methyl 2-(*p*-fluorophenyl)-4-oxobutyrate (5.25 g, 0.025 mol) in glacial acetic acid (90 mL). After 1 h the deep red solution began to lighten. Continued stirring for 17 h at 25 °C produced a pale yellow solution. The crude product was isolated as described for lactone **7e.** Solvent removal provided a light yellow oil (4.58 g) which solidified at −10 °C. Purification by silica gel chromatography (dry-loaded; ligroin–acetone, 4:1) furnished a yellow solid (ca. 1.74 g) that proved to be 3-(*p*-fluorophenyl)-5-bromo-2(5*H*)-furanone (**7f**). The lactone was decolorized with activated charcoal and recrystallized from acetone–hexane to provide colorless plates: mp 97–98 °C; IR (KBr) 3100, 1760, 1620, 1601, 1510, 1310, 1293, 1245, 1175, 1160, 1115, 1063, 974, 953, 885, 838, 670 cm^{-1}; ^1H NMR δ 7.08 (d, 1 H, J = 2 Hz, CH), 7.20–7.33 (m, 2 H, aromatic), 7.64 (d, 1 H, J = 2 Hz, vinyl CH), 7.84–8.10 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 258 (2), 256 (2), 178 (29), 177 (100), 159 (2), 150 (3), 149 (37), 122 (12), 121 (69), 120 (54), 101 (38); UV λ_{max} (EtOH, 100%) 282 nm (ϵ 9100).

Anal. Calcd for $C_{10}H_6BrFO_2$: C, 46.72; H, 2.35; Br, 31.08; F, 7.39. Found: C, 46.83; H, 2.32; Br, 31.14; F, 7.50.

Methyl 2-(*p*-Fluorophenyl)-3-formylacrylate (8). To a stirred solution of methyl 2-(*p*-fluorophenyl)-4-oxobutyrate (6.12 g, 0.029 mol) in glacial acetic acid (50 mL) was added bromine (4.63 g, 0.029 mol) in glacial acetic acid (50 mL) in 10-mL increments over a 2.3-h period. Additional bromine–acetic acid solution was not added to the reaction mixture until the color (deep red) from the previous addition became light yellow. Immediately after the color had disappeared from the last bromine–acetic acid addition, water (200 mL) was added and the resulting solution extracted with chloroform. The combined extract was washed with water, saturated sodium bicarbonate solution, 10% sodium thiosulfate, and water. The chloroform solution was dried (sodium sulfate), and the solvent was removed to afford a yellow oil (2.28 g) that was subjected to silica gel chromatography (hexane–ethyl acetate, 9:1). The first compound eluted was identified as olefin 8 (0.434 g). Recrystallization from pentane afforded yellow needles: mp 64–65 °C; IR (KBr) 3100, 2850 sh, 2750 sh, 1725, 1675, 1600, 1510, 1430, 1395, 1250, 1160, 1108, 1025, 910, 838, 767, 737 cm^{-1}; ^1H NMR δ 3.86 (s, 3 H, OCH_3), 7.00 (d, 1 H, J = 8 Hz, vinyl CH), 7.19–7.51 (m, 4 H, aromatic), 9.66 (d, 1 H, J = 8 Hz, CHO); mass spectrum, *m/e* (relative intensity) 208 (13), 181 (6), 180 (73), 179 (11), 177 (10), 160 (7), 149 (21), 136 (6), 135 (23), 133 (8), 122 (14), 121 (100), 120 (43); UV λ_{max} (EtOH, 100%) 288 nm (ϵ 7200).

Anal. Calcd for $C_{11}H_9FO_3$: C, 63.46; H, 4.36; F, 9.13. Found: C, 63.43; H, 4.34; F, 9.14.

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Registry No.—**1a,** 67031-03-2; **1b,** 67031-02-1; **1c,** 67031-04-3; **1d,** 67031-05-4; **1e,** 67031-06-5; **4a,** 14815-73-7; **4b,** 67031-08-7; **4c,** 67031-09-8; **4d,** 67031-10-1; **4e,** 67031-11-2; **5a,** 67031-12-3; 5a DNP, 67031-13-4; **5b,** 67031-14-5; **5b** DNP, 67031-15-6; **5c,** 67031-16-7; **5c** DNP, 67031-17-8; **5d,** 67031-18-9; **5d** DNP, 67031-19-0; **6a,** 54897-85-7; **6b,** 67031-20-3; **6c,** 67031-21-4; **7a,** 67031-07-6; **7b,** 67030-93-7; **7c,** 67030-92-6; **7d,** 67030-91-5; **7e,** 67030-90-4; **7f,** 67030-98-2; **8,** 67030-97-1; ethyl 2-ethyl-4-oxobutyrate, 67030-96-0; ethyl 2-ethyl-4-pentenoate, 67030-95-9; ethyl 2-ethyl-4-oxobutyrate DNP, 3601-51-2; ethyl 2-ethyl-3,3-dibromo-4-oxobutyrate, 67030-94-8; phenylacetic acid, 103-82-2; *p*-fluorophenylacetic acid, 405-50-5; *p*-chlorophenylacetic acid, 1878-66-6; *p*-methoxyphenylacetic acid, 104-01-8; 3,4,5-trimethoxyphenylacetic acid, 951-82-6.

Supplementary Material Available: Complete IR, NMR, and mass spectral data are available for compounds 4–6 (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Contribution 58 in the series Antineoplastic Agents. For paper 57, see J. Polonsky, Z. Varon, V. Arnoux, C. Pascard, G. R. Pettit, J. H. Schmidt, and L. M. Lange, *J. Am. Chem. Soc.*, **100**, 2575 (1978). Abstracted in part from the Ph.D. Dissertation of Mark T. Edgar, Arizona State University, Tempe, Ariz., July 1977.
(2) (a) Y. Kamano, G. R. Pettit, M. Tozawa, and S. Yoshida, *J. Org. Chem.*, **42**, 906 (1977); (b) Y. Kamano, G. R. Pettit, and M. Tozawa, *J. Chem. Soc., Perkin Trans. 1*, 1972 (1975); (c) *ibid.*, 1976 (1975); (d) G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970).
(3) G. R. Pettit, B. Green, A. K. Das Gupta, P. A. Whitehouse, and J. P. Yardley, *J. Org. Chem.*, **35**, 1381 (1970).
(4) (a) For a review of furanone chemistry, see Y. S. Rao, *Chem. Rev.*, **64**, 353 (1964); (b) *ibid.*, **76**, 625 (1976).
(5) Furanones have also been of interest as fungicides; see, for example, ref 4b, p 666.
(6) (a) For leading references, see M. Semonsky, H. Skvorova, V. Zikan, B. Kakac, and V. Jelinek, *Collect. Czech. Chem. Commun.*, **35**, 96 (1970); (b) M. Semonsky, V. Zikan, H. Skvorova, and B. Kakac, *ibid.*, **33**, 2690 (1968); (c) B. Kakac, K. Mnoucke, P. Zuman, M. Semonsky, V. Zikan, and A. Cerney, *ibid.*, **33**, 1256 (1968); (d) V. Zikan, M. Semonsky, N. Kucharczyk, and E. Svatek, *ibid.*, **35**, 3475 (1970); (e) V. Zikan, L. Vrba, B. Kakac, and M. Semonsky, *ibid.*, **38**, 1091 (1973).
(7) Thomas H. Smith, Ph.D. Dissertation, Arizona State University, Tempe, Ariz., 1974.
(8) B. Akermark, *Acta Chem. Scand.*, **16**, 599 (1962).
(9) F. F. Blicke and P. E. Wright, *J. Org. Chem.*, **25**, 693 (1960).
(10) P. L. Creger, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 58.
(11) J. B. Gin and C. A. Dekker, *Biochemistry*, **7**, 1413 (1968).
(12) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).
(13) J. R. McNesby and C. A. Heller, Jr., *Chem. Rev.*, **54**, 325 (1954).
(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 163.
(15) The structure for hydroxy lactone **7d** is consistent with all spectral data; however, as a referee noted the lactone should be somewhat unstable, and this was not observed. Since this lactone structure was not rigorously proven, the assignment should be regarded as tentative. Scheme III suggests possible mechanistic routes to lactone **7d**. Usually bromination of a pseudoacid results in displacement of the hydroxy group, but a small amount of C-5 bromination with hydroxy group retention may be possible. Alternatively, the 5-bromo-5-hydroxyfuranone could arise by partial hydrolysis of the 5,5-dibromofuranone (**7a**).
(16) The pseudomixed anhydride **10** (Scheme III) was also detected by ^{1}H NMR spectroscopy.
(17) Ethyl 2-ethyl-3,3-dibromo-4-oxobutyrate was isolated in 7% yield (see Experimental Section) and was found to decompose upon standing at 10 °C for 72 h. Only a ^{1}H NMR spectrum was obtained. Ethyl 2-ethyl-3-bromo-4-oxobutyrate was probably present as a reaction intermediate but was not isolated.
(18) I. L. Doerr and R. E. Willette, *J. Org. Chem.*, **38**, 3878 (1973).
(19) A satisfactory elemental analysis could not be obtained for this compound. But upon conversion to the corresponding 4-oxobutyrate 2,4-dinitrophenylhydrazone a good elemental analysis was obtained.

Alkyl Nitrite–Metal Halide Deamination Reactions. 5. In Situ Generation of Nitrosyl Halides. Effective Product Control from Nitrosyl Chloride Diazotization of Primary Aliphatic Amines in *N,N*-Dimethylformamide[1]

Michael P. Doyle,*[2a] Richard J. Bosch, and Paul G. Seites[2b]

Department of Chemistry, Hope College, Holland, Michigan 49423

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Nitrosyl chloride and nitrosyl bromide are formed by an efficient halide/alkoxide exchange between titanium tetrahalides and alkyl nitrites. Complete replacement of halide by alkoxide occurs and results in the formation of titanium tetraalkoxides. Reactions of primary aliphatic amines with in situ generated nitrosyl halides in *N,N*-dimethylformamide effectively minimizes elimination, rearrangement, and oxidation processes normally encountered in alternate diazotization procedures and facilitates product recovery in high yield. Comparative results for the diazotization of benzylamine by nitrosyl chloride generated from selected metal halides and *tert*-butyl nitrite are reported; the generality of chloride/alkoxide exchange for the early transition metal halides is indicated. Diazotization of primary aliphatic amines by in situ generated nitrosyl chloride in dimethylformamide produces unrearranged alkyl chlorides, alcohols, and formate esters.

Methods for deaminaton of aliphatic amines by nitrosyl halides have received considerably less attention than corresponding processes that employ nitrous acid or dinitrogen tetroxide.[3] The gaseous nitrosyl halide reagents require special handling techniques and, as is characteristic in diazotization reactions of primary aliphatic amines, generally effect the production of complex reaction mixtures in moderate yields.[4-6] In chemical operations that employ nitrosyl halides in aprotic media, these reagents are generated externally and then passed into the reaction solution from a collection vessel employed to measure the volume of the nitrosyl halide. Methods for in situ generation of nitrosyl halides, based on known reactions of hydrogen halides with sodium nitrite,[7] dinitrogen tetroxide,[8] or alkyl nitrites,[9] have not been advanced for use in deaminaton or addition procedures due to their production of potentially interfering byproducts;[10] in addition, excess amounts of hydrogen halides are often used to facilitate nitrosyl halide formation or to avoid the normally complex stoichiometric measurement of the gaseous acid. In this paper we report general methods for in situ generation of nitrosyl chloride and nitrosyl bromide that avoid the complexities usually observed with the use of hydrogen halides.

In his recent thorough examinations of deamination reactions of aliphatic amines by nitrosyl chloride at low temperatures in aprotic media, Bakke[11] identified five principal reaction pathways of the intermediate alkyldiazonium chlorides: chloride substitution, elimination, rearrangement, displacement by solvent, and diazoalkane formation (eq 1–5).

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCH_2CH_2Cl + N_2 \quad (1)$$

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCH{=}CH_2 + HCl + N_2 \quad (2)$$

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCHClCH_3 + N_2 \quad (3)$$

$$RCH_2CH_2N_2^+Cl^- + Sol: \rightarrow RCH_2CH_2{-}Sol^+Cl^- + N_2 \quad (4)$$

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCH_2CH{=}N_2 + HCl \quad (5)$$

Reactions were performed at −70 °C in ether solvents to minimize rearrangement and, under these conditions, the process represented by eq 1 was dominant (88% of products from eq 1–4).[11a] In hydrocarbon and chlorocarbon solvents, however, the production of both aldehydes and oximes, presumed formed from the corresponding nitrosoalkane, was dominant.[11c] These and prior reports of diazotization efficiency in reactions of aliphatic amines with nitrosyl chloride

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Table I. Product Yields from Reactions of Benzylamine with Titanium Tetrachloride–*tert*-Butyl Nitrite in Dimethylformamide[a]

$[C_6H_5CH_2NH_2]/[TiCl_4]$	relative yield, %[b]				isolated yield, %[c]
	$C_6H_5CH_2Cl$	$C_6H_5CH_2OH$	$C_6H_5CH_2O_2CH$	C_6H_5CHO	
10.0	41	59	0	0	37
4.00	72	25	1	2	88
3.33	73	24	1	2	90
3.33[d]	68	28	2	2	94
2.00	77	20	1	2	98
1.00	80	17	1	2	99

[a] Unless indicated otherwise, reactions were performed at 25 °C by adding 10 mmol of benzylamine to the combination of titanium tetrachloride and 10 mmol of *tert*-butyl nitrite in 50 mL of DMF. [b] Based on the isolated yield of these products as determined by GC and NMR analyses. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. [c] Combined actual yield of benzyl chloride, benzyl alcohol, benzyl formate, and benzaldehyde. [d] Reaction was performed at 25 °C by adding 10 mmol of *tert*-butyl nitrite to the combination of titanium tetrachloride and 10 mmol of benzylamine in 50 mL of DMF.

describe a multiplicity of reaction pathways that cast doubt on the general usefulness of this reagent in deamination procedures. However, diazotization reactions that employ nitrosyl halides in dipolar aprotic solvents (solvent media expected to moderate the reactivity of the nitrosyl halides and significantly modify the reaction pathways for deamination) have not been reported. Results from reactions between aliphatic amines and in situ generated nitrosyl halides in these solvents are described in this paper. The use of *N,N*-dimethylformamide as the reaction solvent effectively minimizes elimination, rearrangement, and oxidation processes in deamination reactions and facilitates product recovery in high yield.

Results and Discussion

In Situ Generation of Nitrosyl Halides. Halides of the early transition metal series exhibit a marked sensitivity toward moisture that reflects both the lability of the metal–halogen bond to solvolytic substitution and the tendency of these metals to form strong metal–oxygen bonds.[13] As Lewis acids[14] these metal halides form stable adducts with electron donor ligands such as nitriles, tertiary amines, and ethers that are also sensitive to nucleophilic substitution of halide.[13] These properties of the early transition metal halides (Lewis acidity, lability of metal–halogen bonds, and comparative strength of metal–oxygen bonds) are precisely those required for effective halide/oxide interchange. However, although numerous methods for the generation of nitrosyl chloride from dinitrogen tetroxide or alkyl nitrites and a variety of inorganic halides have been reported,[10,15] there is a surprising absence of similar information for the early transition metal halides.

We have found that titanium tetrachloride reacts rapidly with alkyl nitrites at or above 0 °C to form nitrosyl chloride. In contrast to comparable uncatalyzed reactions of titanium tetrachloride with alcohols in which only two of the four chloride substituents of titanium are effectively exchanged,[16] use of an equivalent amount of alkyl nitrite (based on chloride) results in quantitative chloride/alkoxide interchange.

$$TiCl_4 + 4RONO \rightarrow Ti(OR)_4 + 4NOCl \qquad (6)$$

Both isopentyl nitrite and *tert*-butyl nitrite exhibit similar reactivities in reactions with titanium tetrachloride.

Nitrosyl chloride was identified by its characteristic nitrosyl infrared absorption.[17] Titanium tetra-*tert*-butoxide was formed in reactions between *tert*-butyl nitrite and 0.25 molar equiv of titanium tetrachloride and, even without elaborate precautions, the purified product could be isolated in yields that were comparable to those from the standard, but more complex, process involving the use of anhydrous ammonia.[18] Thus reactions of alkyl nitrites with titanium tetrachloride serve not only as a convenient preparative method for nitrosyl chloride but, also, as a superior process for the formation of the tetravalent alkoxides of titanium. Nitrosyl bromide is similarly produced from the combination of alkyl nitrites and titanium tetrabromide, but titanium tetrafluoride is unreactive toward alkyl nitrites and no evidence for nitrosyl fluoride formation could be obtained. The generality of halide/alkoxide or amide exchange for the in situ generation of a wide variety of reactive halide reagents from the early transition metal halides is currently under investigation.

Diazotization of Benzylamine. The utility of the titanium tetrachloride–alkyl nitrite generative method for the production of nitrosyl chloride was evaluated through investigations of amine diazotization reactions. Because of the complexity of products and the relatively low yields of substitution products in prior investigations of nitrosyl chloride diazotization reactions, we were surprised to find that benzylamine was converted to benzyl chloride and benzyl alcohol nearly quantitatively in reactions with nitrosyl chloride performed at 25 °C in dimethylformamide (Table I). Benzyl formate and benzaldehyde were also observed, but in a combined yield of less than 4%; neither benzyl *tert*-butyl ether nor dibenzyl ether were detected. The mole ratio of evolved gas to amine was 1.0 when at least 1 equiv of nitrosyl chloride was employed. These deamination reactions were characteristically exothermic; the reaction temperature was controlled by the slow addition of the amine to the solution containing nitrosyl chloride or by the slow addition of *tert*-butyl nitrite to the amine–titanium tetrachloride combination in solution. The mode of addition had no apparent effect on the yield of isolated products.

Results from a stoichiometric study (Table I) of the reaction between benzylamine and nitrosyl chloride (formed by the combination of *tert*-butyl nitrite and titanium tetrachloride) established the dependence of the benzyl chloride/benzyl alcohol product ratio on the relative molar amount of titanium tetrachloride employed. These results suggest that the water produced in the diazotization reaction was partially trapped by a chlorotitanium compound and, consequently, inhibited from reaction with the benzyldiazonium ion. The use of phosphorus pentoxide to effect a similar result in nitrosyl halide deamination reactions has recently been described.[19] Alternatively, hydrogen chloride produced by hydration of titanium tetrachloride may have been responsible for the higher benzyl chloride/benzyl alcohol product ratio at the lower benzylamine/titanium tetrachloride ratios. Control experiments established that benzyl chloride was not formed in reactions between benzyl alcohol and titanium tetrachloride under the same conditions.[20]

The dramatic effect of solvent on the products from deamination of benzylamine by nitrosyl chloride is evidenced

Table II. Product Yields from Reactions of Benzylamine with Titanium Tetrachlorine–*tert*-Butyl Nitrite in Aprotic Solvents[a]

solvent	relative yield, %[b] $C_6H_5CH_2Cl$	$C_6H_5CH_2OH$	C_6H_5CHO	isolated yield, %[c]
$(CH_3)_2NCHO$	81	17	2	98[d]
$[(CH_3)_2N]_3PO$	76	22	2	74
CH_3CN	80	18	2	83[e]
$(CH_3CH_2)_2O$	78	17	5	64
C_6H_6	66	22	12	65[f]
CH_2Cl_2	69	14	17	78

[a] Reactions were performed at 25 °C by adding 10 mmol of benzylamine to the combination of titanium tetrachloride (10 mmol) and *tert*-butyl nitrite (10 mmol) in 50 mL of the aprotic solvent. [b] Based on the isolated yields of these products as determined by GC and NMR analyses. [c] Combined actual yield of benzyl chloride, benzyl alcohol, and benzaldehyde. [d] Benzyl formate was formed in 1% yield. [e] *N*-Benzylacetamide was produced in 3% yield. [f] Diphenylmethane was formed in 6% yield.

by the data presented in Table II. The most significant differences are found in isolated product yields and in the percentage yield of benzaldehyde. Higher yields of substituted products, benzyl chloride and benzyl alcohol, are formed from reactions performed in dipolar aprotic solvents. Solvents such as benzene and methylene chloride that are less capable of stabilizing the reaction intermediates formed by diazotization of benzylamine promote oxidation. Both nitrous oxide and nitric oxide are produced during the deamination of benzylamine in methylene chloride. The formation of these gaseous products suggests that benzaldehyde is formed by direct oxidation of benzylamine.[21]

$$C_6H_5CH_2NH_2 + NOCl \rightarrow C_6H_5CH{=}NH_2^+ Cl^- + HNO \quad (7)$$

Disproportionation of nitrosyl hydride to nitrous oxide and water[22] or subsequent reaction of nitrosyl hydride with nitrosyl chloride to form nitric oxide[23] accounts for the observed gaseous products.

Products from solvent interception of the benzyl cation were evident, although as minor constituents of the reaction mixtures, in reactions performed in dimethylformamide, acetronitrile, and benzene (Table II). The production of benzyl formate is consistent with the process outlined in eq 8.

$$C_6H_5CH_2N_2^+ + HCON(CH_3)_2 \xrightarrow{(-N_2)} C_6H_5CH_2OCH{=}N^+(CH_3)_2 \xrightarrow{H_2O} C_6H_5CH_2OCHO \quad (8)$$

Although alkyl ethyl ethers have been detected in low-temperature nitrosyl chloride deaminations of aliphatic amines in ethyl ether,[11a,24] benzyl ethyl ether was not observed as a product from reactions performed at 25 °C in this study. Corresponding solvent-intercepted products from reactions in hexamethylphosphoramide were not isolated.

The generation of nitrosyl chloride from dinitrogen tetroxide or alkyl nitrites by reactions with a wide variety of metal halides, including aluminum chloride and stannic chloride,[10c] has been reported. However, the comparative facility of these conversions has not been determined. In addition, metal halides of the early transition metal series such as tantalum pentachloride form stable complexes with nitrosyl chloride[25] that may be expected to significantly modify the reactions and reactivities of nitrosyl chloride. To compare the utility of these methods for nitrosyl chloride production with the titanium tetrachloride–alkyl nitrite generative method, the deamination of benzylamine in dimethylformamide has been investigated. The results from this study are presented in Table III. Data for the hydrogen chlorde–*tert*-butyl nitrite deamination process are provided for comparison.

The combination of aluminum chloride, ferric chloride, or stannic chloride and *tert*-butyl nitrite in dimethylformamide at 25 °C did not result in the formation of nitrosyl chloride in observable amounts. Product yields from benzylamine deaminations were characteristically low, and relatively high yields of benzaldehyde were obtained. In contrast, hydrogen chloride and representative metal halides of the early transition series uniformly produced nitrosyl chloride. Addition of benzylamine to these reaction media effected a rapid and quantitative evolution of gas and resulted in the production of high yields of substitution products. The ratios of benzyl chloride to benzyl alcohol for deamination reactions employing comparable amounts of titanium tetrachloride and molybdenum pentachloride were nearly identical at the low molar ratios of benzylamine to MX_n. Hydrogen chloride and tantalum pentachloride exhibited similar capabilities in forming benzyl chloride at the expense of benzyl alcohol, presumably by substitutive conversion of benzyl alcohol to benzyl chloride.[26] Complete chloride/alkoxide exchange is observed from the combination of either molybdenum pentachloride or tantalum pentachloride with 5.0 molar equiv of *tert*-butyl nitrite in diazotization reactions with benzylamine; in contrast, only three of the six chlorides of tungsten hexachloride are effectively utilized, and results similar to those from the stannic chloride promoted diazotization are obtained when the molar ratio of benzylamine to WCl_6 is 6.0.

The addition of benzylamine to nitrosyl bromide generated from *tert*-butyl nitrite and 0.25 molar equiv of titanium tetrabromide in dimethylformamide at 0 °C results in low product recovery (55% isolated yield) and the dominant production of benzaldehyde (51% relative yield). The low product recovery is predictably due to the utilization of 2 molar equiv of the nitrosyl compound for oxidative formation of benzaldehyde. Although alteration of the mode of addition through treatment of the combination of benzylamine and 0.25 molar equiv of titanium tetrabromide at 0 °C with *tert*-butyl nitrite results in a decreased yield of benzladehyde (20% relative yield, 65% isolated yield of products), only when an equivalent amount of titanium tetrabromide is employed do the product yields resemble those from nitrosyl chloride diazotization of benzylamine: 70% benzyl bromide, 22% benzyl alcohol, 2% benzyl formate, and 6% benzaldehyde (94% isolated yield). Nitrosyl bromide is apparently a more active oxidant than is nitrosyl chloride. However, complexation of the amine with titanium tetrabromide is effective in minimizing hydrogen abstraction from the α position of the amine.

Diazotization of Primary Aliphatic Amines. The superior capability of nitrosyl chloride in dimethylformamide to effect deamination of aliphatic primary amines is evident from the results presented in Table IV. Comparative data are given for reactions in which nitrosyl chloride is generated from the combination of *tert*-butyl nitrite with tantanium tetrachloride, tantalum pentachloride, and hydrogen chloride. Reactions that employ the *tert*-butyl nitrite–titanium tetrachloride combination do not exhibit capabilities for substitutive conversions of alcohols to alkyl halides that are evident in reactions that utilize tantalum pentachloride or hydrogen chloride. Product accountability is high in these deaminative conversions, the yields of aldehyde products are low (<2%), elimination is a minor competitive process (<4%), and there is a notable absence of rearranged products (<1%). However, in contrast to deamination reactions of benzylamine, the for-

Table III. Product Yields from Reactions of Benzylamine with *tert*-Butyl Nitrite and Selected Metal Halides in Dimethylformamide[a]

MCl_n	$[C_6H_5CN_2NH_2]/[MCl_n]$	relative yield, %[b]				isolated yield, %[c]
		$C_6H_5CH_2Cl$	$C_6H_5CH_2OH$	$C_6H_5CH_2O_2CH$	C_6H_5CHO	
HCl	*d*	84	12	3	1	88
$AlCl_3$[e,f]	1.0	75	15	1	9	35
$TiCl_4$	1.0	80	17	1	2	99
$FeCl_3$[f]	1.0	28	57	7	8	61
$MoCl_5$	1.7	81	15	1	3	78
$SnCl_4$	1.0	10	8	3	80	40
$TaCl_5$	1.0	88	3	2	7	85
WCl_6	1.5	81	13	4	2	90

[a] Unless indicated otherwise, reactions were performed at 25 °C by adding 10 mmol of benzylamine to the combination of the metal halide and 10 mmol of *tert*-butyl nitrite in 50 mL of DMF. [b] Based on the isolated yield of these products as determined by GC and NMR analyses. From duplicate runs, experimentally determined percentage yields were accurate to within ±3% of the reported values. [c] Combined actual yield of benzyl chloride, benzyl alcohol, and benzaldehyde. [d] Reaction performed at 0 °C after passing gaseous hydrogen chloride through the reaction solution (100 mL) for 5 min (30 mL/min) prior to the addition of benzylamine. [e] Identical results were obtained when *tert*-butyl nitrite was added to the combination of aluminum and benzylamine. [f] Slow evolution of gas after addition of amine. Reaction solution was heated to 65 °C after complete gas evolution was observed at 25 °C.

Table IV. Product Yields from Reactions of Primary Amines with *tert*-Butyl Nitrite and Selected Metal Halides in Dimethylformamide[a]

amine	registry no.	MCl_n	$[RNH_2]/[MCl_n]$	RCH_2Cl	relative yield, %[b]					isolated yield, %[c]
					registry no.	RCH_2OH	registry no.	RCH_2O_2CH	registry no.	
$C_6H_5CH_2CH_2NH_2$	64-04-0	$TiCl_4$	4.0[d]	76	622-24-2	10	104-62-1	14	4830-93-7	82
		$TaCl_5$	2.5	80		8		12		59
		HCl	*e*	79		5		16		54
$C_6H_5(CH_2)_3CH_2NH_2$	13214-66-9	$TiCl_4$	4.0	59	4830-93-7	19	3360-41-6	22	67421-63-0	80[f]
$CH_3(CH_2)_6CH_2NH_2$	111-86-4	$TiCl_4$	3.3	53	111-85-3	22	111-87-5	25	112-32-3	72
		$TaCl_5$	2.5	48		28		24		71
		HCl	*e*	64		13		23		79
$CH_3(CH_2)_8CH_2NH_2$	2016-57-1	$TiCl_4$	3.3	52	1002-69-3	21	112-30-1	27	5451-52-5	77
		$TaCl_5$	2.5	58		9		33		66
		HCl	*e*	62		7		31		84

[a] Unless indicated otherwise, reactions were performed at 25 °C by adding 10 mmol of the amine to the combination of metal halide and 10 mmol of *tert*-butyl nitrite in 50 mL of DMF. [b] Based on the isolated yield of these products as determined by GC analyses. From duplicate runs, experimentally determined percentage yields were within ±2% of the reported values for reactions with $TiCl_4$ and $TaCl_5$ and within ±4% of the reported values for RCH_2Cl and RCH_2OH for reactions with hydrogen chloride. [c] Combined actual yield of reported products. The yields of secondary alkyl chloride and secondary alcohol were less than 0.5% for reactions with $TiCl_4$ and were 1–3% for reactions with hydrogen chloride and $TaCl_5$. Yields of styrene from reactions of 2-amino-1-phenylethane were less than 2%; olefin yields (>95% terminal alkene) from reactions of 1-aminodecane, 1-aminooctane, and 1-amino-4-phenylbutane were 2–4%. [d] Nearly identical results were obtained with $[RNH_2]/[TiCl_4] = 3.3$ (isolated yield = 75%). [e] Reaction performed at 0°C after passing gaseous hydrogen chloride through the reaction solution (100 mL) for 5 min (30 mL/min) prior to the addition of amine. [f] Tetralin was not produced under these reaction conditions.

mation of formate esters is an important product-forming process. The production of formate esters in remarkably consistent yields, despite the variation in reaction conditions,[28] indicates that interception of the intermediate diazonium ion by dimethylformamide (eq 9) is not a reversible process.[29]

$$RCH_2N_2^+ + HCON(CH_3)_2 \rightarrow RCH_2OCH{=}N^+(CH_3)_2 + N_2 \quad (9)$$

Variation of the reaction temperature from −15 °C does not appreciably affect the relative yield of formate ester formed by nitrosation of 1-amino-2-phenylethane in dimethylformamide.[30]

Reactions of titanium tetrachloride/*tert*-butyl nitrite generated nitrosyl chloride with 1-amino-2-phenylethane and with 1-aminodecane in acetonitrile or in benzene result in a considerably greater yield of rearranged products than those observed from comparable reactions in dimethylformamide. In acetonitrile at 25 °C, 7–13% of the alkyl chloride (60% yield) and 40–60% of the alcohol (10% yield) products result from 1,2-hydrogen transfer. In benzene at 25 °C, 7–10% of the alkyl chloride (58% yield) and 55–65% of the alcohol (8% yield) products result from 1,2-hydrogen transfer. In addition, both rearranged and unrearranged acetamide products (6:8, 14% yield) are produced from reactions of nitrosyl chloride with 1-aminodecane in acetronitrile. Thus, the use of dimethylformamide as the reaction solvent for nitrosyl chloride diazotizations of primary aliphatic amines minimizes structural rearrangement and elimination as well as oxidation. However, a multiplicity of product-forming pathways remain. Methods for the effective control of this product distribution through selective capture of diazotization reaction intermediates are currently under investigation.

Experimental Section

General. Instrumentation has been previously described.[31] Analytical gas chromatographic analyses were performed on a Varian Aerograph Model 2720 gas chromatograph with thermal conductivity detectors; a Varian Model 485 digital integrator was used to determine peak areas. Use was made of 5–7-ft columns of 10% DEGS, 20% SE-30, and 20% Carbowax 20M, all on Chromosorb P. *tert*-Butyl nitrite was

prepared from *tert*-butyl alcohol according to the procedure of Noyes;[32] isopentyl nitrite was obtained commercially. The amines that were employed in this study were commerically available and were used without prior purification. Titanium tetrafluoride, tetrachloride, and tetrabromide, tantalum pentachloride, molybdenum pentachloride, and tungsten hexachloride were obtained commercially from Alfa and were stored in a desiccator. Reagent grade *N,N*-dimethylformamide, acetronitrile, hexamethylphosphoramide, and benzene were distilled from calcium hydride prior to their use as reaction solvents. Ethyl ether was distilled from lithium aluminum hydride.

Nitrosyl Chloride. To 4.74 g of titanium tetrachloride (0.025 mol) in 25 mL of benzene contained in a three-necked flask fitted with a gas bubbler, a reflux condenser joined to a gas trap cooled to −78 °C, and a rubber septum was added 10.3 g of *tert*-butyl nitrite (0.100 mol) over a 20-min period. Dry nitrogen was slowly bubbled through the reaction solution during the addition and continued until the dark orange-red solution color disappeared. The reaction temperature was maintained at 25 °C. The volume of nitrosyl chloride collected in the cold trap was 3.8 mL which corresponded to an 82% isolated yield of product. IR analysis of the collected gas showed exact correspondance with published spectra of nitrosyl chloride.[17]

In separate experiments the combination of titanium tetrachloride and 4 molar equiv of *tert*-butyl nitrite in carbon tetrachloride, acetonitrile, and dimethylformamide was analyzed by IR spectroscopy. Although nitrosyl chloride formation was rapid at temperatures above 0 °C, the reaction was substantially slower at −10 °C. The conversion of titanium tetrachloride and *tert*-butyl nitrite to nitrosyl chloride was estimated to be only 25% complete after 1 h at −10 °C.

Titanium Tetra-*tert*-butoxide. *tert*-Butyl nitrite (10.3 g, 0.100 mol) was added to 2.75 mL of titanium tetrachloride (4.75 g, 0.025 mol) in 30 mL of carbon tetrachloride at room temperature over a 15-min period. After addition was complete, nitrosyl chloride and carbon tetrachloride were removed under reduced pressure and the resulting solution was vacuum distilled through a 12.5-cm Vigreux column. The fraction boiling at 74 °C (0.50 Torr) was collected, and this colorless transparent liquid was identified as titanium tetra-*tert*-butoxide by comparison of its physical and spectral properties with those reported in the literature[18,33] (4.63 g, 55% yield).

In separate experiments titanium *tert*-butoxide and titanium isopentoxide were identified from reactions between the corresponding alkyl nitries and titanium tetrachloride and tetrabromide in dimethylformamide by ^{1}H NMR spectroscopy. The shift in the $-CH_2O-$ proton absorption from δ 4.28 (CH_2ONO) to 4.75 was immediate following addition of isopentyl nitrite to the titanium tetrahalide in dimethylformamide at 37 °C.

Diazotization of Primary Aliphatic Amines. General Procedure. Reaction solutions of titanium tetrachloride in dimethylformamide were prepared by three methods: (a) direct addition of the desired weight of the moisture-sensitive liquid reagent to dimethylformamide, (b) use of a separately prepared saturated solution of the yellow $TiCl_4$·2DMF adduct [13b] which by silver nitrate gravimetric titration was determined to be 0.60 ± 0.05 M in titanium tetrachloride at 25 °C, or (c) direct employment of the solid $TiCl_4$·2DMF adduct.[24] Results obtained for diazotination of benzylamine in dimethylformamide were independent of the method of reaction solution preparation. For the preparation of reaction solutions of titanium tetrachloride in solvents other than dimethylformamide, direct addition by syringe was employed. The solid reagents titanium tetrabromide, tantalum pentachloride, molybdenum pentachloride, tungsten hexachloride, aluminum chloride, and ferric chloride were rapidly weighed in the reaction flask prior to addition of dimethylformamide. All glassware was oven dried prior to use with these moisture-sensitive reagents.

To a rapidly stirred solution of the metal halide in 40 mL of the appropriate solvent maintained at 25 °C in a three-necked flask fitted with a reflux condenser, gas outlet tube, and rubber septum was added the appropriate amount of the alkyl nitrite in 5 mL of the reaction solvent. An immediate color change to orange-red was observed. The primary aliphatic amine in 5 mL of the reaction solvent was then added to this reaction solution over a 20-min period. In dimethylformamide a color change from orange-red to yellow was observed during the addition of the amine.[35] Gas evolution was immediate, continued throughout the addition, and was complete within 5 min following complete addition of the amine. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret. For reactions in dimethylformamide the yield of gaseous products was 220 ± 20 mL (based upon 10.0 mmol of the limiting reagent). After complete gas evolution, the reaction solution was poured into 200 mL of 20% aqueous hydrochloric acid and extracted with two 100-mL portions of ether. The organic layer was washed once with 100 mL of aqueous hydrochloric acid, the resulting ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. Ether solutions containing volatile products were distilled at atmospheric pressure through a 12.5 cm Vigreux column.

For reactions performed with hydrogen chloride, the dry gaseous acid was bubbled through a gas trap containing mineral oil and into a transparent solution of *tert*-butyl nitrite (10.0 mmol) in 100 mL of dimethylformamide at −10 °C for 5 min at 30 mL/min. A color change from yellow to orange was observed as the solution became saturated with hydrogen chloride. Addition of the amine in 20 mL of dimethylformamide to the reaction solution from an addition funnel produced an initial rise in the reaction temperature to 0 °C that was maintained at that temperature by slow addition of the amine over a 20-min period. The addition of gaseous hydrogen chloride was continued until amine addition was complete. As in the previously described reactions, a color change from orange to yellow was observed during the addition of the amine. After complete addition of the amine, the reaction mixture was allowed to warm up to room temperature and was then subjected to the previously described product isolation procedures.

Product Analyses. Structural assignments for the products produced in diazotization reactions were made following extraction by ^{1}H NMR spectral comparisons and GC retention time and peak enhancement with authentic samples. To ensure accurate determination of the extent of rearrangement in diazotization reactions of 1-amino-2-phenylethane in dimethylformamide, the reaction mixture was fractionally distilled and analyzed by 1H NMR spectroscopy; within detection limits no 1-phenylethyl product was detected. Symmetrical ethers, nitrite esters, nitriles, and geminal dihalides were not observed as reaction products from amine diazotization reactions. Formate esters were identified by NMR and IR spectroscopy following isolation of these products from their reaction solutions by GC separation. The gaseous products from nitrosation of benzylamine in methylene chloride were identified by infrared spectral analysis.

Product yields were determined by GC analyses for the reactions reported in this study. Prior to workup a weighed amount of dibenzyl ether or diphenylmethane was added to the reaction mixture as an internal standard. The average integrated area ratio from at least two GC traces was employed in each yield determination. Absolute yields were calculated with the use of experimentally determined thermal conductivities for each of the alkyl halides, alcohols, formate esters, and aldehydes examined by this method. Thermal conductivity ratios were determined immediately prior to product analyses to ensure accuracy in these calculations. Olefin yields were determined by ^{1}H NMR spectral analyses.

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Registry No.—Benzaldehyde, 100-52-7; benzylamine, 100-46-9; dimethylformamide, 68-12-2; *tert*-butyl nitrite, 540-80-7; benzyl chloride, 100-44-7; benzyl alcohol, 100-51-6; nitrosyl chloride, 2696-92-6; titanium tetrachloride, 7550-45-0; titanium tetra-*tert*-butoxide, 3087-39-6.

References and Notes

(1) Part 4 in this series: M. P. Doyle, B. Siegfried, and W. F. Fobare, *Tetrahedron Lett.*, 2655 (1977).
(2) (a) Camille and Henry Dreyfus Foundation Teacher–Scholar Grant Awardee, 1973–1978; (b) National Science Foundation Undergraduate Research Participant, Summer, 1976.
(3) (a) L. Friedman in "Carbonium Ions", Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1970; (b) J. H. Ridd, *Q. Rev., Chem. Soc.*, **15**, 418 (1961); (c) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group", S. Patai, Ed., Interscience, New York, N.Y., 1968; (d) H. Zollinger, "Azo and Diazo Chemistry", Interscience, New York, N.Y., 1961; (e) P. A. S. Smith, "Open-Chain Nitrogen Compounds", Vol. I, W. A. Benjamin, New York, N.Y. 1965.
(4) (a) P. A. S. Smith, D. R. Baer, and S. W. Ege, *J. Am. Chem. Soc.*, **76**, 4564 (1954); (b) H. Felkin, *C. R. Hebd. Seances Acad. Sci.*, **236**, 298 (1953); (c) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **103**, 373 (1933), and references therein.
(5) D. Y. Curtin, J. A. Kampmeier, and M. L. Farmer, *J. Am. Chem. Soc.*, **87**, 874 (1965).
(6) L. Friedman, J. H. Bayless, and F. D. Mendicino, *J. Am. Chem. Soc.*, **87**, 5790 (1965).

(7) J. R. Morton and H. W. Wilcox, *Inorg. Synth.*, **4**, 48 (1953).
(8) P. J. Talbot and J. H. Thomas, *Trans. Faraday Soc.*, **55**, 1884 (1959).
(9) (a) A. Baeyer and H. Caro, *Ber.*, **7**, 809 (1874); (b) L. I. Smith and F. L. Taylor, *J. Am. Chem. Soc.*, **57**, 2460 (1935).
(10) The production of nitrosyl chloride and esters from reactions of acyl chlorides and alkyl nitrites has been reported: (a) H. Franzen and F. Zimmermann, *Ber.*, **40**, 2009 (1907); (b) C. O. Weber, *ibid.*, **35**, 1947 (1902). Analogous methods using thionyl chloride and silicon tetrachloride with alkyl nitrites have also been described; (c) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951). Because of the reactivity of amines with these halide reagents, these methods for nitrosyl chloride formation have not been employed in deamination procedures.
(11) (a) J. Bakke, *Acta Chem. Scand.*, **21**, 1007 (1967); (b) J. Bakke, *ibid.*, **22**, 1833 (1968); (c) J. Bakke, *ibid.*, **25**, 859 (1971).
(12) Deaminative conversions of adenosine and related compounds by nitrosyl chloride in dimethylformamide have been reported: H. Sigel and H. Brintzinger, *Helv. Chim. Acta*, **48**, 433 (1965).
(13) (a) R. J. H. Clark, "The Chemistry of Titanium and Vanadium", Elsevier, Amsterdam, 1968; (b) R. Feld and P. L. Cowe, "The Organic Chemistry of Titanium", Butterworths, London, 1965; (c) R. A. Walton, *Prog. Inorg. Chem.*, **16**, 1 (1972).
(14) (a) T. Mukaiyama, T. Izawa, and K. Saigo, *Chem. Lett.*, 323 (1974); (b) T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **16**, 817 (1977).
(15) (a) E. E. Aynsley, *J. Chem. Soc.*, 3016 (1953); (b) formation of nitrosyl chloride by the reaction of $TiCl_4$ with N_2O_4 at room temperature has been reported: J. R. Partington and A. L. Whynes, *J. Chem. Soc.*, 3135 (1949).
(16) D. C. Bradley, *Prog. Inorg. Chem.*, 2, 303 (1960).
(17) (a) J. H. Wise and J. T. Elmer, *J. Chem. Phys.*, **18**, 1441 (1950); (b) R. H. Pierson, A. N. Fletcher, and E. St. C. Gantz, *Anal. Chem.*, **28**, 1218 (1956).
(18) D. C. Bradley, R. C. Mehrota, and W. Wardlaw, *J. Chem. Soc.*, 4202 (1952).
(19) G. Heublein and D. D. Rang, *Tetrahedron*, **28**, 1873 (1972).
(20) Titanium tetrachloride has been employed in a variety of alcohol dehydration reactions: (a) J. P. Wilson and H. Weingarten, *Can. J. Chem.*, **48**, 983 (1971); (b) W. Lehnert and W. Kiinger, *Tetrahedron Lett.*, 1501 (1971); (c) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).
(21) Nitrosative oxidation of amines and *N*-alkylimines have been reported: (a) M. P. Doyle, M. A. Zaleta, J. E. DeBoer, and W. Wierenga, *J. Org. Chem.*, **38**, 1663 (1973); (b) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, **89**, 1147 (1967).
(22) (a) G. A. Olah, G. Salem, J. S. Staral, and T.-L. Ho, *J. Org. Chem.*, **43**, 173 (1978); (b) F. Q. Kohant and F. W. Lamps, *J. Am. Chem. Soc.*, **87**, 5795 (1965).
(23) E. J. Strojny, R. T. Iwamasa, and L. K. Frevel, *J. Am. Chem. Soc.*, **93**, 1171 (1971).
(24) M. Wilheim and D. Y. Curtin, *Helv. Chim. Acta*, **40**, 2129 (1957).
(25) (a) J. MacCordick and R. Rohmer, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **263**, 1369 (1966); (b) J. MacCordick, C. Devine, R. Perrot, and R. Rohmer, *ibid.*, **274**, 278 (1972).
(26) By continuing the flow of hydrogen chloride through the reaction solution during the addition of benzylamine, benzyl chloride was produced with the total exclusion of benzyl alcohol.
(27) The deamination of 1-aminobutane by RONO/HCl in chloroform has been reported to form 1-butene in 92% yield;[6] deamination of 1-aminooctane by nitrosyl chloride in ethyl ether at −70 °C produces octene in 5% yield;[11a] 3–5% yields of styrene are formed from nitrosyl chloride deaminations of 1-amino-2-phenylethane in ether, chloroform, hexane, and carbon tetrachloride.[19]
(28) No apparent variation in the percentage yield of formate esters was observed in separate experiments in which 1 equiv of water (relative to amine) was added to the NOCl/DMF reaction solution prior to introduction of the amine.
(29) (a) Carbenium ion trapping by the less basic solvent acetonitrile is an irreversible process for the benzyl and primary or secondary aliphatic cations: M. P. Doyle and W. Wierenga, *J. Am. Chem. Soc.*, **94**, 3901 (1972); (b) irreversible intramolecular carbenium ion trapping by O-alkylation of the amido functional group has been reported: S. P. McManus, J. T. Carroll, and C. U. Pittman, Jr., *J. Org. Chem.*, **35** 3768 (1970).
(30) Observed percentage yields were within ±2% of the results reported for $TiCl_4$-generated nitrosyl chloride in Table IV. However, significant variation in the relative yields of alcohol product was observed: % RO_2CH/% ROH (temp, C°) = 4.3 (−15), 2.0 (0), 1.4 (25), 1.0 (50).
(31) M. P. Doyle, B. Siegfried, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2426 (1977).
(32) W. A. Noyes, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 108.
(33) H. A. Ory, *Anal. Chem.*, **32**, 509 (1960).
(34) P. Ehrlich and W. Siebert, *Z. Anorg. Allgem. Chem.*, **303**, 96 (1960).
(35) A blue solution indicative of the presence of aliphatic nitroso compounds was not observed during these diazotization reactions. Except for reactions in methylene chloride that resulted in an orange solution, the final color of the reaction solutions was yellow.

Azoloquinoxaline *N*-Oxides

Berkeley W. Cue, Jr.,* Leonard J. Czuba, and John P. Dirlam*

Department of Agricultural Organic Chemistry, Pfizer Central Research, Groton, Connecticut 06340

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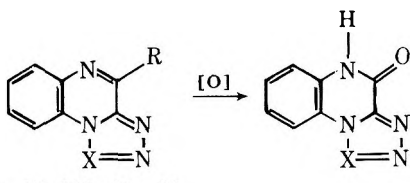
The previously inaccessible *v*-triazolo[1,5-*a*]quinoxaline 5-oxide (**3**), *s*-triazolo[4,3-*c*]quinoxaline 5-oxide (**6**), and tetrazolo[1,5-*a*]quinoxaline 5-oxide (**7**) ring systems have been prepared from *N*-oxide precursors. Previous attempts by others to prepare these compounds by N-oxidation of the appropriate azoloquinoxalines led to C-4 oxidation instead of N-oxidation. This study shows that by introducing the *N*-oxide function at an early stage in the synthetic sequence, the problem of ring carbon oxidation at C-4 is avoided.

Although the chemistry of *s*-triazolo[4,3-*c*]quinoxalines has been extensively studied[1-10] and there is one report[11] concerning the preparation of the *v*-triazolo[1,5-*a*]quinoxaline ring system, the corresponding *N*-oxides in either system have not been prepared. Similarly, tetrazolo[1,5-*a*]quinoxalines are known,[12,13] but the *N*-oxides are not. Attempts by others to prepare these *N*-oxides by oxidation of the known azoloquinoxalines with hydrogen peroxide in acetic acid, alkaline potassium permanganate, or acidic chromic anhydride resulted in oxidation at C-4 instead of N-oxidation (eq 1).[1] We reasoned that these compounds could be prepared from *N*-oxide precursors, thereby avoiding the necessity for N-oxidation at a late stage in the synthesis. Until recently, there were few methods available for the selective synthesis of suitable 3-substituted quinoxaline 1-oxide (**1**) precursors, but it has been demonstrated in these laboratories that certain quinoxaline 1,4-dioxides bearing an electron-withdrawing group in the 2 position can be selectively monodeoxygenated to afford good yields of the desired starting materials.[14] Following this concept, we have developed general procedures for the synthesis of *v*-triazolo[1,5-*a*]quinoxaline 5-oxides (**3**), s-triazolo[4,3-*c*]quinoxaline 5-oxides (**6**), and tetrazolo[1,5-*a*]quinoxaline 5-oxides (**7**).



(1)

R = H, CH_3; X = N
R = H, CH_3; X = CH

None of the known methods for preparing *v*-triazolopyridine and *v*-triazoloquinoline derivatives[15-17] proved to be satisfactory for the preparation of the corresponding quinoxaline analogues. Eventually, we succeeded in obtaining *v*-triazolo[1,5-*a*]quinoxaline 5-oxides (**3**) by modifying a procedure for preparing α-pyridyldiazomethane *N*-oxides.[18,19] The requisite 3-substituted quinoxaline 1-oxides (**1**) were available from the corresponding quinoxaline 1,4-dioxides by selective monodeoxygenation.[14] Treatment of **1** with *p*-toluenesulfonylhydrazine in methanol gave the tosylhydrazones

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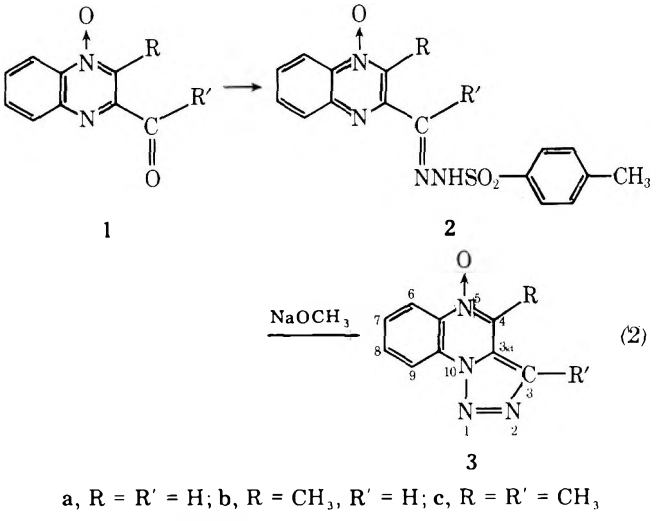
in high yield (eq 2). In most cases, stirring a methanolic solution of **2** with 1 equiv of sodium methoxide led to the formation of the *v*-triazolo[1,5-*a*]quinoxalines. However, when R = R′ = CH_3, the sodium salt of the tosylhydrazone was isolated instead. Heating this salt in dimethylformamide at 100 °C led to the corresponding triazole. Conversion of the tosylhydrazones to the triazoles occurred in good yields.

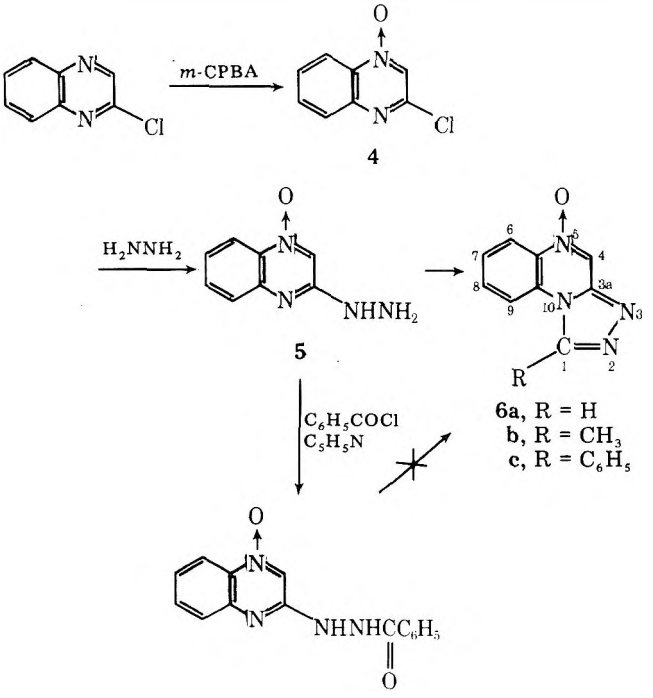


1 2 3 (2)

a, R = R′ = H; b, R = CH_3, R′ = H; c, R = R′ = CH_3

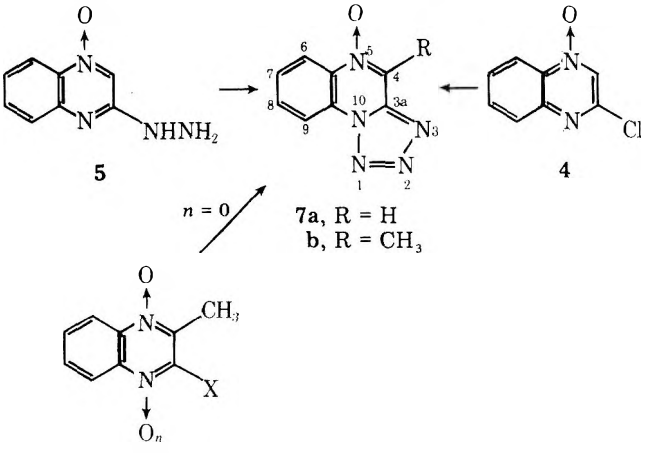
The triazoles were characterized on the basis of their spectral properties and combustion analysis. For example, the NMR spectrum of **3a** (R = R′ = H) exhibits a singlet at δ 9.20 (H-4), a multiplet at δ 8.50 (H-6 and H-9), a singlet at δ 8.37 (triazole H), and a multiplet at δ 8.00 (H-7 and H-8). By comparison, the triazole ring proton in *v*-triazolo[1,5-*a*]-quinoline appears as a singlet at δ 8.04.[16] The mass spectrum of **3a** exhibits a molecular ion at *m/e* 186 with principal fragments at *m/e* 170 ($M^+ - O$) and 158 ($M^+ - N_2$). No absorption due to the diazo tautomer (ca. 2000 cm^{-1}) was detected in the infrared spectrum of **3a.** The other compounds of the type **3** exhibit similar spectral properties.

From a consideration of the methods available for the preparation of *s*-triazolo[4,3-*c*]quinoxalines,[2,3] we felt that the corresponding *N*-oxides (**6**) would be accessible through similar chemistry. The requisite 3-hydrazinoquinoxaline 1-oxide (**5**) was prepared in 63% yield by the action of hydrazine hydrate on 3-chloroquinoxaline 1-oxide (**4**).[20] Heating **5** in refluxing triethyl orthoformate gave **6a** in 61% yield, while heating **5** in acetic acid gave **6b** in 30% yield. Attempts to prepare **6c** from **5** and benzoyl chloride in refluxing pyridine led only to benzoylation of the hydrazino moiety, and the resulting hydrazide resisted cyclization.



4 5 6a, R = H; b, R = CH_3; c, R = C_6H_5

We have used intermediate **5** to also prepare tetraazolo[1,5-*a*]quinoxaline 5-oxide (**7a**), in 60% yield, by diazotization in aqueous acetic acid. Alternatively, displacement of **4** by sodium azide in Me_2SO gave **7a** in 46% yield. None of the azide tautomer could be detected in the product by infrared spectroscopy. The mass spectrum of **7a** exhibits a molecular ion at *m/e* 187 with loss of nitrogen and hydrogen cyanide to give a principal fragment at *m/e* 132. In the NMR spectrum of **7a,** H-4 appears as a singlet at δ 9.50. This chemical shift compares favorably with that assigned to H-4 for the triazole **3a.**



5 4 7a, R = H; b, R = CH_3

8a, X = SO_2CH_3; *n* = 1
b, X = N_3; *n* = 1
c, X = N_3; *n* = 0
d, X = SO_2CH_3; *n* = 0

An alternate route was used for the preparation of the 4-methyl analogue **7b.** Since 3-chloro-2-substituted quinoxaline 1-oxides (**4**) were unknown at the time of this study[24] and could not be conveniently prepared from the corresponding 1,4-dioxides, we explored the use of methylsulfonylmethylquinoxaline 1,4-dioxides (e.g., **8a**), which were readily available.[25] In a related study[26] we found that 2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide (**8a**) afforded 2-azido-3-methylquinoxaline 1,4-dioxide (**8b**) in high yield. We expected the corresponding mono *N*-oxide **8c,** in which N-4 is not oxidized, to exist predominantly as the tetrazole tautomer **7b,** but the thermal instability of **8b** precluded its deoxygenation. However, **8a** was selectively deoxygenated[14] with trimethyl phosphite in refluxing 1-propanol to give **8d** in 73% yield, and reaction of **8d** with sodium azide in Me_2SO gave **7b** in 89% yield.

In summary, we have shown that the previously unaccessible *v*-triazolo[1,5-*a*]-, *s*-triazolo[4,3-*c*]-, and tetrazolo[1,5-*a*]quinoxaline 5-oxides can be prepared in good yield. By introducing the *N*-oxide function at an early stage in the synthetic sequence, the problem of ring carbon oxidation at C-4 is avoided.

Experimental Section

General. Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer; UV spectra were recorded on a Cary Model 14 spectrophotometer; and mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo using either a water aspirator or a vacuum pump.

2-Methylquinoxaline-3-carboxaldehyde 1-Oxide (1b). 2-Hydroxymethyl-3-methylquinoxaline 1,4-dioxide[27] (4.29 g, 20.8 mmol) was added cautiously in several portions with stirring to concentrated sulfuric acid (10 mL) at room temperature (the addition is exothermic). The dark reaction mixture was stirred at room temperature for 3 h, and then it was heated to 70 °C for 30 min. After the reaction mixture had cooled to room temperature, it was poured onto crushed ice. Insoluble material was removed by filtration and the filtrate extracted with several portions of chloroform. The combined chloroform layers were dried ($MgSO_4$) and evaporated to give a residue which was purified by column chromatography on silica gel. Elution of the column with benzene gave 200 mg of an unidentified solid. Further elution with chloroform gave 1.40 g (36%) of **1b** after recrystallization from acetone: mp 167–169 °C; NMR ($CDCl_3$) δ 3.00 (3, s, CH_3), 7.90 (2, m, H-6, H-7), 8.30 (1, m, H-8), 8.65 (1, m, H-5), 10.2 (1, s, CHO); IR (KBr) 2740, 1725 cm^{-1}; mass spectrum, *m/e* 188 (M^+). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.25; N, 14.89. Found: C, 63.57; H, 4.45; N, 14.63.

Quinoxaline-3-carboxaldehyde 1-Oxide *p*-Toluenesulfonylhydrazone (2a). A solution of quinoxaline-3-carboxaldehyde 1-oxide[14] (0.95 g, 5.4 mmol) and *p*-toluenesulfonylhydrazine (2.10 g, 11.2 mmol) in methanol (100 mL) was heated on a steam bath for 30 min and cooled, and the precipitate was filtered and washed with ether to give 1.82 g (98%) of **2a:** mp 160 °C dec; NMR (CF_3COOH) δ 2.43 (3, s, CH_3), 7.57 (4, q, aromatic H's), 8.10 (3, m, H-5, H-6, H-7), 8.13 (1, s, CH), 8.57 (1, m, H-8), 9.06 (1, s, H-2); mass spectrum, *m/e* 342 (M^+). Anal. Calcd for $C_{16}H_{14}N_4O_3S$: C, 56.13; H, 4.12; N, 16.36. Found: C, 55.84; H, 4.35; N, 15.94.

2-Methylquinoxaline-3-carboxaldehyde 1-Oxide *p*-Toluenesulfonylhydrazone (2b). A solution of 2-methylquinoxaline-3-carboxaldehyde 1-oxide (0.64 g, 3.38 mmol) and *p*-toluenesulfonylhydrazine (0.66 g, 3.38 mmol) in absolute methanol (50 mL) was warmed on a steam bath for 1 h and cooled, and the precipitate was filtered to give 0.94 g (78%) of **2b:** mp 142–143 °C dec; NMR (CF_3COOH) δ 2.02 (3, s, CH_3), 2.37 (3, s, CH_3), 7.27 (4, q, aromatic H's), 7.50–8.00 (3, m, H-5, H-6, H-7), 8.00 (1, s, CH), 8.25 (1, m, H-8); IR (KBr) 1333, 1163 cm^{-1}; mass spectrum, *m/e* 356 (M^+). Anal. Calcd for $C_{17}H_{16}N_4O_3S$: C, 57.29; H, 4.52; N, 15.72. Found: C, 57.48; H, 4.62; N, 15.92.

3-Acetyl-2-methylquinoxaline 1-Oxide *p*-Toluenesulfonylhydrazone (2c). A solution of 3-acetyl-2-methylquinoxaline 1-oxide[14] (1.70 g, 8.4 mmol) and *p*-toluenesulfonylhydrazine (1.55 g, 8.4 mmol) in methanol (25 mL) was heated under reflux for 1 h and then cooled, and the precipitate was filtered to give 2.53 g (80%) of **2c:** mp 190–193 °C dec; NMR (Me_2SO-d_6) δ 2.37 (3, s, CH_3), 2.40 (3, s, CH_3), 2.70 (3, s, $COCH_3$), 7.60 (4, q, aromatic H's), 7.80 (3, m, H-5, H-6, H-7), 8.40 (2, m, H-8, HN); IR (KBr) 2985, 1333, 1162, 917, 772 cm^{-1}; mass spectrum, *m/e* 370 (M^+). Anal. Calcd for $C_{18}H_{18}N_4O_3S$: C, 58.31; H, 4.86; N, 15.12. Found: C, 58.00; H, 4.80; N, 15.10.

***v*-Triazolo[1,5-*a*]quinoxaline 5-Oxide (3a).** To a stirred solution of sodium methoxide (180 mg, 3.36 mmol) in methanol (50 mL) at room temperature was added portionwise quinoxaline-3-carboxaldehyde 1-oxide *p*-toluenesulfonylhydrazone (1.15 g, 3.36 mmol). During the addition the solution took on a deep red color. After stirring for 1 h, the precipitate which formed was collected by filtration and recrystallized from methanol to give 425 mg (70%) of **3a:** mp 202–204 °C dec; NMR (Me_2SO-d_6) δ 8.00 (2, m, H-7, H-8), 8.37 (1, s, H-3), 8.50 (2, m, H-6, H-9), 9.20 (1, s, H-4); mass spectrum, *m/e* 186 (M^+). Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 57.75; H, 3.28; N, 30.25.

4-Methyl-*v*-triazolo[1,5-*a*]quinoxaline 5-Oxide (3b). A stirred suspension of 2-methylquinoxaline-3-carboxaldehyde 1-oxide *p*-toluenesulfonylhydrazone (773 mg, 2.17 mmol) in methanol (25 mL) was treated portionwise with a solution of sodium methoxide (117 mg, 2.17 mmol) in methanol (5 mL). After stirring at room temperature for 2 h, the precipitate was collected by filtration and recrystallized from ethyl acetate to give 225 mg (52%) of **3b:** mp 219–220 °C dec; NMR (Me_2SO-d_6) δ 2.83 (3, s, CH_3), 7.80 (2, m, H-7, H-8), 8.45 (1, s, H-3), 8.60 (2, m, H-6, H-9); IR (KBr) 1740, 1280, 1110 cm^{-1}; mass spectrum, *m/e* 200 (M^+). Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.36; H, 3.99; N, 27.95.

3,4-Dimethyl-*v*-triazolo[1,5-*a*]quinoxaline 5-Oxide (3c). A stirred suspension of 3-acetyl-2-methylquinoxaline 1-oxide *p*-toluenesulfonylhydrazone (2.50 g, 6.75 mmol) in methanol (30 mL) was treated dropwise with a solution of sodium methoxide (356 mg, 6.75 mmol) in methanol (5 mL) at room temperature. After the mixture was stirred for 1 h with no precipitate formation, the solvent was evaporated in vacuo to give a yellow solid which was heated in dry dimethylformamide (80 mL) at 100 °C for 1 hr. The colorless solution then was poured into water (200 mL) and extracted with two 100-mL portions of ethyl acetate. Evaporation of the dried ($MgSO_4$) ethyl acetate solution gave 670 mg (53%) of **3c:** mp 199–202 °C dec (recrystallization from methanol); NMR ($CDCl_3$) δ 2.83 (3, s, CH_3), 2.92 (3, s, CH_3), 7.78 (2, m, H-7, H-8), 8.55 (2, m, H-6, H-9); mass spectrum, *m/e* 214 (M^+). Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.70; N, 26.16. Found: C, 61.42; H, 4.67; N, 26.43.

3-Chloroquinoxaline 1-Oxide (4). 2-Chloroquinoxaline (98.8 g, 0.60 mmol) was suspended in methylene chloride (1 L) that was cooled with an icebath, and 85% *m*-chloroperbenzoic acid (122 g, 0.60 mmol) was added to the suspension in ca. 10-g portions over a period of 40 min. After the reaction mixture was stirred at room temperature for 72 h, the resulting precipitate was collected by filtration and washed with methylene chloride. The mother liquor and the methylene chloride washings were combined and washed with a solution of 5% sodium bicarbonate. The organic layer was then dried over anhydrous magnesium sulfate and evaporated to afford a solid product. The crude product was recrystallized from methanol to give 6.89 g (63%) of **4** as colorless needles: mp 150–152 °C (lit.[21] mp 150–152 °C); NMR ($CDCl_3$) δ 6.65–7.35 (3, m, H-5, H-6, H-7), 7.55 (1, s, H-2), 7.55–7.80 (1, m, H-8); UV λ_{max} (MeOH) 243 nm (ϵ 40 900), 320 (8510); mass spectrum, *m/e* 182 ($M^+ + 2$), 180 (M^+). Anal. Calcd for $C_8H_5N_2OCl$: C, 53.20; H, 2.79; N, 15.51. Found: C, 53.10; H, 2.80; N, 15.09.

3-Hydrazinoquinoxaline 1-Oxide (5). To a suspension of 3-chloroquinoxaline 1-oxide (1.50 g, 8.3 mmol) in ethanol (15 mL) was added hydrazine hydrate (80%, 1.5 mL), and the mixture was heated under reflux for 40 min. The solid that separated on cooling the mixture was recrystallized from water to give 0.92 g (63%) of **5** as bright yellow crystals: mp 199–200 °C dec; mass spectrum, *m/e* 176 (M^+). Anal. Calcd for $C_8H_8N_4O$: C, 54.60; H, 4.58; N, 31.83. Found: C, 54.57; H, 4.59; N, 31.81.

***s*-Triazolo[4,3-*a*]quinoxaline 5-Oxide (6a).** 3-Hydrazinoquinoxaline 1-oxide (0.60 g, 3.4 mmol) was added to triethyl orthoformate (7 mL) and the mixture heated under reflux for 3 h. Upon cooling the resulting solution, almost pure product separated. This was washed with cold methanol and then recrystallized from methanol to yield 0.39 g (61%) of **6a** as pink needles: mp 272–273 °C dec; NMR (Me_2SO-d_6) δ 7.59 (2, m, H-7, H-8), 8.21 (2, m, H-6, H-9), 8.93 (s, 1, H-1), 9.70 (1, s. H-4); UV λ_{max} (MeOH) 228 nm (shoulder), 263 (ϵ 7400), 322 (10 900); mass spectrum, *m/e* 186. Anal. Calcd for $C_9H_6N_4O$: C, 58.12; H, 3.25; N, 30.12. Found: C, 58.31; H, 3.43; N, 29.56.

1-Methyl-*s*-triazolo[4,3-*a*]quinoxaline 5-Oxide (6b). A mixture of 3-hydrazinoquinoxaline 1-oxide (**5**) (4.00 g, 22.7 mmol) and glacial acetic acid (30 mL) was heated under reflux for 2 h and cooled, and the solvent was removed in vacuo. The brick-red residue was dissolved in 250 mL of boiling water, the resulting solution was treated with activated carbon and filtered through a pad of Super Cel, and the filtrate was kept in the refrigerator overnight to give 1.35 g (30%) of **6b:** mp 238–242 °C dec (recrystallization from methanol); NMR (Me_2SO-d_6) δ 2.63 (3, s, CH_3), 7.56 (2, m, H-7, H-8), 8.10 (2, m, H-6, H-9), 8.83 (1, s, H-4); mass spectrum, *m/e* 200 (M^+). Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.88; H, 3.95; N, 28.42.

Tetrazolo[1,5-*a*]quinoxaline 5-Oxide (7a). A. To an ice-cooled solution of 3-hydrazinoquinoxaline 1-oxide (1.00 g, 5.7 mmol) in acetic acid (12%, 35 mL) was added dropwise a solution of $NaNO_2$ (0.44 g, 6.4 mmol) in water (4 mL), and the mixture was kept at room temperature for 3 h. The resulting tan precipitate was collected by filtration and washed with methanol to afford 0.60 g (60%) of **7a:** mp 179–180 °C dec; NMR (Me_2SO-d_6) δ 7.70–8.25 (2, m, H-7, H-8), 8.40–8.70 (2, m, H-6, H-9), 9.50 (1, s, H-4); IR (KBr), no absorption in the $-N_3$ region (ca. 2150 cm^{-1}) was detected; UV λ_{max} (MeOH) 230 nm (ϵ 19 850), 262 (shoulder), 317 (9350); mass spectrum, *m/e* 187 (M^+). An analytical sample of **7a** was obtained by recrystallization from methanol. mp 189–190 °C dec. Anal. Calcd for $C_8H_5N_5O$: C, 51.38; H, 2.70; N, 37.43. Found: C, 51.00; H, 2.91; N, 37.04.

B. To a solution of 3-chloroquinoxaline 1-oxide (1.00 g, 5.5 mmol) in Me_2SO (15 mL) was added sodium azide (0.36 g, 5.5 mmol). After stirring the solution for 72 h at room temperature, it was diluted with water (100 mL) and a precipitate formed that was collected by filtration to afford 0.47 g (46%) of **7a,** mp 178–180 °C dec. Similar results were found when the above reaction was heated under reflux overnight in ethanol–water (1:1 v/v), and crude product **7a** was obtained in 52% yield.

2-Methyl-3-methylsulfonylquinoxaline 1-Oxide (8d). 2-Methyl-3-methylsulfonylquinoxaline 1,4-dioxide[25] (7.60 g, 30 mmol) was added to 1-propanol (75 mL) containing trimethyl phosphite (4.09 g, 33 mmol). The reaction mixture was heated under reflux for 3 h and then cooled to room temperature to afford a crystalline precipitate. The solid was collected by suction filtration and washed with 1-pro-

panol to give 5.24 g (73%) of **8d**: mp 185–187 °C dec; NMR (Me_2SO-d_6) δ 2.80 (3, s, CH_3), 3.65 (3, s, CH_3SO_2), 7.90–8.20 (3, m, H-5, H-6, H-7), 8.30–8.60 (1, m, H-8); UV λ_{max} (MeOH) 274 nm (ε 39 590), 330 (8120); mass spectrum, *m/e* 238 (M^+). Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.47; H, 4.24; N, 11.77. Found: C, 50.51; H, 4.24; N, 11.57.

4-Methyltetrazolo[1,5-*a*]quinoxaline 5-Oxide (7b). To a solution of 2-methyl-3-methylsulfonylquinoxaline 1-oxide (4.00 g, 16.8 mmol) in Me_2SO (90 mL) was added sodium azide (1.10 g, 16.8 mmol). After the solution was stirred overnight at room temperature, it was diluted with water (300 mL) and a precipitate formed that was collected by suction filtration to afford 3.02 g (89%) of **7b**: mp 205–206 °C; NMR (Me_2SO-d_6) δ 2.80 (3, s, CH_3), 7.80–8.25 (2, m, H-7, H-8), 8.40–8.70 (2, m, H-6, H-9); UV λ_{max} (MeOH) 232 nm (ε 22 200), 262 (shoulder), 317 (11 000); mass spectrum, *m/e* 201 (M^+). Anal. Calcd for $C_9H_7N_5O$: C, 53.78; H, 3.51; N, 34.84. Found: C, 53.66; H, 3.62; N, 34.62.

Acknowledgment. We wish to thank Anne Krech, Kerry Gombatz, Richard James, and Raymond Sumner for their technical assistance.

Registry No.—**1a**, 61522-60-9; **1b**, 67452-55-5; **1c**, 61522-56-3; **2a**, 67452-56-6; **2b**, 67452-57-7; **2c**, 67452-58-8; **3a**, 67452-59-9; **3b**, 67452-60-2; **3c**, 67452-61-3; **4**, 5227-59-8; **5**, 67452-62-4; **6a**, 67452-63-5; **6b**, 67452-64-6; **7a**, 61148-19-4; **7b**, 67452-65-7; **8a**, 39576-77-7; **8d**, 67464-71-5; 2-hydroxymethyl-3-methylquinoxaline 1,4-dioxide, 16915-79-0; *p*-toluenesulfonylhydrazine, 1576-35-8; 2-chloroquinoxaline, 1448-87-9.

References and Notes

(1) N. G. Koshel, E. G. Kovalev, and I. Y. Postovskii, *Khim. Geterotsikl. Soedin.*, **6**, 851 (1970).
(2) D. Shiho and S. Tagami, *J. Am. Chem. Soc.*, **82**, 4044 (1960).
(3) K. T. Potts and S. N. Schneller, *J. Heterocycl. Chem.*, **5**, 485 (1968).
(4) I. Y. Postovskii and N. G. Koshel, *Khim. Geterotsikl. Soedin.*, **6**, 981 (1970).
(5) K. Y. Tserng and L. Bauer, *J. Heterocycl. Chem.*, **11**, 637 (1974).
(6) K. Saikachi and S. Tagami, *Yakugaku Zasshi*, **82**, 1246 (1962).
(7) S. Tagami, K. Sasayama, and D. Shiho, *Yakugaku Zasshi*, **86**, 622 (1966).
(8) S. Tagami, M. Sawaki, and D. Shiho, *Chem. Pharm. Bull.*, **17**, 1963 (1969).
(9) H. W. Heine and R. P. Henzel, *J. Org. Chem.*, **34**, 171 (1969).
(10) S. Yurugi, A. Miyake, M. Tomimoto, and T. Fushimi, *Takeda Kenkyusho Ho*, **32**, 111, 118 (1973); *Chem. Abstr.*, **80**, 37056a (1974).
(11) J. C. Kauer and R. A. Carboni, *J. Am. Chem. Soc.*, **89**, 2633 (1967).
(12) I. N. Goncharov and I. Y. Postovskii, *Zh. Obshch. Khim.*, **32**, 3323 (1962); *Chem. Abstr.*, **58**, 1255 (1963).
(13) R. Stolle and F. Hanusch, *J. Prakt. Chem.*, **136**, 9 (1933).
(14) J. P. Dirlam and J. W. McFarland, *J. Org. Chem.*, **42**, 1360 (1977).
(15) J. H. Boyer, R. Borgers, and L. T. Wolford, *J. Am. Chem. Soc.*, **79**, 678 (1957).
(16) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).
(17) Y. Tamura, J.-H. Kim, Y. Miki, H. Hayashi, and M. Ikeda, *J. Heterocycl. Chem.*, **12**, 481 (1975).
(18) Y. Mizuno, T. Endo, and T. Nakamura, *J. Org. Chem.*, **40**, 1391 (1975).
(19) R. A. Abramovitch, C. S. Menon, M. Murata, and E. M. Smith, *J. Chem. Soc., Chem. Commun.*, 693 (1974).
(20) Several attempts to prepare **4** according to literature procedure[21–23] failed to give satisfactory results. We have found that oxidation of 2-chloroquinoxaline with *m*-chloroperbenzoic acid in methylene chloride gave reproducibly high yields of **4** (see Experimental Section).
(21) J. K. Landquist, *J. Chem. Soc.*, 2816 (1953).
(22) E. Hayashi, C. Iijima, and Y. Nagasawa, *Yakugaku Zasshi.*, **84**, 163 (1964).
(23) Y. Ahmad, M. S. Habib, M. Ikram Qureshi, and M. A. Farooqi, *J. Org. Chem.*, **38**, 2176 (1973).
(24) C. E. Mixan and R. G. Pews, *J. Org. Chem.*, **42**, 1869 (1977).
(25) E. Abushanab, *J. Org. Chem.*, 38, 3105 (1973).
(26) J. P. Dirlam, B. W. Cue, Jr., and K. J. Gombatz, *J. Org. Chem.*, **43**, 76 (1978).
(27) J. Francis, J. K. Landquist, A. A. Levi, J. A. Silk, and J. M. Thorp, *Biochem. J.*, **63**, 455 (1956).

1,2-Diphenyl-3-azanaphtho[*b*]cyclobutadiene

A. Afzali Ardakani,* N. Maleki, and M. R. Saadein

Department of Chemistry, Pahlavi University, Shiraz, Iran

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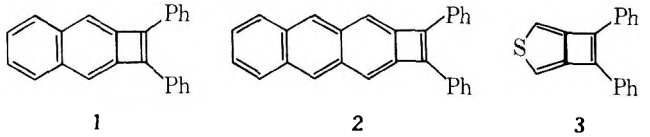
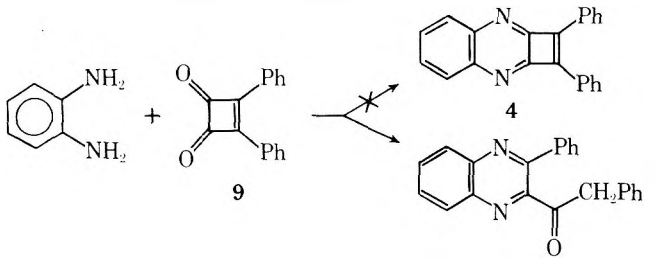
1,2-Diphenyl-3-azanaphtho[*b*]cyclobutadiene (**12**) has been synthesized. The cyclopentadienone derivative **13** and its iron tricarbonyl complex **14** were also formed during the final reduction step. The title compound, obtained as red crystals, undergoes addition reactions (reduction, oxidation) at the 1,2-double bond; it also undergoes a Diels–Alder reaction with 1,3-diphenylisobenzofuran and on heating with triiron dodecacarbonyl it is converted to a mixture of **13** and **14**. The iron tricarbonyl complex **14** is easily oxidized with Ce^{4+} to give **13**.

The synthesis of the first stable aromatic-fused cyclobutadiene, namely 1,2-diphenylnaphtho[*b*]cyclobutadiene (**1**), was reported by Cava[1] in 1963. Since then, 1,2-diphenylanthra[*b*]cyclobutadiene (**2**),[2] 6,7-diphenyl-3-thiabicyclo[3.2.0]heptatriene (**3**),[3] and a few other aromatic-fused cyclobutadienes[4,5] have been synthesized. Compound **3** represents the first known heteroaromatic-fused cyclobutadiene.



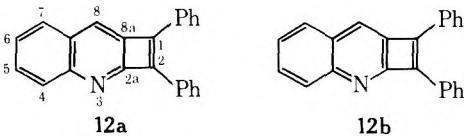
1 **2** **3**



9 **4** **5**

In 1961, Blomquist and Lalancette[6] attempted the synthesis of the diaza analogue **4** of the hydrocarbon **1** by condensation of the dione **9** with *o*-phenylenediamine; they isolated the ring cleavage product **5** rather than the desired cyclobutadiene derivative **4**.

In this paper we report the synthesis and some chemical properties of 1,2-diphenyl-3-azanaphtho[*b*]cyclobutadiene



12a **12b**

(**12**), the first example of a heteroaromatic-fused cyclobutadiene with nitrogen as the heteroatom.

Results and Discussion

o-Nitrobenzyl bromide (**6**) was converted to *o*-nitrobenzyltriphenylphosphonium bromide (**7**) in excellent yield. Wittig condensation of dione **9** with the ylide **8**, derived from the phosphonium salt **7**, afforded a mixture of *cis*- and *trans*-nitroaryls **10a** and **10b** in 85% yield. These isomers, found in the ratio of 87:13, respectively, were separated by

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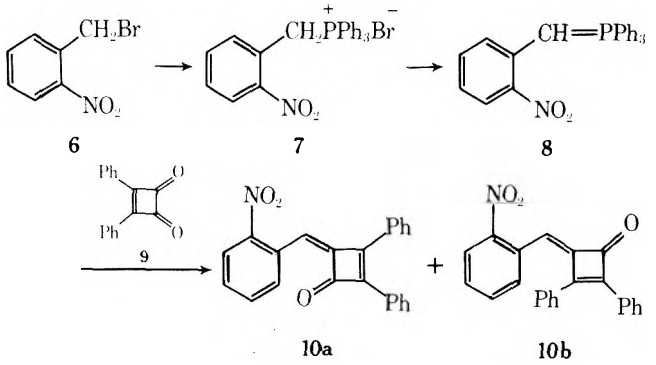
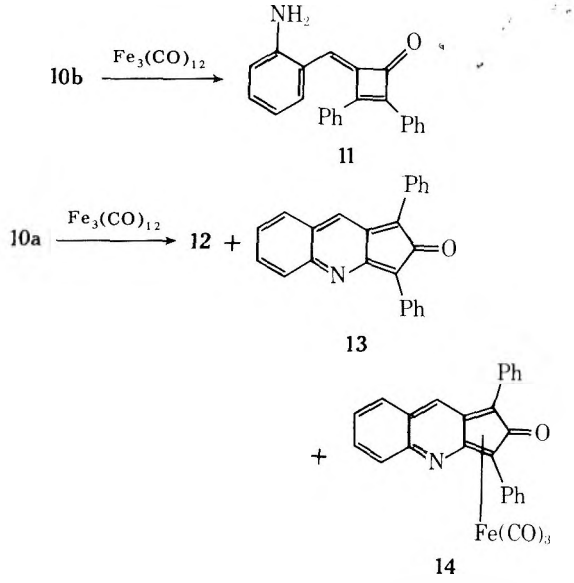


either column chromatography or fractional crystallization from ethanol.

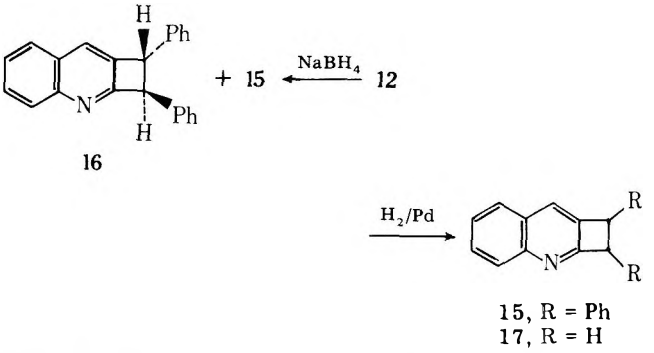
Assignment of the cis and trans geometries to **10a** and **10b** was easily achieved by reduction of these compounds and identification of the product(s) obtained in each case. Although attempts to reduce selectively the nitro group of either **10a** or **10b** by conventional reduction methods, e.g, metals and acid, failed, application of the method of Landesberg[7] to **10a** and **10b** gave the desired products in each case. Thus, reduction of **10b** with triiron dodecacarbonyl afforded the corresponding amino ketone **11**. On the other hand, reduction of **10a** under the same conditions was accompanied by spontaneous ring B closure to give the desired 1,2-diphenyl-3-azanaphtho[*b*]cyclobutadiene (**12**) in 16.5% yield, along with two



other products, the cyclopentadienone derivative **13** (13% yield) and its iron tricarbonyl complex **14** (12.5% yield).

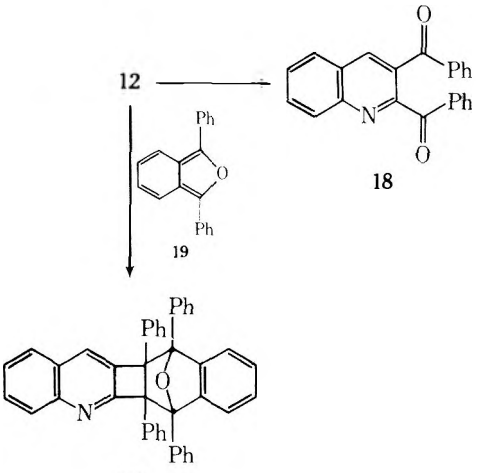
The structural assignment of the latter compounds is based upon spectral and chemical evidence. Compound **12,** isolated as red crystals, mp 163–164 °C, shows a parent ion at *m/e* 305 in its mass spectrum; in addition to a multiplet in the aromatic region in its NMR spectrum, there appears a singlet for one hydrogen at the relatively high-field position of δ 6.55. The position of this proton, undoubtedly that at C-8, is very close to that (δ 6.55) of the olefinic protons of *cis*-stilbene[8] and is strong evidence that the bonds 2a–3 and 8–8a in **12** are fixed to a remarkable degree as in **12a**. A similar suggestion was made to explain the NMR spectrum of **1**.[1] The ultraviolet–visible spectrum of **12** is quite similar to that of hydrocarbon **1**.[1]

Although 1,2-diphenyl-3-azanaphtho[*b*]cyclobutadiene (**12**) appears to be stable indefinitely, it undergoes addition reactions at its 1,2-unsaturated bond of the four-membered ring very easily. Thus, absorption of 1 molar equiv of hydrogen in the presence of palladium afforded *cis*-1,2-diphenyl-3-azanaphtho[*b*]cyclobutene (**15**), whose UV spectrum is quite



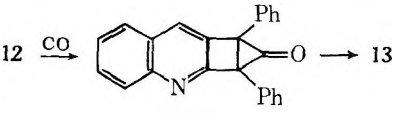
similar to that of nonphenylated analogue **17**, prepared by Wilk.[9] Compound **12** also undergoes facile reduction with sodium borohydride to give largely *trans*-1,2-diphenyl-3-azanaphtho[*b*]cyclobutene (**16**) and a trace of the cis isomer **15**.

Oxidation of **12** with potassium permanganate in dilute hydrochloric acid proceeds smoothly to give 2,3-dibenzoylquinoline (**18**). The diketone **18** could also be obtained by irradiation of a dilute acetone solution of **12** with direct sunlight for 48 h. Finally, the Diels–Alder reaction of **12** with 1,3-di-



phenylisobenzofuran (**19**) resulted in the formation of the expected adduct **20,** whose structure follows from its mass (M^+ 475) and NMR (δ 7.8, s, 1 H).

The dark violet crystalline compound **13,** mp 202–204 °C, exhibits the following spectral data; its NMR spectrum has a singlet at δ 7.3 in addition to a multiplet in the aromatic region, and shows a parent ion at *m/e* 333 in its mass spectrum. Its IR spectrum shows an intense absorption at 1700 cm^{-1} due to a carbonyl group. Compound **13** is probably formed by a chelotropic addition of carbon monoxide to the 1,2-unsaturated bond of the four-membered ring of **12**, giving the in-



termediate **21** which undergoes homolytic ring cleavage to the observed product.[10]

In fact, when **12** was heated with triiron dodecacarbonyl under the conditions of reduction, both **13** and **14** were formed.

$$12 \xrightarrow[C_6H_6,\ \text{heat}]{Fe_3(CO)_{12}} 13 + 14$$

The iron tricarbonyl complex **14** is an orange crystalline compound, mp 297–299 °C dec. It undergoes oxidation with ceric ammonium nitrate very easily, giving back the violet

compound **13**. In its IR spectrum, a carbonyl absorption appears at 1675 cm^{-1} in addition to three distinct absorptions at 2060, 2000, and 1980 cm^{-1}, attributable to three carbonyl groups attached to the iron.

Experimental Section

General. Melting points were determined with a Thomas Unimelt apparatus and are uncorrected. Ultraviolet–visible spectra were determined in ethanol. Spectra were recorded on a Perkin–Elmer 157G IR spectrophotometer, a Varian Cary 118 UV–visible spectrophotometer, a Varian T-60 NMR spectrometer, and a Varian CH5 or Varian Mat. 112 mass spectrometer. Elemental analyses were performed by Alfred Bernhardt Microanalytical Laboratories, West Germany.

o-Nitrobenzyltriphenylphosphonium Bromide.[11] A solution of o-nitrobenzyl bromide (2.16 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) in chloroform (20 mL) was stirred at room temperature for 48 h. Diethyl ether (20 mL) was added and the resulting solution was kept at room temperature for an additional 24 h. The deposited crystals were filtered, washed with dry diethyl ether, and air dried. Recrystallization from ethanol afforded colorless prisms (4.15 g, 87%): mp 161–162 °C; NMR ($CDCl_3$) δ 6.05 (d, 2 H, J = 7 Hz), 7.9 (m, 19 H). Anal. Calcd for $C_{25}H_{21}BrNO_2$: C, 62.76; H, 4.39; N, 2.93. Found: C, 62.55; H, 4.56; N, 2.83.

Wittig Condensation of 8 with Dione 9. A solution of dione **9**[6] (2.43 g, 10 mmol) and phosphonium salt **7** (4.78 g, 10 mmol) in dry acetonitrile (50 mL) was heated to reflux under a slight pressure of nitrogen. Triethylamine (6 mL) was added dropwise to the refluxing solution over a period of 30 min. After the addition was completed, the dark violet solution was refluxed for an additional 4 h. The solution was cooled, the solvent was evaporated on a rotary evaporator, and the oily residue was triturated under ethanol to give 3.0 g (85%) of a mixture of **10a** and **10b** as a yellow solid. The mixture was chromatographed on a column of silica gel using a 1:1 mixture of petroleum ether–benzene as eluent. The leading band afforded, after the evaporation of the solvent, 2.4 g (84% of the mixture) of **10a** as yellow solid. Crystallization from ethanol gave the analytical sample of **10a**: mp 124–126 °C; IR (KBr) 1765 cm^{-1}; NMR ($CDCl_3$) δ 7.10 (s, 1 H), 7.50 (m, 14 H); M^+ 353. Anal. Calcd for $C_{23}H_{15}NO_3$: C, 78.18; H, 4.20; N, 3.96. Found: C, 78.18; H, 4.25; N, 3.97.

The second fraction obtained from the column afforded, after evaporation of the solvent and crystallization of the solid residue from methanol, yellow needles of **10b** (450 mg, 16% of the mixture): mp 162.5–164 °C; M^+ 353; NMR ($CDCl_3$) δ 7.0 (s, 1 H), 7.50 (m, 14 H). Anal. Calcd for $C_{23}H_{15}NO_3$: C, 78.18; H, 4.20; N, 3.96. Found: C, 78.0; H, 4.34; N, 4.07.

Reduction of 10b. Triiron dodecacarbonyl (2.5 g, 5 mmol) was added to a solution of **10b** (870 mg, 2.5 mmol) in dry benzene (30 mL) containing absolute methanol (2 mL), and the resulting solution was refluxed under nitrogen for 7 h. The solvent was evaporated on a rotary evaporator and the residue was taken up into chloroform. The chloroform solution was concentrated and chromatographed on a column of silica gel using a 25:75 mixture of benzene–petroleum ether as eluent. Evaporation of the solvent and crystallization of the solid residue from ethanol afforded an analytical sample (350 mg, 54%) of **11** as orange needles: mp 164–165 °C; IR (KBr) 3400, 1765 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (s, 1 H), 7.25 (m, 14 H); M^+ 323. Anal. Calcd for $C_{23}H_{17}NO$: C, 85.44; H, 5.26; N, 4.33. Found: C, 85.50; H, 5.08; N, 4.23.

Reduction of 10a. Triiron dodecacarbonyl (5.04 g, 0.01 mol) was added to a solution of **10a** (3.53 g, 0.01 mol) in dry benzene (150 mL) containing absolute methanol (2 mL) and the resulting solution was refluxed under nitrogen for 7 h. The reaction mixture was cooled to room temperature and filtered. Evaporation of the filtrate gave a dark red gummy material which was dissolved in a small amount of chloroform and chromatographed on a column of basic alumina. Elution of the column with diethyl ether afforded two different fractions. The first fraction, which was a red solution, was evaporated on a rotary evaporator. Trituration of the residue under ether gave a red solid which was crystallized from n-hexane to give the analytical sample of **12** (0.5 g, 16.5%): mp 163–164 °C; M^+ 305; NMR ($CDCl_3$) δ 6.5 (s, 1 H), 7.42 (m, 14 H); UV λ_{max} (EtOH) 282 (log ϵ 5.62), 444 nm (3.35). Anal. Calcd for $C_{23}H_{15}N$: C, 90.49; H, 4.91; N, 4.59. Found: C, 90.22; H, 5.06; N, 4.45.

Evaporation of the second fraction gave a deep violet solid, which was crystallized from n-hexane to give deep violet crystals of **13** (450 mg, 13.5%): mp 202–204 °C; IR (KBr) 1700 cm^{-1} (C=O); M^+ 333; NMR ($CDCl_3$) δ 7.32 (s, 1 H), 7.43 (m, 14 H); UV λ_{max} (EtOH) 269 (log ϵ 6.5), 477 (5.9), 552 nm (5.6). Anal. Calcd for $C_{24}H_{15}NO$: C, 86.00; H, 4.50; N, 4.20. Found: C, 85.67; H, 4.62; N, 4.15.

Further elution of the column with a 95:5 mixture of chloroform–methanol afforded, after evaporation of the solvent, an orange solid which was crystallized from ethanol to give orange needles of **14** (600 mg, 12.6%). Another crystallization from ethanol gave the analytical sample of **14**: mp 297–299 °C dec; M^+ 473; IR (KBr) 2060, 2000, 1980, 1670 cm^{-1}; NMR (CD_3CO_2H) δ 7.82 (s, 1 H), 7.11 (m, 14 H). Anal. Calcd for $C_{27}H_{15}NO_4Fe$: C, 68.49; H, 3.17; N, 2.95; Fe, 11.83. Found: C, 68.18; H, 3.28; N, 3.06; Fe, 11.94.

Hydrogenation of 1,2-Diphenyl-3-azanaphtho[*b*]cyclobutadiene (12). A solution of **12** (305 mg, 1 mmol) in a mixture of benzene (10 mL) and ethanol (8 mL) was shaken under hydrogen (atmospheric pressure, room temperature) in the presence of 5% palladium on charcoal (0.1 g) until the red color vanished (~45 min). Solvent evaporation followed by crystallization from n-hexane–ether gave pure *cis*-1,2-diphenyl-3-azanaphtho[*b*]cyclobutene (**15**; 200 mg, 67%): mp 107–108 °C; M^+ 356; NMR ($CDCl_3$) AB system as two doublets centered at δ 4.73 and 4.93 (2 H, J = 3 Hz), 8.53 (s, 1 H); UV λ_{max} (EtOH) 234 (log ϵ 4.77), 306 (4.07), 312 (4.04), 320 nm (4.11). Anal. Calcd for $C_{23}H_{17}N$: C, 89.90; H, 5.53; N, 4.56. Found: C, 89.97; H, 5.72; N, 4.36.

Reduction of 12 with Sodium Borohydride. Sodium borohydride (100 mg) was added portionwise to a solution of **12** (305 mg, 1 mmol) in a mixture of diethyl ether (20 mL) and ethanol (10 mL) and the resulting solution was stirred at room temperature for 30 min. The solvent was evaporated and water (50 mL) was added to the oily residue and extracted with three portions (50 mL each) of methylene chloride. The combined extracts were dried (Na_2SO_4) and evaporated on a rotary evaporator. The residue was chromatographed on a thick layer of silica gel using chloroform as eluent. Separation of the two different bands afforded **15** (10 mg) and the trans isomer **16** (180 mg, 58%): mp 127–129 °C; M^+ 356; NMR ($CDCl_3$) AB system as two doublets centered at δ 5.33 and 5.63 (2 H, J = 8 Hz), 8.37 (s, 1 H); UV λ_{max} (EtOH) 235 (log ϵ 4.75), 306 (4.07), 312 (4.05), 320 nm (4.12). Anal. Calcd for $C_{23}H_{17}N$: C, 89.90; H, 5.53; N, 4.56. Found: C, 89.76; H, 5.65; N, 4.36.

Diels–Alder Reaction of 12 with 1,3-Diphenylisobenzofuran. A solution of **12** (305 mg, 1 mmol) and 1,3-diphenylisobenzofuran (270 mg, 1 mmol) in dry benzene (50 mL) was refluxed for 3 h. The reaction mixture was cooled to room temperature and the solvent was evaporated on a rotary evaporator. Crystallization of the solid residue afforded **20** as microcrystals (305 mg, 52%). Recrystallization from ethanol gave an analytical sample of **20**: mp 278–279 °C; M^+ 575; NMR (Me_2SO-d_6) δ 8.15 (s, 1 H). Anal. Calcd for $C_{43}H_{29}NO$: C, 89.73; H, 5.04; N, 2.43. Found: C, 89.40; H, 5.25; N, 2.32.

Chemical Oxidation of 12 by Potassium Permanganate. A saturated solution of potassium permanganate in acetone (1 mL) was added to a solution of **12** (305 mg, 1 mmol) in 10 mL of acetone. Dilute hydrochloric acid (15 drops) was added and the reaction mixture was heated on a steam bath for 30 min. The solution was cooled to room temperature and basified with dilute ammonium hydroxide. The basic solution was extracted with ether, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on a column of basic alumina. Elution with chloroform gave, after evaporation of the solvent, a solid residue which was crystallized twice with ether to give the analytical sample of **18** (55 mg, 16.5%): mp 172–173 °C; IR (KBr) 1670 and 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.25 (s, 1 H); M^+ 337. Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.89; H, 4.45; N, 4.15. Found: C, 81.45; H, 4.32; N, 4.20.

Photochemical Oxidation of 12. A solution of **12** (305 mg, 1 mmol) in acetone (300 mL) in a 500-mL flask was stoppered and kept in direct sunlight for 48 h. The solution was then evaporated on a rotary evaporator to a solid residue which was chromatographed on a column of basic alumina. Elution with chloroform gave a solid residue which was crystallized from diethyl ether to give a crystalline compound (65 mg, 20%), identical in all respects with an authentic sample of **18** obtained from chemical oxidation of **12**.

Reaction of 12 with Triiron Dodecacarbonyl. A mixture of **12** (305 mg, 1 mmol) and triiron dodecacarbonyl (405 mg, 1 mmol) in dry benzene (20 mL) containing few drops of methanol was refluxed under nitrogen for 1 h. The reaction mixture was filtered and the filtrate was evaporated on a rotary evaporator. The residue was chromatographed on a thick layer of silica gel using a mixture of 95:5 chloroform–methanol as eluent. Isolation of the leading and slowest bands afforded compounds **13** (25 mg, 6%) and **14** (65 mg, 12%) identical in their IR and melting points with authentic samples of **13** and **14**, respectively, obtained from the reduction of **10a**.

Oxidation of 14 with Ce^{4+}. A solution of **14** (235 mg, 0.5 mmol) and ceric ammonium nitrate (270 mg, 0.5 mmol) in dry acetone was

stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was evaporated on a rotary evaporator. The solid residue was chromatographed on a column of silica gel eluting with diethyl ether. Evaporation of the solvent afforded a deep violet solid which was crystallized from *n*-hexane to give deep violet crystals (50 mg, 30%), identical in all respects with an authentic sample of **13**.

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Registry No.—**7**, 23308-83-0; **8**, 42546-50-9; **9**, 24234-76-2; **10a**, 59625-73-9; **10b**, 66809-63-0; **11**, 66809-64-1; **12**, 66809-65-2; **13**, 66809-66-3; **14**, 66809-78-7; **15**, 66809-67-4; **16**, 66809-68-5; **18**, 52260-38-5; **19**, 5471-63-6; **20**, 66809-69-6; *o*-nitrobenzyl bromide, 3958-60-9; triphenylphosphine, 603-35-0.

References and Notes

(1) M. P. Cava, B. Hwang, and J. P. Van Meter, *J. Am. Chem. Soc.*, **85**, 4032 (1963).
(2) M. P. Cava, H. Firouzabadi, and M. Krieger; *J. Org. Chem.*, **39**, 480 (1974).
(3) P. J. Garratt, K. Peter, and C. Vollhardt, *J. Am. Chem. Soc.*, **94**, 1022 (1972).
(4) H. Straub, *Angew. Chem., Int. Ed. Engl.*, **13**, 405 (1974).
(5) (a) F. Toda and M. Ohi, *J. Chem. Soc., Chem. Commun.*, 506 (1975); (b) F. Toda and N. Dam; *ibid.*, 30 (1976).
(6) A. T. Blomquist and E. A. LaLancette, *J. Am. Chem. Soc.*, **83**, 1387 (1961).
(7) J. M. Landesberg, L. Katz, and J. Olson, *J. Org. Chem.*, **37**, 930 (1972).
(8) Spectrum No. 305, Varian Associates NMR Spectra Catalogue.
(9) M. Wilk, H. Schwab, and J. Rochlitz, *Justus Liebigs Ann. Chem.*, **698**, 149 (1966).
(10) Huebel and Barge have observed the formation of the same kind of product on heating diphenylacetylene with triiron dodecacarbonyl: W. Huebel and E. H. Barge. *J. Nucl. Inorg. Chem.*, **10**, 250 (1959).
(11) Although compound **7** has been generated previously, its isolation and characterization have not been described: G. P. Schiementz, J. Becker, and J. Stoekigt, *Chem. Ber.*, **103**, 2077 (1970).

Stereocontrolled Preparation of Chiral (*E*)-1-Alkenyl Sulfoxides. Efficient Reduction of Alkenyl Sulfoxides to the Corresponding Alkenyl Sulfides

Gary H. Posner* and Ping-Wah Tang

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

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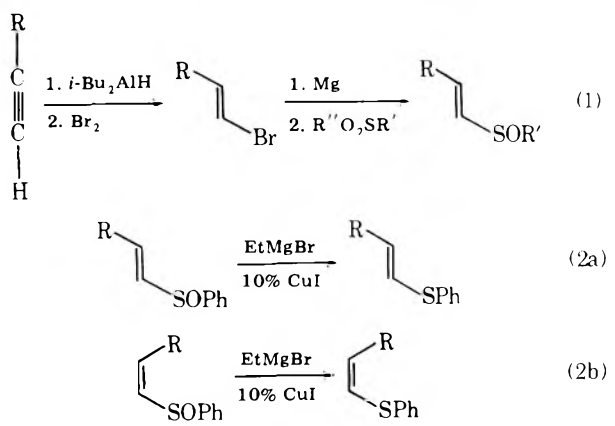
(*E*)-1-Alkenylmagnesium bromides react cleanly and stereospecifically with chiral menthyl sulfinate esters to produce chiral (*E*)-1-alkenyl sulfoxides; no alkenyl sulfide is formed in this process. 1-Alkenyl and 2-alkenyl aryl sulfoxides are easily reduced to the corresponding vinylic sulfides upon treatment with ethylmagnesium bromide/10% cuprous iodide at 0 °C for 1 h. No double bond isomerization occurs during this sulfoxide deoxygenation, and 1,3-butadienyl sulfoxides are reduced cleanly to 1,3-butadienyl sulfides. Proton NMR indicates an upfield chemical shift of about 0.1 and 0.6 ppm for H_α and H_β in the α,β-ethylenic *sulfides* relative to the corresponding *sulfoxides*.

Pursuing our interest in reactions of organometallic reagents with α,β-unsaturated sulfur compounds,[1] we have sought a stereocontrolled method for preparing either (*Z*)-1-alkenyl or (*E*)-1-alkenyl sulfoxides. The Carey–Hernandez synthesis using carbonyl compounds and 1-(trimethylsilyl)-1-(phenylsulfinyl)methyllithium leads to a mixture of (*Z*)- and (*E*)-vinylic sulfoxides,[2] and the Horner–Wittig procedure using carbonyl compounds and sulfinyl methylphosphonate anions also leads to a mixture of geometrical isomers in which the *E* isomer often predominates.[3] Separation of vinylic sulfoxide geometrical isomers is often difficult and time consuming, and the overall yields of pure *E* or *Z* isomers are usually low.[2,3] We report here our recent success in stereospecifically converting (*E*)-vinylic bromides via the corresponding Grignard reagents into (*E*)-vinylic sulfoxides in good yields via eq 1. We report also our discovery that (*Z*)- and (*E*)-vinylic phenyl sulfoxides are easily reduced by ethylmagnesium bromide/10% cuprous iodide with retention of double bond configuration to the corresponding (*Z*)- and (*E*)-vinylic phenyl sulfides under mild conditions and in high yields (eq 2).



Results and Discussion

Preparation of (*E*)-1-Alkenyl Sulfoxides. Reaction of Grignard reagents with chiral sulfinate esters is one of the oldest and most often used procedures for preparation of chiral sulfoxides.[4] Harpp has recently summarized this area and has emphasized that a major byproduct in this type of reaction is often the sulfide derived from the initially formed sulfoxide.[5] Harpp recommends general use of organocopperlithium reagents for conversion of sulfinate esters into the corresponding sulfoxides with formation usually of only small amounts of sulfides. We have found that menthyl *p*-toluenesulfinate reacts with isopropenylmagnesium bromide/10% cuprous iodide to give substantial (e.g., 30–40%) amounts of sulfide. Surprisingly, however, we have found that vinylic Grignard reagents in the absence of any copper salts react cleanly with menthyl sulfinate esters in tetrahydrofuran to give only the corresponding vinylic sulfoxides and no detectable amounts of vinylic sulfides as indicated by the comparison with authentic sulfides (Table I).

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Table I. Reaction of (−)-Menthyl (−)-(*S*)-Sulfinate Esters with Vinylic Grignard Reagents in Tetrahydrofuran

menthyl-OS(O)R′ (1 equiv), R′ =	registry no.	Grignard (1.3 equiv)	time, h	temp, °C	isolated purified product	% yield of purified product	registry no.
p-tolyl	1517-82-4	CH_2=C(CH_3)MgBr	20 11	25 66	CH_2=C(CH_3)S(O)-Tol (1)	75	59336-69-5
p-tolyl		(*E*)-C_6H_{13}CH=CHMgBr	12	25	(*E*)-C_6H_{13}CH=CHS(O)-Tol (2)	60	66967-38-2
phenyl	34513-32-1	(*E*)-C_6H_{13}CH=CHMgBr	12	25	(*E*)-C_6H_{13}CH=CHS(O)-Ph (3)	65	66967-39-3
t-Bu	66967-37-1	(*E*)-C_6H_{13}CH=CHMgBr	4	0	(*E*)-C_6H_{13}CH=CHS(O)-Bu-*t* (4)	51	66967-40-6

Proton NMR coupling constants of 15–16 ppm for the vinylic protons in 1-alkenyl sulfoxides **2–4** confirmed the *E* stereochemistry of these alkenes; coupling constants of 10–12 ppm have been reported for the vinylic protons of (*Z*)-1-alkenyl sulfoxides.[3]

Andersen[4b,c] and Mislow[4d,e] have firmly established that Grignard reaction with chiral sulfinate esters proceeds stereospecifically to give sulfoxides of high optical purity. Vinylic sulfoxides **1–4**, formed via Grignard attack on chiral menthyl sulfinate esters, have high specific rotations; although they are new compounds for which no specific rotation data are available in the literature, we assume them to be of high optical purity.[6]

Acetylenes can be converted cleanly into (*Z*)- and (*E*)-1-alkenyl halides,[7] and (*Z*)- and (*E*)-1-alkenyl Grignard reagents can thus be prepared. We expect, therefore, that (*Z*)-1-alkenyl sulfoxides could be produced as cleanly and effectively as are the (*E*)-1-alkenyl sulfoxides **1–4** in this report.

It is noteworthy that vinylic sulfoxides have recently been used as functionalized dienophiles in diverse Diels–Alder reactions, leading to products difficult to obtain by older methods.[8,9]

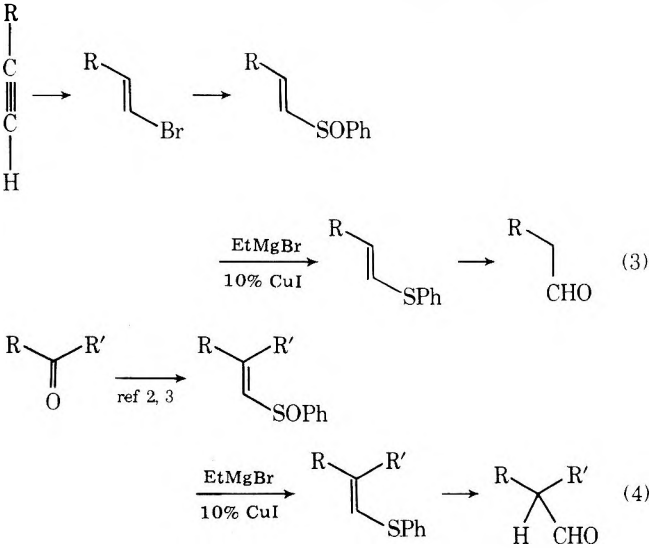
Reduction of α,β-Ethylenic Phenyl Sulfoxides to α,β-Ethylenic Phenyl Sulfides. Among the many methods developed recently for reduction of sulfoxides to sulfides,[10] including our own photochemical deoxygenation procedure,[11] not one has been applied to reduction of *vinylic* sulfoxides. In studying the behavior of vinylic sulfoxides toward some organometallic reagents, we discovered that ethylmagnesium bromide/10% cuprous iodide cleanly and effectively reduces a wide structural variety of vinylic phenyl sulfoxides to the corresponding vinylic sulfides under very mild conditions and in 60–93% yields (Table II).[12]

Several important generalizations emerge from the data in Table II. First, this deoxygenation method proceeds without any change in the configuration of the vinylic group; (*Z*)- and (*E*)-1-alkenyl sulfoxides give geometrically pure (*Z*)- and (*E*)-1-alkenyl sulfides. Second, 2-alkenyl sulfoxide **10** also is reduced to the corresponding 2-alkenyl sulfide. Third, 1,3-butadienyl sulfoxides **7, 8,** and **11** are reduced cleanly to the corresponding 1,3-butadienyl sulfides, even in an isoprenoid system in which cyclized products are often encountered in reactions proceeding by ionic or radical pathways. Fourth, phenyl sulfoxides are reduced somewhat more easily than benzylic sulfoxide **12** and much more easily than *tert*-butyl sulfoxide **13.** Furthermore, in the absence of cuprous iodide, ethylmagnesium bromide causes no sulfoxide reduction, and magnesium and lithium dialkylcuprates[13] also cause no sulfoxide reduction. Finally, 1-alkenyl aryl *sulfones*[1a] undergo only β addition of an ethyl group (i.e., no reduction) when exposed to ethylmagnesium bromide/10% cuprous iodide.

Proton NMR data (see Table III, Experimental Section) indicate that the chemical shifts of H_α and H_β in the α,β-ethylenic *sulfides* are about 0.1 and 0.6 ppm, respectively, upfield from those of H_α and H_β in the corresponding α,β-ethylenic *sulfoxides.* This substantial deshielding effect especially on H_β in the alkenyl sulfoxides suggests a significant π-electron shift away from the β-carbon atom. Furthermore, the upfield shift of H_β in the series α,β-ethylenic sulfones,[1c] sulfoxides, and sulfides correlates with the expected ease of reduction of these alkenyl sulfur compounds (sulfones > sulfoxides > sulfides).[13d]

The mechanism for this copper-catalyzed Grignard reduction of sulfoxides is not clear; it will probably turn out to be a complex process. Our observation that phenyl sulfoxides are more easily reduced than benzylic and nonaryl sulfoxides seems to suggest the possibility of an electron transfer from the organometallic reagent(s) to the aryl sulfoxide unit.[13c,d] Our observation that *methyl*magnesium bromide is less effective than *ethyl*magnesium bromide raises the question of whether a metal hydride mechanism is operative.[14] More information is needed before firm mechanistic conclusions can be drawn.

Vinylic sulfides can be deprotonated and alkylated α to sulfur, and they are synthetically equivalent to carbonyl compounds (i.e., masked or latent acyl anions).[15] Hydrolysis[16] of our vinylic sulfoxides would afford an overall method for anti-Markownikoff hydration of terminal acetylenes[17] (eq 3)

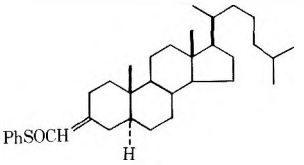
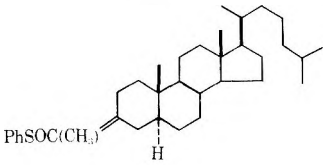
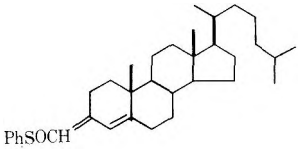


and also a new procedure for reductive nucleophilic acylation of aldehydes and ketones[16,18] (eq 4). Some prostacyclin vinylic sulfoxides and sulfides have recently been reported to possess biological activity.[10h]

Conclusion

Chiral vinylic sulfoxides can be prepared easily and without contamination by vinylic sulfides via reaction of readily available vinylic Grignard reagents with chiral menthyl sulfinate esters. No advantage is achieved by using vinylic copper

Table II. Reduction of Vinylic Phenyl Sulfoxides by 3.0 equiv of Ethylmagnesium Bromide and 0.3 equiv of Cuprous Iodide in Ether at 0 °C for 1 h (eq 2a and 2b)

registry no.	sulfoxide	% yield of purified sulfide[a]	registry no.
	$C_5H_{11}CH{=}CHS(O)Ph$ (5)		
66967-42-8	(*Z*)-5	85	66967-47-3
66967-41-7	(*E*)-5	90	66967-48-4
	$PhCH{=}CHS(O)Ph$ (6)		
40110-65-4	(*Z*)-6	91	7214-56-4
40110-66-5	(*E*)-6	93	7214-53-1
40110-72-3	(*E*,*E*)-$PhCH{=}CHCH{=}CHS(O)Ph$ (7)	81	66967-49-5
	$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHS(O)Ph$[b] (8)	85	
			
66967-43-9	(*Z*)-9[c]	68[d]	66967-50-8
66967-44-0	(*E*)-9	70[d]	66967-51-9
			
66967-45-1	10	80–90[e]	66967-52-0
			
	11[c]	60[f]	
621-08-9	$PhCH_2S(O)CH_2Ph$ (12)	41[g]	538-74-9
67010-46-2	(*E*)-$C_5H_{11}CH{=}CHS(O)Bu\text{-}t$ (13)	0[h]	

[a] Identification was based on IR, NMR, and mass spectral analysis and by comparison with authentic sulfides prepared from the appropriate carbonyl compounds and lithium diethyl phenylthiomethylphosphonate (ref 3). [b] A mixture of (*E*)-1,(*Z*)-3 and (*E*)-1,(*E*)-3 was used (see Experimental Section). [c] The sulfoxide was dissolved in a minimum volume of THF and was added to the Grignard reagent in ether. [d] About 18% of starting material was recovered. [e] 25 °C, 19 h. [f] About 30% of starting material was recovered. [g] Starting material was recovered in 40% yield. [h] Quantitative recovery of starting material.

Table III. Spectroscopic Data for Vinylic Sulfoxides 5-11 and for the Corresponding Sulfides Formed via Equation 2

	sulfoxide		sulfide	
	IR, cm^{-1} (liquid film)	NMR, δ (CCl_4, *J* in Hz) $-CH_2CH{=}CHSO$ γ β α	NMR δ (CCl_4, *J* in Hz) $-CH_2CHCHS-$ γ β α	*m/e* (M^+)
(*Z*)-5	1042	2.52 (m, γ, CH_2), 5.92–6.20 (m, H_α, H_β)	2.08 (m, γ, CH_2), 5.68 (t of d, H_β, $J_{\alpha,\beta}$ = 9, $J_{\beta,\gamma}$ = 7), 6.08 (d, H_α, $J_{\alpha,\beta}$ = 9)	206
(*E*)-5	1042	2.0–2.4 (m, γ, CH_2), 6.14 (d, H_α, $J_{\alpha,\beta}$ = 15.6), 6.45 (d of t, H_β, $J_{\alpha,\beta}$ = 15.6, $J_{\beta,\gamma}$ = 6.6)	2.0–2.3 (m, γ, CH_2), 6.08 (d, H_α, $J_{\alpha,\beta}$ = 14.8), 5.86 (t of d, H_β, $J_{\alpha,\beta}$ = 14.8, $J_{\beta,\gamma}$ = 6.4)	
(*Z*)-6		7.08 (d, H_α, $J_{\alpha,\beta}$ = 10.6),[a] 6.40 (d, H_β, $J_{\alpha,\beta}$ = 10.6)	6.29, 6.38 ($J_{\alpha,\beta}$ = 11.6)	212
(*E*)-6	1045	6.75 (d, $J_{\alpha,\beta}$ = 15.6)[a]	6.58, 6.71 ($J_{\alpha,\beta}$ = 16)	
7[b]	1032	6.44 (H_α), 6.64–6.90 (m, 3 H, vinyl H)[a]	6.30–6.88 (m, 4 H, vinyl H)	238
8[c]	1040	1.52–1.60 (m, 6 H, $Me_2C{=}$), 1.88 (s, 3 H, C_4-Me), 5.02–5.20 (m, C_7-H), 5.88 (d, C_3-H, J_{2-3} = 11.3), 6.20 (d, C_1-H, J_{1-2} = 14.3), 7.16 (d of d, C_2-H)	1.76 (s, 3 H, C_4-Me), 5.0 (br s, C_7-H), 5.80 (d, C_3-H, J_{2-3} = 10.8), 6.10 (d, C_1-H, $J_{1,2}$ = 14.4), 6.54 (d of d, C_2-H)	258
9	1020	5.98 (s, H_α)	5.88 (s, H_α)	
10[d]		1.55 (s, vinyl Me)	1.95 (s, vinyl Me)	
11	1018	0.69 (s, C_{18}-Me), 0.83 (s, C_{19}-Me), 5.78 (s, H_α),[e] 6.68 (s, C_4-H)[e]	0.68 (s, C_{18}-Me), 0.83 (s, C_{19}-Me), 5.70 (s, H_α),[f] 6.28 (s, C_4-H)[f]	

[a] $CDCl_3$. [b] Mp 80 °C; *m/e* 254 (M^+); sulfide mp 72–73 °C. [c] Spectral data recorded only for the mixture of geometrical (*E*)-1, (*Z*)-3 and (*E*)-1, (*E*)-3 1,3,7-nonatriene isomers. [d] Mp 168–169 °C. Anal. Calcd for $C_{35}H_{54}OS$: C, 80.40; H, 10.41; S, 6.13. Found: C, 80.06; H, 10.19; S, 6.39. Sulfide mp 138.5–139.5 °C. Anal. Calcd for $C_{35}H_{54}S$: C, 82.94; H, 10.65; S, 6.32. Found: C, 83.03; H, 10.69; S, 6.24. [e] The minor geometrical isomer had δ 5.94 (s, H_α) and 5.74 (s, C_4-H). [f] The minor geometrical isomer had δ 5.88 (s, H_α) and 5.78 (s, C_4-H).

reagents instead of vinylic Grignards. Exposing vinylic sulfoxides to ethylmagnesium bromide/10% cuprous iodide causes clean deoxygenation and produces vinylic sulfides with retained double-bond configuration.

Experimental Section

General. Infrared spectra were taken with a Perkin-Elmer 457 infrared grating spectrophotometer as liquid films or in $CHCl_3$ solutions. NMR spectra were recorded with Jeol MH-100 or Varian A-60 spectrometers in $CDCl_3$ or in CCl_4 solution with Me_4Si as internal standard and chemical shifts were given in δ (ppm). UV spectra were taken with a Cary Model 15 spectrophotometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Melting points were determined with a Mel-Temp melting point apparatus and boiling points are uncorrected. Thin-layer chromatography was done on commercial Analtech silica gel plates. Analytical gas chromatography was performed on a Varian Aerograph Model 1200 chromatograph using a 10 ft × 1/8 in., 2.5% SE-30 on 100–140 mesh Chromosorb G column. Analyses were done by Chemalytics Inc., Tempe, Ariz.

All reactions reported here were carried out in oven-dried three-neck round-bottom flasks equipped with serum stoppers, a Teflon-coated magnetic stirring bar, the copper salt if needed, and a T joint to which an argon-filled balloon had been attached. The flask was evacuated while being heated, then purged with argon from the balloon. This operation was repeated three times before addition of any reagent or solvent.

Reagents and Solvents. The *n*-butyllithium in hexane solution, the methyllithium and the methylmagnesium bromide in ether solution, and the diisobutylaluminum hydride in hexane solution were purchased from Alfa Inorganics Inc., or from Aldrich Chemical Co. Ethylmagnesium bromide, methylmagnesium iodide, and 2-propenylmagnesium bromide were prepared respectively from ethyl bromide, methyl iodide, and 2-propenyl bromide with magnesium turnings in THF or in ether. All organometallic reagents were titrated according to Watson's method.[19] Diethyl ether and tetrahydrofuran (THF) were distilled from a purple suspension of disodium benzophenone dianion and stored under argon over molecular sieves.

The purified grade cuprous iodide (Fisher Chemical Co.) was continuously extracted with THF in a Soxhlet extractor overnight and dried under vacuum at room temperature. The following chemicals were obtained from commercial sources and were used without further purification: hexanal, citral (cis–trans mixture), cholestan-3-one, 4-cholesten-3-one, 2-methylpropanethiol dibenzyl sulfoxide, menthol, and octyne. (−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate was prepared by the method of Estep and Tavares[20] (50%): mp 108 °C (lit.[5] mp 102–104.5 °C; lit.[20] mp 108–109 °C); $[\alpha]_D$ −200° (c 0.2, acetone) (lit.[5,20] −210°).

Reaction of (−)-Menthyl (−)-(*S*)-*p*-Toluenesulfinate with 2-Propenylmagnesium Bromide. To a stirred solution of 7.5 mL (2.6 mmol) of 2-propenylmagnesium bromide in 8 mL of THF at 25 °C 588 mg (2.0 mmol) of (−)-menthyl (−)-(*S*)-*p*-toluenesulfinate dissolved in THF was syringed. After 20 h at 25 °C and 11 h at reflux the reaction was worked up by quenching with a saturated aqueous ammonium chloride solution and extracting with ether. The ether layer was dried over K_2CO_3, filtered, and flash evaporated. By repeated Kugelrohr distillation, the major part of menthol was removed [bp 50–60 °C (0.5 mmHg)]. The 2-propenyl tolyl sulfoxide (**1**) was purified by column chromatography on silica gel using 25% diethyl ether in petroleum ether as eluent to give 269 mg (75%) of an oil: NMR ($CDCl_3$) δ 1.6 (s, 3 H), 2.4 (s, 3 H), 5.4 (s, 1 H), 5.85 (s, 1 H), 7.2–7.5 (m, 4 H); IR (film) 1090, 1040, 820 cm^{-1}; *m/e* 180 (M^+); $[\alpha]_D$ −15.7° (c 0.06, acetone).

Preparation of (*E*)-1-Bromooctene and the Corresponding Grignard Reagent. Following the procedure of Zweifel,[7] to a stirred solution of 5.5 g of 1-octyne (50 mmol) in 10 mL of hexane under nitrogen was added dropwise 50 mmol of diisobutylaluminum hydride in hexane solution. The reaction mixture was maintained below 40 °C during the addition. When the initial exothermic reaction had subsided, the reaction mixture was heated for 2 h at 50 °C. The hexane was removed under aspirator pressure. The residue was diluted with 20 mL of anhydrous THF and was cooled to −50 °C. To this vinylalane solution was added dropwise via addition funnel 8 g of bromine (50 mmol) in 20 mL of THF. The resulting mixture was allowed to warm to room temperature and then cooled to −20 °C for 20 min, at which time 100 mL of 20% aqueous solution of sulfuric acid was added very slowly to decompose the diisobutylalane. A very exothermic reaction was observed. After stirring for 1 h, the heat evolution had subsided and the reaction mixture was poured into a mixture of ice–20% H_2SO_4 solution. The organic product was extracted with petroleum ether (three times). The combined petroleum ether layer was successively washed with an aqueous solution of sodium thiosulfate, a saturated solution of sodium bicarbonate, and brine, dried over K_2CO_3, and concentrated by solvent removal under reduced pressure. The vinyl bromide was distilled, bp 76–77 °C (15 mmHg), to give 7.16 g (75%) of an oil: IR (neat) 1623 ($\nu_{C=C}$ trans), 938 cm^{-1} (δ-HC=CH trans); NMR (CCl_4) δ 0.80–1.60 (m, 11, aliphatic chain) 1.92–2.24 (m, 2, allylic CH_2), 5.98 (d, 1, vinyl proton α to Br, $J_{H_\alpha-H_\beta}$ (trans) = 13.6 Hz), 6.18 (t of d, vinyl proton β to Br, $J_{H_\alpha-H_\beta}$ (trans) = 13.6 Hz, $J_{H_\beta-\text{allylic } CH_2}$ = 6 Hz).

The (*E*)-1-octenylmagnesium bromide was prepared in THF according to the procedure of Normant.[21]

Synthesis of (*E*)-1-Octenyl Tolyl (+)-(*R*)-Sulfoxide (2). To a stirred solution of 37.5 mL of 0.4 M (*E*)-1-octenylmagnesium bromide (15 mmol) in THF at 0 °C under argon was added dropwise 2.21 g of (−)-menthyl (−)-(*S*)-*p*-toluenesulfinate (7.5 mmol) in 5 mL of THF. After the addition was complete, the mixture was stirred overnight at room temperature, and then quenched with a saturated solution of ammonium chloride and diluted with ether. After stirring, the layers were separated and the aqueous phase was extracted with ether. The combined etheral phases were washed with brine and dried over potassium carbonate. Removal of ether by rotoevaporation gave an oil (3.10 g) as crude product. The NMR spectrum as well as the TLC analysis showed the sulfoxide and the regenerated menthol.

The alkenyl sulfoxide was purified by column chromatography on silica gel using petroleum ether–ether (60:40) as eluent. Sulfoxide **2** (1.125 g) was isolated (60%, based on sulfinate ester): R_f 0.175 (eluent: hexane–ether, 60:40); NMR ($CDCl_3$) δ 0.80–1.56 (m, 11, aliphatic chain), 2.00–2.18 [t of d, 2, allylic CH_2, J_{cd} = $J_{c\beta}$ = 6 Hz, $CH_2^dCH_2^cC(H_\beta)$=$C(H_\alpha)S(\rightarrow O)$-], 2.36 (s, 3, CH_3 of the toluene), 6.06 (d, 1, vinyl proton α to the sulfoxide, $J_{H_\alpha-H_\beta}$ = 14 Hz), 6.46 (t of d, 1, vinyl proton β to sulfoxide, $J_{H_\alpha-H_\beta}$ (trans) = 14 Hz, $J_{H_\beta-\text{allylic}}$ = 6 Hz), 7.14 (AA′XX′ system, 4 protons of the toluene ring); IR (film) 1050 cm^{-1}; *m/e* 250 (M^+, 14), 131 (100); $[\alpha]_D$ +104° (*c* 0.05, acetone). Achiral **2** was prepared via the Horner–Wittig procedure[3] and had spectral properties identical with those of chiral **2**.

Benzensulfinyl Chloride. To 179 g (108 mL, 1.5 mol) of freshly distilled thionyl chloride contained in a 500-mL round-bottom flask equipped with a calcium chloride drying tube was added in small portions at room temperature 32.8 g (0.2 mol) of powdered sodium benzenesulfinate. A vigorous reaction occured with evolution of gas. The resulting reaction mixture, a clear yellow viscous oil, was stirred for 2 h at room temperature. The excess thionyl chloride was removed by evaporation under reduced pressure with bath temperature <50 °C. Anhydrous ether (50 mL) was added to the residue and the solvent was evaporated in order to eliminate any trace of thionyl chloride. This procedure was repeated twice. Anhydrous ether (25 mL) was added to the residue. After stirring for 10 min, the sulfinyl chloride in ethereal solution was separated from the inorganic material by filtration under an inverted funnel connected to a source of nitrogen to provide an inert atmosphere during the filtration. Removal of the solvent by distillation at reduced pressure first at 15–20 mmHg, then at 1 mmHg for 3 h, gave a clear pale yellow oil.

(−)-Menthyl (−)-(*S*)-Benzenesulfinate. In a 3-L three-neck round-bottom flask equipped with a long magnetic stirring bar, an addition funnel, glass stopper, and a long Vigreux column with a calcium chloride drying tube, benzenesulfinyl chloride (from 0.2 mol of the corresponding sodium salt), 31.2 g (0.2 mol) of (−)-menthol, and 300 mL of dry ether were placed. To this well-stirred ethereal solution at room temperature was added very fast 32.5 mL (0.4 mol) of pyridine (freshly distilled over CaH_2). The resulting reaction mixture was stirred at room temperature. After stirring overnight, the reaction mixture was filtered with suction to remove pyridinium hydrochloride, which was washed with ether (three times). The combined ethereal filtrate was washed with 50-mL portions of cold water (four times) and 50-mL portions of 10% hydrochloric acid (four times) followed by water (two times) and dried over magnesium filtrate. After removal of ether by rotevaporation a colorless oil was obtained. This oil was not easily crystallized upon cooling to −78 °C. Attempts were made to crystallize in aqueous methanol with careful cooling, and colorless needle crystals were obtained, mp 46 °C. Another recrystallization from methanol and three recrystallizations from pentane gave a solid: mp 51–51.5 °C (lit.[22] 49–51 °C; lit.[5] 51–52 °C); NMR ($CDCl_3$) δ 0.68–1.00 (m, 10, $(CH_3)_2CH$ and CH_3 of the cyclohexane ring), 1.00–2.40 (m, 8, protons of the cyclohexane), 4.05 (d of d of d, 1, axial proton α to the sulfinate group, $J_{H_{ax}-H_{ax}}$ = 10.4 Hz, $J_{H_{ax}-H_{eq}}$ = 5.2 Hz), 7.48 (m, 3, 2 meta protons and para protons of the benzene ring), 7.64 (m, 2 ortho protons of the benzene ring); $[\alpha]_D$ −200° (c 0.2, acetone) (lit.[22] −205.5°).

Synthesis of (*E*)-1-Octenyl Phenyl (+)-(*R*)-Sulfoxide (3). To the (*E*)-1-octenylmagnesium bromide prepared in THF (19.6 mL of 0.82 M, 16.0 mmol) at ca. 0 °C 2.24 g (8 mmol) of benzenesulfinate ester in 5 mL of THF was added dropwise. The reaction was stirred and warmed to room temperature overnight. NH_4Cl-saturated solution (20 mL) was added. The usual workup afforded an oil which contained the regenerated menthol. The menthol was removed by distillation under vacuum [50–60 °C (0.5 mmHg)]. The product was distilled under vacuum [100 °C (0.2 mmHg)] and further purified by short column chromatography on silica gel using 30% ether–petroleum ether as solvent. The product (3) was obtained as an oil (1.23 g, 65%): NMR (CCl_4) δ 0.72–1.64 (m, 11, aliphatic chain), 2.04–2.4 (m, allylic CH_2), 6.20 (d, 1, vinyl proton α to the sulfoxide group, $J_{H_\alpha-H_\beta}$ = 16 Hz), 6.54 (t of d, vinyl proton β to the sulfoxide group, $J_{H_\alpha-H_\beta}$ = 16 Hz, $J_{\beta\text{-allylic } CH_2}$ = 6.4 Hz), 7.36–7.72 (m, 5, aromatic protons); IR (film) 1050 cm^{-1}; *m/e* 236 (M^+, 15), 104 (100); $[\alpha]_D$ +81.8° (*c* 0.16, acetone). Achiral **3** was prepared via the Horner–Wittig procedure[3] and had the same spectral properties as those for chiral **3**.

Synthesis of *tert*-Butylsulfinic Acid. To an oven-dried argon-flushed three-neck 250-mL round-bottom flask space equipped with an efficient mechanical stirring device and glass stopper, 2.25 g of 2-methylpropanethiol (*tert*-butyl mercaptan) (25 mmol)[23] dissolved in 10 mL of dry methylene dichloride was placed and cooled to ~−40 °C. At 0.5-h intervals a slurry (10 mL) of a precooled suspension (−78 °C) prepared from 50 mmol of *m*-chloroperoxybenzoic acid in 100 mL of dry methylene chloride was pipetted into the mercaptan solution with vigorous stirring (exothermic reaction). After 20 times addition, the resulting white suspension was stirred at −30 °C overnight. The suspension was then cooled to −78 °C and filtered rapidly on a sintered glass funnel. The filtrate containing some white suspension was cooled to −78 °C and filtered to remove all *m*-chloroperbenzoic acid. The filtrate was evaporated to yield a white solid. The product was kept in an evacuated desiccator (P_2O_5) to remove the last traces of moisture: 2.62 g (86%); IR($CHCl_3$) 3000–2500 (δ-COOH), 1060 cm^{-1} ($\nu_{S=O}$); NMR ($CDCl_3$) δ 1.20 (s, 9, *tert*-butyl), 10.48 (s, 1, COOH, exchangeable with D_2O); *m/e* 122 (M^+); a larger scale reaction with 0.15 mol of *t*-BuSH gave the same result.

Preparation of (−)-Menthyl (−)-(*S*)-*tert*-Butylsulfinate. (A) Preparation of Sulfinyl Chloride. To the obtained *tert*-butylsulfinic acid (prepared from 0.15 mol of *tert*-butyl mercaptan) cooled at −40 °C was added 89.2 g (0.75 mol) of freshly distilled thionyl chloride with exclusion of moisture. During addition, the reaction mixture was vigorously stirred. A yellow solution resulted. The mixture was allowed to warm to room temperature and stirred for 2 h at that temperature. Excess thionyl chloride was removed under vacuum with complete exclusion of moisture. A brown thick oil was obtained. The crude sulfinyl chloride was used in the following step without further purification.

(B) Preparation of Sulfinate Ester. To the solution of sulfinyl chloride in 200 mL of dry ether under argon with stirring at −78 °C was added dropwise a solution of 23.4 g of (−)-menthol (0.15 mol) in 30 mL of dry pyridine. An immediate white precipitate was formed. After completion of the addition, the mixture was stirred at −78 °C for 3 h. The reaction was allowed to warm to 5 °C and stirred at that temperature overnight. More ether was added and the suspension was added to a solution of 5% $NaHCO_3$. The organic products were extracted with ether. The ethereal layer was washed successively with 5% cold HCl solution, 5% sodium bicarbonate solution, and brine, and dried over potassium carbonate. After evaporation of ether a yellow oil was obtained (32 g). The NMR spectrum of the crude product showed a mixture of the desired ester and the 1-menthol. Some crude product (7.45 g) was purified by column chromatography on silica gel using pentane–ether (85:15) as eluent to yield 4.33 g. The overall yield of the three forementioned steps (from mercaptan to sulfinate ester) was 48%: IR (neat) 1125 ($\nu_{S=O}$ of sulfinate), 1350, 1365 cm^{-1} (*gem*-dimethyl group); UV (C_2H_5OH) λ_{max} 217.5 nm; NMR ($CDCl_3$) δ 0.72–1.00 (m, 10, $(CH_3)_2CH$- and CH_3 on the cyclohexane), 1.00–2.16 (m, 8, protons of the cyclohexane), 1.10 (s, 9, *tert*-butyl), 3.97 (t of d of d, 1, axial proton α to the sulfinate group, J_{ax-ax} = 10 Hz, J_{ax-eq} = 4 Hz); mass spectrum[24] *m/e* 260 (M^+), 203 (M^+ − *t*-Bu), 155 (M^+ − *O*-menthyl), 139 (menthyl$^+$), 105 (*t*-BuS=O$^+$), 57 (*t*-Bu$^+$, base peak); $[\alpha]_D$ −110.5° (*c* 0.04, acetone).

Synthesis of *tert*-Butyl (*E*)-1-Octenyl (+)-(*R*)-Sulfoxide (4). To a stirred solution of 14.4 mL of 0.55 M (*E*)-1-octenylmagnesium bromide (7.92 mmol) in THF at 0 °C under argon was added dropwise 1.56 g of menthyl *tert*-butylsulfinate (6.0 mmol) in 2.5 mL of dry ether. The reaction mixture was stirred at 0° for 4 h and 1 h at room temperature, and then quenched with 50 mL of a saturated aqueous solution of ammonium chloride and diluted with ether. After stirring, the layers were separated and the aqueous phase was extracted twice with ether. The combined organic phases were washed with brine and dried over potassium carbonate. Rotoevaporation of ether left the crude product, 2.55 g (theoretical, 1.30 g). The vinyl sulfoxide was purified by column chromatography on silica gel using petroleum ether–ether (75:25) as eluent; 0.658 g of vinyl sulfoxide 4 (51% yield based on sulfinate ester) was isolated. The sulfoxide was further purified by bulb-to-bulb distillation: bp 100 °C (1.3 mmHg); IR (liquid film) 1630 (HC=CH trans), 1050 cm^{-1} ($\nu_{S=O}$ sulfoxide); NMR ($CDCl_3$) δ 0.80–1.52 (m, 11, aliphatic chain), 1.21 (s, 9, *tert*-butyl), 2.10–2.36 (m, 2, allylic CH_2), 6.10 (d, 1, vinyl proton α to sulfoxide, $J_{H_\alpha-H_\beta}$ (trans) = 15.2 Hz), 6.44 (t of d, 1, vinyl proton α to sulfoxide, $J_{H_\alpha-H_\beta}$ (trans) = 15.2 Hz, $J_{H_\alpha-\text{allylic } CH_2}$ = 6.4 Hz); *m/e* 216 (M^+), 57 (*t*-Bu$^+$, base peak); $[\alpha]_D$ −35.3° (*c* 0.52, acetone).

Anal. Calcd for $C_{12}H_{24}OS$: C, 66.60; H, 11.18; S, 14.82. Found: C, 66.87; H, 10.92; S, 14.62.

General Procedure for Synthesis of Achiral Alkenyl Phenyl Sulfoxides. The alkenyl phenyl sulfoxides were prepared according to the Horner–Wittig method from the corresponding carbonyl compounds and lithium diethyl phenylsulfinomethylphosphonate in THF.[3] A representative example is given below.

Cholestane Sulfoxides (*Z*)-9 and (*E*)-9. 5α-Cholestan-3-one (1.933 g, 5 mmol) was added to a stirred solution of lithium diethyl phenylsulfinomethylphosphonate (5.5 mmol) in THF at −78 °C. The reaction was stirred for 4 h at −78 °C, and then at room temperature overnight. The crude product obtained after the usual workup contained two isomeric vinyl sulfoxides. The TLC analysis (hexane–ether, 1:1) showed two spots (R_f 0.333 and 0.174). By column chromatography on silica gel using hexane–ether (70:30), these two isomeric sulfoxides were separated: isomer (*E*)-**9** 1.285 g (50%, R_f 0.33, mp 164–165 °C) and isomer (*Z*)-**9** (geometry tentatively assigned) 0.810 g (32%, R_f 0.17, mp 147–148 °C); IR ($CHCl_3$) (*E*)-**9** 1618 ($\nu_{C=C}$), 1580, 1475, 1470, 1445 (aromatic), 1020 cm^{-1} ($\nu_{S=O}$); (*Z*)-**9** 1618 ($\nu_{C=C}$), 1580, 1472, 1465, 1445 (aromatic), 1020 cm^{-1} ($\nu_{S=O}$). The NMR spectra ($CDCl_3$) of these two isomers were identical: δ 0.68 (s, 3, CH_3 at C-18) 0.84 (s, 3, CH_3 at C-19), 5.98 (s, 1, vinyl proton), 7.40–7.74 (m, 5, aromatic protons).

Anal. Calcd for $C_{34}H_{52}OS$ [(*E*)-**9**]: C, 80.25; H, 10.30; S, 6.30. Found: C, 80.35; H, 10.33; S, 6.23.

Anal. Calcd for $C_{34}H_{52}OS$ [(*Z*)-**9**]: C, 80.25; H, 10.30; S, 6.30. Found: C, 80.10; H, 10.44; S, 6.28.

Reduction of Phenyl Vinyl Sulfoxides with Ethylmagnesium Bromide and 10% CuI. General Procedure. To a stirred suspension of 0.3 equiv of purified CuI in dry ether at 0 °C under argon, 3 equiv of ethylmagnesium bromide in ether solution was added via syringe. The resulting mixture was stirred for 15 min and 1 equiv of vinyl sulfoxide in ether solution was added. The reaction was stirred at 0 °C for 1 h, and then quenched by addition of 10 mL of saturated ammonium chlorine solution. The organic product was extracted into the ethereal layer, which was washed with brine, dried over potassium carbonate, filtered, and rotoevaporated to yield the sulfide. A representative example is given below. Authentic sulfides for comparison were prepared by the Corey–Shulman procedure.[16]

Reduction of Cholestane Sulfoxide (*E*)-9. The reaction was carried out according to the general method with 0.127 g (0.25 mmol) of the sulfoxide. The sulfoxide was dissolved in a minimum volume of THF and was added to the reaction mixture Grignard–CuI in ether. After chloroform extraction, TLC (using petroleum ether–ether, 8:2) analysis of the crude product indicated the presence of the vinyl sulfide (R_f 0.6) and the starting material (R_f 0). By preparative TLC (*n*-pentane) 86.2 mg of vinyl sulfide was isolated (70%) and 20 mg (16%) of the starting material was recovered: IR ($CHCl_3$) 1605 ($\nu_{C=C}$), 1582, 1475, 1465, 1445 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 0.68 (s, CH_3 of C-18), 0.84 (s, CH_3 of C-19), 5.88 (s, 1, vinyl proton), 7.24–7.42 (m, 5, aromatic protons). These spectral data were the same as those of an authentic sample of the sulfide.

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Registry No.—(*E,Z*)-8, 66967-56-4; (*E,E*)-8, 55816-11-0; (*E,Z*)-8 sulfide, 66967-57-5; (*E,E*)-8 sulfide, 66967-58-6; (*Z*)-**11**, 66967-46-2; (*E*)-**11**, 66967-54-2; (*Z*)-**11** sulfide, 66967-53-1; (*E*)-**11** sulfide, 66967-55-3; (*E*)-1-bromooctene, 51751-87-2; 1-octyne, 629-05-0; benzenesulfinyl chloride, 4972-29-6; sodium benzenesulfinate, 873-55-2; (−)-menthol, 2216-51-5; *tert*-butylsulfinic acid, 29099-08-9; *tert*-butyl mercaptan, 75-66-1; *tert*-butylsulfinyl chloride, 31562-43-3; 5α-cholestan-3-one, 566-88-1; diethyl phenylsulfinomethylphosphonate, 50746-65-1.

References and Notes

(1) (a) G. H. Posner and D. J. Brunelle, *J. Org. Chem.*, **38**, 2747 (1973); (b) *Chem. Commun.*, 903 (1973); (c) *J. Org. Chem.*, **37**, 3547 (1972).
(2) F. A. Carey and O. Hernandez, *J. Org. Chem.*, **38**, 2670 (1973).
(3) (a) M. Mikolajczyk, S. Grzejszczak, and A. Zatorski, *J. Org. Chem.*, **40**, 1979 (1975); (b) M. Mikolajczyk, W. Midura, S. Grzejszczak, A. Zatorski, and A. Chefrzynska, *ibid.*, **43**, 473 (1978).
(4) (a) H. Gilman, J. Robinson, and N. Beaber, *J. Am. Chem. Soc.*, **48**, 2715 (1926); (b) K. K. Anderson, *Tetrahedron Lett.*, 93 (1962); (c) K. K. Anderson, J. Foley, R. Perkins, W. Gaffield, and N. Papanikalaou, *J. Am. Chem. Soc.*, **86**, 5637 (1964); (d) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *ibid.*, **90**, 4835 (1968); (e) K. Mislow, M. M. Green, P. Laur, J. Melillo, T. Simmons, and A. L. Ternay, Jr., *ibid.*, **87**, 1958 (1965); (f) H. Hope U. de la Camp, G. D. Homer, A. W. Messing, and L. H. Sommer, *Angew. Chem., Int. Ed. Engl.*, **8**, 612 (1969); (g) C. J. H. Stirling, *J. Chem. Soc.*, 5741 (1963); (h) K. K. Anderson, *J. Org. Chem.*, **29**, 1953 (1964).
(5) D. N. Harpp, S. M. Vines, J. P. Montillier, and T. H. Chan, *J. Org. Chem.*, **41**, 3987 (1976).
(6) A similar assumption has been made by D. J. Abbott, S. Cologna, and C. J. M. Stirling, *Chem. Commun.*, 471 (1971).
(7) (a) G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.*, **89**, 2753 (1967); (b) H. C. Brown and G. Zweifel, *ibid.*, **83**, 3834 (1961).
(8) (a) L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978); (b) D. A. Evans, C. A. Bryan, and C. L. Sims, *ibid.*, **94**, 2891 (1972).
(9) S. Danishefsky and M. Hirama, *J. Am. Chem. Soc.*, **99**, 7740 (1977).
(10) (a) For a review, see S. Oae et al., *Org. Prep. Proced. Int.*, **9**, 63 (1977); (b) S. Oae and J. Drabowicz, *Synthesis*, 404 (1977); (c) J. Drabowicz and S. Oae, *Chem. Lett.*, 767 (1977); (d) D. J. Clive, W. A. Kiel, S. M. Menchen, and C. K. Wang, *J. Chem. Soc., Chem. Commun.*, 657 (1977); (e) R. Tanikaya et al., *Chem. Lett.*, 395 (1977); (f) T. L. Ho, *Synth. Commun.*, **7**, 321 (1977); (g) R. G. Nuzzo and J. San Filippo, Jr., *J. Org. Chem.*, **42**, 568 (1977). (h) Cf. K. C. Nicalaou, W. E. Barnette, and R. L. Magolda, *J. Am. Chem. Soc.*, **100**, 2567 (1978); K. C. Nicalaou, R. L. Magolda, and W. E. Barnette, *J. Chem. Soc., Chem. Commun.*, 375 (1978).
(11) G. H. Posner and G. M. Gurria, *J. Org. Chem.*, **38**, 2419 (1973).
(12) For a recent report on Grignard reduction and α-alkylation of sulfoxides, see M. Hojo, R. Masuda, T. Salki, K. Fujimori, and S. Tsutsumi, *Tetrahedron Lett.*, 3883 (1977).
(13) (a) G. H. Posner, *Org. React.*, **19**, 1 (1972); **22**, 253 (1975); (b) J. F. Normant, *J. Organomet. Chem. Libr.*, **1**, 219 (1976); (c) H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976); (d) H. O. House, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **17**, 101 (1973).
(14) Cf. G. M. Whitesides, E. R. Stedronsky, C. P. Casey, and J. San Filippo, Jr., *J. Am. Chem. Soc.*, **92**, 1426 (1970).
(15) (a) K. Oshima, K. Shimoji, H. Takahashi, H. Yamomoto, and H. Zonaki, *J. Am. Chem. Soc.*, **95**, 2694 (1973); (b) R. H. Everhardus, H. G. Euwhorst, and L. Brandsma, *J. Chem. Soc., Chem. Commun.*, 801 (1977).
(16) E. J. Corey and J. I. Shulman, *J. Org. Chem.*, **35**, 777 (1970).
(17) Terminal acetylenes can be converted into aldehydes by treatment with diisobutylaluminum hydride and then oxygen and water: G. Wilke and H. Mueller, *Justus Liebigs Ann. Chem.*, **618**, 267 (1958).
(18) For use of epoxysilanes as intermediates in reductive nucleophilic acylation, see F. Cooke and P. D. Magnus, *J. Chem. Soc., Chem. Commun.*, 513 (1977).
(19) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(20) (a) H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925); (b) R. E. Estep and D. F. Tavares, *Int. J. Sulfur Chem.*, **8**, 279 (1973).
(21) (a) H. Normant, *Bull. Soc. Chim. Fr.*, 728 (1957); (b) H. Normant, *Adv. Org. Chem.*, **2**, 1 (1960).
(22) H. F. Herbrandson and R. T. Dickerson, Jr., *J. Am. Chem. Soc.*, **81**, 4102 (1959).
(23) The reaction was carried out under an efficient hood due to the particular unpleasant odor of this thiol and due to its causing stomach cramps in one of us (cf. G. Cahiez, D. Bernard, J. F. Normant, and J. Villieras, *J. Organomet. Chem.*, **121**, 123 (1976)).
(24) D. H. Harpp and T. G. Back, *Phosphorus Sulfur Chem.*, **1**, 59 (1976).

Preparation of α-Halo Sulfoximines

Carl R. Johnson* and H. Glenn Corkins

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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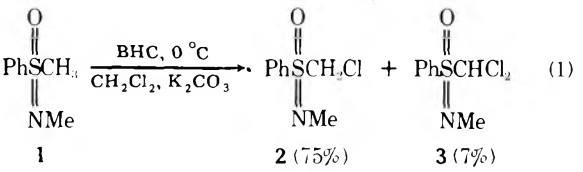
α-Halo sulfoximines have been prepared by the chlorination of *N*-methyl- and *N*-chlorosulfoximines with *tert*-butyl hypochlorite (BHC) and by amination of α-halo sulfoxides with mesitylsulfonyloxyamine. α-Chlorination of *S*-butyl-*N*,*S*-dimethylsulfoximine with BHC occurred only at the *S*-methyl. Reaction of *S*-butyl- or *S*-ethyl-*N*-methyl-*S*-phenylsulfoximine with BHC gave a single diastereomer.

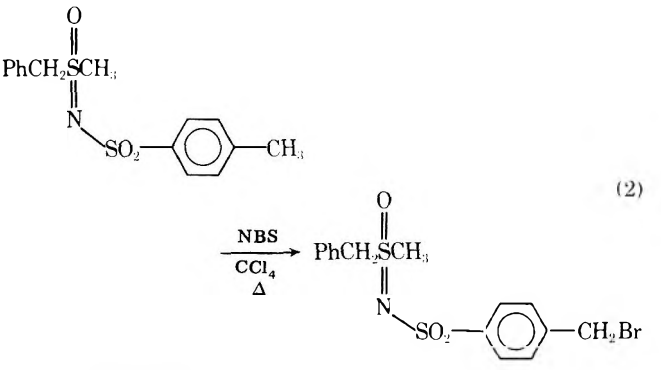
This paper describes the preparation of a new class of compounds, α-halo sulfoximines.

Chlorination of Sulfoximines. We have found that *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine (**2**) is produced by reaction of **1** with *tert*-butyl hypochlorite (BHC) in dichloromethane with potassium carbonate present (eq 1).



(1)

The base suppresses the formation of the hydrochloride of **1** (isolated in about 10% yield in the absence of base), which results from HCl production in a side reaction. Production of the hydrochloride increases to about 50% when the reaction is conducted at ambient temperature in *tert*-butyl alcohol. The presence of added hydroquinone has little effect on the product distribution, suggesting that a radical process is not operating. The ability of the sulfonimidoyl group to deactivate the α position in radical reactions is revealed by the lack of production of a bromomethylsulfoximine when **1** is treated with *N*-bromosuccinimide in the presence of light and peroxide and by the result shown in eq 2. We suggest the mechanism shown in Scheme I (X = O-*t*-Bu) for the BHC reaction. Support for the ylide mechanism comes from an independent generation of **5**. When *N*-chloro-*S*-methyl-*S*-phenylsulfoximine is treated with trimethyloxonium fluoroborate and the



(2)

Scheme I

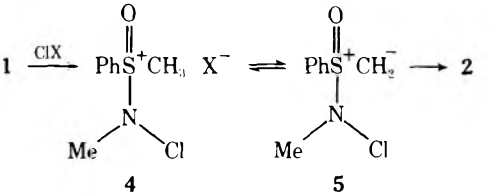


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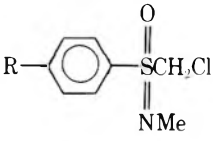
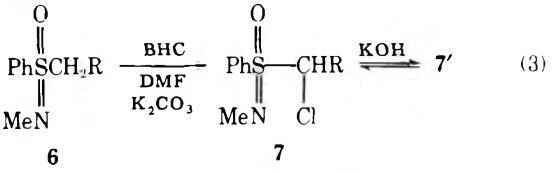
Table I. Products of Reaction of *tert*-Butyl Hypochlorite and *S*-Aryl-*N,S*-dimethylsulfoximes in Dichloromethane/K_2CO_3 at 0 °C



R	registry no.	isolated yield, %	mp [bp], °C
H	67069-79-8	75	[122–125 (0.2 mm)]
CH_3	67087-28-9	61	99.5–100
OCH_3	67087-58-5	56	75.5–76.5
Cl	67087-56-3	58	[95–98 (0.1 mm)]
NO_2	67087-55-2	60	136.5–138

resulting salt (**4**, X = BF_4) is subjected to base, **2** is produced. Various *S*-aryl-*N,S*-dimethylsulfoximines were halogenated with BHC. The summary in Table I shows that chlorination occurs in good yield with either electron-donating or -withdrawing substituents on the aryl group.

The reaction of BHC with the *S*-ethylsulfoximine **6a** in dichloromethane/K_2CO_3 was unsatisfactory; the major product was the hydrochloride of **6**. α-Chlorination was achieved in fair yield with BHC in dimethylformamide (DMF); interestingly, this chlorination resulted in the production of a single diastereomer, **7a** (eq 3). This diastereomer could be equilibrated with its epimer **7'a** in refluxing methanolic KOH. The well-separated *N*-methyl singlets in the NMR spectra of mixtures of **7a** and **7'a** provided a sensitive probe for analysis. Under the above conditions an equilibrium ratio of 56% **7a**/44% **7'a** was observed. The *S*-butylsulfoximine **6b** also gave rise to a single α-halo diastereomer **7b**, which could be equilibrated to a 58% **7b**/42% **7'b** mixture in refluxing methanolic KOH (eq 3). At this time we cannot provide in-



(3)

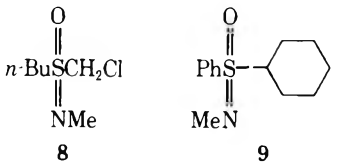
6 **7**

a, R = CH_3; b, R = $CH_2CH_2CH_3$

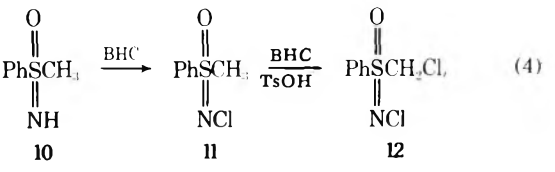
formation about the relative stereochemistries of the chiral sulfur and carbon centers in **7a** and **7b**. The remarkable stereoselectivity in these halogenations may stem from an intramolecular halogen transfer, e.g., from **5** to **2**, Scheme I.

Chlorination of *S*-butyl-*N,S*-dimethylsulfoximine with BHC resulted only in substitution at the *S*-methyl to yield **8**. We were unable to achieve chlorination with BHC at the methine of **9**. The reactivity and regiochemistry appear to be controlled by α-CH acidity.[1]

The reaction of BHC with *S*-methyl-*S*-phenylsulfoximine (**10**) yields the *N*-chloro derivative **11**, as expected (eq 4).[2]



8 **9**



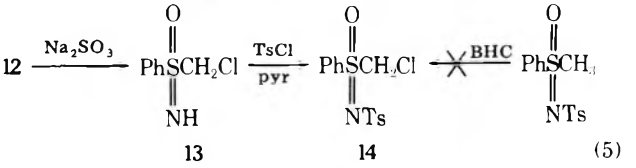
(4)

10 **11** **12**

Compound **11** is recovered after being subjected to a refluxing solution of excess BHC in dichloromethane for 3 days. No reaction had occurred after **11** had stood for 18 h at room temperature in the dark in neat BHC. If, however, a crystal of *p*-toluenesulfonic acid (TsOH) is added to either a neat or dichloromethane solution of the reactants at room temperature, a rapid reaction ensues resulting in a 90% yield of *N*-chloro-*S*-(chloromethyl)-*S*-phenylsulfoximine (**12**) (eq 4). The two most obvious possibilities for the role of the acid are: (1) protonation of BHC at oxygen to generate a more powerful electrophilic reagent; and/or (2) protonation of the sulfoximine at nitrogen to give a salt, the precursor of an ylide which accepts a positive halogen in an intra- or intermolecular reaction.

N-Tosyl- and *N*-benzoylsulfoximines failed to yield α-chloro derivatives when exposed to BHC at room temperature or above. Addition of acid had no effect.

α-Chloro derivatives of "free" sulfoximines were prepared by reduction of the above mentioned *N*,α-dichloro compounds with sodium sulfite. Such "free" sulfoximines can be transformed to *N*-tosyl derivatives by reaction with *p*-toluenesulfonyl chloride in pyridine (e.g., eq 5).



(5)

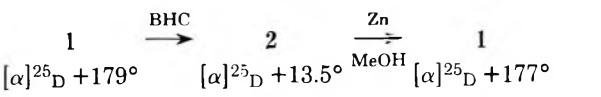
13 **14**

Although it was anticipated that all of the reactions described above occur without perturbation of the configuration of the sulfonimidoyl sulfur, several stereochemical reaction cycles were completed to verify this expectation (Schemes II and III).

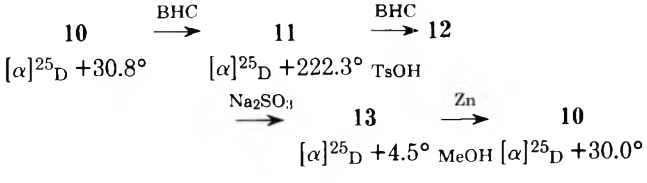
Amination of α-Halo Sulfoxides. An alternative approach to the synthesis of the unsubstituted α-halo sulfoximines was developed which differs from those descirbed above in that the halogen is added at the sulfoxide stage. Recent reports in the literature indicate several good methods are available for preparing the acid-sensitive halo sulfoxide.[3] For example, chloromethyl phenyl sulfoxide can be obtained in 55% yield by treating methyl phenyl sulfoxide with *N*-chlorosuccinimide in the presence of a catalytic amount of *p*-toluenesulfonic acid. α-Halo sulfoxides can be converted to sulfoximines by successive treatment with mesitylsulfonyloxyamine (MSA) and base, usually sodium hydroxide.[4]

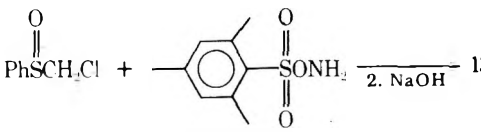
Although high yields of sulfoximines are generally obtained by the "MSA method",[4] the introduction of an α-halo substituent was found to reduce the yield substantially. For example, treatment of the chloromethyl phenyl sulfoxide with excess MSA in dichloromethane followed by basic workup resulted in only 30% of α-halo sulfoximine **13** with a considerable recovery of starting halo sulfoxide (eq 6). By comparison, methyl phenyl sulfoxide is converted to the *S*-methyl-*S*-phenylsulfoximine under these conditions in 95% yield. The

Scheme II



Scheme III





(6)

addition of more MSA (2–3 equiv) over a period of 18 h did not increase the yield of chloro sulfoximine. Presumably the lower yield of halo sulfoximines results from a decrease in reactivity of the halo sulfoxide toward MSA due to the inductive effect of the halide. The slower reaction between these reagents allows decomposition of the oxidizing agent, MSA, to compete with amination.

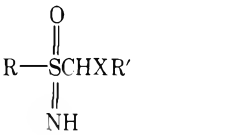
The nature of the MSA decomposition is thought to proceed according to Scheme IV. The stoichiometric ratio of MSA to nitrogen determined experimentally (4:1, respectively) is consistent with that indicated. A benzene solution of MSA at room temperature gives off nitrogen slowly. A white precipitate is formed in the reaction, presumably the salt of mesitylenesulfonic acid and hydrazine. The presence of diimide was inferred by carrying out the decomposition in the presence of cyclohexene. Cyclohexane was identified by VPC. A similar decomposition of hydroxylamine-*O*-sulfonic acid has been observed.[5]

It was found that yields up to ~60% of halo sulfoximines can be obtained if the amination is carried out in acetonitrile or nitromethane. These results are summarized in Table II.

Experimental Section

The following *N*-methylsulfoximines were prepared by the Eschweiler–Clarke methylation of the corresponding N-unsubstituted sulfoximines:[6] *N,S*-dimethyl-*S*-phenylsulfoximine, 77.5% yield, colorless oil, bp 110 °C (0.4 mm) (Kugelrohr distillation); (+)-(*S*)-*N,S*-dimethyl-*S*-phenylsulfoximine, $[\alpha]_D$ +179° (*c* 1.02, acetone);[6] *N,S*-dimethyl-*S*-*p*-tolylsulfoximine, 80.3% yield, colorless oil, bp 108–110 °C (0.5 mm) (Kugelrohr distillation); *S*-(*p*-methoxyphenyl)-*N,S*-dimethylsulfoximine, 75% yield, colorless oil, bp 123–126 °C (0.5 mm) (Kugelrohr distillation); *S*-(*p*-chlorophenyl)-*N,S*-dimethylsulfoximine, 68% yield, colorless oil; *N,S*-dimethyl-*S*-(*p*-nitrophenyl)sulfoximine, 48.8% yield, pale yellow needles, mp 128–129 °C; *S*-butyl-*N,S*-dimethylsulfoximine, 64.5% yield, colorless oil, bp 89–92 °C (0.1 mm) (Kugelrohr distillation); *S,S*-dibutyl-*N*-methylsulfoximine, isolated by column chromatography ($Al_2O_3/CHCl_3$) in 20.5% yield, colorless oil, bp 98–101 °C (0.1 mm) (Kugelrohr distillation); *S*-ethyl-*N*-methyl-*S*-phenylsulfoximine, 77% yield, colorless oil, bp 97–100 °C (0.1 mm) (Kugelrohr distillation); *S*-butyl-*N*-methyl-*S*-phenylsulfoximine, 75% yield, colorless oil, bp 100–110 °C (0.2 mm) (Kugelrohr distillation). *S*-Cyclohexyl-*N*-methyl-*S*-phenylsulfoximine, bp 108–110 °C (0.1 mm), was prepared by methylating *S*-cyclohexyl-*S*-phenylsulfoximine with trimethyloxonium fluoroborate.

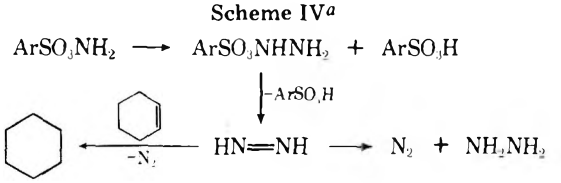
Table II. α-Halosulfoximines from the Reaction of MSA and α-Halo Sulfoxides in Acetonitrile



R	R′	X	registry no.	isolated yield, %	mp, °C
n-Pr	Et	Cl	67087-46-1	45	50–53[a]
n-Bu	*n*-Pr	Cl	67069-95-8	60	42–43[a]
Ph	H	Cl	67087-40-5	63	47.5–48.5
Ph	H	Br	67087-42-7	20[b]	63–64

[a] Single diastereomer. [b] Reaction in dichloromethane.

Scheme IV[a]



[a] Ar = mesityl.

***S*-Benzyl-*S*-methyl-*N*-tosylsulfoximine.** This material was isolated in 36.9% yield as a white solid, mp 128–129 °C, by reacting benzyl methyl sulfoxide with *p*-toluenesulfonyl azide in the presence of Raney–copper catalyst.[7]

Chlorination of *N*-Methylsulfoximines with *tert*-Butyl Hypochlorite[8] (BHC). The apparatus used in this experiment was protected from light by wrapping in aluminum foil. The addition of BHC was made in subdued light. To a solution of the sulfoximine (2.43 mmol) in dichloromethane (10 mL) was added 1.5 equiv of anhydrous potassium carbonate. The stirring mixture was cooled in an ice bath and BHC (5% excess) added slowly via syringe. The ice bath was removed and the mixture was stirred for 15–20 min. After filtration the solution was concentrated by rotary evaporation to give a crude product. The chloro sulfoximines were isolated by either column or thick-layer chromatography (silica gel/ether). If desired small amounts of dichloro sulfoximines and unreacted starting materials could be isolated from the chromatography. The compounds listed in Table I and *S*-butyl-*S*-(chloromethyl)-*N*-methylsulfoximine, bp 93–95 °C, (0.1 mm) were prepared by this method.

***S*-(1-Chloroethyl)-*N*-methyl-*S*-phenylsulfoximine (7a)** was prepared according to the above procedure using DMF as the solvent (4.0 mL/0.2 mmol of sulfoximine) and leaving out the carbonate. After the slow addition of BHC to a cold solution of the sulfoximine, the ice bath was removed and the solution was stirred for 5 h. The colorless solution was poured into an equal volume of saturated sodium chloride solution and extracted with three volumes of diethyl ether. Washing the combined ether extracts with water, drying ($MgSO_4$), and concentrating by rotary evaporation gave a crude oil. The chloro sulfoximine was isolated by thick-layer chromatography (silica gel/diethyl ether) in 44.5% yield as a colorless oil, bp 95–96 °C (0.1 mm) (Kugelrohr distillation). NMR showed this material to be only one diastereomer.

***S*-(1-Chlorobutyl)-*N*-methyl-*S*-phenylsulfoximine (7b).** Using the procedure described for **7a**, **7b** was isolated by thick-layer chromatography (silica gel/diethyl ether) in 43.5% yield as a colorless oil, bp 86–87 °C (0.1 mm) (Kugelrohr distillation). NMR showed this material to be one diastereomer.

Epimerization of *S*-(1-Chloroethyl)-*N*-methyl-*S*-phenylsulfoximine (7a). To 0.138 g (0.689 mmol) of diastereomerically pure **7a** in 6.6 mL of methanol was added 4.2 mL of 1 M KOH. The solution was refluxed for 8.5 h. After cooling, the reaction mixture was concentrated to half its volume by rotary evaporation, saturated with sodium chloride, and extracted with three equal volumes of diethyl ether. The combined ether extracts were washed with 5 mL of water, dried ($MgSO_4$), and concentrated to give 0.125 g (90.6%) of crude oil, bp 96–98 °C (0.1 mm) (Kugelrohr distillation). NMR data revealed a 44:56 mixture of chloro sulfoximines **7a/7′a.**

Epimerization of *S*-(1-Chlorobutyl)-*N*-methyl-*S*-phenylsulfoximine (7b) under reflux for 27 h in methanolic KOH resulted in a 43:57 mixture of chloro sulfoximines **7b/7′b** as ascertained by integration of the *N*-methyl singlets after the addition of europium shift reagent [Eu(fod)$_3$].

Methylation of *N*-Chloro-*S*-methyl-*S*-phenylsulfoximine. To 0.621 g (4.0 mmol) of trimethyloxonium fluoroborate slurried in 25 mL of dichloromethane was added 0.753 g (4.0 mmol) of **11**. The mixture was warmed in hot water for 5 min and then allowed to stir at room temperature for 2 h. A small amount of a white precipitate was removed by filtration. Addition of anhydrous ether to the filtrate caused precipitation of the fluoroborate salts, mp 76–81 °C. After collecting by filtration, the salts were washed with a copious amount of anhydrous ether to remove any unreacted starting sulfoximine. Attempts at recrystallization of the white solid were unsuccessful. The NMR spectrum of this white solid as well as its chemistry was consistent with a mixture of (*N*-chloro-*N*-methylamino)methylphenyloxosulfonium fluoroborate (**4**, X = BF_4) and *N,S*-dimethyl-*S*-phenylsulfoximine hydrofluoroborate.

Reaction of Fluoroborate 4 with Base. A. To 0.254 g of the above mixture of fluoroborate salts dissolved in 20 mL of dichloromethane and cooled to 0 °C with added 0.120 g (0.87 mmol) of anhydrous potassium carbonate and 0.097 g (0.87 mmol) of potassium *tert*-butoxide. After stirring 1 h at 0 °C and 11 h at room temperature, the mixture was filtrated and concentrated to give 0.154 g of crude oil. The *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine and *N,S*-dimethyl-*S*-phenylsulfoximine were found to be components of the oil by TLC and NMR by comparison to that of authentic materials.

B. To 0.202 g of sodium hydride slurried in 10 mL of dry THF was added 0.296 g of the above mixture of fluoroborate salts. A smooth evolution of hydrogen was observed. After stirring at room temperature 30 min the excess hydride was destroyed by the addition of 10 mL of saturated aqueous sodium chloride. Extraction with diethyl ether, drying ($MgSO_4$), and concentrating by rotary evaporation resulted in 0.208 g of oil. The NMR spectrum and TLC of this oil showed the presence of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine along with *N,S*-dimethyl-*S*-phenylsulfoximine by comparison to that of authentic materials. The relative percentages of the sulfoximines were 42.3 and 57.7%, respectively.

Radical Bromination. To 0.3254 g (1.00 mmol) of *S*-benzyl-*S*-methyl-*N*-(*p*-tolylsulfonyl)sulfoximine in 10 mL of benzene was added 0.1869 g (5% excess) of *N*-bromosuccinimide and a few milligrams of benzoyl peroxide. After refluxing 35 min and cooling, the reaction mixture was washed with 5 mL of 5% NaOH and water and dried ($MgSO_4$). Concentration by rotary evaporation gave 0.450 g of crude oil which showed two components by TLC. Thick-layer chromatography of 0.300 g of this oil gave 0.246 g of a mixture of *S*-benzyl-*N*-[(*p*-bromomethyl)phenylsulfonyl]-*S*-methylsulfoximine (63%) and starting sulfoximine (37%). The brominated and unbrominated sulfoximines were not separable to TLC.

***N*-Chloro-*S*-(chloromethyl)-*S*-phenylsulfoximine (12).** To 0.262 g (1.38 mmol) of *N*-chloro-*S*-methyl-*S*-phenylsulfoximine in 2 mL of *tert*-butyl hypochlorite was added a small crystal of *p*-toluenesulfonic acid. After 5 min the solution was concentrated by rotary evaporation. The resulting oils were dissolved in chloroform (10 mL) and washed with 10 mL of 0.5% NaOH and 5 mL of water. Drying ($MgSO_4$) and concentrating gave 0.307 g of crude oil. Spectral data (NMR) showed this oil to be a mixture of 88.7% *N*-chloro-*S*-(chloromethyl)-*S*-phenylsulfoximine, 10.5% *N*-chloro-*S*-(dichloromethyl)-*S*-phenylsulfoximine, and 0.7% starting material. Longer reaction time, e.g., 15 min, results in an increased yield of the dichloromethylsulfoximine (26.1%) at the expense of the chloromethyl derivative (61.2%).

Reduction of *N*-Chloro-*S*-(chloromethyl)-*S*-phenylsulfoximine. A solution of the sulfoximine (1.38 mmol) in diethyl ether (6 mL) was shaken with 3.0 mL of 1 M Na_2SO_3 for 2 min. The progress of the reduction was monitored by TLC (silica gel/ether) of the ether layer. The aqueous phase was removed and extracted with 6 mL of ether. The combined ether layers were washed with water, dried ($MgSO_4$), and concentrated via rotary evaporation to give 0.219 g (86.6%) of an oil. Spectral data (IR and NMR) of this oil were identical with that of an authentic sample of *S*-(chloromethyl)-*S*-phenylsulfoximine prepared by another method.

(+)-(*S*)-*S*-(Chloromethyl)-*N*-methyl-*S*-phenylsulfoximine. Reaction of (*S*)-*N,S*-dimethyl-*S*-phenylsulfoximine, $[\alpha]^{25}_D$ +179° (*c* 1.02, acetone) (98% optically pure),[6] with BHC by the general procedure gave the product as a colorless oil: 69%; bp 110–115 °C (0.1 mm); $[\alpha]^{25}_D$ +13.5° (*c* 1.26, acetone). In addition (−)-(*S*)-*S*-(dichloromethyl)-*N*-methyl-*S*-phenylsulfoximine (3) was isolated by chromatography in 7% yield as a colorless oil: bp 125–130 °C (0.1 mm); $[\alpha]^{25}_D$ − 32.6° (*c* 1.55, acetone).

Reduction of (+)-(*S*)-*S*-(Chloromethyl)-*N*-methyl-*S*-phenylsulfoximine. The chlorosulfoximine (0.357 g, 1.75 mmol), $[\alpha]^{25}_D$ +13.5° (*c* 1.26, acetone), in 10 mL of methanol was treated with 0.660 g (0.01 g-atom) of powdered zinc under reflux for 5 h. The progress of the reaction was monitored by thin-layer chromatography (silica gel/diethyl ether). After cooling, the mixture was filtered. The filtrate was made acidic by the addition of 10 mL of 10% HCl and washed with two portions (10 mL) of chloroform. The aqueous phase was then made basic with 10% NaOH and extracted with three equal volumes of chloroform, dried ($MgSO_4$), and concentrated by rotary evaporation. The resulting crude oil was subjected to preparative TLC to give 0.200 g (67.8%) of (+)-(*S*)-*N,S*-dimethyl-*S*-phenylsulfoximine, $[\alpha]^{25}_D$ +176.7° (*c* 1.695, acetone).

(+)-(*S*)-*N*-chloro-*S*-methyl-*S*-phenylsulfoximine (11). To 0.712 g (4.6 mmol) of (+)-(*S*)-*S*-methyl-*S*-phenylsulfoximine, $[\alpha]^{25}_D$ 30.8° (*c* 1.060, acetone), in dichloromethane (15 mL) was added 1 equiv (0.635 g) of anhydrous potassium carbonate. The mixture was cooled in an ice bath while 0.55 mL (0.497 g, 4.6 mmol) of BHC was added dropwise. After stirring for 30 min the mixture was filtered and concentrated by rotary evaporation. The resulting oil was chromatographed (column, silica gel/ether) to give 0.667 g (76.0%) of **11** as yellow needles: mp 50.5–51 °C; $[\alpha]^{25}_D$ +222.3° (*c* 1.64, acetone).

(+)-(*S*)-*S*-(Chloromethyl)-*S*-phenylsulfoximine (13). To 0.286 g (22.7 mmol) of (+)-(*S*)-*N*-chlorosulfoximine **11** in dichloromethane (1 mL) was added a crystal of *p*-toluenesulfonic acid; 9 equiv of BHC was added in three portions while the progress of the reaction was monitored by TLC (silica gel/ether). The solution was then concentrated by rotary evaporation. The residual oil was dissolved in diethyl ether (5 mL) and shaken for 2 min with 4 mL of 1 M Na_2SO_3 solution. Washing with 3 mL of 0.5% NaOH and 3 mL of water followed by drying ($MgSO_4$) and concentration gave 0.202 g (70.6%) of **13** as a white solid. Recrystallization from diethyl ether gave white needles: mp 76–77 °C; $[\alpha]^{25}_D$ +4.5 ° (*c* 0.95, acetone).

Reduction of (+)-(*S*)-*S*-(Chloromethyl)-*S*-phenylsulfoximine (13). To a solution of **13** (0.155 g, 0.81 mmol) in methanol (10 mL) was added 0.582 g (8.63 mmol) of powdered zinc. The mixture was refluxed for 18 h. After cooling, the mixture was filtered and the filtrate was concentrated by rotary evaporation. The residual oil was dissolved in chloroform and washed with two 10-mL portions of 10% HCl. The acidic aqueous phase was then made basic by the addition of solid Na_2CO_3 (caution: foaming) and 1 mL of 10% NaOH. Extraction with three equal volumes of chloroform was followed by washing the combined extracts with saturated sodium chloride solution (5 mL). Drying ($MgSO_4$) and concentrating gave 0.041 g of *S*-methyl-*S*-phenylsulfoximine, $[\alpha]^{25}_D$ +29.9° (*c* 0.74, acetone). The product was identified by comparison with spectral data (IR and NMR) of authentic material.

Amination of Halo Sulfoxides with Mesitylsulfonyloxyamine (MSA). To a cooled (0 °C) solution of the halo sulfoxide (0.02 mol) in acetonitrile (120 mL) was added 1.4 quiv of MSA. The solution was stirred at 0 °C for 4 h and at room temperature for 48 h. A white precipitate was observed after 30 min. Concentration by rotary evaporation gave a semisolid which was slurried in dichloromethane (40 mL). While cooling in an ice bath, 11.2 mL of 10% NaOH solution was added and the two-phased system was stirred vigorously for 15 min. After removal of the organic layer, the aqueous phase was extracted with an equal volume of dichloromethene. The combined extracts were washed with two 5-mL portions of saturated sodium chloride, dried ($MgSO_4$), and concentrated to give crude product. The halo sulfoximines were then purified by column chromatography (silica gel/30% ether–cyclohexane) and/or recrystallization. The following halo sulfoximines were prepared by this method: *S*-(1-chlorobutyl)-*S*-butylsulfoximine, 59.9% yield (isolated), white crystals, mp 42–43 °C (ether–pentane) (addition of europium shift reagent in progressively increasing amounts showed the presence of one diastereomer); *S*-(1-chloropropyl)-*S*-propylsulfoximine, 45% yield (isolated), white crystals, mp 50–53 °C (ether–cyclohexane) (one diastereomer); *S*-(chloromethyl)-*S*-phenylsulfoximine, 63% yield, as white needles, mp 47.5–48.5 °C (ether–pentane); *S*-(bromomethyl)-*S*-phenylsulfoximine, use of dichloromethane as the solvent gave 22.3% yield of the bromo sulfoximine as a white solid, mp 63–64 °C (ether–pentane).

Preparation of *N*-(*p*-Tolylsulfonyl)-α-chlorosulfoximines from Free α-Chloro Sulfoximines. To a stirring solution of the chloro sulfoximine (1.0 mmol) in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (1.0 mmol). A bright yellow solution was obtained which turned pale yellow after 15 h. The solution was concentrated by rotary evaporation to a semisolid. Addition of 10 mL of chloroform and 10 mL of water resulted in a two-phase system. After removal of the aqueous phase the chloroform layer was washed with 2 mL of 5% HCl, 2 mL of 5% NaOH, and 2 mL of saturated sodium chloride. Drying ($MgSO_4$) and concentrating by rotary evaporation gave pale yellow crystals which were recrystallized from methanol. The following *N*-tosylsulfoximines were prepared by this procedure: *S*-(chloromethyl)-*S*-phenyl-*N*-(*p*-tolylsulfonyl)sulfoximine, 85.4% yield (white needles, mp 155–156 °C); *S*-butyl-*S*-(1-chlorobutyl)-*N*-(*p*-tolylsulfonyl)sulfoximine, 90% yield, white crystals, mp 102–105 °C (one diastereomer); *S*-(1-chloropropyl)-*S*-propyl-*N*-(*p*-tolylsulfonyl)sulfoximine, 90.2% yield, as white crystals, mp 116–118 °C (one diastereomer).

***N*-Chloro-*S*-methyl-*S*-phenylsulfoximine (11).** Treatment of S-methyl-*S*-phenylsulfoximine as described in the procedure for chlorinating *N*-methylsulfoximine derivatives with BHC gave **11**, white needles from methanol, mp 84–84.5 °C (70% yield).

Acknowledgment. This research was supported by a grant from the National Science Foundation.

Registry No.—**1**, 30004-67-2; (*S*)-(+)-**1**, 33993-53-2; **1** HBF_4, 67087-54-1; (*S*)-(+)-**2**, 67087-45-0; **3**, 67087-44-9; **4** (X = BF_4^-), 67124-64-5; **6a**, 67087-37-0; **6b**, 67087-36-9; **7a** isomer 1, 67087-33-6; **7a** isomer 2, 67087-32-5; **7b** isomer 1, 67087-31-4; **7b** isomer 2, 67087-57-4; **8**, 67087-34-7; **9**, 67124-65-6; **10**, 4381-25-3; (*S*)-(+)-**10**, 33903-50-3; **11**, 67087-35-8; (*S*)-(+)-**11**, 39830-45-0; **12**, 67087-49-4; (*S*)-(+)-**13**, 67087-43-8; **14**, 67087-38-1; *N,S*-dimethyl-*S*-*p*-tolylsulfoximine, 67087-52-9; *S*-(*p*-methoxyphenyl)-*N,S*-dimethylsulfoximine, 67087-51-8; *S*-(*p*-chlorophenyl)-*N,S*-dimethylsulfoximine, 67087-50-7; *N,S*-dimethyl-*S*-(*p*-nitrophenyl)sulfoximine, 67087-48-3;

S-butyl-*N*,*S*-dimethylsulfoximine, 67087-39-2; *S*,*S*-dibutyl-*N*-methylsulfoximine, 35362-76-6; *S*-benzyl-*S*-methyl-*N*-tosylsulfoximine, 38401-39-7; benzyl methyl sulfoxide, 824-86-2; *p*-toluenesulfonyl azide, 941-55-9; *S*-benzyl-*N*-[(*p*-bromomethyl)phenylsulfonyl]-*S*-methylsulfoximine, 67087-53-0; *N*-chloro-*S*-dichloromethyl-*S*-phenylsulfoximine, 67087-47-2; *S*-butyl-*S*-(1-chlorobutyl)-*N*-(*p*-tolysulfonyl)sulfoximine, 67070-02-4; S-(1-chloropropyl)-*S*-propyl-*N*-(*p*-tolylsulfonyl)sulfoximine, 67070-01-3; propyl 1-chloropropyl sulfoxide, 67087-41-6; butyl 1-chlorobutyl sulfoximine, 21128-90-5; phenyl chloromethyl sulfoxide, 7205-94-9; phenyl bromomethyl sulfoxide, 31268-20-9.

Supplementary Material Available: Analytical and spectral data of the compounds discussed in this paper (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For a discussion of the acidity of related sulfones, see F. G. Bordwell and J. B. O'Dwyer, *J. Org. Chem.*, **39**, 2519 (1974).

(2) R. Annunziata, R. Fornasier, and F. Montanari, *J. Chem. Soc., Chem. Commun.*, 1133 (1972).

(3) S. Iriuchijima and G. Tsuchihaski, *Synthesis*, 588 (1970); S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **46**, 921 (1973); F. Jung, K. C. Tin, and T. Durst, *Int. J. Sulfur Chem.*, **8**, 1 (1973); T. Durst, *Tetrahedron Lett.*, 4643 (1970); M. Cinquini, S. Colonna, and F. Montanari *Chem. Commun.*, 607 (1969); M. Cinquini, S. Colonna, and D. Landini, *J. Chem. Soc., Perkin Trans. 2*, 296 (1971); M. Cinquini and S. Colonna, *ibid.*, 1883 (1972); M. Cinquini, S. Colonna, R. Fornasier, and F. Montanarei, *J. Chem. Soc., Perkin Trans. 1*, 1886 (1972); C. Venier and J. Barager, *J. Org. Chem.*, **38**, 17 (1973); R. N. Loeppky and D. C. K. Chang, *Tetrahedrom Lett.*, 5415 (1968); C. Y. Meyers and G. J. McCollum, *ibid.*, 289 (1973); P. Calzavara, M. Cinquini, S. Colonna, R. Fornaster, and F. Montanari, *J. Am. Chem. Soc.*, **95**, 7431 (1973).

(4) Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikedo, *Tetrahedron Lett.*, 4137 (1972); C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, *J. Org. Chem.*, **39**, 2458 (1974).

(5) E. Schmitz, R. Ohme, and S. Schramm, *Angew. Chem.*, **73**, 807 (1961).

(6) C. R. Johnson, C. W. Schreck, and J. R. Shanklin, *J. Am. Chem. Soc.*, **95**, 7424 (1973).

(7) C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, **95**, 4287 (1973).

(8) M. J. Minz and C. Walling, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N. Y., 1973, p 184.

Alkenes from Base-Promoted Eliminations of α-Halo Sulfoximines

Carl R. Johnson* and H. Glenn Corkins

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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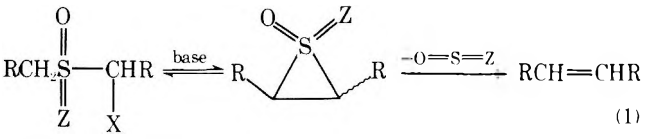
Upon treatment with base α-halc *N*-(*p*-tolylsulfonyl)sulfoximines bearing α hydrogens undergo 1,3 eliminations to yield alkenes in analogy to the Ramberg–Bäcklund reaction of α-halo sulfones. Treatment of benzylic α-bromo *N*-(*p*-tolylsulfonyl)sulfoximines with refluxing methanolic potassium hydroxide gave *cis*-alkenes as the major product, whereas under the same conditions α-chloro dialkylsulfoximines gave largely *trans*-alkenes. Neither NH nor *N*-methyl sulfoximines gave alkenes under the above conditions.

α-Halo sulfones undergo an interesting and facile 1,3 elimination which has occupied the attention of chemical laboratories since its discovery by Ramberg and Bäcklund in 1940.[1] (eq 1, Z = O). The question may then be asked as to



(1)

whether halo sulfoximines undergo a similar transformation (eq 1, Z = NR'). If so, how do various nitrogen substituents effect the reaction?

The stereochemistry observed in the alkene produced upon 1,3 elimination of α-halo dialkyl sulfones may vary from predominantly cis to equal amounts of isomeric alkenes.[2] If indeed, a similar 1,3 elimination may be made to occur with α-halo sulfoximines, bulky nitrogen substituents may promote the formation of *cis*-alkenes.

A series of N-substituted α-halo sulfoximines were prepared[3] and treated with base in order to determine to what extent the reaction occurs. Refluxing diastereomerically pure α-chloro sulfoximines in methanolic potassium hydroxide (6 equiv) gave the results shown in Scheme I.

The differences in the reactions of the various N-substituted sulfoximines in Scheme I with methanolic potassium hydroxide is curious. The production of 1-butanesulfinamide in reaction a can be rationalized in a number of ways, including the transient production of a three-membered S–N heterocycle. At this time, we have insufficient data to justify further speculation. The failure of the *N*-methyl derivative to undergo 1,3 elimination under the conditions of methanolic potassium hydroxide is surprising, since the leaving group, *N*-sulfinylmethylamine, is a stable compound. When the reaction is carried out with potassium deuterioxide in methanol-*O*-*d*, recovered starting material shows complete exchange of the α and α' protons with deuterium. Thus, the anion is capable of being formed, but apparently the elimination is slow under these conditions. A similar situation has been noted in the literature. 2-Bromothiacyclohexane 1,1-dioxide was initially reported not to undergo elimination after prolonged heating in a sodium hydroxide–dioxane solution, but later was found to give cyclopentene in 82% yield when exposed to potassium *tert*-butoxide in THF at 0 °C (eq 18).[4] It may very well turn out that elimination in the present case will occur under other conditions.

The isolation of 4-octene when the *N*-tosyl derivative (Scheme I) was treated with potassium hydroxide suggests that a reaction analogous to the Ramberg–Bäcklund reaction is operative. Several α-halo *N*-tosylsulfoximines were prepared and treated with potassium hydroxide. The cis–trans ratios of the alkenes produced were determined by gas chromatography. The compounds studied can be separated into two structural groups, the benzylic α-bromo and the α-chloro dialkylsulfoximines. The results are summarized in Table I.

In the reactions of the α-bromo sulfoximines **1c–e** and potassium hydroxide approximately 80% of the starting sulfoximines can be accounted for by two reaction pathways. One involves the desired 1,3-dehydrobromination leading to alkene, sulfonamide, and potassium sulfite, while the other is a reduction of the bromo sulfoximines to **4c–e**. The stereochemistry of the alkene produced from **1d** and **1e** is found to be predominately cis. From the α-chloro dialkylsulfoximines **1a** and **1b** only elimination to the alkene was observed. The

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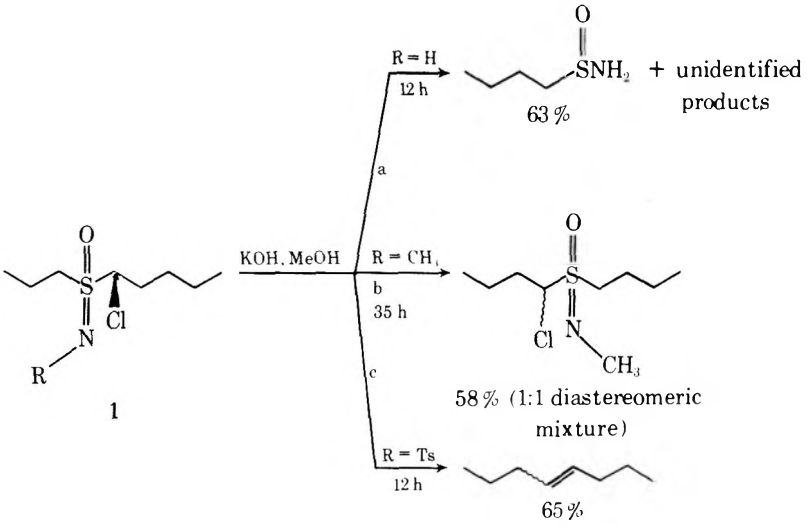
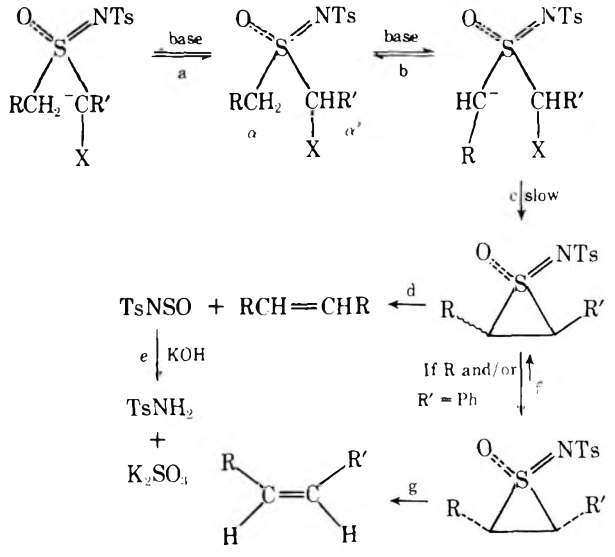
Scheme I



Scheme II

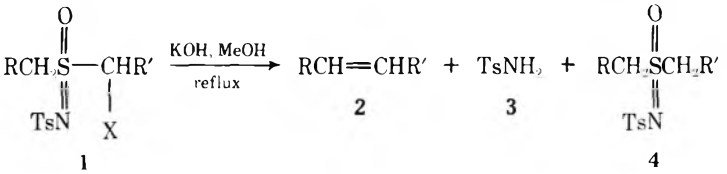


stereochemistry in these cases is found to be about a 1:1 mixture of *cis*- and *trans*-alkenes.

Scheme II rationalizes our results and is compatible with current thinking concerning the Ramberg–Bäcklund reaction. Perhaps the first step (a) is the reversible generation of the α′ anion resulting in epimerization at the α′ carbon. The α anion (formed in step b) can participate in a rate-determining internal nucleophilic displacement of the halide at the α′ position to give an "episulfoximine" intermediate (step c). A double inversion process analogous to that proposed in halo sulfone chemistry[5] is assumed. The stereochemical distribution of the episulfoximines will be controlled by an array of rate constants interlinking both the various configurational combinations at the α′-halo carbon and the α carbanion and the corresponding episulfoximines. Expulsion of the *N*-sulfinyl-*p*-toluenesulfonamide, assumed to occur stereospecifically, will result in alkene formation (step d). (The expulsion of SO_2 from episulfones is known to be stereospecific.) The distribution of diastereomeric alkenes is then determined by the distribution of the diastereomeric episulfoximines.

The benzylic systems, **1d** and **1e**, which yield predominantly *cis*-alkenes, may be special cases. Due to the enhanced acidity episulfoximines with benzylic protons may equilibrate (Scheme II, step f) in favor of an episulfoximine with R and R′ cis to one another and trans to the bulky *N*-Ts group prior to expulsion of TsNSO. Treatment of *cis*-2,3-diphenylthiirane 1,1-dioxide with base results in the exclusive production of *trans*-1,2-diphenylethene, indicating that epimerization (in

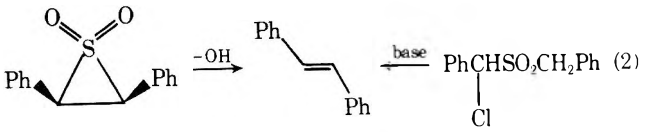
Table I. Reaction of α-Halo *N*-Tosylsulfoximines with Potassium Hydroxide



	R	R′	X	isomer composition of 1[a]	2, % yield (cis/trans)	registry no.	3, % yield[b]	4, % yield	registry no.
a	*n*-Pr	*n*-Pr	Cl	pure[e]	65 (48/52)	7642-15-1 (cis) 14850-23-8 (trans)	81	0	
b	Et	Et	Cl	pure[f]	c (51/49)	7642-09-3	59	0	
c	H	Ph	Br	1:1	34	13269-52-8 (cis) 100-42-5 (trans)	49	37	38401-39-7
d	CH_3	Ph	Br	1:1	49 (92/8)	766-90-5 (trans) 873-66-5 (trans)	76	19	67069-94-7
e[d]	Ph	Ph	Br	1:3	94 (96/4)	645-49-8 (cis) 103-30-0 (trans)	68	2	67-69-93-6

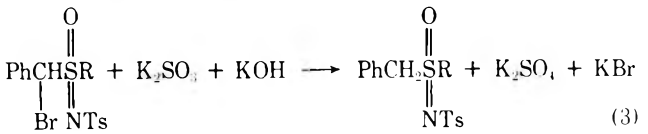
[a] Determined by NMR. [b] Control experiments on the isolation of **3** revealed mechanical loses of 10–20%. [c] Because of volatility the yield was not determined. [d] The reaction was run in aqueous dioxane/KOH. [e] Registry no.: 67070-02-4. [f] Registry no.: 67070-01-3.

this case, the isomer with the aryl groups trans is more stable) occurs prior to loss of SO_2 (eq 2).[6]



(2)

There remains the need for clarification of the mode of production of **4** (Table I). It is believed that potassium sulfite produced in the 1,3-elimination process (Scheme II) may be the agent responsible for the reduction of the bromo sulfoximines to sulfoximines (eq 3). Apparently α-chloro sulfoximines are not as readily reduced with sulfite.[7]



(3)

Experimental Section

The preparation of the following compounds has been reported in an earlier paper:[3] *S*-butyl-*S*-(1-chlorobutyl)sulfoximine; *S*-butyl-*S*-(1-chlorobutyl)-*N*-(*p*-tolylsulfonyl)sulfoximine; *S*-(1-chloropropyl)-*S*-propyl-*N*-(*p*-tolylsulfonyl)sulfoximines.

***S*-Butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine.** To 0.807 g (3.81 mmol) of diastereomerically pure *S*-butyl-*S*-(1-chlorobutyl)-sulfoximine dissolved in 25 mL of dichloromethane and cooled to 0 °C was added 0.5 g of anhydrous potassium carbonate and 0.586 g (3.86 mmol) of trimethyloxonium fluoroborate. The mixture was stirred at 0 °C for 30 min and then at room temperature for 18 h. After filtering, anhydrous ammonia was bubbled through the dichloromethane solution. A white precipitate of ammonium fluoroborate was formed and removed by filtration. The filtrate was washed with two 25-mL portions of water, dried ($MgSO_4$), and concentrated by rotary evaporation to give 0.649 g of a colorless oil. Column chromatography gave 0.566 g (57%) of the desired *N*-methyl derivative. By NMR only one diastereomer was present.

Amination of Sulfoxides with Mesitylsulfonyloxyamine.[8] Several unsubstituted sulfoximines were obtained by the method of Tamura and co-workers. Treatment of a dichloromethane solution of the sulfoxide with mesitylsulfonyloxyamine followed by a basic workup gave the following sulfoximines: *S*-benzyl-*S*-methylsulfoximine (95% yield; fine white needles from benzene–pentane; mp 81–82 °C); *S,S*-dibenzylsulfoximine (84% yield; white needles from methanol; mp 169–170 °C); *S,S*-dibutylsulfoximine (71.9%; colorless oil).

***S*-Benzyl-*S*-methyl-*N*-(*p*-tolylsulfonyl)sulfoximine** was prepared by reaction of *S*-benzyl-*S*-methylsulfoximine with *p*-toluenesulfonyl chloride in pyridine in 73% yield as a white solid, mp 128–129 °C (pentane–ether).

***S*-Benzyl-*S*-ethyl-*N*-(*p*-tolylsulfonyl)sulfoximine.** This material was isolated in 20.8% yield as a white crystalline solid, mp 102.5–103 °C, by reacting the corresponding sulfoxide with *p*-toluenesulfonyl azide in the presence of Raney–copper catalyst.[9]

***S,S*-Dibenzyl-*N*-(*p*-tolylsulfonyl)sulfoximine. Method A.** This material was isolated in 27.6% yield as a white crystalline solid, mp 166–167 °C, by reacting the corresponding sulfoxide with *p*-toluenesulfonyl azide in the presence of Raney–copper catalyst. **Method B.** Treatment of *S,S*-dibenzylsulfoximine with 1 equiv of *p*-toluenesulfonyl chloride in pyridine gave the derivative in 43.4% yield, mp 166–167 °C (pentane–ether).

Bromination of *S*-Alkyl-*S*-benzyl-*N*-(*p*-tolylsulfonyl)sulfoximines. A flame-dried reaction vessel was charged with sodium hydride (6.2 mmol). While maintaining a nitrogen atmosphere, the oil from the sodium hydride dispersion was removed by washing with several small portions of pentane. The last traces of pentane were evaporated in a stream of nitrogen. After adding 5 mL of dimethylformamide (DMF) (distilled from CaH_2), the stirring mixture was cooled in an ice bath. The addition of the sulfoximine (6.0 mmol) in DMF (5 mL) was made slowly via syringe. Hydrogen evolved smoothly for about 40 min, producing a bright red solution of the anion. This solution was added in one portion to a cold (0 °C) solution of bromine (7.0 mmol) in DMF (7 mL). The addition was made by immersing the tip of the syringe beneath the stirring bromine solution. After stirring at room temperature for 30 min the orange solution was poured into 50 mL of saturated ammonium chloride and extracted with three 75-mL portions of chloroform. The extracts were then washed with 50 mL of 1 M Na_2SO_3 solution and concentrated by rotary evaporation. The residual oil was redissolved in a mixture of 300 mL of diethyl ether and 40 mL of chloroform and washed with water. The crude bromo sulfoximines were obtained by drying and concentration of the extracts.

***S*-(1-Bromo-1-phenylmethyl)-*S*-methyl-*N*-(*p*-tolylsulfonyl)sulfoximine (1c).** The crude oil obtained by the general procedure was subjected to thick-layer chromatography (silica gel/ether, developed twice). A 26.5% yield of a diastereomeric mixture (1:1) of the bromo sulfoximines was obtained. Fractional crystallization effected partial separation of the diastereomers. One diastereomer was a white solid, mp 143–145 °C dec, while the other was an oil.

***S*-(1-Bromo-1-phenylmethyl)-*S*-ethyl-*N*-(*p*-tolylsulfonyl)sulfoximine (1d).** A diastereomeric mixture of the bromo sulfoximines was isolated in 26.9% yield by thick-layer chromatography (silica gel/diethyl ether–cyclohexane (4:1), developed three times). A dichloromethane solution of the oil obtained from the chromatography was decolorized with activated charcoal. Addition of anhydrous ether precipitated the bromo sulfoximines as white solid, mp 118–124 °C dec. An NMR spectrum of the crystals obtained prior to the chromatography showed a diastereomeric ratio of 1:1.

***S*-Benzyl-*S*-(1-bromo-1-phenylmethyl)-*N*-(*p*-tolylsulfonyl)sulfoximine (1e).** A diastereomeric mixture of the bromo sulfoximines was isolated as a white crystalline solid, mp 162–166 °C (ether), by thick-layer chromatography (silica gel/30% ether–cyclohexane, developed 12 times). Based on the weight and NMR spectrum of the crude yellow crystals obtained from the general procedure a yield of 61.8% was obtained. The diastereomeric ratio was 1:3.

Reaction of α-Halo Sulfoximines with Potassium Hydroxide. To the halo sulfoximine (1.0 mmol) in 10 mL of methanol was added 6 mL of 1 N KOH. The mixture was refluxed. The disappearance of sulfoximine was monitored by TLC (silica gel/ether). The reaction mixture was cooled, saturated with sodium chloride, and extracted with pentane. The pentane extracts were analyzed for alkene content by gas chromatography using a silver nitrate–ethylene glycol column. The basic solution was extracted with chloroform; the extract was washed with water, dried, and concentrated to give recovered sulfoximine and/or sulfinamide. The basic aqueous phase was made acidic to litmus with 3 M sulfuric acid and extracted with chloroform; the extract was washed, dried, and concentrated to give *p*-toluenesulfonamide when present.

Reaction of *S*-Benzyl-*S*-bromobenzyl-*N*-(*p*-tolylsulfonyl)-sulfoximine (1c) with Potassium Hydroxide. To 0.085 g (0.18 mmol) of a diasteromeric mixture (1:3) of bromo sulfoximines **1c** in 8.0 mL of aqueous dioxane (67% by volume) was added 0.6 mL of 0.1 N KOH (6 equiv). The mixture was refluxed 30 min. The loss of bromo sulfoximine was monitored by TLC (silica gel/ether). After cooling, 5 mL of saturated sodium chloride was added and the solution was acidified with 10% HCl. The solution was extracted with chloroform. The extracts were dried ($MgSO_4$) and concentrated to give 0.052 g of a mixture of *cis*- and *trans*-stilbene (93.5%), *S*-dibenzyl-*N*-(*p*-tolylsulfonyl)sulfoximine (1.7%), and *p*-toluenesulfonamide (67.5%) (mp 136–138 °C). These compounds were identified by GLC, NMR, IR, and TLC. VPC analysis (Apiezon L) showed 96.3% *cis*- and 3.7% *trans*-stilbene. On this column the cis isomer elutes first and then the trans.

Acknowledgment. This research was supported by a grant from the National Science Foundation.

Registry No.—**1c** isomer 1, 67070-00-2; **1c** isomer 2, 67069-99-2; **1d** isomer 1, 67069-98-1; **1d** isomer 2, 67069-97-0; **1e** isomer 1, 67113-89-7; **1e** isomer 2, 67113-90-0; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximinie isomer 1, 67069-96-9; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine isomer 2, 67113-99-9; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine-d_3 isomer 1, 67069-92-5; *S*-butyl-*S*-(1-chlorobutyl)-*N*-methylsulfoximine-d_3 isomer 2, 67069-89-0; *S*-butyl-*S*-(1-chlorobutyl)sulfoximine, 67069-95-8; mesitylsulfonyloxyamine, 36016-40-7; $MeSOCH_2Ph$, 824-86-2; *S*-benzyl-*S*-methylsulfoximine, 38401-38-6; $PhCH_2SOCH_2Ph$, 621-08-9; *S,S*-dibenzylsulfoximine, 67113-91-1; BuSOBu, 2168-93-6; *S,S*-dibutylsulfoximine, 22133-03-5; $EtSOCH_2Ph$, 2843-92-7; 1-butanesulfinamide, 67069-88-9.

Supplementary Material Available: Analytical and spectral data of the compounds discussed in this paper (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) L. A. Paquette, *Acc. Chem. Res.*, **1**, 209 (1968); F. G. Bordwell and B. B. Jarvis, *J. Am. Chem. Soc.*, **95**, 3585 (1973); F. G. Bordwell, E. Doomes, and

P. W. R. Corfield, *ibid.*, **92**, 2581 (1970); F. G. Bordwell and E. Doomes, *J. Org. Chem.*, **39**, 2526 (1974); L. Ramberg and B. Backlund, *Arkiu Kemi Mineral Geol.*, **13A**, No. 27 (1940); *Chem. Abstr.*, **34**, 4725 (1940).
(2) N. P. Neureiter, *J. Am. Chem. Soc.*, **88**, 558 (1966).
(3) C. R. Johnson and H. G. Corkins, *J. Org. Chem.*, companion paper in this issue.
(4) L. A. Paquette, "Advances in Organic Chemistry", Vol 6, E. C. Taylor and H. Wynberg, Eds., Interscience, New York, N.Y., 1969.
(5) The protons and the carbon atom which do not carry the halogen will be referred to as the α' position, while the protons and the carbon atom bearing the halogen will be called the α protons or α carbon; F. G. Bordwell, E. Doomes, and P. W. Corfield, *J. Am. Chem. Soc.*, **92**, 2591 (1970); F. G. Bordwell and B. B. Jarvis, *ibid.*, **95**, 3585 (1973).
(6) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **73**, 5187 (1951).
(7) In an experiment performed by Dr. Susan Goff it was found that *S*-(bromomethyl)-*S*-methyl-*N*-tosylsulfoximine was reduced to *S,S*-dimethyl-*N*-tosylsulfoximine by potassium sulfite in refluxing methanol.
(8) Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 4137 (1972).
(9) C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, **95**, 7418 (1973).

Rearrangement Reaction of 1-Chloro-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone with Potassium Phthalimide

Shiang-Yuan Chen and M. G. Nair*

Department of Biochemistry, College of Medicine, University of South Alabama, Mobile, Alabama 36688

Received June 5, 1078

Treatment of 1-chloro-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone with potassium phthalimide in acetonitrile resulted in skeletal rearrangement with the formation of 1-phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone. The structure of the rearrangement product was established by independent synthesis and mass spectrometry. The isolation of some intermediates from the reaction mixture gave evidence for the mechanism of this reaction; these mechanistic considerations guided the successful synthesis of 1-phthalimido-4-[*p*-(carbomethoxy)-thiophenoxy]-2-butanone.

As part of a continuing program[1-6] aimed at developing folate analogues that are altered at the C^9–N^{10} bridge region for possible use as anticancer agents,[7] we were interested in the synthesis of 11-thiohomofolic acid, which is an analogue of homofolic acid.[8] At the outset, we explored methods for the construction of the partial side chain **2**, which could eventually be elaborated to the title compound **1**. In this regard, we investigated the reaction between chloro ketone **5** and potassium phthalimide. Chloro ketone **5** was conveniently prepared by the nucleophilic addition of *p*-carbomethoxythiophenol[4] to hydroxymethyl vinyl ketone[9] and subsequent treatment of the resulting addition product with thionyl chloride.

Treatment of 1 equiv of chloro ketone **5** with a solution of 2 equiv of potassium phthalimide in acetonitrile containing crown ether for 4 h at ambient temperature and subsequent workup of the reaction mixture gave a product that displayed NMR resonances at 7.9 (d, J = 9 Hz, 2 H), 7.8 (c, 4 H), 7.3 (d, J = 9, 2 H), 3.97 (t, J = 7, 2 H), 3.9 (s, 3 H), 3.8 (s, 2 H), and 3.09 (t, J = 7, 2 H) ppm. These resonances, although they appeared to be consistent with the expected structure **3a**, were proved to be due to the alternate structure **4a**. This compound, on reaction with hydroxylamine, gave an oxime and on ketalization with ethylene glycol gave a crystalline ketal. Treatment of the oxime with hydrazine, in a standard hydrazinolysis reaction, liberated an aminoacetonyl oxime, which was different from **2a**, but reacted with 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine[4] to obtain an intermediate (**7a**). This reaction product, possessing spectral characteristics and giving analytical data consistent with either structure **7a** or **8a**, was deprotected at the carbonyl function using trifluoroacetic acid and 1 N HCl, as previously described.[5] The deprotected nitro ketone thus obtained was subjected to the dithionite reduction and one-step cyclization oxidation technique to generate the homopteroic acid analogue **9**.[4,5,10] Although the dithionite reduction of the nitro group to the amino group worked well, the subsequent cyclization of the pyrimidine to the dihydropteridine did not occur. Repetition of the same reaction sequence using a ketal protective group also resulted in complete failure of its transformation to the pteridine. Since several analogous amino ketones were readily cyclized to the pteridines, and no failures were reported in literature in using such an approach to the general synthesis of pteridines, it became apparent that the crown ether reaction product between chloro ketone **5** and potassium phthalimide did not have the expected structure **3a**. Since this product was a ketone, which could easily be converted to an oxime and an ethylene ketal, the alternate structure **4a** was proposed for this product. Indeed, if this product had structure **4a** rather than **3a**, then the failure to construct the pteridine ring using this material can easily be understood. These expectations were proved correct (vide infra). The transformations are summarized in Scheme I.

In order to prove that the crown ether reaction product has structure **4a**, an unambiguous synthesis of this material was undertaken. Reaction of phthalic anhydride with β-alanine gave *N*-(3-carboxypropyl)phthalimide (**13**), which was converted to an acid chloride by reaction with thionyl chloride. Treatment of the acid chloride with ethereal diazomethane gave the diazo ketone **14**, which was converted to the corresponding chloromethyl ketone **15** by standard procedures.[11] Reaction of *p*-(carbomethoxy)thiophenol[4] with **15** was carried out in acetone using 1 molar equiv of anhydrous sodium carbonate; subsequent workup of the reaction mixture gave a product that was identical with the crown ether reaction product in all respects (TLC, NMR, mp). Thus, the structure of the product obtained by reaction of chloromethyl ketone **5** with potassium phthalimide was unequivocally established as **4a**.

Mechanism of the Reaction

When equimolar amounts of chloromethyl ketone **5** and potassium phthalimide were allowed to react in the presence of crown ether using acetonitrile as a solvent, it was observed by monitoring the reaction by TLC that a product was being

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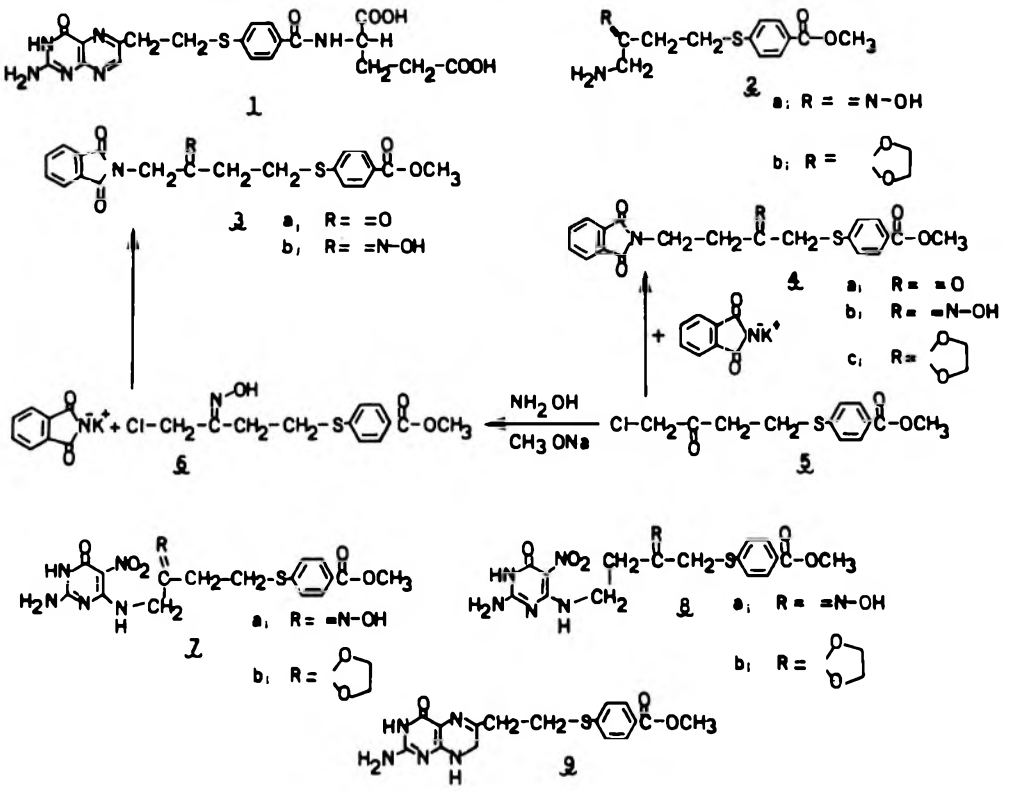
Scheme I

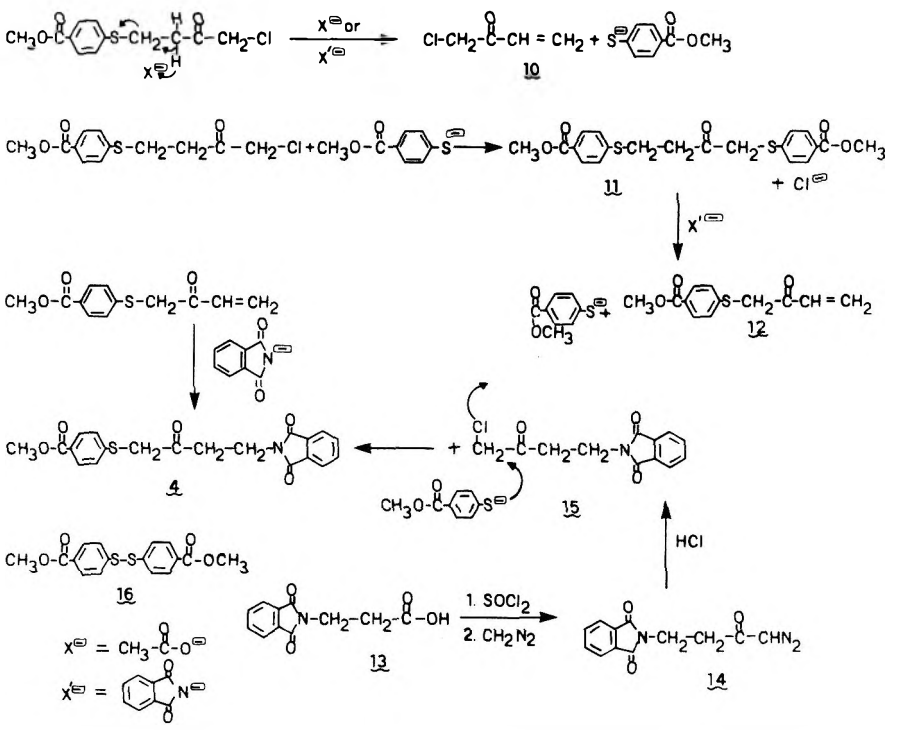


formed in the reaction mixture that was less polar than **4a**. Under these conditions, this product predominates; only very little **4a** is formed (~10%). However, addition of 1 equiv more of potassium phthalimide at this stage resulted in the complete disappearance of this material with the concomitant formation of **4a**. Therefore, it became clear that this reaction occurred in a stepwise fashion; **4a** is formed by reaction of potassium phthalimide with the less polar intermediate. In order to prove this assumption, conditions were optimized so that the less polar intermediate (hereto referred to as **11**) could be isolated and characterized. Compound **11** had a molecular weight of 404, as determined by mass spectrometry, and showed NMR resonances in TFA at 7.95 (d, 4 H), 7.4, 7.33 (d d, 4 H), 4.06 (s, 6 H), 3.93 (s, 2 H), and 3.25 (c, 4 H) ppm. The formation and isolation of **11** requires the formation of *p*-(carbomethoxy)thiophenolate anion in the reaction mixture, which in turn should result from a reverse Michael addition to chloro ketone **5** by potassium phthalimide. If this assumption was correct, then we reasoned that weak nucleophiles, such as sodium acetate, might be used to generate a phenolate anion from **5**, which on reaction with chloro ketone **5** should yield intermediate **11** in quantitative yield. This is because we had prior knowledge that intermediate **11** is stable to sodium acetate in boiling methanol. Thus, treatment of a solution of **5** in boiling methanol with excess sodium acetate gave intermediate **11** in quantitative yield, as required by the proposed mechanism. Next, the fate of 4-chloro-3-butenone, which is a compulsory co-product of the reaction between **5** and sodium acetate, was investigated. Evaporation of the reaction mixture, after removal of **11** by filtration, extraction of the residue with ether, and evaporation of the ether layer, yielded an oil that gave an NMR spectrum that was identical with 4-chloro-3-butenone. This compound, a sample of which was available, was found to be stable to sodium acetate under conditions of the above reaction. These experimental results clearly demonstrated the mechanism by which **11** was generated from **5** on treatment with potassium phthalimide.

Next, we examined the mechanism of the subsequent steps by which **11** was converted to **4a**. Treatment of **11** with potassium phthalimide in acetonitrile, with or without the presence of crown ether, resulted in the formation of two products, one of which was identical with **4a**. The other product, which was less polar than **4a**, was identified as **16** by isolation after workup and chromatography of the reaction mixture. This material was identical in all respects with an authentic sample[4] of **16**. On the other hand, by monitoring the reaction by TLC until all **11** had disappeared, evaporation and ether extraction of the reaction mixture resulted in the isolation of *p*-(carbomethoxy)thiophenol.[4] The isolation of *p*-(carbomethoxy)thiophenol and dimer **16** from the reaction mixture gave evidence for the mechanism of formation of **4a** from **11**. It is postulated that attack of potassium phthalimide on **11** resulted in the formation of an enolate that collapsed to an intermediate **12**; a retro Michael reaction and subsequent addition of phthalimide to **12** in a Michael addition resulted in the formation of **4a** with the liberation of the resonance-stabilized thiophenolate anion. The enhanced stability of **4a** toward potassium phthalimide, compared to **11**, together with the formation of a thermodynamically more stable intermediate (**12**) from **11** facilitates the formation of **4a**. A direct nucleophilic attack of phthalimide anion on **11** with concurrent displacement of the thiophenolate anion is unlikely because one would anticipate the production of both **4a** and **3a** by this mechanism.

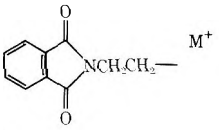
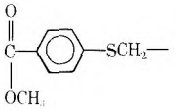
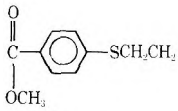
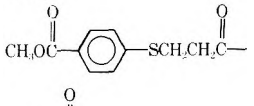
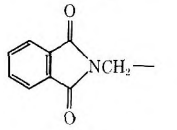
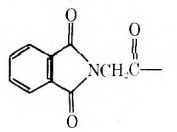
From the preceding discussion, it is apparent that the initial formation of the enolate from **5** leads to the formation of **11**. Due to the ease of formation of **12**, nucleophillic displacement reactions on **5** results in the formation of rearranged products. Therefore, any attempt involving direct displacement of chlorine of **5** by a nucleophile should be carried out under conditions which avoid enolate formation. On reaction of **5** with H_2NOH, chloro ketone **5** could be converted to the chloroacetonyl oxime **6** under carefully controlled conditions. Reaction of **6** with potassium phthalimide in acetonitrile or DMF resulted in the formation of an oxime **3b**, which was not identical with **4b**. Deprotection of the carbonyl group of **3b** with aqueous TFA resulted in the formation of a ketone, which was an isomer of **4a** but was not identical with it. The compound showed relevant NMR signals at 7.98 (m, phthalimido, 4 H), 7.84, 7.35 (d, d, arom, 4 H), 4.53 (s, methylene, 2 H), 3.93

Scheme II



(s, carbomethoxy, 3 H), and at 3.29 and 2.93 (t, t, ethylene, 4 H) ppm and had a different R_f value and melting point. Structure **3a** was assigned to this product after comparing its mass spectral fragmentation pattern with that of **4a**. The relevant fragments and their respective *m/e* values are presented in Table I. The presence of fragments representing *m/e* values of 188, 195, and 223 in the mass spectrum of **3a** and the total absence of these fragments in the spectrum of **4a** establishes the structure of **3a** as written. The mass spectrum of **4a** shows a fragment representing an *m/e* value of 174, which is completely absent in the spectrum of **3a**. Since this value of 174 represents the *N*-ethylphthalimide fragment, the structure of **4a** is also correct as written. In addition, fragments having *m/e* values of 160 and 181 are generated from both compounds, the former being nine times more intense and the latter five times less intense for **3a** compared to **4a**. These observations are in complete agreement with the proposed structures for both **3a** and **4a**.

Table I

fragment	mass to charge ratio (*m/e*) 4a	3a
	404 174	404 absent
	181	181
	absent	195
	absent	223
	160	160
	absent	188

Experimental Section

Melting points are uncorrected and were determined on a Fisher-Johns apparatus. NMR spectra were run in CF_3COOH or $CDCl_3$ on a 90-MHz Perkin Elmer R-32 spectrometer with Me_4Si as internal lock signal. Field strengths of the various proton resonances are expressed in parts per million and coupling constants in hertz. Peak multiplicity is depicted as usual: s, singlet; d, doublet; t, triplet; q, quartet; br, broadened singlet or unresolved miltiplet; and c, complex signal, the center of which is given. UV spectra were determined on a Beckman Model 25 spectrophotometer. Mass spectra were run at Research Triangle Institute in North Carolina. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Yields represent the actual amount of pure compound isolated, assuming 100% reaction.

1-Chloro-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone (5). A solution of *p*-(carbomethoxy)thiophenol, 3.36 g (20 mmol) in 10 mL of benzene, was added to a solution of 2.5 g (22 mmol) of chloromethyl vinyl ketone in 10 mL of benzene under nitrogen. To this mixture 5 drops of triethylamine was added and stirred for 30 min at 25 °C. The solution was then evaporated to dryness in vacuum and the residue was recrystallized from acetone and hexane: mp 94–95 °C; yield 5.15 g (94.5%); NMR ($CDCl_3$) 8.0, 7.3 (d, d arom, 4 H), 4.08 (s, chloromethyl, 2 H), 3.86 (s, carbomethoxy, 3 H), and at 3.21 and 3.0 (t, t, ethylene, 4 H) ppm. Anal. Calcd for $C_{12}H_{13}ClO_3S$: C, 52.85; H, 4.80; Cl, 13; S, 11.75. Found: C, 53.0; H, 4.77; Cl, 12.83; S, 11.86.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-2-butanone (3a). A solution of 2.725 g (10 mmol) of **5** was made in 30 mL of THF and added to a solution prepared by dissolving successively 810 mg (15 mmol) of sodium methoxide and 1.4 g (20 mmol) of hydroxylamine hydrochloride in 200 mL of methanol. After stirring for 1 h, the solution was evaporated to dryness, and the residue thus obtained was suspended in 100 mL of water and extracted repeatedly three times with 100 mL each of chloroform. The combined chloroform layer was washed with water and dried with Na_2SO_4. The chloroform layer was evaporated to dryness to obtain **6**: NMR ($CDCl_3$) 7.86, 7.34 (d, d, J = 9 Hz, aromatic, 4 H); 4.23 (s, chloromethyl, 2 H), 3.80 (s, carbomethoxy, 3 H), 3.23 and 2.83 (t, t, ethylene, 4 H) ppm. Treatment of this compound with potassium phthalimide, as described for the preparation of **4a**, gave **3b**: 80% yield; mp of 145 °C; NMR ($CDCl_3$) 7.87 (c, phthalimido, arom, 6 H), 7.37 (d, J = 9 Hz, arom, 2 H), 4.47

(s, methylene, 2 H), 3.95 (s, carbomethoxy, 3 H), and at 3.2 and 2.7 (t, t, J = 8 Hz, 4 H) ppm. Deprotection of this oxime was accomplished at 55 °C with the use of a 1:1 (v/v) mixture of TFA/H_2O for 30 min. The desired compound **3a** was isolated after dilution and extraction of the reaction mixture with chloroform and was freed of minor impurities by column chromatography over silica gel CC_4. The compound was eluted in chloroform and crystallized from methanol as silky needles, mp 136–138 °C. The rearranged compound **4a** was found to be more polar than **3a** on silica gel CC_4 TLC plates using chloroform as the solvent. Anal. Calcd for $C_{20}H_{17}NO_5S$: C, 62.64; H, 4.47; N, 3.65; S, 8.36. Found: C, 62.48; H, 4.47; N, 3.58; S, 8.17.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone (4a). A solution of 2.73 g (10 mmol) of chloromethyl ketone **5** in 20 mL of acetonitrile was added dropwise to a suspension of 3.7 g (20 mmol) of potassium phthalimide in a solution of 2.64 g of 18-crown-6 ether in 80 mL of acetonitrile. This mixture was stirred at 25 °C for 6 h and filtered, and the filtrate was evaporated to dryness. The residue thus obtained was triturated with water, and the slightly yellow product was collected by filtration and recrystallized from methanol: mp 126–127 °C; yield 2.0 g. Anal. Calcd for $C_{20}H_{17}NO_5S$: C, 62.64; H, 4.47; N, 3.65; S, 8.36. Found C, 62.46; H, 4.30; N, 3.55; S, 8.43.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone Oxime (4b). Compound **4a**, 3.83 g (10 mmol), was dissolved in 70 mL of 1:1 mixture of pyridine and absolute alcohol (v/v). To this solution 695 mg (10 mmol) of hydroxylamine hydrochloride was added and the mixture was heated under reflux for 2 h and then evaporated to remove solvent. The resulting gum was triturated with water, and the solid thus formed was filtered and recrystallized form ethyl acetate/hexane: mp 152–153 °C; yield 3.56 g. This compound was not identical with **3b** in all respects (TLC, NMR, mp). For example, the methylene resonance of **4b** appeared as a singlet at 3.8, and the ethylene protons as two triplets as 4.0 and 2.9 ppm. Anal. Calcd for $C_{20}H_{18}N_2O_5S$: C, 60.29; H, 4.55; N, 7.03; S, 8.05. Found: C, 60.40; H, 4.58; N, 6.92; S, 8.07.

1-Phthalimido-4-[*p*-(carbomethoxy)thiophenoxy]-3-butanone Ethylene Ketal (4c). In a round-bottom flask 1.99 g (5 mmol) of **4a** was suspended, and 10 mL of ethylene glycol was added to it, followed by the addition of 200 mg of *p*-toluenesulfonic acid monohydrate. The mixture was heated to ~150 °C, when most of the ketone dissolved. To this hot solution, benzene was very carefully added, and the flask was attached to a Dean–Stark apparatus and refluxed with continuous removal of water for 8 h. After this period, benzene was removed by flash evaporation, and 3.0 g of solid potassium bicarbonate was added to the flask and diluted to 500 mL with a saturated solution of potassium bicarbonate in water. The precipitated solid was filtered and recrystallized from methanol: yield 1.5 g; mp 103 °C. Anal. Calcd for $C_{22}H_{21}NO_6S$: C, 61.83; H, 4.92; O, 22.48. Found: C, 61.67; H, 4.80; O, 22.31.

Hydrazinolysis of 3b and 4b: Preparation of 7a and 8a. The experimental procedures were carried out in an analogous fashion as previously reported from our laboratory.[4-6] As a typical example, 1 equiv of either **3b** or **4b** was dissolved in the minimum required amount of absolute ethanol, and exactly 1 equiv of 95% hydrazine hydrate was added to it under an atmosphere of N_2. The reaction was frequently monitored by TLC for the complete disappearance of the starting material. When complete, which usually takes about 72 h at 25 °C, the solution was treated with 1 molar equiv of 1 N HCl, evaporated to dryness, and extracted with water. The clear aqueous solution was basified to pH 8.0 by the addition of NH_4OH, and the gummy material thus obtained was isolated by extraction with ethyl acetate. The ethyl acetate layer was washed, dried with Na_2SO_4, filtered, and evaporated to a gum. The NMR spectrum did not exhibit resonances due to the phthalimide moiety, but was otherwise consistent with the required structures in both instances. An alcoholic solution of this amine was treated with a solution of 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine in absolute alcohol and refluxed for 1.5 h in the presence of 1 molar equiv of *N*-methylmorpholine. Both compounds **7a** and **8a** were precipitated during the reaction and were removed by filtration, washed, and dried to obtain analytical samples. The compounds were formed in ~60–70% yield based on the amine used for the reaction: mp 145–148 °C (**7a**) and 135–136 °C (**8a**). Only one of these two isomeric compounds (**7a**) could be converted to the pterdine structure **9** by subsequent synthetic procedures. Details of these reactions will be published elsewhere. Anal. Calcd for $C_{16}H_{18}N_6O_6S$: C, 45.5; H, 4.29; N, 19.89. Found for **8a:** C, 45.62; H, 4.18; N, 19.76. Found for **7a:** C, 45.27; H, 4.32; N, 20.07.

***N*-(4-Chloro-3-oxobutyl)phthalimide (15).** Treatment of *N*-(2-carboxyethyl)phthalimide with thionyl chloride according to the procedure of Viscontini[11] gave the corresponding acid chloride (mp 108 °C). A solution of 4.75 g (20 mmol) of this acid chloride in dry THF was treated with ethereal alcohol-free diazomethane prepared from 10 g of diazald at 0–5 °C. After 30 min, gaseous HCl was passed through the reaction mixture for 5 min. The solution was stirred for an additional 30 min and evaporated to dryness in vacuum. The residue thus obtained was crystallized from methanol: mp 109–110 °C; yield 4.2 g. The compound exhibited NMR resonances expected of the desired structure. Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.26; H, 3.98; Cl, 14.12; N, 5.57. Found: C, 57.31; H, 4.10; Cl, 14.16; N, 5.66.

Preparation of 4a from 15 and *p*-(Carbomethoxy)thiophenol. To a mixture of 503 mg (2 mmol) of **14**, 336 mg (2 mmol) of *p*-(carbomethoxy)thiophenol, and 212 mg (2 mmol) of anhydrous sodium carbonate, 10 mL of acetone was added and the mixture was stirred under nitrogen for 6 h. The white suspension thus obtained was evaporated to dryness, diluted with 50 mL of water, and extracted with ethyl acetate. The ethyl acetate layer was evaporated after washing and the residue was crystallized from methanol: mp 126–127 °C (undepressed by mixing with **4a**); yield 720 mg. This compound was identical in all respects with **4a** prepared by the crown ether reaction.

Reaction of Chloromethyl Ketone 5 with Sodium Acetate: Preparation of 11. A solution of 5.45 g (20 mmol) of **5** in 300 mL of hot methanol was treated with 10.88 g (80 mmol) of sodium acetate trihydrate. The clear solution thus obtained was heated to boiling on a hot plate and the volume was reduced to ~150 mL when white crystals of **11** began to separate. At this point, the reaction mixture was allowed to cool to 25 °C, and after 1 h the crystals were collected by filtration, washed with water, and recrystallized from methanol: yield 3.92 g (theoretical yield 4.04 g); mp 167 °C. Anal. Calcd for $C_{20}H_{20}O_5S_2$: C, 59.41; H, 4.95; S, 15.84. Found: C, 58.98; H, 4.94; S, 15.53.

The original filtrate prior to washings was evaporated at 25 °C, in vacuum, and the residue was extracted repeatedly with ether. The combined ether layer was dried over anhydrous Na_2SO_4 and evaporated. The NMR spectrum of the oily resudue thus obtained was identical with an authentic spectrum of 4-chloro-3-butenone.

Reaction of 11 with Potassium Phthalimide: Formation of 4a and Isolation of 16. To a mixture of equimolar amounts of **11** and potassium phthalimide (1 mmol each) 30 mL of acetonitrile was added, followed by the addition of 100 mg of 18-crown-6 ether. The mixture was allowed to stir at 25 °C, and the reaction was frequently monitored by TLC for the complete disappearance of **11**. When all of **11** had reacted, which took 2.5 h, the reaction mixture was evaporated to dryness at 25 °C. Ice was added to the residue and triturated, and the solid thus obtained was separated by filtration. The filtrate was acidified to pH 4.0 by glacial acetic acid and the solution was extracted with ether. The ether layer was washed, dried with Na_2SO_4, and on evaporation gave a solid residue that was identified as *p*-(carbomethoxy)thiophenol by comparison with an authentic sample. The solid residue was purified by chromatography over silica gel CC-7. Benzene eluted a crystalline material from the column that was identified as **16.** Chloroform eluted **4a,** which was identical in all respects with the material obtained by reaction of potassium phthalimide with **5.**

Acknowledgment. This investigation was supported by Grant CH-53A from the American Cancer Society, Inc.

Registry No.—**3a,** 67425-98-3; **3b,** 67425-99-4; **4a,** 67426-00-0; **4b,** 67426-01-1; **4c,** 67426-02-2; **5,** 67426-03-3; **6,** 67426-04-4; **7a,** 67416-04-4; **7a,** 67426-05-5; **8a,** 67426-06-6; **11,** 67426-07-7; **13,** 3339-73-9; 13 acid chloride, 17137-11-0; **14,** 7504-49-6; **15,** 65495-45-6; **16,** 35190-68-2; *p*-(carbomethoxy)thiophenol, 6302-65-4; chloromethyl vinyl ketone, 25476-89-5; potassium phthalimide, 1074-82-4; 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine, 1007-99-4.

References and Notes

(1) M. G. Nair and C. M. Baugh, *J. Org. Chem.*, **38,** 2185 (1973).
(2) M. G. Nair and C. M. Baugh, *J. Med. Chem.*, **17,** 223 (1974).
(3) M. G. Nair, L. P. Mercer, and C. M. Baugh, *J. Med. Chem.*, **17,** 1268 (1974).
(4) M. G. Nair, P. T. Campbell, and C. M. Baugh, *J. Org. Chem.*, **40,** 1745 (1975).
(5) M. G. Nair, and P. T. Campbell, *J. Med. Chem.*, **19,** 825 (1976).
(6) M. G. Nair, P. C. O'Neal, C. M. Baugh, R. L. Kisliuk, Y. Gaumont, and M. Rodman, *J. Med. Chem.*, **21,** 673 (1978).
(7) H. R. Hornbeak and M. G. Nair, *Mol. Pharmacol.*, **14,** 299 (1978).
(8) J. I. DeGraw, J. P. Marsh, Jr., E. M. Acton, O. P. Crews, C. W. Mosher, A. N. Fujiwara, and L. Goodman, *J. Org. Chem.*, **30,** 3404 (1965).
(9) Y. A. Arbuzov and A. M. Korolev, *Zh. Obshch. Khim.*, **32,** 3674 (1962).
(10) M. G. Nair, P. T. Campbell, E. Braverman, and C. M. Baugh, *Tetrahedron Lett.*, **31,** 3745 (1975).
(11) M. Viscontini, W. Kaiser, and H. A. Leiduer, *Helv. Chim. Acta.*, **48,** 1221 (1965).

Chemistry of α,β-Unsaturated Thione Dimers. 1. Preparation of α,β-Unsaturated Thione Dimers and Thermolysis of These Dimers in the Presence of Acrylonitrile or Acrylamide

Takayuki Karakasa and Shinichi Motoki*

Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162 Japan

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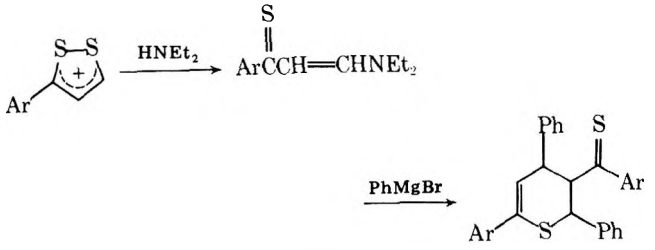
Thiochalcone, 4'-methoxythiochalcone, 2-benzylidene-1-thiotetralone, 2-(*p*-methoxybenzylidene)-1-thiotetralone, and 2-(*p*-chlorobenzylidene)-1-thiotetralone dimers have been prepared by the reaction of corresponding α,β-unsaturated ketones with P_4S_{10}. When these dimers were heated in the presence of acrylonitrile or acrylamide, monomeric unsaturated thiones generated by the decomposition of the dimers reacted with the acrylic compounds to give some cycloadducts of the Diels–Alder type, such as 3,4-dihydro-2*H*-thiopyran or 5,6-dihydrobenzo[*h*]thiochroman derivatives.

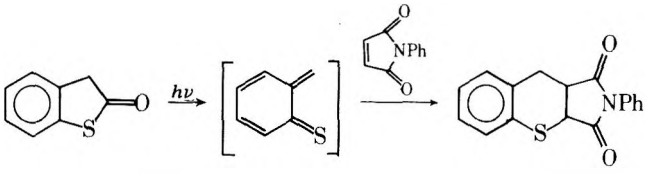
α,β-Unsaturated thiones are little known because of their instability in the monomeric form[1] and tendency to undergo [4 + 2] cycloaddition in which the thione itself may serve as a dienophile or a diene.

For example, Quiniou et al.[2] reported that treatment of vinylogous thioamide with phenylmagnesium bromide gave 3-methoxythiobenzoyl-6-methoxyphenyl-2,4-diphenyl-3,4-dihydro-2*H*-thiopyran, via a thiochalcone intermediate.

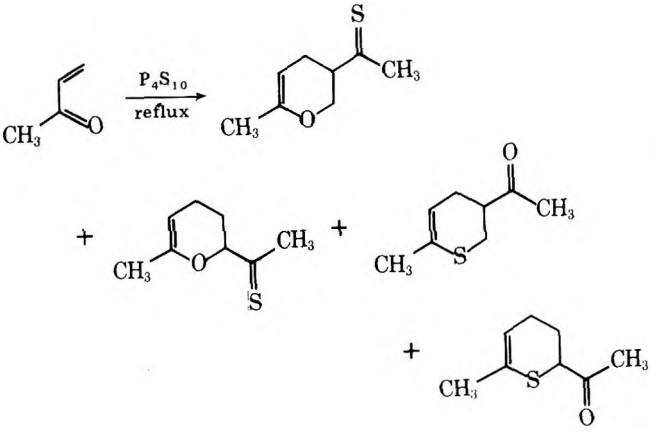


Ar = *p*-CH_3O–C_6H_4

The photoreaction of the thiolactone in the presence of *N*-phenylmaleimide afforded good chemical evidence for the intermediacy of the ortho-quinoid thioketone.[3]



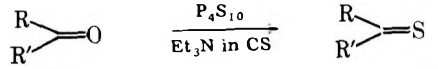
Recently, Lipkowitz et al.[4] reported that treatment of methyl vinyl ketone with P_4S_{10} in pyridine gave four isomeric products. This work also provided some suggestions for the cycloaddition of α,β-unsaturated thiones.



In this paper we wish to describe the satisfactory preparation of α,β-unsaturated thione dimers and the thermolysis of these dimers in the presence of acrylonitrile or acrylamide.

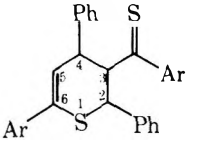
Preparation of α,β-Unsaturated Thione Dimers

Tetraphosphorus decasulfide (P_4S_{10}) is well known as a reagent for the thionation of nonenolisable ketones. The reactions are usually carried out by refluxing the ketone dissolved in toluene or xylene with suspended P_4S_{10}.[5] Under the same conditions, however, thionation of α,β-unsaturated ketones was unsuccessful. We have investigated other procedures for the preparation of ordinary thiones (**2**), and found that treatment of ketones (**1**) with P_4S_{10} takes place with ease in carbon disulfide solution in the presence of triethylamine.



1a, R = R' = C_6H_5 **2a**, R = R' = C_6H_5
b, R = CH_3; R' = C_6H_5 **b**, R = CH_3; R' = C_6H_5

Under these conditions, the reaction of chalcone or 4'-methoxychalcone with P_4S_{10} proceeded readily to give the corresponding thione dimer in moderate yield. The results are shown in Table I. The NMR spectrum of 4'-methoxythiochalcone dimer **3b** was identical with that reported by Quiniou et al.[2] and thiochalcone dimer **3a** gave a similar NMR spectrum.



3a, Ar = C_6H_5
b, Ar = *p*-CH_3O–C_6H_4

Similarly, 2-arylidene-1-thiotetralone dimers (**4**) were obtained by the reaction of 2-arylidene-1-tetralone with P_4S_{10}. The structures of **4** are supported by analytical and spectral data. The elemental analyses of mass spectra were in agreement with the proposed structures **4** or **5**. The NMR spectra showed sharp one-proton singlets at δ 3.6 and 5.6 ppm; these were assigned to the C-4 and the C-2 protons in the 3,4-dihydro-2*H*-thiopyran ring, respectively, so the structure **5** can be excluded. However these spectral data do not enable the stereochemistry of **4** to be deduced.

It would be probable that the formation of these dimers (**9**) proceed via an α,β-unsaturated thione intermediate (**7**), from which **9** is formed via path A or path B as illustrated in Scheme I, and the structure of **9** suggests that the cycloaddition re-

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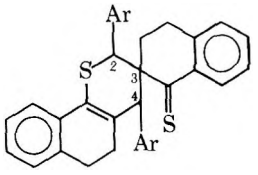
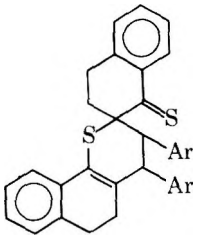
Table I. Preparation of Thiones

product	registry no.	reaction conditions: temp °C	reaction conditions: time	yield, %[a]
thioacetophenone	16696-68-7	10–15	1 h	27
thiobenzophenone	1450-31-3	reflux	1 h	76
3a	67254-57-3	20–25	1 day	38
3b	67314-93-6	20–25	1 day	50
4a	67254-58-4	20–25	1 week	45
4b	67254-59-5	20–25	1 week	50
4c	67254-60-8	20–25	1 week	62

[a] Based on the ketone.



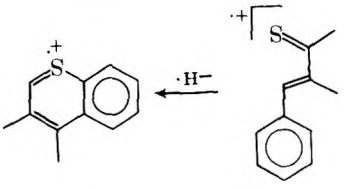
4a, Ar = C_6H_5
b, Ar = p-CH_3O–C_6H_4
c, Ar = p-Cl–C_6H_4



5a, Ar = C_6H_5
b, Ar = p-CH_3O–C_6H_4
c, Ar = p-Cl–C_6H_4

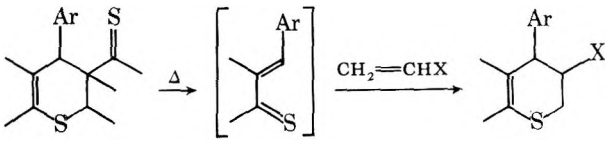
action of 7 shows the opposite regioselectivity to that of α,β-unsaturated ketones.[4,6]

The mass spectra of 3 and 4 showed evidence for the retro-Diels–Alder reaction: intense ions for α,β-unsaturated thiones, and the characteristic peak recognized by the assumption that the α,β-unsaturated thione ion loses a hydrogen to give the stable thiopyrrylium ion.



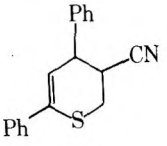
The Thermolysis of α,β-Unsaturated Thione Dimers in the Presence of Acrylonitrile or Acrylamide

In the preparation of α,β-unsaturated thione dimers, we observed that the yield of the dimer decreased and the formation of polymeric substances increased with raising reaction temperature. This suggested the dissociation of the dimers into unstable thione monomers upon heating so trapping of the monomers by the thermolysis of the dimer in the presence of acrylonitrile or acrylamide has been examined.

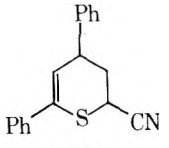


X = CN, $CONH_2$

The thermolysis of **3a** in the presence of acrylonitrile gave the cycloadduct **10a** in 44% yield. The IR spectrum of the product showed a sharp band at 2250 cm^{-1}, attributable to the nitrile group and the elemental analysis and mass spectra are in agreement with the proposed structure, **10a** or **11a**. The

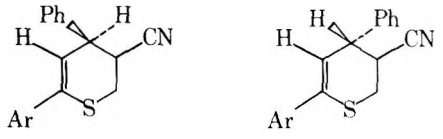


10a



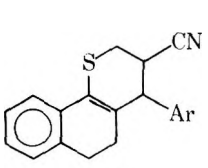
11a

NMR spectrum showed signals at δ 3.0–3.5 (m, 3 H), 3.9 (t, 1 H), 6.1 (d, 1 H), and 7.2–7.8 (m, 10 H). The doublet at δ 6.1 (J = 4.8 Hz) is assigned to the olefinic proton while the triplet at δ 3.9 is attributed to the benzylic proton by spin decoupling. Therefore the isomeric structure **11a** can be excluded.[7] In addition to providing the molecular weight, the mass spectra showed evidence for the retro-Diels–Alder reaction: an intense ion at 224 for thiochalcone was observed. The NMR spectrum of 2-cyano-6-methoxyphenyl-4-phenyl-3,4-dihydro-2*H*-thiopyran (**10b**) showed signals at δ 5.9 (d, 0.5 H, J = 4.0 Hz) and 6.0 (d, 0.5 H, J = 4.8 Hz). These signals suggest that the product is a mixture of the two epimers **10b**.

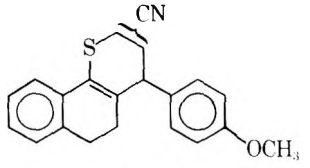


10b, Ar = p-CH_3O–C_6H_4

Similarly, the reaction of **4** and acrylonitrile gave the cycloadducts **12**. The analytical and spectral data of **12a** and **12c** were in agreement with the proposed structure, but the position of the nitrile group was not determined in **12b**.



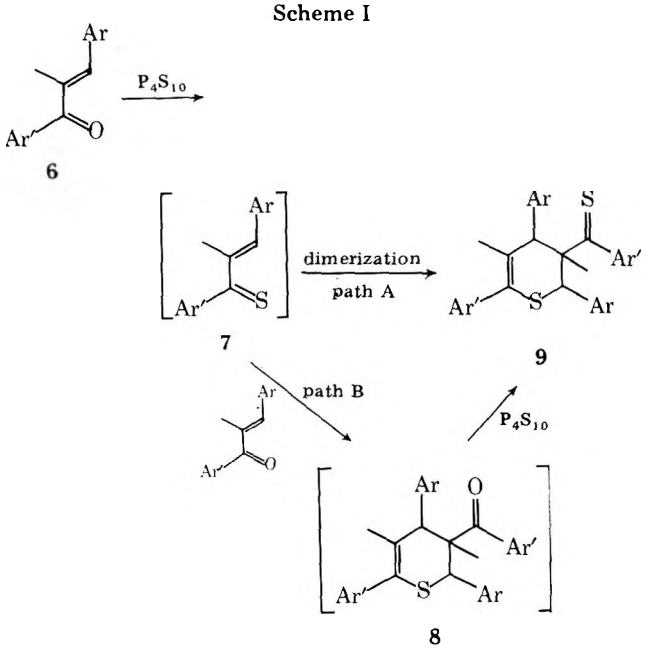
12a, **12c**

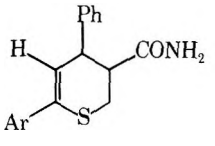


12b

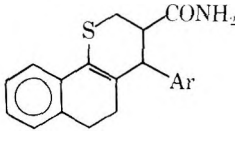
3a reacted with acrylamide in dry benzene to give the adduct **13a** in 40% yield. The IR spectrum showed bands at 3400 (NH_2), 3200 (NH_2), and 1660 cm^{-1} (C=O). The molecular ion (m/e 277) and thiochalcone fragment (m/e 224) were observed in the mass spectra. In the NMR spectrum, the doublet at δ 6.2 (J = 7.0 Hz) is assigned to the olefinic proton while the

Scheme I





13



14

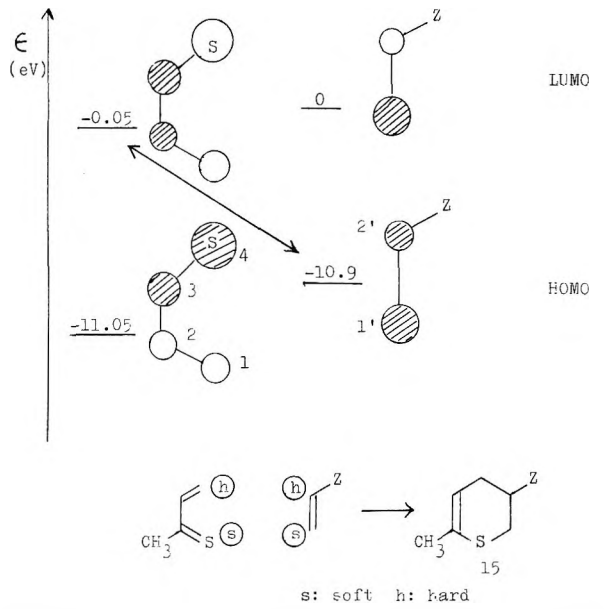


Figure 1. Estimated π frontier orbital energies for methyl vinyl thione and olefins (Z = CN, CHO). (Solid arrow indicates the dominant interaction).

Table II. Reaction of α,β-Unsaturated Thiones with Acrylonitrile and Acrylamide

product	registry no.	reaction time, min	yield, %
	Acrylonitrile		
10a	67254-61-9	30	44
10b		60	74
12a	67254-62-0	120	53
12b	67254-47-1	15	53
12c	67254-63-1	60	59
	Acrylamide		
13a	67254-64-2	30	40
13b	67254-65-3	60	48
14a	67254-66-4	60	71
14b	67254-67-5	20	49
14c	67254-68-6	70	71

double doublet at δ 4.16 is attributed to the benzylic proton by spin decoupling. The reaction of **3b–4c** with acrylamide afforded the corresponding adducts (**13b, 14a, 14b,** and **14c**). The results are presented in Table II.

Experimental Section

All melting and boiling points are uncorrected. Column chromatography was performed on a 100–200 mesh Florisil column by eluting with ligroin–benzene (1:1). ^{1}H-NMR spectra were recorded at 60 MHz on a JEOL JNM-PMX 60 spectrometer using Me_4Si as internal standard. IR spectra were obtained on an Hitachi Model 260-10 infrared spectrometer. Mass spectral data were obtained with an Hitachi double focusing mass spectrometer RMU-7M. Commercial acetophenone and benzophenone were used without further purification. All α,β-unsaturated ketones were prepared by the Aldol condensation of the corresponding ketone with aldehyde.[8] Acrylonitrile and acrylamide were obtained commercially. Acrylonitrile was dried over molecular sieves 3A and was carefully fractionated at atomospheric pressure. Acrylamide was recrystallized from benzene.

Thioacetophenone. To a stirred suspension of acetophenone (9.6 g) and P_4S_{10} powder (7.1 g) in dry carbon disulfide (30 mL) was added dropwise triethylamine (6 mL) at 10–15 °C. The mixture was stirred at room temperature for 1 h and filtered and the filtrate was evaporated. The deep-purple residue was distilled to give thioacetophenone (**3 g**): bp 55 °C (0.3 mm) [lit.[5] bp 78–82 °C (1 mm)].

Thiobenzophenone. A suspension of benzophenone (18.2 g), P_4S_{10} powder (6.7 g), and triethylamine (10 mL) was gently refluxed for 1 h under nitrogen atmosphere. After the reaction was over, the mixture was filtered and the filtrate was evaporated. The deep-blue residue was distilled to give thiobenzophenone (**15 g**): bp 127–131 °C (0.04–0.06 mm) [lit.[5] bp 129–133 °C (0.06 mm)].

A Typical Procedure for the Preparation of α,β-Unsaturated Thione Dimers. A suspension of chalcone (0.01 mol), P_4S_{10} powder (1 g), and triethylamine (1 mL) in dry carbon disulfide (20 mL) was allowed to stand at 20–25 °C under nitrogen atmosphere for 1 day. The reaction mixture was filtered and the filtrate was evaporated. The residue was chromatographed on Florisil gel (25 g) using ligroin–benzene (1:1) as the eluent. The solvent was evaporated and the residue was recrystallized from benzene–ethanol giving thiochalcone dimer (**3a**) as blue crystals: mp 134–135 °C; MS (70 eV) *m/e* 224 (12), 223 (100); NMR (CCl_4) δ 3.96 (dd, 1 H, *J* = 3.5 and 6.6 Hz), 4.95 (d, 1 H, *J* = 11.5 Hz), 5.18 (dd, 1 H, *J* = 3.5 and 11.5 Hz), 6.23 (d, 1 H, *J* = 6.6 Hz), and 6.9–7.8 (m, 20 H). Anal. Calcd for $C_{30}H_{24}S_2$: C, 80.32; H, 5.39; S, 14.29. Found: C, 80.12; H, 5.51; S, 14.20.

4'-Methoxythiochalcone dimer 3b: mp 145–148 °C (lit.[2] mp 151–152 °C); NMR ($CDCl_3$) δ 3.76 (s, 3 H), 3.82 (s, 3 H), 4.06 (dd, 1 H, *J* = 3.6 and 6.6 Hz), 5.06 (d, 1 H, *J* = 11 Hz), 5.38 (dd, 1 H, *J* = 3.6 and 11 Hz), 6.28 (d, 1 H, *J* = 6.6 Hz), and 6.8–7.8 (m, 18 H). Anal. Calcd for $C_{32}H_{28}O_2S_2$: C, 75.55; H, 5.54; S, 12.60. Found: C, 75.64; H, 5.71; S, 12.66. The NMR spectrum is identical with that reported by Quiniou et al.[2].

2-Benzylidene-1-thiotetralone dimer 4a: mp 171–172 °C; MS (70 eV) *m/e* 250 (39), 249 (100); NMR (CCl_4) δ 2.0–3.1 (m, 8 H), 3.6 (s, 1 H), 5.6 (s, 1 H), and 6.9–7.5 (m, 18 H). Anal. Calcd for $C_{34}H_{28}S_2$: C, 81.56; H, 5.63; S, 12.81. Found: C, 81.91; H, 5.78; S, 12.94.

2-(*p*-Methoxybenzylidene)-1-thiotetralone dimer 4b: mp 135–136 °C; MS (15 eV) *m/e* 560 (M^+, 6), 280 (47), 279 (88); NMR ($CDCl_3$) δ 2.0–3.1 (m, 8 H), 3.6 (s, 1 H), 3.7 (s, 3 H), 3.8 (s, 3 H), 5.6 (s, 1 H), and 6.6–7.3 (m, 16 H). Anal. Calcd for $C_{36}H_{32}O_2S_2$: C, 77.11; H, 5.75; S, 11.43. Found: C, 77.42; H, 5.87; S, 11.15.

2-(*p*-Chlorobenzylidene)-1-thiotetralone dimer 4c: mp 173–174 °C: MS (15 eV) *m/e* 569 (M^+, 1), 285 (54), 284 (94), 283 (100), 250 (20), 249 (93); NMR ($CDCl_3$) δ 1.78–2.38 (m, 2 H), 2.62–3.17 (m, 6 H), 3.65 (s, 1 H), 5.60 (s, 1 H), and 6.85–8.27 (m, 16 H). Anal. Calcd for $C_{34}H_{26}S_2Cl_2$: C, 71.69; H, 4.60; S, 11.26. Found: C, 71.49; H, 4.48; S, 11.30.

A Typical Procedure for the Thermolysis of α,β-Unsaturated Thione Dimers with Acrylonitrile. A suspension of thiochalcone dimer (0.448 g, 1 mmol) in acrylonitrile (8 mL) was gently refluxed for 0.5 h under nitrogen atomosphere. The excess acrylonitrile was removed and recrystallization of the residue from 30 mL of ligroin gave 3-cyano-4,6-diphenyl-3,4-dihydro-2*H*-thiopyran (**10a**) (0.245 g) as colorless needles: mp 131–132 °C; MS (70 eV) *m/e* 277 (M^+, 11), 224 (58), 223 (100); IR (KBr) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 3.0–3.5 (m, 3 H), 3.9 (t, 1 H, *J* = 5.0 and 4.8 Hz), 6.1 (d, 1 H, *J* = 4.8 Hz), and 7.2–7.8 (m, 10 H). Anal. Calcd for $C_{18}H_{15}NS$: C, 77.97; H, 5.45; S, 11.55. Found: C, 77.65; H, 5.31; S, 11.46.

3-Cyano-6-(*p*-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-thiopyran (10b): mp 95–98 °C (recrystallized from ligroin); MS (70 eV) *m/e* 307 (M^+, 19), 254 (61), 253 (100); IR (KBr) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 3.0–3.5 (m, 3 H), 3.8 (s, 3 H), 3.8–4.0 (m, 1 H), 5.9 (d, 0.5 H, *J* = 4.0 Hz), 6.0 (d, 0.5 H, *J* = 4.8 Hz), and 6.8–7.5 (m, 9 H). Anal. Calcd for $C_{19}H_{17}NOS$: C, 74.27; H, 5.54; S, 10.43. Found: C, 74.51; H, 5.66; S, 10.22.

3-Cyano-4-phenyl-5,6-dihydrobenzo[*h*]thiochroman (12a): mp 223–225 °C (recrystallized from benzene–ligroin); MS (70 eV) *m/e* 303 (M^+, 28), 250 (39), 249 (100); IR (KBr) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 2.0–3.6 (m, 7 H), 3.8 (d, 1 H, *J* = 3.5 Hz), and 7.0–7.6 (m, 9 H). Anal. Calcd for $C_{20}H_{17}NS$: C, 79.17; H, 5.65; S, 10.57. Found: C, 79.12; H, 5.77; S, 10.70.

2(or 3)-Cyano-4-(*p*-methoxyphenyl)-5,6-dihydrobenzo[*h*]-thiochroman (12b): mp 126–128 °C (recrystallized from ligroin); MS (70 eV) *m/e* 333 (M^+, 54), 280 (69), 279 (100); IR (KBr) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 2.0–2.3 (m, 2 H), 2.56–3.3 (m, 5 H), 3.6–3.86 (4 H), and 6.8–7.56 (m, 8 H). Anal. Calcd for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74; S, 9.61. Found: C, 75.75; H, 5.65; S, 9.74.

3-Cyano-4-(*p*-chlorophenyl)-5,6-dihydrobenzo[*h*]thiochroman (12c): mp 130–132 °C (recrystallized from ligroin); MS (70 eV) *m/e* 337 (M^+, 50), 284 (50), 283 (86), 249 (100); IR (KBr) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 2.0–3.5 (m, 7 H), 3.7 (d, 1 H, *J* = 4.0 Hz), and 7.0–7.6 (m, 8 H). Anal. Calcd for $C_{20}H_{16}ClNS$: C, 71.11; H, 4.74; S, 9.49. Found: C, 71.23; H, 4.80; S, 9.40.

A Typical Procedure for the Thermolysis of α,β-Unsaturated Thione Dimers with Acrylamide. A solution of thiochalcone dimer (0.448 g, 1 mmol) and acrylamide (0.142 g, 2 mmol) in dry benzene (8 mL) was gently refluxed for 0.5 h under nitrogen atomosphere. The benzene was removed and recrystallization of the residue from ethanol

gave 3-carbamoyl-4,6-diphenyl-3,4-dihydro-2*H*-thiopyran (**13a**) (0.236 g) as colorless crystals: mp 223–224 °C; MS (70 eV) *m/e* 295 (M^+, 22), 224 (59), 223 (100); IR (KBr) 1660 cm^{-1} (C=O); NMR (Me_2SO) δ 4.16 (dd, 1 H, J = 7 and 4 Hz), 6.2 (d, 1 H, J = 7 Hz), 6.9 (br band, 2 H), and 7.0–7.6 (m, 10 H). Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; S, 10.85. Found: C, 73.21; H, 5.86; S, 10.88.

3-Carbamoyl-6-(*p*-methoxyphenyl)-4-phenyl-3,4-dihydro- (14a): mp 174–176 °C (recrystallized from benzene); MS (70 eV) *m/e* 321 (M^+, 52), 250 (44), 249 (100); IR (KBr) 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.7–2.26 (m, 2 H), 2.56–3.2 (m, 5 H), 3.9 (d, 1 H, J = 6 Hz), 5.6 (br band, 2 H), and 6.9–7.6 (m, 9 H). Anal. Calcd for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; S, 9.97. Found: C, 74.98; H, 6.04; S, 9.95.

3-Carbamoyl-4-(*p*-methoxyphenyl)-5,6-dihydrobenzo[*h*]- thiochroman (14b): mp 175–176 °C (recrystallized from benzene); MS (70 eV) *m/e* 351 (M^+, 79), 280 (42), 279 (64); IR (KBr) 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.9–3.1 (m, 7 H), 3.7 (s, 3 H), 3.9 (d, 1 H, J = 6 Hz), 5.5 (br band, 2 H), and 6.7–7.5 (m, 8 H). Anal. Calcd for $C_{21}H_{21}NO_2S$: C, 71.79; H, 5.98; S, 9.12. Found: C, 71.74; H, 5.96; S, 9.00.

3-Carbamoyl-4-(*p*-chlorophenyl)-5,6-dihydrobenzo[*h*]thio- chroman (14c): mp 138–140 °C (recrystallized from benzene); MS (70 eV) *m/e* 355 (M^+, 28), 284 (17), 283 (29), 249 (36); IR (KBr) 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.9–3.1 (m, 7 H), 3.9 (d, 1 H, J = 3 Hz), 5.8 (br band, 2 H), and 7.0–7.5 (m, 8 H). Anal. Calcd for $C_{20}H_{18}ClNOS$: C, 67.51; H, 5.06; S, 9.01. Found: C, 67.52; H, 5.11; S, 8.97.

Registry No.—**10b** isomer 1, 67254-69-7; **10b** isomer 2, 67254-70-0; acrylonitrile, 107-13-1; acrylamide, 79-06-1; acetophenone 98-86-2; tetraphosphorus decasulfide, 12066-62-5; chalcone, 94-41-7; 4′-methoxychalcone, 959-33-1; 2-benzylidene-1-tetralone, 6261-32-1; 2-(*p*-methoxybenzylidene)-1-tetralone, 49629-37-0; 2-(*p*-chlorobenzylidene)-1-tetralone, 49545-70-2.

References and Notes

(1) D. C. Sen, *J. Indian Chem. Soc.*, **13**, 268 (1936); D. A. Winkler and S. A. Ballard, U.S. Patent 2443811 (1948); R. Bourdon, *Bull. Soc. Chim. Fr.*, 722 (1958); F. A. King, *Chem. Ber.*, **93**, 1043 (1960); Y. Kitahara and M. Funamizu, *Bull. Chem. Soc. Jpn.*, **37**, 1897 (1964); T. Eicher and G. Frenzel, *Z. Naturforsch.*, **20**, 274 (1965); P. Metzner and J. Vialle, *Bull. Soc. Chim. Fr.*, 3739 (1970); H. Hartmann and R. Mayer, D.D.R. Patent 73753, *Chem. Abstr.*, **71**, 53302j (1971); P. Metzner, *Bull. Soc. Chim. Fr.*, 3138 (1972).
(2) J. P. Pradere, G. Bouet, and H. Quiniou, *Tetrahedron Lett.*, 3471 (1972).
(3) G. Jacqmin, J. Nasielsky, G. Billy, and M. Remy, *Tetrahedron Lett.*, 3655 (1973).
(4) K. B. Lipkowitz and B. P. Mundy, *Tetrahedron Lett.*, 3417 (1977).
(5) E. Campaigne, "The Chemistry of the Carbonyl Group", S. Patai, Ed., Interscience, New York, N.Y., 1966, p 934; J. W. Scheeren, P. H. J. Ooms, and R. J. F. Nivard, *Synthesis*, 149 (1973).
(6) O. Eisenstein, J. M. Lefour, and NG. T. Anh, *Tetrahedron*, **33**, 523 (1977).
(7) We can account for the regioselectivity in these cycloadditions by frontier molecular orbital theory. A simple qualitative frontier orbital treatment of the reaction between methyl vinyl thione,[4] selected as a model for α,β-unsaturated thiones, and olefins,[7a] (C=CZ, Z = CN, CHO) is represented in Figure 1, and application of the "hard and soft" concept allows us to predict that the first bond would link the softest centers,[7b] i.e., atom 4 with 1′ to give **15**. (a) K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973). (b) G. Desimoni and G. Tacconi, *Chem. Rev.*, **75**, 651 (1975).
(8) E. P. Kohler and H. M. Chadwell, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1932, p 78. A. Hassner, N. H. Cromwell, and S. J. Davis, *J. Am. Chem. Soc.*, **79**, 230 (1957).

Synthesis and Reactions of Some *N*-Acylated and *N*-Sulfonylated *N,N′*-Dialkylureas

R. Richter,* B. Tucker, and H. Ulrich

The Upjohn Company, D. S. Gilmore Research Laboratories, North Haven, Connecticut 06473

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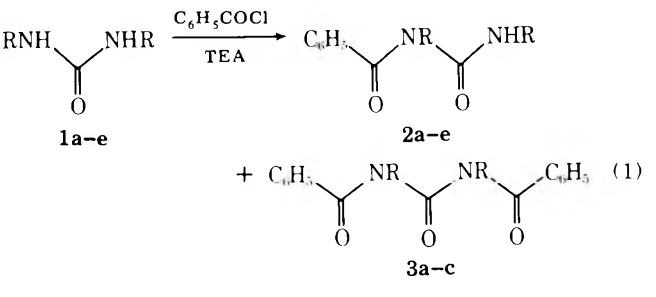
N,N′-Dialkylureas (**1**) are *N*-mono or *N,N′*-diacylated on treatment with various acyl chlorides: benzoyl chloride/base leads to *N*-benzoyl- and/or *N,N′*-dibenzoylureas (**2** and **3**). Similarly, cyclic *N*-mono- and *N,N′*-bisarenesulfonyl) ureas (**4** and **5**) are formed on reacting arenesulfonyl chlorides with imidazolidin-2-one and perhydropyrimidin-2-one. *N*-Benzoyl-*N′*-oxamoylureas (**12**) are obtained on successive treatment of **2** with oxalyl chloride and arylamine. Several *N*-benzoyl-*N′*-oxamoylureas undergo facile skeletal rearrangement on heating in methanol, yielding 1-aryl-3-(ω-benzamidoalkyl)imidazolidine-2,4,5-triones (**13**).

N,N′-Disubstituted ureas react with acylating agents on either the nitrogen or the carbonyl oxygen with formation of *N*- or *O*-acylated products. Evidence has been presented that many *N*-acylations of amides involve an initial attack on the more nucleophilic carbonyl oxygen; the thereby formed *O*-acylated intermediates rapidly rearrange to the thermodynamically more stable *N*-acylated products.[1] Detailed reports describing the synthetically important reactions of substituted ureas with phosgene and thionyl and phosphoryl chloride have been published.[2] Recently, we reported the *N*-benzoylation of cyclic *N,N′*-dialkylureas which lead to products of potential interest as masked isocyanates.[3] In conjunction with this work we investigated the feasibility of acylating and sulfonylating certain linear and cyclic *N,N′*-dialkylureas on both nitrogen atoms[4] and studied subsequent reactions of some of the obtained products. Treatment of *N,N′*-dimethylurea (**1a**) with molar amounts of benzoyl chloride in methylene chloride solution, using triethyl amine as an HCl scavenger, produces *N,N′*-dimethyl-*N*-benzoylurea (**2a**) in 81% yield and small amounts of *N,N′*-dimethyl-*N,N′*-dibenzoylurea (**3a**) (excess benzoyl chloride produces **3a** exclusively). Cyclic five- and six-membered ring ureas, such as imidazolidin-2-one (**1b**) and hexahydropyrimidin-2-one (**1c**), give mixtures of *N*-mono and



(1)

R = CH_3; R–R = $-(CH_2)_n-$; n = 2–5

N,N′-dibenzoylated products **2b,c** and **3b,c** under identical conditions while seven- and eight-membered ring ureas, i.e., perhydro-1,3-diazepin-2-one (**1d**) and perhydro-1,3-diazocin-2-one (**1e**), again produce *N*-monobenzoylated products exclusively.[3] Yields and melting points of all new compounds are presented in Table I.

The reaction of *N,N′*-dialkylureas with arenesulfonyl chlorides proceeds by O attack and subsequent elimination of sulfonic acid to give carbodiimides.[5,6] Treatment of the acyclic urea **1a** with benzenesulfonyl chloride and triethylamine in chloroform solution does indeed give *N,N′*-di-

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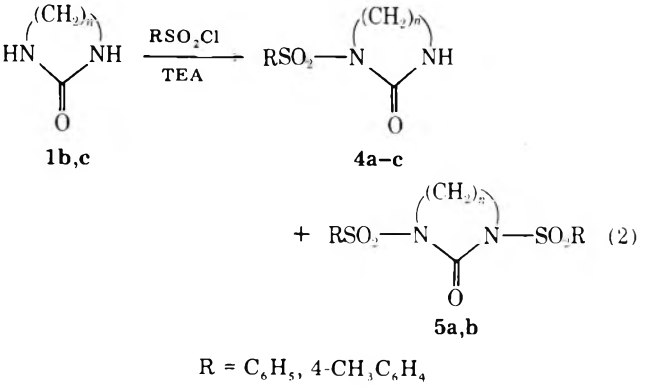
Table I. *N*-Acylated and -Sulfonylated Ureas and Their Rearrangement Products [a]

compd no.	registry no.	R	R'	*n*	mp, °C	yield, %
2a	67488-19-1	CH_3			97–98	88
2b	27034-77-1	$-(CH_2)_2-$			171–172	53[b]
2c	54236-66-7	$-(CH_2)_3-$			144–145	30[c]
3a	67488-20-4	CH_3			162–163	66
3b	5391-42-4	$-(CH_2)_2-$			240	27
3c	54236-74-7	$-(CH_2)_3-$			230[e]	50
4a	57451-91-9	C_6H_5		2	153–154	18[d]
4b	67488-21-5	p-$CH_3C_6H_4$		2	165–167	15
4c	67488-22-6	C_6H_5		3	208	18[f]
5a	67488-23-7	C_6H_5		2	193–194	60
5b	67488-24-8	p-$CH_3C_6H_4$		2	218	36
11b	67488-25-9			2	210	82
12a	67488-26-0	C_6H_5	H	2	205–207	84
12b	67488-27-1	C_6H_5	H	3	257	86
12c	67488-28-2	C_6H_5	H	4	166–168	quant
12d	67488-29-3	C_6H_5	H	5	160–161	81
12e	67488-30-6	C_6H_5	CH_3	2	182	95
12f	67488-31-7	C_6H_5	CH_3	5	108–110	50
13a	67488-32-8			2	174–176	74[g]
13b	67488-33-9			3	123	86
13c	67488-34-0			4	128	91
13d	67488-35-1			5	132–133	93[h]

[a] Satisfactory analytical values (±0.3% for C,H,N) were reported for all compounds. [b] 27% of **3b** is obtained as byproduct. [c] 50% of 3c is obtained as byproduct. [d] 20% of **5a** is obtained as byproduct. [e] Soft at 218 °C. [f] A 37% yield is obtained with 2 equiv of benzenesulfonyl chloride. [g] From *N*-phenyl-*N'*-(β-benzamidoethyl)urea and oxalyl chloride. [h] A 45% yield is obtained from *N*-phenyl-*N'*-(5-benzamidopentyl)urea and oxalyl chloride.

methylcarbodiimide as evidenced by infrared spectroscopy. Since it is unlikely that carbodiimides are produced from the cyclic ureas **1b–e** on treatment with arenesulfonyl chloride it was of interest to investigate if rearrangement to *N*-sulfonylated products would occur.[7]

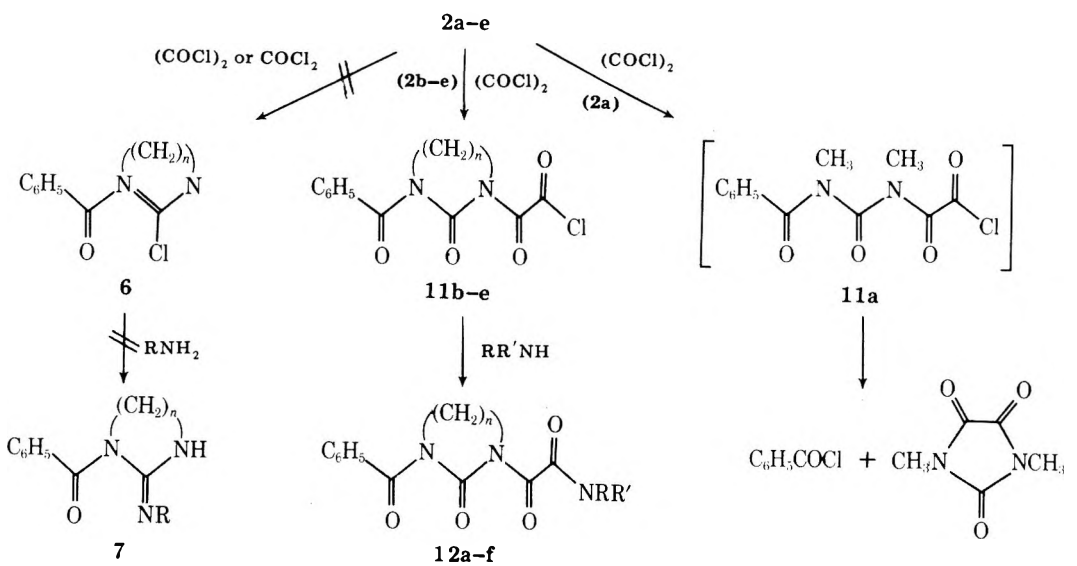
Treatment of **1b** and **1c** with benzene or *p*-toluenesulfonyl chloride in hot dimethoxyethane solution in the presence of triethylamine indeed gives mixtures of *N*-mono and/or *N,N'*-disulfonylated products **4a,b** and **5a,b** depending upon reaction conditions. Heating of molar amounts of **1b** and benzenesulfonyl chloride produces a mixture of **4a** (20%) and **5a** (18%) while reaction of **1b** with *p*-toluenesulfonyl chloride under similar conditions affords only the monosulfonylated urea **4b.** Heating of **1b** with 2 equiv of benzene or *p*-toluenesulfonyl chloride leads to formation of only the disulfonylated products **5a** and **5b.** The propyleneurea **1c** gives solely the monosulfonylurea **4c** on heating with benzenesulfonyl chloride in the presence of base regardless of reaction conditions. No



R = C_6H_5, 4-$CH_3C_6H_4$

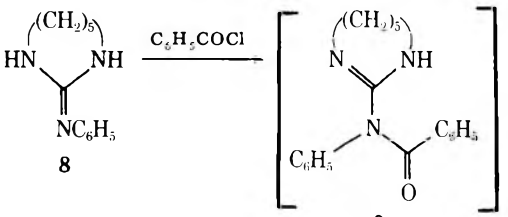
sulfonylated products could be obtained with the larger ring ureas **1d** and **1e** under a variety of conditions. The yields of all sulfonylated ureas (**4** and **5**) are low when compared with the *N*-benzoylated products (see Table I). This could in part

Scheme I

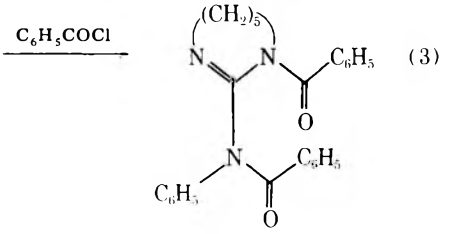


be due to a failure of *O*-sulfonylated intermediates to rearrange to *N*-sulfonylated products.[8] Compounds **4a–c** and **5a,b** are, to our knowledge, the only ureas of this kind obtained by sulfonylation with sulfonyl chlorides, a reaction which previously has not been observed.[11]

It was anticipated that the cyclic benzoylated ureas of type **2** would react with phosgene or oxalyl chloride via *O*-acylated intermediates to form *N*-benzoylated chloroformamidines **6** (Scheme I) which, on treatment with amine, would afford alicyclic guanidines **7** bearing a benzoyl group on one of the ring nitrogens. An attempt to prepare these compounds by benzoylation of the parent guanidines failed: octahydro-1,3-diaza-2-(*N*-phenylimino)cyclooctane (**8**) (prepared from **2e**, phosphoryl chloride, and aniline by analogy to a known procedure[12]) does not yield the 2-(*N*-phenylbenzamido) derivative **9**. Instead, the *N,N'*-dibenzoylated guanidine **10** is formed, regardless of the molar ratio of benzoyl chloride used (eq 3). H-NMR analysis of **10** excluded the presence of the equally possible dibenzoylated guanidine with both aroyl groups on the ring nitrogens.



8 **9**

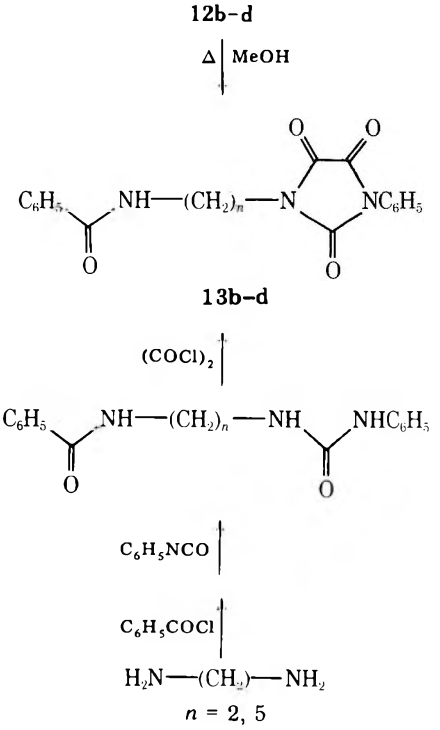


10

In pursuing the approach outlined above, we found that phosgene does not react with **2e** at room or slightly elevated temperature. Oxalyl chloride, however, reacts readily with **2e** as well as all the other cyclic benzoylated ureas affording *N*-benzoyl-*N'*-chlorooxoacetylureas **11b–11e** in virtually quantitative yield. The reactions, which are followed by IR, are generally completed within a few hours. Only in the case of **11b** was the chloride isolated in pure form; the compound proved to be surprisingly stable at ordinary conditions and could be recrystallized from acetone/hexane without noticeable decomposition. In all other cases, however, the crude reaction solutions of **11b–e** when treated with aromatic amines afford the corresponding *N*-benzoyl-*N'*-(*N*-aryloxamoyl)-ureas **12b–e** in high yields. The highly crystalline oxamides show a characteristic carbonyl band in the IR spectra (in $CHCl_3$) at 1680 cm^{-1} and a weaker band for the urea carbonyl group between 1715 and 1770 cm^{-1}, depending upon ring size. All H-NMR spectra are in agreement with the proposed structural formulas. A similar reaction between the acyclic urea **2a** and oxalyl chloride requires about 40 h for completion and produces a mixture of 1,3-dimethylimidazolidinetrione (*N,N'*-dimethylparabanic acid) and benzoyl chloride in high yield. Both compounds are probably formed via internal quaternization of the initially formed chloride **11a** (see Scheme I).

Several of the diacylureas of type **12** prepared from aniline and **11** proved to be rather labile compounds and were readily rearranged to 1-aryl-3-(ω-benzamidoalkyl)imidazolidine-2,4,5-triones **13** (parabanic acid derivatives) on brief heating in methanol. The rearrangement of this type was so facile in

Scheme II



the case of **12d** that methanol workup of crude products from the reaction of **11d** with aniline (Scheme I) lead to complete conversion to **13d.** The imidazolidintriones **13** show in the IR spectra (in $CHCl_3$) carbonyl bands characteristically different from the isomeric ureas **12:** a very sharp and intense band is found around 1740 cm^{-1} for all compounds; the H-NMR spectra are also in agreement with the proposed structure. Additional proof for the proposed structural formulas was obtained through independent synthesis of **13d** from 1,5-diaminopentane in several steps (see Scheme II). Since **13b** is formed readily on opening the relatively stable pyrimidine ring in **12b,** it was surprising to find that the ethyleneurea derivative **12a** could not be rearranged to the corresponding parabanate **13a** even on heating in methanol for 18 h (which led only to partial degradation of the molecule). To assure that **12a** had indeed the proposed structure, the isomeric **13a** was synthesized via the sequence outlined for **13d** in Scheme II.

The fact that the rearrangements proceed in a protic solvent like methanol seems to suggest an addition–elimination step involving ROH. It is remarkable that these reactions are relatively clean and produce high yields of **13** especially since bond cleavage prior to ring closure could occur at several places and not exclusively between the urea 1,2-(N–C) linkage. In an attempt to catalyze the rearrangememt of **12b** by adding small amounts of aniline to the methanolic reaction medium *N,N'*-diphenyl oxanilide was formed as byproduct resulting from cleavage of the exocyclic N–C bond at position 3 of the urea.

Since only oxamoyl derivatives with NH protons are capable of recyclization to parabanates, it was not expected that the fully substituted **12e** and **12f** would undergo a similar rearrangement in methanol. However, it was hoped that opening of the urea ring would occur, giving some insight into the reaction mechanism which operates in the above described ring rearrangements. It was, therefore, surprising to find that **12f** does not undergo ring opening in refluxing methanol.

Experimental Section[13]

A. Benzoylation of Ureas. *N,N'*-Dimethyl-*N*-benzoylurea (2a) was prepared by adding a solution of 5.0 g (0.05 mol) of triethylamine in 30 mL of dichloromethane dropwise over a period of 50 min to 4.40

g (0.05 mol) of N,N'-dimethylurea (**1a**) and 7.0 g (0.05 mol) of benzoyl chloride, dissolved in 30 mL of dichloromethane. Toward the end of the addition triethylamine hydrochloride precipitated. After 2.5 h of reaction time, the solvent was removed in vacuo and the solid residue was suspended in water. Solid **2a** (8.48 g) was collected and dried. Recrystallation from methanol containing small amounts of water gave colorless crystals; yield and mp are given in Table I.

Occassionally, samples of **2a** were contaminated by trace amounts of **3a**, which were difficult to remove by recrystallization, but both compounds could be separated by column chromatography on silica gel (Biorad Bio-Sil A) with toluene–acetone (9:1) as eluent.

***N,N'*-Dimethyl-*N,N'*-dibenzoylurea (3a)** was obtained in a procedure similar to the one given above: 0.02 mol of N,N'-dimethylurea (**1a**) was reacted with 0.04 mol of benzoyl chloride and triethylamine each and gave on trituration with water 3.90 g (66%) of **3a**, which was recrystallized from methanol (large prisms); for yield and mp see Table I.

1-Benzoylimidazolidin-2-one (2b) and 1,3-Dibenzoylimidazolidin-2-one (3b). To a suspension of 10.0 g (0.116 mol) of imidazolidin-2-one (**1b**) in 70 mL of chloroform, containing 10.0 g (0.1 mol) of triethylamine, was added dropwise 14.0 g (0.1 mol) of benzoyl chloride in 40 mL of chloroform over a period of 100 min. A clear solution was obtained from which triethylamine hydrochloride separated on standing for several hours. Removal of solids left a filtrate which was evaporated to dryness in vacuo. The obtained solid residue was treated with ca. 100 mL of water, stirred for 30 min, and filtered and gave 14.30 g of a mixture of **2b** and **3b** as evidenced by IR. Repeated treatment of the crude product with methanol (3 × 75 mL) left 4.0 g of **3b**, which was recrystallized from acetone/hexane (colorless needles). The monobenzoyl derivative was obtained on evaporating the methanolic filtrates, which left 10.1 g of crude **2b**, which was recrystallized from acetone/hexane (colorless plates); yields and mp are given in Table I.

1-Benzoylhexahydropyrimidin-1-one (2c) and 1,3-Dibenzoylhexahydropyrimidin-2-one (3c). A solution of benzoyl chloride (70 g, 0.05 mol) in 40 mL of acetonitrile was added dropwise over a period of 30 min to a stirred suspension of 5.0 g (0.05 mol) of hexahydropyrimidin-2-one (**1c**) in 75 mL of acetonitrile at 80 °C. On additional stirring for 60 min a clear solution was obtained to which 5.0 g (0.05 mol) of triethylamine in 20 mL of acetonitrile was added dropwise, causing the separation of a colorless precipitate which dissolved on heating the mixture for another 2 h at 90 °C. Triethylamine hydrochloride precipitated on cooling in an ice bath.

Filtration and concentrating the filtrate in vacuo left a semisolid mass which was diluted with water and filtered. The residue, 3.95 g, contained exclusively the dibenzoylated urea **3c** which was recrystallized for analysis from DMF/MeOH/H_2O (colorless needles). The acetonitrile/water filtrate was further diluted with water leading to separation of 3.10 g of **2c**. Recrystallization from acetone/hexane gave colorless prisms of **2c**; yield and mp's are given in Table I.

The monobenzoylated ureas **2d** and **2c** were prepared as described earlier.[3]

B. Sulfonylation of Ureas. 1-Benzenesulfonylimidazolidin-2-one (4a) and 1,3-Bis(benzenesulfonyl)imidazolidin-2-one (5a). A suspension of 4.3 g (0.05 mol) of **1b** in 40 mL of 1,2-dimethoxyethane (DME) containing also 5.0 g (0.05 mol) of triethylamine and 8.8 g (0.05 mol) of benzenesulfonyl chloride was kept for 4.5 h in an oil bath at 65–70 °C during which time the urea slowly dissolved. Cooling the reaction solution to room temperature led to precipitation of triethylamine hydrochloride which was removed by filtration. A crystalline mixture of **4a** and **5a** (5.36 g) was obtained on evaporating the filtrate in vacuo to dryness and treating the oily residue with a small amount of water. Fractional crystallization of the crude mixture from acetone and gradual addition of water led to separation of **5a** (1.81 g, colorless needles) as first fraction followed by **4a** (2.01 g, colorless plates from methanol/water) as second fraction. Purity of both fractions was checked by IR and TLC; yields and mp's are given in Table I.

1,3-Bis(benzenesulfonyl)imidazolidin-2-one (5a) was formed exclusively on reacting **1b** with 2 equiv of benzenesulfonyl chloride and triethylamine under conditions as given in the procedure above (7 h reaction duration). Workup of the triethylamine hydrochloride free DME filtrate yielded 60% of **5a** in the form of colorless needles (acetone), identical by IR comparison with material obtained according to the procedure above.

1-(*p*-Toluenesulfonyl)imidazolidin-2-one (4b). A suspension of **1b** (4.3 g, 0.05 mol) in 40 mL of DME containing equimolar quantities of triethylamine and *p*-toluenesulfonyl chloride was kept at 90–95 °C for 7 h. Triethylamine hydrochloride precipitated during the reaction while **1b** slowly dissolved. After cooling the mixture to room temperature, the salt was filtered off and the yellow filtrate was concentrated in vacuo to yield an oil which was treated with water/methanol. Colorless crystals precipitated while unreacted *p*-toluenesulfonyl chloride was kept in solution. Filtration gave 1.86 g of **4b** which was recrystallized for analysis from chloroform/hexane yielding colorless prisms; yield and mp are given in Table I.

1,3-Bis(*p*-toluenesulfonyl)imidazolidin-2-one (5b) was prepared following a procedure similar to the one given above for **4b** using 2 equiv of *p*-toluenesulfonyl chloride and triethylamine per equiv of urea. The reaction filtrate, obtained after salt removal, concentrated in vacuo gave a semisolid mass which was taken up in a small amount of methanol. The product **5b**, which remained undissolved, was isolated by filtration and purified for analysis by recrystallization from acetone/water (colorless needles); for mp and yield see Table I.

1-Benzenesulfonylhexahydropyrimidin-2-one (4c) was obtained on heating a DME solution of 5.0 g (0.05 mol) of **1c** with 0.1 mol each of benzenesulfonyl chloride and triethylamine for 7 h at 90 °C. The product **4c** was isolated from the reaction mixture following procedures given for the preparation of **4a** and **4b**; the crude product was recrystallized from acetone/water (colorless prisms). Using an excess of sulfonyl chloride/base in this reaction produced a higher yield (37%) while equivalent amounts of all reagents gave only an 18% yield of **4c**.

Octahydro-1,3-diaza-2-(*N*-phenylimino)cyclooctane (8). Dropwise addition of a benzene solution (10 mL) of 1.35 g (0.01 mol) of phosphoryl chloride to 1.28 g (0.0 mol) of urea **1d** in 10 mL of benzene was leading to separation of a colorless oil which solidified after several hours. After 8 h of standing at room temperature aniline (1.86 g, 0.02 mol), dissolved in 10 mL of benzene, was added dropwise to the stirred suspension thereby transforming the phosphoryl chloride adduct into an amber oil. The mixture was refluxed for 5–6 h after which the benzene was decanted from the honeylike residue. Treatment of the residue with aqueous sodium hydroxide led to separation of solid **8** mixed with aniline; filtration after cooling in ice left 2.0 g (quantitative) of **8** which was recrystallized from methanol/water giving colorless crystals: mp 127–129 °C; IR ($CHCl_3$) 1620 cm^{-1} (C=N). Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.54; H, 8.77; N, 20.57.

Hexahydro-1,3-diaza-1-benzoyl-2-(*N*-phenylbenzamido)cyclooctene-2 (10). A solution of guanidine **8** (0.41 g, 0.002 mol) in 10 mL of chloroform was treated with 0.56 g (0.004 mol) of benzoyl chloride dissolved in 10 mL of chloroform followed by addition of excess triethylamine (1.0 g, 0.01 mol) to neutralize the formed hydrogen chloride. After brief heating to 50–60 °C the reaction mixture was kept at room temperature for 1 h. Solvent evaporation in vacuo left a semisolid residue which crystallized on scratching and treatment with water. Filtration afforded 0.32 g (100%) of **10**: mp 172 °C (methanol); IR ($CHCl_3$) 1630 cm^{-1} (C=N) with shoulders at 1650 cm^{-1} (C=O). Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21. Found: C, 75.78; H, 6.25; N, 10.77.

C. *N*-Benzoyl-*N'*-oxamidoureas and Precursors. Reaction of *N,N'*-Dimethyl-*N*-benzoylurea (2a) with Oxalyl Chloride. A solution of 3.82 g (0.02 mol) of **2a** and 2.52 g (0.02 mol) of oxalyl chloride in 30 mL of dichloromethane was kept at room temperature for 68 h. The progress of the reaction was observed by IR. Removal of the solvent in vacuo left a semisolid which, after trituration with hexane, was collected by filtration. Thus, 2.12 g (75%) of **1,3-dimethylimidazolidine-2,4,5-trione** was obtained. Evaporation of the filtrate gave 2.00 g (71% yield) of **benzoyl chloride.** Both products were identical in IR comparison and melting point with authentic samples.

1-Benzoyl-3-chlorooxoacetylimidazolidin-2-one (11b). Colorless crystals separated from a solution of 1.9 g (0.01 mol) of benzoylurea **1b** and 1.26 g (0.01 mol) of oxalyl chloride in 20 mL of chloroform on standing for 18 h. Filtration and washing with chloroform left 2.30 g of **11b** which was recrystallized for analysis from acetone/hexane (colorless needles); yield and mp are given in Table I.

1-Benzoyl-3-oxamoylimidazolidon-2-ones 12a and 12e were prepared by reacting the oxamoyl chloride **11b** with 3 equiv of aniline or *N*-methylaniline in chloroform at room temperature. The clear reaction solutions were concentrated after standing for 1 h and the solid residues were treated with water or water–methanol and **12a** and **12e** were collected by filtration. The crude products were recrystallized from acetone/water or acetone/hexane; yields and mp's are given in Table I.

1-Benzoyl-3-(*N*-phenyloxamoyl)hexahydropyrimidin-2-one (12b). Solutions of *N*-benzoylurea **1c** (2.04 g, 0.01 mol) in 50 mL of dichloromethane and oxalyl chloride (1.27 g, 0.01 mol) in 20 mL of the same solvent were mixed and kept at room temperature for 2 h after which 2.80 g (0.03 mol) of aniline, dissolved in 15 mL of CH_2Cl_2, was added slowly with stirring causing precipitation of aniline hydro-

chloride. The resulting suspension was kept at room temperature for 12 h. Filtration and concentration left a syrup which crystallized on scratching. The solid was suspended in water, filtered, and recrystallized from acetone/hexane giving colorless crystals.

The ***N*-benzoyl-*N'*-oxamoylureas 12c, 12d and 12f** were prepared following procedures similar to the one presented above employing dichloromethane or chloroform as solvents. Melting points and yields are given in Table I.

D. 1-Aryl-3-(ω-benzamidoalkyl)imidazolidine-2,4,5-triones (13b–d) from 12b–d (General Procedure). Suspensions of 1-benzoyl-3-oxamoylureas **12b–d** in methanol (ca. 1.0 g per 20–50 mL of solvent) were heated to reflux. The starting materials dissolved slowly and progress of the rearrangement was followed by TLC or IR. As soon as the reactions were complete (10 min to 2.5 h), part of the solvent was removed and water was added to precipitate the products, which were collected and purified for analysis by recrystallization from methanol/water. Extended heating of the methanolic solutions after completed rearrangement can cause further degradation of the parabanates and thus result in lower yields.

No rearrangement to **13a** was observed on prolonged heating of **12a** in methanol (18 h; the odor of methyl benzoate indicated partial cleavage in a different manner) or briefly in DMF or DMF/water.

1-Phenyl-3-(2-benzamidoethyl)imidazolidine-2,4,5-trione (13a) via Cyclization. *N*-Phenyl-*N'*-(2-benzamidoethyl)urea[14] (2.83 g, 0.01 mol) and oxalyl chloride (1.26 g, 0.01 mol) were heated to reflux for 1 h in 50 mL of dichloromethane. The resulting reaction solution was evaporated leaving an oily residue which was dissolved in acetone. Gradual addition of water to beginning turbidity and scratching caused separation of 2.48 g of **13a**; the crude material was recrystallized from methanol/water (colorless crystals); yield and mp are given in Table I.

In a similar manner, **1-phenyl-3-(5-benzamidopentyl)imidazolidine-2,4,5-trione (13d)** was obtained from *N*-phenyl-*N'*-(5-benzamidopentyl)urea[15] and oxalyl chloride in refluxing chloroform (45% yield).

Hydrolytic cleavage of **13d** in aqueous potassium hydroxyde–methanol (1:3) at room temperature yielded the corresponding *N*-phenyl-*N'* (5-benzamidopentyl)urea in 90% yield.

Registry No.—**1a**, 96-31-1; **1b**, 120-93-4; **1c**, 1852-17-1; **1d**, 19055-93-7; **8**, 67488-36-2; **10**, 67488-37-3; *N*-phenyl-*N'*-(β-benzamidoethyl)urea, 67488-38-4; oxalyl chloride, 79-37-8; *N*-phenyl-*N'*-(5-benzamidopentyl)urea, 67488-39-5; benzoyl chloride, 98-88-4; benzenesulfonyl chloride, 98-09-9; *p*-toluenesulfonyl chloride 98-59-9; aniline, 62-53-3; 1,3-dimethylimidazolidine-2,4,5-trione, 5176-82-9; 1,5-diaminopentane, 462-94-2; *N*-(5-aminopentyl)-*N'*-phenylurea, 67488-40-8.

References and Notes

(1) R. Huisgen and H. Brade, *Chem. Ber.*, **90**, 1432 (1957).
(2) H. Ulrich, "The Chemistry of Imidoylhalides", Plenum Press, New York 1968, p 117; H. Ulrich and A. A. R. Sayigh, *Angew. Chem., Int. Ed. Engl.*, **8**, 704 (1966).
(3) H. Ulrich, B. Tucker, and R. Richter, *J. Org. Chem.*, **43**, 1544 (1978).
(4) The acylation of urea with acyl halides has been reported in detail: R. G. Stoughton, *J. Org. Chem.*, **2**, 514 (1938); R. G. Stoughton, H. L. Dickison, and O. G. Fitzhugh, *J. Am. Chem. Soc.*, **61**, 408 (1939).
(5) G. Amiard and R. Heynes, *Bull. Soc. Chim. Fr.*, 1360 (1956).
(6) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961).
(7) The formation of the eight-membered pentamethylene carbodiimide on desulfurizing the thiourea has been observed in solution: H. Behringer and H. Meier, *Justus Liebigs Ann. Chem.*, **607**, 67 (1957).
(8) There is only a small energy difference between S–N (111 ± 5 kcal/mol)[9] and S–O bonds (124.7 kcal/mol).[10]
(9) V. N. Kondratiev, "Bond Dissociation Energies, Ionization Potentials and Electron Affinities", Nauka Publishing House, Moscow, 1974.
(10) L. Brewer and G. M. Rosenblatt, *Adv. High Temp. Chem.*, **2**, 1 (1969).
(11) For references, see F. Kurzer, *Chem. Rev.*, **50**, 1 (1952).
(12) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).
(13) All melting points are uncorrected. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn., IR spectra (in $CHCl_3$) were determined using a Beckman Acculab 4 spectrophotometer; ^1H NMR spectra were determined with a Varian T-60 and ^{13}C NMR spectra with a Varian CFT 20 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard.
(14) O. Stoutland, L. Helgen, and C. L. Agre, *J. Org. Chem.*, **24**, 818 (1959).
(15) This urea, mp 118–120 °C (Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.25; H, 7.13; N, 12.89) was prepared in quantitative yield in analogy to literature procedures[14] from 1,5-diaminopentane via *N*-(5-aminopentyl)-*N'*-phenylurea, mp 124–125 °C (4% yield; Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.12; H, 8.65; N, 18.99. Found: C, 65.15; H, 8.81; N, 18.87).

Pteridines. 45. Synthesis and Properties of Some Isothiazolo[4,5-*b*]pyrazines and Isothiazolo[4,5-*g*]pteridines[1,2]

Edward C. Taylor* and Eberhard Wachsen

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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Several isothiazolo[4,5-*b*]pyrazines and isothiazolo[4,5-*g*]pteridines were prepared utilizing 3-methyl- and 3-methylmercapto-4-nitroso-5-acetamidoisothiazole (**5a,b**) as key starting materials. All attempts to desulfurize these fused isothiazoles were uniformly unsuccessful. Reaction of 3-methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine (**6b**) with diethyl malonate in the presence of base unexpectedly resulted in the formation of the pyrido[2,3-*b*]isothiazolo[4,5-e]pyrazine **14** rather than cleavage of the isothiazole ring.

The classical synthetic route to pteridines involves condensation of a preformed 4,5-diaminopyrimidine with an appropriately functionalized two-carbon unit (e.g., an α-keto, α-hydroxy, or α-bromocarbonyl compound).[3] This so-called Isay route to pteridines, despite its attractive simplicity, suffers from the serious disadvantage that a mixture of structural isomers is formed when the two-carbon reaction component is itself unsymmetrical.[4] In addition, however, the requisite pyrimidine intermediates are often extremely insoluble and difficult to manipulate, and there are obvious structural limitations in the other reaction component which provides carbons 6 and 7 of the pteridine ring along with their associated substituents. Furthermore, pteridines are notoriously insoluble and chemically recalcitrant compounds whose chemical manipulation by the usual methods of synthetic organic chemistry poses severe problems. We have developed and exploited over the past few years an alternative synthetic pathway to pteridines which involves the prior synthesis of pyrazine (as opposed to pyrimidine) intermediates, followed by final annelation of the fused pyrimidine ring. This procedure possesses many chemical and manipulative advantages which have been summarized elsewhere.[5] However, since certain types of pteridine derivatives have thus far not been directly accessible by this latter pathway (e.g., acyl derivatives), we have a continuing interest in exploring new synthetic methodologies. The present paper describes a projected strategy for the preparation of 6-acyl derivatives via isothiazolo[4,5-*b*]pyrazines and isothiazolo[4,5-*g*]pteridines, both

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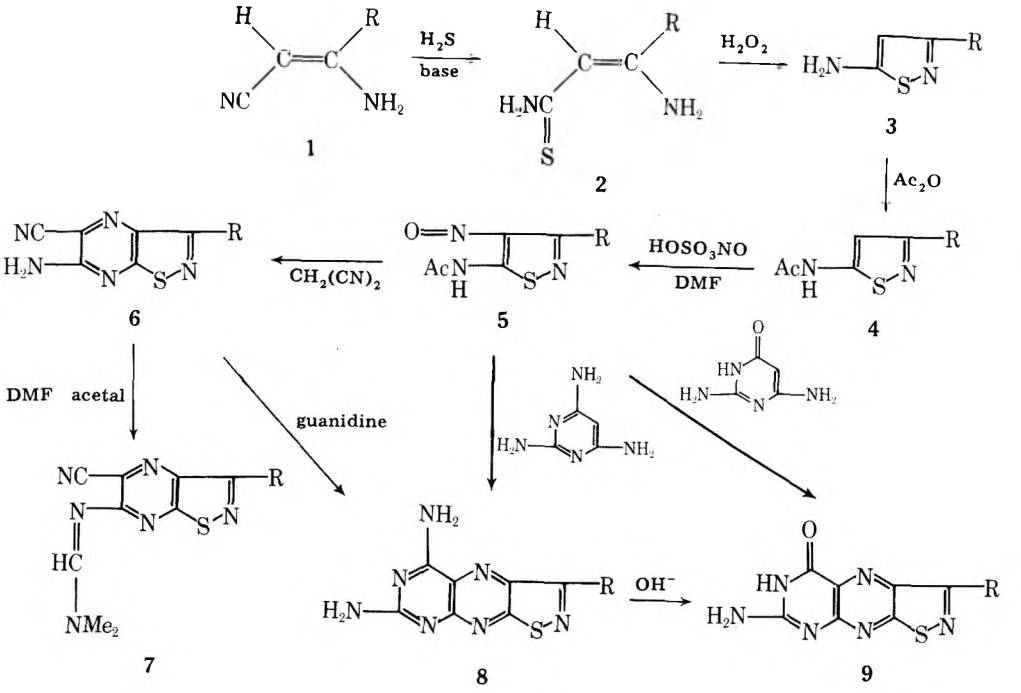
Scheme I



a, R = CH_3
b, R = SCH_3

of which possess potential carbonyl groups in the C=N unit of the isothiazole ring. Fused isothiazoles can be considered as latent amines, alkyl, or acyl groups, since they can be carried through a long synthetic sequence unscathed, to be destroyed in a final step by reductive desulfurization with release of the desired functionality (see, for example, Woodward's elegant colchicine synthesis,[6] and the recently described preparation of 6-amino-5-methylpyrimidines from isothiazolo[3,4-*d*]-pyrimidines).[7]

We have prepared several isothiazolo[4,5-*g*]pteridines as outlined in Scheme I. 5-Amino-3-methylisothiazole (**3**) was synthesized by the general method of Slack[8] and Goerdeler[9] by hydrogen peroxide oxidation of the thioamide **2a,** which is readily prepared by base-catalyzed addition of hydrogen sulfide to acetonitrile dimer (**1a**).[10] We found it best not to isolate **3a,** but to convert it directly with acetic anhydride to 3-methyl-5-acetamidoisothiazole (**4a**). The latter is a known compound,[9] but various modifications in the above synthetic sequence have resulted in a much improved preparation. The key intermediate in our projected synthesis of isothiazolo[4,5-*g*]pteridines was 3-methyl-4-nitroso-5-acetamidoisothiazole (**5a**), but its preparation from **4a** was not straightforward. Classical nitrosation procedures in acetic acid either with isoamyl nitrite or with sodium nitrite under many attempted reaction conditions were unsuccessful; in one attempt utilizing isoamyl nitrite a transient deep green color was observed, indicative of the formation of the desired **5a,** but this color shortly faded and the reaction mixture turned dark brown. Successful nitrosation of **4a** was finally achieved, however, utilizing nitrosyl hydrogen sulfate in dimethylformamide at room temperature.

Condensation of **5a** with malononitrile provided the isothiazolopyrazine **6a** in low (25–30%) yield.[11] Many variations in reaction conditions with aprotic and protic solvents, the use of varying amounts of different bases such as triethylamine, sodium methoxide, and pyridine, and inverse addition of reactants were explored, but in every case the reaction mixtures turned dark brown and contained large amounts of tarry material. We attribute this decomposition or polymerization to base-catalyzed reactions involving the acidic 3-methyl group[10] of the isothiazole component **5a,** since analogous cyclizations involving the corresponding 3-methylmercapto derivative (**5b,** vide infra) proceeded without complication in quantitative yield.

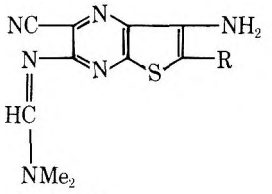
Condensation of the isothiazolopyrazine **6a** with guanidine gave 3-methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine (**8a**), which could alternatively be prepared in a single step by condensation of **5a** with 2,4,6-triaminopyrimidine. Similarly, condensation of **5a** with 2,4-diamino-6(1*H*)-pyrimidone gave the isothiazolo[4,5-*g*]pterin **9a,** which was also prepared by alkaline hydrolysis of the 5-amino group of **8a.**

We then explored the possible desulfurization of these fused isothiazole derivatives in an attempt to generate 2-amino-3-cyano-5-acetylpyrazine (from **6a**) and the corresponding 6-acetyl derivatives of 2,4-diaminopteridine (from **8a**) and of pterin itself (from **9a**). Raney nickel desulfurization is a well-established synthetic procedure in organic chemistry;[12] deactivation of the nickel by boiling in acetone for a short period is known to allow retention of desulfurization capabilities but to inhibit the reduction of carbonyl and other functional groups sensitive to hydrogenation.[13,14] Furthermore, the pyrazine ring should be stable to Raney nickel desulfurization conditions, since 3-hydroxypyrazolo[*b*]pyrazines are readily converted under these conditions to 2-amino-3-carboxamidopyrazines in moderate to good yield.[15]

All attempts to effect desulfurization of these isothiazole intermediates, however, proved fruitless. Neither **6a** nor its dimethylaminomethyleneamino derivative **7a** (prepared from **6a** and dimethylformamide dimethyl acetal) gave any identifiable product. Many different types of freshly prepared Raney nickel, such as W7,[16] W4,[17] and the modification described by Fieser and Fieser,[14] under many different types of conditions in which solvents, temperature, amounts of reagents, and time of reaction were all varied, were explored with **6a,** but similar discouraging results were obtained from every experiment. Reaction mixtures were all monitored by TLC until starting material had disappeared, but separation of the nickel and evaporation of solvent led only to small amounts of tarry residues which were completely absorbed on charcoal

in attempted purifications. Control experiments showed that pyrazines and pteridines closely related to the anticipated products could be treated with charcoal under similar conditions without any loss by absorption, and we conclude that complete destruction of the substrates took place under the above reaction conditions.

Similar discouraging results were obtained upon attempted Raney nickel desulfurization of thieno[2,3-*b*]pyrazines **10** (which should lead to 5-(1-aminoalkyl)pyrazines) and the 6-methylmercaptopyrazine **11**;[18] only small amounts of oily



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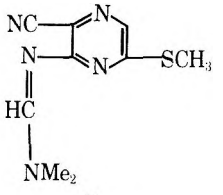

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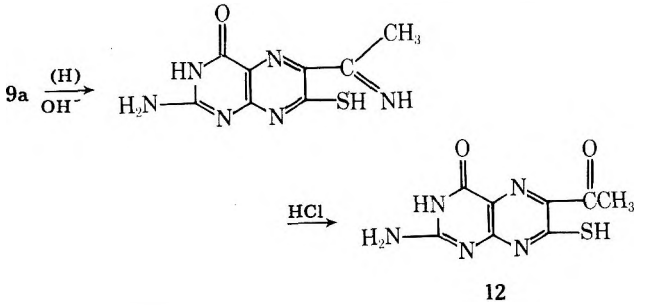
polymeric tars were formed, regardless of variations in the reaction conditions. It appears that pyrazinyl radicals, which are presumably formed upon homolytic cleavage of the C–S bond,[12] are inherently unstable and that, as a consequence, reductive desulfurization of sulfur-substituted pyrazines, regardless of the nature of the sulfur substituent, will probably be unsuccessful. This conclusion is unfortunately reinforced by our attempts to desulfurize the isothiazolopteridines **8a** and **9a**. Thus, attempted desulfurization of **9a** in 1% sodium hydroxide solution resulted again in the formation of a polymeric tar. Since 3-methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine (**8a**) was only soluble in acid, reductive desulfurization was attempted with Raney nickel (once prewashed with concentrated formic acid) in concentrated formic acid as solvent,[19] but a complex mixture of dark solids was obtained from which no identifiable single compound could be isolated.[20]

Chemical reduction of **9a** was also explored. Addition of sodium hydrosulfite to an alkaline solution of **9a** resulted in the immediate precipitation of the trihydrate of the sodium salt of **9a** (see Experimental Section). Addition of concentrated hydrochloric acid to this reaction mixture, followed by several hours of stirring at room temperature, gave an orange solid whose physical and spectral properties were consistent with structure **12**, the product of S–N hydrogenolysis followed



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by acid hydrolysis of the resulting imine. Once again, however, reductive desulfurization had not been achieved, despite the successful introduction of the desired acetyl grouping into the pteridine nucleus.

By a sequence of reactions analogous to those described in Scheme I for the preparation of **6a**, we prepared the corresponding 3-methylmercaptoisothiazolo[4,5-*b*]pyrazine **6b**. Thus, methylation of malonic acid dithioamide with methyl iodide gave 3-amino-3-methylmercaptoacrylthioamide (**2b**), which was oxidized with hydrogen peroxide to 3-methylmercapto-5-aminoisothiazole (**3b**); in contrast to the very labile **3a**, **3b** proved to be a stable crystalline solid. Acetylation of **3b** with acetic anhydride followed by nitrosation with nitrosyl hydrogen sulfate in dimethylformamide solution gave **5b**, which was condensed with malononitrile to **6b** in quantitative yield.

In view of the difficulties experienced above in attempted desulfurization of **6a**, **8a**, and **9a**, we did not explore reductive desulfurization of **6b**. Instead, we envisioned **6b** as a potentially versatile intermediate for the introduction of functionality at position 3 by nucleophilic displacement either of the methylthio grouping or the corresponding methylsulfone, thus providing (assuming an eventually successful reductive cleavage) a route to a variety of 6-acylpteridine derivatives.

We report here on the reaction of **6b** with the sodium salt of diethyl malonate. It is known that 3-chloro-1,2-benzoisothiazole may react with nucleophiles either at C-3, with displacement of chloride ion, or at the ring sulfur atom with concomitant ring opening, elimination of chloride ion, and generation of an ortho-substituted nitrile.[21] When C–H acidic methylene compounds such as diethyl malonate are employed as the nucleophile, the ring-opened o-cyano substituted intermediate subsequently cyclizes to a benzo[*b*]thiophene derivative.[22] We thus anticipated, based on this close analogy, that reaction of **6b** with the sodium salt of diethyl malonate would probably follow path a indicated in Scheme II to give the thieno[*b*]pyrazine **13**. An analogous isothiazole to thiophene rearrangement has been reported with some isothiazolo[5,4-*b*]pyridines.[23] In fact, this ring transformation might be expected to proceed even more readily in the present case because of the better leaving-group capabilities of the methylthio grouping compared with chloride ion. However, under the same reaction conditions employed by Clarke et al. for the conversion of 3-chloro-1,2-benzoisothiazole to benzo[*b*]thiophenes, **6b** and diethyl malonate gave the pyrido[2,3-*b*]isothiazolo[4,5-e]pyrazine **14**. No displacement either on carbon or on sulfur takes place; instead, acylation of the amino group in the pyrazine ring by diethyl malonate (path b) is followed by intramolecular cyclization across the ortho-situated nitrile grouping to generate the 5-amino fused pyridine derivative **14**.

In an attempt to avoid initial reaction of diethyl malonate with the 6-amino function in **6b**, the latter was converted to its 6-dimethylaminomethyleneamino derivative **7b** with dimethylformamide dimethyl acetal. However, **7b** failed to react with diethyl malonate in the presence of sodium ethoxide at room temperature, even after 6 days. When the reaction mixture was heated, starting material disappeared completely within a few hours, but TLC indicated the simultaneous formation of at least ten compounds.

Experimental Section

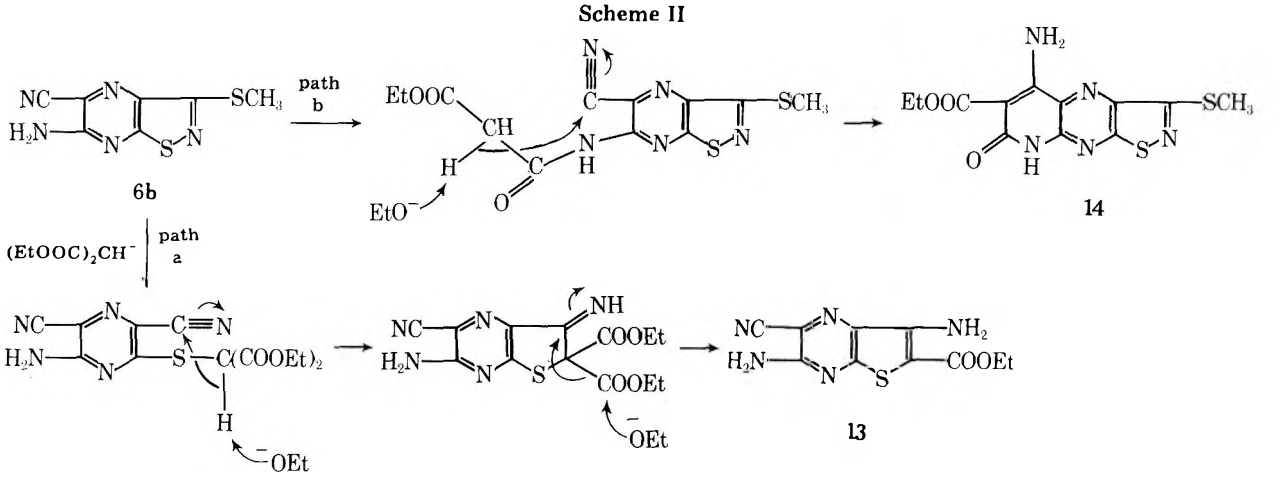
3-Methyl-5-acetamidoisothiazole (4a). To a chilled (0 °C) solution of 11.4 g (0.1 mol) of β-iminothiobutyramide in 200 mL of methanol was added dropwise 11.5 g (0.1 mol) of 30% hydrogen peroxide. After 15 min of stirring, the methanol was removed by evaporation under reduced pressure, the residual solid was dissolved in ether, and the resulting solution was dried over anhydrous $MgSO_4$. The dried ether solution was then reduced to a small volume by evaporation under reduced pressure and 40 mL of acetic anhydride was added. The reaction was exothermic, and a white precipitate separated. After 3 h of stirring, the solid was removed by filtration and recrystallized from water (Norite) to give 12.6 g (81%) of **4a** as white needles, mp 173–174 °C (lit.[8] mp 180–181 °C).

3-Methyl-4-nitroso-5-acetamidoisothiazole (5a). To a solution of 7.8 g (50 mmol) of 3-methyl-5-acetamidoisothiazole in 48 mL of dry dimethylformamide, chilled to 0 °C, was added in small portions 6.35 g (50 mmol) of nitrosyl hydrogen sulfate. After 2 h of stirring, the green solution was poured into water and the light green solid collected by filtration and recrystallized from ether to give 5.0 g (57%) of **5a** as a bright green crystalline solid, mp 166–167 °C.

Anal. Calcd for $C_6H_7N_3O_2S$: C, 38.91; H, 3.81; N, 22.69; S, 17.31. Found: C, 38.86; H, 3.70; N, 22.76; S, 17.11.

3-Methyl-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine (6a). To a slurry of 3.7 g (20 mmol) of 3-methyl-4-nitroso-5-acetami-

Scheme II



doisothiazole in 80 mL of ethanol, chilled to 0 °C, was added a solution of 4.0 g (40 mmol) of triethylamine and 1.6 g (24 mmol) of malononitrile in 20 mL of ethanol. After addition was complete, the reaction mixture was stirred to 0 °C for 8 h and the separated solid then was removed by filtration and recrystallized from ethanol (Norite) to give 2.0 g (26%) of **6a** as bright yellow needles, mp 203–205 °C (followed by resolidification).

Anal. Calcd for $C_7H_5N_5S$: C, 43.96; H, 2.64; N, 36.63; S, 16.77. Found: C, 44.03; H, 2.50; N, 36.39; S, 16.78.

3-Methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine (8a). Method A. A mixture of 4.65 g (25 mmol) of 3-methyl-4-nitroso-5-acetamidoisothiazole and 3.17 g (25 mmol) of 2,4,6-triaminopyrimidine in 50 mL of acetic acid was heated with stirring to 100 °C. A clear solution was thus obtained, which was then stirred at room temperature. After 2 h, a yellow solid started to separate and after 5 h of stirring, the reaction mixture was filtered and the collected yellow solid was washed with acetic acid followed by ether and then dried in vacuo. The crude product was stirred vigorously for 1 h in hot acetone, removed by filtration, rinsed with acetone, and then dried under reduced pressure at 140 °C: yield, 5.72 g (98%); mp >310 °C.

Anal. Calcd for $C_8H_7N_7S$: C, 41.20; H, 3.02; N, 42.04; S, 13.75. Found: C. 41.13, H, 2.84; N, 42.16; S, 14.23.

Method B. A solution of 86 mg (0.5 mmol) of 3-methyl-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine in 8 mL of methanol was treated with 1 equiv of guanidine in methanol (prepared by dissolving equivalent amounts of guanidine hydrochloride and sodium methoxide in methanol, and filtering off the precipitated sodium chloride), and the reaction mixture was heated under reflux for 5 h. The precipitated yellow solid was removed by filtration, washed well with methanol followed by ether, and dried [140 °C (0.01 Torr)], yield 90 mg (77%). It was analytically pure without further purification and was identical in all respects with the material prepared by method A.

3-Methylisothiazolo[4,5-*g*]pterin (9a). Method A. A mixture of 2.82 g (15 mmol) of 3-methyl-4-nitroso-5-acetamidoisothiazole and 2.16 g (15 mmol) of 2,4-diamino-6(1*H*)-pyrimidinone in 75 mL of acetic acid was heated on a steam bath for 1.5 h, at which point no residual isothiazole could be detected by TLC (benzene/acetone (9:1) on silica gel). The hot reaction slurry was then filtered and the collected solid was washed with acetic acid followed by ethanol and ether. The crude product was further purified by dissolution in 50 mL of 0.1 N NaOH, acidification with concentrated HCl, and dilution with 50 mL of water; filtration then gave 1.85 g (79%) of **9a** as a light green-yellow solid, mp >360 °C.

Anal. Calcd for $C_8H_6N_6OS$: C, 41.02; H, 2.58; N, 35.87; S, 13.69. Found: C, 41.08; H, 2.31; N, 35.63; S, 13.90.

Method B. A slurry of 100 mg of 3-methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine in 5 mL of 1 N NaOH was heated under reflux with stirring until complete solution was achieved (30 min). Cooling of the reaction mixture resulted in the separation of yellow crystals of the hydrated sodium salt of **9a**. The mixture was cooled overnight at 2–5 °C and filtered, and the collected solid was triturated with dilute hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried [140 °C (0.01 Torr)] to give 65 mg (65%) of analytically pure **9a**, identical in all respects with the material prepared by method A.

6-Acetyl-7-mercaptopterin (12). To a solution of 250 mg of 3-methylisothiazolo[4,5-*g*]pterin in 25 mL of 0.1 N NaOH was added in two portions 370 mg of sodium hydrosulfite. The clear solution rapidly turned turbid with the separation of 3-methylisothiazolo[4,5-*g*]pterin sodium salt trihydrate as a yellow solid, mp >360 °C. (Anal. Calcd for $C_8H_5N_6OSNa{\cdot}3H_2O$: C, 30.97; H, 3.57; N, 27.09. Found: C, 31.28; H, 3.59; N, 27.13.) After 15 min at room temperature, the slurry was treated with 1 mL of concentrated HCl and then stirred overnight. The resulting bright yellow-orange solid was collected by filtration, suspended in water, and then dissolved by the careful addition of 0.1 N NaOH. The resulting orange solution was treated with Norite and filteraid and filtered, and the filtrate was acidified with concentrated HCl to give 230 mg of **12** as an orange-yellow solid, mp >300 °C dec.

Anal. Calcd for $C_8H_7N_5O_2S{\cdot}1.5H_2O$: C, 39.00; H, 3.28; N, 28.46; S, 13.05. Found: C, 39.53; H, 3.03; N, 28.52; S, 12.58.

3-Methyl-5-cyano-6-(dimethylaminomethyleneamino)isothiazolo[4,5-*b*]pyrazine (7a). To a mixture of 5 mL of tetrahydrofuran and 5 mL of dimethylformamide dimethyl acetal was added 1.0 g of 3-methyl-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine. Immediate solution was achieved, but after a few minutes the product started to precipitate. It was removed by filtration (a small amount of additional product could be obtained by concentration of the filtrate) and recrystallized from ether to give 1.05 g (81%) of **7a** as a colorless solid, mp 152–153.5 °C.

Anal. Calcd for $C_{10}H_{10}N_6S$: C, 48.76; H, 4.09; N, 34.12; S, 13.02. Found: C, 48.93; H, 4.06; N, 34.05; S, 12.96.

3-Amino-3-methylmercaptoacrylthioamide (2b). To a slurry of 26.8 g (0.20 mol) of malonic acid dithioamide in 80 mL of dimethylformamide at room temperature was added dropwise 32.0 g (0.23 mol) of methyl iodide at such a rate that the temperature of the reaction mixture did not rise above 37 °C. The reaction mixture was then stirred for 2 h after addition was complete, by which time all of the remaining malonic acid dithioamide had dissolved. The reaction mixture was then chilled to 0 °C and poured slowly into a chilled solution of 19.0 g (0.23 mol) of sodium bicarbonate in 500 mL of water. Filtration then gave 19.3 g of crude product which still contained a small amount of unreacted malonic acid dithioamide. The crude product was extracted with ether, utilizing a Soxhlet extractor, from which pure **2b** crystallized upon concentration: yield, 16.0 g (54%); mp 104.5–105.5 °C. The product may be obtained in the form of colorless crystals upon recrystallization from methanol or ether.

Anal. Calcd for $C_4H_8N_2S_2$: C, 32.41; H, 5.44; N, 18.90; S, 43.26. Found: C, 32.65; H, 5.22; N, 19.14; S, 43.18.

3-Methylmercapto-5-aminoisothiazole (3b). To a solution of 1.48 g (10 mmol) of 3-amino-3-methylmercaptoacrylthioamide in 20 mL of methanol, chilled to 0 °C, was added dropwise 1.15 g (10 mmol) of 30% hydrogen peroxide. After addition was complete, the reaction mixture was stirred for 1 h at room temperature and then evaporated to dryness. The residue was dissolved in 40 mL of ether, the ether solution was dried over anhydrous $MgSO_4$, and the reaction mixture was concentrated by evaporation to induce crystallization: yield, 1.1 g (75%); mp 116.5–118 °C. The product was obtained in the form of colorless crystals by recrystallization from ether (Norite).

Anal. Calcd for $C_4H_6N_2S_2$: C, 32.85; H, 4.14; N, 19.16; S. 43.85. Found: C, 33.09; H, 3.89; N, 19.25; S, 43.78.

3-Methylmercapto-5-acetamidoisothiazole (4b). A solution of 2.19 g of 3-methylmercapto-5-aminoisothiazole in 6 mL of acetic anhydride and 10 mL of tetrahydrofuran was stirred at room temperature for 3 h. The reaction mixture became warm after a few minutes of stirring, and after 1 h the product started to separate. The reaction slurry was cooled to 0 °C and filtered, and the product was crystallized from methanol (Norite) to give 2.6 g (92%) of **4b** as colorless crystals, mp 196–197 °C.

Anal. Calcd for $C_6H_8N_2OS_2$: C, 38.28; H, 4.27; N, 14.88; S, 34.06. Found: C, 38.49; H, 4.45; N, 14.67; S, 34.14.

3-Methylmercapto-4-nitroso-5-acetamidoisothiazole (5b). To a solution of 0.94 g (5 mmol) of 3-methylmercapto-5-acetamidoisothiazole in 4 mL of dry dimethylformamide was added in small portions 0.72 g (5.5 mmol) of nitrosyl hydrogen sulfate. The reaction mixture was stirred for 1 h, diluted with 20 mL of water, and filtered to give a dark green solid which was collected by filtration, washed with water, and recrystallized from ethanol: yield, 0.95 g (79%); mp 230 °C dec.

Anal. Calcd for $C_6H_7N_3O_2S_2$: C, 33.17; H, 3.25; N, 19.35; S, 29.52. Found: C, 33.45; H, 3.14; N, 19.66; S, 29.37.

3-Methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine (6b). A mixture of 2.42 g (11.1 mmol) of 3-methylmercapto-4-nitroso-5-acetamidoisothiazole, 1.0 g (15 mmol) of malononitrile, and 1.2 g (12 mmol) of triethylamine in 20 mL of ethanol was refluxed for 1 h and the resulting greenish yellow precipitate was collected by filtration and washed with ethanol followed by ether. Recrystallization from ethanol (Norite) gave 2.23 g (94%) of **6b** as yellow crystals, mp >270 °C dec (with decomposition starting with 210 °C).

Anal. Calcd for $C_7H_5N_5S_2$: C, 37.65; H, 2.26; N, 31.37; S, 28.72. Found: C, 37.47; H, 2.29; N, 31.18; S, 28.75.

3-Methylmercapto-5-cyano-6-(dimethylaminomethyleneamino)isothiazolo[4,5-*b*]pyrazine (7b). A slurry of 1.0 g of 3-methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine in 15 mL of dimethylformamide dimethyl acetal was stirred at room temperature for 24 h, by which time TLC indicated complete disappearance of starting material. The reaction mixture was evaporated to dryness, the residue was triturated with ether and filtered, and the product was recrystallized from ethanol (Norite) to give 1.24 g (quantitative) of **7b** as a greenish yellow solid, mp 211–213 °C.

Anal. Calcd for $C_{10}H_{10}N_6S_2$: C, 43.15; H, 3.62; N, 30.19; S, 23.04. Found: C, 42.87; H, 3.62; N, 30.09; S, 23.15.

3-Methylmercapto-5-amino-6-carboethoxypyrido[2,3-*b*]isothiazolo[4,5-*e*]pyrazin-7(8H)-one (14). A slurry of 0.565 g (2.5 mmol) of 3-methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]-pyrazine, 400 mg (2.5 mmol) of diethyl malonate, and 20 mL of ethanol containing 120 mg (5 mmol) of sodium was stirred at room temperature for 4 days, by which time TLC indicated that no starting material remained. The reaction mixture was concentrated under reduced pressure and filtered to give 0.8 g (98%) of the orange-yellow sodium salt of **14**. Dissolution of this salt in dimethylformamide followed by addition of a small amount of acetic acid resulted in the separation of analytically pure bright yellow **14**, mp 305–310 °C dec.

Anal. Calcd for $C_{12}H_{11}N_5O_3S_2$: C, 42.72; H, 3.29; N, 20.76; S, 19.01. Found: C, 42.66; H, 3.30; N, 20.81; S, 18.96.

Registry No.—**2b**, 67209-06-7; **3b**, 67209-07-8; **4a**, 67209-08-9; **4b**, 67209-09-0; **5a**, 67209-10-3; **5b**, 67209-11-4; **6a**, 67209-12-5; **6b**, 67209-13-6; **7a**, 67209-14-7; **7b**, 67209-15-8; **8a**, 67209-16-9; **9a**, 67209-17-0; **9a** Na salt, 67209-18-1; **12**, 67209-19-2; **14**, 67209-20-5; **14** Na salt, 67209-21-6; β-iminothiobutyramide, 32081-55-3; nitrosyl hydrogen sulfate, 7782-78-7; malononitrile, 109-77-3; 2,4,6-triaminopyrimidine, 1004-38-2; guanidine, 113-00-8; 2,6-diamino-4(3*H*)-pyrimidinone, 56-06-4; dimethylformamide dimethyl acetal, 4637-24-5; malonic acid dithioamide, 6944-34-9; diethyl malonate, 510-20-3.

References and Notes

(1) For the previous paper in this series, see E. C. Taylor, R. N. Henrie II, and R. C. Portnoy, *J. Org. Chem.*, **43**, 736 (1978).
(2) We are indebted for the support of this work to the National Cancer Institute, National Institutes of Health (Grant No. CA 12876), Eli Lilly & Co., Lonza AG, and Hoffmann-La Roche & Co., Ltd.
(3) For general references on pteridine chemistry, see (a) W. Pfleiderer and E. C. Taylor, Ed., "Pteridine Chemistry", Pergamon Press, London, 1964; (b) W. Pfleiderer, *Angew. Chem., Int. Ed. Engl.*, **3**, 114 (1964); (c) R. C. Elderfield and A. C. Mehta, *Heterocycl. Compd.*, **9**, 1–117 (1967); (d) W. Pfleiderer, Ed., "Chemistry and Biology of Pteridines", Walter de Gruyter, Berlin, 1975.
(4) For a discussion of these orientation problems, see E. C. Taylor, K. L. Perlman, I. P. Sword, M. Séquin-Frey, and P. A. Jacobi, *J. Am. Chem. Soc.*, **95**, 6407 (1973).
(5) See, for example, E. C. Taylor in ref 3d, pp 543–573, as well as previous papers in this series.
(6) R. B. Woodward, I. Gougoutas, and G. Volpp, *Harvey Lect.*, **59**, 31 (1963).
(7) Y. Furukawa, O. Miyashita, and S. Shima, *Chem. Pharm. Bull. Jpn.*, **24**, 970 (1976).
(8) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).
(9) I. Goerdeler and H. W. Pohland, *Chem. Ber.*, **94**, 2950 (1961).
(10) For a discussion of this general route to isothiazoles, see (a) R. Slack and K. R. H. Wooldridge, *Adv. Heterocycl. Chem.*, **4**, 107 (1964); (b) K. R. H. Wooldridge, *Adv. Heterocycl. Chem.*, **14**, 1 (1972).
(11) This ring system has apparently been reported only once before; condensation of 3-methyl-4,5-diaminoisothiazole with *n*-butyl glyoxylate gives 3-methyl-6-hydroxyisothiazolo[4,5-*b*]pyrazine [A. Holland, R. Slack, T. F. Warren, and D. Buttimore, *J. Chem. Soc.*, 7277 (1965)].
(12) G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 356 (1960).
(13) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, pp 131 ff.
(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 729.
(15) E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.*, **80**, 421 (1958).
(16) H. Adkins and H. R. Billics, *J. Am. Chem. Soc.*, **70**, 695 (1948).
(17) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).
(18) E. C. Taylor and L. A. Reiter, unpublished observations.
(19) F. Pochat and E. Levas, *Tetrahedron Lett.*, 1491 (1976).
(20) The failure of all these desulfurization attempts stands in marked contrast with the report that urothione, a presumed thieno[2,3-*g*]pteridine, is smoothly desulfurized to a 6-alkylpterin with Raney nickel [M. Goto, A. Sakurai, K. Ohta, and Y. Yamakami, *J. Biochem.*, **65**, 611 (1967)].
(21) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. C*, 3262 (1971).
(22) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. C*, 3903 (1971).
(23) K. Gewald, H. Schäfer, and U. Schlegel, *J. Prakt. Chem.*, **318**, 779 (1976).

Total Synthesis of Anthracyclinones via Intramolecular Base-Catalyzed Cyclizations[1]

Fumio Suzuki, Steven Trenbeath, Robert D. Gleim, and Charles J. Sih*

Contribution from the School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

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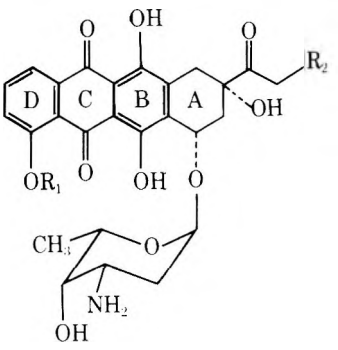
Methods for the preparation of anthracyclinones from substituted anthraquinone derivatives are described. The construction of the alicyclic A ring was achieved via intramolecular base-catalyzed cyclizations of dihydroanthraquinones.

Daunorubicin[2] (1), doxorubicin[3] (2), and carminomycin[4] (3) are members of a large family of anthracycline antibiotics



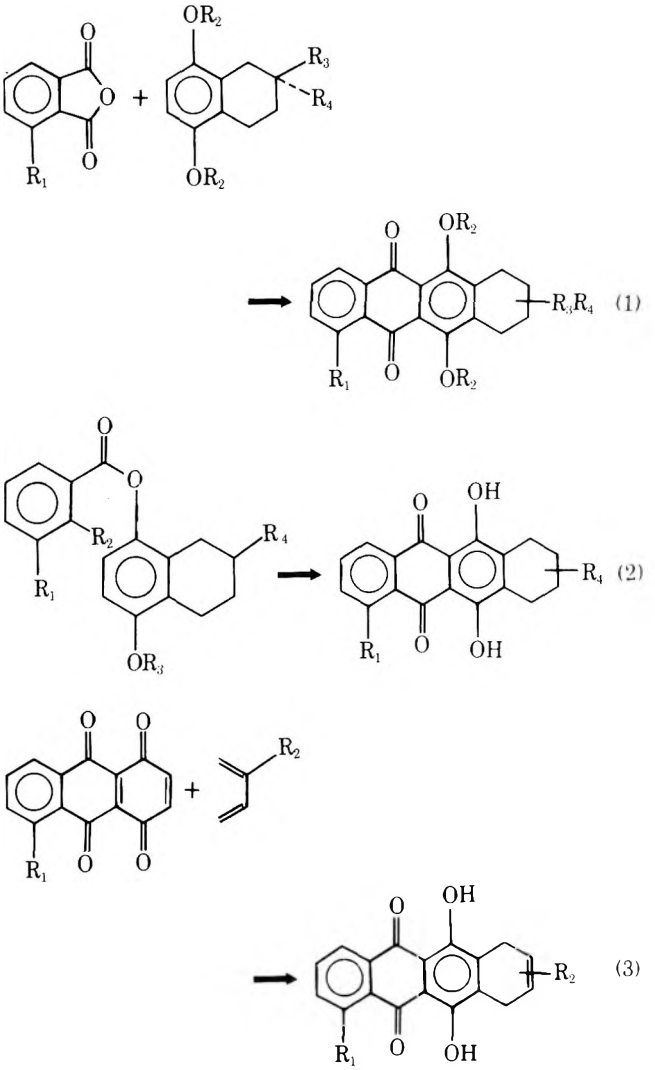
1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = CH_3$; $R_2 = OH$
3, $R_1 = H$; $R_2 = H$

produced by *Streptomyces* sp. The structures of these compounds were established by a combination of spectral analyses[5b] and chemical degradations[2a,5a] and further confirmed by X-ray analysis,[5c] which revealed these molecules to consist of a tetracyclic aglycon attached to the amino sugar daunosamine via a β-glucosidic bond. The stereochemistry of both asymmetric centers of the aglycons is of the *S* configuration, and the amino sugar is of the L configuration.

In recent years, these antibiotics have attracted considerable attention because of their remarkable effectiveness in combating a variety of human malignancies.[6] However, like many cytotoxic drugs, they also display untold side effects, the most serious being their cardiotoxicities.[7] Due to the lack of an efficient fermentation process[3b] and that a small structural difference between doxorubicin and daunorubicin can so favorably affect therapeutic characteristics,[6] there has been continual chemical interest aimed at the development of an efficient total synthesis of these antibiotics and totally synthetic analogues with improved therapeutic properties. As several suitable syntheses of daunosamine[8] and its coupling to daunomycinone[9] have already been accomplished, our research efforts have been directed to the synthesis of the aglycone moieties (anthracyclinones) of these antitumor antibiotics.

Several synthetic approaches to the tetrahydro-5,12-naphthacenedione ring system have been developed utilizing Friedel–Crafts[10] (eq 1), photo-catalyzed or Lewis acid catalyzed Fries[11] (eq 2), and Diels–Alder reactions[12] (eq 3) as illustrated in Scheme I. With a few exceptions,[11a,13] most of these synthetic schemes lack regiochemical control with respect to the orientation of ring A and D substituents. Recently, we developed a fundamentally different approach to the synthesis of anthracyclinones[1] from appropriately substituted anthraquinone derivatives. In this paper, we record the precise experimental procedures required for the successful elaboration of the alicyclic ring A since these methods are likely to find frequent use in the synthesis of anthracyclinones.

Scheme I



Anthraquinone derivatives are potential starting materials for anthracyclinone synthesis because they are readily available from microbial[14] and plant[15] sources or as intermediates of dye synthesis.[16] While one can readily envisage a regiospecific synthesis of anthracyclinones via the cyclization of appropriately substituted anthraquinone derivatives such as **4**, the success of this approach rests heavily on the development of a suitable method for the construction of ring A. To examine the feasibility of this synthetic scheme, we selected **5** as a model compound for our initial ring closure explorations, for it may be more readily prepared than **4**. Also, 4-demethoxydaunorubicin is a compound of considerable clinical importance for it possesses an improved therapeutic index[17] as compared to daunorubicin in animal studies.

Condensation of phthalic anhydride with methylhydroquinone in an $AlCl_3$–NaCl melt at 190 °C afforded 2-

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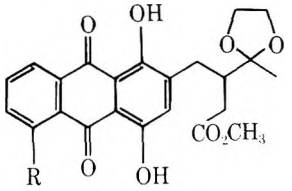
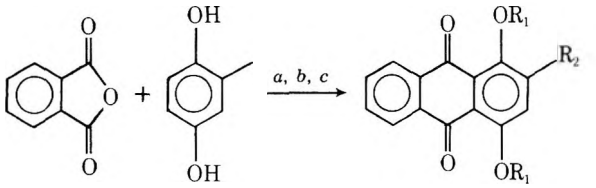


4, R = OCH_3
5, R = H

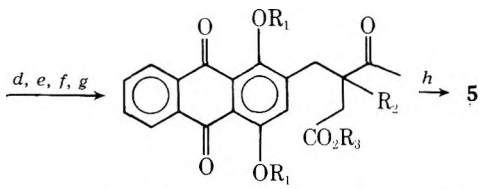
methyl-1,4-dihydroxyanthraquinone (**6**) in 79% yield. After methylation, **7** was brominated to give **8a** (55%), accompanied by residual **7** and dibromide **8b**, but **8a** was isolated by recrystallization. It is interesting to note that while bromination of **7** was comparatively rapid (2 h), bromination of 1,4-diacetoxy-2-methylanthraquinone was very slow (16 h), presumably due to the electron-withdrawing acetyl groups. Alkylation of **8a** with ethyl 3-acetyllevulinate gave **9** (88%). Simultaneous ester hydrolysis and cleavage of β-diketone were achieved by treating **9** with 8% NaOH at 60 °C. The model compound **5** was obtained by esterification of **10** with diazomethane, demethylation with BBr_3 at −78 °C, and ketalization. Operationally, the conversion of 2-methylhydroquinone to **5** may be easily executed with one chromatography in an overall yield of 23% (Scheme II).

Having the tricyclic ketal **5** in hand, we proceeded to examine experimental conditions required for cyclization using a variety of bases (NaH, LDA, NaOMe, *t*-BuOK), acids (BF_3 ethereate, PPA, HF, H_2SO_4), and solvents (DMF, HMPA, THF, MeOH, *t*-BuOK) at varying temperatures (25–160 °C), but unfortunately no cyclization of **5** was observed. We surmised that this resistance of **5** toward cyclization is attributed to the apparent strong electron-withdrawing property of the anthraquinone system. To surmount this obstacle, it appeared necessary to alter the electronic configuration of the anthraquinone system (Scheme III). This was achieved by reduction of **5** with zinc dust in acetic acid[12f] to yield a single diastereomer **13**, as evidenced by the two sharp singlets at δ 3.92 and 3.66 corresponding to the protons of the ethylene ketal and the methyl ester. When **13** was refluxed with BaO and zinc dust in acetone (condition 5, Table I), another diastereomer

Scheme II



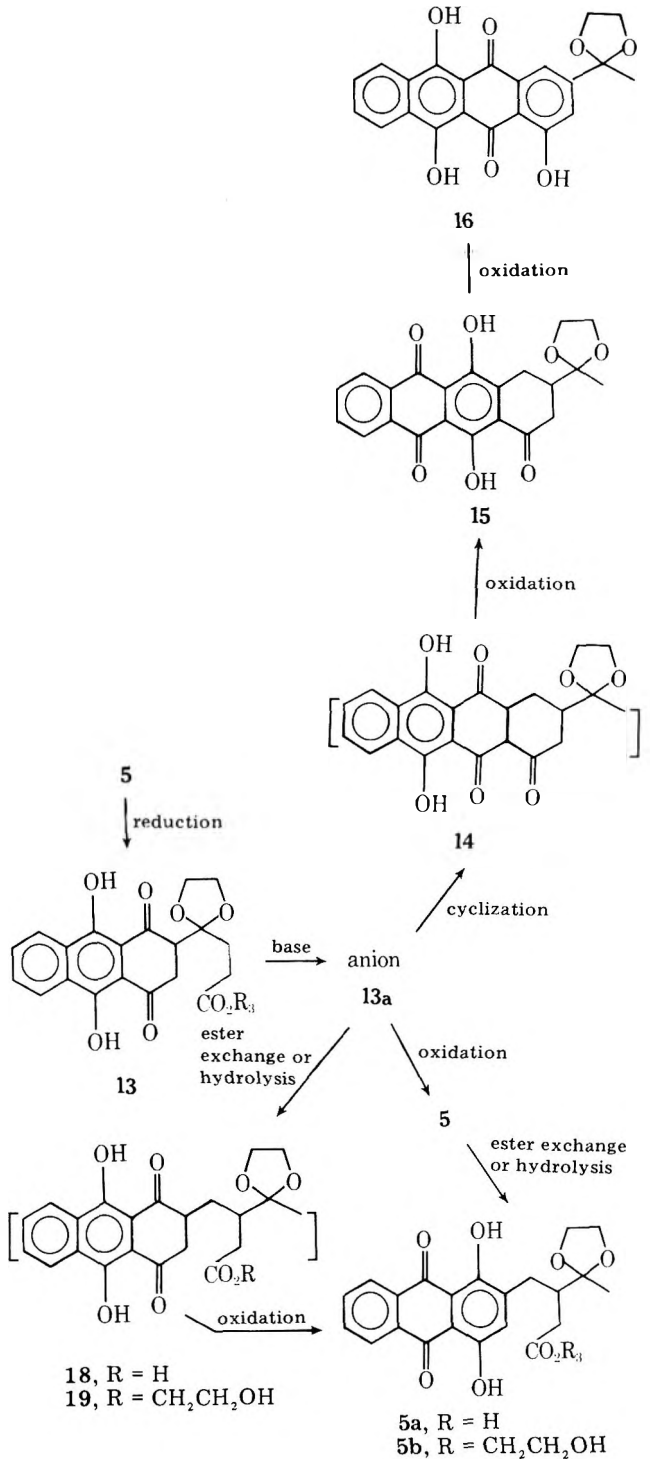
6, R_1 = H; R_2 = CH_3
7, R_1 = R_2 = CH_3
8a, R_1 = CH_3; R_2 = CH_2Br
8b, R_1 = CH_3; R_2 = $CHBr_2$



9, R_1 = CH_3; R_2 = CH_3CO; R_3 = Et
10, R_1 = CH_3; R_2 = R_3 = H
11, R_1 = CH_3; R_2 = H; R_3 = CH_3
12, R_1 = R_2 = H; R_3 = CH_3

[a] $AlCl_3$–NaCl, 190 °C. [b] $(CH_3)_2SO_4$–K_2CO_3–acetone, reflux. [c] NBS–BPO–CCl_4, reflux. [d] NaH–ethyl 3-acetyllevulinate–DMF, 25 °C. [e] 8% NaOH, 60 °C. [f] CH_2N_2. [g] BBr_3–CH_2Cl_2, −78 °C. [h] Ethylene glycol–benzene, reflux.

Scheme III



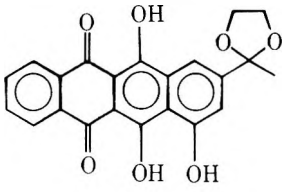
was formed as indicated by the appearance of another pair of singlets of equal intensity at δ 3.94 and 3.62. An exhaustive study of the cyclization of the leuco form **13** using a variety of conditions is tabulated in Table I. Conditions 1–4 catalyzed the oxidation of **13** back to **5**. However, the reaction path was dramatically altered when Zn dust was included in the reaction mixture (condition 6). This is evidenced by the appearance of four colored compounds on TLC plates ($CHCl_3$–acetone, 95:5): pink-red (R_f 0.52); orange and yellow (both have R_f 0.32); and brownish red (R_f 0.25). The orange and yellow compounds corresponded to **5** and residual starting material **13** respectively, by comparison with authentic samples. After preparative TLC, the brownish red band was isolated and characterized to be **15** on the basis of mass spectral and NMR data. The pink-red band was identified as an oxidation product of **15** and was assigned the structure **16**. This struc-

Table I. Reaction Conditions and Product Yield Data for the Cyclization of 5.

run	base	solvent	reducing reagents	temp, °C	time, min	major products
1	NaH or LDA	THF–HMPA			30	**5**
2	BaO	HMPA		140	18	**5**
3	NaH	DMF		140	4	**5**
4	CaO	DMF	Zn	140	35	**5**
5	BaO	acetone	Zn	reflux	180	**13**[a] + **5**
6	BaO	DMF	Zn	140	25	**15** (20%), **16** (14%), **5** & **13** (12%)[b]
7	NaH	DMF	Zn	25	3	**5**
8	NaH	DMF	$Na_2S_2O_4$	25	10	**5**
9	CaO	HMPA	Zn	140	10	**5**
10	CaO	diglyme	Zn	140	35	**15** (12%), **5** & **13** (50%)
11	CaO	*t*-BuOH	Zn	reflux	30	**5, 13**
12	CaO	ethylene glycol	Zn	140	3	**15** (49%), **5a, 5b**
13	CaO	ethylene glycol	Zn	25~80	60	**5, 5b**
14	MgO	ethylene glycol	Zn	140	9	**5, 13**
15	CaO	ethylene glycol–diglyme (3:2)	Zn	140	3	**15** (52%), **5a, 5b**

[a] Two diastereomers. [b] Values in parentheses indicate isolated yields.

tural assignment was deduced from the NMR data which showed three strongly hydrogen-bonded proton signals at δ 13.35, 12.25, and 10.37, rendering structure **17** an unlikely



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possibility. Also, from thermodynamic considerations, one would expect that aerial oxidation of **15** would preferentially give rise to an isomer with maximum hydrogen bonding.

It is noteworthy that conditions 7 (NaH–Zn–DMF) and 8 (NaH–$Na_2S_2O_4$–DMF) afforded only **5** as a result of back oxidation of **13**. This suggests that the anion **13a** thus generated appears to be rather unstable, and neither Zn nor $Na_2S_2O_4$ suppressed the oxidation of the anion (**13a**) to the anthraquinone anion via electron transfer or some other mechanism. On the other hand, anion **13a**, generated by the use of divalent bases such as BaO or CaO, appears to be less unstable. Presumably, these divalent counterions may be involved in stabilization via complexation to allow cyclization to occur. To some extent, Zn appeared to suppress back oxidation.

Since **13** is ipso facto the diketo form of the 1,4,9,10-tetrahydroxyanthracene derivative, one may consider this cyclization to be analogous to C acylation of ambident anions of hydroquinones. It is well known that hydroxylic solvents (e.g., H_2O, CF_3CH_3OH, etc.) favor C- vs. O-alkylation of ambident anions of phenoxides or naphthoxides.[18] Conceivably, O-acylation may also occur, giving rise to the acid **18** upon workup, but this possibility appears remote in view of the involvement of seven- or eight-membered rings.

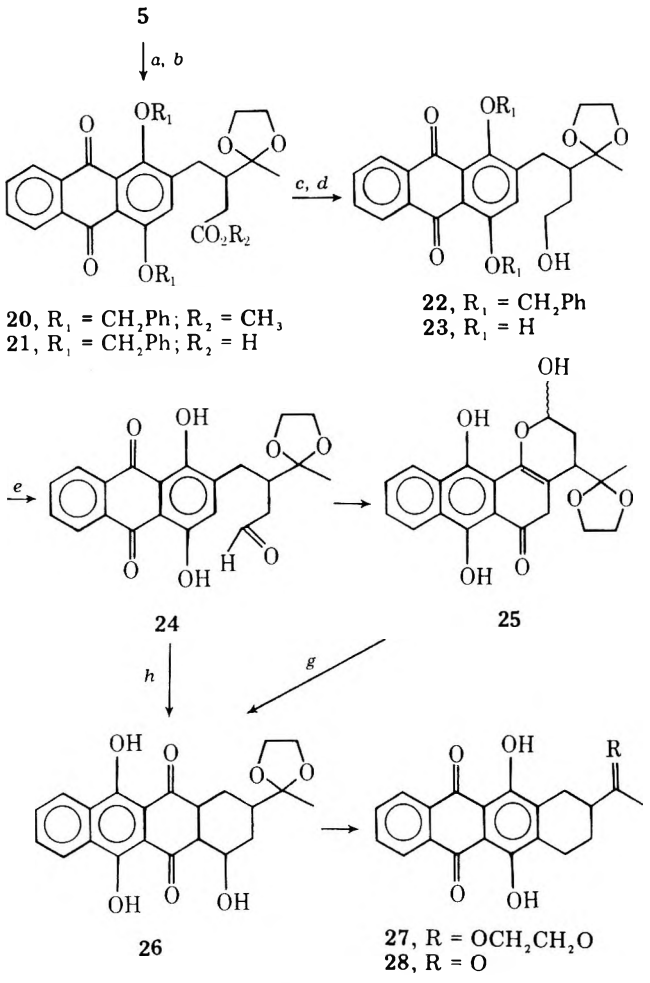
Polyhydroxylic solvents with high boiling points such as ethylene glycol were found to be the best solvent for this cyclization since in general intramolecular acylation reactions require high activation energies. For optimum results, cyclization of **13** should be carried out using the following procedure: CaO (8 equiv), Zn (2 equiv), ethylene glycol–diglyme (3:2), and heating at 140 °C for 3 min; diglyme was used for better dissolution of **13** (condition 15). It is important to emphasize that after mixing the solvents, base and **13** at −78 °C, to minimize ester exchange and back oxidation, the temperature of the reaction flask should be brought to 140 °C as quickly as possible because the glycolic ester **19** (leuco form) failed to undergo cyclization under these reaction conditions (Scheme III). This suggests that the rate of cyclization is determined by entropies of activation.

Since the intramolecular Claisen cyclization requires rather rigid experimental conditions to suppress side reactions, it may not be suitable for large-scale operations. We reasoned that if the ester grouping is transformed into an aldehyde, cyclization may be more facile due to a lowering of activation energy and may minimize competitive reactions such as back oxidation. Thus, **5** was converted into **24** via a five-step reaction sequence in 35% overall yield (Scheme IV). This included benzylation of **5** to give **20** (91%), hydrolysis of **20** (92%), reduction of **21** with diborane (68%), debenzylation of **22** (87%), and oxidation of **23** with pyridinium chlorochromate (66%). It was found that **5** was easily reduced to its corresponding anthracene derivative with either diborane or $LiAlH_4$ at 25 °C, presumably via intramolecular hydride transfer and dehydration. Thus, the hydroxyls of **5** were protected as benzyl ethers. Reduction of **24** with zinc dust in acetic acid afforded two diastereomers (**25**; 94% which were separated by preparative TLC. Both compounds gave identical mass spectra, and each diastereomer exhibited a signal at δ 13.50 or 13.58, characteristic of one hydrogen-bonded proton, but no signals corresponding to aldehydic protons were observed. These spectral data are consistent with the supposition that the expected dihydroanthraquinone derivative preferentially exists in its enol hemiacetal forms, **25**. This mixture of diastereomers (**25**) was cyclized directly without further purification using condition 15 of Table I to yield **27** as red crystals in 56% yield. Presumably, this transformation proceeds via the unstable intermediate **26**, which upon dehydration and tautomerism affords **27**. Acid deketalization of **27** afforded **28** in 92% yield.

This sequence of reduction of **24** into its leuco form, followed by base-catalyzed cyclization is mechanistically equivalent to an intramolecular Marschalk reaction. In fact, it was subsequently found that this transformation of **24** into **27** was conveniently affected in one step using $Na_2S_2O_4$ in 8% NaOH and *p*-dioxane at 90 °C in comparable yield (50%).

The successful development of methods for ring A closure in the 4-demethoxy series prompted us to focus our attention to the regiochemical synthesis of **4** from the readily available starting material 1-hydroxy-5-methoxyanthraquinone[19] (**29**) (Scheme V). Methylation of **29** at the C-2 position using dithionite and aqueous formaldehyde in 1.5 N NaOH (Marschalk reaction)[20] afforded **30** in 60% yield after silica gel chromatography. Acylation of **30** with acetic anhydride in the presence of a catalytic amount of concentrated H_2SO_4 at 25 °C gave **31** in quantitative yield. Treatment of **31** with 1.3 equiv of NBS yielded the desired bromide **32a** (60%) and di-

Scheme IV

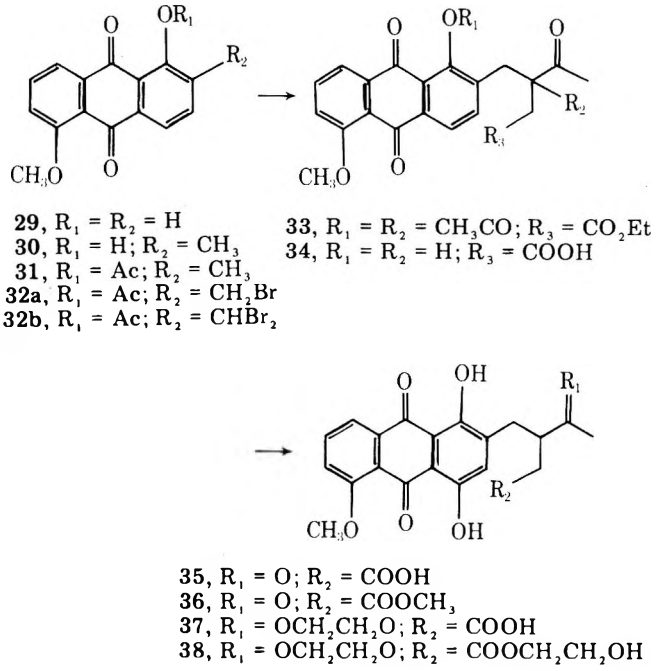


[a] $PhCH_2Br$, K_2CO_3–acetone, reflux. [b] 8% NaOH, *p*-dioxane, 90 °C. [c] BH_3, THF, 25 °C. [d] 5% Pd–$BaSO_4$, H_2. [e] PCC–CH_2Cl_2. [f] Zn–ACOH, 25 °C. [g] CaO, ethylene glycol–diglyme, Zn, 140 °C. [h] $Na_2S_2O_4$, 8% NaOH, *p*-dioxane, 90 °C.

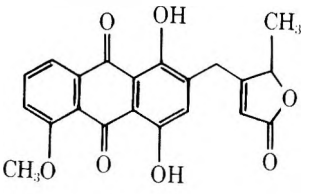
bromide **32b** (27%). The monobromide **32a** was conveniently separated from the mixture by several crystallizations from $CHCl_3$–CCl_4 and silica gel chromatography. Alkylation (NaH, DMF, 25 °C) of **32a** with ethyl 3-acetyllevulinate gave **33** in 96% yield. Hydrolysis of the ester grouping and cleavage of the β-diketone (reverse Claisen) were simultaneously effected by the reaction of **33** with 5% NaOH at 65 °C (91%). The overall yield of **34** from **30** was 52%.

Introduction of the hydroxyl function at C-4 in **34** was accomplished using the Elbs oxidation procedure.[21] After expending a considerable amount of effort in defining the optimum reaction conditions, moderate yields of **35** (42%) were obtained along with unreacted **34** (38%), which was conveniently separated from the product without chromatography and recycled. Attempts to introduce the C-4 hydroxylation step at an earlier stage in our synthesis using **30** as substrate were unsuccessful. Apparently, this failure may be attributed to the poor solubility of **30** in the aqueous oxidative medium, and addition of DMF, Me_2SO, or THF to the reaction medium did not improve the hydroxylation process. In our experience, the presence of a carboxylic acid function is a prerequisite to obtaining reasonable yields of the hydroxylated product in the Elbs reaction since it greatly improves the solubility of the compound in the aqueous oxidative medium. The use of mixed solvents has not been fruitful, for lower yields of **35** were obtained in each instance. Attempts to oxidize **34** at C-4 using other oxidation reagents (Fremy salt, CrO_3–OAC, H_2O_2–$AlCl_3$, O_2–salcomine) did not give significant quantities of the desired product.

Scheme V



Having the desired key intermediate **35** at hand, we proceeded to examine conditions required for its cyclization using acidic reagents such as HF, concentrated H_2SO_4, PPA, and BF_3 ethereate at varying temperatures. In each instance, a complex mixture of products was formed, but no anthracyclinones were detected. When **35** was treated with HF at 100 °C,[22] with PPA at 70 °C, or with BF_3–Et_2O at 120 °C, a major product was formed which was characterized as the unsaturated lactone **39**, mp 294–297 °C.



39

Since attempts to catalyze the cyclization of **4** with conventional acidic reagents were unsuccessful, we decided to call upon the cyclization method that was used in the 4-demethoxy series. Thus, **35** was quantitatively converted into **36** with diazomethane, which was then transformed into its ethylene ketal **4** in 82% yield. However, in contrast to the 4-demethoxy series, **4** was only sluggishly and incompletely reduced into its leuco form, **40**, using zinc dust in acetic acid. It was difficult to separate **40** from **4** via preparative TLC because of the susceptibility of **40** to undergo aerial oxidation back into **4**. Attempts to accelerate this reduction process through the addition of formic or hydrochloric acid were without success. On the other hand, **4** was found to be smoothly converted into **40** in 85% yield using dithionite in 5% NaOH; a small quantity of dioxane was needed to ensure the dissolution of **4**.

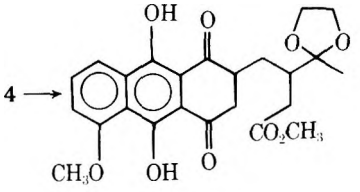
Having the dihydroanthraquinone derivative at hand, we subjected it to the same cyclization conditions (Zn, ethylene glycol–diglyme, CaO, 140 °C) successfully applied to the 4-demethoxy compounds. However, contrary to our expectations, the major products that formed were **37** and **38** and only traces of **41** (<1%) were detected. Treatment of **40** with a variety of conventional bases (NaH, LDA, *t*-BuOK, MeONa, BaO) in several solvents (DMF, THF, HMPA) with zinc dust or dithionite failed to yield detectable quantities of **41**. As

Table II. Conditions for the Cyclization of 40

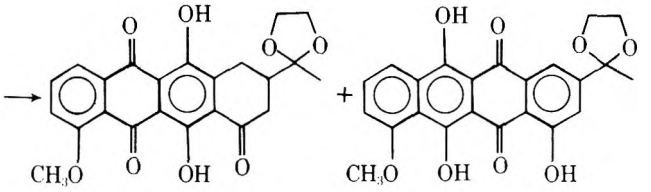
run	solvent	base	reducing reagent	reaction time, min	temp, °C	yield of 19,[a] %
1	1,2-propanediol	CaO	Zn	3	140	1–3
2	2,3-butanediol	CaO	Zn	3	140	1–3
3	2,2-dimethylpropanediol	CaO	Zn	3	140	1–3
4	glycerol	CaO	Zn	3	140	5
5	glycerol–H_2O (4:1)	CaO	Zn	3	140	8.4
6	sorbitol (10 equiv)–DMF	CaO	Zn	3	140	1
7	phenol	CaO	Zn	3	140	*b*

[a] Isolated yields. All reactions were carried out using 50 mg of **40**. Major products were different esters of **38**, depending on the solvent used. [b] The major product was **4**.

transesterification appeared to be a major side reaction and the resulting glycolic ester. **38** resisted cyclization, a series of more bulky glycols and polyhydroxylic compounds was evaluated as potential solvents for the ring closure reaction, with the hope of minimizing exchange reactions. The experimental conditions and results are summarized in Table II. It was found that by substituting glycerol–H_2O (4:1) for ethylene glycol as solvent, 8.4% of **41** was obtained, along with a trace of **42**.



40

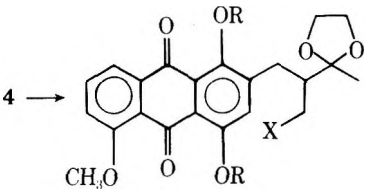


41 **42**

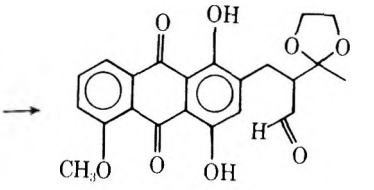
It was somewhat surprising to find that the presence of the 4-methoxyl group markedly altered the electronic properties of **40** as compared to the 4-demethoxy series. One may speculate that the substitution of a methoxyl for hydrogen on an aromatic ring raises the energy level of the LUMO as a rule,[23] thereby accelerating the oxidation of the anion, via electron transfer. However, it is also possible that the 4-methoxyl group may sterically interfere with the proper chelation of the divalent metal, thus retarding cyclization. It would be interesting to distinguish the relative importance of electronic vs. steric effects by the substitution of the methoxyl with a methyl group.[24] This unexpected turn of events forces us to utilize the intramolecular Marschalk reaction to bring our synthetic strategy into fruition. Thus, the ketal **4** was transformed into **47** via a five-step reaction sequence involving benzylation ($PhCH_2Br$, K_2CO_3–acetone; 99% yield), hydrolysis (8% NaOH, dioxane, 90 °C; 92%), reduction (BH_3, THF, 25 °C; 79%), debenzylation (H_2, Pd–$BaSO_4$, ethyl acetate; 90%), and oxidation (PCC, CH_2Cl_2, 25 °C; 65%) in 42% overall yield from **4** (Scheme VI).

Treatment of **47** with basic sodium dithionite at 90 °C followed by acidification afforded red crystalline tetracyclic compound **50**, mp 177–178.5 °C, in 55% yield. By analogy to the 4-demethoxy series, this cyclization proceeds via the intermediates **48** and **49**. We surmised that this aldol-type condensation (**48** to **49**) requires considerably less activation energy than that of the Claisen-type condensation (**40** to **41**), and thus the excess dithionite in aqueous base completely

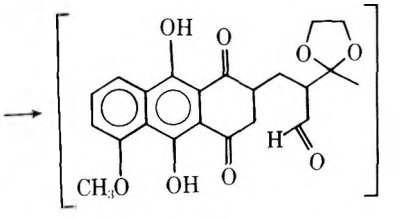
Scheme VI



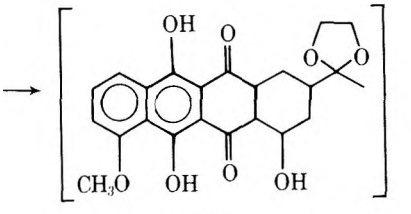
43, R = CH_2Ph; X = CO_2CH_3
44, R = CH_2Ph; X = CO_2H
45, R = CH_2Ph; X = CH_2OH
46, R = H; X = CH_2OH



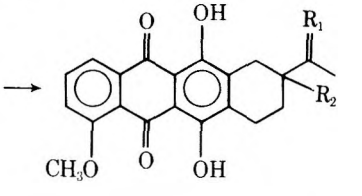
47



48



49



50, R_1 = OCH_2CH_2O; R_2 = H
51, R_1 = O; R_2 = H
52, R_1 = O; R_2 = OH

suppressed the back oxidation of **48** to **47**. Unfortunately, this aqueous basic condition readily cleaved the ester grouping in **40**, so that it is unsuitable for Claisen-type condensation. Moreover, dithionite is unstable at the high temperature required for the Claisen-type cyclization. Deketalization of **50**

with 5% H_2SO_4 in a mixture of THF–acetone afforded **51**, whose spectral properties were found to be identical with an authentic sample.[11c] Hydroxylation at C-9 in **51** was achieved via a four-step reaction sequence, which has been used for the introduction of the C-17 hydroxyl group into steroids.[25] This involved enol acetylation via continuous distillation of the reaction mixture containing **51** and a large excess of *p*-toluenesulfonic acid in acetic anhydride at 145 °C seems to favor the formation of the thermodynamically more stable $\Delta^{9,13}$ enol ether. After epoxidation with *m*-chloroperbenzoic acid, the epoxy acetate was treated successively with base and acid to ensure complete hydrolysis and rearrangement to (±)-7-deoxydaunomycinone (**52**), which was isolated by silica gel chromatography in 50% overall yield from **51**. As methods for the introduction of hydroxyl functions at C-7[12c,26] and C-14[12c,26] have already been described, this route formally constitutes a regiospecific synthesis of adriamycinone.

Equally important, these modes of base-catalyzed cyclizations will probably prove to be of general utility in other regiospecific syntheses of anthracyclinones from anthraquinone derivatives. More direct routes to the preparation of **47** from islandicin methyl ether are currently being investigated.

Experimental Section

Melting points are uncorrected. Unless otherwise stated, IR spectra were taken in $CHCl_3$ using a Perkin-Elmer Model 257 grating spectrophotometer. ^1H NMR data ($CDCl_3$) were obtained with a Varian Associates Model EM 390. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ = 0). Mass spectra were recorded using an AEI-MS-9 double focusing mass spectrometer or a Finnigan 1015 spectrometer at an ionizing voltage of 70 eV. All compounds which were submitted to mass spectrometric molecular weight determination were of high purity as determined by NMR anslysis and TLC. Carbon–hydrogen analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thin-layer chromatograms (TLC) were obtained on 250 μm silica gel G plates. Preparative layer chromatograms (PLC) were obtained on 20 × 20 × 0.25 cm silica gel 60F-254 plates (E. Merck). Column chromatography was performed with silica gel, 70–270 mesh ASTM (Macherey and Nagel). Solvent extracts of aqueous solution were dried over anhydrous $MgSO_4$. Solutions were concentrated under reduced pressure using a rotary evaporator.

2-Methyl-1,4-dihydroxyanthraquinone (6). A mixture of 184 g (1.38 mol) of $AlCl_3$ and 36 g (0.62 mol) of NaCl was added to a 2-L beaker and heated with a Bunsen burner to 180–190 °C for several minutes. To this melt was added 20 g (0.135 mol) of phthalic anhydride and 16.7 g (0.135 mol) of methylhydroquinone, and this mixture was stirred for 8 min at 180–190 °C. After cooling, the reaction was quenched with 750 mL of ice water and concentrated HCl (150 mL). After heating the mixture for 1 h on a steam bath, it was extracted with $CHCl_3$ three times. The combined $CHCl_3$ extract was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to dryness. The residue was washed with dry methanol and recrystallized from $CHCl_3$–CCl_4 to afford 27.2 g (0.107 mol, 79.3%) of pure **6**: mp 178–179 °C; IR (KBr) 1628, 1583, 1460, 1434, 1350, 1273, 1260, 1249, 1218, 726 cm^{-1}; NMR δ 13.21 (s, 1 H), 12.83 (s, 1 H), 8.25 (m, 2 H), 7.75 (m, 2 H), 7.06 (s, 1 H), 2.30 (s, 3 H); MS *m/e* (%) 254 (100, M^+), 253 (53), 239 (11), 197 (22), 152 (26), 141 (31), 140 (18), 115 (30), 105 (21), 102 (47), 77 (29).

Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.33; H, 4.13.

2-Methyl-1,4-dimethoxyanthraquinone (7). A mixture containing 27 g (0.106 mol) of **6**, 96.6 g (1.55 mol) of K_2CO_3, and 30 mL (0.316 mol) of dimethyl sulfate in 1.2 L of dry acetone was stirred under N_2 at reflux for 15 h. After filtration, the filtrate was evaporated to dryness under reduced pressure. The residue (yellow solid) was washed with methanol to remove any unreacted dimethyl sulfate and crystallized from $CHCl_3$–CCl_4 to give 27.5 g (0.097 mol, 92%) of pure **7**: mp 132.5–133.5 °C; IR (KBr) 1668, 1592, 1330, 1248, 975, 730 cm^{-1}; NMR δ 8.17 (m, 2 H), 7.69 (m, 2 H), 7.20 (s, 1 H), 4.01 (s, 3 H), 3.89 (s, 3 H), 2.42 (s, 3 H); MS *m/e* (%) 282 (100, M^+), 253 (48), 165 (62), 152 (58), 139 (59). On TLC ($CHCl_3$–acetone, 98:2), **6** and **7** possessed R_f values of 0.55 and 0.36, respectively.

Anal. Calcd for $C_{17}H_{14}O_4$: 72.33; H, 5.00. Found: C, 71.86; H, 4.93.

2-Bromomethyl-1,4-dimethoxyanthraquinone (8a). A mixture containing 25.6 g (0.0908 mol) of **7**, 17.0 g (0.0955 mol) of *N*-bromosuccinimide, and 50 mg of benzoyl peroxide in 3.1 L of carbon tetrachloride was stirred under N_2 at reflux for 2 h. During this period the reaction contents were irradiated with a sunlamp. After cooling, the succinimide (white solid) was removed by filtration, and the filtrate was evaporated under reduced pressure. Crystallization of the residue from $CHCl_3$–CCl_4 gave 19.7 g (0.0546 mol, 60%) of **8a**: mp 184–186 °C; IR (KBr) 1670, 1590, 1323, 1266, 1240, 1038, 1008, 972, 731 cm^{-1}; NMR δ 8.15 (m, 2 H), 7.70 (m, 2 H), 7.38 (s, 1 H), 4.61 (s, 2 H), 4.01 (s, 3 H). 4.00 (s, 3 H); MS *m/e* (%) 362 (98, M + 1), 360 (100), 281 (65), 252 (51), 223 (84).

Anal. Calcd for $C_{17}H_{13}O_4Br$: C, 56.53; H, 3.63. Found: C, 56.44; H, 3.71.

The mother liquor contained a mixture of **7**, **8a**, and **8b**, possessing R_f values of 0.36, 0.43, and 0.54 on TLC ($CHCl_3$–acetone, 98:2), in a ratio of 2:1:3.4, respectively. The dibromide **8b** was isolated by preparative TLC using two developments in $CHCl_3$–acetone (95:5). Crystallization of **8b** from $CHCl_3$–hexane afforded pure **8b**: mp 175–178 °C; IR ($CHCl_3$) 3018, 2940, 1672, 1593, 1462, 1394, 1318, 1266, 1237, 1037, 1002. 978 cm^{-1}; NMR δ 8.3–7.1 (m, 6 H), 4.10 (s, 3 H), 4.00 (s, 3 H); MS *m/e* (%) 442 (3), 441 (4), 440 (7) 439 (6), 438 (5), 437 (3), 361 (67), 360 (50), 359 (70), 358 (39), 280 (21), 279 (53), 273 (21), 263 (65), 262 (30), 251 (93), 243 (100), 242 (38), 237 (20).

Anal. Calcd for $C_{17}H_{12}O_4Br_2$: C, 46.39; H, 2.75. Found: C, 46.42; H, 2.78.

2-(2′-Acetyl-2′-carbethoxymethyl-3′-oxobutyl)-1,4-dimethoxyanthraquinone (9). To a suspension of 1.4 g (0.0585 mol) of NaH (prewashed with pentane) in 150 mL of dry DMF was added dropwise to 10.8 g (0.0582 mol) of ethyl 3-acetyllevulinate dissolved in 50 mL of DMF under N_2 at 25 °C. After completion of the addition, the mixture was heated at 40 °C until hydrogen evolution ceased (ca. 30 min). A solution containing 20.6 g (0.0571 mol) of **8a** in 50 mL of DMF was added dropwise to this suspension at 25 °C, and the reaction mixture was stirred for 15 h. The reaction was terminated by the addition of dilute HCl (20 mL), and the contents were extracted with ethyl acetate (150 mL × 4). The combined extract was successively washed with saturated $NaHCO_3$ and brine, dried, and evaporated to dryness. The residue was washed with dry methanol and crystallized from $CHCl_3$–ether to afford 23.5 g (0.0504 mol, 88%) of pure **9**: mp 163–163.5 °C; IR (KBr) 1724, 1700, 1670, 1281, 1262, 1242, 1157, 1042 cm^{-1}; NMR δ 8.13 (m, 2 H), 7.69 (m, 2 H), 4.07 (q, J = 7.2 Hz, 2 H), 3.93 (s, 3 H), 3.78 (s, 3 H), 3.57 (s, 2 H), 2.90 (s, 2 H), 2.20 (s, 6 H, 1.19 (t, J = 7.2 Hz, 3 H); MS *m/e* (%) 462 (8, M^+), 423 (15), 391 (51), 377 (53), 43 (100).

Anal. Calcd for $C_{26}H_{26}O_8$: C, 66.94; H, 5.62. Found: C, 66.70; H, 5.57.

2-(2′-Carboxymethyl-3′-oxobutyl)-1,4-dimethoxyanthraquinone (10). The reaction mixture contained 24.2 g (0.0519 mol) of **9** in 70 mL of 8% aqueous NaOH. After stirring the contents at 60 °C under N_2 for 3 h (a small amount of an insoluble oil was removed by Et_2O extraction), the alkaline solution was cooled and acidified with HCl. The yellow solution was separated by filtration after stirring for 30 min. The precipitate was collected by filtration, washed twice with water, dried, and evaporated to dryness. The yield of crude **10** was 18.7 g (0.0472 mol, 91%). Crystallization of **10** from $CHCl_3$–benzene gave mp 200–201.5 °C; IR (KBr) 3300–2800 (broad), 1715, 1668, 1592, 1330, 1260, 1243, 1039 cm^{-1}; NMR δ 8.73 (br, 1 H), 8.21 (m, 2 H), 7.76 (m, 2 H), 7.16 (s, 1 H), 4.03 (s, 3 H), 3.97 (s, 3 H), 2.4–3.6 (m, 5 H), 2.22 (s, 3 H); MS *m/e* (%) 396 (74), 353 (100), 265 (48), 263 (49), 165 (75), 152 (59), 151 (56), 43 (66). The relative mobilities of **9** and **10** on TLC plates were 0.55 and 0.49, respectively, when developed in ethyl acetate–acetic acid–isooctane–water (110:20:50:100 v/v).

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.67; H, 5.10.

2-(2′-Carbomethoxymethyl-3′-oxobutyl)-1,4-dimethoxyanthraquinone (11). To 18.1 g (0.0457 mol) of **10** in 300 mL of chloroform was added an excess of ethereal diazomethane at 0 °C. After stirring for 1 h, a few milliliters of acetic acid were added to destroy the unreacted diazomethane. Evaporation of the solvent and crystallization of the residue from $CHCl_3$–CCl_4 afford 17.0 g (0.0415 mol, 91%) of pure **11**: mp 129–130 °C; IR (KBr) 1726, 1703 (sh), 1669, 1329, 1314, 1260, 1242, 1039 cm^{-1}; NMR δ 8.19 (m, 2 H), 7.71 (m, 2 H), 7.13 (s, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.61 (s, 3 H), 2.4–3.6 (m, 5 H), 2.19 (s, 3 H); MS *m/e* (%) 410 (75, M^+), 379 (23), 367 (100), 165 (67), 152 (48), 43 (45).

Anal. Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found: C, 67.14; H, 5.42.

2-(2′-Carbomethoxymethyl-3′-oxobutyl)-1,4-dihydroxyanthraquinone (12). To 16.0 g (0.0390 mol) of **11** dissolved in 200 mL

of dichloromethane was added dropwise a dichloromethane (282 mL of 0.5 M solution) solution of BBr_3 (0.141 mol) under N_2 at −78 °C. After stirring for 7 h at −78 °C, aqueous $NaHCO_3$ was added and the contents were warmed up to room temperature. The organic layer was washed with brine three times, dried, and evaporated to dryness. The residue was crystallized from $CHCl_3$–CCl_4 to afford 12.7 g (0.0332 mol, 85%) of pure **12:** mp 170–180 °C; IR (KBr) 1730, 1703, 1625, 1588, 1450, 1433, 1410, 1365, 1308, 1260, 1240, 1225, 1205, 790 cm^{-1}; NMR δ 13.36 (s, 1 H), 12.81 (s, 1 H), 8.34 (m, 2 H), 7.82 (m, 2 H), 7.11 (s, 1 H), 3.62 (s, 3 H), 2.4–3.6 (m, 5 H), 2.28 (s, 3 H); MS *m/e* (%) 382 (8, M^+), 364 (42), 279 (57), 187 (100), 43 (60). The relative mobilities of **11** and **12** on TLC plates were 0.13 and 0.34, respectively, in $CHCl_3$–acetone (98:2). The monomethyl ether had an R_f value of 0.22.

Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 65.39; H, 4.96.

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-1,4-dihydroxyanthraquinone (5). A mixture consisting of 12.0 g (0.0314 mol) of **12,** 25 mL of ethylene glycol, 170 mL of benzene, and 30 mg of *p*-toluenesulfonic acid was stirred at reflux; water was collected with a Dean-Stark condenser. After 16 h, the mixture was cooled, diluted with 5% $NaHCO_3$, and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried, and evaporated to dryness. The residue (14.5 g) was chromatographed over 450 g of silica gel. Elution of the column with $CHCl_3$–EtOAC (95:5) gave 11.4 g (0.0268 mol, 85%) of pure **5:** mp 140.5–141 °C ($CHCl_3$–CCl_4); IR (KBr) 1729, 1625, 1587, 1432, 1267, 1232, 1052, 792 cm^{-1}; NMR δ 13.38 (s, 1 H), 12.86 (s, 1 H), 8.31 (m, 2 H), 7.78 (m, 2 H), 7.16 (s, 1 H), 3.96 (s, 4 H), 2.0–3.3 (m, 5 H), 1.39 (s, 3 H); MS *m/e* (%) 426 (3, M^+), 395 (3), 364 (23), 86 (52), 87 (100). The mobility of **13** on TLC plates was 0.26 when developed with $CHCl_3$–acetone (98:2).

Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.97; H, 5.21.

Zinc Reduction of 5. To 1.01 g (2.37 mmol) of **5** in 40 mL of glacial acetic acid was added 1.00 g (15.3 mmol) of zinc dust, and the reaction mixture was stirred under N_2 for 30 min at 25 °C. After dilution of the contents with 5% $NaHCO_3$, the mixture was extracted with $CHCl_3$ three times. The combined extract was washed successively with 5% $NaHCO_3$ and brine, dried, and evaporated to afford 0.92 g (2.14 mmol, 91%) of the yellow dihydroanthraquinone **13:** NMR δ 13.53 (s, 1 H), 13.50 (s, 1 H), 8.44 (m, 2 H), 7.69 (m, 2 H), 3.92 (br s, 4 H), 3.66 (s, 3 H), 1.29 (s, 3 H); MS *m/e* (%) 428 (1.8, M^+), 366 (8), 351 (5), 254 (23), 111 (18), 87 (100). On TLC plates, **13** possessed an R_f value of 0.35, whereas 5 had an R_f value of 0.32 when the plates were developed in $CHCl_3$–acetone (95:5). Compound **13** was too unstable to allow C, H analysis.

9-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-5,7,12-naphthacenetrione (15). (a) Condition 6. To 93 mg (0.21 mmol) of **18** in 3 mL of DMF was added 16 mg (0.24 mmol) of zinc dust and 300 mg (1.95 mmol) of BaO at −78 °C. After repeated flushing of the system with N_2 to remove oxygen, the mixture was heated for 25 min at 140 °C. The reaction was quenched by the addition of dilute HCl at 0 °C, and the resulting mixture was exhaustively extracted with $CHCl_3$. The combined extract was washed with brine, dried, and evaporated to dryness. The residue was subjected to preparative TLC ($CHCl_3$–acetone, 95:5). Four colored bands were noted: brownish red band (R_f 0.25); orange and yellow bands (R_f 0.32); and pink-red band (R_f 0.52). Elution of the brownish red band afforded 16 mg of **15** (20%): mp 185–187 °C ($CHCl_3$–EtOAc); IR 1690, 1669, 1630, 1586, 1405, 1235, 1210, 1048, 734 cm^{-1}; NMR δ 13.97 (s, 1 H), 13.17 (s, 1 H), 8.28 (m, 2 H), 7.80 (m, 2 H), 4.00 (s, 4 H), 2.3–3.7 (m, 5 H), 1.38 (s, 3 H); MS *m/e* (%) 394 (2, M^+), 392 (24), 377 (43), 87 (100), 43 (52).

Anal. Calcd for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 66.85; H, 4.62.

Elution of the pink-red band gave 12 mg (14%) of **16:** mp 231–233 °C ($CHCl_3$–hexane); IR 1595, 1465, 1260, 1045 cm^{-1}; NMR δ 13.35 (s, 1 H), 12.25 (s, 1 H), 10.37 (s, 1 H), 8.48 (m, 2 H), 8.10 (d, 1 H, J = 1.6 Hz), 7.80 (m, 2 H), 7.44 (d, 1 H, J = 1.6 Hz), 4.10 (m, 2 H), 3.85 (m, 2 H), 1.72 (s, 3 H); MS *m/e* (%) 392 (8, M^+), 377 (20), 87 (40), 41 (100); molecular ion at *m/e* 392.0875 (theory for $C_{22}H_{16}O_7$, 392.0894.

The orange and yellow bands consisted of a mixture of **13** and **5** as indicated by the NMR spectrum of the eluate, which totaled 10 mg.

(b) Condition 15. To 30 mg (0.07 mmol) of **18** in 0.6 mL of ethylene glycol and 0.4 mL of diglyme was added 13.7 mg (0.21 mmol) of zinc dust and 31.4 mg (0.56 mmol) of CaO at −78 °C (to minimize ester exchange). After repeated flushing of the system with N_2 to remove the last trace of oxygen, the mixture was heated for 3 min at 140°C. The reaction was quenched by the addition of dilute HCl at 0 °C, and the resulting mixture was exhaustively extracted with $CHCl_3$. The combined extract was washed with brine, dried, and evaporated to dryness. TLC analysis ($CHCl_3$–acetone, 95:5) of the residue revealed the presence of three components with relative mobilities of 0.25 (brownish red) (**15**), 0.1 (orange-red) (**5b**), and 0.00 (orange-red) (**5a**). PLC of this mixture ($CHCl_3$–acetone, 95:5) afforded 15 mg (54%) of **15.** Initially, the bottom band was composed mainly of **18** and **19,** as evidenced by a characteristic bright blue fluorescence under long wave ultraviolet light, which upon standing underwent aerial oxidation to **5a** and **5b,** respectively. As a rule, the R_f values of the leuco forms are very similar to their oxidized forms. The bottom red band (10 mg) was further purified after elution and developed in $CHCl_3$–MeOH (95:5), which gave 3 mg of **5a** [R_f 0.2; mp 198–199 °C ($CHCl_3$–acetone); IR 1720, 1624, 1589, 1430, 1266, 1204 cm^{-1}; NMR δ 13.55 (s, 1 H), 12.81 (br s, 1 H), 8.31 (m, 2 H), 7.78 (m, 2 H), 7.14 (s, 1 H), 3.94 (s, 4 H), 3.3–1.8 (m, 5 H), 1.37 (s, 3 H); MS *m/e* (%) 412 (7, M^+), 394 (22), 350 (48), 349 (23), 307 (17), 305 (16), 304 (19), 280 (20), 279 (43), 278 (17), 262 (15), 253 (35), 225 (19), 187 (13), 87 (28), 86 (21), 43 (100)] and 3 mg of **5b** [R_f 0.4; IR 3500, 2950, 1730, 1624, 1589, 1430, 1410, 1339, 1266, 1233, 1205, 1045, 951 cm^{-1}; NMR δ 13.35 (s, 1 H), 12.84 (s, 1 H), 8.28 (m, 2 H), 7.78 (m, 2 H), 7.14 (s, 1 H), 4.11 (m, 2 H), 3.98 (s, 4 H), 3.72 (m, 2 H), 3.3–1.8 (m, 5 H), 1.45 (s, 3 H); MS *m/e* (%) 456 (3, M^+), 455 (2), 395 (17), 394 (40), 393 (18), 351 (10), 350 (12), 305 (24), 304 (36), 279 (34), 253 (24), 225 (16), 87 (100), 86 (47), 43 (91)].

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-1,4-dibenzyloxyanthraquinone (20). A mixture consisting of 1.0 g (2.35 mmol) of 5, 3.1 g (22.4 mmol) of anhydrous K_2CO_3, and 2.0 g (12 mmol) of benzyl bromide in 60 mL of acetone was refluxed under N_2 for 16 h. After filtration, the filtrate was evaporated to yield a yellow solid. After washing with methanol, crystallization from $CHCl_3$–MeOH afforded 1.29 g (2.13 mmol, 91%) of pure **20:** mp 120–122 °C; IR 1730, 1670, 1597, 1582, 1326, 1260, 1235, 1205 cm^{-1}; NMR δ 8.4–7.0 (m, 15 H), 5.30 (s, 2 H), 5.01 (s, 2 H), 3.90 (m, 4 H), 3.48 (s, 3 H), 3.2–1.5 (m, 5 H), 1.21 (s, 3 H); MS *m/e* (%) 471 (7, M − 107), 105 (3), 91 (100), 90 (51), 89 (11), 65 (4), 43 (5).

Anal. Calcd for $C_{37}H_{34}O_8$: C, 73.25; H, 5.65. Found: C, 73.41; H, 5.80.

2-(2′-Carboxymethyl-3′-ethylenedioxybutyl)-1,4-dibenzyloxyanthranthraquinone (21). A mixture containing 1.25 g (2.06 mmol) of **20** in 10 mL of 8% aqueous NaOH and 4 mL of *p*-dioxane was stirred under N_2 at 90 °C for 2 h. After cooling, dilute HCl was added and the resulting solution was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to give 1.12 g (1.89 mmol, 92%) of **21:** IR 3300–2500, 1705, 1667, 1595, 1583, 1322, 1258, 1235, 1204, 1039 cm^{-1}; NMR δ 8.18 (m, 2 H), 7.9–7.0 (m, 13 H), 5.25 (s, 2 H), 4.97 (br s, 2 H), 3.78 (m, 4 H), 3.2–1.6 (m, 5 H), 1.15 (s, 3 H); MS *m/e* (%) 575 (1.2, M − 17), 574 (0.5, M − 18), 502 (4), 486 (6), 485 (5), 440 (5), 394 (10), 279 (12), 105 (14), 91 (77), 90 (32), 87 (100).

2-[2′-(2-Hydroxyethyl)-3′-ethylenedioxybutyl]-1,4-dibenzyloxyanthraquinone (22). To 1.02 g (1.72 mmol) of **21** in 5 mL of THF was added dropwise 3.4 mL (3.4 mmol) of a THF solution of borane (1 M) at room temperature. After stirring for 1 h, 3 mL of ethanol was added and the resulting mixture was evaporated. Chromatography of the residue on 30 g of silica gel eluting the column with $CHCl_3$–MeOH (99:1) gave 671 mg (68%) of **22:** IR 3050, 2950, 2880, 1667, 1593, 1580, 1321, 1259, 1232, 1203 cm^{-1}; NMR δ 8.20 (m, 2 H), 7.9–7.1 (m, 13 H), 5.30 (br s, 2 H), 4.97 (br s, 2 H), 3.81 (m, 4 H), 3.30 (m, 2 H), 3.02 (m, 1 H), 2.7–1.3 (m, 4 H), 1.25 (s, 3 H); MS *m/e* (%) 470 (1, M^+ − 180), 469 (1), 432 (7), 431 (6), 425 (10), 424 (8), 342 (5), 335 (5), 325 (5), 173 (5), 105 (16), 92 (18), 91 (100), 90 (43), 87 (30), 86 (12).

2-[2′-(2-Hydroxyethyl)-3′-ethylenedioxybutyl]-1,4-dihydroxyanthraquinone (23). To a suspension of 427 mg of 5% Pd–$BaSO_4$ in 5 mL of ethyl acetate (presaturated with H_2) was added a solution of 427 mg (0.739 mmol) of **22** dissolved in 3 mL of ethyl acetate. The mixture was stirred under hydrogen at 25 °C for 1 h, and the contents were then filtered through Celite. The solvent was evaporated to dryness, and the residue was chromatographed over 15 g of silica gel. Elution of the column with $CHCl_3$–MeOH (99:1) afforded 258 mg (87%) of **23:** IR 3480, 2990, 2940, 2880, 1641, 1586, 1410, 1340, 1265, 1232, 1201 cm^{-1}; NMR δ 13.46 (br s, 1 H), 12.87 (br s, 1 H), 8.28 (m, 2 H), 7.78 (m, 2 H), 7.15 (s, 1 H), 3.89 (s, 4 H), 3.61 (m, 2 H), 3.09 (dd, J_1 = 12.3 Hz, J_2 = 4.2 Hz, 1 H), 2.7–1.6 (m, 4 H), 1.40 (s, 3 H); MS *m/e* (%) 398 (0.4, M^+), 336 (10), 318 (4), 304 (4), 291 (3), 254 (4), 87 (100), 86 (39), 43 (23); molecular ion at *m/e* 398.1384 (theory for $C_{22}H_{22}O_7$, 398.1363).

2-(2′-Formylmethyl-3′-ethylenedioxybutyl)-1,4-dihydroxyanthraquinone (24). To 60 mg (0.28 mmol) of pyridinium chlorochromate suspended in 3 mL of CH_2Cl_2 was added dropwise a solution

of **23** (53 mg, 0.13 mmol) in 2 mL of CH_2Cl_2 at room temperature. After stirring for 1 h, 25 mL of dry ether was added and the resulting mixture was filtered through Celite. The filtrate was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to dryness. Preparative TLC ($CHCl_3$–acetone, 95:5) afforded 34 mg (66%) of **24:** IR 2980, 1729, 1622, 1589, 1445, 1430, 1371, 1265 (sh), 1245, 1204, 1039 cm^{-1}; NMR δ 13.41 (s, 1 H), 12.88 (s, 1 H), 9.53 (m, 1 H), 8.31 (m, 2 H), 7.83 (m, 2 H), 7.14 (s, 1 H), 3.94 (s, 4 H), 1.44 (s, 3 H); MS *m/e* (%) 396 (2, M^+), 334 (3), 305 (6), 253 (2), 225 (2), 149 (11), 87 (100), 43 (55); molecular ion at *m/e* 396.1217 (theory for $C_{22}H_{20}O_7$, 396.1207).

Zinc Reduction of 24. A mixture containing 17.3 mg (0.0436 mmol) of **24**, 17 mg (0.26 mmol) of zinc dust, and 1 mL of glacial acetic acid was stirred under N_2 at 25 °C. After 30 min, 5% $NaHCO_3$ was added and the resulting solution was extracted with $CHCl_3$ three times. The combined extract was washed successively with 5% $NaHCO_3$ and brine, dried, and evaporated to give 16.4 mg (0.0412 mmol, 94%) of crude **25**. This crude material, consisting of two products, was separated by PLC ($CHCl_3$–acetone, 95:5). The more polar band was the predominant product and exhibited the following spectral properties: NMR δ 13.58 (s, 1 H), 8.46 (m, 2 H), 7.76 (m, 2 H), 3.98 (s, 4 H), 1.33 (s, 3 H); MS *m/e* (%) 398 (3, M^+), 390 (11), 365 (4), 336 (5), 318 (13), 293 (9), 275 (7), 254 (20), 87 (100), 86 (64). The less polar band showed the following: NMR δ 13.50 (s, 1 H), 8.43 (m, 2 H), 7.74 (m, 2 H), 4.01 (s, 4 H), 1.31 (s, 3 H); MS *m/e* (%) 398 (9, M^+), 380 (3), 365 (1), 336 (8), 318 (3), 293 (6), 275 (2), 254 (46), 87 (100).

8-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (27). A. To a mixture of 12.1 mg (0.0304 mmol) of **25**, 0.4 mL of ethylene glycol, and 0.3 mL of diglyme was added 5.0 mg (0.076 mmol) of zinc dust and 11.2 mg (0.2 mmol) of CaO under N_2 at 25 °C. The mixture was heated at 140 °C for 3 min. The reaction was quenched with dilute HCl at 0 °C, and the resulting mixture was extracted with $CHCl_3$ three times. The combined extracts were washed with brine, dried, and evaporated to dryness. Purification via PLC (silica gel; $CHCl_3$–acetone, 95:5) gave 6.5 mg (0.017 mmol, 56%) of **27:** mp 183–184 °C ($CHCl_3$–MeOH); IR 1635 (sh), 1625, 1592, 1450, 1400, 1380, 1280, 1266, 1242 cm^{-1}; NMR δ 13.51 (s, 1 H), 13.48 (s, 1 H), 8.35 (m, 2 H), 7.78 (m, 2 H), 4.00 (s, 4 H), 3.3–1.5 (m, 7 H), 1.40 (s, 3 H); MS *m/e* (%) 380 (21, M^+), 318 (22), 293 (16), 275 (9), 87 (100), 86 (100).

Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.17; H, 5.46.

B. To 13.1 mg (0.033 mmol) of **24** in 0.3 mL of *p*-dioxane was added 0.4 mL of 5% aqueous NaOH and 120 mg (0.689 mmol) of $Na_2S_2O_4$ under N_2 at 25 °C. After stirring for 30 min (color turned from purple to yellow after 5 min), the reaction mixture was heated at 90 °C for 1 h. Additional $Na_2S_2O_4$ (20 mg) was then added, and the heating was continued for another 30 min. The reaction was quenched with dilute HCl at 0 °C and the resulting mixture extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated. PLC purification of the residue (silica gel; $CHCl_3$–acetone, 95:5) gave 6.2 mg (0.016 mmol, 50%) of **27.**

8-Acetyl-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (28). To 2 mL of the acidic solution THF–5% H_2SO_4–acetone (1:1:1) was added 10.1 mg (0.0265 mmol) of **27.** After stirring the reaction mixture at 50 °C for 3 h, 3 mL of 5% $NaHCO_3$ was added and the contents were extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. PLC purification (silica gel; $CHCl_3$–acetone, 95:5) gave 8.2 mg (92%) of **28:** mp 180–182 °C ($CHCl_3$–MeOH); IR 1710, 1625, 1410, 1400, 1378, 1342, 1277, 1265, 1240, 1208 cm^{-1}; NMR δ 13.41 (s, 1 H), 13.36 (s, 1 H), 8.29 (m, 2 H), 7.77 (m, 2 H), 3.3–1.5 (m, 7 H), 2.27 (s, 3 H); MS *m/e* (%) 336 (18, M^+), 293 (45), 275 (30), 187 (32), 105 (21), 77 (26), 43 (100); molecular ion at *m/e* 336.1002 (theory for $C_{20}H_{16}O_5$, 336.0998).

1-Hydroxy-2-methyl-5-methoxyanthraquinone (30). To 1-hydroxy-5-methoxyanthraquinone (**29**; 26.5 g, 104 mmol) in 1.5% NaOH (2.65 L) under N_2 was added 20.5 g (117 mmol) of $Na_2S_2O_4$ at 25 °C. After stirring the mixture for 10 min at 90 °C, 8.97 g (120 mmol) of 40% CH_2O solution was added (color turned from orange-red to deep red within 10 min). After stirring at 90 °C for 60 min, the reaction mixture was cooled to 50 °C and a current of air was passed through the solution for 60 min (color changed from deep red to purple. The reaction mixture was then acidified with 10% H_2SO_4, heated at 50 °C for 1 h, and extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated. Chromatography of the residue over 700 g of silica gel (elution with $CHCl_3$) afforded 16.8 g (62.2 mmol, 60%) of **30:** mp 185–186 °C ($CHCl_3$–CCl_4); IR (KBr) 1668, 1636, 1585, 1281, 1266, 1011, 791, 781 cm^{-1}; NMR δ 12.73 (s, 1 H), 7.95 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 4.02 (s, 3 H), 2.33 (s, 3 H); MS *m/e* (%) 268 (100, M^+), 253 (88), 251 (16), 239 (17), 225 (14), 165 (16), 152 (24), 139 (17), 115 (16), 105 (10), 76 (21), 63 (16).

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.66; H, 4.65.

1-Acetoxy-2-methyl-5-methoxyanthraquinone (31). A mixture containing 15.1 g (56.3 mmol) of **30**, 1 mL of concentrated H_2SO_4, and 300 mL of acetic anhydride was stirred at 25 °C for 3.5 h. The reaction mixture was then poured into 3 L of ice water, and the resulting suspension was extraced with $CHCl_3$ three times. The combined $CHCl_3$ extract was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to yield 17.3 g (55.8 mmol, 99%) of **31:** mp 195–197 °C ($CHCl_3$–CCl_4); IR (KBr) 1750, 1672, 1588, 1263 cm^{-1}; NMR δ 8.12 (d, J = 7.8 Hz, 1 H), 7.85 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.67 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.29 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 4.02 (s, 3 H), 2.50 (s, 3 H), 2.30 (s, 3 H); MS *m/e* (%) 310 (20, M^+), 268 (100), 267 (43), 254 (37), 253 (100), 252 (34), 251 (26), 239 (26), 225 (22), 222 (15), 168 (16), 165 (24), 153 (26), 152 (44), 139 (36), 115 (13), 76 (16), 41 (81).

Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.80; H, 4.71.

1-Acetoxy-2-bromomethyl-5-methoxyanthraquinone (32a). A mixture containing 30 g (97 mmol) of **31**, 17.8 g (100 mmol) of *N*-bromosuccinimide (NBS), and 200 mg of benzoyl peroxide in 3.5 L of CCl_4 was stirred under N_2 at reflux. After 3 h, an additional 4 g (22 mmol) of NBS and 100 mg of benzoyl peroxide were added and the contents were refluxed for an additional 5 h. During reflux, the reaction mixture was irradiated with a sunlamp. After cooling, the succinimide (white solid) was removed by filtration and the filtrate was evaporated under reduced pressure. Crystallization of the residue from $CHCl_3$–CCl_4 gave 15 g (38 mmol) of **32a:** mp 213–216 °C; IR (KBr) 1762, 1672, 1587, 1267 cm^{-1}; NMR δ 8.18 (d, J = 8.0 Hz, 1 H), 7.95–7.7 (m, 2 H), 7.67 (dd, J_1 = J_2 = 7.8 Hz), 7.28 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 4.46 (s, 2 H), 4.02 (s, 3 H), 2.51 (s, 3 H); MS *m/e* (%) 390 (1, M^+ for ^{81}Br), 388 (1, M^+ for ^{79}Br), 348 (7), 346 (7), 268 (16), 267 (100), 266 (31), 239 (17), 152 (24), 76 (9), 41 (52).

Anal. Calcd for $C_{18}H_{13}O_5Br$: C, 55.54; H, 3.37. Found: C, 55.50; H, 3.47.

The mother liquor, containing residual **31**, **32a**, and dibromide **32b**, was chromatographed on a silica gel column (6.25 × 90 cm). The column was eluted with $CHCl_3$, and 17-mL fractions were collected. Fractions 1–140 gave 12 g (26 mmol) of dibromide **32b:** mp 196–198 °C; IR 3015, 2940, 1781, 1674, 1589, 1578, 1265, 1167, 1005 cm^{-1}; NMR δ 8.28 (s, 2 H), 8.1–7.1 (m, 3 H), 6.90 (s, 1 H), 4.01 (s, 3 H), 2.54 (s, 3 H); MS *m/e* (%) 468 (2), 467 (2), 466 (1), 426 (6), 425 (4), 424 (4), 347 (100), 346 (55), 345 (100), 238 (40), 237 (34), 152 (47), 151 (58), 150 (40), 105 (31), 104 (19), 85 (23), 83 (27). Fractions 210–305 afforded an additional 7 g (18 mmol) of **32a.** Fractions 141–209 (5 g) consisted of a mixture of **32b** and **32a** in an approximately 1:1 ratio; fractions 306–356 (3.5 g) contained **32a** and **31** in a ratio of 2:1.

1-Acetoxy-2-(2′-acetyl-2′-carbethoxymethyl-3′-oxobutyl)-5-methoxyanthraquinone (33). To 0.865 g (36 mmol) of NaH (prewashed with dry pentane) in 50 mL of dry THF under N_2 was added dropwise a solution of 6.51 g (35 mmol) of 3-acetyllevulinic acid ethyl ester dissolved in 50 mL of dry THF at 25 °C. After completion of this addition, the mixture was heated at 40 °C until hydrogen evolution ceased (ca. 30 min). A solution of 200 mL of dry DMF containing 13.4 g (34.4 mmol) of **32a** was added dropwise at −21 °C (dry ice–CCl_4) to the reaction mixture. After warming to 25 °C, the mixture was stirred for 10 h. The reaction was quenched with dilute HCl and the resulting mixture extracted three times with ethyl acetate. The combined extract was washed with brine, dried, and evaporated to dryness. The residue was washed with dry methanol to give 16.5 g (33.5 mmol, 97%) of **33,** which was used for the subsequent reaction. Crystallization of **33** from $CHCl_3$–ether afforded an analytical sample: mp 181–182 °C; IR (KBr) 1771, 1729, 1712, 1700, 1670, 1363, 1269, 1177 cm^{-1}; NMR δ 7.85 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.8 (AB q, ν_A = 8.11, ν_B = 7.49, J_{AB} = 8.1 Hz, 2 H), 7.69 (dd, J_1 = J_2 = 7.8 Hz), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.04 (s, 3 H), 3.57 (s, 2 H), 2.92 (s, 2 H), 2.47 (s, 3 H), 2.22 (s, 6 H), 1.23 (t, J = 7.1 Hz, 3 H); MS *m/e* (%) 494 (0.1, M^+), 452 (1), 434 (7), 409 (12), 392 (51), 391 (100), 390 (74), 389 (20), 363 (41), 362 (23), 335 (16), 279 (14), 278 (13), 267 (14), 43 (78).

Anal. Calcd for $C_{27}H_{26}O_9$: C, 65.58; H, 5.30. Found: C, 64.98; H, 5.19.

2-(2′-Carboxymethyl-3′-oxobutyl)-1-hydroxy-5-methoxyanthraquinone (34). A mixture containing 16.5 g (33.5 mmol) of **33** in 40 mL of 5% NaOH was stirred at 65 °C under nitrogen for 5 h. After cooling, the reaction mixture was acidified and a yellow precipitate was formed after stirring for 30 min. The precipitate was collected by filtration, washed twice with water and methanol, and dried under reduced pressure to yield 11.6 g (30.4 mmol, 91%) of crude **34,** which

was used for the Elbs oxidation. Two crystallizations of **34** from $CHCl_3$–EtOAc afforded an analytical sample: mp 197–200 °C; IR (KBr) 3400–2500, 1710, 1666, 1631, 1587, 1430, 1265 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 12.85 (s, 1 H), 7.98 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 7.9–7.3 (m, 4 H), 6.60 (br s, 1 H), 4.06 (s, 3 H), 3.7–2.3 (m, 5 H), 2.21 (s, 3 H); MS *m/e* (%) 382 (40, M^+), 339 (16), 321 (16), 305 (33), 294 (33), 279 (32), 267 (28), 266 (21), 239 (11), 165 (20), 152 (23), 139 (18), 77 (12), 41 (100).

Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 66.07; H, 4.93.

2-(2′-Carboxymethyl-3′-oxobutyl)-1,4-dihydroxy-5-methoxyanthraquinone (35). To a solution of 8 mL of 2 M aqueous KOH containing 601 mg (1.57 mmol) of **34** was added 20 mL of aqueous $K_2S_2O_8$ (800 mg, 2.96 mmol) solution under N_2. After stirring the reaction mixture for 2 days at 25 °C, the contents were acidified with 10% HCl to pH 4.0 to precipitate the unreacted starting material (yellow solid). After extraction of the filtrate with ethyl acetate to remove traces of **34**, 575 mg (4.56 mmol) of Na_2SO_3 and 4 mL of concentrated HCl were then added. The resulting mixture was heated on a steam bath for 1 h, and the solution was exhaustively extracted with $CHCl_3$. The combined extract was washed with brine, dried, and evaporated to give 262 mg (0.658 mmol, 42%) of **35:** mp 124–125 °C ($CHCl_3$–EtOAc); IR 3300, 2500, 1705, 1613, 1575, 1440, 1275, 1217, 774 cm^{-1}; NMR δ 13.29 (s, 1 H), 13.18 (br s, 1 H), 7.99 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.76 (t, J_1 = J_2 = 7.8 Hz), 7.40 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.10 (s, 1 H), 6.87 (br s, 1 H), 4.09 (s, 3 H), 2.7–2.4 (m, 5 H), 2.24 (s, 3 H); MS *m/e* (%) 398 (20, M^+), 390 (43), 315 (17), 334 (16), 321 (16), 309 (37), 295 (16), 293 (12), 291 (12), 283 (17), 255 (22), 217 (17), 41 (100).

Anal. Calcd for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.03; H, 4.90.

The residual starting material (yellow solid) was purified by chromatography over silica gel. Elution of the column with $CHCl_3$–MeOH (5:1) afforded 227 mg of **34** (0.597 mmol, 38%).

2-(2′-Carbomethoxymethyl-3′-oxobutyl)-1,4-dihydroxy-5-methoxyanthraquinone (36). To 1.52 g (3.8 mmol) of **35** dissolved in 30 mL of $CHCl_3$ was added an excess of ethereal diazomethane at 0 °C. After stirring for 1 h, 1 drop of acetic acid was added and the solvent was evaporated under reduced pressure to yield 1.57 g (3.81 mmol, 99.7%) of **36.** Crystallization of **36** from $CHCl_3$–hexane afforded a sample: mp 147–148 °C; IR (KBr) 1733, 1715, 1620, 1580, 1281, 1262, 1222 cm^{-1}; NMR δ 13.30 (s, 1 H), 13.17 (s, 1 H), 8.02 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.75 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.38 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.08 (s, 1 H), 4.07 (s, 3 H), 3.60 (s, 3 H), 3.6–2.4 (m, 5 H), 2.26 (s, 3 H); MS *m/e* (%) 412 (49, M^+), 394 (70), 381 (19), 370 (23), 369 (21), 337 (21), 321 (25), 310 (37), 309 (81), 308 (30), 295 (27), 293 (20), 255 (34), 217 (42), 43 (100), 41 (38).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.07; H, 4.87. Found: C, 64.04; H, 5.15.

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-1,4-dihydroxy-5-methoxyanthraquinone (4). The reaction mixture, containing 1.57 g (3.81 mmol) of **36,** 3 mL of ethylene glycol, and 15 mg of *p*-toluenesulfonic acid in 50 mL of benzene, was refluxed for 14 h. The water was collected through a Dean-Stark condenser. After cooling, the contents were diluted with 5% $NaHCO_3$ and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried, and evaporated to dryness. The residue (1.74 g) was chromatographed over 46 g of silica gel. Elution of the column with $CHCl_3$–EtOAc (95:5) gave 1.42 g (82%) of **4:** mp 164–165 °C ($CHCl_3$–CCl_4); IR (KBr) 1720, 1615, 1574, 1435, 1275, 1257, 1218, 1025, 780 cm^{-1}; NMR δ 13.30 (s, 1 H), 13.19 (s, 1 H), 7.93 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.68 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.13 (s, 1 H), 4.04 (s, 3 H), 4.00 (s, 4 H), 3.52 (s, 3 H), 3.13 (dd, J_1 = 12.1 Hz, J_2 = 3.0 Hz, 1 H), 3.0–2.0 (m, 4 H), 1.41 (s, 3 H); MS *m/e* (%) 456 (5, M^+), 425 (2), 349 (20), 379 (3), 335 (3), 334 (3), 321 (5), 309 (3), 87 (100), 41 (26).

Anal. Calcd for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Found: C, 63.22; H, 5.40.

9-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-4-methoxy-5,7,12-naphthacenetrione (41). To 64 mg (0.14 mmol) of **4** in 0.4 mL of *p*-dioxane was added 200 mg (1.15 mmol) of $Na_2S_2O_4$ in 0.8 mL of 5% aqueous NaOH under N_2. After stirring at 25 °C for 30 min (color turned from dark red to yellow), 50 mg of additional $Na_2S_2O_4$ was added and the mixture was stirred for another 30 min. After quenching the reaction with dilute HCl, the resulting mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to afford 59 mg (92%) of crude **40** as a mixture of two diastereomers: IR 1730, 1630, 1609, 1585, 1395, 1265 cm^{-1}; NMR δ 14.60 (s, 1 H), 13.47 (s, 0.5 H), 13.43 (s, 0.5 H), 8.03 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.54 (t, J = 7.8 Hz, 1 H), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 4.03 (s, 3 H), 3.93 (s, 2 H), 3.91 (br s, 2 H), 3.64 (s, 1.5 H), 3.60 (s, 1.5 H), 1.5–3.4 (m, 8 H), 1.27 (s, 3 H); MS *m/e* (%) 458 (0.6, M^+), 396 (2), 284 (9), 187 (4), 155 (5), 149 (8), 111 (31), 87 (100). This mixture was used for the following cyclization reaction.

To 51 mg (0.11 mmol) of **40** suspended in 1.1 mL of glycerol and 0.28 mL of water was added 50 mg (0.87 mmol) of CaO and 20 mg (0.31 mmol) of zinc dust at −78 °C (to minimize ester exchange). After repeated flushing of the system with N_2 to remove the last traces of oxygen, the reaction mixture was heated to 140 °C for exactly 5 min. After cooling, the reaction was quenched by the addition of dilute HCl at 0 °C and the mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. TLC analysis ($CHCl_3$–acetone, 95:5) of the mixture revealed the presence of three components with relative mobilities of 0.35 (brownish red), 0.54 (red), and 0.01 (red). Purification of this mixture using PLC afforded 3.9 mg (8.4%) of **41** (R_f 0.35): mp 234–236 °C ($CHCl_3$–MeOH); IR 1625, 1593, 1285, 1205, 730 cm^{-1}; NMR δ 14.33 (s, 1 H), 13.10 (s, 1 H), 7.98 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.73 (t, J_1 = 7.8 Hz), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 4.05 (s, 4 H), 3.98 (s, 3 H), 3.6–1.5 (m, 5 H), 1.39 (s, 3 H); MS *m/e* (%) 424 (7, M^+), 423 (31), 422 (79), 407 (100), 406 (9), 363 (9), 348 (9), 335 (15), 320 (11), 87 (53); molecular ion at *m/e* 424.1159 (theory for $C_{23}H_{20}O_8$, 424.1159.

Elution of the top red band (R_f 0.54) gave 15 mg of **4,** and the bottom band (R_f 0.01) afforded 14 mg of **37 37.** [IR (KBr) 3300–2500, 1720, 1620, 1582, 1440, 1280, 1225 cm^{-1}; NMR δ 13.35 (s, 1 H), 13.22 (s, 1 H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.72 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.36 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.18 (s, 1 H), 6.94 (br s, 1 H), 4.06 (s, 3 H), 3.98 (s, 4 H), 3.13 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1 H), 3.0–2.0 (4H), 1.40 (s, 3 H)], which was esterified to **4** and recycled.

Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01. Found: C, 62.40; H, 5.02.

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-5-methoxy-1,4-dibenzyloxyanthraquinone (43). A mixture consisting of 550 mg (1.21 mmol) of **4,** 1 g (7.2 mmol) of anhydrous K_2CO_3, and 0.51 g (3 mmol) of benzyl bromide in 50 mL of acetone was refluxed under N_2 for 20 h. The reaction mixture was then filtered, and the filtrate was evaporated to dryness. The residue was washed with methanol to remove the unreacted benzyl bromide, and 761 mg (99%) of crude **43** was obtained. Crystallization of **43** from $CHCl_3$–MeOH gave a sample: mp 134–136 °C; IR 1759, 1670, 1588, 1205, 1015 cm^{-1}; NMR δ 7.8–7.1 (m, 14 H), 5.29 (s, 2 H), 4.99 (s, 2 H), 3.97 (s, 3 H), 3.77 (m, 4 H), 3.45 (s, 3 H), 2.97 (d, J = 9.6 Hz, 1 H), 2.65 –1.75 (m, 4 H), 1.25 (s, 3 H); MS *m/e* (%) 636 (6, M^+), 546 (5), 530 (4), 484 (4), 483 (4), 394 (6), 372 (5), 356 (4), 105 (7), 92 (20), 91 (100), 87 (93).

Anal. Calcd for $C_{38}H_{36}O_9$: C, 71.68; H, 5.70. Found: C, 71.10; H, 5.80.

2-(2′-Carboxymethyl-3′-ethylenedioxybutyl)-5-methoxy-1,4-dibenzyloxyanthraquinone (44). A mixture of 720 mg (1.13 mmol) of **43,** 8 mL of 8% aqueous NaOH, and 3 mL of *p*-dioxane was stirred under N_2 at 90 °C for 3 h. After cooling, dilute HCl was added and the resulting solution was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to yield 646 mg (92%) of crude **44.** Crystallization of **44** ($CHCl_3$–MeOH) afforded a sample: mp 173–174 °C; IR 1740, 1718, 1680, 1598, 1275, 1216 cm^{-1}; NMR δ 7.8–7.1 (m, 14 H) 6.52 (br s, 1 H), 5.24 (s, 2 H), 4.97 (s, 2 H), 3.94 (s, 3 H), 3.74 (m, 4 H), 2.93 (br d, J = 10.2 Hz, 1 H), 2.61–1.76 (m, 4H), 1.14 (s, 3 H); MS *m/e* (%) 622 (3, M^+), 532 (4), 516 (2), 514 (2), 469 (4), 442 (4), 379 (5), 372 (6), 309 (5), 283 (3), 105 (4), 92 (21), 91 (100), 87 (49).

Anal. Calcd for $C_{37}H_{34}O_9$: C, 71.37; H, 5.50. Found: C, 71.49; H, 5.60.

2-[2′-(2′-Hydroxyethyl)-3′-ethylenedioxybutyl]-5-methoxy-1,4-dibenzyloxyanthraquinone (45). To 302 mg (0.486 mmol) of **44** in 2 mL of dry THF was added dropwise 0.97 mL (0.97 mmol) of a BH_3–THF solution (1 M) at room temperature. After stirring for 1 h, 2 mL of ethanol was added and the resulting mixture was evaporated to dryness. PLC purification (silica gel; $CHCl_3$–MeOH, 95:5) of the crude material gave 235 mg (80%) of **45:** IR 1678, 1596, 1455, 1325, 1270, 1213, 1020 cm^{-1}; NMR δ 7.8–7.0 (m, 14 H), 5.31 (s, 2 H), 4.99 (s, 2 H), 4.00 (s, 3 H), 3.83 (m, 4 H), 3.32 (m, 2 H), 3.02 (dd, J_1 = 13.5 Hz, J_2 = 3.0 Hz, 1 H), 2.54–1.65 (m, 4 H), 1.25 (s, 3 H); MS *m/e* (%) 500 (4, M − 108), 91 (46), 87 (100); molecular ion at *m/e* 608.2393 (theory for $C_{37}H_{36}O_8$, 608.2410).

2-[2′-(2-Hydroxyethyl)-3′-ethylenedioxybutyl]-5-methoxy-1,4-dihydroxyanthraquinone (46). To a suspension of 5 mL of ethyl acetate and 200 mg of 5% Pd–$BaSO_4$ (presaturated with hydrogen) was added a solution of 202 mg (0.332 mmol) of **45** in 3 mL of ethyl

acetate. After stirring the mixture under H_2 for 1 h, the contents were filtered through Celite. The filtrate was evaporated, and the crude **46** was purified by PLC (elution with $CHCl_3$–MeOH, 95:5), which afforded 101 mg (71%) of pure **46:** IR 1625, 1593, 1454, 1445, 1285, 1272, 1246, 1040 cm^{-1}; NMR δ 13.35 (s, 1 H), 13.17 (s, 1 H), 7.92 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1 H), 7.68 (dd, $J_1 = J_2$ = 8.0 Hz, 1 H), 7.31 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1 H), 7.09 (s, 1 H), 4.02 (s, 3 H), 3.95 (s, 4 H), 3.61 (m, 2 H), 3.06 (dd, J_1 = 12.0 Hz, J_2 = 3.0 Hz), 2.85–1.43 (m, 4 H), 1.37 (s, 3 H); MS *m/e* (%) 428 (0.2, M^+), 366 (2), 348 (1), 335 (1), 243 (4), 165 (3), 87 (100), 86 (19); molecular ion at *m/e* 428.1471 (theory for $C_{23}H_{24}O_8$, 428.1471).

2-(2′-Formylmethyl-3′-ethylenedioxybutyl)-5-methoxy-1,4-dihydroxyanthraquinone (47). To a suspension of 60 mg (0.28 mmol) of pyridinium chlorochromate (PCC) in 3 mL of CH_2Cl_2 was added dropwise a solution of CH_2Cl_2 (2 mL) containing 60 mg (0.14 mmol) of **46** at room temperature. After stirring for 1 h, 25 mL of ether was added and the mixture was filtered through Celite. The filtrate was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to dryness. PLC purification (elution with $CHCl_3$–MeOH, 95:5) of the crude **47** (48 mg) gave 39 mg (65%) of pure **47:** IR 1740, 1619, 1585, 1260, 1205 cm^{-1}; NMR δ 13.31 (s, 1 H), 13.11 (s, 1 H), 9.52 (dd, J_1 = 3.3 Hz, J_2 = 1.2 Hz), 8.02 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 1 H), 7.75 (dd, $J_1 = J_2$ = 7.8 Hz, 1 H), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.11 (s, 1 H), 4.06 (s, 3 H), 3.95 (m, 4 H), 3.17 (dd, J_1 = 12.0 Hz, J_2 = 3.1 Hz, 1 H), 3.0–2.0 (m, 4 H), 1.41 (s, 3 H); MS *m/e* (%) 426 (2, M^+), 364 (3), 335 (5), 321 (2), 255 (2), 115 (2), 87 (100); molecular ion at *m/e* 426.1291 (theory for $C_{23}H_{22}O_8$, 426.1267).

8-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (50). To a solution of 15.1 mg (0.035 mmol) of **47** in 0.3 mL of *p*-dioxane was added 0.5 mol of 5% aqueous NaOH and 130 mg of $Na_2S_2O_4$ under N_2 at room temperature. After stirring at 25 °C for 30 min, the reaction mixture was heated at 90 °C for 1 h. Additional $Na_2S_2O_4$ (20 mg) was then added, and heating was continued for another 30 min. The reaction was quenched with HCl at 0 °C, and the reaction mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. PLC purification ($CHCl_3$–acetone, 95:5) of the crude residue gave 7.9 mg (55%) of **50:** mp 177–178.5 °C ($CHCl_3$–MeOH); IR 1610, 1580, 1445, 1278, 1260 cm^{-1}; NMR δ 13.82 (s, 1 H), 13.48 (s, 1 H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.71 (t, $J_1 = J_2$ = 7.8 Hz, 1 H), 7.33 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 4.05 (s, 4 H), 4.00 (s, 3 H), 3.14 (br d, J = 18 Hz, 2 H), 2.8–1.6 (m, 5 H), 1.38 (s, 3 H); MS *m/e* (%) 410 (4, M^+), 348 (2), 323 (2), 305 (1), 87 (100), 86 (30); molecular ion at *m/e* 410.1378 (theory for $C_{23}H_{22}O_7$, 410.1365).

8-Acetyl-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (51). A solution consisting of 4.2 mg (0.01 mmol) of **50** in 2 mL of the acidic solution THF–5% H_2SO_4–acetone (1:1:1) was stirred at 50 °C. After 3, 3 mL of 5% $NaHCO_3$ was added and the resulting mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. PLC purification ($CHCl_3$–acetone, 95:5) afforded 3.3 mg (90%) of **51**, mp 243–245 °C, identical in all respects (NMR, IR, and mass spectra) with an authentic specimen.[5c]

(±)-7-Deoxydaunomycinone (52). To 226 mg (0.617 mmol) of **51** in 60 mL of acetic anhydride was added 705 mg (3.7 mmol) of *p*-toluenesulfonic acid (monohydrate). Continuous slow distillation of acetic anhydride and acetic acid was carried out over 6 h. An additional 135 mg of *p*-toluenesulfonic acid was then added, and the distillation was continued for another 3 h. After removing the residual acetic anhydride in vacuo, the residue was dissolved in $CHCl_3$ and chromatographed over a silica gel column (1.5 × 21 cm). The column was eluted with $CHCl_3$, and 15-mL fractions were collected. Fractions 7–11 were combined to give 254 mg (0.517 mmol) of a mixture of enol acetates as an orange-yellow solid. To this partially purified material (254 mg) in 10 mL of dry CH_2Cl_2 was added 315 mg (1.55 mmol) of *m*-chloroperbenzoic acid. After 1 h at room temperature, TLC ($CHCl_3$–acetone, 9:1) analysis showed only one major new component (epoxy acetate). To this solution was added 160 mg of Na_2SO_3, and the contents were washed with saturated $NaHCO_3$, dried, and evaporated to yield 273 mg of a yellow oil, which was treated with 8.5 mL of 0.3 N NaOH in 50% ethanol for 40 min at room temperature. After acidification and extraction with CH_2Cl_2, the residue containing partially hydrolyzed material was treated with 11 mL of an acidic solution of 150 mL of glacial acetic acid, 0.75 mL of concentrated H_2SO_4, and 5 mL of H_2O for 75 min. After dilution with water, the reaction mixture was extracted with CH_2Cl_2, washed with water, dried, and evaporated to yield 196 mg of crude red solid. Chromatography of this crude material over a small silica gel column (elution with $CHCl_3$–acetone, 99:1) afforded pure **52**, mp 229–231 °C, whose (NMR, IR, MS) spectra were indistinguishable from an authentic sample.

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Registry No.—**4**, 66644-11-9; **5**, 67408-45-1; **5a**, 67408-46-2; **5b**, 67408-47-3; **6**, 2589-39-1; **7**, 52541-72-7; **8a**, 63965-48-0; **8b**, 63965-49-1; **9**, 65127-10-8; **10**, 67408-48-4; **11**, 67408-49-5; **12**, 67408-50-8; **13**, 65127-15-3; **15**, 67408-51-9; **16**, 65127-17-5; **18**, 67408-52-0; **20**, 67408-53-1; **21**, 67408-54-2; **22**, 67408-55-3; **23**, 67408-56-4; **24**, 67408-57-5; **25** (isomer 1), 67408-58-6; **25** (isomer 2), 67408-59-7; **27**, 67408-60-0; **28**, 67122-26-3; **29**, 52869-21-3; **30**, 64809-72-9; **31**, 64809-77-4; **32a**, 66644-06-2; **32b**, 67408-61-1; **33**, 66644-07-3; **34**, 67408-62-2; **35**, 66644-09-5; **36**, 66644-10-8; **37**, 67408-63-3; **40** (isomer 1), 67408-64-4; **40** (isomer 2), 67408-65-5; **41**, 66644-13-1; **43**, 67408-66-6; **44**, 67408-67-7; **45**, 67408-68-8; **46**, 67408-69-9; **47**, 67408-70-2; **50**, 67408-71-3; **51**, 61857-05-4; **52**, 59367-18-9; phthalic anhydride, 85-44-9; methylhydroquinone, 95-71-6; ethyl 3-acetylevulinate, 18835-02-5.

References and Notes

(1) For preliminary reports, see F. Suzuki, R. D. Gleim, S. Trenbeath, and C. J. Sih, *Tetrahedron Lett.*, 2303 (1977), and F. Suzuki, S. Trenbeath, and C. J. Sih, *J. Am. Chem. Soc.*, **100**, 2272 (1978).

(2) (a) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbieri, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1964); (b) J. Bernard, R. Paul, M. Boiron, C. Jacquillot, and R. Masai, Ed., "Rubidomycin", Springer-Verlag, New York, N.Y., 1969.

(3) (a) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, 1007 (1969); (b) F. Arcamone, G. Cassinelli, G. Fantini, A. Grein, P. Orezzi, C. Pol, and C. Spalla, *Biotechnol. Bioeng.*, **11**, 1109 (1969).

(4) M. G. Brazhnikova, V. B. Zbarsky, V. I. Ponomarenko, and N. P. Patapova, *J. Antibiot.*, **27**, 254 (1974).

(5) (a) F. Arcamone, G. Franceschi, P. Orezzi, S. Penco, and R. Mondelli, *Tetrahedron Lett.*, 3349, 3353 (1968); (b) R. H. Iwamoto, P. Lim, and N. S. Bhacca, *ibid.*, 3891 (1968); (c) R. Angiuli, E. Foresti, L. Riva di Sanseverino, N. W. Isaacs, O. Kennard, W. D. S. Motherwell, D. L. Wampler, and F. Arcamone, *Nature (London), New Biol.*, **234**, 78 (1971).

(6) R. H. Blum and S. K. Carter, *Ann. Intern. Med.*, **80**, 249 (1974); (b) D. W. Henry, *ACS Symp. Ser.*, **No. 30**, Chapter 2, (1976); (c) F. Arcamone, *Lloydia*, **40**, 45 (1977).

(7) (a) E. A. Lefrak, J. Pitha, S. Rosenheim, and J. A. Gottlieb, *Cancer (Philadelphia)*, **32**, 302 (1973); (b) L. Lenaz and J. A. Page, *Cancer Treat. Rev.*, **3**, 111 (1976).

(8) (a) J. P. Marsh, C. W. Mosher, E. M. Acton, and L. Goodman, *Chem. Commun.*, 973 (1967); (b) T. Yamaguchi and M. Kojima, Symposium on the Chemistry of Natural Products, Abstracts, Tokyo, 205 (1973); (c) D. Horton and W. Weckerle, *Carbohydr. Res.*, **44**, 227 (1975); (d) C. M. Wong, T. L. Ho, and W. P. Niemczma, *Can. J. Chem.*, **53**, 3144 (1975); (e) F. Arcamone, *Carbohydr. Res.*, **46**, 3 (1976).

(9) E. M. Acton, A. N. Fujiwara, and D. W. Henry, *J. Med. Chem.*, **17**, 659 (1974).

(10) (a) Z. Horii, H. Hakusui, T. Momose, and E. Yoshino, *Chem. Pharm. Bull.*, **16**, 1251 (1968); (b) J. Finkelstein and J. A. Romano, *J. Med. Chem.*, **13**, 568 (1970); (c) H. Brockmann, *Tetrahedron Lett.*, **45** (1966); (d) C. M. Wong, D. Popien, R. Schwenk, and J. Rao, *Can. J. Chem.*, **49**, 2712 (1971); (e) C. M. Wong, D. Popien, R. Schwenk and T. L. Ho, *ibid.*, **51**, 466 (1973); (f) W. Trueb and C. H. Engster, *Helv. Chim. Acta*, **55**, 969 (1972).

(11) (a) A. S. Kende, J. Belletire, T. J. Bentley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97**, 4425 (1975); (b) D. M. Miller, S. Trenbeath, and C. J. Sih, *Tetrahedron Lett.*, 1637 (1976); (c) R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *ibid.*, 3385 (1976).

(12) (a) F. Farina and J. C. Vega, *Tetrahedron Lett.*, 1655 (1972); (b) R. Winkler, *Chimia*, **20**, 122 (1966); (c) A. K. Kende, Y. G. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976); (d) A. S. Kende, D. P. Curran, Y. S. Tsay, and J. E. Mills, *Tetrahedron Lett.*, 3537 (1977); (e) T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr., and J. M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977); (f) W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, **41**, 2296 (1976).

(13) P. W. Raynolds, M. J. Manning, and J. S. Swenton, *Tetrahedron Lett.*, 2383 (1977).

(14) W. B. Turner, "Fungal Metabolites", Academic Press, New York, N.Y., 1971.

(15) R. H. Thomson, "Naturally Occurring Quinones", 2nd ed, Academic Press, New York, N.Y., 1971.

(16) J. Houben "Das Anthracen und die Anthrachinone", Georg Thieme, Leipzig, 1929.

(17) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976).

(18) (a) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959); (b) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963); (c) D. R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964); (d) P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1291 (1973).

(19) K. Klemore and G. Gehrke, German Patent 1 178 441, 1964; *Chem. Abstr.* **61P**, 16027f (1964).

(20) C. Marschalk, *Bull. Soc. Chim. Fr.*, **6**, 655 (1939).

(21) S. M. Sethna, *Chem. Rev.*, **49**, 91 (1951).

(22) A considerable amount of destruction of compounds was noted at this temperature, resulting in low material balance.

(23) (a) J. Petruska, *J. Chem. Phys.*, **34**, 1120 (1961); (b) F. Suzuki and M. Oki, *Bull. Chem. Soc. Jpn.*, **49**, 596 (1975).

(24) It is interesting to note the difference in the apparent cardiac toxicities of daunorubicin vs. 4-demethoxydaunorubicin: F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. D. Marco, A. M. Cassazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976).
(25) (a) C. Marshall, T. Kritchevsky, S. Lieberman, and T. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948); (b) J. Attenburrow, L. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson, *J. Chem. Soc.*, 4547 (1961).
(26) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, **42**, 3653 (1977).

New Synthesis of (±)-Emetine from Tetrahydroprotoberberine Precursors via an α-Diketone Monothioketal Intermediate

Seiichi Takano,* Makoto Sasaki, Hideyuki Kanno,
Kozo Shishido, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan 980

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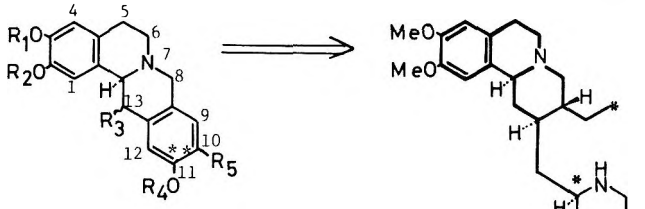
A new route to (±)-emetine (**2**) via the protoemetine derivative **29** has been developed. Protoberberine derivatives **3, 4, 5,** and **6** were converted into the α-diketone monothioketal **25,** which upon cleavage with potassium hydroxide, followed by desulfurization and esterification, yielded the protoemetine derivative **29.**

Because of the structural and biosynthetic parallelism between the ipecac and various indole alkaloids,[1] the development of efficient synthetic methods which could cover both of these classes of alkaloids has a significant practical value. We report here a new synthesis of (±)-emetine (**2**),[2] a representative ipecac alkaloid and one of the most synthesized natural products known,[3] by a completely new method which would be generally applicable to the synthesis of both the ipecac and the indole alkaloids.[4]



1 : $R_1=R_2=R_3=R_4=H$, $R_5=OH$

3 : $R_1=R_2=R_4=Me$, $R_3=R_5=H$

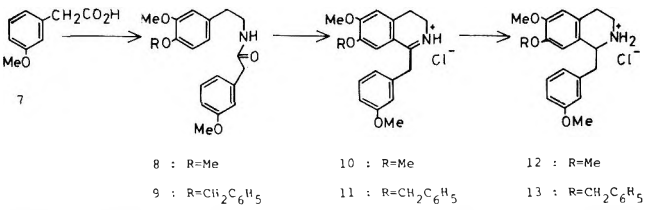
4 : $R_1=R_2=R_4=Me$, $R_3=CN$, $R_5=H$

5 : $R_1=R_4=Me$, $R_2=CH_2C_6H_5$, $R_3=R_5=H$

6 : $R_1=R_4=Me$, $R_2=CH_2C_6H_5$, $R_3=CN$, $R_5=H$

The present method proceeds through Woodward fission,[5] which had been once thought to be involved in the biogenetic pathways of the ipecac and some of the indole alkaloids. The fission between C-10 and C-11 of a tetrahydroprotoberberine precursor (e.g., **1**) was realized chemically by the cleavage reaction[6] of an α-diketone monothioketal intermediate **25** derived from tetrahydroprotoberberine precursors **3, 4, 5,** and **6.**

The starting tetrahydroprotoberberine framework was prepared by two different approaches. In the first approach, the tetrahydroprotoberberine **3** was obtained in 47% overall yield from 3-methoxybenzyl cyanide. Hydrolysis of 3-methoxybenzyl cyanide, prepared from *o*-chloroanisole and acetonitrile by a benzyne reaction[7] with methanolic potassium hydroxide, gave 3-methoxyphenylacetic acid (**7**), which on condensation with homoveratrylamine at 180 °C yielded the phenylacetamide **8** in 92% yield. The Bischler–Napieralski cyclization by phosphorus oxychloride provided the 3,4-dihydroisoquinoline **10** in 98% yield. This material was reduced with sodium borohydride followed by treating with ethereal hydrogen chloride to form the 1,2,3,4-tetrahydroisoquinoline hydrochloride **12** nearly quantitatively. Mannich condensation of the hydrochloride with 35% formalin in methyl alcohol produced the crystalline hydrochloride of 2,3,11-trimethoxytetrahydroprotoberberine (**3**) in 85% yield.



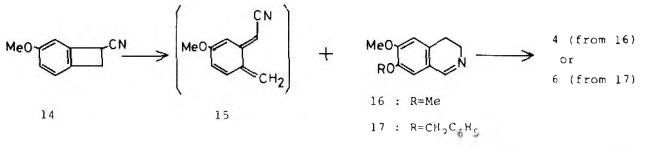
7

8 : R=Me
9 : $R=CH_2C_6H_5$

10 : R=Me
11 : $R=CH_2C_6H_5$

12 : R=Me
13 : $R=CH_2C_6H_5$

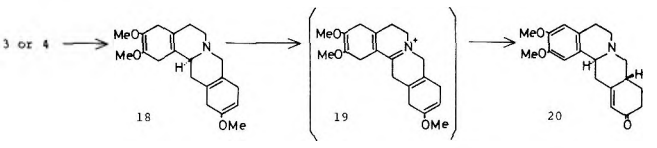
In the second approach, the tetrahydroprotoberberine **4,** a synthetic equivalent of **3,** was prepared by a more straightforward way using the method developed by Kametani et al.[8] Thermolysis of a 1:1 mixture of 1-cyano-5-methoxybenzocyclobutene (**14**)[9] and 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**)[10] without solvent at 140–150 °C resulted in regioselective intermolecular cycloaddition to form 13-cyano-2,3,11-trimethoxytetrahydroprotoberberine (**4**) via the o-quinodimethane intermediate **15** in 50% yield. The product **4** possessed a superfluous cyano group at C-13. However, this could be easily removed in a subsequent stage.



14 15 16 : R=Me 17 : $R=CH_2C_6H_5$

4 (from 16) or 6 (from 17)

Dissolving metal reduction of the tetrahydroprotoberberines **3** and **4** using lithium in liquid ammonia in the presence of *tert*-butyl alcohol afforded the enol ether **18** in 76 and 74% yields, respectively. In the latter case, reductive decyanation occurred in preference to reduction of the aromatic rings, as observed in a related system.[11] Although attempts at selective reduction of ring D to give **23** under Birch conditions were unsuccessful, a selective aromatization of ring A of the enol

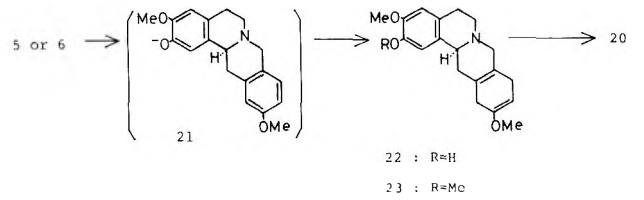


3 or 4 18 19 20

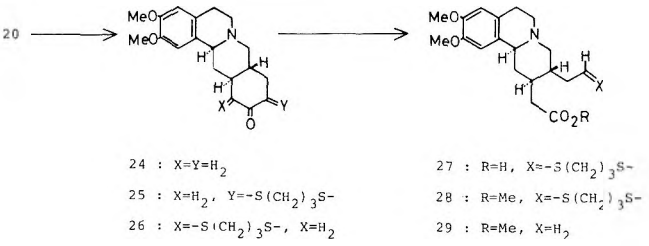
ether **18** could be accomplished by using *N*-chlorosuccinimide.

Upon treatment of the enol ether **18** with an equivalent molar amount of *N*-chlorosuccinimide in methylene chloride, the α,β-unsaturated ketone **20**[12] was obtained directly in 63% yield. During the conversion an immonium salt **19** could be formed initially,[13] and concurrent hydrolysis of the enol ether group on the D ring by moisture contained in the solvent and subsequent isomerization of the double bonds could occur to give the thermodynamically more stable compound **20.**

In order to avoid overreduction under the Birch conditions, alternative tetrahydroprotoberberines, **5** and **6,** possessing a 2-benzyloxy group as a regiocontrol element were prepared by employing the same two approaches as above. Birch reduction of the protoberberine **5,** obtained in 62% overall yield from the phenylacetic acid **7** by the first approach, followed by treating with ethereal diazomethane afforded the ring D enol ether **23** in 84% yield. Similarly, the 13-cyanoprotoberberine **6,** generated in 60% yield of thermolysis of the 3,4-dihydroisoquinoline **17**[14] and the benzocyclobutene **14,**[9] afforded the identical enol ether **23**[9] in 76.5% yield. In these conversions, initial formation of the phenolate anion **21** through reductive cleavage of the benzyl ether could allow a preferential reduction of the D ring to give **23.** Conversion of the enol ether **23** into the α,β-unsaturated ketone **20**[12] was achieved in 84% yield by heating with methanolic hydrochloric acid.



Catalytic hydrogenation of the α,β-unsaturated ketone **20** on 10% palladized carbon in methyl alcohol achieved a highly stereospecific reduction to furnish the C/D trans ketone **24** in 89% yield, although an actual stereochemistry could not be determined at this stage since none of the characteristics appeared spectroscopically.



Treatment of the ketone **24** with pyrrolidine in boiling benzene for 2 h followed by trimethylene dithiotosylate[15] yielded the α-diketone monothioketal **25** in 65% yield accompanied by its regioisomer **26** in 9% yield. Similar to the ketone **24,** the actual structures of the products could not be assigned at this point. In this transformation, the ratio of the products was greatly influenced by the amount of enamine formed. Longer heating resulted in a higher yield of the unwanted isomer **26,** while a minimum heating period was desirable for the preferential formation of the target compound **25.**

Cleavage of the α-diketone monothioketal **25** by potassium hydroxide[16] afforded the crude thioacetal carboxylic acid **27,** which on esterification with diazomethane gave rise to the corresponding thioacetal ester **28** in a well-defined crystalline form in 94% overall yield. Heating **28** with Raney nickel catalyst (W-2) in boiling methyl alcohol effected the desulfurization of the thioacetal group to give the crystalline protoemetine derivative **29** in 92% yield. Although the physical properties were in agreement with the reported data[17] and the synthesis of the compound **29** constitutes a formal synthesis of (±)-emetine (**2**), further structure confirmation was made by the conversion into (±)-emetine (**2**) via a three-step sequence developed by Battersby and Turner.[18] Complete identity with the authentic material led to confirmation of structures **24, 25,** and **28.**

Since the indole analogues of the tetrahydroprotoberberines have been prepared,[19] the synthesis of structurally parallel indole alkaloids, such as the corynantheine-type alkaloids, can be conceived by appropriate modification of the present approach.

Experimental Section

Melting points were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. Infrared absorption spectra were recorded on a Shimadzu IR 400 instrument, and proton magnetic resonance spectra, for deuteriochloroform solutions, were recorded on Jeol PS 100 and PMX 60 spectrometers with tetramethylsilane as an internal reference. Mass spectra were recorded on a Hitachi RMU-7 spectrometer.

3-Methoxyphenylacetic Acid (7). A solution of 3-methoxybenzyl cyanide (58.0 g, 0.41 mol) in ethyl alcohol (1110 mL) containing KOH (132.2 g, 2.2 mol) was refluxed for 14 h. The solvent was removed in vacuo, and the residue was dissolved in water (300 mL). The aqueous layer was washed twice with methylene chloride and acidified with concentrated HCl to liberate the carboxylic acid. The mixture was extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from *n*-hexane to give **7** (59.6 g, 91%) as colorless prisms: mp 67.5–68.5 °C (lit.[20] mp 67 °C); IR ν_{max} (Nujol) ~2400, 1695 cm^{-1}; NMR δ 11.9 (1 H, s), 7.4–6.85 (4 H, m), 3.75 (3 H, s), 3.6 (2 H, s).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methoxyphenylacetamide (8).** A mixture of 2-(3,4-dimethoxyphenyl)ethylamine (1.34 g, 7.4 mmol) and 3-methoxyphenylacetic acid (**7;** 1.23 g, 7.4 mmol) was heated at 130 °C for 0.5 h and then at 170–180 °C for 2.5 h, removing water by means of an aspirator. After cooling, the crystalline residue was recrystallized from benzene and *n*-hexane to give **8** (2.26 g, 92%) as colorless prisms: mp 104.5–106 °C; IR ν_{max} (Nujol) 3270, 1640 cm^{-1}; NMR δ 5.50 (1 H, brd s; disappeared with D_2O), 3.80 (3 H, s), 3.75 (3 H, s), 3.70 (3 H, s), 3.45 (2 H, s), 3.40 (2 H, t, J = 7.0 Hz), 2.70 (2 H, t, J = 7.0 Hz); MS *m/e* 329 (M^+). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.26; H, 7.19; N, 4.29.

3,4-Dihydro-6,7-dimethoxy-1-(3-methoxybenzyl)isoquinoline Hydrochloride (10). A solution of **8** (37.15 g, 113 mmol) in benzene (250 mL) was refluxed with phosphorus oxychloride (34.94 g, 226 mmol) for 4 h. The solvent was removed in vacuo, and the residue was washed several times with hot *n*-hexane to leave a crystalline mass which was recrystallized from isopropyl alcohol and *n*-hexane to give **10** (39 g, 98%) as colorless prisms: mp 118.5–120 °C; IR ν_{max} (Nujol) 1640 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 4.38 (2 H, s), 4.10 (3 H, s), 3.87 (3 H, s), 3.82 (3 H, s), 3.11 (2 H, t, J = 8.0 Hz); MS *m/e* 311 (M^+). Anal. Calcd for $C_{19}H_{22}NO_3Cl{\cdot}H_2O$: C, 62.35; H, 6.61; N, 3.83. Found: C, 62.43; H, 6.13; N, 3.64.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl)isoquinoline Hydrochloride (12). To an ice-cooled solution of **10** (2.5 g, 6.8 mmol) in methyl alcohol (20 mL) was added $NaBH_4$ (1.55 g, 41 mmol) in small portions with stirring. The solvent was evaporated in vacuo, and the residue was treated with 10% NH_4OH (40 mL) and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over K_2CO_3, and evaporated to leave a crystalline residue (1.53 g, 71.3%) which was converted into the hydrochloride **12** by treating with saturated ethereal hydrogen chloride in isopropyl alcohol: colorless prisms; mp 102–104 °C; NMR ($CDCl_3$ + CF_3CO_2H) δ 3.80 (3 H, s), 3.77 (3 H, s), 3.75 (3 H, s); MS *m/e* 313 (M^+). Anal. Calcd for $C_{19}H_{24}NO_3Cl{\cdot}H_2O$: C, 62.03; H, 7.12; N, 3.81; Cl, 9.64. Found: C, 61.79; H, 6.81; N, 3.82; Cl, 9.57.

2,3,11-Trimethoxytetrahydroprotoberberine Hydrochloride (3). A solution of **12** (0.1 g, 0.29 mmol) in ethyl alcohol (10 mL) was refluxed with 37% formalin (0.54 g, 18 mmol) for 45 min. Removal of the solvent in vacuo left a crystalline mass which was recrystallized from isopropyl alcohol to give **3** (0.085 g, 85%) as colorless prisms: mp 185–187 °C; IR ν_{max} (Nujol) 2850–2700, 1600 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 3.85 (3 H, s), 3.80 (3 H, s), 3.75 (3 H, s); MS *m/e* 325 (M^+). Anal. Calcd for $C_{20}H_{24}NO_3Cl{\cdot}H_2O$: C, 63.23; H, 6.90; N, 3.69; Cl, 9.33. Found: C, 63.45; H, 6.94; N, 3.65; Cl, 9.45.

13-Cyano-2,3,11-trimethoxytetrahydroprotoberberine (4). A mixture of 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**; 2.32 g, 12.2 mmol) and 1-cyano-5-methoxybenzocyclobutene (**14**; 1.93 g, 12.2 mmol) was heated at 150 °C for 5.5 h under an atmosphere of nitrogen. The reaction mixture was crystallized from ethyl alcohol to give practically pure **4** (2.09 g, 50%) as pale yellow prisms: mp 174–176 °C; IR ν_{max} (Nujol) 2850–2750, 2230 cm^{-1}; NMR δ 6.67 (1 H, s), 6.64 (1 H, s), 4.29 (1 H, d, J = 3.0 Hz), 3.92 (6 H, s), 3.84 (3 H, s); MS m/e 350 (M^+). Anal. Calcd for $C_{21}H_{22}O_3N_2$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.94; H, 6.25; N, 8.00.

1,4,9,12-Tetrahydro-2,3,11-trimethoxytetrahydroprotoberberine (18). A. To a stirring solution of **3** (3.5 g, 10.7 mmol) in a mixture of tetrahydrofuran (48 mL), *tert*-butyl alcohol (48 mL), and liquid ammonia (200 mL) was added lithium (2.56 g, 0.37 g-atom) in small portions. After the stirring was continued for 1 h, the reaction mixture was treated with NH_4Cl (25 g) and ammonia was evaporated. The residue was extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from isopropyl alcohol to give **18** (2.7 g, 76%) as pale yellow prisms: mp 111.5–114 °C; NMR δ 4.60 (1 H, brd s), 3.62 (3 H, s), 3.60 (3 H, s), 3.50 (3 H, s); MS m/e 329 (M^+). Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.07; H, 8.12; N, 4.19.

B. To a stirring solution of **4** (0.7 g, 2 mmol) in a mixture of tetrahydrofuran (5 mL), *tert*-butyl alcohol (6 mL), and liquid ammonia (130 mL) was added lithium (1.5 g, 0.22 g-atom) in small portions. After the stirring was continued for 6 h, the reaction mixture was treated with NH_4Cl (10 g) and ammonia was evaporated. The residue was extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from isopropyl alcohol to give **18** (0.487 g, 74%) as pale yellow prisms, mp 111.5–114 °C.

5,6,8,8a,9,10,13,13a-Octahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (20). To a stirring solution of **18** (0.15 g, 0.46 mmol) in methylene chloride (35 mL) was added *N*-chlorosuccinimide (0.061 g, 0.46 mmol) in methylene chloride (5 mL) dropwise at −10 °C, and the stirring was continued for 10 h at room temperature. The reaction mixture was washed with saturated $NaHCO_3$, and the organic layer was dried over Na_2SO_4. Removal of the solvent in vacuo left a crystalline residue which was recrystallized from isopropyl alcohol to give **20** (0.1 g, 63%) as yellow prisms: mp 187–189 °C (lit.[12] mp 185–187 °C) IR ν_{max} (Nujol) 2750–2650, 1660 cm^{-1}; NMR δ 6.70 (1 H, s), 6.68 (1 H, s), 6.05 (1 H, s), 3.89 (3 H, s), 3.88 (3 H, s); MS m/e 313 (M^+), 282.

***N*-[2-(4-Benzyloxy-3-methoxyphenyl)ethyl]-3-methoxyphenylacetamide (9).** A mixture of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (27.1 g, 100 mmol) and 3-methoxyphenylacetic acid (**7**; 16.5 g, 100 mmol) was heated at 170–180 °C for 1 h, removing generated water by means of an aspirator. The crystalline residue thus formed was recrystallized from benzene to give **9** (37.6 g, 93%) as colorless needles: mp 116.5–117 °C; IR ν_{max} (Nujol) 3280, 1640 cm^{-1}; NMR δ 5.35 (1 H, brd s; disappeared with D_2O), 5.08 (2 H, s), 3.83 (3 H, s), 3.80 (3 H, s), 3.47 (2 H, s), 2.63 (2 H, t, J = 7.5 Hz); MS m/e 405 (M^+). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.42; H. 6.25; N, 3.47. Found: C, 74.16; H, 6.53; N, 3.53.

7-Benzyloxy-3,4-dihydro-6-methoxy-1-(3-methoxybenzyl)-isoquinoline Hydrochloride (11). A solution of **9** (5.03 g, 12.5 mmol) in benzene (85 mL) was refluxed with phosphorus oxychloride (3.06 g, 20 mmol) for 2.5 h. The solvent was removed in vacuo, and the residue was washed several times with hot *n*-hexane to leave a crystalline mass which was recrystallized from isopropyl alcohol to give **11** (4.92 g, 93%) as pale yellow needles: mp 180.5–181.5 °C; IR ν_{max} (Nujol) 1640 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 7.42 (5 H, s), 5.12 (2 H, s), 4.32 (2 H, s), 4.03 (3 H, s), 3.80 (3 H, s), 3.09 (2 H, t, J = 7.5 Hz); MS m/e 387 (M^+). Anal. Calcd for $C_{25}H_{26}NO_3Cl$: C, 70.82; H, 6.18; N, 3.30; Cl, 8.37. Found: C, 71.03; H, 6.14; N, 3.16; Cl, 8.04.

7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(3-methoxybenzyl)isoquinoline Hydrochloride (13). To an ice-cooled solution of **11** (4.21 g, 10 mmol) in methyl alcohol (30 mL) was added $NaBH_4$ (2.4 g, 60 mmol) in small portions with stirring. The solvent was removed in vacuo, and the residue was extracted with benzene, washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was dissolved in isopropyl alcohol and treated with saturated ethereal hydrogen chloride to give **13** (3.7 g, 87%) as colorless prisms: mp 194–197 °C; NMR ($CDCl_3$ + CF_3CO_2H) δ 7.40 (5 H, s), 4.99 (2 H, s), 4.78 (1 H, brd s; disappeared with D_2O), 3.88 (3 H, s), 3.76 (3 H, s); MS m/e 389 (M^+). Anal. Calcd for $C_{25}H_{28}NO_3Cl$: C, 70.49; H, 6.63; N, 3.29; Cl, 8.33. Found: C, 70.37; H, 6.37; N, 3.21; Cl, 8.18.

2-Benzyloxy-3,11-dimethoxytetrahydroprotoberberine Hydrochloride (5). A solution of **13** (9.0 g, 23.1 mmol) in isopropyl alcohol (120 mL) was refluxed with 37% formalin (16.7 g, 205 mmol) for 1 h. After cooling, the separating cyrstalline mass was filtered off and recrystallized from isopropyl alcohol to give **5** (8.0 g, 86%) as pale yellow needles, mp 194–196 °C. The free base obtained from the hydrochloride was recrystallized from methyl alcohol to give pale yellow needles: mp 92–94 °C; NMR δ 7.43 (5 H, s), 5.01 (2 H, s), 3.89 (3 H, s), 3.80 (3 H, s); MS m/e 401 (M^+). Anal. Calcd for $C_{26}H_{27}O_3N$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.49; H, 6.65; N, 3.28.

2-Benzyloxy-13-cyano-3,11-dimethoxytetrahydroprotoberberine (6). A mixture of 7-benzyloxy-3,4-dihydro-6-methoxyisoquinoline (**17**; 1.15 g, 5 mmol) and 1-cyano-5-methoxybenzocyclobutene (**14**; 0.9 g, 5.6 mmol) was heated at 135–140 °C for 3.5 h under an atmosphere of nitrogen. The reaction mixture was treated with ethyl alcohol to give practically pure **6** (1.16 g, 60%) as colorless needles: mp 172–174 °C; IR ν_{max} (Nujol) 2850–2750, 2230 cm^{-1}; NMR δ 7.33 (5 H, s), 5.08 (2 H, s), 3.83 (3 H, s), 3.73 (3 H, s); MS m/e 426 (M^+). Anal. Calcd for $C_{27}H_{26}O_3N_2$: C, 76.03; H, 6.15; N, 6.57. Found: C, 76.34; H, 6.13; N, 6.49.

9,12-Dihydro-2-hydroxy-3,11-dimethoxytetrahydroprotoberberine (22). A. To a stirring solution of **5** (11.0 g, 25 mmol) in a mixture of tetrahydrofuran (60 mL), *tert*-butyl alcohol (70 mL), and liquid ammonia (300 mL) was added lithium (5.5 g, 0.79 g-atom) in small portions. After the stirring was continued for 1 h, the reaction mixture was treated with NH_4Cl (30 g) and ammonia was evaporated. The residue was neutralized with concentrated hydrochloric acid, extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from methyl alcohol to give **22** (6.4 g, 82%) as colorless needles: mp 179.5–180.5 °C; IR ν_{max} (Nujol) 3400, 2750–2650, 1660 cm^{-1}; NMR δ 6.71 (1 H, s), 6.53 (1 H, s), 4.85 (1 H, brd s; disappeared with D_2O), 4.62 (1 H, brd s), 3.80 (3 H, s), 3.53 (3 H, s); MS m/e 313 (M^+). Anal. Calcd for $C_{19}H_{23}O_3N$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.52; H, 7.51; N, 4.55.

B. To a stirring solution of **6** (0.91 g, 2.14 mmol) in a mixture of tetrahydrofuran (5 mL), *tert*-butyl alcohol (5 mL), and liquid ammonia (130 mL) was added lithium (1.5 g, 0.22 g-atom) in small portions. After the stirring was continued for 6 h, the reaction mixture was treated with NH_4Cl (10 g) and ammonia was evaporated. The residue was neutralized with concentrated hydrochloric acid, extracted with methylene chloride, washed with water, and dried over Na_2SO_4, and the solvent was evaporated in vacuo to leave a crystalline mass which was recrystallized from methyl alcohol to give **22** (0.52 g, 78%) as colorless needles, mp 179.5–180.5 °C.

9,12-Dihydro-2,3,11-trimethoxytetrahydroprotoberberine (23). A solution of **22** (1.25 g, 4 mmol) in methyl alcohol (100 mL) was treated with ethereal diazomethane under cooling for 1.5 h. Removal of the solvent left a crystalline residue which was recrystallized from methyl alcohol to give **23** (1.28 g, 98%) as colorless needles: mp 168.5–170 °C; IR ν_{max} (Nujol) 2750–2650, 1660 cm^{-1}; NMR δ 6.62 (1 H, s), 6.53 (1 H, s), 4.60 (1 H, brd s), 3.83 (6 H, s), 3.51 (3 H, s); MS m/e 327 (M^+). Anal. Calcd for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.26; H, 7.70; N, 4.18.

5,6,8,8a,9,10,13,13a-Octahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (20) Hydrochloride from the Enol Ether 23. A solution of **23** (1.3 g, 4 mmol) in a mixture of methyl alcohol (100 mL), concentrated hydrochloric acid (1 mL), and water (3 mL) was refluxed for 27 h. Removal of the solvent in vacuo left a crystalline residue which was recrystallized from methyl alcohol to give the hydrochloride of **20** (1.12 g, 84%) as pale yellow needles, mp 214–217 °C. The free base converted from the hydrochloride was identical in all respects with an authentic specimen prepared by the above method.

5,6,8,8a,9,10,12,12a,13,13a-Decahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (24). A solution of **20** (1.15 g, 3.7 mmol) in methyl alcohol (70 mL) was hydrogenated over 10% Pd–C (300 mg) at atmospheric pressure at room temperature for 13 h until the calculated amount of hydrogen was consumed. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. Purification of the residue by silica gel column chromatography followed by recrystallization from methyl alcohol gave **24**, (1.02 g, 89%) as pale yellow prisms: mp 139–140 °C; IR ν_{max} (Nujol) 2850–2700, 1700 cm^{-1}; NMR δ 6.66 (1 H, s), 6.58 (1 H, s), 3.87 (6 H, s); MS m/e 315 (M^+), 205, 191. Anal. Calcd for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.31; H, 7.97; N, 4.38.

5,6,8,8a,9,10,12,12a,13,13a-Decahydro-2,3-dimethoxy-10,10-(propane-1,3-dithio)-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (25) and 5,6,8,8a,9,10,12,12a,13,13a-Decahydro-2,3-dimethoxy-12,12-(propane-1,3-dithio)-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (26). A solution of **24** (1.47 g, 4.7 mmol) in benzene (80 mL) was refluxed with pyrrolidine (0.63 mL, 7.5 mmol) for 2 h with removal of

water by means of a Dean-Stark apparatus. Removal of the solvent in vacuo left the crude enamine which was mixed with 1,3-propane dithiotosylate (1.93 g, 4.7 mmol) and triethylamine (5 mL) in acetonitrile (80 mL), and the mixture was refluxed for 4 h. After evaporation of solvent in vacuo, the residue was extracted with methylene chloride, washed with 3% HCl and 5% $NaHCO_3$, and dried over Na_2SO_4. Removal of the solvent in vacuo left an orange-red caramel (2.13 g) which on silica gel column chromatography followed by recrystallization from methyl alcohol afforded **25** (1.27 g, 65%) as pale yellow needles [mp 202.5–204 °C; IR ν_{max} (Nujol) 2800–2700, 1680 cm^{-1}; NMR δ 6.60 (1 H, s), 6.52 (1 H, s), 3.84 (6 H, s); MS *m/e* 419 (M^+), 232, 205, 191. Anal. Calcd for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34; S, 15.28. Found: C, 62.68; H, 7.08; N, 3.24; S, 15.46.] and the isomeric **26** (0.18 g, 9.2%) as pale yellow needles [mp 225.5–227 °C; IR ν_{max} (Nujol) 2800–2700, 1680 cm^{-1}; NMR δ 6.57 (1 H, s), 6.54 (1 H, s), 3.84 (6 H, s); MS *m/e* 419 (M^+), 232, 205, 191. Anal. Calcd for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34; S, 15.28. Found: C, 62.71; H, 6.84; N, 3.22; S, 15.29.].

1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-[2,2-(propane-1,3-dithio)ethyl]-2*H*-benzo[*a*]quinolizine-2-acetic Acid Methyl Ester (28). To a solution of **25** (0.073 g, 0.17 mmol) in a mixture of *tert*-butyl alcohol (2 mL) and tetrahydrofuran (2 mL) was added KOH (65 mg, 1 mmol), and the mixture was heated at 60 °C for 3 h with stirring. After cooling, the reaction mixture was acidified with concentrated hydrochloric acid and then treated with ethereal diazomethane. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with methylene chloride, washed with water, and dried over K_2CO_3. The solvent was evaporated in vacuo to leave **28** (0.075 g, 94%) as amorphous powder: IR ν_{max} (neat) 2850–2700, 1720 cm^{-1}; NMR δ 6.70 (1 H, s), 6.62 (1 H, s), 3.90 (6 H, s), 3.70 (3 H, s); MS *m/e* 451 (M^+), 205, 149. Anal. Calcd for $C_{23}H_{33}NO_4S_2$: C, 61.16; H, 7.37; N, 3.10; S, 14.20. Found: C, 60.94; H, 7.22; N, 3.13; S, 14.00.

3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo-[*a*]quinolizine-2-acetic Acid Methyl Ester (29). A suspension of W-2 Raney nickel (ca. 3 mL) and **28** (0.447 g, 1 mmol) in methyl alcohol (42 mL) was refluxed for 20 h. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography followed by recrystallization from petroleum ether to give **29** (0.32 g, 92.4%) as colorless prisms: mp 77–78.5 °C (lit.[17] mp 78.9–79.2 °C); IR ν_{max} (neat) 2850–2700, 1720 cm^{-1}; NMR δ 6.65 (1 H, s), 6.56 (1 H, s), 3.84 (6 H, s), 3.72 (3 H, s), 0.92 (3 H, collapsed t, J = 7.0 Hz); MS *m/e* 347 (M^+), 246, 205, 191.

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Registry No.—**2,** 65910-27-2; **3** HCl, 19779-81-8; **4,** 67237-59-6; **5,** 67237-60-9; **5** HCl, 67237-61-0; **6,** 67237-62-1; **7,** 1798-09-0; **8,** 67237-63-2; **9,** 67237-64-3; **10,** 1860-59-9; **11,** 67237-65-4; **12** HCl, 67237-66-5; **13** HCl, 67237-67-6; **14,** 1199-31-1; **16,** 3382-18-1; **17,** 15357-92-3; **18,** 65341-27-7; **20,** 19778-10-0; **20** HCl, 19778-11-1; **22,** 67237-68-7; **23,** 67237-69-8; **24,** 65378-14-5; **25,** 65341-28-8; **26,** 65341-29-9; **28,** 65341-30-2; **29,** 3332-90-9; 3-methoxybenzyl cyanide, 19924-43-7; 2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; formalin, 50-00-0; 2-(4-benzyloxy-3-methoxyphenyl)ethylamine, 22231-61-4; 1,3-propane dithiotosylate, 3866-79-3.

References and Notes

(1) Cf. A. R. Battersby and R. J. Parry, *Chem. Commun.*, 901 (1971); A. R. Battersby and K. H. Gibson, *ibid.*, 902 (1971).
(2) Cf. T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1974, p 263.
(3) Cf. M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, N.Y., 1972, pp 426–457.
(4) A part of the present work has been published as a preliminary form: S. Takano, M. Sasaki, H. Kanno, K. Shishido, and K. Ogasawara, *Heterocycles*, **7,** 143 (1977).
(5) R. B. Woodward, *Angew. Chem.*, **68,** 13 (1956).
(6) Cf. S. Takano and K. Ogasawara, *Yuki Gosei Kagaku Kyokai Shi*, **35,** 795 (1977).
(7) T. Kametani, K. Ogasawara, T. Terui, K. Yamaki, and K. Fukumoto, *Chem. Pharm. Bull.*, **16,** 1584 (1968).
(8) T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *J. Org. Chem.*, **39,** 447 (1974).
(9) J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8,** 255 (1965).
(10) W. M. Whaley and M. Meadow, *J. Chem. Soc.*, 1067 (1953).
(11) P. Arapakos, M. Scott, and F. Huber, Jr., *J. Am. Chem. Soc.*, **91,** 2059 (1969).
(12) A. Brossi, H. Bruderer, A. I. Rachlin, and S. Teitel, *Tetrahedron*, **24,** 4277 (1968).
(13) Cf. J. Lundström and S. Agurell, *Tetrahedron Lett.*, 4437 (1968).
(14) T. Kametani and K. Ohkubo, *Chem. Pharm. Bull.*, **15,** 608 (1967).
(15) R. B. Woodward, I. J. Pachter, and M. L. Scheinbaum, *J. Org. Chem.*, **36,** 1137 (1971); *Org. Synth.*, **54,** 39 (1974).
(16) J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **39,** 1814 (1974).
(17) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1461 (1963).
(18) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 717 (1960).
(19) Cf. T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 737 (1975).
(20) R. Pschorr, *Justus Liebigs Ann. Chem.*, **391,** 40 (1912).

Studies on Total Synthesis of the Olivomycins

Robert P. Hatch, Jayant Shringarpure and Steven M. Weinreb*[1]

Department of Chemistry, Fordham University, Bronx, New York 10458

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Studies directed toward total synthesis of olivin (**4**), the aglycon of the olivomycin antitumor antibiotics, are described. The key aldehyde **23,** containing the tricyclic nucleus of olivin, has been prepared in 14 steps from 3,5-dimethoxybenzyl chloride. Methods for construction of the olivin hydroxy ketone side chain were also investigated. Attempted addition of trianion **24** to simple aldehydes was unsuccessful. Cyclohexanecarboxaldehyde, a model for aldehyde **23,** was converted to dithiane **36,** which in two steps was transformed to ketone **38.** Hydroxylation of **38** with *m*-CPBA via a kinetic enolate and trimethylsilyl ether **39** produced a single acyloin, having either structure **40** or **42.**

The olivomycins are a group of antitumor antibiotics first isolated in 1962 from a strain of *Actinomyces olivoreticuli.*[2] The crude antibiotic was subsequently found to be a mixture of three components, olivomycin A, B, and C.[3] Extensive chemical studies led to assignment of absolute stereostructures **1, 2,** and **3,** respectively, to these compounds.[4] The olivomycin antibiotics differ from each other only in the nature of the sugar moieties, and upon hydrolysis all three compounds afford the same aglycon, olivin (**4**). The chromomycins[5] and mithramycins[6] are closely related groups of antitumor antibiotics which differ from the olivomycins in the nature of the carbohydrate residues. In addition both contain a methyl group at the C-7 position of the aglycon. Hydrolysis of the chromomycins and mithramycins affords an aglycon,

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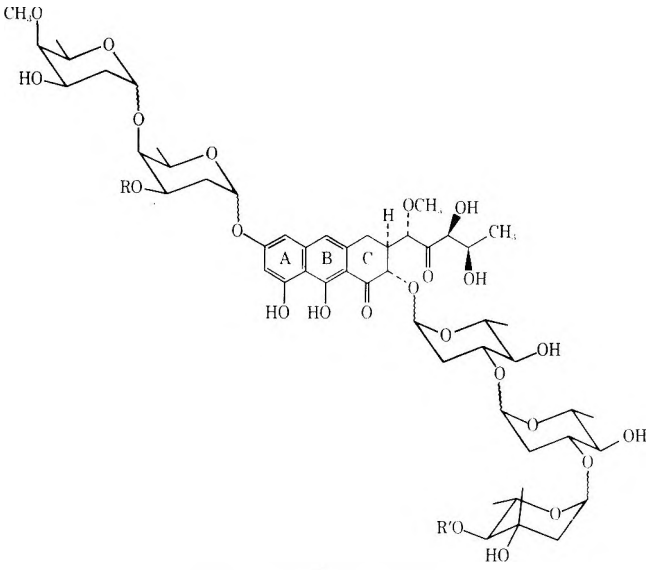
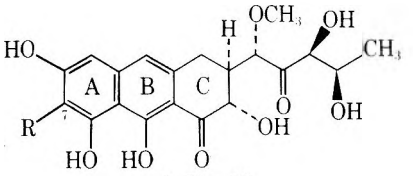


1, R = CH_3CO; R' = $(CH_3)_2CHCO$
2, R = CH_3CO; R' = CH_3CO
3, R = H; R' = $(CH_3)_2CHCO$

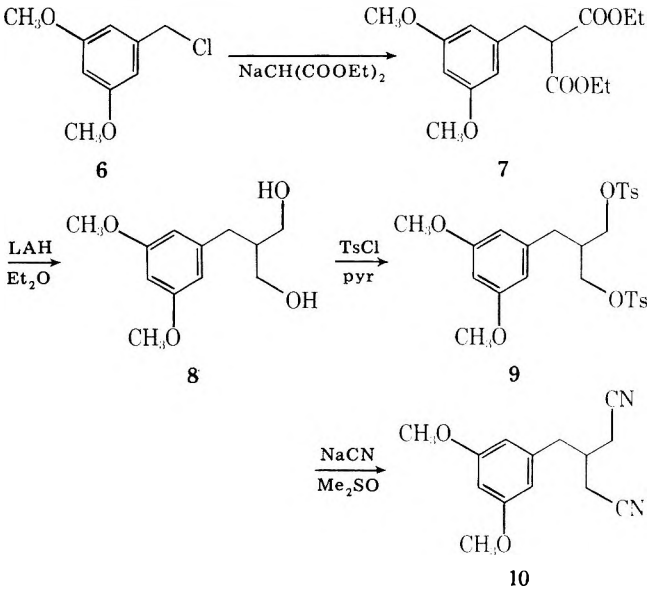


4, R = H
5, R = CH_3

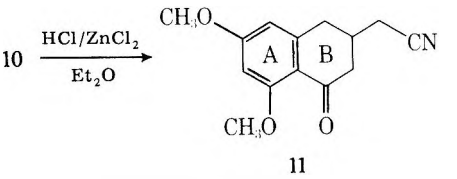
chromomycinone (**5**). The olivomycins, as well as the chromomycins and mithramycins, are currently being evaluated clinically in human cancer chemotherapy.[7]

We are presently attempting to develop a total synthesis of olivin (**4**) and ultimately a synthesis of the olivomycins. Described in this paper are synthetic studies which hopefully will lead to the preparation of olivin, and which with minor modification should also produce chromomycinone (**5**).

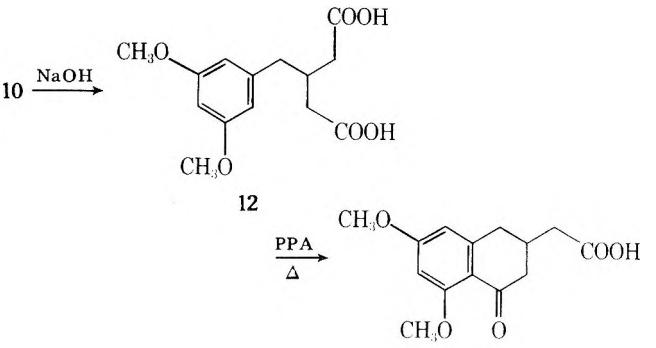
Our strategy for construction of the tricyclic nucleus of olivin involves sequential annulation of nonaromatic B and C rings on to a preformed A ring, followed by B-ring aromatization. Thus, readily available chloride **6**[8] was alkylated with sodiodiethyl malonate (93% yield) and the resulting product **7** was reduced to diol **8** with lithium aluminum hydride (95%).



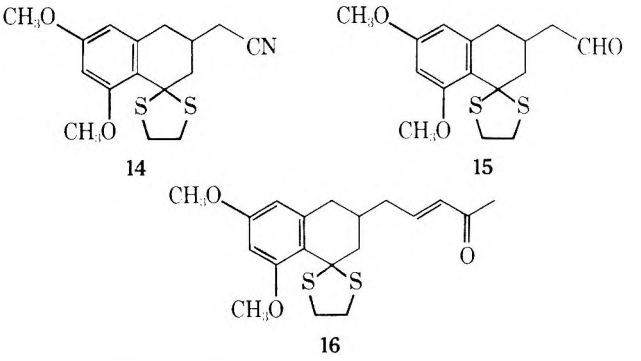
Diol **8** was then transformed via ditosylate **9** to dinitrile **10**. Intramolecular Hoesch condensation[9] of dinitrile **10**



(ZnCl/HCl), followed by hydrolysis of the intermediate imine, provided bicyclic ketone **11** in good yield. An alternative but longer and less attractive route to the bicyclic system involved the basic hydrolysis of dinitrile **10** to the diacid **12** which was cyclized with polyphosphoric acid to ketoacid **13**.[10]

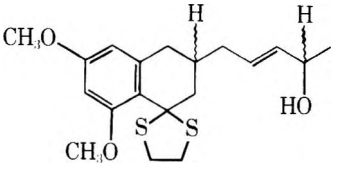


A number of attempts were then made to convert ketonitrile **11** into the corresponding ethylene ketal, but **11** was recovered unchanged in all of these reactions. However, treatment of **11** with ethane dithiol/BF_3 etherate produced a stable crystalline thioketal **14** (90%).[11] Reduction of **14** with Dibal yielded aldehyde **15** (90%), and condensation of this aldehyde with di-



methylphosphonoacetone (sodium hydride/benzene) afforded the trans-α,β-unsaturated ketone **16** (90%).[12] Reduction of **16** with either lithium aluminum hydride or Dibal gave an inseparable mixture of diastereomeric alcohols **17**, which cleanly underwent the Johnson modification[13] of the Claisen rearrangement (triethyl orthoacetate/propionic acid) to afford esters **18**, again as an inseparable diastereomeric mixture (50%). Cleavage of the dithiolane group of **18** was best effected with methyl iodide in wet methanol,[14] giving ketoesters **19**. Base-catalyzed cyclization of ketoester **19** afforded the tricyclic diketones **20** (or a tautomer[15]).

Aromatization of the B ring of **20** could be effected by chloranil to give the desired tricyclic ketone **21** as a crystalline solid. Ultimately, the O-methyl groups of **21** will have to be removed for synthesis of olivin, but in order to continue with some model studies we decided to prepare the trimethyl ether **22**. Methylation of the chelated hydroxyl group of **21** proved difficult, and attempts to use methyl iodide or dimethyl sulfate in conjunction with various bases for formation of ether **22** were generally discouraging. However, treatment of phenol **21** with methyl fluorosulfonate and potassium *tert*-butoxide in glyme gave ether **22** in good yield.[16] Cleavage of alkene **22** with osmium tetroxide/periodate afforded keto aldehyde **23**.



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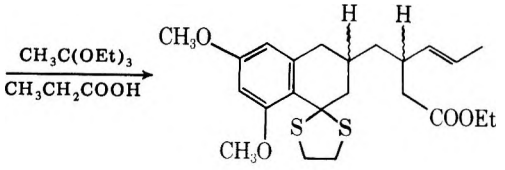

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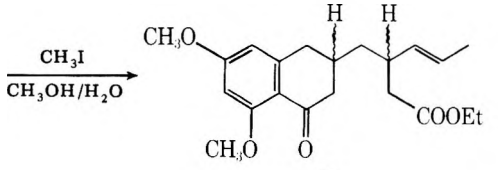

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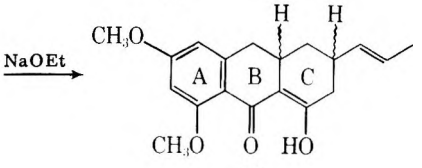

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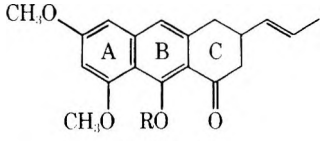
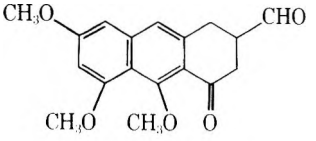
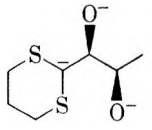


21, R = H
22, R = CH_3

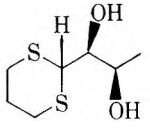


23

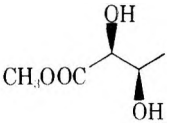
With the key aldehyde **23** now in hand, it was our intention to couple it with trianion **24**.[17] This anion should be available by deprotonation of dithiane diol **25**, which we prepared from readily available methyl *threo*-2,3-dihydroxybutyrate (**26**)[18] as described below.



24

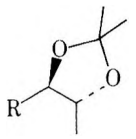


25

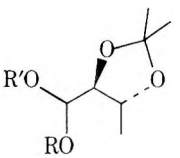


26

Ester **26** on treatment with acetone/$CuSO_4$/*p*-TsOH was converted to acetonide **27a**. Reduction of **27a** with Dibal, followed by either aqueous or methanolic quench, produced either the hydrate **28** or hemiacetal **29**, respectively. Although hydration of an aldehyde such as **27b** is not without precedent,[19] we felt it would be prudent to confirm the structures assigned to **28** and **29** by synthesizing them via an alternative route.

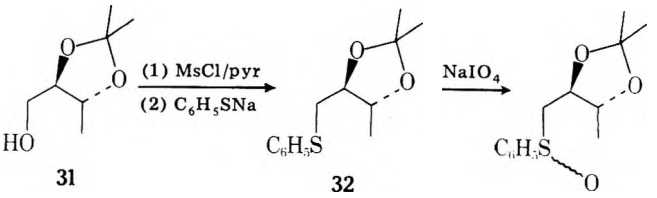


27a, R = $COOCH_3$
b, R = CHO

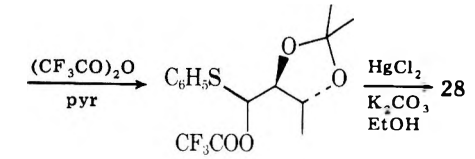


28, R = R′ = H
29, R = CH_3; R′ = H
30, R = CH_3; R′ = $COCH_3$

Reduction of ester **27a** with lithium aluminum hydride afforded alcohol **31** (93%) which on treatment with mesyl chloride/pyridine followed by sodium thiophenoxide gave sulfide **32**. Oxidation of **32** with sodium periodate yielded a



31 32 33

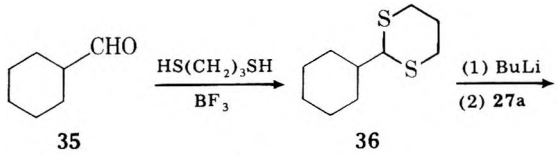


34

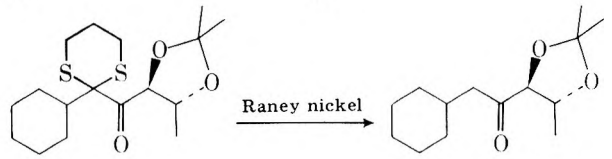
1/1 mixture of diasteromeric sulfoxides **33**. A Pummerer rearrangement of these sulfoxides was effected with trifluoroacetic anhydride/pyridine to give trifluoroacetate **34**, which upon mercury(II)-catalyzed hydrolysis was converted to hydrate **28**, identical to material prepared by Dibal reduction of ester **27a**, followed by an aqueous quench.

Conversion of hemiacetal **29** to dithane **25** was effected in 73% yield with 1,3-propanedithiol/boron trifluoride etherate. Compound **25** could be successfully deprotonated with 3-equiv of *n*-butyllithium (as evidenced by a D_2O quench yielding C-deuterated **25**) but attempted addition of trianion **24** to some simple aldehydes was disappointing. In general, only low yields of addition products could be isolated, and therefore this approach to construction of the olivin side chain was abandoned.

Using cyclohexanecarboxaldehyde (**35**) as a model for aldehyde **23** we have investigated an alternative sequence for synthesis of this side chain. Aldehyde **35** was converted to dithiane **36** by standard means,[20] and after metallation with *n*-butyllithium was acylated with ester **27a** to produce **37**. Raney nickel desulfurization of **37** afforded ketone **38**.

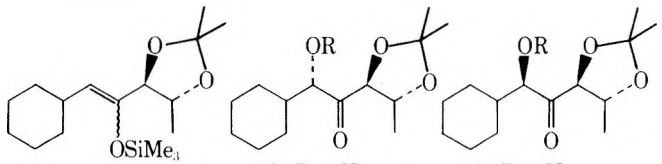


35 36



37 38

This ketone can be deprotonated kinetically with LDA, followed by silylation to afford a silyl enol ether **39**.[21] Without complete characterization, **39** was treated with *m*-chloro-



39

40, R = H
41, R = $COCH_3$

42, R = H
43, R = $COCH_3$

perbenzoic acid in methylene chloride and after acidic workup only a *single* stereoisomeric α-hydroxy ketone was obtained.[22] This acyloin has either structure **40** or **42**, but we are unable to distinguish between these two possibilities by simple spectral means.[23] The acyloin was further characterized by conversion to a single acetate (either **41** or **43**) with acetic anhydride/pyridine (single sharp $COCH_3$ in the ^1H NMR).

We anticipate that it should be possible to convert an acyloin such as this to the corresponding methyl ether with in-

version if **42** or with retention if **40**.[23] This work is in progress, and the chemistry described in this paper will be used in the synthesis of olivin.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on either a Perkin-Elmer 137 or 197 spectrometer. NMR spectra were taken at 60 MHz on Varian A60A or Perkin-Elmer R-12 spectrometers; 100-MHz spectra were recorded on a Varian XL-100 instrument. All NMR spectra were taken in deuteriochloroform unless otherwise noted. NMR spectra (270 MHz) were obtained on a Bruker HX instrument at Yale University on a facility supported by NIH grant PR00798. Low-resolution mass spectra were obtained on a CEC 21-104 instrument. High-resolution mass spectra were obtained on a CEC 21-110B spectrometer at MIT under NIH grant PR-00317. Elemental analyses were done by Microtech Laboratories, Skokie, Ill. E.M. Merck Silica Gel 60 (0.05–0.20 mm) was used for column chromatography and Silica Gel PF_{254} was used for both analytical and preparative TLC.

Diethyl 3,5-Dimethoxybenzylmalonate (7). Sodium metal (55 g, 2.39 mol) was dissolved in 900 mL of absolute ethanol and diethyl malonate (225 g, 1.4 mol) was added over a 30-min period at 60 °C. A solution of 3,5-dimethoxybenzyl chloride (**6**) (130 g, 0.69 mol)[8] in 400 mL of absolute ethanol was added over 1 h at 70–75 °C with stirring. The mixture was refluxed overnight and the alcohol was distilled off. The residue was treated with 3% hydrochloric acid and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was distilled to provide diester **7**: bp 160–5 °C (0.1 mm) (200 g, 93%); NMR δ 1.20 (6 H, t, J = 9 Hz), 3.15 (2 H, d, J = 6 Hz), 3.75 (6 H, s), 4.18 (4 H, q, J = 9 Hz), 6.35 (3 H, s).

2-(3,5-Dimethoxybenzyl)-1,3-propanediol (8). Diester **7** (100 g, 0.32 mol) in 425 mL of dry THF was slowly added over 3 h to a slurry of lithium aluminum hydride (50 g) in dry THF (1.2 L). The mixture was stirred at room temperature overnight and excess $LiAlH_4$ was destroyed by slow addition of 100 mL of ethyl acetate, followed by 50 mL of saturated NH_4Cl. The solid precipitate was removed by filtration and washed with ethyl acetate. The combined organic phase was evaporated in vacuo and the residual oil was taken up in ether, washed with H_2O, and dried ($MgSO_4$) to afford 69 g (95%) of a colorless viscous oil which slowly crystallized upon standing: mp 32–34 °C; IR (film) 3450 and 1600 cm^{-1}; NMR δ 1.20 (1 H, m), 2.5 (2 H, br, s), 2.60 (2 H, d, J = 3 Hz), 3.8 (10 H, m), 6.38 (3 H, s).

2-(3,5-Dimethoxybenzyl)-1,3-propanediol Ditosylate (9). Diol **8** (66 g, 0.29 mol) was dissolved in 200 mL of dry pyridine and the resulting solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (166 g, 0.87 mol) was added at such a rate that the temperature was maintained between 0 and 10 °C. The mixture was stirred in ice for 4 h and stored in a refrigerator overnight. The mixture was poured onto ice and extracted with ether. The organic layer was thoroughly washed with dilute HCl and water, dried over $MgSO_4$, and evaporated to afford a white solid. Recrystallization from ether/chloroform gave 126 g (91%) of crystals: mp 87–88 °C; IR ($CHCl_3$) 1600 and 1460 cm^{-1}; NMR δ 1.20 (1 H, t), 2.41 (8 H, br s), 3.71 (6 H, s), 3.91 (4 H, d, J = 5 Hz), 6.10 (2 H, d, J = 2 Hz), 6.30 (1 H, d, J = 2 Hz), 7.33 (4 H, d, J = 9 Hz), 7.75 (4 H, d, J = 9 Hz).

Anal. Calcd for $C_{26}H_{30}O_8S_2$: C, 58.44; H, 5.61. Found: C, 58.37; H, 5.69.

3-(3,5-Dimethoxybenzyl)glutaronitrile (10). To a solution of 65 g (0.12 mol) of ditosylate **9** in 200 mL of Me_2SO was added over 30 min a suspension of 20 g of sodium cyanide in 100 mL of Me_2SO with stirring at room temperature. After stirring at room temperature for 3 h, the mixture was heated on a steam bath for 1 h, poured onto ice, and extracted with ether. After drying ($MgSO_4$) and evaporation a white crystalline solid (28 g, 86%) was isolated. Recrystallization from CH_2Cl_2/hexane gave an analytical sample: mp 52–53 °C; IR ($CHCl_3$) 2250 and 1600 cm^{-1}; NMR δ 1.20 (1 H, t), 2.53 (4 H, d, J = 2 Hz), 2.80 (2 H, d, J = 6 Hz), 3.83 (6 H, s), 6.41 (3 H, s).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.87; H, 6.55. Found: C, 68.85; H, 6.50.

1-Oxo-3,4-dihydro-6,8-dimethoxy-(2*H*)-naphthalene-3-acetonitrile (11). Dinitrile **10** (31 g, 0.12 mol) was dissolved in 700 mL of dry ether and 30 g of fused zinc chloride was added. Hydrogen chloride gas was passed through the mixture for 1.5 h. The ether was evaporated and the residue was refluxed with 100 mL of water for 2 h. On cooling a solid precipitated was collected, dried, and recrystallized from methylene chloride to afford 29 g (93%) of crystals: mp 144–145 °C; IR ($CHCl_3$) 2250, 1685, and 1600 cm^{-1}; NMR δ 2.46 (5 H, m), 2.93 (2 H, m), 3.86 (6 H, s), 6.35 (2 H, s).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.50; H, 5.93.

4-(3,5-Dimethoxybenzyl)glutaric Acid (12). Dinitrile **10** (3.8 g, 1.56 mmol), 50 mL of 5% sodium hydroxide, and 50 mL of ethylene glycol monomethyl ether were refluxed for 18 h. The solvent was evaporated in vacuo and the residue was dissolved in water and washed with ether. The aqueous layer was acidified with HCl, extracted with ethyl acetate, and dried ($MgSO_4$). Upon evaporation of the solvent 4.16 g (94%) of oily diacid **12** was isolated. A sample crystallized from ethyl acetate/hexane had mp 128–130 °C; IR (film) 2500–3500, 1710, and 1600 cm^{-1}; NMR δ 2.1–2.5 (7 H, m), 3.75 (6 H, s), 6.3 (3 H, s).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.36; H, 6.34.

1-Oxo-3,4-dihydro-6,8-dimethoxy-(2*H*)-naphthalene-3-acetic Acid (13). To 1.8 g of polyphosphoric acid heated on a steam bath was added 30 mg of diacid **12**. The mixture was heated for 20 min and cooled. Ice water was added and the mixture was swirled until the PPA had dissolved. Extraction with ether gave only 5 mg of **13**, but filtration of the aqueous phase afforded another 15 mg. The two solid crops were combined to afford a total of 72% of **13**, mp 209–211 °C. An analytical sample crystallized from methanol had mp 214–216 °C: NMR (Me_2SO-d_6) δ 2.5 (7 H, m), 3.80 (3 H, s), 3.87 (3 H, s), 6.5 (2 H, s).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.49; H, 5.81.

3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′(2′*H*)-naphthalene]-1-acetonitrile (14). Ketone **11** (10 g, 0.04 mol) was dissolved in 150 mL of methylene chloride and 6 g (0.06 mol) of 1,2-ethanedithiol was added, followed by 1 mL of boron trifluoride etherate. The solution was stirred at room temperature overnight and 50 mL of 5% sodium hydroxide was added. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to afford 12 g (90%) of white crystals. An analytical sample was recrystallized from methylene chloride/hexane: mp 148–149 °C; IR ($CHCl_3$) 1600, 1580, and 1460 cm^{-1}; NMR δ 2.48 (5 H, m), 2.96 (2 H, m), 3.48 (4 H, m), 3.76 (3 H, s), 3.88 (3 H, s), 6.20 (1 H, d, J = 2 Hz), 6.36 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{16}H_{19}NO_2S_2$: C, 59.81; H, 5.91; S, 19.95. Found: C, 59.87; H, 5.68; S, 19.95.

3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′(2′*H*)-naphthalene]-3′-acetaldehyde (15). Nitrile **14** (10 g, 0.031 mol) was dissolved in dry benzene (225 mL) and the solution was cooled to 10 °C. Diisobutylaluminum hydride (37 mL of a 1 M solution in hexane, 0.037 mol) was added dropwise under nitrogen while maintaining the temperature below 10 °C. The solution was stirred for 4 h at 10 °C and dilute HCl was added. The benzene layer was separated, washed with water, dried ($MgSO_4$), and evaporated in vacuo to afford 9 g (90%) of an amorphous solid which appeared pure by TLC analysis: IR ($CHCl_3$) 1720, 1600, and 1580 cm^{-1}; NMR δ 2.40 (7 H, m), 3.35 (4 H, m), 3.65 (3 H, s), 3.75 (3 H, s), 6.15 (1 H, d, J = 2 Hz), 6.30 (1 H, d, J = 2 Hz), 10.05 (1 H, s).

5-(3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′-(2′*H*)-naphthalen]-3′-yl)-3-penten-2-one (16). A slurry of sodium hydride (5 g of 50% in mineral oil) in 60 mL of dry benzene was treated with 10 g (0.06 mol) of dimethyl phosphonoacetone in 60 mL of dry benzene slowly with stirring. The mixture was stirred for 30 min at room temperature and a solution of aldehyde **15** (9 g, 27 mmol) in 100 mL of benzene was added dropwise. The mixture was stirred overnight and 20 mL of water was added. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to afford a white solid. Recrystallization from benzene/hexane gave 9 g (90%) of crystals: mp 112–113 °C; IR ($CHCl_3$) 1670, 1600, and 1580 cm^{-1}; NMR δ 2.10 (9 H, m), 3.35 (4 H, m), 3.62 (3 H, s), 3.75 (3 H, s), 5.99–6.25 (4 H, m).

Anal. Calcd for $C_{19}H_{24}O_3S_2$: C, 62.64; H, 6.58. Found: C, 62.71; H, 6.60.

5-(3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′-(2′*H*)-naphthalen]-3′-yl)-3-penten-2-ol (17). Ketone **16** (9.5 g, 26 mmol) was dissolved in 200 mL of dry benzene and cooled to 10 °C. Diisobutylaluminum hydride (40 mL of a 1 M solution in hexane, 39 mmol) was added slowly while maintaining the temperature below 10 °C. The mixture was stirred at 10 °C for 4 h and dilute HCl was added. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (200 g) with benzene/ethyl acetate (9/1) to afford the alcohols **17** as a gummy solid (3.3 g, 60%): IR ($CHCl_3$) 3450, 1600, and 1580 cm^{-1}; NMR δ 1.27 (3 H, d, J = 6 Hz), 2.13 (8 H, m), 3.50 (4 H, m), 3.78 (3 H, s), 3.90 (3 H, s), 5.70 (2 H, m), 6.26 (1 H, d, J = 2 Hz), 6.41 (1 H, d, J = 2 Hz).

Ethyl 3′,4′-Dihydro-6′,8′-dimethoxy-β-1-propenylspiro[1,3-dithiolane-2,1′(2′*H*)-naphthalene]-1-butanoate (18). A mixture of alcohols **17** (5.1 g, 13 mmol), 21 mL of triethyl orthoacetate, and

70 μL of propionic acid was heated at 135–140 °C for 5 h while a slow stream of nitrogen was flushed through the system to remove ethanol. The reaction mixture was evaporated in vacuo and the residue was chromatographed on 100 g of silica gel eluting with benzene/ethyl acetate (9/1) to afford esters **18** as a gummy solid (3 g, 50%): IR ($CHCl_3$) 1740, 1600, and 1580 cm^{-1}; NMR δ 1.26 (3 H, t, J = 7 Hz), 1.64 (3 H, d, J = 5 Hz), 2.36–2.03 (7 H, m), 3.50 (4 H, m), 3.76 (3 H, s), 3.88 (3 H, s), 4.15 (2 H, q, J = 7 Hz), 5.68 (2 H, m), 6.23 (1 H, d, J = 2 Hz), 6.43 (1 H, d, J = 2 Hz).

Ethyl 1-Oxo-3,4-dihydro-6,8-dimethoxy-β-1-propenylnaphthalene-3-butyrate (19). Thioketal **18** (0.93 g, 2 mmol) was dissolved in 30 mL of methanol containing 5% water and 2 mL of methyl iodide was added.[14] The solution was refluxed overnight, the solvent was evaporated, and the residue was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to afford a gum which was chromatographed on 25 g of silica gel eluting with benzene/ethyl acetate (95/5). A gummy product (0.49 g, 50%) was obtained which appeared pure by TLC: IR ($CHCl_3$) 1720, 1660, and 1600 cm^{-1}; NMR δ 1.26 (3 H, t, J = 7 Hz), 1.63 (3 H, d, J = 6 Hz), 2.81–2.16 (6 H, m), 4.15 (2 H, q, J = 7 Hz), 5.45 (2 H, m), 6.40 (2 H, d, J = 2 Hz).

3,4,4a,10-Tetrahydro-6,8-dimethoxy-3-(1-propenyl)-1,9(2*H*,9a*H*)-anthracenedione (20). Ketoester **19** (250 mg, 0.7 mmol), 7 mL of dry toluene, 5 μL of ethanol, and 38 mg (0.79 mmol) of a 50% oil dispersion of sodium hydride were refluxed under nitrogen for 5.5 h. The mixture was diluted with ether and washed with 3% HCl and saturated $NaHCO_3$. The combined aqueous fraction was back extracted twice with CH_2Cl_2 and the organic extracts were combined and dried ($MgSO_4$). Upon evaporation of solvent 205 mg of crude material was obtained. This residue was dissolved in about 4 mL of hot benzene. Hexane was added and the mixture was slowly cooled to room temperature and stored at −20 °C overnight. The solid which formed was collected and dried to give 105 mg of **20,** mp 135–145 °C. Preparative TLC of the recrystallization residue (10% ether/CH_2Cl_2) gave an additional 38 mg of **20.** Total yield: 143 mg (64%); NMR δ 6.41 (2 H, m), 3.92 (3 H, s), 3.85 (3 H, s), 2.62 (4 H, m), 2.48–2.2 (2 H, m), 2.4–1.7 (4 H, m), 1.65 (1.5 H, d, J = 8 Hz), 1.58 (1.5 H, d, J = 8 Hz); IR ($CHCl_3$) 1600 cm^{-1}; λ_{max} (CH_3OH) 347, 280 nm (ε 14 000, 4800).

1,2,3,4-Tetrahydro-5,7-dimethoxy-10-hydroxy-4-oxo-3-propenylanthraeene (21). Diketone **20** (0.23 g, 0.7 mmol) and chloranil (0.24 g, 1 mmol) were dissolved in 20 mL of dry benzene and heated at reflux for 48 h under nitrogen. The solvent was removed and the residue was chromatographed on 5 g of silica gel. Elution with benzene gave unconsumed chloranil and elution with benzene/ethyl acetate (95/5) provided **21.** Recrystallization from benzene/hexane gave 0.11 g (50%) of **21:** mp 127–128 °C; IR ($CHCl_3$) 3400, 1620, and 1605 cm^{-1}; NMR δ 1.70 (3 H, d, J = 5 Hz), 2.75–2.95 (5 H, m), 3.96 (3 H, s), 4.08 (3 H, s), 5.75 (2 H, m), 6.61–6.91 (3 H, m), 15.15 (1 H, s); mass spectrum (70 eV), m/e (rel intensity) 312 (M^+, 12), 270 (12), 245 (8), 57 (100).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.72; H, 6.40. Found: C, 72.92; H, 6.78.

1,2,3,4-Tetrahydro-5,7,10-trimethoxy-4-oxo-3-propenylanthracene (22). Phenol **21** (280 mg, 0.9 mmol) and potassium *tert*-butoxide (112 mg, 1.34 mmol) in 1 mL of 1,2-dimethoxyethane was treated with 105 mg (0.92 mmol) of methyl fluorosulfonate. The mixture was stirred for 30 min at room temperature and an additional 20 mg (0.18 mmol) of methyl fluorosulfonate was added. The mixture was stirred for 5 min longer, diluted with methylene chloride, washed with 5% sodium hydroxide and brine, and dried over $MgSO_4$. Evaporation of the solvent yielded 300 mg of crude product which was chromatographed on 10 g of silica gel, eluting with 5% ether/methylene chloride to afford 250 mg (85%) of crystalline ether **22** along with 5 mg of unreacted phenol **21.** Recrystallization of **22** from ether yielded light orange prisms: mp 138–139 °C; IR ($CHCl_3$) 1675, 1615, and 1560 cm^{-1}; NMR δ 1.65 (3 H, d, J = 5 Hz), 2.3–3.2 (5 H, m), 3.92 (6 H, s), 3.95 (3 H, s), 5.40–5.60 (2 H, m), 6.44 (1 H, br s), 6.58 (1 H, d, J = 2 Hz), 7.19 (1 H, s).

Anal. Calcd for $C_{20}H_{22}O_4$: m/e 326.1516. Found: m/e 326.1519.

1,2,3,4-Tetrahydro-5,7,10-trimethoxyl-4-oxo-3-formylanthracene (23). To a solution of **21** mg (0.065 mmol) of alkene **22** in 2 mL of dioxane/water (3/1) was added 2 mg of osmium tetroxide and the mixture was stirred for 30 min. Sodium metaperiodate (65 mg, 0.3 mmol) was added in portions over a 5-h period. The reaction mixture was diluted with methylene chloride and washed with saturated sodium sulfite, 5% sodium hydroxide, and brine. The organic layer was dried ($MgSO_4$) and evaporated to yield 11 mg (55%) of a red gum, which was further purified by preparative TLC developing with ethyl acetate: NMR δ 2.8–3.4 (5 H, m), 3.90 (6 H, s), 3.94 (3 H, s), 6.44 (1 H, d, J = 2 Hz), 6.58 (1 H, d, J = 2 Hz), 7.23 (1 H, s), 9.76 (1 H, s); IR (film) 1720, 1680, 1620, and 1560 cm^{-1}; mass spectrum m/e (rel intensity) 314 (100), 285 (27), 257 (22), 165 (29), 147 (60).

Methyl *trans*-2,2,5-Trimethyl-1,3-dioxolane-4-carboxylate (27a). Diol **26** (12.5 g, 108 mmol), 300 mg of *p*-toluenesulfonic acid, and 3 g of anhydrous cupric sulfate in 50 mL of acetone were stirred at room temperature for 14 h. The mixture was filtered and evaporated. The residue was dissolved in ether and washed with 5% sodium hydroxide and brine and dried with $MgSO_4$. Evaporation of the solvent in vacuo, followed by distillation (22 °C (0.08 mm)), afforded 7.7 g (47%) of acetonide **27a:** IR (film) 1760 and 1735 cm^{-1}; NMR δ 1.4–1.98 (9 H, m), 3.8 (3 H, s), 4.4–4.05 (2 H, m).

α-Methoxy-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-methanol (29). Diisobutylaluminum hydride (4.7 mL of a 1 M solution in hexane) was added over 5 min to a solution of 0.72 g (4.1 mmol) of ester **27a** in 15 mL of ether at −78 °C. The mixture was stirred for 30 min and 2.5 mL of methanol was added. The reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was filtered and the filter cake was washed thoroughly with ether. Evaporation of the solvent afforded 0.61 g (85%) of hemiacetal **29:** IR (film) 3435 and 1080 cm^{-1}; NMR δ 1.3 (3 H, d, J = 7 Hz), 1.4 (6 H, s), 3.5 (3 H, s), 3.7–4.7 (3 H, m); CI mass spectrum (isobutane), m/e (rel intensity) 145 (100), 115 (10), 101 (15).

Hemiacetal **29** (110 mg, 0.635 mmol) was stirred with 12 mL of acetic anbydride in 1 mL of anhydrous pyridine for 2 h at room temperature. The mixture was diluted with ether, washed with 3% HCl, 5% NaOH, and brine, dried ($MgSO_4$), and evaporated to afford 51 mg of an oil. Bulb-to-bulb distillation (80 °C (2 mm)) gave 40 mg (34%) of pure acetate **30:** IR (film) 1750 and 1090 cm^{-1}; NMR δ 1.35–1.45 (9 H, m), 2.20 (3 H, s), 3.55 (3 H, s), 3.75 (1 H, m), 4.2 (1 H, m).

***trans*-2,2,5-Trimethyl-1,3-dioxolane-4-methanol (31).** Ester **27** (2 g, 11.3 mmol) in 10 mL of ether was added dropwise to a slurry of 0.46 g (11.3 mmol) of lithium aluminum hydride in 30 mL of dry ether. The mixture was cooled and water was cautiously added. The mixture was filtered and the filter cake was thoroughly washed with ether. The combined filtrate was evaporated to afford 1.55 g (93%) of alcohol **31:** IR (film) 3450 cm^{-1}; NMR δ 1.25 (3 H, d, J = 4 Hz), 1.35 (6 H, s), 2.4–2.8 (1 H, br s, OH), 3.5–4.1 (2 H, m).

***trans*-4-Phenylthiomethyl-2,2,5-trimethyl-1,3-dioxolane (32).** To a solution of 0.144 g (1.46 mmol) of triethylamine and 0.145 g (1 mmol) of alcohol **31** in 1.5 mL of methylene chloride cooled to 0 °C was added dropwise 0.135 g (1.2 mmol) of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. The mixture was diluted with methylene chloride and washed with 3% hydrochloric acid, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), and evaporated to afford 164 mg (75%) of mesylate. This material was added to a solution of sodium thiophenoxide (formed from 43 mg (2.9 mmol) of sodium metal and 0.32 g (2.9 mmol) of thiophenol) in 2 mL of absolute ethanol and stirred at room temperature overnight. The ethanol was evaporated and the residue was dissolved in ether, washed with 5% NaOH and brine, dried ($MgSO_4$), and evaporated to afford 135 mg (78% based on mesylate) of crude sulfide **32:** IR (film) 3100 and 1590 cm^{-1}; NMR δ 1.35 (3 H, d, J = 6 Hz), 1.40 (6 H, s), 3.15 (2 H, m), 3.65–4.0 (2 H, m), 7.35 (5 H, m).

Preparation of Sulfoxides 33. Sulfide **32** (1.11 g, 4.7 mmol) was stirred for 22 h with 1.44 g (6.8 mmol) of sodium metaperiodate in 10 mL of methanol. The mixture was filtered and evaporated. The residue was dissolved in ether and washed with 5% NaOH and brine, dried ($MgSO_4$), and evaporated. The residue was rapidly chromatographed on 20 g of silica gel in ether to remove some residue of diphenyl disulfide affording 0.96 g (73%) of a 1:1 mixture of diastereomeric sulfoxides **33:** IR (film) 3100, 1590, and 1040 cm^{-1}. Samples of pure sulfoxide isomers were separated by chromatography on activity III alumina eluting with ether/methylene chloride (1/1). More polar diastereomer: NMR δ 1.28 (3 H, d, J = 6 Hz), 1.42 (3 H, s), 1.46 (3 H, s), 2.8–3.1 (2 H, m), 3.6–4.4 (2 H, m). Less polar diastereomer: NMR δ 1.22 (3 H, d, J = 6 Hz), 1.35 (3 H, s) 1.40 (3 H, s), 2.9–3.1 (2 H, m), 3.4–4.4 (2 H, m).

α-Hydroxy-*trans*-2,2,5-trimethyl-1,3-dioxoline-4-methanol (28). Trifluoroacetic anhydride (79 mg, 0.35 mmol) was added to a solution of 69 mg (0.27 mmol) of sulfoxides **33** in 1 mL of benzene and the solution was stirred at room temperature for 5 min. Pyridine (0.05 mL, 6.2 mmol) was added and the mixture was stirred for an additional 20 min. The mixture was diluted with ether, washed with 3% HCl, 5% NaOH, and brine, dried ($MgSO_4$), and evaporated to afford 72 mg (84%) of oily trifluoroacetate **34:** IR (film) 3100, 1795, and 1595 cm^{-1}; NMR δ 1.3–1.5 (9 H, m), 3.8–4.5 (2 H, m), 6.3 (1 H, m), 7.35 (5 H, m).

The trifluoracetate **34** was stirred with 69 mg of mercuric chloride and 56 mg of potassium carbonate in 2 mL of 95% ethanol at room temperature overnight. The solvent was removed in vacuo and the

residue was taken up in methylene chloride and filtered. Evaporation of the solvent gave 25 mg (78%) of hydrate **28**. This material was identical to a sample prepared by an aqueous workup of a Dibal reduction of ester **27a**: IR (film) 3450 and 1090 cm^{-1}; NMR δ 1.2 (3 H, s), 1.42 (6 H, s), 3.2–4.7 (3 H, m).

***threo*-2,3-Dihydroxy-3-(1,3-dithian-2-yl)-propane (25).** Hydrate **28** (200 mg, 1.13 mmol) was stirred at room temperature with 0.35 g (3.3 mmol) of 1,3-propanedithiol and 0.02 mL of BF_3·etherate in 5 mL of methylene chloride for 14 h. The solvent was removed in vacuo and the residue was chromatographed on 10 g of silica gel, eluting first with methylene chloride to remove 1,3-propanedithiol and 2,2-dimethyl-1,3-dithane, then with ether/methylene chloride (10/90) to remove minor products, and finally with ether/methylene chloride (20/80) to afford 155 mg (73%) of dithiane **25**: IR (film) 3450 cm^{-1}; NMR δ 1.25 (3 H, d, J = 8 Hz), 2.1 (2 H, m), 2.5–3.0 (6 H, m), 3.60 (1 H, dd, J = 4, 8 Hz), 3.9–4.4 (1 H, m).

***trans*-(2-Cyclohexyl-1,3-dithian-2-yl)(2,2,5-trimethyl-1,3-dioxolan-4-yl)methanone (37).** *n*-Butyllithium (7.4 mL of a 2.2 M solution in hexane, 15.5 mmol) was added to a −20 °C solution of 3 g (14.5 mmol) of cyclohexyl dithiane **36** in 60 mL of dry THF.[20] The mixture was stirred for 1.5 h at −20 °C and cooled to −78 °C and 3 g (17 mmol) of ester **27a** was added dropwise. After stirring for 1 h, the mixture was warmed to room temperature and was evaporated in vacuo. Ether and water were added to the residue and the organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on 120 g of silica gel in CH_2Cl_2/hexane (1/1) to afford 3 g (60%) of a waxy solid. A sample recrystallized from hexane had mp 70–72 °C: IR (film) 1705 cm^{-1}; NMR δ 1.1–2.1 (13 H, m), 1.35 (3 H, d, J = 6 Hz), 1.42 (3 H, s), 1.48 (3 H, s), 2.4–2.65 (4 H, m), 3.15 (1 H, dt, J = 12, 2 Hz), 4.35 (1 H, m), 4.58 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{17}H_{28}O_3S_2$: C, 59.29; H, 8.19. Found: C, 59.68; H, 8.37.

***trans*-2-Cyclohexyl-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)-ethanone (38).** Thioketal **37** (300 mg, 0.87 mmol) was stirred 30 min at room temperature with 5 g of freshly prepared Raney nickel (activity W-2) in 10 mL of absolute ethanol. The reaction mixture was filtered and evaporated in vacuo to 180 mg of crude ketone **38** which was purified by bulb-to-bulb distillation (85 °C (0.1 mm)) and then by chromatography on silica gel eluting with methylene chloride to afford 120 mg (60%) of pure ketone: IR (film) 1705 cm^{-1}; NMR δ 0.9–2.1 (11 H, m), 1.38 (3 H, d, J = 7 Hz), 1.45 (6 H, s), 2.55 (2 H, d, J = 7 Hz), 3.9–4.4 (2 H, m).

[4α,5β]-2-Cyclohexyl-2-hydroxy-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)ethanone (40 or 42). A solution of lithium diisopropylamide was formed at −20 °C by addition of 0.21 mL (0.34 mmol) of 1.6 M *n*-butyllithium to a solution of 36 mg (0.355 mmol) of diisopropylamine in 2 mL of THF. The solution was cooled to −70 °C and 50 mg (0.21 mmol) of ketone **38** in 0.5 mL of dry hexane was added dropwise over a 3-min period. The solution was stirred for 30 min and 0.15 mL (1.2 mmol) of chlorotrimethylsilane was added. The mixture was warmed to room temperature and poured onto aqueous sodium bicarbonate. The mixture was extracted with methylene chloride, and the organic phase was dried ($MgSO_4$) and evaporated to yield 55 mg (88%) of crude silylenol ether **39**: IR (film) 1665, 1245, and 840 cm^{-1}; δ 0.28 (9 H, s), 1.0–2.5 (11 H, m), 1.45, (3 H, d, J = 6 Hz), 1.70 (6 H, s), 3.7–4.3 (2 H, m), 4.78 (1 H, d, J = 10 Hz).

This material in 2 mL of dry hexane was cooled to −20 °C and treated with 40 mg (0.23 mmol) of purified *m*-chloroperbenzoic acid. The reaction mixture was stirred for 1 h during which time the flask was warmed to +10 °C. The mixture was diluted with aqueous sodium sulfate and extracted with methylene chloride. The organic phase was washed with 3% HCl, saturated sodium bicarbonate, and brine, dried with $MgSO_4$, and evaporated to give 40 mg (79%) of crude acyloin. Preparative TLC of this material eluting with methylene chloride gave 25 mg (50%) of pure acyloin as a colorless oil: IR (film) 3450 and 1710 cm^{-1}; NMR (270 MHz) δ 1.0–2.5 (1 H, m), 1.36 (3 H, d, J = 6 Hz), 1.39 (3 H, s), 1.40 (3 H, s), 3.94 (1 H, dq, J = 8, 6 Hz), 4.04 (1 H, d, J = 8 Hz), 4.20 (1 H, br s).

[4α,5β]-2-Cyclohexyl-2-acetoxy-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)ethanone (41 or 43). Ketoalcohol **40** or **42** (5 mg, 0.02 mmol) was stirred at room temperature for 12 h with excess acetic anhydride in 0.5 mL of dry pyridine. The mixture was diluted with methylene chloride, washed with 3% HCl and saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated to give 5 mg (86%) of acetate: IR (film) 1740 and 1725 cm^{-1}; NMR δ 1.0–2.2 (11 H, m), 1.42–1.52 (9 H, m), 2.12 (3 H, s), 3.9–4.3 (2 H, m), 5.02 (1 H, d, J = 4 Hz).

Anal. Calcd for $C_{16}H_{26}O_5$: *m/e* 298.1780. Found: *m/e* 298.1777.

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Registry No.—**6**, 6652-32-0; **7**, 5859-68-7; **8**, 67194-88-1; **9**, 67194-89-2; **10**, 67194-90-5; **11**, 67194-91-6; **12**, 67194-92-7; **13**, 41651-06-3; **14**, 67194-93-8; **15**, 67194-94-9; **16**, 67194-95-0; *erythro*-**17**, 67194-96-1; *threo*-**17**, 67194-97-2; *erythro*-**18**, 67208-76-8; *threo*-**18**, 67194-98-3; *erythro*-**19**, 67194-99-4; *threo*-**19**, 67194-69-8; **20**, 67195-00-0; **21**, 67195-01-1; **22**, 67195-02-2; **23**, 67195-03-3; **25**, 67195-04-4; **26**, 5057-95-4; **27a**, 63640-49-3; **28**, 67195-05-5; **29**, 67195-06-6; **30**, 67226-41-9; **31**, 67195-07-7; **32**, 67195-08-8; **33** isomer 1, 67195-09-9; **33** isomer 2, 67252-86-2; **34**, 67195-10-2; **36**, 56698-00-1; **37**, 67195-11-3; **38**, 67195-12-4; **39**, 67195-13-5; **40** or **42**, 67195-14-6; **41** or **43**, 67195-15-7; diethyl malonate, 105-53-3; *p*-toluenesulfonyl chloride, 98-59-9; 1,2-ethanedithiol, 540-63-6; dimethylphosphonoacetone, 4202-14-6.

References and Notes

(1) (a) A. P. Sloan Foundation Fellow, 1975–1979; recipient of a Research Career Development Award, 1975–1980, from the National Heart, Blood and Lung Institute (HL00176); (b) Address correspondence to this author at Department of Chemistry, The Pennsylvania State University, University Park, Pa. 16802.
(2) G. F. Gauze, R. S. Ukholino, and M. A. Sveshnikova, *Antibiotiki*, **7**, 34 (1962); M. G. Brazhnikova, E. G. Krugliak, and I. N. Kovsharova, *ibid.*, **7**, 39 (1962).
(3) M. G. Brazhnikova, E. G. Kugliak, and V. N. Borisova, *Antibiotiki*, **9**, 141 (1964).
(4) G. P. Bakhaeva, Y. A. Berlin, D. A. Chuprunova, M. N. Kolosov, G. Y. Peck, L. A. Piotrovich, M. M. Shemyakin, and I. A. Vasina, *J. Chem. Soc., Chem. Commun.*, 10 (1967), and references cited.
(5) N. Harada, K. Nakanishi and S. Tatsuoka, *J. Am. Chem. Soc.*, **91**, 5896 (1969), and references cited.
(6) G. P. Bakhaeva, Y. A. Berlin, E. F. Boldyreva, O. A. Chuprunova, M. N. Kolosov, V. S. Soifer, T. E. Vasiljeva, and I. V. Yartseva, *Tetrahedron Lett.*, 3595 (1968).
(7) (a) "U.S.A.-U.S.S.R. Monograph, Methods of Development of New Anticancer Drugs", National Cancer Institute Monograph 45, DHEW Publication No. (NIH)76-1037 (1977); (b) G. R. Pettit, "Biosynthetic Products for Cancer Chemotherapy", Vol. 1, Plenum Press, New York, N.Y., 1977, p 143.
(8) R. Adams, S. Mackenzie, Jr., and S. Loewe, *J. Am. Chem. Soc.*, **70**, 664 (1948).
(9) P. E. Spoerri and A. S. DuBois, *Org. React.*, **5**, 387 (1949).
(10) Cf. A. S. Kende, T. L. Fields, J. H. Boothe, and S. Kushner, *J. Am. Chem. Soc.*, **83**, 439 (1961).
(11) J. A. Marshall, N. H. Anderson, and J. W. Schlicher, *J. Org. Chem.*, **35**, 858 (1970).
(12) W. S. Wadsworth, Jr., and W. D. Emmons, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 547; F. A. Cotton and R. A. Schunn, *J. Am. Chem. Soc.*, **85**, 2394 (1963).
(13) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.*, **92**, 1 (1970).
(14) M. Fetizon and M. Jurion, *J. Chem. Soc., Chem. Commun.*, 382 (1972).
(15) J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Am. Chem. Soc.*, **90**, 439 (1968).
(16) P. C. Belanger, C. S. Rooney, F. M. Robinson, and L. H. Sarett, *J. Org. Chem.*, **43**, 906 (1978).
(17) Cf. H. Paulsen, K. Roden, V. Sinnwell, and W. Kaebernick, *Chem. Ber.*, **110**, 2146 (1977), and references cited.
(18) F. W. Bachelor and G. A. Miana, *Can. J. Chem.*, **47**, 4089 (1969).
(19) I. T. Harrison and V. R. Fletcher, *Tetrahedron Lett.*, 2729 (1974).
(20) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(21) S. R. Wilson, M. E. Walters, and B. Orbaugh, *J. Org. Chem.*, **41**, 378 (1976).
(22) A. Hassner, R. H. Reuss, and H. W. Pinnick, *J. Org. Chem.*, **40**, 3426 (1975); G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Lett.*, 4319 (1974).
(23) We hope to make a stereochemical correlation with natural olivin when we have actually attached the side chain to aldehyde **23**.

C-12 Substituted Prostaglandins: Synthesis and Biological Evaluation of (±)-12-Hydroxyprostaglandin $F_{2\alpha}$ Methyl Ester

Paul A. Grieco,* Yuusaku Yokoyama, Gregory P. Withers, Francis J. Okuniewicz, and C.-L. J. Wang

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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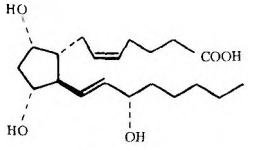
The synthesis of (±)-12-hydroxyprostaglandin $F_{2\alpha}$ methyl ester (**5**) and (±)-15-*epi*-12-hydroxyprostaglandin $F_{2\alpha}$ methyl ester (**35**) along with the corresponding 11,12-*O*-isopropylidene derivatives **33** and **34** is detailed starting from the known bromo ester **6**. Prostaglandins **5**, **33**, **34**, and **35** have been evaluated for pregnancy interruption in the hamster and smooth muscle stimulating effects on gerbil colon and hamster uterine strips.

Since the observation that prostaglandin $F_{2\alpha}$ (**1**) has a luteolytic action in a variety of laboratory and farm animals,[1] derivatives of natural $PGF_{2\alpha}$ possessing luteolytic activity in animals have been reported.[2] Our efforts in this area have been primarily concerned with finding prostaglandin derivatives which possess luteolytic properties with no undesirable effects (e.g., nausea, vomiting, diarrhea). We have been involved in the synthesis and biological evaluation of C-12 substituted derivatives of natural $PGF_{2\alpha}$ in order to investigate the effect on luteolytic activity. Our early work centered on the preparation of (±)-12-methyl-$PGF_{2\alpha}$ (**2**).[3] More recently we have described the synthesis of (±)-12-fluoro-$PGF_{2\alpha}$ methyl ester (**3**)[4] and (±)-12-hydroxymethyl-$PGF_{2\alpha}$ methyl ester (**4**).[5] We



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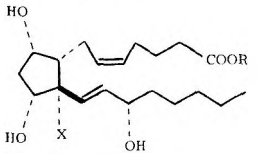
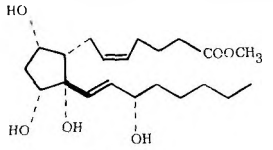


2 X = CH_3, R = H
3 X = F, R = CH_3
4 X = CH_2OH, R = CH_3

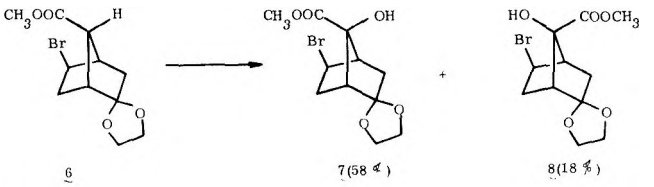
detail below the synthesis of (±)-12-hydroxy-$PGF_{2\alpha}$ methyl ester (**5**) and present the preliminary biological data.



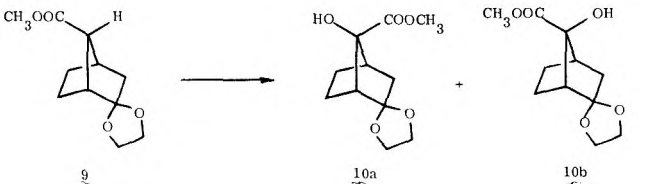
5

The previously described bicyclo[2.2.1]heptane derivative **6**, mp 74–75 °C, which had been employed in the synthesis of the C-12 methyl, fluoro, and hydroxymethyl derivatives,[3-6] was subjected to α-hydroxylation.[7] Treatment in tetrahydrofuran of the enolate derived from ester **6** with oxygen at low temperature provided in 76% yield a 3:1 mixture of the two crystalline hydroxy esters **7** (mp 102 °C) and **8** (mp 126 °C), respectively, along with recovered starting material (17%). In contrast, the corresponding bicyclo[2.2.1]heptane **9** upon α-hydroxylation afforded a 4:1 mixture of α-hydroxy esters **10a** and **10b**, respectively.[8] The presence of the bulky *exo*-2-bromo substituent in compound **6** is undoubtedly responsible for the observed predominance of hydroxy ester **7** during α-hydroxylation of ester **6**.

The anti relationship between the 7-hydroxy group and the *exo*-2-bromo substituent in compound **7** was based primarily

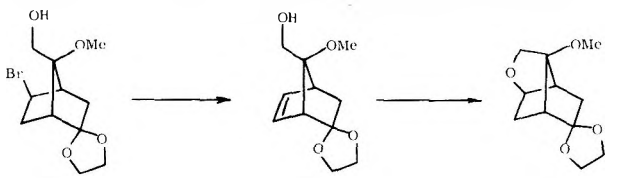


6 **7** (58%) **8** (18%)



9 **10a** **10b**

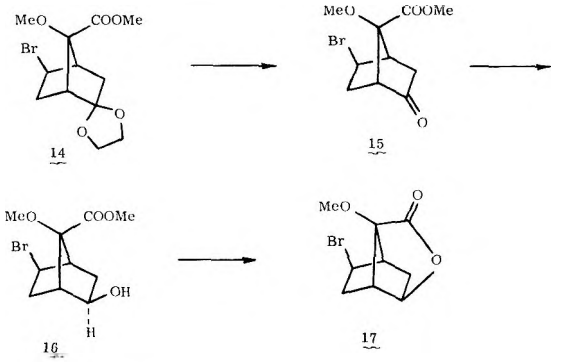
(vide infra) on two sets of experiments. The lower melting isomer (**7**) was methylated (sodium hydride, tetrahydrofuran, methyl iodide, room temperature, 13 h) and reduced (90% overall) in refluxing anhydrous ether with lithium aluminum hydride. The resulting bromo alcohol **11** was dehydrobrominated (80%) with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing toluene providing the bicyclo[2.2.1]heptene **12**.



11 **12** **13**

Oxymercuration–demercuration[9] [a, mercuric acetate (1.0 equiv), tetrahydrofuran–water (1:1), 25 °C; b, sodium hydroxide, sodium borohydride] gave cyclic ether **13** (83%) whose spectral data were in complete agreement with the assigned structure.

In a second series of experiments the higher melting hydroxy ester **8** was methylated (94%) [sodium hydride, tetrahydrofuran, methyl iodide, room temperature, 21 h] giving rise to methyl ether **14**. Hydrolysis [acetic acid–water (1:1), 95 °C, 3 h] of the ketal function provided (90%) keto ester **15** [IR ($CHCl_3$) 1760, 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.08 (q, 1 H, J = 5 Hz, 8 Hz, –CHBr), 3.81 (s, 3 H, $-COOCH_3$), 3.40 (s, 3 H,



14 **15** **16** **17**

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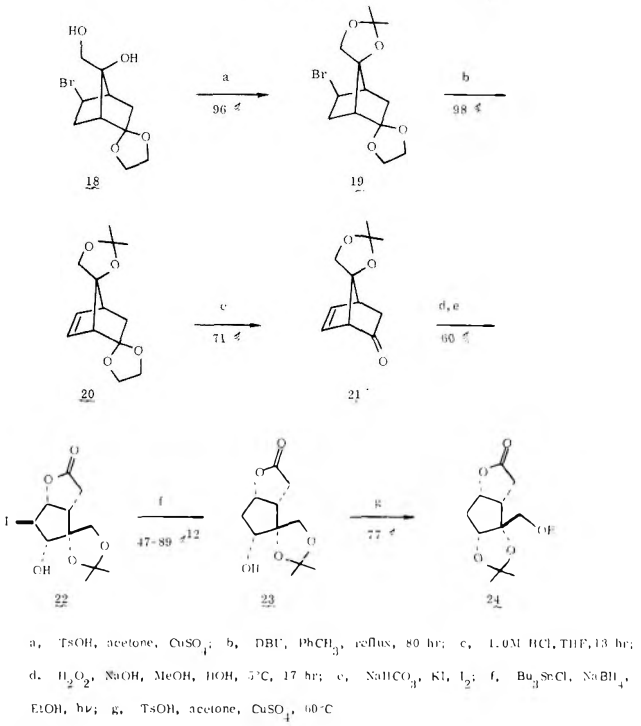
Scheme I



a, TsOH, acetone, $CuSO_4$; b, DBU, $PhCH_3$, reflux, 80 hr; c, 1.0 M HCl, THF, 13 hr; d, H_2O_2, NaOH, MeOH, HOH, 5°C, 17 hr; e, $NaHCO_3$, KI, I_2; f, Bu_3SnCl, $NaBH_4$, EtOH, hν; g, TsOH, acetone, $CuSO_4$, 60°C

OCH_3)]. Reduction of bicyclo[2.2.1]heptanone **15** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at 0 °C gave (85%) the exo alcohol **16** [IR ($CHCl_3$) 3615, 3500, 1735] which upon treatment with *p*-toluenesulfonic acid in refluxing benzene (1 h) gave exclusively in near quantitative yield γ-lactone **17** [IR ($CHCl_3$) 1790 cm^{-1}; NMR ($CDCl_3$) δ 4.44 (t, 1 H, J = 3 Hz, -CHO-), 4.17 (t, 1 H, J = 5 Hz, -CHBr), 3.60 (s, 3 H, $-OCH_3$)].

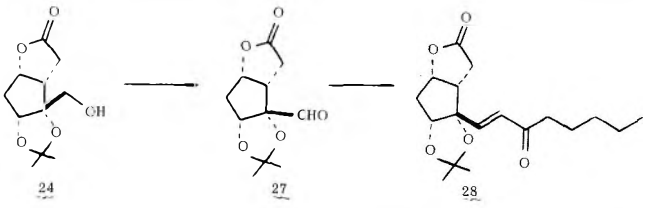
Having established the structures of the two α-hydroxy esters **7** (vide infra) and **8**, we proceeded with conversion of **7** into the key cyclopentanoid intermediate **24** (Scheme I) which possesses the necessary functionality for elaboration of the α and ω side chains. Reduction of ester **7** with lithium aluminum hydride in refluxing tetrahydrofuran provided diol **18**, mp 84.5–86.0 °C. Treatment of crystalline diol **18** with anhydrous *p*-toluenesulfonic acid in acetone containing anhydrous copper sulfate gave rise to a 96% yield of crystalline acetonide **19**,[10] mp 103.0–103.5 °C, as evidenced by the presence of a six-proton singlet (broad) located at δ 1.42 and an AB quartet (J = 9 Hz, $\Delta\nu_{AB}$ = 15.6 Hz) centered at 4.22 in the NMR spectrum. Dehydrobromination was carried out utilizing DBU in refluxing toluene in near quantitative yield giving rise to the crystalline bicyclo[2.2.1]heptene **20**, mp 33.0–34.5 °C. The NMR spectrum clearly revealed the presence of a two-proton multiplet at δ 6.29, indicative of the olefinic protons. Selective hydrolysis of the ketal function in compound **20** was achieved in 71% yield with 1.0 M hydrochloric acid in tetrahydrofuran. The acetonide moiety was reasonably stable to the reaction conditions for short periods of time; however, prolonged treatment with acid resulted in cleavage of the acetonide as well.

Baeyer-Villiger oxidation of ketone **21** followed by iodolactonization gave in ca. 60% overall yield the crystalline iodo lactone **22**, mp 133.5–134.5 °C. The above two-step sequence was necessary due to the sensitive nature of the Baeyer-Villiger product **25** which cyclized upon standing to the bicyclic lactone **26**. Deiodination employing the recently described procedure by Corey and Suggs[11] furnished the bicyclic acetonide **23**, mp 129.0–129.5 °C, in varying yields.[12]

Of critical importance to the success of our scheme was the ability at some point in the synthesis to transform **23** into the corresponding acetonide **24**. We were gratified to find that

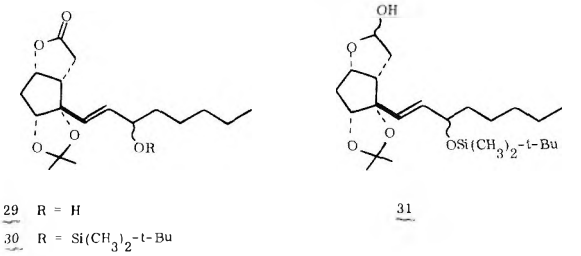
treatment of a solution of acetonide **23** in acetone with anhydrous *p*-toluenesulfonic acid in the presence of anhydrous copper sulfate at 55 °C gave, as evidenced by TLC analysis, a single product (ca. 80%) which was not starting material. The spectral data are completely consistent with the assigned structure **24**. The smooth transformation of **23** into acetonide **24** further supports the α configuration of the hydroxyl group at C-12 (prostaglandin numbering).

It was anticipated that once alcohol **24** was in hand the completion of the synthesis of 12-hydroxy-$PGF_{2\alpha}$ methyl ester would proceed in a straightforward manner (cf. **24** → **28**). It



was assumed that standard prostaglandin methodology[13] for elaboration of the α and ω side chains could be utilized. Indeed this was a reasonable assumption based on the vast amount of data that has now accumulated in the literature. Our assumption proved to be incorrect. Oxidation of alcohol **24** with Collins reagent[14] followed by treatment of the intermediate aldehyde **27** with the sodio derivative of dimethyl (2-oxoheptyl)phosphonate[15] gave only disappointingly low yields (0–10% overall) of enone **28**. Use of pyridinium chlorochromate,[16] *N*-chlorosuccinimide–dimethyl sulfide,[17] dimethyl sulfoxide–chlorine,[18] dimethyl sulfoxide–sulfur trioxide–pyridine,[19] dimethyl sulfoxide–acetic anhydride,[20] and dimethyl sulfoxide–dicyclohexylcarbodiimide–pyridinium trifluoroacetate[21] also gave discouraging results. Fortunately, utilization of a Moffatt-Pfitzner oxidation (Me_2SO-DCC)[22] in the presence of dichloroacetic acid[21,23] followed by a nonaqueous workup gave in 82% yield aldehyde **27** which after purification was condensed (tetrahydrofuran, 0 °C, 1 h) with the standard phosphonate carbanion giving rise to the crystalline product **28**, mp 89–90 °C, in 88% yield. Analysis of the infrared spectrum of enone **28** revealed absorptions at 1780, 1698, 1680, and 1632 cm^{-1}. Further support for the structure came from the NMR spectrum which displayed an AB quartet centered at δ 6.58 (J = 15 Hz), highly characteristic of a trans-enone system possessing no γ hydrogens.

Reduction of enone **28** gave in near quantitative yield alcohol **29** which was directly protected as its *tert*-butyldimethyl

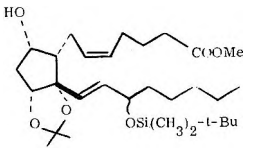


silyl ether.[24] Intermediate **32** was prepared from lactone **30** employing the standard sequence of reactions:[13] (a) reduction with diisobutylaluminum hydride, (b) Wittig reaction, and (c) esterification. Cleavage of silyl ether **32** with tetra-*n*-butylammonium fluoride gave in 76% yield a 1:1 mixture of

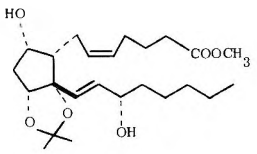
Table I. Smooth Muscle Data[28]

	registry no.	gerbil colon contraction[a] (in vitro)	hamster uterine contraction[a] (in vitro)
(±)-12-hydroxy-$PGF_{2\alpha}$ methyl ester	67237-12-1	0.004	0.023
(±)-15-*epi*-12-hydroxy-$PGF_{2\alpha}$ methyl ester	67237-13-2	0.001	0.004
(±)-acetonide **33**	67237-14-3	0.0005	0.0005
(±)-acetonide **34**	67237-15-4	0.0005	0.0005

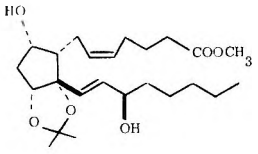
[a] $PGF_{2\alpha}$ = 1.



32



33



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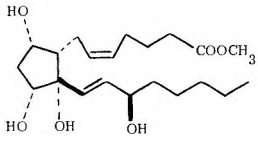

35

acetonides **33** and **34** which were separated. Cleavage of the acetonide unit in both **33** and **34** with methanol containing *p*-toluenesulfonic acid gave in only modest yield (±)-12-hydroxy-$PGF_{2\alpha}$ methyl ester **5** and (±)-15-*epi*-12-hydroxy-$PGF_{2\alpha}$ methyl ester **35**.[25]

Preliminary results obtained with acetonide **33** and the corresponding C-15 epimer **34** indicate that both compounds are ineffective in terminating pregnancy in hamsters when dosed (125 μg/hamster) subcutaneously on day five of pregnancy.[26] Similar results were encountered with racemic 15-*epi*-12-hydroxy-$PGF_{2\alpha}$ methyl ester **35** at a dose level of 25 μg/hamster. In sharp contrast, racemic 12-hydroxy-$PGF_{2\alpha}$ methyl ester **5** gave 100% inhibition of pregnancy in the hamster at a subcutaneous dose level of 25 μg/hamster. Experiments are presently underway to determine the minimum effective dose of (±)-**5** to terminate pregnancy in hamsters. Our initial data indicate that the enantiomerically pure 12-hydroxy-$PGF_{2\alpha}$ methyl ester is at least as potent as natural $PGF_{2\alpha}$.[26]

Testing of these compounds in both the gerbil colon and hamster uterine strip smooth muscle assays revealed (Table I) that they are only very weakly effective. For example, the compound of interest, (±)-**5**, possessed only 2.3% the potency of natural $PGF_{2\alpha}$ in the hamster uterine strip assay and 0.4% the potency of $PGF_{2\alpha}$ in the isolated gerbil colon assay. Of significant interest is the dissociation in compound **5** of smooth muscle stimulating activity from antifertility (luteolytic) activity.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded on a 60-MHz (Varian A-60A or T-60) spectrometer or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (Me_2SO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.

Methyl (1α,4α,5α,7*R)-5-Bromo-7-hydroxyspiro[bicyclo-[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-carboxylate (7).** A solution of bromo ester **6** (9.52 g, 32.7 mmol) in 40 mL of dry tetrahydrofuran was added over 30 min to a cooled (−78 °C) solution of lithium diisopropylamide, prepared from 5.09 g (50.4 mmol) of diisopropylamine in 130 mL of anhydrous tetrahydrofuran and 31.5 mL (50.4 mmol) of *n*-butyllithium (1.6 M in hexane) at −78 °C. After approximately 90 min, oxygen was gently bubbled into the reaction mixture at −78 °C. After an additional 20 min the temperature was raised to 0 °C at which time oxygen was passed into the reaction mixture for an additional 2 h. The reaction was quenched with 35 mL of a 20% aqueous solution of sodium sulfite. The reaction mixture was concentrated in vacuo and treated with saturated brine solution. The product was extracted with ethyl acetate (4 × 70 mL), and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 11.37 g of a clear oil which was chromatographed on 450 g of silica gel. Elution with hexane–ether (1:1) gave in order of elution 1.64 g (17%) of starting bromo ester **6**, 1.71 g (18%) of hydroxy ester **8**, mp 126 °C, and 5.52 g (58%) of hydroxy ester **7**, mp 102 °C: IR ($CHCl_3$) 3500, 3050, 2950, 2895, 1740, 1450, 1440, 1330, 1264, 1106, 1058, 1040, 950 cm^{-1}; NMR ($CDCl_3$) δ 4.17–3.80 (m, 5 H), 3.84 (s, 3 H, $-COOCH_3$), 2.85–2.25 (m, 5 H), 1.72 (d, 1 H, J = 14 Hz, 3-endo proton). An analytical sample was prepared by recrystallization from hexane–chloroform. Anal. Calcd for $C_{11}H_{15}BrO_5$: C, 43.01; H, 4.92. Found: C, 42.72; H, 4.78.

(1α,4α,5α,7*R)-5-Bromo-7-hydroxy-7-hydroxymethylbicyclo-[2.2.1]heptane-2,2'-[1,3]dioxolane (18).** To a stirred suspension of 1.80 g (47.3 mmol) of lithium aluminum hydride in 120 mL of anhydrous tetrahydrofuran cooled to 0 °C was slowly added 5.06 g (16.5 mmol) of bromo ester **7** in 65 mL of dry tetrahydrofuran. Upon completion of the addition, the reaction was heated to reflux. After 2 h, the reaction mixture was cooled to 0 °C and quenched with 90 mL of wet ether, followed by careful addition of water (15 mL). The reaction mixture was dried ($MgSO_4$) and filtered. The precipitate was washed exhaustively with ethyl acetate. The combined organic layers were concentrated in vacuo under high vacuum, yielding 4.43 g (96%) of diol **18** as a white solid, mp 82–83 °C. Recrystallization from ether–pentane gave analytically pure diol: mp 84.5–86.0 °C; IR ($CHCl_3$) 3525, 3000, 2895, 1380, 1332, 1120, 1100, 1054, 1020, 1000, 948, 896 cm^{-1}; NMR ($CDCl_3$) δ 4.4–3.6 (m, 7 H), 3.0–2.5 (m, 6 H); mass spectrum *m/e* (rel intensity) 263 (8), 262 (15, $M^+ - H_2O$), 261 (9), 260 (14, $M^+ - H_2O$), 249 (11), 247 (10), 199 (38), 181 (76), 180 (24), 163 (12), 145 (20), 137 (100), 136 (44), 93 (16), 91 (25), 87 (25), 86 (46). Anal. Calcd for $C_{10}H_{15}BrO_4$: C, 43.02; H, 5.42. Found: C, 43.20; H, 5.28.

(1α,4α,5α,7*R)-5-Bromo-2'',2''-dimethylspiro[bicyclo[2.2.1]-heptane-2,2'-[1,3]dioxolane]-7,4''-[1,3]dioxolane (19).** To a stirred solution of 7.01 g (25.1 mmol) of crystalline diol **18** in 250 mL of acetone was added 8.14 g (51.2 mmol) of anhydrous copper sulfate and a catalytic amount of anhydrous *p*-toluenesulfonic acid. After 12 h at room temperature, the reaction mixture was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent in vacuo gave 7.73 g (96%) of acetonide **19** as a solid, mp 98–99 °C. Recrystallization of **19** from ether–pentane gave analytically pure acetonide: mp 103.0–103.5 °C; IR ($CHCl_3$) 2996, 2950, 2880, 1384, 1372, 1336, 1244, 1160, 1115, 1090, 1070, 1060, 862 cm^{-1}; NMR ($CDCl_3$) δ 4.22 (ABq, 2 H, J = 9 Hz, $\Delta\nu$ = 15.6 Hz, $-CH_2OC(Me)_2-$), 4.1–3.6 (m, 5 H), 2.9–1.7 (m, 6 H), 1.42 (s, 6 H); mass spectrum *m/e* (rel intensity) 305 (22, $M^+ - CH_3$), 303 (22, $M^+ - CH_3$), 261 (23), 239 (43), 238 (16), 182 (100), 125 (35). Anal. Calcd for $C_{13}H_{19}BrO_4$: C, 48.92; H, 6.00. Found: C, 49.04; H, 6.12.

(1α,4α,7*S)-2'',2''-Dimethylspiro[bicyclo[2.2.1]hept-5-ene-2,2'-[1,3]-dioxolane]-7,4''-[1,3]dioxolane (20).** A solution of 8.71 g (27.3 mmol) of acetonide **19** and 81.0 g (533 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 300 mL of toluene was heated at reflux for

80 h. The reaction mixture was concentrated under reduced pressure and the resulting crude product was dissolved in ethyl acetate. The organic layer was washed repeatedly with cold 1% hydrochloric acid until the aqueous layer was clear. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated under high-vacuum pump, yielding 5.54 g (98%) of olefin **20** as a light-yellow solid. An analytical sample of **20,** mp 33.0–33.5 °C, was prepared by column chromatography on silica gel using hexane–ether (1:1): IR ($CHCl_3$) 3075, 3000, 2955, 2885, 1475, 1455, 1430, 1380, 1370, 1330, 1310, 1165, 1150, 1105, 1075, 1060, 1040, 1009, 966, 948, 905, 878, 860, 835 cm^{-1}; NMR ($CDCl_3$) δ 6.29 (m, 2 H, –CH=CH–), 4.10–3.80 (m, 6 H), 2.82–2.55 (m, 2 H), 2.32 (dd, 1 H, J = 12 Hz, 4 H, 3-exo proton), 1.62 (d, 1 H, J = 12 Hz, 3-endo proton), 1.45 (s, 6 H); mass spectrum m/e (rel intensity) 238 (3, M^+), 223 (4, $M^+ - CH_3$), 180 (9), 162 (10), 91 (10), 86 (100), 79 (11), 66 (19), 44 (27), 43 (20). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.37; H, 7.65.

(1α,4aα,7S*)-2′,2′-Dimethylspiro[bicyclo[2.2.1]hept-5-ene-7,4′-[1,3]dioxolan]-2-one (21). A solution of 3.49 g (14.7 mmol) of ketal **20** in 250 mL of tetrahydrofuran was cooled to 0 °C and treated with 40 mL of 1 M hydrochloric acid. The reaction was warmed to room temperature and stirring was continued for 13 h. The reaction mixture was neutralized with 2 N sodium hydroxide solution and the product was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated, and evaporated in vacuo leaving 2.72 g of a yellow oil which was purified on 260 g of silica gel. Elution with hexane–ether (3:2) gave 2.02 (71%) of pure crystalline ketone: mp 52.5–53.0 °C; IR ($CHCl_3$) 2990, 2940, 2875, 1742, 1391, 1374, 1252, 1225, 1201, 1098, 1075, 1060, 1041, 862 cm^{-1}; NMR ($CDCl_3$) δ 6.51 (m, 1 H, –C=CH), 6.06 (m, 1 H, –C=CH), 4.15 (s, 2 H, $-OCH_2-$), 3.00 (m, 2 H), 2.45 (dd, 1 H, J = 16 Hz, 4 Hz, 3-exo proton), 2.00 (d, 1 H, J = 16 Hz, 3-endo proton), 1.28 (s, 6 H); mass spectrum m/e (rel intensity) 194 (1, M^+), 179 (24, $M^+ - CH_3$), 137 (34), 136 (100), 108 (67), 95 (31), 94 (86), 92 (20), 91 (26), 66 (27), 59 (12). An analytical sample was prepared by recrystallization from cold hexane. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.06; H, 7.27. Found: C, 67.96; H, 7.41.

(3aβ,4α,5α,6β,6aβ)-Tetrahydro-5-hydroxy-6-iodo-2′,2′-dimethylspiro[4*H*-cyclopenta[*b*]furan-4,4′-[1,3]-dioxolan]-2(3*H*)-one (22). To a solution of 1.02 g (5.27 mmol) of ketone **21** in 22.5 mL of methanol and 1.4 mL of water cooled in an ice–water bath was added 16.7 mL (41.8 mmol) of 10% aqueous sodium hydroxide solution, followed by the slow dropwise addition of 5.03 mL (74.0 mmol) of 50% aqueous hydrogen peroxide. After stirring at ca. 5 °C for 17 h the reaction was quenched by the addition of sodium thiosulfate. The reaction mixture was concentrated in vacuo and acidified to pH 5.5 with 2 M hydrochloric acid. The aqueous layer was extracted exhaustively with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure leaving 1.17 g (97%) of crude hydroxy acid **25** which was not purified further, but used directly in the next reaction.

To a solution of 1.30 g (15.5 mmol) of sodium bicarbonate in 18.5 mL of water cooled in an ice–water bath was added 1.17 g (5.11 mmol) of hydroxy acid **25** (from above), and a solution of 5.07 g (30.6 mmol) of potassium iodide and 2.58 g (10.2 mmol) of iodine in 13 mL of water. The reaction was quenched after 48 h at 5 °C with sodium thiosulfate. The aqueous layer was saturated with sodium chloride and was extracted with ethyl acetate (6 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo yielding 1.56 g of a white solid. The iodolactone was purified on 200 g of silica gel. Elution with hexane–ethyl acetate (2:3) gave 1.19 g (66%) (60% overall from ketone **21**) of pure iodolactone as a crystalline substance. Recrystallization from ether gave analytically pure iodolactone **22:** mp 133.5–134.5 °C; IR ($CHCl_3$) 3560, 3000, 2950, 2880, 1790, 1390, 1379, 1163, 1140, 1116, 1066, 1060, 1030, 1000, 982, 910, 895, 871, 855 cm^{-1}; NMR ($CDCl_3$) δ 5.1 (m, 1 H), 4.3–3.9 (m, 4 H), 3.2–2.4 (m, 4 H), 1.45 (s, 6 H); mass spectrum m/e (rel intensity) 327 (16, $M^+ - OH$), 227 (13, $M^+ - I$), 154 (100), 127 (52), 97 (55), 84 (11), 68 (40), 59 (45), 57 (23), 55 (19), 44 (98). Anal. Calcd for $C_{11}H_{15}IO_5$: C, 37.31; H, 4.27. Found: C, 37.51; H, 4.31.

(3aα,4β,5β,6aα)-Tetrahydro-5-hydroxy-2′2′-dimethylspiro[4*H*-cyclopenta[*b*]furan-4,4′-[1,3]dioxolan]-2[3*H*]-one (23). A solution of 1.21 g (3.42 mmol) of iodolactone **22** in 40 mL of absolute ethanol cooled to 0 °C was treated with 0.32 mL (1.18 mmol) of tri-*n*-butyltin chloride and 0.17 g (4.50 mmol) of sodium borohydride. The solution was irradiated with a sunlamp for 15 min. After an additional 20 min the reaction was quenched with oxalic acid and the product was extracted with ethyl acetate. The organic layer was washed with dilute hydrochloric acid, saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 1.08 g of an oil which was purified by column chromatography using 40 g of silica gel. Elution with hexane–ethyl acetate (1:2) yielded 368 mg (47%) of crystalline hydroxy lactone **23:** mp 129.0–129.5 °C; IR ($CHCl_3$) 3580, 3030, 2998, 2948, 2880, 1772, 1390, 1380, 1306, 1255, 1230, 1184, 1155, 1118, 1090, 1065, 1030, 982, 864 cm^{-1}; NMR ($CDCl_3$) δ 4.95 (m, 1 H, –CHOCO), 4.01–3.70 (m, 3 H, $-CH_2O$, –CHOH), 2.87–2.65 (m, 3 H), 2.30–2.01 (m, 3 H), 1.45 (s, 6 H); mass spectrum m/e (rel intensity) 213 (100, M^+ – Me), 172 (11), 153 (15), 142 (12), 98 (17), 59 (10). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.90; H, 7.18.

(3aα,4aα,7aα,7bα)-Hexahydro-7b-(hydroxymethyl)-2,2′-dimethyl-6*H*-furo[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxol-6-one (24). To a stirred solution of 682 mg (2.99 mmol) of spiroacetonide **23** in 40 mL of acetone was added 690 mg (4.33 mmol) of anhydrous copper sulfate and four crystals of *p*-toluenesulfonic acid. After a total of 13 h at 60 °C, the reaction mixture was diluted with ethyl acetate and filtered. Removal of the solvent afforded 791 mg of a light-brown oil. The product was purified on 40 g of silica gel. Elution with hexane–ethyl acetate (1:5) provided 525 mg (77%) of pure alcohol **24** as a clear oil: IR ($CHCl_3$) 3600, 3500, 3030, 3010, 2990, 2940, 2875, 1770, 1460, 1421, 1415, 1390, 1380, 1370, 1355, 1334, 1301, 1240, 1198, 1170, 1148, 1120, 1090, 1040, 1020, 996, 970, 960, 900 cm^{-1}; NMR ($CDCl_3$) δ 5.02 (t, 1 H, J = 5 Hz, –CHOCO), 4.67 (d, 1 H, J = 5 Hz, –CHO-C), 3.66 (s, 2 H, $-CH_2OH$), 3.10 (s broad, 1 H, OH), 3.00–2.00 (m, 5 H), 1.45 (s, 3 H), 1.40 (s, 3 H); mass spectrum m/e (rel intensity) 213 (100, M^+ – Me), 197 (6), 171 (5), 135 (4), 107 (3), 59 (3), 58 (10), 43 (10). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.81; H, 7.20.

[3aα,4aα,7aα,7bα(*E*)]-Hexahydro-2,2-dimethyl-7b-(3-oxo-1-octenyl)-6*H*-furo[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxol-6-one (28). To a solution of 328 mg (1.44 mmol) of alcohol **24** in 12 mL of dry dimethyl sulfoxide was added 978 mg (4.75 mmol) of *N,N′*-dicyclohexylcarbodiimide and 75 μL (0.91 mmol) of dichloroacetic acid. The reaction was stirred at room temperature for 20 h. The reaction was diluted with methylene chloride and the precipitated urea was removed by filtration. The filtrate was concentrated in vacuo and the residue was once again washed with methylene chloride and filtered. This procedure was repeated several times. The product was purified by column chromatography on 50 g of silica gel. Elution with ether–ethyl acetate (10:1) gave 268 mg (82%) of pure aldehyde **27** which was used directly in the next reaction.

To a stirred suspension of 62 mg (1.29 mmol) of 50% sodium hydride dispersion in 15 mL of anhydrous tetrahydrofuran cooled to 0 °C under nitrogen was added dropwise a solution of 350 mg (1.58 mmol) of dimethyl (2-oxoheptylphosphonate in 5 mL of dry tetrahydrofuran. Upon completion of the addition, the reaction was warmed to 25 °C (1 h). The phosphonate anion was cooled to 0 °C and treated with a solution of 254 mg (1.12 mmol) of aldehyde **27** in 2 mL of dry tetrahydrofuran. The reaction was quenched at 0 °C after 1 h with saturated aqueous ammonium chloride solution. The product was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product (474 mg) was purified on 50 g of silica gel. Elution with ether–ethyl acetate (10:1) gave 318 mg (88%) of pure crystalline enone **28:** mp 89–90 °C: IR ($CHCl_3$) 1780, 1698, 1680, 1632 cm^{-1}; NMR ($CDCl_3$) δ 6.58 (ABq, 2 H, J = 15 Hz, $\Delta\nu_{AB}$ = 23.6 Hz, –CH=CH), 4.95 (t, 1 H, J = 5 Hz, –CHOCO), 4.60 (d, 1 H, J = 5 Hz, $-CHOC(CH_3)_2$), 1.47 (s, 3 H), 1.29 (s, 3 H), 0.88 (t, 3 H); mass spectrum m/e (rel intensity) 307 (60. M^+ – Me), 265 (29), 205 (9), 193 (25), 167 (15), 165 (11), 164 (12), 121 (10), 107 (15), 99 (97), 95 (10), 91 (11), 81 (15), 79 (12), 71 (29), 69 (15), 60 (17), 56 (15), 55 (45), 44 (35), 43 (100). A sample was prepared by recrystallization from hexane–ether, mp 90–91 °C. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.10; H, 8.08. Found: C, 67.36; H, 8.22.

[3aα,4aα,7aα,7bα(*E*)]-Hexahydro-2,2-dimethyl-7b-[3(*RS*)-*tert*-butyldimethylsilyloxy-1-octenyl]-6*H*-furo[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxol-6-one (30). Sodium borohydride (139 mg, 3.7 mmol) was added to a solution of 590 mg (1.8 mmol) of trans-enone **28** in 15 mL of 95% ethanol cooled to −10 °C. The reaction was quenched at −10 °C after 1 h with 60% aqueous acetic acid and neutralized with solid sodium bicarbonate. The solvent was concentrated under reduced pressure and the residue was taken up in water (5 mL). The product was isolated by extraction with ether (3 × 100 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The crude product was subjected to column chromatography on 30 g of silica gel prior to silylation. Elution with ether–ethyl acetate (10:1) gave 592 mg (96%) of alcohol **29** as a colorless oil which was a mixture of epimers at C-15. Alcohol **29** was used directly in the next reaction.

A solution of the above alcohol (592 mg, 1.8 mmol) in 4.8 mL of dry dimethyl formamide was treated at room temperature with 554 mg (3.6 mmol) of *tert*-butyldimethylsilyl chloride and 245 mg (3.6 mmol) of imidazole. After 2 h the reaction mixture was diluted with benzene

and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. The crude product was purified on 40 g of neutral silica gel (SilicAR CC-7). Elution with hexane–ether (1:1) gave 680 mg (86%) of pure silyl ether **30** as a colorless solid: IR (CCl_4) 2960, 2940, 2900, 2855, 1795, 1695, 1472, 1460, 1415, 1385, 1375, 1362, 1350, 1340, 1328, 1295, 1260, 1215, 1192, 1155, 1090, 1060, 1044, 1009, 990, 974, 954, 940, 895, 876, 838 cm^{-1}; NMR (CCl_4) δ 5.72 (m, 2 H), 4.80 (t, broad, 1 H, J = 5 Hz), 4.44 (d, broad), 1 H, J = 6 Hz), 4.15 (m, 1 H), 1.41 (s, 3 H), 1.24 (s, 3 H), 0.90 (s, 9 H), 0.00 (s, 6 H).

Wittig Reaction on Lactol 31. To a solution of 145 mg (0.33 mmol) of lactone **30** in 5 mL of dry toluene cooled to −78 °C under nitrogen was added dropwise via syringe 0.71 mL (0.99 mmol) of a 20% solution of diisobutylaluminum hydride in toluene. The reaction was quenched at −78 °C after 30 min by the careful dropwise addition of methanol. The reaction was diluted with 40 mL of ether and was warmed to room temperature. Water (0.5 mL) was added and stirring was continued for 40 min, followed by direct drying over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo provided 136 mg of hemiacetal **31** which was used directly in the next reaction.

A suspension of 313 mg (6.27 mmol) of 50% sodium hydride dispersion (washed with hexane prior to use) in 3.0 mL of freshly distilled dimethyl sulfoxide was heated at 75 °C for 1 h under nitrogen. To the above solution cooled to room temperature was added 1.46 g (3.3 mmol) of (4-carboxybutyl)triphenyl phosphonium bromide in 4.0 mL of dry dimethyl sulfoxide. A 4.0-mL aliquot of the dark-red ylid solution was added to a solution of 136 mg of hemiacetal **31** in 1.0 mL of dry dimethyl sulfoxide. After 18 h at 25 °C, the reaction mixture was heated at 60 °C for 20 min. The reaction was quenched by the addition of 10 mL of ice–water and carefully acidified to pH 5 with 0.5 N sodium hydrogen sulfate. The product was isolated by extraction with ether (4 × 150 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The yellow residue was esterified with ethereal diazomethane. The crude product was chromatographed on 20 g of silica gel. Elution with hexane–ether (1:1) gave 85 mg (48% overall yield from 30) of hydroxy ester **32** as a colorless oil: IR (CCl_4) 3555, 2990, 2950, 2930, 2855, 1740, 1460, 1439, 1385, 1375, 1365, 1258, 1217, 1175, 1060 cm^{-1}; NMR ($CDCl_3$) 5.60 (m, 2 H), 5.38 (m, 2 H), 4.41 (m, 1 H), 4.10 (m, 2 H), 3.61 (s, 3 H), 1.47 (s, 3 H), 1.25 (s, 3 H), 0.87 (s, 9 H).

(±)-12-Hydroxy-PGF$_{2\alpha}$-(11,12-*O*-isopropylidene) Methyl Ester (33). A solution of 50 mg (0.09 mmol) of silyl ether **32** in 3.0 mL of tetrahydrofuran was treated at 25 °C for 4 h with 70 mg (0.27 mmol) of tetra-*n*-butylammonium fluoride. The reaction mixture was diluted with 50 mL of ether and washed with a saturated solution of sodium bicarbonate. The ether layer was dried over anhydrous magnesium sulfate and evaporated, leaving 35 mg of crude product as a mixture of epimers at C-15 which was purified on 15 g of silica gel. Elution with ether–ethyl acetate (10:1) gave 29 mg (76%) of a colorless oil. The product (20 mg) was separated into the C-15 α and β epimers 33 (more polar) and 34 (less polar) on 10 g of silica gel using benzene–ethyl acetate (3:1). There was obtained in order of elution, 5 mg of pure **34**, a mixture (10 mg) of **33** and **34**, and 3 mg of pure **33**: IR ($CHCl_3$) 3540, 3005, 2960, 2935, 2865, 1730, 1470, 1460, 1440, 1418, 1386, 1378, 1365, 1335, 1315, 1260, 1235, 1205, 1171, 1138, 1105, 1059, 1021, 985 cm^{-1}; NMR ($CDCl_3$) δ 5.75 (m, 2 H), 5.40 (m, 2 H), 4.48 (m, 1 H), 4.08 (m, 2 H), 3.67 (s, 3 H), 1.52 (s, 3 H), 1.35 (s, 3 H), 0.90 (t, 3 H).

(±)-12-Hydroxy-PGF$_{2\alpha}$ Methyl Ester (5). A 1:1 mixture of acetonides **33** and **34** (48 mg, 0.11 mmol) in 2.0 mL of methanol was treated at room temperature with a catalytic amount of *p*-toluenesulfonic acid for 24 h. The reaction mixture was diluted with 50 mL of chloroform and washed with a saturated solution of sodium bicarbonate. After drying over anhydrous magnesium sulfate and evaporation of the solvent in vacuo, the crude product was chromatographed on 15 g of neutral silica gel (SilicAR CC-7). Elution with ether–ethyl acetate–methanol (10:10:1) provided 11 mg (26%) of a mixture of (±)-12-hydroxy-PGF$_{2\alpha}$ methyl ester (**5**) and (±)-15-*epi*-12-hydroxy-PGF$_{2\alpha}$ methyl ester (**35**). The mixture of **5** and **35** was separated on SilicAR CC-7 employing ether–ethyl acetate (1:1). There was obtained in order of elution 5 mg of **35**, 6 mg of a mixture of **35** and **5**, and 3 mg of (±)-12-hydroxy-PGF$_{2\alpha}$ methyl ester (**5**) as a solid. Recrystallization of **5** from ether–pentane gave pure **5**: mp 65–67 °C; IR ($CHCl_3$) 3620, 3425, 3030, 2960, 2945, 2865, 1738, 1463, 1420, 1241, 1210, 1165, 1110, 1055, 982, 938 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.78 (dd, 1 H, J = 15 Hz, 7 Hz), 5.50 (d, 1 H, J = 15 Hz), 5.38 (m, 2 H, *cis*-CH=CH–), 4.12 (m, 2 H), 3.92 (m, 1 H), 3.66 (s, 3 H), 0.88 (t, 3 H).

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Registry No.—**6**, 54701-91-6; **7**, 67237-16-5; **8**, 67314-16-3; **18**, 67237-17-6; **19**, 67237-18-7; **20**, 67237-19-8; **21**, 67237-20-1; **22**, 67237-21-2; **23**, 67237-22-3; **24**, 67237-23-4; **25**, 67237-24-5; **27**, 67237-25-6; **28**, 67237-26-7; **29**, 67237-27-8; **30**, 67237-28-9; **31**, 67237-29-0; **32**, 67292-17-5; dimethyl (2-oxoheptyl)phosphonate, 36969-89-8; *tert*-butyldimethylsilyl chloride, 18162-48-6; (4-carboxybutyl)triphenyl phosphonium bromide, 17814-85-6.

References and Notes

(1) J. R. Weeks, *Ann. Rev. Pharmacol.*, **12**, 317 (1972); E. K. Insheep, *J. Anim. Sci.*, **36**, 1149 (1973).
(2) (a) N. S. Crossley, *Prostaglandins*, **10**, 5 (1975) and references cited therein; (b) J. Fried, M.-S. Lee, B. Gaede, J. C. Sih, Y. Yoshikawa, and J. A. McCracken, *Adv. Prostaglandin Thromboxane Res.*, **1**, 183 (1976).
(3) P. A. Grieco, C. S. Pogonowski, S. D. Burke, M. Nishizawa, M. Miyashita, Y. Masaki, C.-L. J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 4111 (1977); also see P. A. Grieco, N. Fukamiya, and M. Miyashita, *J. Chem. Soc., Chem. Commun.*, 573 (1976).
(4) C.-L. J. Wang, P. A. Grieco, and F. J. Okuniewicz, *J. Chem. Soc., Chem. Commun.*, 468 (1976).
(5) P. A. Grieco, C.-L. J. Wang, and F. J. Okuniewicz, *J. Chem. Soc., Chem. Commun.*, 939 (1976).
(6) For other C-12 substituted prostaglandins, see N. Nakamura and K. Sakai, *Tetrahedron Lett.*, 2049 (1976); L. Godoy, A. Guzman, and J. M. Muchouski, *Chem. Lett.*, 327 (1975); E. J. Corey, C. S. Shiner, R. P. Volante, and C. R. Cyr, *Tetrahedron Lett.*, 1161 (1975).
(7) H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 4611 (1975); H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 4613 (1976); W. Adam and O. Cueto, *J. Org. Chem.*, **42**, 38 (1976).
(8) Unpublished results of David Moore, University of Pittsburgh, Pittsburgh, Pa.
(9) H. C. Brown and P. Geoghegan, *J. Am. Chem. Soc.*, **89**, 1522 (1967).
(10) Rigorously anhydrous conditions are required for the formation of acetonide **19**. Traces of moisture will inhibit the formation of **19**.
(11) E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **40**, 2554 (1975).
(12) Yields ranged from a low of 47% to a high of 89%. Small-scale reactions consistently gave high yields whereas large-scale reactions proceeded in ca. 50% yield.
(13) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5677 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, N. M. Weinshenker, *ibid.*, **92**, 397 (1970); (c) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971).
(14) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(15) For routes to β-keto phosphonates see B. A. Arbusov, *Pure Appl. Chem.*, **9**, 307 (1964); G. Sturtz, *Bull. Soc. Chim. Fr.*, 2340 (1964); G. Sturtz, C. Charrier, and H. Normant, *ibid.*, 1707 (1966); E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5654 (1966); G. Sturtz, *Bull. Soc. Chim. Fr.*, 1345 (1967); M. S. Chatta and A. M. Aguiar, *J. Org. Chem.*, **37**, 1845 (1972); P. A. Grieco and C. S. Pogonowski, *J. Am. Chem. Soc.*, **95**, 3071 (1973); M. S. Chatta and A. M. Aguiar, *J. Org. Chem.*, **38**, 2908 (1973); P. Savignac and F. Mathey, *Tetrahedron Lett.*, 2829 (1976).
(16) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(17) E. J. Corey and C. U. Kim, *Tetrahedron Lett.*, 287 (1974).
(18) E. J. Corey and C. U. Kim, *Tetrahedron Lett.*, 919 (1973).
(19) J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
(20) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).
(21) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).
(22) For a review of the Moffatt-Pfitzner oxidation see J. G. Moffatt, "Oxidation: Techniques and Applications in Organic Synthesis", Vol. 2, Marcel Dekker, New York, N.Y., 1971, p 1.
(23) Dichloroacetic acid has previously been employed in oxidations using dimethyl sulfoxide–dicyclohexylcarbodiimide.[21] Also see, P. Turnbull, K. Syhora, and J. H. Fried, *J. Am. Chem. Soc.*, **88**, 4764 (1966).
(24) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(25) By analogy to the TLC behavior of natural and 15-epi prostaglandins, the more polar isomer has been assigned the natural 15S configuration (N. H. Andersen, *J. Lipid Res.*, **10**, 316 (1969).
(26) The interruption of pregnancy test was carried out as described by Giannina and co-workers[27] with the exception that one male per female was used instead of one male per three females. Ten hamsters (80–90 g bodyweight) were used for each compound. The compounds were dissolved in ethanol and a single dose of each compound was administered subcutaneously on day five of pregnancy. Whereas natural PGF$_{2\alpha}$ exhibited 100% interruption of pregnancy at a dose of 12.5 μg/hamster, ICI 81008, Equimate, was completely effective at 0.125 μg/hamster.[2a]
(27) T. Giannina, M. Butler, W. K. Sawyer, and B. G. Steinetz, *Contraception*, **9**, 507 (19).
(28) The oxytocin-like activity was determined using the assay as described by Holton[29] with the exception that hamsters were used in place of rats.
(29) P. Holton, *Brit. J. Pharmacol.*, **3**, 328 (1948).

Stereospecific Cyclizations of Iminium Salts from α-Amino Acid Decarbonylation. Synthesis of 8- and 13-Methylberbines

Richard T. Dean and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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Berbines containing methyl substituents at C-8 and C-13 have been synthesized by stereospecific cyclizations of iminium salts generated by α-amino acid decarbonylation. (8*S*,13a*R*)-(+)-8-Methyl-2,3,10,11-tetramethoxyberbine [(+)-*O*-methylcorytenchirine (**5**)] was synthesized starting from dihydroxyphenyl-L-alanine (**7**) via a previously described stereoselective introduction of the 1-methyl substituent to give (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic acid (**8**). This was efficiently converted to ethyl (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylate (**10**) by esterification, N-formylation, methylation of the phenolic hydroxyls, and selective deformylation. Alkylation, hydrolysis, iminium salt formation, and cyclization then proceeded in high yield stereospecifically to give (+)-*O*-methylcorytenchirine (**5**). β-Methyl(3,4-dimethoxyphenyl)alanine was synthesized with the methyl substituent enantiomerically pure by resolving 3-(3,4-dimethoxyphenyl)butyric acid and then aminating via the malonate derivative **31** using chloramine. Hydrolysis and decarboxylation of the optically active aminomalonate proceeded with little stereoselectivity. The resulting β-methyl(3,4-dimethoxyphenyl)alanine (**19**) was then converted to 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylic acid (**23**), decarbonylated to the iminium salt **1**, and cyclized stereospecifically to give racemic *trans*-13-methyl-2,3,10-11-tetramethoxyberbine (**2**). Disproportionation was observed as a side reaction, and modified conditions are considered which decrease this disproportionation of the intermediate dihydroisoquinoline.

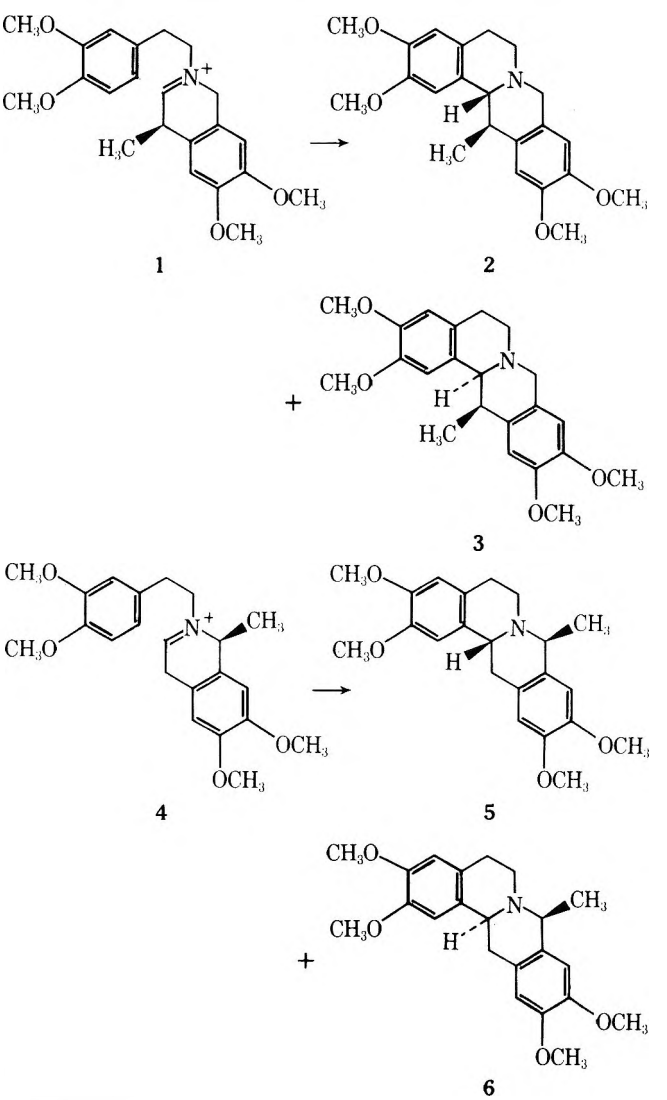
The decarbonylation of α-tertiary amino acids has been demonstrated to be an efficient method for regiospecifically generating iminium salts.[1] That the starting material, an α-amino acid, also may be asymmetric suggests two additional potential advantages. Although the α-carbon asymmetry is lost on iminium salt generation, the chirality of the amino acid may be used to induce asymmetry in earlier reactions introducing additional substituents. Secondly, enantiomerically pure products may be possible by prior resolution of the amino acid or amino acid precursors. To address these questions, we chose to investigate the synthesis of 8- and 13-methylberbines, applying the general method for synthesis of berbines described in our earlier work.[2] The synthesis of both classes of compounds presents a stereochemical question in the outcome of the cyclization step since diastereomers are possible (Scheme I).

8-Methylberbines. Obligatory to the synthesis of berbines by the general method we have developed is an intermediate 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid. A substituent at C-8 of the subsequently formed berbine requires a corresponding C-1 substituent in the tetrahydroisoquinoline. Such a compound has been described[3] in the asymmetric synthesis of (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic acid (**8**) from dihydroxyphenyl-L-alanine (**7**) (Scheme II). This reaction allows for the preparation of an 8-methylberbine enantiomerically pure at the 8 position. However, the phenolic secondary amine **8** must be N-alkylated and the phenolic hydroxyls converted to methyl ethers to realize the α-tertiary amino acid necessary for iminium salt generation.

The simplest route to the required dimethoxy tertiary amine would be to selectively methylate the phenols and then N-alkylate. However, treatment of ethyl ester **9** with diazomethane gave mostly the permethylated compound **11** with a small amount of the selectively alkylated compound **10**.[4] Applying a method which had previously[5] been selective for the methylation of phenols, the phenolic amine **8** was treated with *N,N'*-diisopropyl-*O*-methylisourea, but gave exclusively the permethylated compound **11** with partial racemization. This unexpected racemization foreshadowed difficulties in this seemingly simple conversion.

Another scheme was to protect the catechol portion of the molecule, alkylate the nitrogen, and then deprotect and methylate the phenols. Thus, **9** was treated with phenylboronic anhydride to form the cyclic borate ester **12**, which was N-alkylated to give **13**. The catechol was deprotected during

Scheme I. Iminium Salt Cyclization to Diastereomeric 8- and 13-Methyl-2,3,10,11-tetramethoxyberbines



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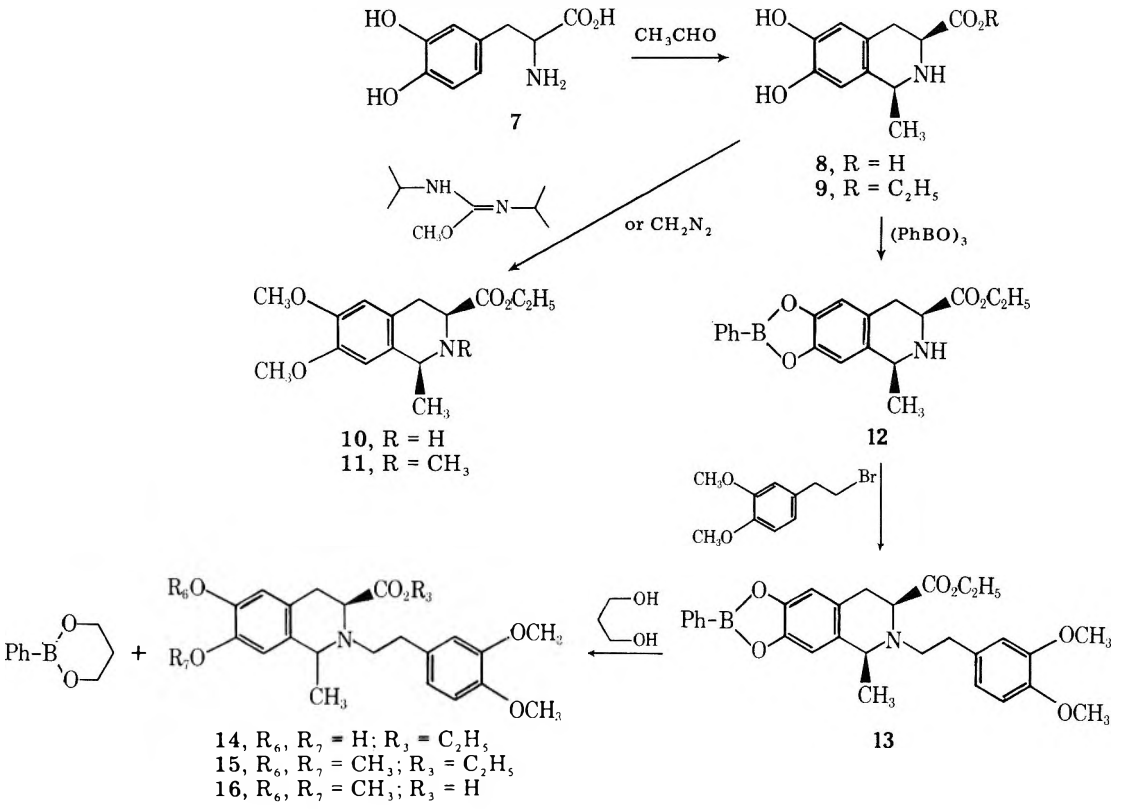
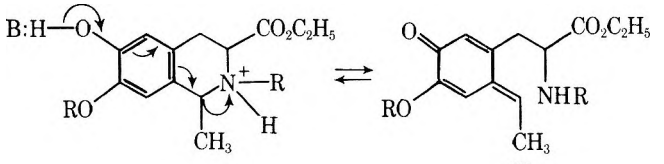
Scheme II. Synthesis of 6,7-Dimethoxy-1-methyltetrahydro-3-isoquinolinecarboxylates with Partial Racemization



isolation by exchange with 1,3-propanediol, and the phenolic tertiary amine was methylated with *N,N'*-diisopropyl-*O*-methylisourea to give **15** in 57% overall yield (Scheme II). This ester was hydrolyzed, the acid **16** was decarbonylated, and the iminium salt **4** was cyclized to give the berbine. Ring closure took place exclusively to form isomer **5** with the 8-methyl and 13a-hydrogen cis as shown in Scheme I. To our surprise, however, the optical rotation of the product indicated that only 16% of the optical activity had been retained through this series of reactions.

In considering where this substantial racemization might have occurred, we focused on the conversion of the catechol **14** to the veratrole **15.** Either the catechol or its monomethyl ether, with a free hydroxyl at C-6, could lead to racemization at C-1 of the tetrahydroisoquinoline through methide inter-



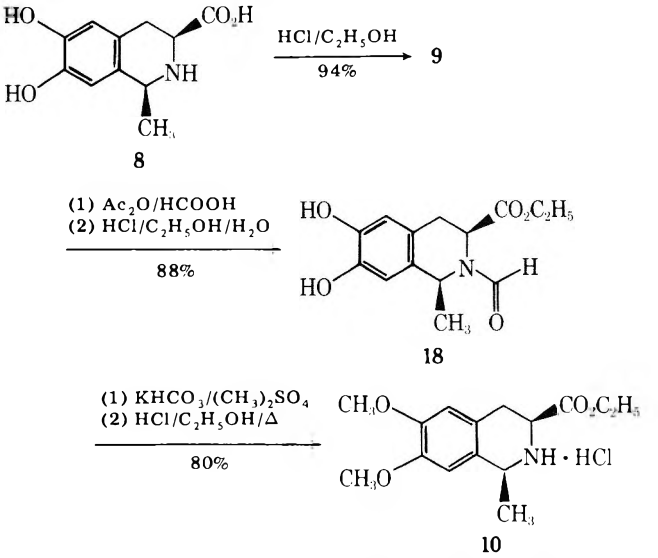
17

mediate **17.** Racemizations of various tetrahydroisoquinolines analogous to ours have been observed.[6]

Thus, it became mandatory, for a chirally specific synthesis, to avoid conversions of the type **14** → **15,** that is, to avoid methylation of the phenolic tertiary amine. Actually, the desired transformation of the dihydroxytetrahydroisoquinoline **8** to the dimethoxy secondary amine **10** has been accomplished[4] with complete chiral integrity. However, the overall yield was poor (~6%). The transformation was effected by selectively protecting the amine as its acetyl derivative after esterification, but difficulties in removing the *N*-acetyl were responsible in part for the poor yield.

We have modified this process and improved the overall yield to 66%. A key change was the use of the formyl group to protect the nitrogen. This allowed its facile selective removal in the presence of the ethyl ester and avoided the additional

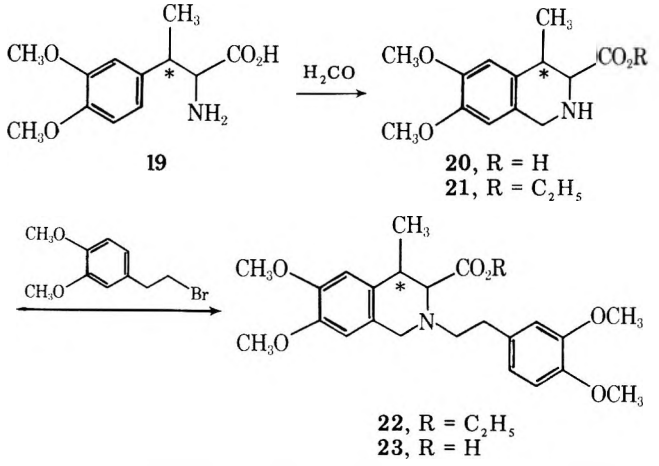
Scheme III. Synthesis of Chirally Pure 6,7-Dimethoxy-1-methyltetrahydro-3-isoquinolinecarboxylates



reesterification step. Also, a possible side reaction in the methylation step is conversion of the *N*-formyl group to methyl imidate salt. This is accommodated by using an alkaline isolation procedure at this stage of the synthesis. The product, a mixture of amine and amide, was heated with HCl/C_2H_5OH to remove all remaining formyl residues, and chirally pure ethyl (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-1-methyl-6,7-dimethoxy-3-isoquinolinecarboxylate (**10**) was isolated as its hydrochloride (Scheme III).

To form berbine, ester hydrochloride **10** was then converted to the free amine, alkylated with the phenylethyl bromide, hydrolyzed, decarbonylated, and cyclized in the usual manner to give **5** in high yield with an optical rotation for the hydrochloride of $[\alpha]_D$ +136° (lit.[4] $[\alpha]_D$ +148°), corresponding to 94% retention of optical purity from isoquinoline **10.** Ring closure of iminium salt **4** was stereospecific with less than 1% of isomer

Scheme IV



6 as established by LC and GC. The product was identical with (+)-*O*-methylcorytenchirine (**5**) by comparison of its physical and spectral properties with those reported.[7]

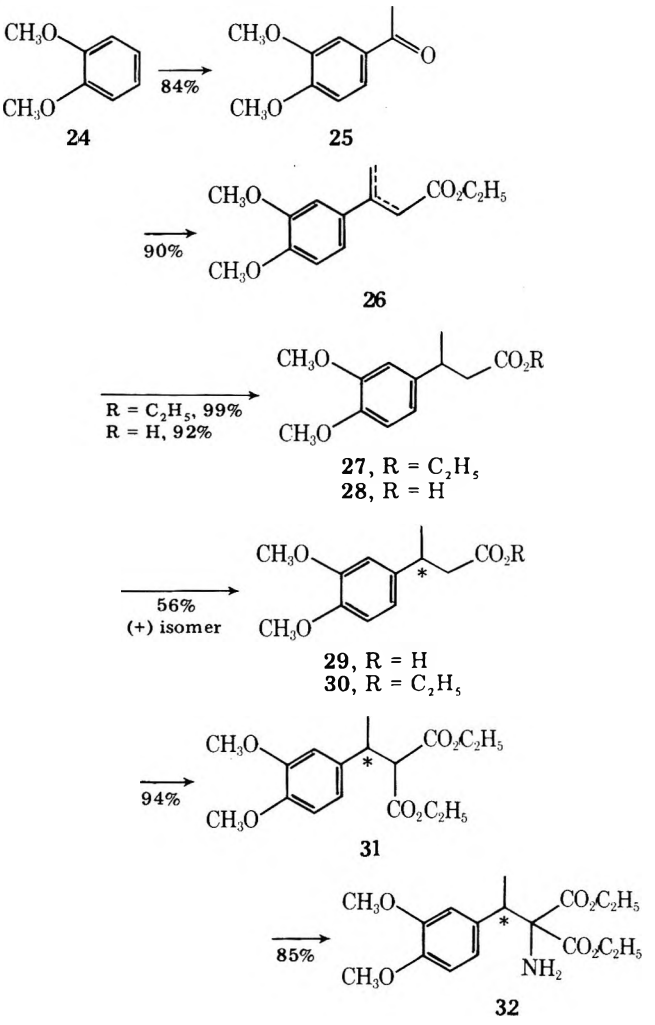
Thus, the optically active amino acid was able to effect a stereospecific introduction of what ultimately became the 8-methyl group of the berbine. Even if the α carbon of the amino acid may have racemized in subsequent steps, its function of inducing asymmetry was complete and it need only serve to create iminium salt regiospecifically by a self-destruction process. The methyl group, now of a single stereochemistry, directed a stereospecific ring closure to a single, optically pure compound. Interestingly, the methyl group did this from a position relatively remote from the bond-forming site. This can be rationalized by assuming that the methyl group influenced the conformation of the transition state and thus the mode of attack by the aromatic ring of the iminium salt.

13-Methylberbines. The complimentary substitution pattern with a 13-methyl substituent can be envisioned as being derived from a β-methylphenylalanine derivative (**19**; Scheme IV). Our plan was to resolve the asymmetry due to the methyl group at some point in the scheme prior to iminium salt cyclization. This should allow a chirally specific synthesis and the direct preparation of an optically active final product. Thus, we chose to synthesize the β-methylphenylalanine **19** with the chirality at the β carbon resolved. Since the carboxyl group would be lost in decarbonylation to form iminium salt, its stereochemistry was of no concern and we sought the diastereomeric pair with only the β carbon configurationally pure.

The synthetic options at this point were to prepare all four isomeric β-phenylalanines, separate diastereomers, and then resolve to obtain a single compound. Alternatively, we could resolve only the asymmetry resulting from the β-methyl group by resolving 3-(3,4-dimethoxyphenyl)butyric acid (**28**) and then aminate to obtain the phenylalanine derivative. The former method has been reported,[8] but is troublesome and inefficient. The target then became **28**. Our synthesis (Scheme V) began with veratrole (**24**), which was converted to acetoveratrone[9] (**25**) and thence in a carefully controlled Reformatsky reaction to give, after dehydration, a mixture of the three isomeric unsaturated esters **26** in 90% yield. Catalytic reduction gave a single product, ethyl 3-(3,4-dimethoxyphenyl)butyrate (**27**). This was hydrolyzed to the free acid **28** for resolution.

The resolution of 3-(3,4-dimethoxyphenyl)butyric acid (**28**), after a series of preliminary tests,[10] was effected with *d*-α-phenylethylamine in chloroform for the (−) isomer and quinine in acetone for the (+) isomer. In four recrystallizations, constant rotation (+) acid was obtained in 56% yield. Acid thus obtained was established as optically pure by quantitative amide formation using *d*-α-phenylethylamine-*d* and analysis for diastereomeric purity by GC. This classical resolution is quite efficient and superior to kinetic resolution available through optically active oxazolines.[11] The comparable 3-phenylbutyric acid was obtained by the latter process in 50% yield, 13% optically pure.

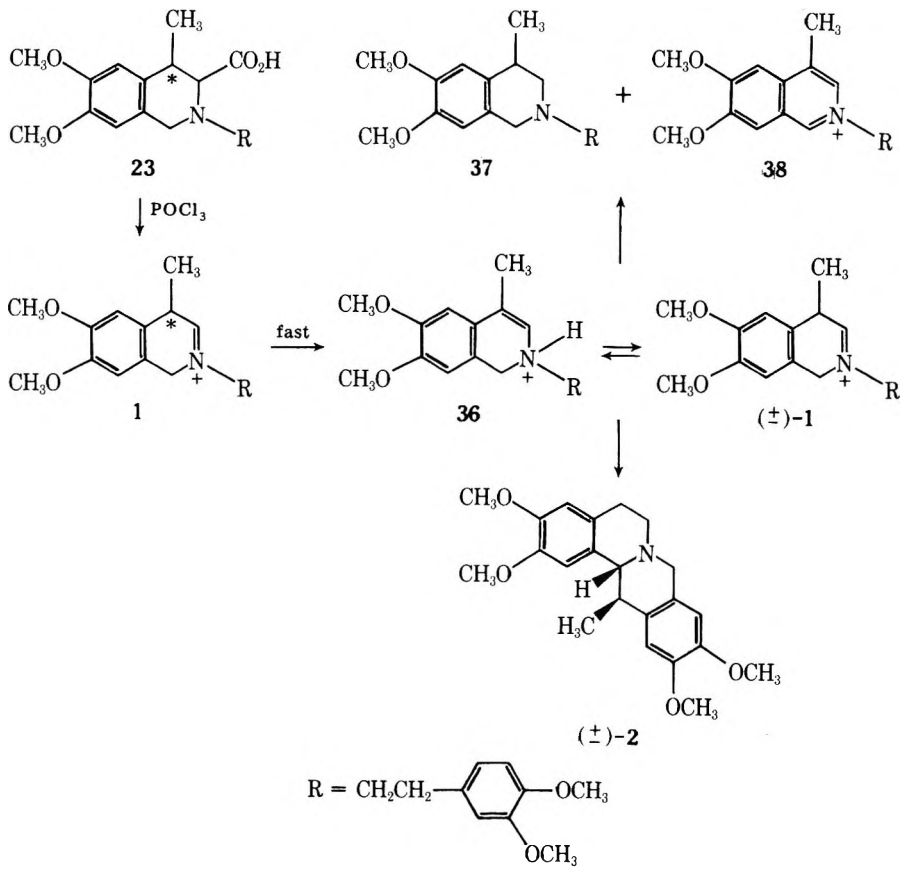
Scheme V. Intermediates in the Synthesis of β-Methyl-3,4-dimethoxyphenylalanine Enantiomerically Pure at the β Position



Conversion of (+)-3-(3,4-dimethoxyphenyl)butyric acid (**29**) to the desired β-methylphenylalanine (**19**) requires an α-amination, which was attempted first through the α-bromo acid. The acid chloride was brominated with *N*-bromosuccinimide (NBS) in carbon tetrachloride,[12] using 2 equiv of NBS since ring bromination was more facile than α-bromination. The α-bromo ester resulting from addition of methanol was treated with potassium phthalimide in DMF.[13] Removal of the aromatic bromine by hydrogenolysis and hydrazinolysis–hydrolysis of the α-phthalimido ester give the desired amino acid **19**; however, it was obtained in less than 15% overall yield for seven steps.

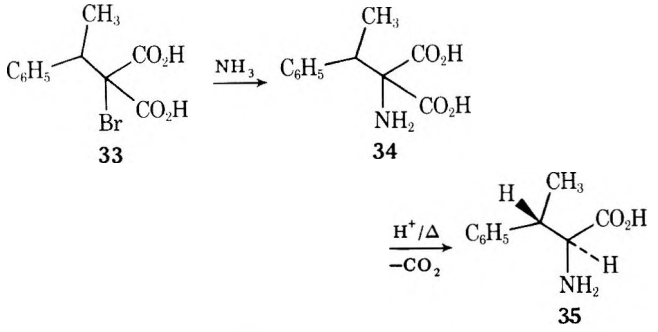
Amination of the acid was considered but dismissed since poor results have been reported.[14] Amination of the ester by first forming the enolate with lithium diisopropylamide followed by treatment with chloramine yielded product, but again in less than 15% yield. A possible reason for the poor amination yields of these strong bases with chloramine is that chloramine has a pK_a of 14 ± 2.[15] Proton transfer could be occurring faster than amination. On this basis, amination should be more successful on the anion of malonate **31**, a weaker base. Indeed, when the anion of **31** was treated with chloramine in ether, an 85% yield of amino ester **32** was ob-

Scheme VI



tained. Chloramine was conveniently prepared by adding an NaOCl solution to a cold NH_4OH solution buffered with NH_4Cl and then extracting into ether.[16] This avoids decomposition caused by excess alkali and gives >90% yields of chloramine without the troublesome distillation.[17] The malonate needed, **31**, was prepared from ethyl ester **30** in 94% yield by forming the enolate with lithium diisopropylamide and treating with 150 mol % of ethyl chloroformate at −78 °C.[18] The aminomalonate **32** was then converted to amino acid **19** by hydrolysis followed by decarboxylation.

Of interest was a report[19] that aminomalonic acid **34** could be decarboxylated to phenylalanine **35** sterospecifically. We were interested in applying this process to our aminomalonate



32 and thereby obtaining a single amino acid. No experimental details were given, and **35** was stated to be obtained in 47% yield from **33**.

We hydrolyzed **32** in refluxing 1 N HCl to produce amino acid **19** as a 4:3 mixture of diastereomers in 89% yield. When **32** was hydrolyzed with alkali, the dipotassium salt isolated, and this subjected to decarboxylation in 1 N HCl, a 3:2 mixture of diastereomers was obtained. In the last case, our aminomalonic acid intermediate prior to decarboxylation should be identical (except for the two methoxyls) with the reported[19] example **34**. One possible explanation for this apparent difference might be that the reported reaction was not stereospecific but slightly stereoselective and that only the erythro isomer was isolated (47% yield) by fractional crystallization. Indeed, in a similar report of the hydrolysis and decarboxylation of ethyl (±)-2-acetylamino-2-ethoxycarbonyl-3-phenylbutyrate to (±)-α-methylphenylalanine [(±)-**35**], the erythro isomer predominates (1.5–1.7:1), but is not exclusive, in the product.[8]

The amino acid **19**, enantiomerically pure at C-3 and mixed at C-2, was converted to the 3-isoquinolinecarboxylic acid **20**, and the ethyl ester **21** was formed in 79% overall yield. The secondary amine was then alkylated to give **22** in 76% yield. Hydrolysis proceeded in 89% yield to acid **23** (Scheme IV), now ready for iminium salt formation and ring closure.

When **23** was subjected to the standard decarbonylation and cyclization conditions, a mixture of the desired berbine **2** and one of the dihydroisoquinoline disproportionation products, 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-4-methylisoquinoline (**37**), was obtained. These two compounds were isolated as the only basic products from this reaction. Berbine **2** was established to have the stereochemistry shown (Scheme VI) with the hydrogens at C-13 and C-13a trans. This assignment is based on the NMR absorption, which for trans 13- and 13a-hydrogens shows a chemical shift for the 13-methyl group of ca. δ 1.5 compared to ca. δ 1.0 for the case where the hydrogens are cis.[20–24] This is the expected mode of attack by the aromatic ring on an iminium salt with a substituted carbon adjacent to the bond-forming site and provides synthetically based evidence corroborating earlier assignments. Finally, both products are racemic, indicating a loss of optical integrity at the 4 position of the isoquinoline prior to ring closure.

Disproportionation of 4-alkyldihydroisoquinolines has been previously reported. For example, when 4-alkyl-1,2-dihydroisoquinolines were treated with acid in an attempt to obtain the iminium salt (i.e., the 1,4-dihydroisoquinolinium salt), disproportionation was reported as the exclusive result.[25,26] The mechanism and conditions promoting this dispropor-

tionation are poorly understood. In an attempt to evaluate some of the possible variables, the effect of conditions on the production of berbine **2** was briefly investigated. The factors studied were concentration, time, and temperature during both iminium salt formation and acid cyclization and acid strength in the latter. The results show that **2** is favored over the disproportionation products under (1) minimum time, lower temperatures, and lower concentrations during decarbonylation in $POCl_3$ and (2) higher acidity in the aqueous cyclization step. Concentration of reactant in the aqueous medium appears unimportant.

These data suggest that disporportionation is a bimolecular reaction and that it occurs primarily in the $POCl_3$ solution. Earlier studies showed that no cyclization occurs in the $POCl_3$ with this system, but takes place only in the subsequent aqueous acid treatment. The loss of optical activity in all products is explicable only if a rapid equilibrium between initially formed iminium salt **1** and enamine **36** is established prior to cyclization and disproportionation. Scheme VI summarizes our observations and hypothesis. Our results are suggestive of additional steps now under investigation which might avoid disproportionation in this system such as formation of an activated acyl derivative under milder conditions and decarbonylation under strongly acidic or catalytic conditions.

Experimental Section[27]

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarhoxylate (15a).[27a] To ethyl (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dihdroxy-1-methyl-3-isoquinolinecarboxylate (**9**)[4] (3.24 g, 12.9 mmol) was added phenylboronic anhydride (1.39 g, 4.5 mmol), benzene (60 mL), and DMF (10 mL), and this mixture was refluxed for 1 h, followed by distillation of 40 mL over 2.5 h. To the remaining mixture was added K_2CO_3 (3.82 g, 26 mmol) and 1-(2-bromoethyl)-3,4-dimethoxybenzene (3.94 g, 1.6 mmol), and the mixture was refluxed for 22 h and cooled. Ether (100 mL), H_2O (20 mL), 1,3-propanediol (0.3 mL, 40 mmol), and then 1 N HCl (52 mL) were added; after 2 h, the ether layer was separated and extracted with 1 N HCl (50, 25, and 25 mL). The acidic extracts were neutralized to pH 8 with $NaHCO_3$, and extracted with $CHCl_3$ (50, 25, 25, and 20 mL), and the dried $CHCl_3$ extracts were evaporated to give a crude residue (8.4 g). To this residue was added *N,N'*-diisopropyl-*O*-methylisourea (16.5 g, 104 mmol), and heating was maintained at 100 °C for 26 h until all of the material was converted to a single product by TLC ($CHCl_3$/MeOH, 9:1; R_f 0.73). The mixture was distilled, collecting ester **15a** between 150–210 °C (0.01 torr), to give 3.25 g (7.3 mmol, 57%): NMR δ 6.8–6.5 (5 H, m), 4.3–3.5 (2 H, m), 4.1 (2 H, q), 3.9 (12 H, s), 3.0–2.7 (6 H, m), 1.35 (3 H, d), 1.15 (3 H, t); IR 1728 cm^{-1}; MS *m/e* (relative intensity) 443 (1), 428 (4), 370 (13), 292 (100).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylic Acid (16a). To ester **15a** (3.22 g, 7.3 mmol) was added ethanolic KOH (800 mg in 50 mL), and the mixture was heated at reflux for 3 h. The solvent was evaporated, water and decolorizing carbon were added, the mixture was filtered, and the pH was adjusted to 6 with 6 N HCl. The filtered solution was extracted with $CHCl_3$ (3 × 20 mL) and the $CHCl_3$ evaporated to a residue, which was recrystallized from 15 mL of CH_3OH/ether (1:2) to give 1.27 g (3.1 mmol, 42%) of acid **16a,** mp 157–158 °C with softening at 152 °C. A second crop of 328 mg was obtained, and chromatography of the mother liquor gave 606 mg (80% total yield): NMR δ 6.64–6.30 (5 H, m), 4.47 (1 H, t), 3.84, 3.81, and 3.75 (12 H, s, s, s), 4.10–3.54 (1 H, m), 3.54–2.84 (6 H, m), 1.64 (3 H, d); IR 1644 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.5; H, 7.0; N, 3.4. Found: C, 66.2; H, 7.0; N, 3.3.

8-Methyl-2,3,10,11-tetramethoxyberbine (5a). Acid **16a** (211 mg, 0.51 mmol) and $POCl_3$ (1.0 mL, 11 mmol) were heated at 70 °C for 10 min. The mixture was cooled (ice bath) and H_2O (11 mL) added, and then it was heated at 100 °C for 1.25 h, cooled, extracted with $CHCl_3$ (3 × 10 mL), saturated with NaCl, and extracted again with $CHCl_3$ (5 mL). The dried extracts were evaporated to give 210 mg which was chromatographed (after treatment with ethanolic HCl) on silica (1.1 × 11.5 cm) eluting with $CHCl_3$ (20 mL) and then acetone (260 mL) to give 66 mg of an oily hydrochloride, $[\alpha]_D$ +24° (c 1, $CHCl_3$) [lit.[7] $[\alpha]_D$ +148° c 1, $CHCl_3$)]. This was converted to the free base by addition to a saturated Na_2CO_3 solution, extraction with CH_2Cl_2, drying, and evaporating to a residue which was a single spot by TLC (EtOAc; R_f 0.16 compared to coralydine, R_f 0.27, and *O*-methylcorytenchirine, R_f 0.16, both prepared according to the literature[7]): NMR δ 6.63, 6.53 (4 H, m), 4.37–3.97 (1 H, m), 3.87 (12 H, s), 3.16 (1 H, m), 2.90 (5 H, m), 1.40 (3 H, d, J = 7 Hz); MS *m/e* (relative intensity) 369 (15), 354 (100).

Ethyl (1*S*,3*S*)-(−)-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylate Hydrochloride (9). Acid **8** (12.44 g, 56 mmol) in ethanol (100 mL) and saturated HCl/ethanol (50 mL) was refluxed for 6 h, the solvent evaporated, and the residue recrystallized from acetic acid to give ester **9** hydrochloride: 15.16 g (52.6 mmol, 94%); mp 220–221 °C dec (lit.[3] mp 229–230 °C); $[\alpha]_D$ −110.5° (c 1.2, CH_3OH)].

Ethyl (1*S*,3*S*)-(+)-2-Formyl-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylate (18). To **9** (12.32 g, 42.8 mmol) was added 97% HCO_2H (107 mL), HCO_2K (3.96 g, 47 mmol), and then Ac_2O (43 mL) dropwise over 5 min while maintaining the internal temperature at 5 °C. The mixture was stirred at room temperature for 3 h, and then ethanol (140 mL) was added, the solvent was evaporated, ethanol (200 mL) and 1 N HCl (4 mL) were added, and this mixture was stirred at room temperature for 14 h. The solvent was evaporated, and to the residue was added 1 N HCl (20 mL) and EtOAc (200 mL). The crystalline precipitate was washed with H_2O (2 × 20 mL) and dried to give 5.42 g (19.5 mmol), mp 174.5–175 °C. The EtOAc layer was washed with saturated $NaHCO_3$ (2 × 20 mL) and saturated NaCl (50 mL), dried, and evaporated to give an additional 5 g (18 mmol; total 37.5 mmol, 88%) of formyl derivative **18:** mp 170–172 °C; single spot by TLC ($CHCl_3$/EtOH, 9:1), R_f 0.28; $[\alpha]_D$ +6.0° (c 1, EtOH); NMR (Me_2SO-d_6) δ 8.80 (2 H, s), 8.33 and 8.20 (2 H, s, s, 1:1), 6.66–6.56 (2 H, m), 5.17–3.90 (4 H, m), 3.11–2.87 (2 H, m), 1.55–0.94 (6 H, m); IR 3320, 2990, 1738, 1656 cm^{-1}.

Ethyl (1*S*,3*S*)-(−)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylate Hydrochloride (10). Formyl derivative **18** (3.90 g, 14 mmol), acetone (100 mL), $KHCO_3$ (12, g, 120 mmol), and $(CH_3)_2SO_4$ (5.3 mL, 56 mmol) were refluxed for 18.5 h, the solvent was evaporated, and EtOAc (200 mL), saturated Na_2CO_3 (50 mL), and H_2O (10 ml) added. After separation, the ethyl acetate was washed with saturated NaCl (100 mL), dried and evaporated, and excess $(CH_3)_2SO_4$ was removed by distillation at 50 °C (0.03 torr). The residue, EtOH (50 mL), and saturated HCl/EtOH (25 mL) were refluxed for 3 h. Evaporating to 20 mL and cooling gave crystals which were washed with cold Et_2O/EtOH (4:3) and then Et_2O to yield 3.54 g (11.2 mmol. 80%) of ester hydrochloride **10:** mp 213 °C (lit.[4] mp 219–220°C); $[\alpha]_D$ −92.9° (c 1, EtOH) [lit.[4] $[\alpha]_D$ −95.8° (c 1, EtOH)]; single spot by TLC ($CHCl_3$/EtOH, 9:1), R_f 0.59; NMR δ 6.65 and 6.58 (2 H, s, s), 4.70 (1 H, m), 4.22 (2 H, q), 4.20 (1 H, m), 3.85 (6 H, s), 3.30 (2 H, m), 1.95 (2 H, d), 1.30 (3 H, t); IR 1750 cm^{-1}.

(1*S*,3*S*)-2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylic Acid (16b).[27b] To ester hydrochloride **10** (2.53 g, 8.0 mmol) was added saturated Na_2CO_3 (50 mL), and this was extracted with $CHCl_3$ (3 × 20 mL). The extracts were dried and evaporated. To the residue was added 1-(2-bromoethyl)-3,4-dimethoxybenzene (2.45 g, 10 mmol), benzene (10 mL), DMF (10 mL), and K_2CO_3 (2.21 g, 16 mmol), and this mixture was heated at 110 °C under reflux for 23 h. More 1-(2-bromoethyl)-3,4-dimethoxybenzene (1 g, 4.1 mmol) was added, and reflux was continued for 8 h; this addition was repeated and reflux continued for 13 h more. The mixture was cooled and added to H_2O (50 mL) and Et_2O (100 mL), the aqueous layer was separated, saturated NaCl (25 mL) was added, and the mixture was extracted with Et_2O (3 × 17 mL). The combined Et_2O extracts were extracted with 0.5 N HCl (50, 25, and 25 mL), and the acid extracts were basified with saturated Na_2CO_3 (60 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried, and evaporated. To the residue was added EtOH (40 mL), H_2O (10 mL), and KOH (1 g). The mixture was refluxed for 5.5 h. The solvent was evaporated, H_2O (40 mL) added followed by washing with Et_2O (20 mL), and then the aqueous phase adjusted to pH 6 with 6 N HCl and stored in the cold overnight. The resulting mixture was filtered, the filtrate was extracted with $CHCl_3$ (3 × 17 mL), and the extracts were dried and evaporated to give 1.58 g (3.8 mmol, 48%). This tertiary amino acid **16b** was recrystallized from EtOH/Et_2O (1:2): mp 157–158 °C dec; NMR and IR were identical with **16a.**

(8*S*,13a*R*)-(+)-5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-8-methyl-6*H*-dibenzo[*a,g*]quinolizine [(8*S*,13a*R*)-(+)-8-Methyl-2,3,10,11-tetramethoxyberbine, (+)-*O*-Methylcorytenchirine] (5b). Tertiary amino acid **16b** (207 mg, 0.50 mmol) and $POCl_3$ (1 mL, 11 mmol) were heated at 70 °C for 10 min and then cooled (ice bath), and H_2O (11 mL) was added. The mixture was heated at 100 °C for 1.5 h, cooled, added to 2 N NaOH (30 mL), and

extracted with CH_2Cl_2 (3 × 10 mL), and the extracts were dried and evaporated to give 169 mg (0.46 mmol, 92%) of crude oily base which was chromatographed (3 g of silica, eluting with EtOAc) and converted to hydrochloride by dissolving in hot Et_2O and adding saturated HCl/EtOH (2 drops). The hydrochloride of **5b** was recrystallized from isopropyl alcohol: 162 mg, 80% yield; mp 193–194 °C (lit.[7] mp 205–206 °C); $[\alpha]_D$ +136° (c 0.35, $CHCl_3$) [lit.[7] $[\alpha]_D$ +148° (c 1, $CHCl_3$)]. The diastereomeric integrity was established by GC (5% Dexsil 300 GC on Anachrom Q, He flow rate of 30 cm^3/min, oven 262 °C, injection port 260–270 °C, detector 295 °C) using coralydine and *O*-methylcorytenchirine prepared according to the literature[7] for comparison (R_t 47.2 and 51.6 min, respectively), by TLC (Brinkman HR, EtOAc; R_f 0.16) (coralydine, R_f 0.26), (coralydine, R_f 0.26), and by LC (<1% of coralydine; silica, EtOAc); NMR and mass spectra were identical with **5a**.

Reformatsky Reaction on 3,4-Dimethoxyacetophenone (25). Formation of 26. To zinc (88 g, 1.35 mol, 30 mesh granulated; treated with 1 N HCl, washed with water, ethanol, and acetone, and dried at 160 °C) in a three-neck 5-L round-bottom flask fitted with a paddle stirrer, a 500 mL pressure equalized addition funnel, and a series of two Liebig condensors connected with adapters to the mouth of a 6-L Erlenmeyer flask was added a portion of a solution of acetoveratrone (**25**) (198 g, 1.10 mol) and ethyl bromoacetate (200 g, 1.32 mol) in benzene (1.23 L) to just cover the zinc, and the mixture was heated to reflux. Induction was observed as a rapid generation of solvent vapor condensing in the apparatus. The remaining solution was then added dropwise while applying enough heat to maintain a vigorous reflux (over 30 min). The mixture was gently refluxed for an additional 45 min and then quenched with an equal volume of 10% H_2SO_4. The organic layer was washed with 1 N NaOH (1 vol), H_2O (1 vol), and saturated NaCl (0.5 vol) and then dried. The solvent was evaporated and the residue distilled at 195–207 °C (7–11 torr) (in a 15-cm vacuum-jacketed column with platinum gauze) to give 244 g (0.98 mol, 90%) as a mixture of the three isomeric unsaturated esters **26**: GC (200 °C, 4 ft, 3% OV-17 Aeropak 30, 100–120 mesh), R_t 1.5, 2.4 min; IR 1732, 1712 cm^{-1}.

Ethyl 3-(3,4-Dimethoxyphenyl)butyrate (27). Unsaturated esters **26** (400 g, 1.6 mol) in EtOH (450 mL) were hydrogenated using 10% Pd/C (50 g) as catalyst. After uptake of hydrogen was complete (7.5 h), the mixture was filtered through Celite, the catalyst was washed with ethanol, the filtrate was evaporated, and the residue was distilled at 155 °C (0.1 torr) [lit.[28] 107 °C (0.008 torr)] to give 397 g (1.58 mol, 99%) of the saturated ester **27**: IR (neat) 1732 cm^{-1}; NMR (CCl_4) δ 6.7 (3 H, s), 4.2–3.8 (2 H, q), 3.8 (6 H, d), 3.4–3.0 (1 H, m), 2.6–2.4 (2 H, d), 1.4–1.2 (3 H, d), 1.3–1.0 (3 H, t).

3-(3,4-Dimethoxyphenyl)butyric Acid (28). Ester **27** (397 g, 1.58 mol), EtOH (1 L), KOH (119 g, 1.8 mol), and H_2O) (60 mL) were refluxed for 2 h. The solvent was evaporated, H_2O (1 L) and 6 N H_2SO_4 (350 mL) were added to the residue, the aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL), and then the organic phase was washed successively with H_2O (1 vol) and saturated NaCl (1 vol). The filtered CH_2Cl_2 solution was evaporated, benzene was added to a volume of 600 mL, and solvent was slowly evaporated in a stream of N_2 passed over the cooled solution; total yield of crystalline acid **28** (in three crops) was 334 g (92%): mp 83–84 °C (lit.[8] mp 84–85 °C); IR 1701 cm^{-1}; NMR δ 6.8 (3 H, s), 3.9 (6 H, d), 3.5–3.0 (1 H, m), 2.7–2.5 (2 H, m), 1.4–1.2 (3 H, d).

(+)-3-(3,4-Dimethoxyphenyl)butyric Acid (29). To acetone (1.3 L) was added racemic 3-(3,4-dimethoxyphenyl)butyric acid (**28**; 224 g, 1.0 mol) and quinine (324 g, 1.0 mol). Dissolution was complete at the boiling point. The mixture was allowed to cool slowly to room temperature for 24 h. The salt was recrystallized three more times from acetone to a constant rotation to give 160 g, mp 125–127 °C. Before liberating the acid, this corresponded to a 60% overall yield of the (+) isomer. The acid was recovered by adding the salt to 1 N NaOH (1.5 L) and extracting the quinine with CH_2Cl_2 (3 × 100 mL). The aqueous layer was then acidified with 6 N HCl to pH 1 and extracted with CH_2Cl_2 (3 × 167 mL), and the combined organic layers were dried and evaporated to give 57.4 g of carboxylic acid **29** (93% from salt, 56% overall for resolution): mp 78.5–79.5 °C; $[\alpha]^{20}D$ +30.2° (c 5.6, CH_3OH); TLC ($CHCl_3$/MeOH, 9:1), R_f 0.56 (single spot); IR 1728 cm^{-1}; NMR δ 6.8 (3 H, s), 3.8 (6 H, s), 3.4–3.0 (1 H, m), 2.7–2.5 (2 H, m), 1.4–1.2 (3 H, d). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.4; H, 7.1.

The optical purity of this acid was established by making the amide with *d*-α-phenylethylamine and determining the diastereomeric purity by GC. Thus, both racemic and resolved *d*-3-(3,4-dimethoxyphenyl)butyric acid were treated with *d*-α-phenylethylamine as follows.

To 3-(3,4-dimethoxyphenyl)butyric acid (103 mg, 0.46 mmol) was added thionyl chloride (1 mL, 13.94 mmol) and pyridine (1 drop). The mixture was stirred at room temperature for 60 min, and excess thionyl chloride was evaporated. To the residue was added CH_2Cl_2 (2.5 mL), then *d*-α-phenylethylamine (0.10 mL, 0.78 mmol; $[\alpha]^{20}D$ +39.6°), and finally 5% Na_2CO_3. The mixture was stirred vigorously for 15 min. The CH_2Cl_2 layer was removed and dried, acetone (2 mL) was added, and the solutions were analyzed by GC.

For the amide from racemic carboxylic acid: GC (6 ft, 6% OV-25 on Chromosorb W, acid washed, treated with dichlorodimethylsilane, 100–120 mesh, ⅛ in. diam, oven 223 °C, injection port 267 °C, detector 292 °C), R_{t-1} 52.4 min (area, 179), R_{t-2} 57.6 min (area, 182). For the amide made with the resolved carboxylic acid: GC (same conditions), R_{t-1} 52.2 min (area, 0.35), R_{t-2} 57.2 min (area, 444); purity 99.92%.

The solution containing the two diasteriomeric amides was evaporated in a stream of nitrogen. Ether (1 mL) and then hexane (1 mL) were added, and the crystals that developed melted at 90–94 °C. Anal. Calcd for $C_{20}H_{25}NO_3$:C, 73.4; H, 7.7; N, 4.3. Found: C, 73.4; H, 7.7; N, 4.4.

(+)-3-(3,4-Dimethoxyphenyl)butyric Acid Ethyl Ester (30). Acid **29** (10 g, 44 mmol), EtOH (50 mL), toluene (100 mL), and concentrated H_2SO_4 (0.5 mL) were refluxed for 12.5 h, removing H_2O with a Dean-Stark trap. The solvent was evaporated to 25 mL, the mixture cooled, and Et_2O (50 mL) added. This was washed with 5% Na_2CO_3 (50 mL) and then saturated NaCl (50 mL), the Et_2O) was evaporated, and the residue was distilled (bult-to-bulb) at 115 °C (0.05 torr) to yield 10.94 g (43.5 mmol, 98%) of ester **30**: mp 34.5–35 °C; $[\alpha]^{20}D$ +34° (c 6.3, CH_3OH). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.6; H, 7.9.

Diethyl (+)-2-(3,4-Dimethoxyphenyl)propane-1,1-dicarboxylate (31). To diisopropylamine (9.1 g, 90 mmol) in tetrahydrofuran (90 mL) was added *n*-butyllithium (30.6 mL of a 2.95 M solution, 90 mmol) at −10 to −20 °C followed after 10 min by ester **30** (21.39 g, 85 mmol) at −70 °C (internal temperature rising to −45 °C). After cooling to −73 °C, ethyl chloroformate (19.5 g, 180 mmol) was added as fast as possible (temperature rising to −10 °C). After stirring for 20 min, the solvent was evaporated and to the residue was added H_2O (200 mL) and Et_2O (200 mL). The Et_2O layer was washed with saturated NaCl (20 mL), dried, and evaporated, and the residue was distilled at 135 °C (0.08 torr) to yield 26.6 g (94%) of malonate **31**: IR 1731, 1751 cm^{-1}; NMR δ 6.8 (3 H, s), 4.4–3.5 (12 H, m), 1.4–0.9 (9 H, m).

Diethyl (+)-1-Amino-2-(3,4-dimethoxyphenyl)propane-1,1-dicarboxylate (32). To malonate **31** (14.2 g, 43.7 mmol) in THF (120 mL) was added a 50% NaH dispersion in oil (2.1 g, 43.7 mmol) and EtOH (0.2 mL). The mixture was stirred at room temperature until after gas evolution ceased (9 h total), and to the stirred mixture at room temperature was added a cooled solution of dry chloramine (170 mL of a 0.49 M Et_2O solution, 83.3 mmol), continuing the stirring at room temperature for 20 h. The solvent was evaporated and the residue distributed between Et_2O (200 mL) and 5% $Na_2S_2O_3$ (100 mL). The Et_2O layer was separated and extracted with 1 N HCl (3 × 60 mL), and the aqueous phase was basified with 10% Na_2CO_3 and extracted with CH_2Cl_2 (3 × 60 mL). Evaporation of the CH_2Cl_2 followed by distillation at 143 °C (0.25 Torr) yielded 12.6 g (37 mmol, 85%) of aminomalonate **32**: $[\alpha]^{20}D$ +46.4° (c 4.0, CH_3OH); MS *m/e* (relative intensity) 339 (0.3), 293 (0.6), 226 (3), 243 (1), 192 (2), 176 (2), 166 (11), 165 (100); IR 3380, 3320, 1736 cm^{-1}; NMR δ 6.9–6.7 (3 H, m), 4.5–3.5 (11 H, m), 1.9 (2 H, s), 1.4–1.0 (9 H, m). Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.2; H, 7.4; N, 4.1. Found: C, 60.0; H, 7.4; N, 4.1.

(2*R*,*S*; 3*R* or *S*)-2-Amino-3-(3,4-dimethoxyphenyl)butyric Acid (19). To aminomalonate **32** (8.95 g, 26.4 mmol) was added 1 N HCl (100 mL), and the mixture was refluxed for 5 days. The solvent was evaporated, the residue dissolved in H_2O (100 mL), and the mixture adjusted with concentrated NH_4OH to pH 6. The solution was evaporated, the residue was again dissolved in H_2O (100 mL) at the boiling point, and the solution was then reduced to 25 mL and cooled. After 1 day, the crystals were collected and washed with H_2O (2 × 5 mL, ice cold) to give 5.6 g (23.5 mmol, 89%) of amino acid **19**: mp 182–192 °C; amino acid analysis under standard conditions[29] (Phe, R_t 180 min) showed 2 peaks, R_t 199 (area 6.2) and 212 min (area, 4.3); IR 3240, 3220, 2080, 1612 cm^{-1}; NMR (CF_3CO_2H) δ 7.5–6.9 (3 H, brd), 7.0 (3 H, s), 4.8–4.2 (1 H, brd), 4.0 (6 H, s), 3.9–3.3 (1 H, brd), 1.7–1.5 (3 H, d). Anal. Calcd for $C_{12}H_{17}O_4N$: C, 60.2; H, 7.2; N, 5.9. Found: C, 60.0; H, 7.1; N, 5.9.

Dipotassium 1-Amino-2-(3,4-dimethoxyphenyl)propane-1,1-dicarboxylate. To aminomalonate **32** (4.0 g, 11.9 mmol) was added 95% EtOH (50 mL) and KOH (2 g, 36 mmol). The solution was refluxed for 20 h, and the precipitate that formed on cooling was recrystallized (aqueous EtOH, toluene) to give the dipotassium salt, mp 317–319 °C dec. Anal. Calcd for $C_{13}H_{15}K_2NO_6$: C, 43.4; H, 4.2; N, 3.9. Found: C, 43.2; H, 4.4; N, 3.7.

Decarboxylation of Dipotassium 1-Amino-2-(3,4-dimethox-

yphenyl)propane-1,1-dicarboxylate. To potassium 1-amino-2-(3,4-dimethoxyphenyl)propane-1,1-dicarboxylate (324 mg, 0.90 mmol) was added 1 N HCl (50 mL), and the mixture was refluxed for 20 h. The crude hydrolysate was subjected to amino acid analysis[29] and showed the diastereomeric β-methyl-(3,4-dimethoxyphenyl)-alanines at 203 and 217.5 min in a ratio of 61:39. The volume was reduced and the pH adjusted to 6. After several days, the crystals were collected to give 2.06 g (8.63 mmol, 73%) of amino acid **19.**

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylic Acid (20). Amino acid **19** (4.55 g, 19.1 mmol), a 37% formaldehyde solution (18 mL, 213 mmol), and 6 N HCl (38 mL) were heated at 95 °C for 35 min, the solvent was evaporated at 60–70 °C. and the residue was dried to give 5.66 g of crude product. A sample for analysis was recrystallized from EtOH/EtOAc: mp 259–263 °C dec; NMR (CF_3CO_2H) δ 7.0–6.83 (2 H, m), 4.67 (3 H, m), 4.02 (6 H, s), 3.74 (1 H, m), 1.69 and 1.50 (3 H, d, d); IR 1748 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_4 \cdot 0.25H_2O$: C, 61.0; H, 6.9; N, 5.5. Found: C, 61.2; H, 6.7; N, 5.4.

Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylate (21). To crude acid **20** (5.44 g, 18.9 mmol) was added *p*-TsOH·H_2O (3.8 g, 20 mmol), EtOH (100 mL), and toluene (100 mL), and the solution was refluxed through 4A molecular sieves in a Soxhlet extractor for 3.5 days, changing drying agent 3 times during this period. The solvent was evaporated, CH_2Cl_2 (20 mL), saturated Na_2CO_3 (20 mL), and H_2O (10 mL) were added, and the aqueous layer was extracted further with CH_2Cl_2 (2 × 20 mL). The dried organic extracts were evaporated, and the residue was distilled at 130 °C (0.01 torr) to give 4 g (14.4 mmol, 79% based on starting phenylalanine derivative **19**) of ester **21:** mp 67–78 °C; TLC (CH_3OH), R_f 0.60; two products by GC; IR 3350, 1736 cm^{-1}.

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylate (22). Ester **21** (11.2 g, 40.2 mmol), benzene (50 mL), DMF (50 mL), 1-(2-bromoethyl)-3,4-dimethoxybenzene (12.3 g, 50 mmol), and K_2CO_3 (11 g, 80 mmol) were heated at 110 °C for 24 h. The mixture was added to Et_2O (200 mL) and H_2O (100 mL), and the Et_2O layer was extracted with 0.5 N HCl (100, 50, and 50 mL). Basification of the aqueous layer with excess saturated Na_2CO_3, extraction into CH_2Cl_2 (100, 50, 50, and 25 mL), drying, and evaporating the extracts left a residue which was distilled. Collecting between 120–185 °C (0.03 torr) gave 13.5 g (30.5 mmol, 76%) of tertiary amino ester **22:** NMR δ 6.80–6.48 (5 H, m), 4.27–3.97 (4 H, m), 3.87 (12 H, s), 3.80–2.86 (6 H, m), 1.36–0.86 (6 H, m); IR 1730 cm^{-1}; MS *m/e* (relative intensity) 443 (5), 370 (24), 292 (100), 264 (27), 239 (15), 239 (15), 204 (15), 164 (35), 151 (13).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylic Acid (23). Ester **22** (4.0 g, 9.0 mmol), 95% EtOH (50 mL), and KOH (800 mg, 14.4 mmol) were refluxed for 21 h, after which time more KOH (300 mg) was added and refluxing continued for 5 h. After stirring for an additional 16 h at room temperature, the solvent was evaporated, water added, and the solution adjusted to pH 6.5 with 6 N HCl and cooled to give in two crops 2.29 g. The mother liquors were extracted with $CHCl_3$ (3 × 17 mL), and the extracts were dried and evaporated to give 1.04 g more (total 3.33 g, 89%): mp 160–162 °C dec (from methanol); NMR δ 6.70 (5 H, m), 4.14 (3 H, m), 3.85 (12 H, s), 3.52–2.99 (6 H, m), 1.40 (3 H, d); IR 1612 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.5; H, 7.0; N, 3.4. Found: C, 66.4; H, 7.0; N, 3.3.

***trans*-5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-13-methyl-6*H*-dibenzo[*a,g*]quinolizine (*trans*-13-Methyl-2,3,10,11-tetramethoxyberbine) (2) and 2-[2-(3,4-Dimethoxyphenyl)-ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methylisoquinoline (37).** Acid **23** (208 mg, 0.5 mmol) and $POCl_3$ (4 mL) were heated at 50 °C for 4 min and cooled (ice bath), 3 N HCl (40 mL) was added, and the solution was heated at reflux for 1.5 h. After cooling the mixture, it was basified with Na_2CO_3 and NaOH and extracted with $CHCl_3$ (3 × 7 mL). The extract consisted of a mixture of two basic products in a ratio of 87:13, the major one being *trans*-13-methyl-2,3,10,11-tetramethoxyberbine (**2**) in 24% yield. The components were separated by chromatography (EtOAc) to give the pure components.

(a) *trans*-13-Methyl-2,3,10,11-tetramethoxyberbine (**2**): mp 148 °C; $[\alpha]_D$ 0° (c 1, $CHCl_3$); TLC (EtOAc), R_f 0.08, single spot; NMR δ 6.71, 6.68, 6.58, and 6.52 (4 H, s, s, s, s), 4.16 (1 H, d, J = 18 Hz), 3.86 (12 H, s), 3.69–3.34 (1 H, m), 2.90 (6 H, m), 1.47 (3 H, d, J = 7 Hz); MS *m/e* (relative intensity) 369 (22), 354 (9), 192 (7), 178 (100), 163 (18). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.4; H, 7.4; N, 3.8. Found: C, 71.5 H, 7.3; N, 3.8.

(b) 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methylisoquinoline (**37**): mp 84–85 °C; $[\alpha]_D$ 0° (c 1, $CHCl_3$); TLC (EtOAc), R_f 0.27, single spot; NMR δ 6.77, 6.67, and 6.47 (5 H, s, s, s), 3.84 (12 H, s), 3.60 (2 H, s), 2.95 (6 H, m), 1.28 (3 H, d, J = 7 Hz); MS *m/e* (relative intensity) 371 (1), 279 (1), 220 (100). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.1; H, 7.9; N, 3.8. Found: C, 71.2; H, 7.8; N, 3.8.

Registry No.—**2,** 67408-99-5; **5a,** 58116-10-2; **5a** HCl, 58116-11-3; **5b** HCl, 58165-69-8; **8,** 35287-23-1; **9,** 55863-04-2; **9** HCl, 35287-18-4; **10** HCl, 67409-00-1; **15a,** 67409-01-2; **16a,** 67409-02-3; **16b,** 67409-03-4; **18,** 67409-04-5; **19,** 67409-05-6; **20,** 67409-06-7; **21,** 67409-07-8; **22,** 67409-08-9; **23,** 67409-09-0; **25,** 120-14-9; **26** (isomer 1), 67409-10-3; **26** (isomer 2), 67409-11-4; **26** (isomer 3), 67409-12-5; **27,** 67409-13-6; **28,** 67409-14-7; **29,** 67409-15-8; **29** quinine salt, 67409-16-9; **29** *d*-α-phenylethylamide (isomer 1), 67409-17-0; **29** *d*-α-phenylethylamide (isomer 2), 67409-22-7; **30,** 67409-18-1; **31,** 67425-68-7; **32,** 67409-19-2; **32** acid 2K salt, 67409-20-5; **37,** 67409-21-6; 1-(2-bromoethyl)-3,4-dimethoxybenzene, 40173-90-8; *d*-α-phenylethylamine, 3886-69-9.

References and Notes

(1) R. T. Dean, H. C. Padgett, and H. Rapoport, *J. Am. Chem. Soc.*, **98,** 7448 (1976).
(2) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43,** 2115 (1978).
(3) A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **55,** 15 (1972).
(4) H. Bruderer, A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **58,** 795 (1975).
(5) J. Musich and H. Rapoport, *J. Org. Chem.*, **42,** 139 (1977).
(6) T. Kametani and M. Ihara, *Heterocycles*, **5,** 649 (1976).
(7) H. Bruderer, J. Metzger, A. Brossi, and J. Daly, *Helv. Chim. Acta*, **59,** 2793 (1976).
(8) Y. Kataaka, Y. Seto, M. Yamamoto, T. Yamada, S. Kuwata, and H. Watanabe, *Bull. Chem. Soc. Jpn.*, **49,** 1081 (1976).
(9) J. B. Koepfli and W. H. Perkin, *J. Chem. Soc.*, 289 (1928).
(10) (a) H. Gustafsson, *Ark. Kemi*, **29,** 587 (1968); (b) B. Sjoberg, *ibid.*, **12,** 573 (1958).
(11) A. I. Meyers and K. Kamata, *J. Am. Chem. Soc.*, **98,** 2290 (1976).
(12) J. G. Gleason and D. N. Harpp, *Tetrahedron Lett.*, 3431 (1970).
(13) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72,** 2786 (1950).
(14) T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, **23,** 167 (1975).
(15) W. L. Jolly, *J. Phys. Chem.*, **60,** 507 (1956).
(16) E. Schmitz, S. Schramm, W. Flamme, and U. Bicker, *Z. Anorg. Allg. Chem.*, **396,** 178 (1973).
(17) G. H. Coleman and H. L. Johnson, *Inorg. Synth.*, **1,** 59 (1939).
(18) T. J. Brocksom, N. Petrognani, and R. Rodrigues, *J. Org. Chem.*, **39,** 2114 (1974).
(19) H. Arold, M. Eule, and S. Reissmann, *Z. Chem.*, **9,** 447 (1969).
(20) (a) P. W. Jeffs, *Experientia*, **21,** 690 (1965); (b) M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, **42,** 1111 (1977), also present an elegant synthesis of some (+)-*trans*-13-methylberbines via condensation of a 3,4-dihydroisoquinoline with a homophthalic anhydride.
(21) M. Shamma and C. D. Jones, *J. Am. Chem. Soc.*, **92,** 4943 (1970).
(22) T. R. Govindachari, K. Nagarajan, S. Natarajan, and B. P. Rai, *Indian J. Chem.*, **9,** 1313 (1971).
(23) T. R. Govindachari, K. Nagarajan, R. Charubala, B. P. Rai, and P. S. Subramanian, *Indian J. Chem.*, **8,** 769 (1970).
(24) C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Can. J. Chem.*, **48,** 3673 (1970).
(25) S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, **24,** 1467 (1968).
(26) S. F. Dyke, *Adv. Heterocycl. Chem.*, **14,** 279 (1972).
(27) All reactions were performed under nitrogen with magnetic stirring unless otherwise indicated, and all solvents were dried with $MgSO_4$ prior to evaporation in vacuo using a Berkeley rotary evaporator. Melting points are uncorrected, and distillation was bulb-to-bulb, Kugelrohr type. NMR spectra were determined in $CDCl_3$ solution, unless otherwise indicated, with a Varian T-60 instrument using internal Me_4Si; IR spectra were recorded neat for liquids and in a paraffin oil mull for solids on a Perkin-Elmer 337 spectrophotometer; CEC-103 and 110B mass spectrometers were used for determining mass spectra. GC was done on 4 ft 2% OV-17 on 100–120 mesh Chromosorb W (AW) or 3% OV-17 on 100–200 mesh Aeropak 30 columns unless otherwise indicated. TLC was done on SiO_2 (Eastman, Brinkman HR, or E. M. silica gel 60, 63–200 μm), and column chromatography was done on E. M. silica gel 60, 63–200 μ. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. (a) Compound numbers followed by **a** indicate those in which the configuration at C-1 of the isoquinoline has been largely racemized, based on the optical purity of **5a.** (b) Compound numbers followed by **b** indicate those in which the configuration at C-1 of the isoquinoline is essentially optically pure, based on the optical purity of **5b.**
(28) R. B. Moffett, *J. Med. Chem.*, **7,** 319 (1964).
(29) Amino acid analysis was done on a Beckman Model 120C AA analyzer using a 0.9 × 55 cm column of Beckman type AA-15 resin at 55 °C and a flow rate of 70 mL/h. The acid and neutral runs were done using pH 3.25 buffer from 0.85 min and pH 4.25 buffer from 85 min on. The buffer change to pH 4.25 was detected on the output graph at 133 min.

Liquid-Phase Syntheses of Protected Peptides on the New 3-Nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) Support

Foe-Siong Tjoeng,[1] E. K. Tong, and Robert S. Hodges*[2]

Department of Biochemistry and the Medical Research Council Group on Protein Structure and Function, University of Alberta, Edmonton, Alberta, Canada T6G 2H7

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A further application of the 3-nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) support to the liquid-phase syntheses of protected peptides possessing free C-terminal carboxyl groups is described. The syntheses were performed using the in situ symmetrical anhydride coupling method and the protected peptides were cleaved from the support by photolysis at 350 nm. The five protected peptides Boc-L-Lys(Z)-L-Leu-L-Glu(OBzl)-L-Ala-OH, Boc-L-Lys(Z)-L-Leu-L-Glu(OBzl)-L-Ala-L-Leu-L-Glu(OBzl)-L-Ala-OH, Boc-L-Lys(Z)-L-Ala-L-Glu(OBzl)-L-Ala-L-Leu-L-Glu(OBzl)-L-Ala-OH, Boc-L-Lys(Z)-L-Leu-L-Glu(OBzl)-L-Ala-L-Ala-L-Glu(OBzl)-L-Ala-OH, and Boc-L-Lys(Z)-L-Ala-L-Glu(OBzl)-L-Ala-L-Ala-L-Glu(OBzl)-L-Ala-OH were prepared to be used in the synthesis of sequential polypeptides as models for the double-stranded coiled-coil structure of tropomyosin.

The liquid-phase method of peptide synthesis using soluble poly(ethylene glycol) as the C-terminal protecting group was introduced by Bayer et al. in 1971.[3] This method offers many advantages over the classical and solid-phase methods of peptide synthesis.[4-6] Its major disadvantage, low yields of final peptide obtained by cleavage under drastic conditions such as saponification of hydrazinolysis,[7-9] was overcome by the introduction of a photosensitive 3-nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) support.[10] This support provides a convenient and high yield photolytic method to cleave protected peptides from the poly(ethylene glycol) support and offers increased acid stability of the peptide–polymer ester bond during peptide synthesis. This paper describes a further application of this photosensitive support to the syntheses of fully protected peptides for use in the preparation of sequential polypeptides as models for the double-stranded coiled-coil structure of tropomyosin.

Tropomyosin is involved in the calcium-regulated system of contraction and relaxation.[11] Understanding the essential features required to form the coiled-coil structure should provide a means of determining the detailed molecular interactions that occur between tropomyosin, actin, and troponins, as well as the conformational changes that take place in tropomyosin during the contraction process.

Analysis of the primary structure of tropomyosin led Hodges et al.[12] to propose that the two-stranded coiled-coil was stabilized by hydrophobic residues situated at positions 2 and 5 of the repeating heptad sequence $(X\text{-}N\text{-}X\text{-}X\text{-}N\text{-}X\text{-}X)_n$, where N is a nonpolar residue. This hypothesis was further supported by the complete sequence of tropomyosin[13] and the preliminary conformation studies on the polyheptapeptide $(Lys\text{-}Leu\text{-}Glu\text{-}Ser\text{-}Leu\text{-}Glu\text{-}Ser)_n$.[14] The peptide sequences described in this paper were chosen to determine the effect that varying the size of the hydrophobic residue in positions 2 and 5 has on the formation and stabilization of the coiled-coil structure.

The peptides were synthesized using N^{α}-*tert*-butyloxycarbonyl amino acids under the same conditions employed for conventional liquid-phase peptide synthesis. As shown in Scheme I, 3-nitro-4-(bromomethyl)benzoic acid (I) was esterified to poly(ethylene glycol), average mol wt 6000–7500, via the dicyclohexylcarbodiimide method in the presence and absence of 1-hydroxybenzotriazol (HOBt). The preparation of 3-nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) (IIIA) in the presence of HOBt resulted in a decreased substitution of 3-nitro-4-(bromomethyl)benzoic acid to the poly(ethylene glycol) as indicated by the bromine substitution of 0.076 mmol of Br/g in the presence of HOBt and 0.141 mmol of Br/g in the absence of HOBt. This may be due to a side reaction between the poly(ethylene glycol) and HOBt in the presence of DCC as reported recently by Hemmasi and Bayer.[15] A higher substitution (0.23 mmol of Br/g) of I to the poly(ethylene glycol) could be obtained using the procedure for compound IIIB with a few milliliters of pyridine added as a catalyst.

N^{α}-*tert*-Butyloxycarbonyl amino acids were attached to the support by heating under gentle reflux with diisopropylethylamine in ethyl acetate for 5 days. In the following steps of the synthesis the N^{α}-*tert*-butyloxycarbonyl amino acids were coupled to the growing chain in a stepwise fashion using the symmetrical anhydride method. The coupling step was monitored for completion using the qualitative ninhydrin method. In most cases, the coupling reactions were complete in a single coupling. The peptide–polymer ester bond was stable to the conditions used for peptide synthesis since the peptide substitution remained unchanged. The protected peptides were cleaved from the support by photolysis at a wavelength of 350 nm in anhydrous methanol or DMF in the absence of oxygen and purified by gel filtration on Sephadex LH-20 in methanol–dichloromethane (30:70 v/v).

To achieve maximum cleavage yield, the peptide–PEG was irradiated for 18 h, although 10 h of irradiation was found to be sufficient as shown in the case of the model tetrapeptide Boc-Leu-Ala-Gly-Val-nitro-PEG (Figure 1). The yields obtained for the five peptides prepared in this paper were 95% for Boc-Lys(Z)-Leu-Glu(OBzl)-Ala (IX), 87% for Boc-Lys(Z)-Leu-Glu(OBzl)-Ala-Leu-Glu(OBzl)-Ala (XIV), 96% for Boc-Lys(Z)-Ala-Glu(OBzl)-Ala-Leu-Glu(OBzl)-Ala (XVII), 90% for Boc-Lys(Z)-Leu-Glu(OBzl)-Ala-Ala-Glu(OBzl)-Ala (XXIV), and 92% for Boc-Lys(Z)-Ala-Glu(OBzl)-Ala-Ala-Glu(OBzl)-Ala (XXVII) based on the quantity of alanine on the Boc-Ala-nitro-PEG support as determined by amino acid analysis. The yields of cleaved peptide were determined after removal of the poly(ethylene glycol) by precipitation followed by evaporation of the filtrate to dryness and a water wash of the protected peptide. At this stage, the peptides showed excellent amino acid ratios. Four of the five protected peptides were obtained in an average yield of 92% after photolysis at a concentration of 5 mL of methanol per gram of peptide support. The heptapeptide support XXVI (Scheme II) showed a limited solubility in methanol and was chosen to study the effect of solvent and concentration on the photolysis cleavage yield (Table I). The yield of this peptide was improved by reducing the concentration to 150 mL of methanol per gram peptide support; however, to obtain a 92% yield DMF had to be used as the solvent for photolysis. The protected peptides were purified on a column of Sephadex LH-20 in methanol–dichloromethane. A representative elution profile is shown in Figure 2. Peak 2 gave the analytically pure product and peak 1 contained the

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Scheme I

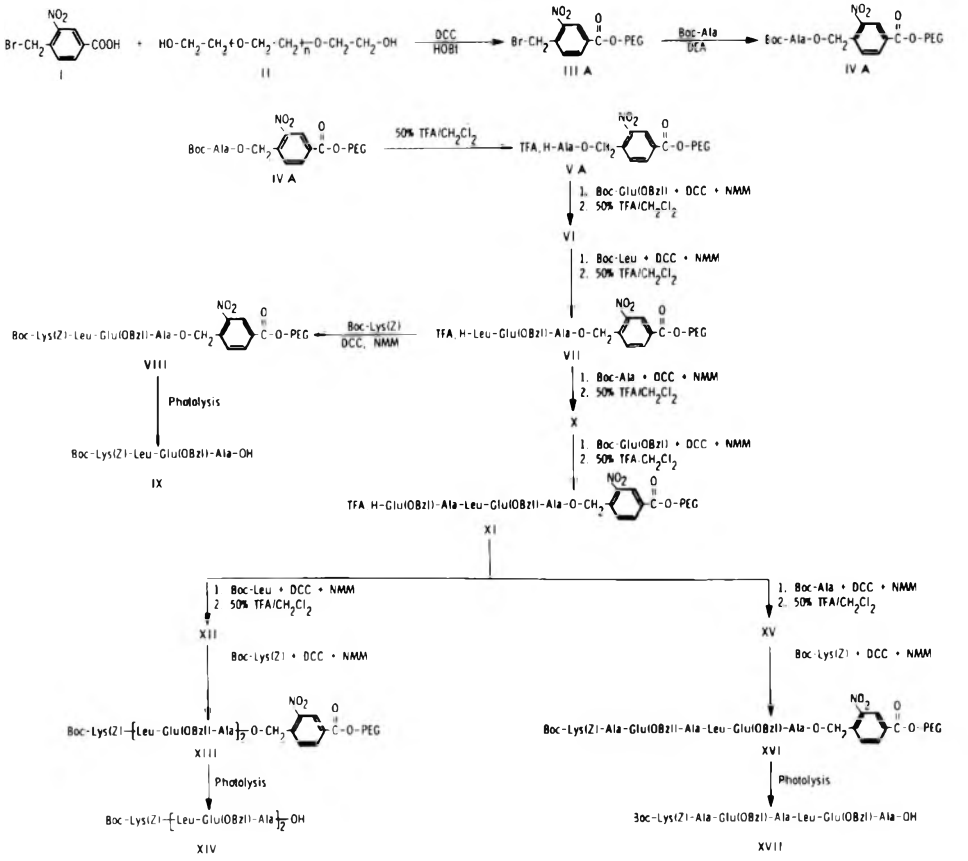


Table I. Effect of Concentration of Peptide–PEG and Solvent on Photolysis Cleavage Yields[a]

solvent volume per gram of peptide–PEG, mL	cleavage yield, %	
	DMF	methanol
7.5	39	21
30	47	35
150	92	47

[a] Determined using peptide–PEG (XXVI).

poly(ethylene glycol) that was not removed during the workup. The LH-20 chromatography gave an average yield of 70%.

To further demonstrate the usefulness of the nitro-PEG support, the tripeptide Boc-Ala-Gly-Val-Nitro-PEG[10] was cleaved from the support with 10% hydrazine hydrate in DMF (v/v) for 15 min. The yield of cleaved peptide hydrazide was 85% based on the quantity of valine on the Boc-Val-nitro-PEG support as determined from amino acid analysis. Based on these results and those obtained from previous work, this new support provides a convenient method for the synthesis of fully protected peptide fragments to be used in the preparation of larger peptides by fragment coupling or polymerization.

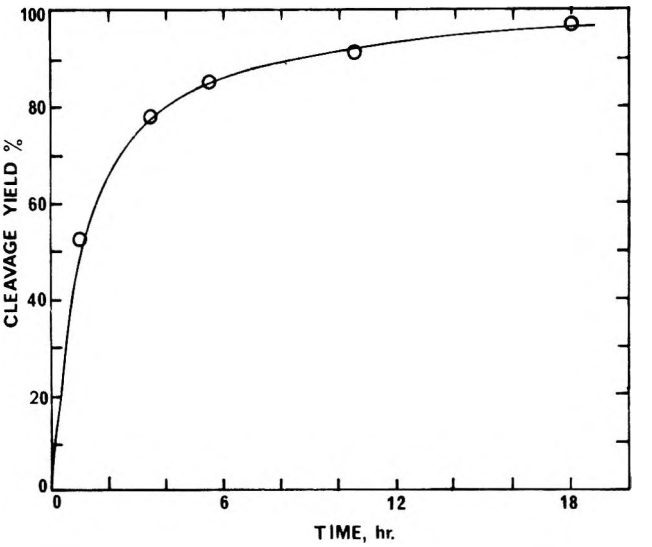
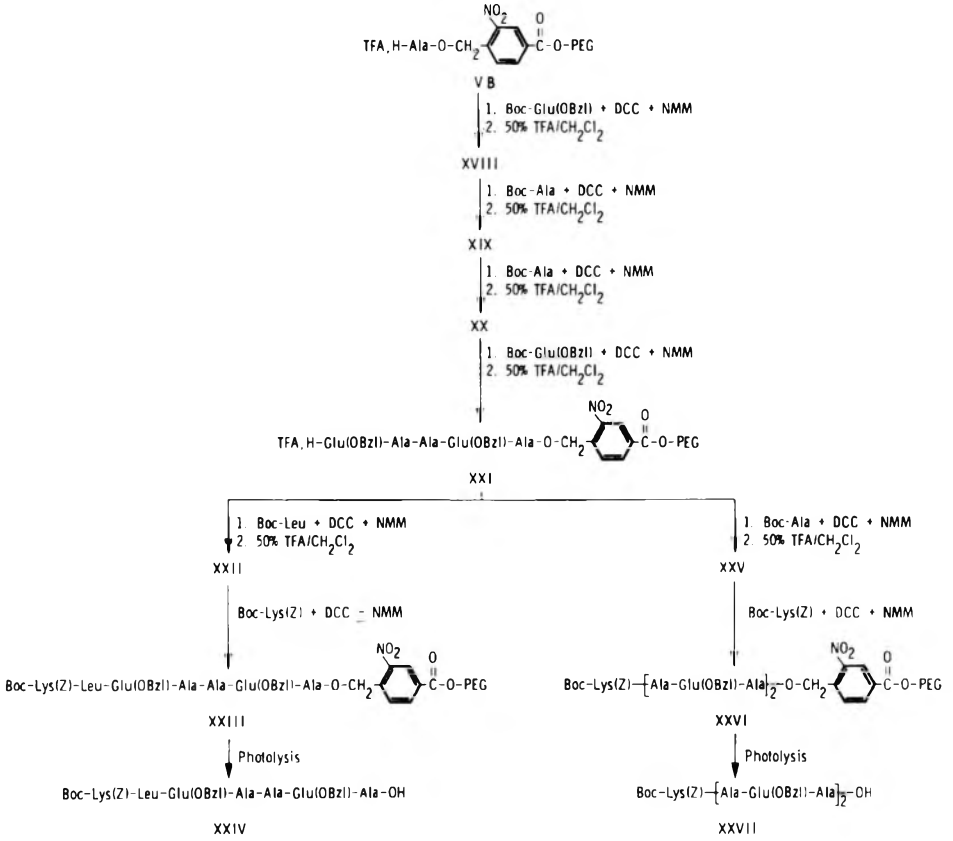


Figure 1. Cleavage yield in percent of Boc-Leu-Ala-Gly-Val obtained by photolysis of the peptide–support as a function of time. The quantity of the cleaved peptide was determined by amino acid analysis. Samples of protected peptide–support (50 mg) were dissolved in 2 mL of absolute methanol.

Experimental Section

Melting points were determined on an Electrochemical melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with either a Varian Model T-60 or a 270 MHz Brüker spectrometer. The NMR data include the frequency, integration, and assignment of the principal functional groups or characteristic side chains of the five protected peptides (compounds IX, XIV, XVII, XXIV, and XXVII) shown in Schemes I and II. The data refer mainly to the resonances of Boc and Bzl and to the protons of the leucyl, glutamyl, alanyl, and lysyl side chains (β, γ, and δ) which gave the best resolution. Deuteriochloroform or deuterated CH_3OH (99%) was used as solvent with tetramethylsilane as an internal reference. Elemental analyses were performed at the Microanalytical Laboratory, Department of Chemistry, University of Alberta. IR spectra were recorded with a Beckman IR 12 spectrometer using KBr pellets with 0.5% of sample. All photolyses were done in a RPR 208 preparative reactor (Rayonet, The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with RPR 3500-Å lamps. With the reactor at room temperature, the air temperature surrounding the sample was maintained at 32 °C by an electric fan. Amino acid analyses were obtained on a Durrum Model D-500 high-pressure automatic analyzer after hydrolysis of the samples with 6 N HCl in sealed evacuated tubes at 110 °C for 24 h for cleaved peptides and 36 h for peptide–PEG support. TLC was performed with precoated silica gel plates with a fluorescent indicator obtained from Eastman Kodak

Scheme II



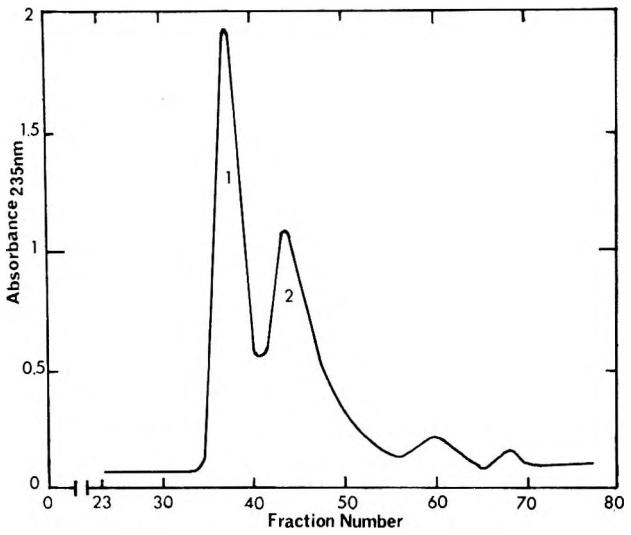


Figure 2. Chromatographic purification of synthetic heptapeptide XVII, Boc-Lys(Z)-Ala-Glu(OBzl)-Ala-Leu-Glu(OBzl)-Ala-OH, on Sephadex LH-20. The column, 2.2 × 40 cm, was equilibrated with methanol–dichloromethane (3:7 v/v), and a sample of 24 mg dissolved in 0.5 mL was applied. The flow rate was 12 mL/h, and 2-mL fractions were collected. The effluent was monitored by the absorbance of 235 nm.

(No. 6060) or Analtech silica gel GF plates (0.25 mm). The following solvent systems were used: 1-butanol–acetic acid–water, 3:1:1 (system A); 1-butanol–concentrated NH_4OH, 7:3 (system B); and 1-butanol–acetic acid–water, 4:1:1 (system C). The compounds were visualized directly under ultraviolet light or by spraying with ninhydrin in acetone followed by heating after removal of the Boc group by exposure to HCl fumes. The peptides were homogeneous in the solvent systems described when 300 μg of peptide was applied to the thin-layer plate.

The following abbreviations were used: DCC, *N,N'*-dicyclohexylcarbodiimide; DCU, dicyclohexylurea; DEA, diisopropylethylamine; NMM, *N*-methylmorpholine; HOBt, 1-hydroxybenzotriazole; Boc, N^{α}-*tert*-butyloxycarbonyl; PEG, poly(ethylene glycol); nitro-PEG, 3-nitro-4-(bromomethyl)benzoylpoly(ethylene glycol); THF, tetrahydrofuran; DMF, *N,N*-dimethylformamide.

The general procedures of deprotection, coupling, photolysis, and peptide purification are described below along with the characterization of the five finished protected peptides.

Deprotection Procedure. All amino acids were protected on the α-amino position with the Boc group. The Boc groups were removed at each cycle of the synthesis by treatment for 30 min with 50% TFA–CH_2Cl_2 (v/v) using 10 mL of this solution per gram of peptide support. The volume of the solution was then reduced by flash evaporation to an oil which was triturated with anhydrous ether to give a precipitate. After standing for 1 h at −20 °C, the precipitate was filtered, washed thoroughly with ether, and dried in vacuo.

Coupling Procedure. All couplings were made via the in situ symmetrical anhydride method, using a 5-fold molar excess of Boc amino acid and a 2.5-fold molar excess of DCC. The Boc amino acid was dissolved in 15 mL of dichloromethane, and the solution was cooled to 0 °C. A solution of DCC in 15 mL of dichloromethane was prepared and cooled to 0 °C. Both solutions were combined and allowed to stand at 0 °C for 1 h. This solution containing the symmetrical anhydride of the Boc amino acid was filtered directly into a flask containing the deprotected peptide support dissolved in 7–10 mL of dichloromethane per gram of peptide support. NMM was added to neutralize the trifluoracetate salt (pH 7.5–8.0 as measured on moistened indicator paper). After stirring the reaction mixture for 1 h at room temperature, the pH was readjusted to 7.5–8.0 if necessary by further addition of NMM and the reaction mixture was stirred for an additional 1–3 h. The solution was reduced to a small volume by evaporation in vacuo. The peptide–PEG support was precipitated by the slow addition of anhydrous ether, filtered, washed with ether, and dried in vacuo. A small sample was taken for TLC in system A to check for the complete removal of uncoupled Boc amino acid during precipitation.

The extent of coupling was monitored by a qualitative ninhydrin test. A sample of the peptide support (10–20 μmol of peptide) in 1 mL of water was added to 1 mL of ninhydrin reagent (1 L of 4 N NaAc buffer (pH 5.5), 1 L of methylcellosolve, 80 g of ninhydrin, and 7.6 mL of a 20% solution of titanium trichloride and the mixture was heated at 90 °C for 20 min. The coupling was judged to be complete when no blue color could be detected on visual observation. A second coupling was carried out if this test was positive.

Photolytic Cleavage of the Peptide from the Support. The

peptide support was dissolved in absolute methanol (5 mL/g of support). The solution was deaerated with nitrogen for 2 h and irradiated for 18 h at 350 nm. After irradiation, the solution containing the cleaved peptide, the peptide–PEG, and the PEG was diluted with absolute methanol to a volume of 1 L. It was allowed to stand at −20 °C for 3 h and then rapidly filtered. This procedure was repeated twice, and the combined filtrates containing the protected peptide were evaporated to dryness. The crude product was twice suspended in water (5 mL/g of peptide support used for photolysis) and centrifuged, and the supernatant was removed by decantation and discarded. The precipitate containing the protected peptide was further purified by Sephadex LH-20 chromatography.

Cleavage of the Peptide from the Support by Hydrazinolysis. The peptide support, Boc-Ala-Gly-Val-PEG[10] (59 mg containing 0.113 mmol of peptide per gram), was dissolved in 25 mL of DMF, and 3 mL of hydrazine hydrate was added with constant stirring. The solution was stirred for 15 min at room temperature and evaporated to dryness. The residue was dissolved in 20 mL of ethanol, evaporated to dryness, and redissolved in 10 mL of ethanol, and 90 mL of anhydrous ether was added. The mixture was left at −20 °C for 2 h and filtered at 4 °C. The filtrate containing the cleaved peptide hydrazide was evaporated to dryness. The cleavage yield was 85%, as determined by quantitative amino acid analysis.

Chromatographic Purification on Sephadex LH-20. The protected peptide was chromatographed on Sephadex LH-20 in a 2.2 × 40 cm column equilibrated with methanol–dichloromethane (3:7 v/v). The flow rate was 12–15 mL/h, and fractions of 2 mL were collected. The complete removal of PEG and peptide–PEG from the protected peptide was determined on TLC (system A) and by IR spectroscopy from the disappearance of the intensive and characteristic ether band of PEG at 1100 cm^{-1}.

3-Nitro-4-(bromomethyl)benzoic Acid (I). This compound was prepared by adding 4-(bromomethyl)benzoic acid (60 g, 0.23 mol) to 500 mL of 90% HNO_3 (white fuming) as previously described[16] to yield 64 g (89%), mp 132–135 °C (lit.[15] mp 125–126 °C).

Anal. Calcd for $C_8H_6NBrO_4$: C, 36.95; H, 2.32; N, 5.38; Br, 30.73. Found: C, 36.67; H, 2.20; N, 5.21; Br, 30.55.

3-Nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) (IIIA). 3-Nitro-4-(bromomethyl)benzoic acid (13 g, 50 mmol) and HOBt (7.65 g, 50 mmol) were dissolved in 100 mL of THF and added to poly(ethylene glycol) 6000 (30 g; containing a total of 10 mmol of hydroxyl groups). DCC (10.5 g 50 mmol) in 200 mL of dichloromethane was added, and the reaction mixture was stirred at room temperature for 24 h. The mixture was filtered to remove precipitated DCU. The above quantities of 3-nitro-4-(bromomethyl)benzoic acid, DCC, and HOBt were added to the filtrate, and the mixture was stirred for an additional 3 days. The precipitate of DCU was filtered off, the filtrate was concentrated in vacuo to a small volume, and the product was precipitated by the addition of ether. The product was filtered, washed thoroughly with ether, recrystallized from methanol by the slow addition of ether with rapid stirring, filtered, washed with ether, and dried under vacuum to yield 29.5 g: Br, 1.22 % (0.076 mmol of Br/g).

3-Nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) (IIIB). 3-Nitro-4-(bromomethyl)benzoic acid (13 g, 50 mmol) was added to poly(ethylene glycol) 6000 (30 g; containing a total of 10 mmol of hydroxyl groups) followed by DCC (10.5 g, 50 mmol) in 250 mL of dichloromethane. The reaction conditions and isolation of compound IIIB were the same as those previously described for compound IIIA: yield 29 g; Br, 2.25 % (0.141 mmol of Br/g).

N^{α}-*tert*-Butyloxycarbonyl-L-alanyl-*O*-nitrobenzoylpoly(ethylene glycol) (IVA). 3-Nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) IIIA (17 g) was dissolved in 70 mL of ethyl acetate, followed by 3.024 g (16 mmol) of N^{α}-*tert*-butyloxycarbonyl-L-alanine and 2.08 g (16 mmol) of DEA. The reaction mixture was heated gently at reflux for 5 days. After cooling the solution to room temperature, 400 mL of ether was added and the precipitate was filtered and washed with ether until no traces of N^{α}-*tert*-butyloxycarbonyl-L-alanine were detected by TLC on silica gel (solvent system A). R_f values for compound IVA and N^{α}-Boc-L-alanine were 0 and 0.56, respectively. The precipitate was dried in vacuo to give 17.05 g of compound IVA. The substitution of alanine on the support was 0.044 mmol/g of compound IVA, as determined by quantitative amino acid analysis after a 36-h hydrolysis in 6 N HCl at 110 °C. Compound IVA was deprotected as previously described to yield 17.0 g of compound VA.

N^{α}-*tert*-Butyloxycarbonyl-L-alanyl-*O*-nitrobenzoylpoly(ethylene glycol) (IVB). The esterification of Boc-Ala (2.84 g, 15 mmol) to 3-nitro-4-(bromomethyl)benzoylpoly(ethylene glycol) IIIB (15 g) was carried out in the presence of 1.94 g (15 mmol) of DEA using the same procedure as described for compound IVA. The substitution of alanine on the support was 0.092 mmol/g of compound IVB, as determined by quantitative amino acid analysis. Compound IVB was deprotected as previously described to yield 14.7 g of compound VB.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-carbobenzoxy-L-lysyl-L-leucyl-γ-benzyl-L-glutamyl-L-alanine (IX). Compound VIII (4.0 g, 0.176 mmol) was dissolved in 20 mL of absolute methanol and cleaved from the support as previously described to yield 130 mg (95%) as determined by quantitative amino acid analysis. Further purification on Sephadex LH-20 gave compound IX: yield 100 mg (85%); mp 140–143 °C; R_f (system C) 0.86; NMR analysis in $CDCl_3$–Me_4Si (1%) showed δ 0.95 (6 H, multiplet, leucine methyls), 1.35 (3 H, doublet, alanine methyl), 1.43 (9 H, singlet, Boc methyls), 5.10 (4 H, singlet, methylenes of Bzl and Z), and 7.34 (10 H, singlet, aromatic). Amino acid analysis: Glu, 0.96; Ala, 1.02; Leu, 0.96; Lys, 1.05.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-carbobenzoxy-L-lysyl-L-leucyl-γ-benzyl-L-glutamyl-L-alanyl-L-leucyl-γ-benzyl-L-glutamyl-L-alanine (XIV). Compound XIII (5.9 g, 0.26 mmol of peptide) was dissolved in 25 mL of absolute methanol and irradiated at a wavelength of 350 nm for 18 h as previously described. The yield obtained after photolysis was 265 mg (87%). The peptide was purified by Sephadex LH-20 chromatography to yield 186 mg (70%) of compound XIV: mp 218 °C; R_f (system A) 0.76, R_f (system B) 0.41; NMR analysis in CD_3OD showed δ 0.92 (12 H, 2 doublets, leucine methyls), 1.38 (6 H, doublet, alanine methyls), 1.46 (9 H, singlet, Boc methyls), 5.10 (6 H, singlet, methylenes of Bzl and Z), and 7.34 (15 H, singlet, aromatic). Amino acid analysis: Glu, 2.07; Ala, 1.91; Leu, 2.02; Lys 0.99.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-carbobenzoxy-L-lysyl-L-alanyl-γ-benzyl-L-glutamyl-L-alanyl-L-leucyl-γ-benzyl-L-glutamyl-L-alanine (XVII). Compound XVI (5.1 g, 0.224 mmol of peptide) was dissolved in 25 mL of absolute methanol and irradiated for 18 h, and compound XVII was isolated as previously described to yield 246 mg (96%). This product was purified by Sephadex LH-20 chromatography to yield 186 mg (76%) of pure compound XVII: mp 227 °C dec; R_f (system A) 0.79, R_f (system B) 0.42; NMR analysis in CD_3OD showed δ 0.94 (6 H, 2 doublets, leucine methyls), 1.40 (9 H, doublet, alanine methyls), 1.46 (9 H, singlet, Boc methyls), 5.08 (6 H, singlet, methylenes of Bzl and Z), and 7.34 (15 H, singlet, aromatic). Amino acid analysis: Glu, 1.94; Ala, 2.99; Leu, 1.02; Lys, 1.05.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-carbobenzoxy-L-lysyl-L-leucyl-γ-benzyl-L-glutamyl-L-alanyl-L-alanyl-γ-benzyl-L-glutamyl-L-alanine (XXIV). Compound XXIII (5.2 g, 0.48 mmol of peptide) was dissolved in 25 mL of absolute methanol and irradiated for 18 h, and compound XXIV was isolated as previously described to yield 482 mg (90%). This product was purified on Sephadex LH-20 to yield 361 mg (74%) of pure compound XXIV: mp 227–230 °C dec; R_f (system A) 0.71, R_f (system B) 0.29; NMR analysis in CD_3OD showed δ 0.95 (6 H, multiplet, leucine methyls, 1.32 (9 H, doublet, alanine methyls), 1.42 (9 H, singlet, Boc methyls), 4.81 (6 H, singlet, methylenes of Bzl and Z), and 7.3 (15 H, singlet, aromatic). Amino acid analysis: Glu, 2.01; Ala, 2.92; Leu, 1.01; Lys, 1.05.

N^{α}-*tert*-Butyloxycarbonyl-N^{ϵ}-carbobenzoxy-L-lysyl-L-alanyl-γ-benzyl-L-glutamyl-L-alanyl-L-alanyl-γ-benzyl-L-glutamyl-L-alanine (XXVII). Compound XXVI (6.7 g, 0.62 mmol of peptide) was dissolved in 25 mL of absolute methanol and irradiated for 18 h, and compound XXVII was isolated as previously described to yield 130 mg (19%). This product was purified on Sephadex LH-20 to yield 84 mg (65%) of pure compound XXVII: mp 234 °C dec; R_f (system A) 0.78, R_f (system B) 0.36; NMR analysis in CD_3OD showed δ 1.38 (12 H, doublet, alanine methyls), 1.44 (9 H, singlet, Boc methyls), 5.10 (6 H, singlet, methylenes of Bzl and Z), and 7.42 (15 H, singlet, aromatic). Amino acid analysis: Glu, 2.05; Ala, 3.93; Lys, 1.02.

Registry No.—I, 555715-03-2; II, 25322-68-3; III, 67316-51-2; IV, 67271-86-7; V, 67315-52-0; VII, 67271-87-8; IX, 67271-88-9; XIII, 67271-85-6; XIV, 67316-54-5; XVI, 67271-84-5; XVII, 67271-89-0; XXIII, 67316-52-3; XXIV, 67271-90-3; XXVI, 67271-83-4; XXVII, 67271-91-4; BOC-Ala-Gly-Val-PEG, 67271-82-3; 4(bromomethyl)-benzoic acid, 6232-88-8; N^{α}-*tert*-butyloxycarbonyl-L-alanine, 15761-38-3; BOC-Leu-Ala-Gly-Val-OH, 61165-83-1.

References and Notes

(1) Present address: The Rockefeller University, New York, N.Y., 10021.
(2) This project was supported by the Medical Research Council of Canada.
(3) M. Mutter, H. Hagenmaier, and E. Bayer, *Angew. Chem.*, **83**, 883, 884 (1971).
(4) E. Bayer, M. Mutter, R. Uhmann, J. Polster, and H. Mauser, *J. Am. Chem. Soc.*, **96**, 7333–7336 (1974).
(5) M. Mutter and E. Bayer, *Angew. Chem., Int. Ed. Engl.*, **13**, 88, 89 (1974).

(6) H. Hagenmaier and M. Mutter, *Tetrahedron Lett.*, 767–770 (1974).
(7) W. Gohring and G. Jung, *Justus Liebigs Ann. Chem.*, 1765–1789 (1975).
(8) M. Mutter, R. Uhmann, and E. Bayer, *Justus Liebigs Ann. Chem.*, 901–915 (1975).
(9) G. Jung, G. Bovermann, W. Gohring, and G. Heusel in "Peptides: Chemistry, Structure and Biology," R. Walter and J. Meienhofer, Ed., Ann Arbor Sci. Publ., Ann Arbor, Mich., 1975, pp 433–437.
(10) F.-S. Tjoeng, W. Staines, S. St-Pierre, and R. S. Hodges, *Biochim. Biophys. Acta*, **490**, 489–496 (1977).
(11) L. B. Smillie, *PAABS Revista*, **5**, 183–263 (1976).
(12) R. S. Hodges, J. Sodek, L. B. Smillie, and L. Jurasek, *Cold Spring Harbor Symp. Quant. Biol.*, **37**, 299–310 (1972).
(13) D. Stone, J. Sodek, P. Johnson, and L. B. Smillie *Fed. Eur. Biochem. Soc. Meet.*, [*Proc.*], **31**, 125–126 (1975).
(14) S. A. St-Pierre and R. S. Hodges, *Biochem. Biophys. Res. Commun.*, **72**, 581–588 (1976).
(15) B. Hemmasi and E. Bayer, *Tetrahedron Lett.*, 1599–1602 (1977).
(16) D. H. Rich and S. K. Gurwara, *J. Am. Chem. Soc.*, **97**, 1575–1579 (1975).

Rapid Removal of Protecting Groups from Peptides by Catalytic Transfer Hydrogenation with 1,4-Cyclohexadiene

Arthur M. Felix,* Edgar P. Heimer, Theodore J. Lambros, Chryssa Tzougraki, and Johannes Meienhofer

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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1,4-Cyclohexadiene is a very effective hydrogen donor for catalytic transfer hydrogenation. *N*-Benzyloxycarbonyl, benzyl ester, and benzyl ether (tyrosine) protecting groups can be rapidly removed at 25 °C with 1,4-cyclohexadiene and 10% palladium–carbon catalyst. Removal of the N^{im}-benzyl group from histidine, the N^{g}-nitro group from arginine, and the benzyl ether groups from serine and threonine can be carried out at 25 °C using palladium black as catalyst. Cleavage of *N*-benzyloxycarbonyl groups from sulfur-containing amino acids was also achieved by catalytic transfer hydrogenation with 1,4-cyclohexadiene. *tert*-Butyl-derived protecting groups were completely stable under these conditions. The scope of the 1,4-cyclohexadiene-catalyzed transfer hydrogenation for the removal of benzyl-derived protecting groups used in peptide synthesis was examined.

Recent publications[1,2] from two laboratories described the use of catalytic transfer hydrogenation for the removal of several benzyl-type protecting groups used in peptide synthesis. Good yields of homogeneous and nonracemized products were obtained when cyclohexene was used as hydrogen donor at temperatures of >65 °C (refluxing methanol or ethanol). However, in certain cases, especially when *tert*-butyl-derived protecting groups are also present, the danger of thermal decomposition at elevated temperatures might discourage the use of catalytic transfer hydrogenation.

We have examined other hydrogen donors and now report that 1,4-cyclohexadiene is a much more effective donor and can be used to carry out catalytic transfer hydrogenations at 25 °C in the presence of 10% palladium–charcoal. Under these conditions, removal of *N*-benzyloxycarbonyl, benzyl ester, and tyrosine benzyl ether protecting groups was complete within 2 h and good yields of analytically pure amino acids and peptides were obtained directly. The more efficient palladium-black catalyst was required for cleavage of the N^{im}-benzyl group from histidine, N^{g}-nitro group from arginine, and benzyl ether groups from serine and theonine at 25 °C. The scope of the catalytic transfer hydrogenation reaction was evaluated with respect to hydrogen donor, solvent, concentration, catalyst, and reaction temperature.

Results and Discussion

Nature of the Donor. Catalytic transfer hydrogenation has been used for the reduction of a variety of functional groups (including olefins, acetylenes, imines, hydrazones, azo, and nitro compounds).[3] The availability and reactivity of cyclohexene have rendered this reagent a preferred hydrogen donor.[4,5] The rapid disproportionation reported[6] for 1,3-cyclohexadiene and 1,4-cyclohexadiene prompted us to examine their effectiveness as hydrogen donors for the catalytic transfer hydrogenolysis of benzyl-derived protecting groups used in peptide synthesis. We observed that transfer hydrogenation of *N*-benzyloxycarbonyl-L-alanine in ethanol at 25 °C in the presence of 10% palladium–carbon and 1,4-cyclohexadiene required only 1.5 h for complete deprotection. Under the same conditions, using 1,3-cyclohexadiene as the hydrogen donor, the required reaction time for complete removal of the benzyloxycarbonyl group was 8 h. When cyclohexene was used, there was no deprotection, even after 24 h at 25 °C.

Studies were also carried out to determine the excess of hydrogen donor required for optimum deprotection. An excess of 5–10 equiv of 1,4-cyclohexadiene (per protecting group) is ideal. The rate of transfer hydrogenolysis decreased substantially when only 1 equiv of hydrogen donor was used. On the other hand, a large excess of 1,4-cyclohexadiene (50 equiv) produced only a marginal increase in the rate of reaction compared to that observed when 5–10 equiv were used.

Solvent and Concentration. Most of the solvents employed for catalytic hydrogenolysis of peptides are also useful for the catalytic transfer hydrogenation procedure. Glacial acetic acid was the most effective solvent. Transfer hydrogenation of *N*-benzyloxycarbonyl-L-alanine at 25 °C in the presence of 10% palladium–carbon and 10 equiv of 1,4-cyclohexadiene required only 45 min for complete deprotection in glacial acetic acid. Other solvents were also useful for transfer hydrogenation but required somewhat longer reaction times for complete deprotection: ethanol (1.5 h), dimethylacetamide (3 h), methanol (3.5 h), and dimethylformamide (5 h). The following solvents were impractical for catalytic transfer hydrogenation since only partial deprotection was observed at 25 °C even after prolonged periods of reaction: hexamethylphosphoramide, trifluoroethanol, phenol, trifluoroacetic acid, tetrahydrofuran, dimethyl sulfoxide, and isopropyl alcohol.

Literature[1,2] reports on inhibition of catalytic transfer hydrogenation by sulfur-containing amino acids are conflicting. We have observed that transfer hydrogenation in ethanol (using palladium-black catalyst) removed the *N*-benzyloxycarbonyl group from methionine, but not from *S*-benzylcys-

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Table I. 1,4-Cyclohexadiene Catalyzed Transfer Hydrogenation of Protected Amino Acids and Peptides in EtOH at 25 °C

substrate	registry no.	product[a]	registry no.	yield, %[b]	$[\alpha]^{25}D$, deg, found standard	mp (°C) found reported
Z-Ala-OH	1142-20-7	Ala	56-41-7	95	13.35 (c 1.1, 5 N HCl) 13.45 (c 1.2, 5 N HCl)	
Boc-Lys(Z)-OH	2389-45-9	Boc-Lys-OH	13734-28-6	88	21.3 (c 2, MeOH) 21.5 (c 2, MeOH)	195–199.5 200–201[g]
Z-Ser-OBzl	21209-51-8	Ser	56-45-1	99	12.5 (c 2, 5 N HCl) 12.6 (c 2.1, 5 N HCl)	
Boc-Tyr(Bzl)-OH	2130-96-3	Boc-Tyr-OH	3978-80-1	100	43.2 (c 1, DMF)[c] 41.6 (c 1, DMF)[c]	206.5–208.5 211–212[c,h]
Z-Phe-OH	1161-13-3	Phe	63-91-2	99	−5.01 (c 1, 5 N HCl) −4.48 (c 1, 5 N HCl)	
Z-Met-OH[d]	1152-62-1	Met	63-68-3	83	22.7 (c 1, 5 N HCl) 23.2 (c 1, 5 N HCl)	
Boc-His(N^{im}-Bzl)-OH[d]	20898-44-6	Boc-His-OH	17791-52-5	100	25.6 (c 1, MeOH) 24 (c 1, MeOH)	190.5–192.5 191–191.5[i]
Z-Gly-Pro-OH	1160-54-9	H-Gly-Pro-OH	704-15-4	99	−131.6 (c 2, 5 N HCl) −128.1 (c 2, 5 N HCl)[j]	
Boc-Phe-Gln-OBzl	67452-49-7	Boc-Phe-Gln-OH	67452-53-3	84	−3.16 (c 1.1, MeOH) −3.28 (c 1, MeOH)[j]	116–120
Z-Lys(Boc)-Thr(Bu^t)-OMe	65895-38-7	H-Lys(Boc)-Thr(Bu^t)-OMe	65895-41-2	99	−1.51 (c 1, MeOH)	
Z-Arg(NO_2)-Pro-Pro-OBu^t[d,e]	67452-50-0	H-Arg-Pro-Pro-OBu^t	67452-54-4	99	−90.1 (c 1, MeOH)	
Z-Lys(Boc)-Asn-Phe-Phe-OMe[f]	53054-10-7	H-Lys(Boc)-Asn-Phe-Phe-OMe	62437-66-5	85	−36.0 (c 1, DMF)	199–201
Boc-Tyr(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl[d,e]	67452-51-1	Boc-Tyr-Lys-Lys-Gly-Glu-OH	67452-36-2	95	−1.00 (c 1, DMF)	
Boc-Ile-Ile-Lys(Z)-Asn-Ala-Tyr(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl[d,k]	67452-52-2	Boc-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu-OH	67452-37-3	79	−3.80 (c 0.92, 1 N HCl)	

[a] Satisfactory elemental analyses have been obtained for all products. [b] No attempt was made to optimize these yields. [c] Dicyclohexylammonium salt. [d] Transfer hydrogenation carried out with freshly prepared palladium black. [e] Reaction carried out in glacial acetic acid. [f] Reaction carried out in dimethylacetamide. [g] R. Schwyzer, A. Costopanagiotis, and P. Sieber, *Helv. Chim. Acta*, **46**, 870 (1963). [h] D. D. Van Batenberg and K. E. T. Kerling, *Int. J. Pept. Protein Res.*, **8**, 1 (1976). [i] B. O. Hartford, T. A. Hylton, K. Wang, and B. Weinstein, *J. Org. Chem.*, **33**, 425 (1968). [j] J. Meienhofer, unpublished results. [k] Transfer hydrogenation carried out for 20 h at 25 °C.

teine, even in the presence of glacial acetic acid at elevated temperatures. Since liquid ammonia supports catalytic hydrogenolysis of protecting groups of *S*-benzylcysteine and methionine-containing peptides,[7] we examined the transfer hydrogenation using palladium black in refluxing liquid ammonia and observed that *N*-benzyloxycarbonyl groups are completely cleaved from methionine but only partially from *S*-benzylcysteine.

Catalytic transfer hydrogenation proceeds at the rate described above when the concentrations of amino acid or peptide substrate are in the range of 0.05–0.25 mmol/mL. At lower concentration (<0.025 mmol/mL) the rate of reaction decreases substantially. There was no significant advantage in working at higher concentration (>0.5 mmol/mL) and the heat generated from the exothermic reaction (following a short induction period) was not fully dissipated. We recommend the use of a very slow stream of nitrogen in a vibro-mixer reaction apparatus (Figure 1) for proper agitation and a 25 °C bath for temperature control. The vibro-mixer compared favorably to magnetic stirring and reactions went to completion in almost half the time. Under the conditions outlined above the reaction mixtures remained at 25 °C for the course of the reaction. However, larger scale catalytic transfer hydrogenation reactions (>0.05 mol), even at concentrations of 0.05–0.25 mmol/mL, required initial immersion in an ice bath to ensure dissipation of the heat generated during the addition of 1,4-cyclohexadiene.

Effect of Catalyst. Palladium catalysts have been reported to be most effective for transfer hydrogenation.[8] Removal of a large number of benzyl-derived protecting groups has been carried out with a variety of amino acids and peptides. Table I shows examples of isolated products. *N*-Benzyloxycarbonyl, benzyl ester, and tyrosine benzyl ether protecting groups were removed at 25 °C using 10% palladium–charcoal within 1.5 h. Freshly generated Raney nickel[9] was completely ineffective even after prolonged reaction times. Other palladium catalysts were useful for transfer hydrogenation but required longer reaction times for complete deprotection, e.g., 5% palladium–charcoal (2.5 h), 10% palladium–$BaSO_4$ (6 h), and 5% palladium–$BaSO_4$ (12 h). Freshly prepared palladium black is a much more active catalyst and cleavage of the *N*-benzyloxycarbonyl group was complete within 5 min. This catalyst was required for the removal of the following more stable protective groups: histidine N^{im}-benzyl, threonine and serine benzyl ether, methionine *N*-benzyloxycarbonyl, and *N*-[2-(*p*-biphenyl)-2-propyloxycarbonyl]. Deprotection of the N^g-nitro group of arginine required the use of palladium black in glacial acetic acid.

A large excess of catalyst improved the rate of transfer hydrogenation. We observed the optimal ratio of catalyst to substrate to be 1:1 by weight for each protecting group to be removed. Larger amounts of catalyst resulted in only minor improvement. However, the rate of transfer hydrogenation was significantly slower when smaller amounts of catalyst (catalyst: substrate < 0.5:1) were used.

Effect of Temperature. Temperature is a critical variable in catalytic transfer hydrogenation[10] and depends on the nature of the hydrogen donor. The oxidation potential for 1,4-cyclohexadiene appears to be low and consequently the optimum temperature seems to be ~20 °C (see Table II). At temperatures below 20 °C the rate of deprotection of the *N*-benzyloxycarbonyl group diminished rapidly. At higher temperatures the reaction time showed only marginal improvement.

Thermal decomposition of certain peptides may occur when *tert*-butyl derived protecting groups (including *tert*-butyloxycarbonyl, *tert*-butyl ether, *tert*-butyl ester) are used. This can be a serious problem when reactions are carried out at elevated temperatures over a prolonged reaction time. Ambient temperature is therefore particularly advantageous for catalytic transfer hydrogenation. Table I lists several examples of selective cleavage of benzyl-derived protecting groups in the presence of *tert*-butyloxycarbonyl, *tert*-butyl ether, and *tert*-butyl ester functions. The catalytic transfer hydroge-

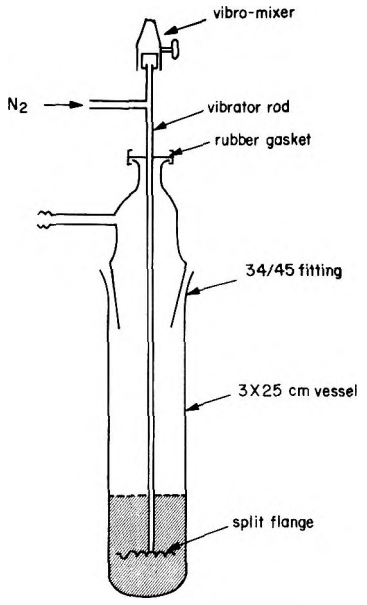

Figure 1. Apparatus for catalytic transfer hydrogenation using vibromixing for uniform suspension of the catalyst throughout the reaction mixture and efficient nitrogen distribution.

nation procedure was successfully applied to the deblocking of a number of representative protected amino acids and peptides shown in Table I including a pentapeptide and decapeptide with multiple benzyl-derived protecting groups.

Experimental Section

1,4-Cyclohexadiene (Aldrich Chemical Co.) was kept refrigerated and used directly. All amino acids were of the L configuration and were either derivatized by standard methods or purchased from Bachem Inc. or Chemical Dynamics Corp. Dimethylformamide (reagent grade, Matheson Coleman and Bell) was distilled from ninhydrin and stored over molecular sieve. All other solvents were of reagent grade and used without purification. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured in a jacketed 1-dm cell on a Perkin-Elmer Model 141 polarimeter. NMR spectra were compatible for all products isolated. Palladium catalysts were obtained from Englehard Industries. Palladium black was freshly generated and introduced directly into the reaction mixture using a syringe filter.[11] The catalytic transfer hydrogenations were carried out in a 3 × 25 cm reaction vessel (Figure 1) connected by means of a standard taper 34/45 fitting to a Vibrator rod (Chemapec Inc., No. 500-10117). The rod was connected to a Vibromixer E1 (No. 500-10180) apparatus which was adjusted for proper agitation. The lower end of the rod was fitted with a split phlange (No. 500-10134) which was immersed just below the surface of the reaction mixture. All the parts for the transfer hydrogenation system were purchased from Chemapec Inc. (Hoboken, N.J.).

Table II. Effect of Temperature on Catalytic Transfer Hydrogenation[a]

temp, °C	react time[b]	temp, °C	react time[b]
0	incomplete (8 h)	25	1.5 h
10	4.5 h	30	1.0 h
20	1.5 h	35	40 min

[a] Z-Ala-OH (0.25 mmol/mL EtOH); 10% Pd-C (catalyst:Z-Ala-OH, 1:1); 1,4-cyclohexadiene (10 equiv). [b] 100% deprotection.

Procedure for Catalytic Transfer Hydrogenation. The substrate (1.0 mmol) was dissolved in 4 mL of absolute ethanol placed in the 3 × 25-cm reaction vessel (see solvent concentration section for alternate solvents depending on solubility of substrate) and immersed in a water bath at 25 °C. A gentle stream of nitrogen was passed through the reaction mixture and thorough agitation was provided by the vibro-mixer. An equal weight of 10% palladium–carbon (per protecting group) was added followed by the addition of 1,4-cyclohexadiene (0.94 mL, 10.0 mmol). The reaction proceeded for a minimum of 2 h and the mixture was filtered (celite), washed with solvent (depending on the solubility of the product, a variety of solvents may be used, e.g., DMF, acetic acid, water), and evaporated under reduced pressure. Products were generally obtained in 90–100% yields.

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Registry No.—1,4-Cyclohexadiene, 628-41-1.

References and Notes

(1) A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1977).
(2) G. M. Anantharamaiah and K. M. Sivanandaiah, *J. Chem. Soc., Perkin Trans. 1*, **5**, 490 (1977).
(3) E. A. Braude, R. P. Linstead, P. W. D. Mitchell, and K. R. H. Woolridge, *J. Chem. Soc.*, 3595 (1954).
(4) A. Giaffe and A. Plotiau, *C. R. Hebd. Seances Acad. Sci.*, **261**, 164 (1965).
(5) P. Scribe and R. Pallaud, *C. R. Hebd. Seances Acad. Sci.*, **256**, 1120 (1963).
(6) R. P. Linstead, E. A. Braude, P. W. D., Mitchell, K. R. H. Woolridge, and L. M. Jackman, *Nature (London)*, **169**, 100 (1952).
(7) K. Kuromizu and J. Meienhofer, *J. Am. Chem. Soc.*, **96**, 4978 (1974).
(8) E. A. Braude, R. P. Linstead, and K. R. H. Woolridge, *J. Chem. Soc.*, 3586 (1954).
(9) R. Mozingo, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 181.
(10) K. Kindler and K. Lührs, *Justus Liebigs Ann. Chem.*, **685**, 36 (1965).
(11) M. Jimenez, *Org. Prep. Proced. Int.*, in press.

Deamination of Cytidine by Bisulfite: Mechanism at Neutral pH

S. Slae and R. Shapiro*

Department of Chemistry, Graduate School of Arts and Sciences, New York University, New York, New York 10003

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The kinetics of cytidine deamination in the presence of bisulfite were studied at elevated temperatures at pH 6.55 and 7.30. The reaction was found to be second order in bisulfite ion. The activation enthalpy and entropy were determined. General base catalysis was observed in the presence of added bases. A mechanism is suggested which describes the kinetic properties of this reaction. By extrapolation of our data, the rate of deamination of cytidine by 10^{-4} M bisulfite within a cell, at 37 °C, has been estimated at 4.0×10^{-12} s^{-1}.

The specific deamination of cytosine derivatives to those of uracil by bisulfite[1,2,3] (for example, I → VI, Scheme I) has been used as a synthetic method in nucleoside chemistry and as a means for the chemical modification of nucleic acids.[4] Treatment of viruses and bacteria by bisulfite induces mutations, which have been ascribed to cytosine deamination within DNA.[5]

In an earlier study, we described the principal mechanistic features of the reaction.[6] Our data were primarily collected in acidic solution, in which the optimal rate of deamination is observed. One unresolved point of uncertainty was the nature of the buffer catalysis observed in the deamination step (IV → V, Scheme I). In order to understand this step more fully, we have recently completed a study of the model compound, 1-methyl-5,6-dihydrocytosine.[7]

In our present work, we have conducted additional studies of the deamination of cytidine at neutral pH. With this data, and the conclusions from our model study, we can describe the deamination mechanism fully, and extrapolate the rate to physiological conditions. This information is necessary for an accurate estimate of the possible hazard of bisulfite as an environmental mutagen.[8]

Results

Kinetic Order of the Reaction. The kinetics of the bisulfite-catalyzed deamination of cytidine were measured at pH 6.55, μ = 3.0 and 75 °C under pseudo-first-order conditions at several bisulfite concentrations. The results shown in Table I conform to a rate equation second order in bisulfite ion.[9]

$$\frac{1}{[\text{Sub}]}\frac{d[P]}{dT} = k_{obsd}^{SO_3} = k'_{SO_3}[HSO_3^-]_{ST}^2 \quad (1)$$

where $k'_{SO_3} = (2.08 \pm 0.1) \times 10^{-5}$ mol^{-1} s^{-1}.

General Base Catalysis. When general-base catalysts were added to solutions of cytidine and bisulfite ion at pH 6.55 and 7.30, μ = 3.0, and 75 °C, an increase in the deamination rate was revealed, the overall reaction rate being described by the rate law

$$\frac{1}{[\text{Sub}]}\frac{d[P]}{dT} = k_{obsd} = k'_{SO_3}[HSO_3^-]_{ST}^2 + k'_B[HSO_3^-]_{ST}[B]_{ST} \quad (2)$$

When this increase in observed reaction rate,

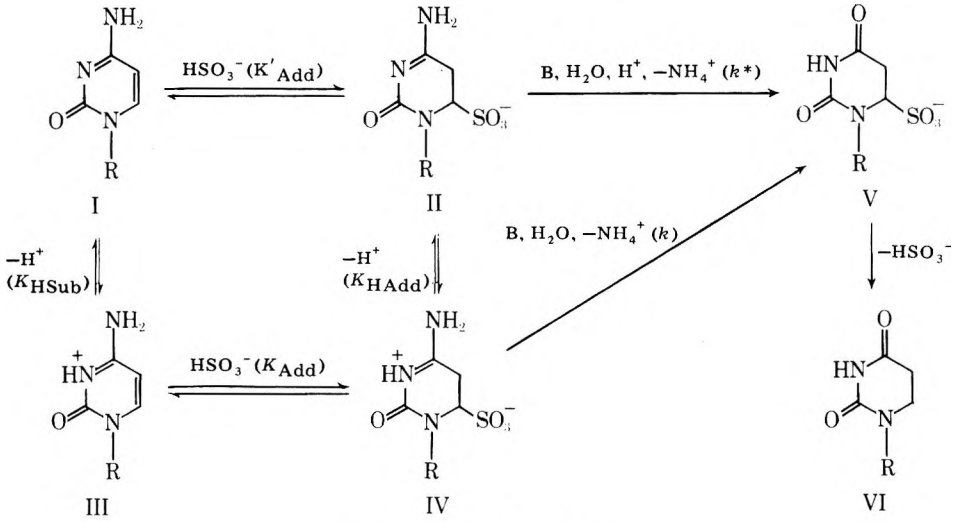
$$\left(\frac{1}{[\text{Sub}]}\frac{d[P]}{dT} - k'_{SO_3}[HSO_3^-]_{ST}^2\right)/[HSO_3^-]_{ST}$$

was combined with the known stoichiometric concentration of base, the catalytic effect of each general-base catalyst, k'_B, was obtained.

In solutions of biphosphate and bisulfite ions, the observed "biphosphate" or "sulfite" catalysis is due to the presence of two catalytic species, $H_2PO_4^-$ and HPO_4^{2-}, or HSO_3^- and SO_3^{2-}. An adjustment can be made to the observed rate constants k_B, for the minor catalytic effects of $H_2PO_4^-$ and HSO_3^-, so that a good estimate of the k's for HPO_4^{2-} and SO_3^{2-} alone, $(k'_B)_{ADJ}$, can be made.[10] A further correction for the actual concentration of free base present under experimental conditions[11] is made in Table II, where the resulting values of k'_{COR} are compiled.

Activation Parameters. Rate constants for bisulfite-catalyzed deamination of cytidine were measured at elevated temperatures at pH 6.55 and 7.30, and the results are summarized in Table III. The activation parameters derived from

Scheme I. Mechanism of Bisulfite-Catalyzed Deamination of Cytidine



R = β-D-ribofuranosyl

Table I. Observed Catalytic Coefficients in Cytidine Deamination in the Presence of Bisulfite[c]

$[HSO_3^-]_{ST}$	$[B]_{ST}$	$10^5 \times k_{obsd}$, s^{-1} [a]	$10^5 \times k'_B$, $M^{-2}\ s^{-1}$ [b]
		pH 6.55	
0.75		1.03 ± 0.01	
0.93		1.79 ± 0.03	
1.0		2.08 ± 0.02	
0.75	0.56 M imidazole	1.40 ± 0.02	0.66 ± 0.01
1.0	0.25 M $H_2PO_4^-$	2.55 ± 0.02	1.88 ± 0.02
1.0	0.50 M $H_2PO_4^-$	3.15 ± 0.17	2.14 ± 0.10
		pH 7.30	
1.0		0.098 ± 0.01	
1.0	0.40 M $CH_3CO_2^-$	0.141 ± 0.006	0.108 ± 0.006
1.0	0.50 M imidazole	0.134 ± 0.005	0.072 ± 0.005
1.0	0.13 M HPO_4^{2-}	0.109 ± 0.005	0.086 ± 0.06

[a] Estimated uncertainties in values of k are the standard deviations. [b] $k'_B = (k_{obsd} - k_{obsd}^{SO_3})/([HSO_3^-]_{ST}[B]_{ST})$ as explained in the text. [c] μ = 3.0, 75 °C.

this data were: pH 6.55, $\Delta H^{\ddagger}$ = 4.1 ± 0.7 kcal/mol, $\Delta S^{\ddagger}$ = −69 ± 2 eu; pH 7.30, $\Delta H^{\ddagger}$ = 7.0 ± 0.5 kcal/mol, $\Delta S^{\ddagger}$ = −66 ± 2 eu.

Discussion

pH Dependence of Reaction Rates. The cytidine deamination reaction in the presence of bisulfite was shown previously to proceed through either a protonated (IV) or neutral (II) intermediate (see Scheme I), depending on the experimental conditions.[6] In the first case, a rapid equilibration between the species I, II, III, and IV is followed by the rate-determining reaction of the protonated intermediate, IV → V. In the second case, the rate-determining reaction of the intermediate, II → V, follows its rapid preequilibrium formation, I → II. Since either step IV → V or II → V may be catalyzed by a base such as sulfite ion, the observation of second-order rate dependence on the stoichiometric bisulfite concentration as well as general base catalysis is consistent with either case. The lack of nucleophilic catalysis is demonstrated by the small ratio of catalytic coefficients for imidazole compared to monohydrogen phosphate ion,[19] $(k/q)_{im}/(k/q)_{HPO_4^{2-}}$ = 3.42 at pH 6.55.

The observed rate constant for this reaction in the presence of bisulfite alone, $k_{obsd}^{SO_3}$, as well as that for the increase in observed rate constant due to the presence of additional base catalysts, k_{obsd}^{B}, exhibit a calculable dependence on pH. The results of these calculations are compared with experimental measurements in Table IV (see the Supplementary Material for the derivation of these calculations). Under the experimental conditions described here, the mechanism involving the protonated intermediate (IV → V) accurately predicts the pH dependence of $k_{obsd}^{SO_3}$ and k_{obsd}^{B}, while the alternative mechanism (I → II → V) is inconsistent with these results.

Activation Parameters. The enthalpies and entropies of activation measured for the bisulfite-catalyzed cytidine deamination differ significantly from those determined for the deamination of 1-methyl-5,6-dehydrocytosine, MDC[7] ($\Delta H^{\ddagger}$ = 20.7 ± 0.8 kcal/mol, $\Delta S^{\ddagger}$ = −11.0 ± 2.6 eu for the reaction in acidic media). The mechanism proposed here for cytidine deamination can account for these differences.

In the bisulfite-catalyzed cytidine deamination, intermediate IV is formed in a rapid preequilibrium, and it is this species that is the equivalent of the protonated MDC, the reacting species under the conditions studied for MDC (pH 0.4). In the mechanism proposed for cytidine deamination, where IV → V is the slow step, the overall activation enthalpy (and entropy) is the sum of the enthalpies (and entropies) for steps I → II (equilibrium), III → IV (equilibrium), and IV → V (kinetic). Based on earlier measurements[6] of the temperature dependence of the cytidine sulfonate adduct formation, an approximate estimate of $\Delta H°$ = −9.3 ± 4 kcal/mol, and $\Delta S°$ = −60 ± 20 eu can be made for transformation III → IV. The transformation equivalent to I → III for cytidine[18] has $\Delta H°$ = −4.4 kcal/mol and $\Delta S°$ = 5.0 eu. Therefore for the step IV → V, the estimated parameters are $\Delta H^{\ddagger}$ = 18 ± 5 kcal/mol and $\Delta S^{\ddagger}$ = −14 ± 25 eu. When MDC deamination is compared with the kinetically equivalent step of cytidine deamination, the activation parameters are similar.

Brønsted Relationship. The relative rate constants of the general bases compared to sulfite ion can be shown to be equal to the equation

$$\frac{k_{obsd}^{B}/([HSO_3^-]_{ST}[B]_{ST})}{k_{obsd}^{SO_3}/[HSO_3^-]_{ST}^2} = \frac{k_B}{k_{SO_3}}\left(\frac{K_{HB}}{[H^+] + K_{HB}}\right)\left(\frac{[H^+] + K_{HSO_3}}{K_{HSO_3}}\right) \quad (3)$$

The relative catalytic coefficients for the rate-determining step of this mechanism, k_B/k_{SO_3}, can be calculated from the relative observed rate constants (see the Supplementary Material for the derivation). Values so obtained are presented in Table II. The Brønsted relationship[21] for the relative rate constants of the rate-determining step at pH 6.55, μ = 3.0 and 75 °C yields[22]

$$\log (k/q) = (0.35 \pm 0.07)[(pK_a + \log (p/q)] - (8.59 \pm 0.47) \quad (4)$$

Studies of the general-base-catalyzed deamination of 1-methyl-5,6-dihydrocytosine[7] (37 °C, μ = 1.0), which proceeds through a similar rate-determining step, yielded a β of 0.19 ± 0.03 for a series of bases including structural types similar to those used in the present study. The agreement between the values of β is good, considering the differences in experi-

Table II. General-Base Catalysis in Cytidine Deamination in the Presence of 1 M Bisulfite Ion[e]

base	pK[a]	$10^6 \times k'_B$ $M^{-1}\ s^{-1}$	$10^6 \times (k'_B)_{adj}$ $M^{-1}\ s^{-1}$ [b]	$K_{HB}/([H^+] + K_{HB})$	$10^6 \times (k'_B)_{cor}$, s^{-1}	$(k'_B)_{cor}$[c]$/(k'_{SO_3^{2-}})_{cor}$
			pH 6.55			
SO_3^{2-}	6.37	20.8	15.6	0.60	26.0 ± 0.3	1.00
imid	7.12	6.61	6.1	0.21	31.5 ± 0.5	1.21 ± 0.06
HPO_4^{2-}	6.27	20.1	18.1	0.65	27.8 ± 1.8	1.07 ± 0.08
			pH 7.30			
SO_3^{2-}	6.37	0.98	0.93	0.90	1.01 ± 1	1.00
imid	7.12	0.72	0.72	0.60	1.20 ± 0.1	1.20 ± 0.10
HPO_4^{2-}	6.27	0.86	0.84	0.915	0.94 ± 0.7	0.94 ± 0.23
$CH_3CO_2^-$	4.76	1.08	1.08	0.997	1.08 ± 0.08	1.08 ± 0.09

[a] pK estimates for these experimental conditions based on extrapolations of the best literature values,[12-18] estimated error limits are ± 0.05. [b] Adjustment made for the catalytic contribution of conjugate acids, $H_2PO_4^-$ and HSO_3^-, as explained in the text. [c] $(k'_B)_{cor} = (k'_B)_{adj}([H^+] + K_{HB})/K_{HB}$. [d] Average of two measurements, see Table I. [e] μ = 3.0, 75 °C.

Table III. Temperature Dependence of Cytidine Deamination Rate Constants in the Presence of 1 M Bisulfite[a]

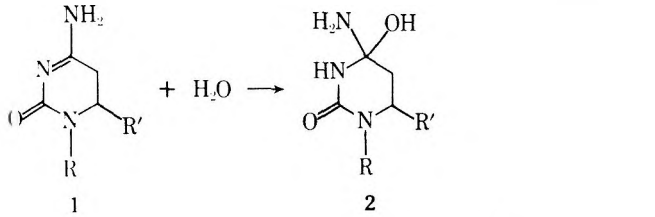
temp, °C	$10^5 \times k_{obsd}$, s^{-1} (pH 6.55)	$10^7 \times k_{obsd}$, s^{-1} (pH 7.30)
55.5	1.31 ± 0.07	5.29 ± 0.30
64.5	1.49 ± 0.04	6.55 ± 0.06
75.0	2.08 ± 0.09	9.80 ± 0.60
86.0	2.42 ± 0.22	14.1 ± 0.30

[a] μ = 3.0.

mental conditions and the uncertainties involved in the estimate of β for cytidine.

Reaction Mechanism. The mechanism presented in Scheme I is consistent with the kinetic order of the reaction, rate dependence on pH, general-base catalysis, absence of nucleophilic catalysis, lack of general-acid catalysis,[6] solvent isotope effect,[6] and activation parameters.

Although the details of transformation IV → V have not been examined, this process probably occurs through a tetrahedral intermediate (**2a**) similar to the mechanism proposed



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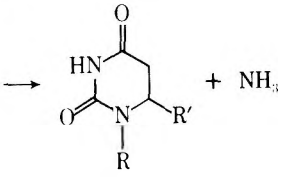

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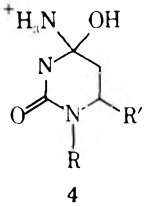
a, R = β-D-ribofuranosyl; R′ = SO_3^-
b, R = CH_3; R′ = H

for the deamination of 1-methyl-5,6-dihydrocytosine (**1b** → **2b** → **3b**) and similar amidines.[7] The rate-determining step of this mechanism is thought to be either the formation of intermediate **2**, or the reaction of the protonated form with which it is in equilibrium under the experimental conditions (**4**). These processes could occur through transition states VII



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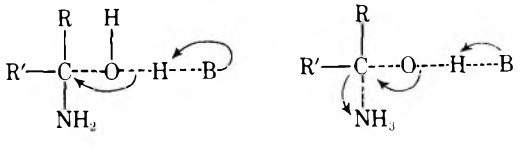
or VIII, respectively.



VII VIII

The Rate of Cytidine Deamination of Bisulfite under Physiological Conditions. It can be shown that in the presence of general base, the rate of cytidine deamination proceeding through intermediate IV can be approximately described by the following rate constant (eq 5)

Table IV. Dependence of Cytidine Deamination Rate Constants on pH in the Presence of 1 M Sulfite and Added Bases

	$[(k'_B)_{6.55}/(k'_B)_{7.30}]$[a]		
	experimental	calculated ratio[b,c]	
base	ratio	case 1	case 2
SO_3^{2-}	17.7 ± 1.1	15.1 ± 2.0	2.6 ± 0.3
imidazole	9.2 ± 0.04	7.7 ± 1.0	1.3 ± 0.2
HPO_4^{2-}	21.5 ± 7.5	16.8 ± 2.0	2.8 ± 0.3

[a] $k'_B = k_{obsd}^{SO_3}/[HSO_3^-]_{ST}^2$ for SO_3^{2-} and $k_{obsd}^{[B]}/[HSO_3^-]_{ST}[B]_{ST}$ for imidazole and HPO_4^{2-}. These are the apparent third-order rate constants corrected for pH to reflect true concentrations of reactive forms; 6.55 and 7.30 are the pH values for the respective determination of k'_{obsd}. [b] See Appendix in supplementary material for the basis of these calculations. [c] Case 1 and 2 as described in the text. [d] μ = 3.0, 75 °C.

$$k_{obsd} = [HSO_3^-]_{ST} k_{obsd}^{SO_3}([HSO_3^-]_{ST} + \sum_i [B_i]_{ST}) \quad (5)$$

(see the Supplementary Material for the derivation). Extrapolation from rate data at elevated temperatures yields

$$k_{obsd}^{SO_3} = 2.5 \times 10^{-7}\ mol^{-2}\ s^{-1}$$

for 37 °C, pH 7.30, μ = 3.0.

In order to estimate the rate of deamination within a living cell, we must introduce into eq 5 the total concentration of bases within the cell, $\sum_i [B_i]_{ST}$. This has been estimated as 0.16 M (μ = 0.16).[23-25]

Thus the physiological deamination rate of cytidine by bisulfite in vivo at 10^{-4} M bisulfite can be estimated at $4.0 \times 10^{-12}\ s^{-1}$, while at 10^{-6} M bisulfite it would be $4.0 \times 10^{-14}\ s^{-1}$. The significance of this data for questions of environmental mutagenesis will be discussed elsewhere.

Experimental Section

Materials and Apparatus. Schwartz Mann cytidine and commercially available reagent grade chemicals were used. Imidazole was recrystallized from benzene three times before use (mp 88.5–89.0 °C; lit. 90–91 °C). Water was doubly distilled in Pyrex vessels and deoxygenated with nitrogen. For reactions in the presence of sulfite ion, 10^{-3} M hydroquinine was added as a radical inhibitor.

Apparatus. Ultraviolet absorbance measurements were recorded on a Cary 15 recording spectrophotometer. pH measurements were made at various temperatures on a Radiometer Model 22 pH meter equipped with a glass electrode which had been precalibrated with pH standard solutions at the temperatures of measurement. pH values are ±0.02.

Kinetics of Cytidine Deamination. Ampules (2 mL) sealed with rubber septum caps were filled with reaction mixtures buffered to the desired pH at appropriate temperatures and kept in a constant temperature bath regulated to ±0.1 °C. Temperatures were measured with a thermometer calibrated by the National Bureau of Standards. Samples (50 μL) were removed with a syringe and stored in pH 11.5 buffer solution of 0.2 M Na_2HPO_4 for at least 24 h. The relative concentrations of the reactant (cytidine) and product (uridine) were calculated for each sample from the observed absorbances at 270 and 280 nm by means of the formulas, [Uridine] = $(A_{270} - 1.21A_{280})/3044$; [Cytidine] = $(2.39\ A_{280} - A_{270})/8805$. A plot of log χ_{Cyt} against time was analyzed by the method of least squares on a Hewlett Packard 3000 computer. Estimated errors in k are the standard deviations of the slopes for these kinetic plots. Catalytic coefficients of general bases were obtained by rate measurements in aqueous buffers kept at constant pH. Ionic strength was held constant by the addition of sodium chloride.

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Supplementary Material Available: An Appendix containing

the derivations mentioned in the text (6 pages). Ordering information is given on any current masthead page.

Registry No.—Cytidine, 65-46-3; bisulfite, 15181-46-1.

References and Notes

(1) R. Shapiro, R. E. Servis, and M. Welcher, *J. Am. Chem. Soc.* **92,** 1422 (1970).
(2) H. Hayatsu, Y. Wataya, and K. Kai, *J. Am. Chem. Soc.* **92,** 724 (1970).
(3) H. Hayatsu, Y. Wataya, and K. Kai, *Biochemistry,* **9,** 2858 (1970).
(4) H. Hayatsu, *Prog. Nucleic Acid Res. Mol. Biol.* **16,** 75 (1976).
(5) R. Shapiro, *Mutation Res.* **39,** 149 (1977).
(6) R. Shapiro, V. DiFate, and M. Welcher, *J. Am. Chem. Soc.* **96,** 906 (1974).
(7) S. Slae and R. Shapiro, *J. Org. Chem* **43,** 1721 (1978).
(8) *Science,* **187,** 502 (1975).
(9) Symbolism used in this paper includes the following: μ is the ionic strength (in molarity); k_{obsd} indicates the observed rate constant; ST indicates the stoichiometric concentration before correction for equilibration of the different species present; Sub indicates Substrate; "Bisulfite" describes the overall effects of a solution of bisulfite and sulfite ions without identifying the specific species causing that effect.
(10) Assuming that the catalytic properties of general bases are similar for the well-characterized deamination of 1-methyl-5,6-dihydrocytosine,[7] and the rate-determining step of cytidine deamination (See Reaction Mechanism), then $k_{SO_3} = 2k_{HSO_3}$; $k_{HPO_4^{2-}} = 5k_{H_2PO_4^-}$. Under the experimental conditions, the relative concentrations of the basic species present can be calculated to be: $[SO_3^{2-}]/[HSO_3^-] = 1.50$ (pH 6.55), 9.00 (pH 7.30); $[HPO_4^{2-}]/[H_2PO_4^-] = 1.86$ (pH 6.55), 10.8 (pH 7.30). The relative catalytic contribution of each species becomes $(k_{SO_3^{2-}}[SO_3^{2-}])/(k_{HSO_3^-}[HSO_3^-]) = 3.0$ (pH 6.55), 18 (pH 7.30); $(k_{HPO_4^{2-}}[HPO_4^{2-}])/(k_{H_2PO_4^-}[H_2PO_4]) = 9.3$ (pH 6.55), 54 (pH 7.30). Should the rate constant ratio $(k_{SO_3^{2-}}/k_{HSO_3^-})$ equal one (a lower limit), the relative catalytic contribution would become $(k_{SO_3^{2-}}[SO_3^{2-}])/(k_{HSO_3^-}[HSO_3^-]) = 1.50$ (pH 6.55), 9.0 (pH 7.30). The possible error introduced into the calculations by this estimate is not significant enough to modify the final conclusions.
(11) Based on best pK estimates vailable from the literature[12-18] for these conditions.
(12) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Methuen, London, 1962.
(13) G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids In Aqueous Solution", Butterworths, London, 1961.
(14) D. D. Perrin, "Dissociation Constants of Inorganic Acids and Bases In Aqueous Solutions", Butterworths, London, 1969.
(15) D. D. Perrin, "Dissociation Constants of Organic Bases In Aqueous Solutions", Butterworths, London, 1965.
(16) L. G. Sillen and A. E. Martell, "Stability Constants of Metal Ion Complexes", 2nd ed, The Chemical Society, London, 1964.
(17) L. G. Sillen and A. E. Martell, "Stability Constants of Metal-Ion Complexes, Supplement No. 1", The Chemical Society, London, 1971.
(18) H. A. Sober, ed., "Handbook of Biochemistry", Chemical Rubber Publishing Co., Cleveland, Ohio, 1970.
(19) Nucleophilic catalysis is characterized by high ratios of $(k/q)_{Im}/(k/q)_{HPO_4}$ of about 1000.[20]
(20) H. S. Johnson, *Adv. Phys. Org. Chem.,* **5,** 237 (1967).
(21) W. P. Jencks, "Catalysis In Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969.
(22) The Brønsted relationship reported here should be considered only illustrative, since bases of different structural types are compared. In addition, errors in the estimated values of K_{HB} and the small change in catalyst strength ($\Delta pK = 0.85$) studied and possible specific salt effects affect the uncertainty in the Brønsted relationship.
(23) J. L. Gamble, "Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid", 6th ed, Howard University Press, Cambridge, Mass., 1954, pp 5, 9, 11.
(24) D. Jensen, "The Principles of Physiology", Appleton-Century-Crofts, New York, N.Y., 1976, p 54.
(25) A. C. Guyton, "Textbook of Medical Physiology", 4th ed, Saunders, Philadelphia, Pa., 1971, p 39.

Fluorinated Pyrimidine Nucleosides. 2.[1] Reaction of 2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine Hydrochloride with Nitrogen and Sulfur Nucleophiles

Alan F. Cook* and Michael J. Holman

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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Reaction of 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine hydrochloride (**1**, anhydro-ara-FC) with ammonia gave 1-β-D-arabinofuranosyl-2,4-diamino-5-fluoropyrimidinium chloride (**2**) by attack at C_2 of the pyrimidine ring. Reaction of **1** with methylamine gave the corresponding 2-methylamino derivative **3**, which was rapidly converted into the 2,4-bis(methylamino)arabinoside **4** by amine exchange at C_4. Treatment of **1** with ethylamine or *n*-propylamine similarly produced the corresponding 2,4-bis(alkylamino) derivatives **14** and **15**. Reaction of **1**, **2**, or **4** with methylamine for a prolonged reaction period resulted in rearrangement with loss of the sugar moiety to produce 2-amino-5-fluoro-1-methyl-4-methyliminopyrimidine hydrohalide (**9**), the structure of which was confirmed by X-ray crystallography. The reaction of **1** with ^{15}N-enriched ammonia was examined; in addition to C_2 attack and amine exchange at C_4, evidence was found for incorporation of ^{15}N into the pyrimidine ring. Reaction of **1** with sodium hydrosulfide or hydrogen sulfide induced defluorination without cleavage of the anhydro bond to give 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (**21**); the oxazolidinethione **22** was also isolated as a byproduct. Treatment of the corresponding sulfur- and nitrogen-bridged analogues **23** and **26** with sodium hydrosulfide also produced the corresponding defluorinated anhydro nucleosides **25** and **27**.

2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine hydrochloride (**1**, anhydro-ara-FC; Scheme I), a compound first synthesized by Fox et al.,[2] has been shown by Burchenal et al.[3] to be a promising new agent for the treatment of acute myeloblastic leukemia. As part of a synthetic program in the area of fluorinated pyrimidine nucleosides, we have employed anhydro-ara-FC as starting material for the preparation of some 5-fluoropyrimidine nucleosides with potential antitumor activity. The reactions of nitrogen and sulfur nucleophiles form the basis for this report.

Reaction of anhydro-ara-FC (**1**) with methanolic ammonia yielded the highly crystalline 2,4-diamino-5-fluoropyrimidine arabinoside **2** by reaction at C_2 of the pyrimidine ring.[4] This reaction is to be expected since Doerr and Fox have previously shown that the corresponding unfluorinated analogue 1-β-D-arabinofuranosyl-2,4-diaminopyrimidinium chloride was produced by the reaction of 2,2′-anhydro-1-β-D-arabinofuranosylcytosine with ammonia.[5] Although difficulty was experienced by Doerr and Fox in the isolation of the unfluorinated analogue due to the hygroscopic nature of the salt, together with its propensity for recrystallization to the 2,2′-anhydro compound, the hydrochloride salt of **2**, in contrast, was found to be stable indefinitely at room temperature. In aqueous solution, **2** was found to be much less stable; storage of a solution for 4 days at room temperature resulted in almost complete conversion to arabinosyl-5-fluorocytosine. A small amount of a byproduct was isolated from the reaction of **1** with ammonia; this was identified as 2-amino-β-D-arabinofu-

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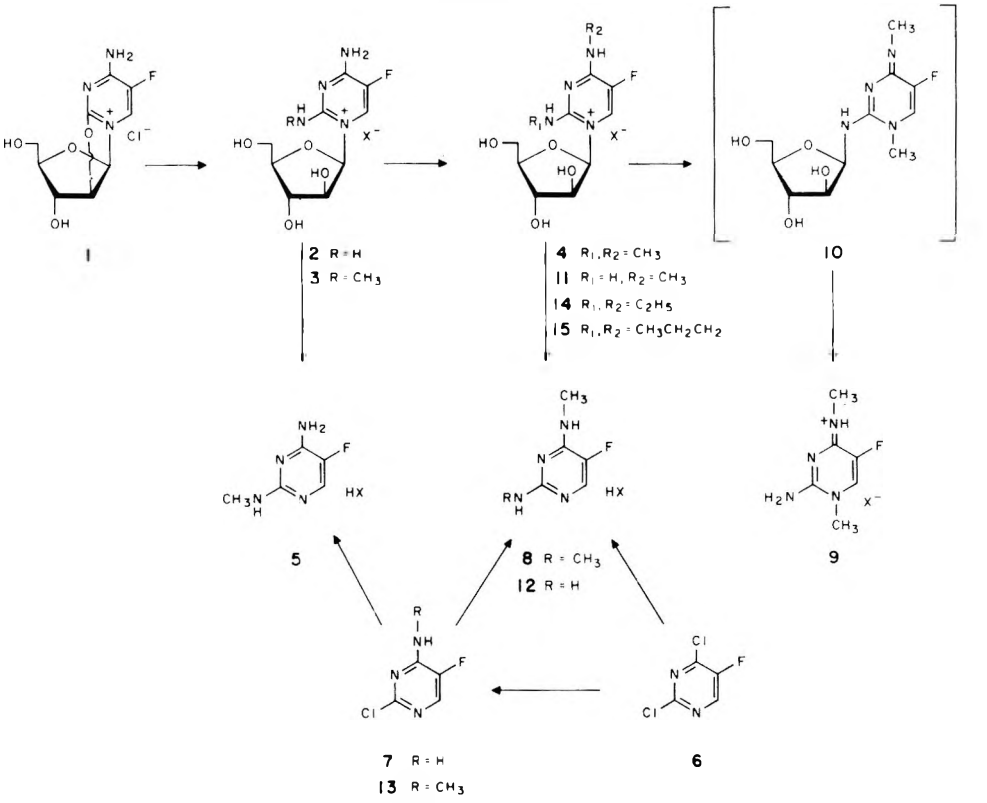
Scheme I



rano[1′,2′:4,5]-2-oxazoline and was found to be identical with a sample prepared from D-arabinose and cyanamide by the method of Shannahoff and Sanchez.[6] This oxazoline was previously isolated by Fox and Otter[7] from the reaction of **1** with sodium hydroxide and presumably arose from degradation of the pyrimidine ring of **1** while preserving the 2,2′-anhydro linkage intact.

Our attention was next focused on the reaction of **1** with methylamine. Reaction with 3 equiv in methanol at room temperature gave initially the arabinosyl-2-methylaminopyrimidine **3** as expected. This compound, however, was rapidly converted by excess methylamine into the 2,4-bis(methylamino)pyrimidine nucleoside **4**; after only 15 min at room temperature, the latter was found to be the major product. Thus, an extremely facile amine exchange reaction had apparently taken place at C_4 in addition to the expected attack of methylamine at C_2. The presence of two methylamino functions in **4** was particularly evident from an examination of its NMR spectrum; two three-proton doublets at δ 2.91 and 3.00 due to two CH_3NH- functions both collapsed to singlets on addition of D_2O.

Further experiments were carried out to examine this amine exchange reaction at C_4 in more detail; reaction of **1** with only 1 equiv of methylamine gave, after 10 min, a complex mixture of starting material, monomethyl compound **3**, and dimethyl compound **4** in a ratio of approximately 3:3:1. After 40 min, the monomethyl derivative **3** was found to be the main product, with substantial amounts of **1** and **4** present; **3** could be isolated with difficulty by conversion into its picrate salt and characterized by its NMR spectrum, which revealed only one doublet (δ 2.87) due to one CH_3NH functionality. Reaction of a sample of **3** with methylamine also produced the dimethyl compound **4**, thus implicating **3** as the probable intermediate in the conversion of **1** to **4**.

The reactivity of the C_4 position in this series of compounds is in distinct contrast to the results obtained by the reaction of 5-fluorocytidine with methylamine in methanol; even after 96 h at room temperature in the presence of 9 equiv of methylamine, no reaction was detected.

A pyrimidine byproduct was obtained from the reaction of **1** with methylamine and was isolated as the hydrochloride. An analysis of its NMR spectrum revealed one three-proton doublet at δ 2.88 due to a CH_3NH group and a broad exchangeable two-proton singlet at δ 8.55 due to a primary amino group in addition to signals due to the CH=CF and NH protons. This material was designated as 4-amino-5-fluoro-2-methylaminopyrimidine hydrochloride (**5**), the formation of which could be accounted for by attack of methylamine on **1** followed by aminolysis of the nucleoside **3** or by acidic hydrolysis of **3** during the preparation of the picrate. Since physicochemical methods were unable to determine the exact location of the methyl group, confirmation of the structural assignment of **5** was obtained by an alternate synthesis. Reaction of 2,4-dichloro-5-fluoropyrimidine **6** with ammonia as previously reported[8] gave 4-amino-2-chloro-5-fluoropyrimidine **7**; treatment of **7** with methylamine for 75 h at room temperature in a stainless steel bomb induced nucleophilic displacement of the relatively unreactive 2-chloro substituent, and **5** was obtained in 21% yield. This material proved to be identical with the sample obtained from the reaction of **1** with methylamine.

Compound **1** was also treated with methylamine for a prolonged reaction period (2–3 days), and thin-layer chromatographic analysis of the reaction mixture indicated the complete absence of **1** and **4** with the formation of a new product which was subsequently isolated in crystalline form as the picrate and as the hydrochloride. The latter gave a correct elemental analysis for a dimethylpyrimidine of empirical formula $C_6H_{10}ClFN_4$. The most likely structure to be expected from such a reaction would be 2,4-bis(methylamino)-5-fluoropyrimidine hydrochloride **8**, the formation of which could be explained by aminolysis of the dimethylated nucleoside **4**. Compound **4** therefore was synthesized by an unambiguous route by reaction of **6** with anhydrous methylamine at room temperature in a stainless steel bomb. This material, however, proved to be different from the dimethyl derivative obtained from the reaction of **1** with methylamine. Moreover, a comparison of the NMR data of these two compounds indicated that **8**, when isolated as the picrate, revealed the presence of two three-proton doublets at ca. δ 2.9 due to two CH_3NH

groups, which on addition of D_2O collapsed to two singlets. The picrate of the dimethylpyrimidine obtained from the reaction of **1** with methylamine, on the other hand, revealed the presence of only one doublet at δ 2.93 due to one CH_3NH function, but a three-proton singlet at lower field suggested the presence of an uncoupled *N*-methyl group, presumably located directly on the pyrimidine ring. Since NMR and UV studies were unable to determine the exact location of the two methyl groups, an X-ray crystallographic analysis of the hydrobromide was carried out. The structure was thus revealed to be 2-amino-5-fluoro-1-methyl-4-methyliminopyrimidine hydrohalide (**9**).

The formation of this compound can be rationalized as follows: (a) formation of the bis(methylamino)pyrimidine arabinoside **4** by attack at C_2 and C_4 as previously discussed, (b) Dimroth rearrangement of **4** to the glycosylamine **10** during which the sugar is transferred to the exocyclic nitrogen, and (c) attack of methylamine at C_1 of the sugar moiety to give the 1-methylpyrimidine **9**. Dimroth rearrangement of 1-alkyl-2-alkyliminopyrimidines has been well documented,[9] and the rearrangement of **4** can be considered as a nucleoside example of this class of reactions. Since the normal driving force for the Dimroth rearrangement, i.e., the production of a formally aromatic ring, is absent in this example, **4** would be expected to undergo rearrangement to produce a mixture of isomers in a ratio controlled by steric and/or electronic factors; in cases where the two alkyl groups are electronically similar, the equilibrium favors the isomer bearing the bulky substituent on the exocyclic nitrogen. Thus, the equilibrium for the Dimroth rearrangement of **4** would be expected to favor the formation of **10** in which the bulky sugar substituent is in the exocyclic N_2 position. The glycosylamine **10** would then be expected to undergo attack by methylamine at the C_1' atom with the formation of the 1-methylpyrimidine **9**. The overall yield of **9** from **1** was found to be 44% by direct cyrstallization of the picrate.

In order to demonstrate the intermediacy of the 2,4-bis(methylamino)arabinosyl nucleoside (**4**) in this scheme, **4** was directly treated with methylamine under essentially the same reaction conditions as for **1**. A thin-layer chromatographic examination of the reaction mixture revealed the presence of two products; the major product proved to be chromatographically identical with the 1-methyl-4-methyliminopyrimidine **9**, and the minor component corresponded to the 2,4-bis(methylamino)pyrimidine **8**. The mixture was resolved by column chromatography on silica, and **9** and **8** were isolated as their picrate salts in yields of 54 and 2.5%, respectively. This latter material could have been produced either by Dimroth rearrangement of the 1-methylpyrimidine **9** in the presence of methylamine or by direct aminolysis of the nucleoside **4**. Since direct treatment of **9** with methylamine failed to produce **8**, the latter was presumably produced by aminolysis of the bis(methylamino) nucleoside **4**. Exposure of **8** to methylamine similarly failed to produce any trace of **9**, providing further evidence that the Dimroth rearrangement to produce **9** occurred at the nucleoside level rather than the pyrimidine level. In contrast, acidic hydrolysis of **4** produced **8** as the only UV-absorbing product; the physicochemical characteristics of the picrate of **8** proved to be identical with the material previously obtained by the reaction of 2,4-dichloro-5-fluoropyrimidine (**6**) with methylamine.

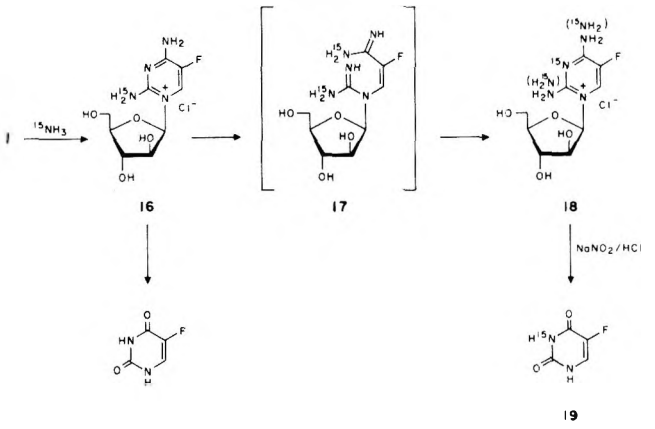
Reaction of 1-β-D-arabinofuranosyl-2,4-diamino-5-fluoropyrimidine (**2**) with methylamine for 1 h produced a new compound which was not isolated in pure form, but which was tentatively assigned to be the 4-methylamino nucleoside **11**, obtained by amine exchange at C_4. The reaction mixture was hydrolyzed with hot aqueous picric acid to give a new monomethyl pyrimidine which was isomeric with but different from the 2-methylaminopyrimidine **5**; its structure was therefore deduced to be 2-amino-5-fluoro-4-methylaminopyrimidine (**12**). The NMR signal for the methyl group in the free base or the hydrochloride appeared as a three-proton doublet in the δ 2.8 region, thus confirming the presence of the CH_3NH function rather than a methyl group located on the pyrimidine ring. The structure of **12** was confirmed by synthesis from **6**; reaction with methylamine in methanol overnight at 5 °C gave 2-chloro-5-fluoro-4-methylaminopyrimidine (**13**), from which **12** was obtained by reaction with ammonia at elevated temperature and pressure. Prolonged reaction of the diamino nucleoside **2** with methylamine (for 2 days) introduced two methyl groups into the pyrimidine ring, and 1-methyl-4-methyliminopyrimidine **9** was produced as the major product, isolated as the picrate in 31% yield. The formation of **9** from **2** can be explained on the basis of (a) amine exchange at both C_2 and C_4 to give the bis(methylamino)pyrimidine **4**, and (b) Dimroth rearrangement of **4** via the intermediate **10** as previously discussed. The bis(methylamino) nucleoside **4** was in fact isolated in small quantities from the reaction mixture, thus providing support for the intermediacy of this compound in the conversion of **2** to **9**. The isolation of the dimethylamino nucleoside **4** demonstrates that amine exchange at C_2 is experimentally possible; amine exchange at C_4 has previously been discussed.

Reactions of anhydro-ara-FC with other amines were also briefly studied. Reaction with excess ethylamine gave the 2,4-bis(ethylamino) compound **14**, and, similarly, reaction with *n*-propylamine gave the di-*n*-propyl derivative **15**; with the conditions employed (5 equiv of amine in methanol, 25 °C, 15 min), starting material was completely consumed and no degradation of the nucleoside linkage was detected. Reaction of **1** with dimethylamine was less successful; after treatment with 6 equiv for 40 min, a complex mixture was obtained, from which no crystalline products could be isolated.

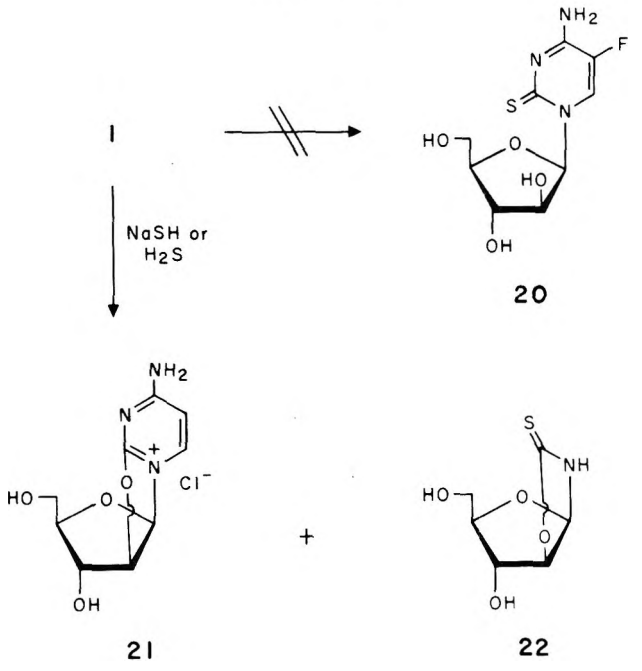
The reactivity of C_4 in this series of compounds prompted us to examine the reaction of anhydro-ara-FC with ^{15}N-enriched ammonia. Using 6 equiv of 99% ^{15}N-enriched ammonia, a reaction with **1** was carried out for 3 h at 25 °C; under these conditions, only the diamino nucleoside could be detected by TLC. The extent of reaction of $^{15}NH_3$ at C_4, in addition to attack at C_2, was calculated by mass spectrometry;[10] although the molecular ion for the nucleoside was not detected, the peaks derived from the 2,4-diamino-5-fluoropyrimidine fragment were observed. A comparison of the relative proportions of these peaks at *m/e* 129 and 130 as compared with those obtained from unenriched material gave an indication of the extent of incorporation of a second molecule of $^{15}NH_3$ in addition to incorporation at C_2. These experiments indicated that incorporation of a second molecule of $^{15}NH_3$ had occurred to the extent of 22%. In addition, a small peak at *m/e* 131 indicated that a small percentage (1%) of incorporation of a third atom of ^{15}N had taken place.

In order to determine the extent of ^{15}N incorporation into the pyrimidine ring, in addition to the exocyclic amino groups, a sample of the diamino nucleoside obtained by treatment of anhydro-ara-FC with ^{15}N-enriched ammonia was hydrolyzed and deaminated using sodium nitrite in aqueous hydrochloric acid to produce 5-fluorouracil. This sample was analyzed by mass spectrometry and again compared with a sample of unenriched material. By this method it was determined that ^{15}N had been incorporated into the pyrimidine ring to the extent of about 6%, in addition to incorporation at the exocyclic amino groups. One suggested mechanism for ring incorporation of ^{15}N is illustrated in Scheme II. Initial attack by $^{15}NH_3$ would produce the singly labeled species **16**, and attack of a second molecule of $^{15}NH_3$ on C_4 followed by ring opening would produce an amidine such as **17**. This molecule is capable of recyclization so that an ^{15}N atom is incorporated into the N_3 position of the pyrimidine ring to give **18**. The exocyclic

Scheme II



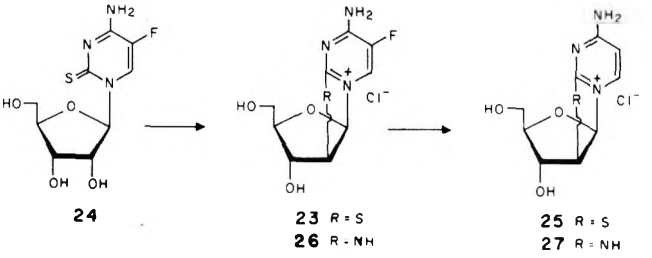
Scheme III



amino groups of 18 would contain either ^{14}N or ^{15}N atoms, depending upon the direction of ring closure and whether subsequent exchange reactions had taken place. This reaction can be considered as another nucleoside example of the Dimroth rearrangement. Subsequent degradation of 18 with sodium nitrite/hydrochloric acid would lead to the production of [^{15}N]-5-fluorouracil (19).

A second series of reactions was carried out by reaction of anhydro-ara-FC (1) and analogues with sodium hydrosulfide or hydrogen sulfide. It was anticipated at the outset that reaction of the sulfur nucleophile would take place at C_2 to yield 2-thio-ara-FC (20; Scheme III). Reaction of 1 with 1.4 equiv of sodium hydrosulfide did not lead to the expected 2-thioarabinoside, but instead yielded the defluorinated anhydro nucleoside 21 in a yield of 49%. Reaction of 1 with hydrogen sulfide was carried out in DMF as solvent in the presence of triethylamine. After 9 h at room temperature, a considerable amount of starting material was still present, but a small amount (5%) of defluorinated anhydro nucleoside 21 was again isolated; in addition, a new product was obtained. This latter material, which was formulated as the oxazolidinethione 22, was presumably produced by reaction of hydrogen sulfide at C_2 followed by degradation of the pyrimidine ring in preference to the 2,2′-anhydro linkage. The preparation of 22 from D-arabinose has previously been described by Ranganathan,[11] although no analytical data were given. Thus,

Scheme IV



the 2,2′-anhydro bond, which has previously been shown to be quite labile under alkaline conditions,[7] is remarkably stable toward sodium hydrosulfide or hydrogen sulfide. The inability of these sulfur nucleophiles to form 20 may be a reflection of the fact that although the SH^- ion is strongly nucleophilic, the sulfur atom forms the C=S bond with reluctance as compared with C=O.

The formation of the defluorinated anhydro nucleoside was not anticipated, even though there is some precedent for debromination of bromouracil derivatives under similar conditions. Szabo, Kalman, and Bardos, for example, have reported that reaction of 1-methyl-5-bromouracil with sodium hydrosulfide gave 1-methyluracil.[12] Deuterium exchange studies led these workers to propose a mechanism of addition, followed by displacement of the bromo substituent by hydrosulfide ion and subsequent elimination; such a mechanism would seem to be applicable to the defluorination reaction, although we have not studied the mechanistic aspects of this reaction. Other workers have described the debromination of 5-bromouracil with either cysteine[13] or sodium bisulfite,[14] and the enzyme thymidylate synthetase has also been reported to catalyze debromination of 5-bromo-2′-deoxyuridylate, although the corresponding 5-chloro and 5-fluoro nucleotides were not dehalogenated under the same conditions.[15] Defluorination has also been observed as a side reaction in the aminolysis of 5-fluoro-4-thiopyrimidine nucleosides.[16]

We have also studied this defluorination reaction using analogues of anhydro-ara-FC in which the oxygen of the 2,2′-anhydro bridge was replaced by sulfur or nitrogen. The sulfur analogue 23 (Scheme IV) was synthesized in a conventional manner[17] by reaction of acetoxyisobutyryl chloride with 2-thio-5-fluorocytidine (24). The latter compound was in turn prepared by reaction of the silyl derivative of 2-thio-5-fluorocytosine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose using the silyl procedure of Vorbrüggen and Strehlke.[18] Reaction of 23 with sodium hydrosulfide (2.6 equiv) for 3 h at room temperature did produce the defluorinated anhydro nucleoside 25, a compound which has been previously synthesized by Russell et al.[17]

The first paper in this series dealt with the synthesis of the nitrogen-bridged analogue 26. Treatment of a small sample of this compound with sodium hydrosulfide gave as the major product a compound with the same chromatographic properties as the defluorinated analogue 27;[19] insufficient material was available for a rigorous characterization. The facility with which these anhydro nucleosides undergo defluorination prompted an examination of a reaction of 5-fluorocytidine with sodium hydrosulfide; even after a prolonged reaction time (3 days at room temperature), no evidence for defluorination could be detected. The lability of the 5-fluoro substituent therefore seems to be particularly enhanced in the anhydro series.

Experimental Section

General. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. NMR spectra were obtained using either a Varian XL-100 or HA-100 spectrometer and IR spectra with either a Perkin-Elmer 621 or a Beckman IR-9 instrument. UV spectra were obtained using a Cary Model 14 recording spectrometer.

1-β-D-Arabinofuranosyl-2,4-diamino-5-fluoropyrimidinium Chloride (2). A suspension of anhydro-ara-FC (**1**; 20 g) in methanolic ammonia (25 mL, saturated) was stirred at room temperature for 20 min. During this time the starting material dissolved and a crystalline precipitate was formed. At this point 2-propanol (400 mL) was added and the suspension was stored at 0 °C for 1 h. The crystals were collected by filtration, washed with 2-propanol, and dried in vacuo to give **2**: 16.2 g (76%); mp 175–176 °C dec; UV (H_2O) λ_{max} 205–206 nm (ε 18 000), 235–237 (11 000), 274–276 (7450); NMR (D_2O) δ 4.6 (m, 4, C_3' H, C_4' H, CH_2), 5.13 (d, 1, C_2' H), 6.55 (q, 1, C_1' H), 8.85 (d, 1, CHCF). Anal. Calcd for $C_9H_{14}ClFN_4O_4$: C, 36.43; H, 4.76; N, 18.88; F, 6.40. Found: C, 36.70; H, 4.87; N, 19.24; F, 6.78.

The liquors were evaporated to ca. 100 mL, and on storage crystals of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline were deposited, 2.6 g (21%). Recrystallization from methanol gave pure material, mp 177–178 °C (lit.[6] mp 175–176 °C).

1-β-D-Arabinofuranosyl-4-amino-5-fluoro-2-methylaminopyrimidinium Picrate (3). A suspension of **1** (629 mg) in methanolic methylamine (4.5 M, 0.5 mL) was stirred at room temperature for 5 h. The residual solid was removed by filtration, and the filtrate was evaporated to dryness and treated with aqueous picric acid (30 mL, saturated). After storage at room temperature overnight, the crystals were collected and recrystallized from water (10 mL) to give **3**, 352 mg (31%), as the hemihydrate: mp 95–103 °C (indefinite); NMR (Me_2SO-d_6) δ 2.87 (d, 3, CH_3NH). Anal. Calcd for $C_{16}H_{18}FN_7O_{11}\cdot 0.5H_2O$: C, 37.51; H, 3.74; F, 3.71; N, 19.14. Found: C, 37.32; H, 3.66; F, 3.68; N, 18.91.

1-β-D-Arabinofuranosyl-5-fluoro-2,4-bis(methylamino)pyrimidinium Chloride (4). A suspension of anhydro-ara-FC (**1**; 3 g) in methanol (50 mL) containing methylamine (1 g) was stirred at room temperature for 15 min. The solution was evaporated to dryness and dried in vacuo for 2 h, and aqueous picric acid (saturated, 190 mL) was added. After 1 h at 0 °C, the crystals were collected by filtration and the liquors were concentrated to ca. 40 mL and cooled to 0 °C. This procedure yielded a second batch of picrate (total 3.27 g, 59%). A sample was recrystallized from water: mp 78 °C (indefinite); UV (MeOH) λ_{max} 213 nm (ε 34 400), 284 (9400), 355 (14 900); NMR (Me_2SO-d_6) δ 2.89 (d, 3, CH_3NH), 2.97 (d, 3, CH_3NH), 5.91 (d, 1, C_1' H), 8.12 (m, 1, NH), 8.50 (d, 1, CHCF), 8.59 (s, 2, picrate), 9.18 (m, 1, NH). Anal. Calcd for $C_{17}H_{20}FN_7O_{11}$: C, 39.46; H, 3.90; F, 3.67; N, 18.95. Found: C, 39.09; H, 3.87; F, 3.43; N, 18.55.

A sample of the picrate (1.07 g) was dissolved in methanol/water (110 mL, 1:10) and stirred with an excess of AG 1-X8 resin (chloride form, Bio-Rad Labs) until a colorless solution was obtained. The resin was filtered off, and the filtrate was evaporated to dryness and dried by repeated coevaporation of ethanol over the residue. The dried material was dissolved in ethanol (4 mL) and added dropwise with stirring to ether (50 mL). The precipitate was collected by centrifugation, washed with ether twice, and dried in vacuo to give the hydrochloride salt of **4** as an amorphous powder: 257 mg; mp 120 °C (indefinite); UV (H_2O) λ_{max} 213 nm (ε 15 380), 247–248 (14 620), 280 sh (7630); NMR (Me_2SO-d_6) δ 2.91 (d, 3, CH_3NH), 3.00 (d, 3, CH_3NH), 8.55 (m, 1, NH), 9.29 (m, 1, NH). Anal. Calcd for $C_{11}H_{18}ClFN_4O_4\cdot 1.5H_2O$: C, 37.55; H, 6.01; N, 15.92. Found: C, 37.90; H, 6.27; N, 16.26.

The combined liquors from the picrate of **4** were concentrated to a small volume, and a third batch of crystals was deposited. Recrystallization from methanol/water yielded the picrate of **5**, 487 mg (12%). Treatment with AG 1-X8 resin (chloride form) in the usual manner and recrystallization from ethanol/ether gave **5** as the hydrochloride: 150 mg (8%); mp 214–215 °C; UV (0.1 N HCl) λ_{max} 210 sh nm (ε 15 720), 222–223 (18 320), 279–281 (3400); NMR (Me_2SO-d_6) δ 2.88 (d, 3, CH_3NH), 8.09 (d, 1, CHCF), 8.23 (m, 1, NH), 8.55 (brd s, 2, NH_2). Anal. Calcd for $C_5H_8ClFN_4$: C, 33.62; H, 4.51; Cl, 19.85; N, 31.37. Found: C, 33.79; H, 4.62; Cl, 19.85; N, 31.05.

4-Amino-5-fluoro-2-methylaminopyrimidinium Chloride (5) from 4-Amino-2-chloro-5-fluoropyrimidine (7). 4-Amino-2-chloro-5-fluoropyrimidine (**7**; 1 g)[8] was treated with methylamine (40 mL) in a stainless steel bomb at room temperature for 75 h. The product was evaporated to dryness, dissolved in methanol, and impregnated onto silica gel (15 g, Merck). This material was applied to the top of a silica column (250 g) which had been packed in chloroform/ethyl acetate (1:1), and the column was eluted with the same solvent (1.5 L) followed by ethyl acetate (2 L). Fractions 125–170 (20-mL size) were evaporated to dryness, dissolved in ethanol (50 mL), and treated with aqueous hydrochloric acid (1 N, 9.2 mL). This solution was evaporated to dryness, coevaporated with ethanol, and recrystallized from the same solvent to give **5**, 256 mg (21%). This material proved to be identical with the sample of **5** previously isolated.

5-Fluoro-2,4-bis(methylamino)pyrimidinium Chloride (8). (a) Via 2,4-Dichloro-5-fluoropyrimidine (6). Liquid methylamine (20 mL) was added to 2,4-dichloro-5-fluoropyrimidine[8] (**6**; 1 g) in a stainless steel bomb which had been cooled in a dry ice–acetone bath. The vessel was sealed and stored at room temperature for 5 days. After this time, the bomb was cooled, opened, and allowed to warm to room temperature to allow methylamine to evaporate. The residue was dissolved in methanol (100 mL) and filtered through Celite, and the filtrate was evaporated to dryness and pumped in vacuo. The residue was dissolved in water (120 mL) and filtered through Celite, and the filtrate was treated with saturated aqueous picric acid (200 mL). Crystals were deposited on storage overnight, and recrystallization gave pure **8** as the picrate: 0.9 g (39%); mp 240–242.5 °C dec; UV (CH_3OH) λ_{max} 209 nm (ε 40 200), 300 (7200), 354 (15 100); NMR (Me_2SO-d_6) δ 9.00 (m, 1, NH), 8.60 (s, 2, picrate), 7.92 (d, 1, CHCF), 7.90 (m, 1, NH), 2.96 (d, 3, CH_3NH). 2.88 (d, 3, CH_3NH). Anal. Calcd for $C_{12}H_{12}FN_7O_7$: C, 37.41; H, 3.14; F, 4.93. Found: C, 37.32; H, 3.34; F, 4.80.

A sample (0.4 g) in methanol/water (500 mL, 1:1) was warmed to dissolve it and was stirred with an excess of AG 1-X8 resin (chloride form). The mixture was applied to the top of a column (20 mL) of the same resin, which was eluted with methanol/water (1:1). The eluate (560 mL) was collected, evaporated to dryness, and crystallized from methanol/ethyl acetate to give **8** as the hydrochloride: 157 mg (79% from the hydrochloride); mp 243–244 °C; UV (H_2O) λ_{max} 215 nm (ε 20 220), 280 sh (5200); NMR (Me_2SO-d_6) δ 9.10 (m, 1, NH), 8.31 (m, 1, NH), 8.01 (d, 1, CHCF), 2.93 and 2.97 (overlapping d, 6, $2CH_3NH$). Anal. Calcd for $C_6H_{10}ClFN_4$: C, 37.41; H, 5.23; F, 9.86; N, 29.09. Found: C, 37.40; H, 5.22; F, 9.69; N, 29.20.

(b) Via Hydrolysis of 4. A solution of the picrate of **4** (0.5 g) in aqueous hydrochloric acid (1 N, 20 mL) was heated at 100 °C for 1 h and then stored at 0 °C for 2 h. The crystals were collected and recrystallized from water to give the picrate of **8**, 90 mg (24%).

2-Amino-5-fluoro-1-methyl-4-methyliminopyrimidinium Chloride (9). (a) Reaction of 1 with Methylamine. A suspension of **1** (15 g) in methanol (80 mL) containing methylamine (15 g) was stirred at room temperature until the solid dissolved. The solution was then stored at room temperature for 36 h, evaporated to dryness, and evacuated for 1 h. The residue was treated with aqueous picric acid (960 mL) with stirring for 1 h, and the crystals were filtered off and recrystallized from water to give **9** as the picrate: 10.4 g (50%); mp 224–226 °C; UV (CH_3OH) λ_{max} 207 nm (ε 46 500), 353 (15 700); NMR (Me_2SO-d_6) δ 8.88 (m, 1, NH), 8.54 (s, 1, picrate), 8.17 (d, 1, CHCF), 8.02 (brd s, 2, NH_2), 3.47 (s, 3, CH_3N), 2.93 (d, 3, CH_3NH). Anal. Calcd for $C_{12}H_{12}FN_7O_7$: C, 37.41; H, 3.14; F, 4.93; N, 25.45. Found: C, 37.64; H, 2.87; F, 4.81; N, 25.75.

The picrate was dissolved in methanol/water (1 L, 4:1), and the solution was treated with an excess of AG 1-X8 resin (chloride form) with stirring for 1 h. The resin was removed by filtration, and the filtrate was treated with carbon and filtered through Celite. The filtrate was evaporated to a solid which was dried and recrystallized from ethanol/ethyl acetate to give **9** as the chloride: 4.5 g (44%); mp 295 °C dec; UV (0.1 N HCl) λ_{max} 239–240 nm (ε 11 550), 275–276 (8400); NMR (Me_2SO-d_6) δ 2.93 (s, 3, CH_3), 3.58 (s, 3, CH_3), 8.42 (d, 1, CHCF), 8.5 (m, 3, 3NH). Anal. Calcd for $C_6H_{10}ClFN_4$: C, 37.41; H, 5.23; N, 29.09; Cl, 18.40; F, 9.86. Found: C, 37.38; H, 5.35; N, 28.93; Cl, 18.50; F, 9.87.

(b) Reaction of 4 with Methylamine. The picrate of **4** (2 g) was converted into the chloride by passage through an AG 1-X8 column (chloride form), and the eluate was evaporated to dryness. The residue was coevaporated with ethanol twice, pumped in vacuo overnight, and then treated with a solution of methylamine in methanol (0.11 g/mL, 15 mL) for 66 h at room temperature. This solution was evaporated to dryness, dissolved in 1-butanol/acetic acid/water (12:3:5, 10 mL), and applied to a silica column (3.5 × 60 cm) which was packed and eluted with the same solvent mixture. Fractions of 20 mL were collected and tubes 35–43 were combined and evaporated to dryness. Treatment of the residue with saturated aqueous picric acid (10.8 mL) gave a crystalline precipitate. After storage overnight, the crystals were collected and dried in vacuo to give **8**, 37 mg (2.5%).

Fractions 46–70 were combined and evaporated, and the residue was dissolved in a minimum amount of water and treated with aqueous picric acid (54 mL). The crystals were collected and dried in vacuo to give **9** as the picrate, 0.81 g (54%).

Crystals of the hydrobromide of **9** are monoclinic, space group $P2_1/a$, with a = 7.137 (1) Å, b = 20.590 (4) Å, c = 6.254 (1) Å, β = 95.39 (1)°, and d_{calcd} = 1.720 g cm^{-3} for Z = 4. X-ray crystallographic intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans). The approximate size of the crystal used for data collection was 0.07 × 0.10 × 0.4 mm; the data

were corrected for absorption. There were 1237 accessible reflections with $\theta < 57°$, of which 1094 were considered to be observed. The structure was solved by a multiple solution procedure and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The final discrepancy indices are $R = 0.055$ and $R_w = 0.065$ for the 1094 observed reflections.[20]

The relatively short C_2–N_3 and C_4–N_4 bond distances (1.317 and 1.320 Å, respectively) as compared with the C_2–N_2 and N_3–C_4 distances (1.349 and 1.342 Å) imply the existence of a 2-amino-4-methylimino tautomer rather than a 2-imino-4-methylamino structure.

2-Amino-5-fluoro-4-methylaminopyrimidinium Chloride (12). (a) From 2. Compound **2** (1 g) was stirred with methylamine in methanol (0.72 M, 30 mL) for 1 h at room temperature and evaporated to dryness. The residue was treated with aqueous picric acid (100 mL) at 100 °C for 6 h, and on cooling crystals were deposited. These crystals were collected and recrystallized from methanol/water to give the picrate of **12**, 332 mg (27%). A second crop of 557 mg (45%) was obtained by evaporation of the liquors. A sample was converted into the chloride form by stirring a methanolic solution of the picrate with AG 1-X8 resin (chloride form). Recrystallization from ethanol/ether gave pure **12** as the hydrochloride: mp 209–210 °C; UV (0.1 N HCl) λ_{max} 206 nm (ϵ 20 500), 235 sh (12 650), 267 (7500); NMR (Me_2SO-d_6) δ 2.92 (d, 3, CH_3NH), 7.90 (s, 2, NH_2), 8.06 (d, 1, CHCF), 8.99 (m, 1, NH). Anal. Calcd for $C_5H_8ClFN_4$: C, 33.62; H, 4.51; Cl, 19.85; N, 31.37. Found: C, 33.84; H, 4.64; Cl, 20.14; N, 31.02.

(b) From 6. A 0 °C solution of **6** (0.95 g) in methanol (10 mL) was treated with methylamine in methanol (3.55 N, 9.6 mL), stored overnight at 5 °C, and evaporated to a white solid which was triturated with water (10 mL). The solid was collected by filtration and dried in vacuo to give crude **13**, 629 mg (68%). For analytical purposes, a sample was recrystallized from water: mp 131.5–132.5 °C; UV (CH_3OH) λ_{max} 240 nm (ϵ 10 800), 280 (5350); NMR (Me_2SO-d_6) δ 2.84 (d, 3, CH_3NH), 8.02 (d, 1, CHCF), 8.08 (brd s, 1, NH). Anal. Calcd for $C_5H_5ClFN_3$: C, 37.17; H, 3.12; Cl, 21.95; N, 26.01. Found: C, 37.05; H, 3.25; Cl, 22.06; N, 26.01.

A sample (249 mg) of crude **13** in liquid ammonia (6 mL) was stored in a steel bomb for 64 h at 100 °C. The bomb was cooled in a dry ice–acetone bath, and methanol (30 mL) was added. The solution was filtered through Celite to remove some insoluble brown material, and the filtrate was evaporated to dryness and dissolved in chloroform/methanol (10:1, 10 mL). This solution was applied to a silica column (100 g) and the column eluted with the same solvent. Fractions of 20 mL were collected, and tubes 42–58 were combined and evaporated to give crude **12** as the free base, 0.1 g (46%). Recrystallization from water gave analytically pure material, mp 158–160 °C. A sample of the picrate was prepared by the usual procedure and found to be identical with the sample obtained from the reaction of **1** with methylamine (melting point, IR, and NMR).

Prolonged Reaction of 2 with Methylamine. A suspension of **2** (3 g) in methanol (25 mL) containing methylamine (2.75 g) was stirred until completely dissolved, and the solution was stored at room temperature for 45 h and then evaporated to dryness. The residual gum was dissolved in methanol (20 mL) and applied to a silica column (700 g) which had been packed in the same solvent. The column was eluted with methanol (2 L) followed by methanol/acetic acid (100:1, 2 L), and fractions of 20 mL were collected. Fractions 158–300 were combined, evaporated to dryness, dissolved in water (10 mL), and treated with saturated aqueous picric acid (116 mL). After storage at 0 °C for 2 h, the yellow precipitate was collected and recrystallized from methanol/water to give the picrate of **9**, 1.2 g (31%).

Fractions 130–150 were combined and evaporated to dryness (1.29 g). A portion (0.89 g) of this material was triturated with ethanol (10 mL), and after storage at 5 °C overnight, a white solid was removed by filtration and discarded. The filtrate was evaporated to a brown gum (450 mg), which was dissolved in a minimum amount of water and treated with picric acid (22 mL). After storage at 5 °C overnight, crystals (33 mg) were deposited. Recrystallization from water gave pure **4**, 21 mg.

1-β-D-Arabinofuranosyl-2,4-bis(ethylamino)-5-fluoropyrimidinium Chloride (14). A suspension of **1** (5 g) in methanol (40 mL) containing ethylamine (3 g) was stirred for 15 min at room temperature. The solution was evaporated to dryness, pumped in vacuo for 1 h, and treated with aqueous picric acid (325 mL). After 1 h at 0 °C, the solid was collected, washed briefly with ice water, and dissolved in methanol/water (1:1, 100 mL). The solution was stirred with an excess of AG 1-X8 (chloride) resin until colorless, and the resin was removed by filtration. The filtrate was evaporated to dryness and triturated with ethyl acetate (50 mL) and methanol (0.1 mL). Crystallization commenced on standing. The solid was recrystallized from methanol (5 mL)/ethyl acetate (50 mL) to give **14**, 2.9 g (46%): mp 147–148 °C; UV (H_2O) λ_{max} 217 nm (ϵ 17 500), 251 (16 200), 285 sh (8300); NMR (Me_2SO-d_6) δ 1.28 (t, 6, $2CH_3CH_2$), 3.55 (m, 4, $2CH_3CH_2$). Anal. Calcd for $C_{13}H_{22}ClFN_4O_4$: C, 44.26; H, 6.29; Cl^-, 10.05; N, 15.88. Found: C, 44.28; H, 6.36; Cl^-, 10.05; N, 15.96.

1-β-D-Arabinofuranosyl-5-fluoro-2,4-bis(*n*-propylamino)-pyrimidinium Chloride (15). Anhydro-ara-FC (**1**; 5 g) was treated with *n*-propylamine (7.35 mL) in methanol (50 mL) for 15 min at room temperature and isolated as described for **14**: 4.0 g (59%); mp 147–149 °C, then resolidified and mp 181 °C dec; UV (0.1 N HCl) λ_{max} 219–220 nm (ϵ 17 500), 253 (16 500), 285 sh (8600); NMR (Me_2SO-d_6) δ 0.90 (t, 6, $2CH_3$), 1.63 (m, 4, $2CH_3CH_2$), 3.35 (m, 4, $2CH_2N$). Anal. Calcd for $C_{15}H_{26}ClFN_4O_4$: C, 47.31; H, 6.88; Cl^-, 9.31; N, 14.71. Found: C, 47.20; H, 6.97; Cl^-, 9.51; N, 14.58.

Reaction of 1 with $^{15}NH_3$. A suspension of **1** (207 mg, 0.74 mmol) in methanol (1 mL) containing ammonia (99% ^{15}N-enriched, 4.46 mmol) was stirred at room temperature for 3 h and then treated with 2-propanol (3 mL). After storage at 0 °C overnight, the solid was collected, washed with 2-propanol, and dried in vacuo. Recrystallization from methanol/ethyl acetate gave the diamino nucleoside (132 mg, 60%), mp 172–173 °C. Mass spectrometric examination of the peaks assigned to the 2,4-diamino-5-fluoropyrimidinium ion (*m/e* 128, 129, 130, and 131), as compared with those obtained from an unenriched sample, gave the results in Table I.

Table I

m/e	no. of ^{15}N atoms	% incorporation
128	0	6
129	1	71
130	2	22
131	3	1

Degradation of ^{15}N-Enriched Diamino Nucleoside to 5-Fluorouracil. A sample of ^{15}N-enriched diamino nucleoside (45 mg) in aqueous hydrochloric acid (1 N, 2 mL) was heated with sodium nitrite (400 mg) at 60 °C for 24 h and then evaporated to dryness. The residue was extracted with methanol, and the extract was applied to a silica gel plate (3 mm thickness) which was developed in tetrahydrofuran/methanol (10:1). The band corresponding to 5-fluorouracil was cut out and extracted with methanol, and the extract was evaporated to dryness and redissolved in methanol. Solids were removed by centrifugation, and the supernatant was evaporated to dryness for examination by mass spectrometry. The relative intensities of the peaks at *m/e* 130 and 131 in the synthetic sample (corresponding to the molecular ion peaks for [^{14}N]- and [^{15}N]fluorouracil, respectively) were compared with those obtained from authentic material. By this method it was determined (after correction for the natural abundance of ^{15}N) that (*m/e* 130)/(*m/e* 131) = 94/6; i.e., 6% of the synthetic sample of 5-fluorouracil contained one ^{15}N atom per molecule.

Reaction of 1 with Sodium Hydrosulfide. A suspension of **1** (580 mg) and sodium hydrosulfide (255 mg) in methanol (50 mL) was stirred at room temperature for 3 h and concentrated to 10 mL. Silica gel (13 g) was added, and the slurry was applied to the top of a silica gel column (125 g) which had been packed in methanol/acetic acid (100:1). After a preliminary wash with methanol (150 mL), the column was eluted with methanol/acetic acid (100:1) and fractions of 20 mL were collected. Tubes 24–60 were combined, evaporated to dryness, and dissolved in water. Some insoluble material was removed by filtration, and the filtrate was evaporated to dryness, dried by evaporation of ethanol over the residue, and crystallized from methanol to give the acetate of **21** (278 mg, 49%), mp 179–180 °C dec (lit.[5] mp 190–192 °C). A sample was converted into the hydrochloride salt by passage through an AG 1-X8 (chloride) column and recrystallized from methanol: mp 249 °C dec (lit.[17] 266–267 °C); UV (H_2O) λ_{max} 231 nm (ϵ 9350), 262 (10 380); NMR (Me_2SO-d_6) δ 6.70 (d, 1, C_5 H), 8.28 (d, 1, C_6 H), 9.21 (s, 1, NH), 9.69 (s, 1, NH). Anal. Calcd for $C_9H_{12}ClN_3O_4$: C, 41.31; H, 4.62; N, 16.06. Found: C, 41.38; H, 4.70; N, 16.02.

Reaction of 1 with Hydrogen Sulfide. Hydrogen sulfide was bubbled into a suspension of **1** (2.8 g) in DMF (100 mL, dry) and triethylamine (3 mL). After 9 h, a stream of nitrogen was bubbled into the solution for 30 min to remove hydrogen sulfide, and the solution was filtered to remove unreacted starting material (1.35 g). Silica gel (25 g) was added to the filtrate, and the slurry was evaporated to dryness and applied to the top of a silica gel column (250 g) which had

been packed in chloroform. The column was initially developed with chloroform, and fractions were evaporated and crystallized from ethanol to give 238 mg (12%) of the oxazolidinethione **22**: mp 132–133.5 °C; UV (CH_3OH) λ_{max} 243 nm (ϵ 18 950), 285 sh (1010); NMR (Me_2SO-d_6) δ 3.27 (m, 2, CH_2), 3.87 (m, 1, CH), 4.23 (m, 1, CH), 4.88 (t, 1, CH_2OH), 5.05 (d, 1, OH), 5.66 (d, 1, OH), 5.79 (d, 1, C_1' H), 10.76 (s, 1, NH). Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33; S, 16.77. Found: C, 37.55; H, 4.69; N, 7.31; S, 16.85.

The column was subsequently eluted with chloroform/methanol (10:1, 5 L) to remove a number of minor impurities which were discarded. Elution with methanol/acetic acid (1 L, 50:1) gave a fraction which was evaporated to dryness and converted into the chloride form in the usual way. Recrystallization from methanol yielded **21**, 125 mg (5%).

5-Fluoro-2-thiocytidine (24). A solution of 4-amino-2-chloro-5-fluoropyrimidine[8] (25.2 g) and sodium hydrosulfide (51 g) in ethylene glycol (75 mL) was heated with stirring to 103 °C. At this point, heating was discontinued since the solution began to foam. After 15 min, the solution was heated to 140 °C and maintained at that temperature for 15 min. The product was cooled, treated with water (250 mL), adjusted to pH 6.5 with aqueous hydrochloric acid (6 N, 50 mL), and cooled to 0 °C for 1 h. The precipitate was filtered, washed with water (3 × 60 mL), and dried in vacuo. Recrystallization from water (2.6 L) yielded 5-fluoro-2-thiocytosine (14.8 g, 60%), mp 265 °C (indefinite) dec. Anal. Calcd for $C_4H_4FN_3S$: C, 33.10; H, 2.78; F, 13.10; N, 28.95; S, 22.09. Found: C, 32.99; H, 2.77; F, 13.00; N, 28.73; S, 22.37.

This material (4.5 g) was suspended in dry dioxane (120 mL) and treated with 1,1,1,3,3,3-hexamethyldisilazane (22.5 mL) and chlorotrimethylsilane (3 mL) under reflux for 5.5 h. The solid was removed by filtration, and the filtrate was concentrated to a yellow paste. This material was dissolved in 1,2-dichloroethane (100 mL, distilled over P_2O_5) and treated with a solution of tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose (14 g) in dry acetonitrile (125 mL). This solution was treated with freshly distilled stannic chloride (3 mL) in dichloroethane (25 mL) for 3 h at room temperature. The reaction mixture was cooled to 0 °C and treated with aqueous sodium bicarbonate (1 M, 450 mL) with vigorous stirring at room temperature for 18 h. The emulsion was filtered through Celite, and the organic layer was washed with water (2 × 400 mL), dried over anhydrous sodium sulfate, and concentrated to a foam. This material was dissolved in chloroform (50 mL), applied to a silica gel column (1.6 kg), and eluted with chloroform/acetone (85:15). Fractions of 20 mL were collected, and tubes 400–660 were combined and evaporated to yield 8.2 g (45%) of 2′,3′,5′-tri-*O*-benzoyl-5-fluoro-2-thiocytidine as a white solid. A sample was crystallized with difficulty from ethanol at 0 °C: mp 165–168 °C dec; NMR (Me_2SO-d_6) δ 7.4–8.0 (m, 15, $3C_6H_5$); UV (CH_3OH) λ_{max} 232 nm (ϵ 46 000), 262 (26 200), 315 sh (3000). Anal. Calcd for $C_{30}H_{24}FN_3O_7S$: C, 61.11; H, 4.10; F, 3.22; N, 7.13; S, 5.44. Found: C, 61.00; H, 4.21; F, 3.22; N, 7.06; S, 5.51.

The crude tribenzoyl derivative (7.05 g) was treated with saturated methanolic ammonia (200 mL) for 18 h at room temperature. After evaporation to dryness, the residue was dissolved in water (200 mL) and extracted with ether (3 × 200 mL). The aqueous layer was evaporated to dryness, and the residue was coevaporated with ethanol. The residue was dissolved in hot methanol (15 mL), treated with activated carbon, and filtered through Celite. On cooling to 0 °C, crystalline 24 (3.02 g, 91%) was deposited: mp 127 °C; UV (H_2O) λ_{max} 217 nm (ϵ 5900), 260 (21 550); NMR (Me_2SO-d_6) δ 3.17 (d, 3, CH_3OH), 3.70 (m, 2, CH_2), 3.95 (m, 4, C_2', C_3', and C_4' H, OH), 4.88 (d, 1, OH) 5.33 (d, 2, OH), 6.44 (brd s, 1, C_1' H), 7.8 (brd s, 1, NH), 8.2 (brd s, 1, NH), 8.72 (d, 1, CHCF). Anal. Calcd for $C_9H_{12}FN_3O_4S$·CH_3OH: C, 38.83; H, 5.21; N, 13.58; S, 10.36. Found: C, 38.38; H, 5.05; N, 13.36; S, 10.55.

2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluoro-2-thiocytosine Hydrochloride (23). A suspension of 24 (2.0 g) in dry acetonitrile (24 mL) was treated with acetoxyisobutyryl chloride (4 mL) for 3.5 h. The solution was added dropwise to anhydrous ether (400 mL), and the precipitate was collected, washed with ether, and treated with methanolic hydrogen chloride (0.15 N, 52 mL) for 72 h. The solution was evaporated, and on trituration with boiling isopropyl alcohol (30 mL) **23** was obtained, 1.4 g (72%). An analytically pure sample was obtained by crystallization from methanol/isopropyl alcohol: mp 211–212 °C; UV (CH_3OH) λ_{max} 247 nm (ϵ 23 500), 285 sh (5100); NMR (Me_2SO-d_6) δ 3.44 (d, 2, CH_2), 4.15 (q, 1, C_4' H), 4.41 (t, 1, C_3' H), 4.55 (q, 1, C_2' H), 6.64 (d, 1, C_1' H), 8.78 (d, 1, CHCF), 9.59 (s, 1, NH), 9.84 (s, 1, NH). Anal. Calcd for $C_9H_{11}ClFN_3O_3S$: C, 36.55; H, 3.75; F, 6.42; N, 14.21; S, 10.84. Found: C, 36.63; H, 3.79; F, 6.25; N, 13.96; S, 10.85.

Reaction of 23 with Sodium Hydrosulfide. A solution of **23** (1 g) in methanol (100 mL, dry) was treated with sodium hydrosulfide (0.81 g) with stirring at room temperature for 3 h. A small amount of insoluble material was removed by filtration, and the filtrate was applied directly to a silica gel column (silica gel 60, size C; E. Merck, Darmstadt). The column was eluted with methanol (600 mL) followed by methanol/acetic acid (50:1, 1 L), and fractions of 20 mL were collected. Fractions 77–100 were combined, evaporated to dryness, dissolved in water (10 mL), and applied to an AG 50-X8 column (1 × 10 cm, chloride form) which was washed with water. The fractions containing UV-absorbing material were pooled and evaporated to dryness, and the residue was triturated with hot 2-propanol (13 mL) to yield **25** as an amorphous solid, 198 mg (21%). An analytically pure sample was obtained by recrystallization from methanol/chloroform, mp 195–197 °C (lit.[17] mp 201–202.5 °C).

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Registry No.—**1**, 40505-45-1; **2**, 67316-25-0; **3**, 67316-27-2; **4** picrate, 67316-29-4; **4** HCl, 67316-30-7; **5** picrate, 67316-32-9; **5** HCl, 67316-33-0; **6**, 2927-71-1; **7**, 155-10-2; **8** picrate, 67316-35-2; **8** HCl, 67316-36-3; **9** picrate, 67316-38-5; **9** HCl, 67316-39-6; **9** HBr, 67360-74-1; **12**, 67316-40-9; **12** picrate, 67316-41-0; **12** HCl, 67316-42-1; **13**, 67316-43-2; **14** HCl, 67316-44-3; **15** HCl, 67316-45-4; **21** HCl, 10212-25-6; **21** acetate, 10212-28-9; **22**, 56270-92-9; **23**, 67316-46-5; **24**, 67316-47-6; **25**, 51392-03-1; methylamine, 74-89-5; 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline, 67316-48-7; ethylamine, 75-04-7; propylamine, 107-10-8; 5-fluoro-2-thiocytosine, 67316-49-8; tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose, 6974-32-9; 2′,3′,5′-tri-*O*-benzoyl-5-fluoro-2-thiocytidine, 67316-50-1.

References and Notes

(1) For Part 1 in this series, see A. F. Cook, *J. Med. Chem.*, **20**, 344 (1977).
(2) J. J. Fox, E. A. Falco, I. Wempen, D. Pomeroy, M. D. Dowling, and J. H. Burchenal, *Cancer Res.*, **32**, 2269 (1972).
(3) J. H. Burchenal, V. E. Currie, M. D. Dowling, J. J. Fox, and I. H. Krakoff, *Ann. N.Y. Acad. Sci.*, **255**, 202 (1975).
(4) This reaction was first performed by Dr. M. Hoffer of these laboratories.
(5) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967).
(6) D. H. Shannahoff and R. A. Sanchez, *J. Org. Chem.*, **38**, 593 (1973).
(7) J. J. Fox and B. A. Otter, *Ann. N.Y. Acad. Sci.*, **255**, 59 (1975).
(8) R. Duschinsky, U.S. Patent 3 185 690, 1965.
(9) D. J. Brown, *Mech. Mol. Migr.*, **1**, 209 (1968).
(10) Special thanks are due to Dr. Benz of these laboratories for carrying out mass spectrometric measurements.
(11) R. Ranganathan, *Tetrahedron Lett.*, 1185 (1975).
(12) L. Szabo, T. I. Kalman, and T. J. Bardos, *J. Org. Chem.*, **35**, 1434 (1970).
(13) F. A. Sedor and E. G. Sander, *Biochem. Biophys. Res. Commun.*, **50**, 328 (1973).
(14) E. G. Sander and C. A. Deyrup, *Arch. Biochem. Biophys.*, **150**, 600 (1972).
(15) Y. Wataya and D. V. Santi, *Biochem. Biophys. Res. Commun.*, **67**, 818 (1975).
(16) I. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 4755 (1961).
(17) A. F. Russell, M. Prystasz, E. K. Hamamura, J. P. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 2182 (1974).
(18) H. Vorbrüggen and P. Strehlke, *Chem. Ber.*, **106**, 3039 (1973).
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Reactions of Phosphorus Compounds. 39. Synthesis and Reactions of [2-(Aziridin-1-yl)alkenyl]triphenylphosphonium Bromides

Mark A. Calcagno[1] and Edward E. Schweizer*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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Aziridines (1) were allowed to react with (2-propynyl)triphenylphosphonium bromide (2) to yield (2-aziridinylallyl)-triphenylphosphonium bromide (3) at low temperature and (2-aziridinyl-1-propenyl)triphenylphosphonium bromide (4) directly, or on heating from 3. (Phenylethynyl)triphenylphosphonium bromide (5a) yields (2-phenyl-2-aziridinylvinyl)triphenylphosphonium bromide (6). The salts from aziridine and 2 or 5a yield (2-methyl- (14a) and (2-phenyl-2-pyrrolin-3-yl)triphenylphosphonium bromide (14b), respectively, on heating in acetonitrile. Treatment of several of the salts, 4a and 4b, with aniline at 70 °C yields the alkylated anilines 13a and 13b, respectively. 2-Vinylaziridines (15) and 2 yield substituted [(2*H*-1,3,4,7-tetrahydroazepin-2-ylidene)methyl]triphenylphosphonium bromides (16), while 15 and 5a or (1-propyn-1-yl)triphenylphosphonium bromide (5b) give (1*H*-2,5-dihydroazepin-6-yl)triphenylphosphonium bromides (17) via hetero-Cope rearrangements. Compounds 14a and 17a are N-alkylated, whereas 16b is alkylated α to the triphenylphosphonium moiety. Compounds 14a and 16a undergo the Wittig reaction with aldehydes in the normal manner. Proton and ^{13}C NMR spectra are reported for most of the compounds.

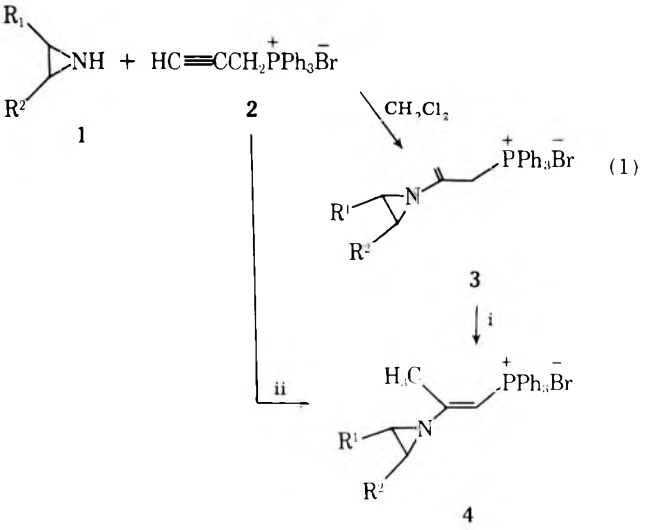
Recent reviews have reflected current interest in the synthesis and chemistry of heterocycles bearing phosphorus-containing substituents.[2,3] Preceding work in this laboratory has dealt with the synthesis of such heterocycles from unsaturated organophosphonium salts.[4a-e] These syntheses have employed both cycloaddition and intramolecular Wittig reaction routes to form the heterocycle. This paper describes our current efforts to prepare phosphorus-substituted heterocycles via the rearrangements of the activated aziridine synthon.

Results and Discussion

When aziridines 1 were allowed to react with (2-propynyl)-triphenylphosphonium bromide (2) in methylene chloride (eq 1) at the temperature given in Table I, the corresponding adducts 3 were usually produced (Scheme I, Table I). From the low temperature addition of 1c to 2, however, only the "conjugated" adduct 4c was isolated. The "conjugated" adducts 4a and 4b were also prepared either via heating the isolated intermediate 3 in chloroform or acetonitrile [eq 1 (i)] or directly by heating 1 and 2 in methylene chloride [eq 1 (ii)] (without isolation of intermediate 3). Similarly, the *N*-vinylaziridine 6 was obtained from the reaction of 1a and (phenylethynyl)triphenylphosphonium bromide (5a) (eq 2, Scheme I).

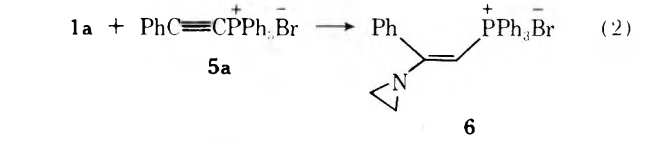
These products were characterized by their field desorption (FDMS) and chemical ionization mass spectra (CIMS), IR, ^1H NMR, and ^{13}C NMR spectra. The IR spectra of compounds 3 showed a weak absorption at ~1630 cm^{-1} corresponding to the terminal double bond, while compounds 4 and 6 showed a strong absorption at ~1560 cm^{-1}, in good agreement with the behavior of double bonds of other β-aminovinylphosphonium salts.[4f,g] The NMR spectra of 3 (with the

Scheme I



(1)

a, $R^1 = R^2 = H$; b, $R^1 = R^2 = (CH_2)_4$; c, $R^1 = Ph$, $R^2 = H$; d, $R^1 = PhCO$, $R^2 = p\text{-}O_2NC_6H_4$



(2)

exception of 3d) could not be obtained at normal probe temperatures (~30–40 °C). Attempts to do so provided only a spectrum of 4. However, ^1H and ^{13}C NMR spectra of 3a were obtained at −10 °C. The ^{13}C NMR spectra are given in Table II for compounds 3a, 4a,[4i] and 4b. The ring protons of adducts

Table I. [2-(Aziridin-1-yl)-2-propenyl]triphenylphosphonium Bromides (3) and [2-(Aziridin-1-yl)-1-propenyl]triphenylphosphonium Bromides (4)

		Equation 1			Equation 1 (i)				Equation 1 (ii)	
	R^1, R^2	3, mp (°C)	% yield	T, °C time, h	4, mp (°C)	% yield	Solvent	T, °C/ time, h	% yield	T, °C/ time, h
a	H, H	132–136	85	0–10/0.5	122–127	84	$CHCl_3$	40/8 × 10^{-4}	81	0[a] → 40/0.5
b	$(CH_2)_4$	110–117	71	0–10/0.5	97–117		CH_3CN	81/16	84	0[a] → 25/0.5
c	Ph, H				153–160				92	0[a] → 5/0.5
d	PhC(O), $p\text{-}O_2NC_6H_4$	124–136	53	25/1.33						

[a] Reactants were mixed at 0 °C over a period of 0.5 h, and then the mixture was warmed briefly to the second temperature for the time given.

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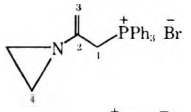
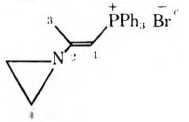
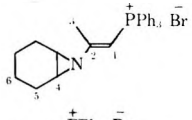
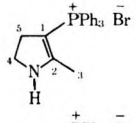
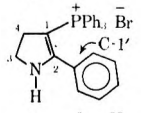
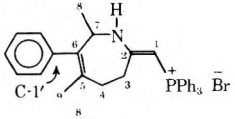
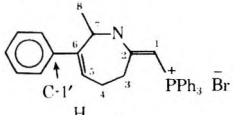
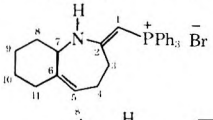
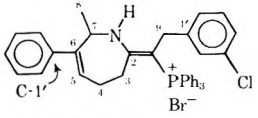
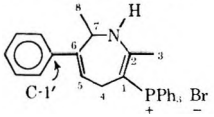
Table II. ^{13}C Chemical Shifts[a] and ^{13}C–^{31}P Coupling Constants[b] of β-Vinylphosphonium Salts

No.	Compd	1	2	3	4	5	6	7	8	9	10	11	C-1	*o*	*m*	*p*	C-1′	Other
3a		31.9 (48.2)	146.4 (11.0)	103.3 (10.4)	28.2								118.2 (87.3)	134.0 (9.8)	130.0 (12.8)	134.7 *		
4a		80.7 (106)	175.8 (10.4)	22.2 (3.7)	28.6								120.3 (91.6)	133.2 (9.8)	130.5 (12.2)	134.7 *		
4b		78.9 (105)	176.7 (9.8)	21.7 *	39.6	23.7	19.7						120.5 (91.6)	133.2 (9.8)	130.5 (12.2)	134.6 *		
14a		64.9 (125.7)	169.7 (22.0)	15.6 *	46.1 (11.0)	31.5 (9.8)							121.9 (91.6)	133.4 (11.0)	130.1 (13.4)	134.2 *		
14b		66.9 (124.5)	170.1 (19.5)	46.3 (9.8)	32.1 (9.8)								120.5 (91.5)	135.5 (9.8)	129.7 (12.2)	134.0 *	134.7 *	*o′*, *m′*, *p′***
16a		56.4 (114)	171 (~14–15)	30.8 (5)	31.6	**	137.8	53.4	22.9	21.3			124.6 (84)	133.0 (10.4)	129.8 (12.2)	133.6 *	142.3	*o′*, *m′*, *p′***
16b		57.6 (123.3)	171 (12.2)	31.2 *	25.7	**	143.2	52.5	22.3				124.0 (91.6)	132.8 (9.8)	129.8 (12.2)	133.7 *	142.4	*o′*, *m′*, *p′***
16c		56.9 (123.3)	172.1 (13.4)	33.2 (4.7)	35.6 (36.9)	121	140	57.5	24.9	27.2	24.9	36.9 (35.6)	124.5 (91.6)	133.0 (11.0)	129.8 (12.2)	133.7 *		
19		69.4 (111.1)	167.2 (19.5)	33.6 *	25.7	**	143.4	53.1	22.4	45.8 (47.6)			122.9 (89.1)	**	**	**	142.1	1′, 138.6 (11.0); *o′*, *m′*, *p′*; 2′, 3′, 4′**
17a		62.6 (109.9)	162.0 (19.5)	21.1 *	26.4 (7.3)		143.8	51.7	22.4				123.0 (89.1)	**	**	**	140.7	*o′*, *m′*, *p′***

17b		69.7 (108.6)	164.3 (22.0)	36.0 (9.7)		138.4	50.9	21.7	19.4		121.4 (89.1)	**	129.7 (12.2)	**	140.1	1′, 137 (~2–3); o′, m′, p′; 2′, 3′, 4′**
17c		69.2 (109.9)	165.0 (20.8)	29.4 (7.9)		145.0	51.9	21.5			121.8 (89.1)	**	**	**	140.1	1′, 137 (~2–3); o′, m′, p′; 2′, 3′, 4′**
20		61.8 (107.4)	161.5 (21)	26.5 *	27.3 (~4)		141.3	47.9	12.2	64.2	122.4 (89.1)	**	**	**	137.7	o′, m′, p′; 2′, 3′, 4′**

[a] The chemical shifts are in ppm referenced to internal Me_4Si. The numbering system for the β-aminopropenyl moiety is shown on the structure. The numbering system for the PPh_3 moiety is as follows:

All samples were run in $CDCl_3$. A double asterisk indicates that the peaks were obscured by the aromatic region. [b] The coupling constants are in parentheses and are in Hz. The digital resolution was ±0.6 Hz; an asterisk indicates that the coupling was less than resolution capable. [c] Reference 4i.

4 exhibited NMR signals with chemical shifts approximately 1 ppm downfield from those of **1**. The chemical shifts of the vinyl protons of these adducts likewise appear considerably downfield from those found for other β-(alkylamino)vinylphosphonium salts.[4f–i] In a similar manner, the chemical shift of the vinyl carbon next to phosphorus in **4** was deshielded relative to the same resonance in other β-(alkylamino)vinylphosphonium salts.[4h] This phenomenon (i.e., the relative deshielding of the vinyl protons and carbons adjacent to phosphorus in β-aziridinylvinylphosphonium salts) has been discussed in a recent publication.[4i]

While IR, ^1H NMR, and ^{13}C NMR spectra were of considerable utility in the characterization of these phosphonium salts, electron-impact mass spectra provided extremely little information, presumably due to the salts' low volatility. Field desorption mass spectroscopy (FD), which has previously been found useful for the molecular weight determination of phosphonium halides,[5] was therefore tried with a number of these salts. Although compounds **7**, **8**, and **10** gave essentially

7, X = $CH_2CH_2CH_2N$–

8, X = $CH_2CH_2CH_2CH_2CH_2N$–

9, X = $(CH_3)_2N$–

10, X = CH_3NH–

one-line spectra providing the correct molecular weight of the corresponding cation, FD spectra of **4a**, **4b**, and **6** were quite complex and could not be used for molecular weight determination. Interestingly, the FD mass spectrum of **3d** showed two main line groups corresponding to the cation (M^+) and a cation/anion cluster (M^+Br^- − 1). Another more general method was sought, however, since the field desorption method was unsuccessful with **4a**, **4b**, and **6**. McLafferty and co-workers[6] have reported a chemical ionization technique wherein relatively involatile compounds react in the solid phase directly with the ionized gas. Munson et al.[7] have recently applied this technique to the analysis of the phosphonium halides reported in this work. From this method correct M^+ lines were obtained for not only **7**, **8**, and **9**, but also for **3**, **4**, and **6**. Thus, the latter technique seems to have wider applicability than FDMS to the analysis of these phosphonium salts. Both methods have been used in the analysis of various other compounds in this paper.

Isolation of compound **3** is consistent with the following mechanism of addition of amines to **2** (Scheme II). The intermediacy of **2′** has been conclusively shown in the conjugate additions of nucleophiles to **2**.[4f] Compounds corresponding to **3** or **3′** from the addition of alcohols to **2** have also been

Scheme II

Table III. 2*H*-1,5,6,7-Tetrahydroazepines (16) and 2*H*-1,5-Dihydroazepines (17)

Compd	R	R^1	R^2	R^3	% yield	Mp, °C	Conditions (T, °C/time, h)
16a		CH_3	Ph	CH_3	95	232–234	0[a] → 20/0.5
16b		CH_2	Ph	H	90	229–234	0[a] → 20.0.5
16c		$(CH_2)_4$		H	74	90–115	0[a] → 20/0.5
17a	CH_3	CH_3	Ph	H	90	242–246	81/6
17b	Ph	CH_3	Ph	CH_3	71	214–222	81/20
17c	Ph	CH_3	Ph	H	73	130–150	81/20

[a] Reactants were mixed at 0 °C over a period of 0.5 h, and then the mixture was warmed briefly to 20 °C for the time given.

isolated,[4f] and a phosphonate analogue of **3a** has been prepared.[8]

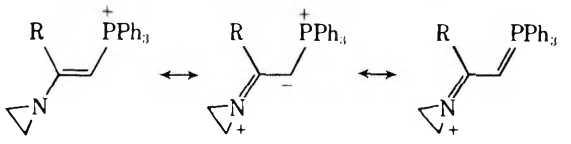
Compounds **4** and **6** are uniquely "activated" aziridines. Many examples of compounds with the general structure **11** (where Z is an electron-withdrawing group) are known.[9-13] Examples containing the phosphorus moiety, iminophosphonates and phosphoramides **12**, have also been synthe-

11 **12**

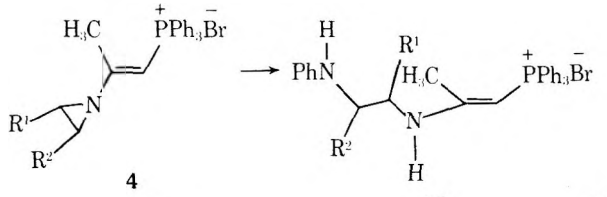
R = Ar, NHAr; R′ = –OPh, –N⟨

sized.[14] However, **4** and **6** are the only examples of **11**, to our knowledge, where Z is a phosphonium group.

Although the resonance forms depicted below for **4** are apparently not as important as those for **7–10**,[4i] consideration of this diminished resonance might nevertheless lead one to predict that **4** and **6** have quite electrophilic ring carbons.



Some alkylation reactions typical of "activated" aziridines were therefore attempted. Thus, when aziridines **4a** and **4b** were treated with aniline at 70 °C, compounds **13** were obtained in 95% yield (eq 3).

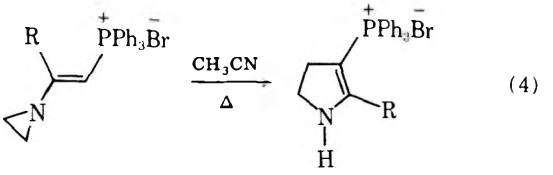


4 **13** (3)

a, $R^1 = R^2 = H$; b, $R^1 = R^2 = (CH_2)_4$

Nucleophile-Catalyzed Rearrangements. Nucleophile-catalyzed rearrangements of *N*-vinylaziridines to pyrrolines[9-11] are rather sparse compared to those of acyl-activated aziridines.[15,16] Indeed, rearrangements of *N*-vinylaziridines in this manner are known to be quite difficult,[17] often producing only ring-opened products.[9-17] In this laboratory, attempts at these rearrangements with 2-(aziridin-1-yl)-vinylphosphonium salts were only partially successful.

In refluxing acetonitrile, compounds **4a** and **6** rearrange to the 2-pyrrolines **14a** and **b** in 65 and 86% yields, respectively (eq 4). The spectral and analytical data support the assigned structures. The ^{13}C NMR spectra of **14** are given in Table II. Compound **4b** under similar conditions was recovered unchanged.



4a, R = CH_3
6, R = Ph

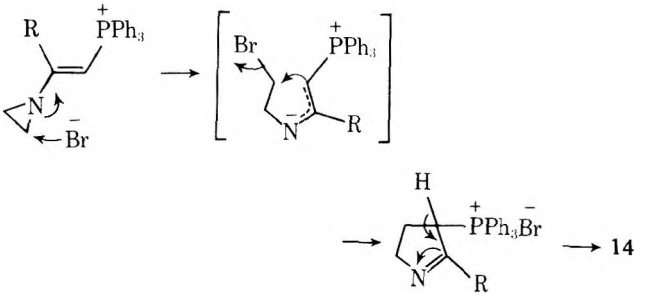
14a, R = CH_3
b, R = Ph

(4)

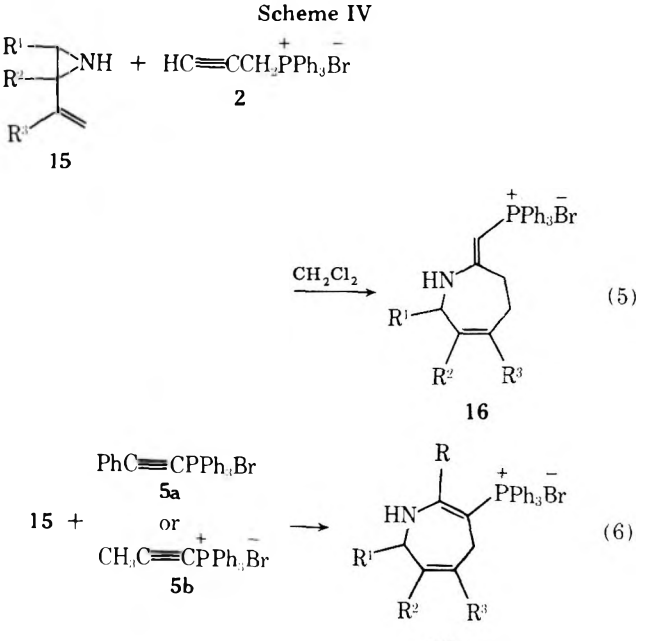
A suggested mechanism for the formation of **14** is depicted in Scheme III. Although analogous phosphonates have been synthesized,[18a] previous attempts to prepare a pyrroline ring containing a triphenylphosphonium substituent have been unsuccessful.[18b,c]

Hetero-Cope Rearrangements. From the reaction of 2-vinylaziridines **15** with **2** in methylene chloride, no compounds corresponding to **3** or **4** were isolated. Instead, the tetrahydroazepine derivatives **16** were obtained (eq 5, Scheme IV, Table III). In a similar manner, treatment of **5a** of (1-propynyl)triphenylphosphonium bromide (**5b**) with **15** in

Scheme III



Scheme IV



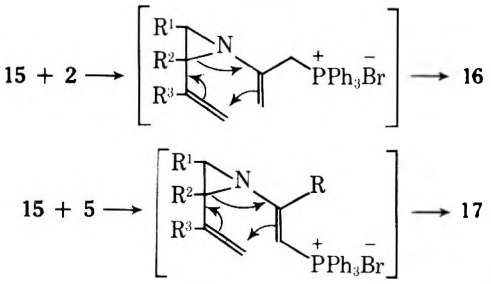
15 **16**

(5)

17

(6)

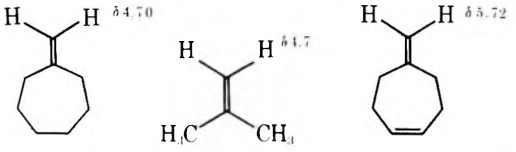
Scheme V



acetonitrile produced the dihydroazepine derivatives **17** (eq 6, Scheme IV, Table III).

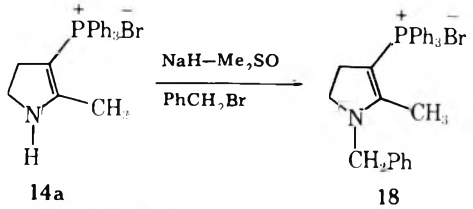
The unique ability to form the dihydroazepine ring where the triphenylphosphonium moiety β to the amino group is placed on the ring 2 position (**17**) or on an exocyclic methylene position at the ring 1 position (**16**) is due to the nature of the intermediate unsaturated phosphonium salt formed prior to the hetero-Cope rearrangement. The reaction of **15** and **2** undoubtedly proceeds by a mechanism similar to that in Scheme II, but the intermediate corresponding to **3′** undergoes a hetero-Cope rearrangement[22] to give **16** (Scheme V) instead of becoming conjugated. The addition of **15** to **5** occurs in the same manner as the addition of aziridines to other activated alkynes,[12a,13] followed by the hetero-Cope rearrangement. The facility of these processes should make them appealing as a ready synthesis of the azepine ring system; such syntheses are scarce in the literature.[22b]

The ^{1}H NMR spectra of compounds **16** exhibit a resonance for the vinyl proton next to phosphorus considerably deshielded (δ 5.30–5.47) from the corresponding shifts of compounds **7–10** (δ 3.68–4.05).[4i] The carbon next to phosphorus in these compounds, on the other hand, gives a ^{13}C chemical shift in good agreement with those of **7–10**.[4i] The reasons for the anomalous ^{1}H shifts are not clear; however, a similar chemical shift difference may be noted in the ^{1}H NMR spectra of methylidenecycloheptane[19] or 2-methylpropene[20] vs. 5-methylidenecycloheptene[21] (below).



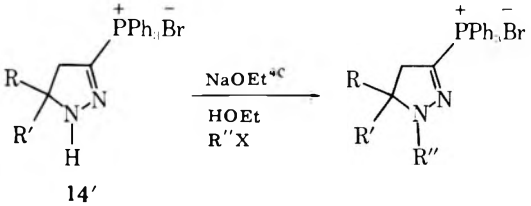
The ^{13}C NMR spectra of **16** and **17** are given in Table II. Additional evidence for the structure of **16a** was provided by an off-resonance decoupling experiment carried out with its ^{1}H NMR spectrum. Irradiation of the broad 1-H multiplet at δ ~4.6 changed the exchangeable proton at δ 9.80 (NH) from a broad doublet to a singlet and the doublet at δ 1.38 (overlapping with the singlet at δ 1.27) to a singlet.

Alkylation of 14, 16, and 17. The alkylation of salt **14a** by benzyl bromide in sodium hydride–dimethyl sulfoxide (eq 7)



(7)

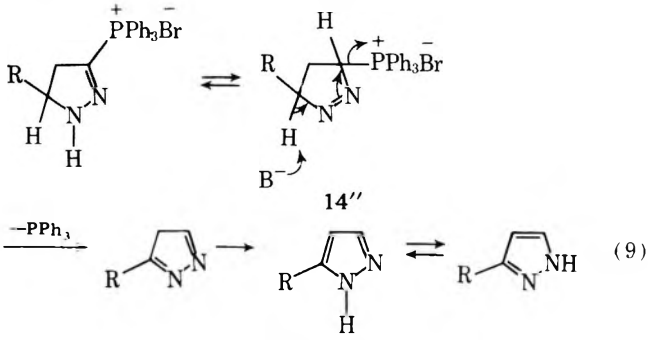
14a **18**



(8)

14′

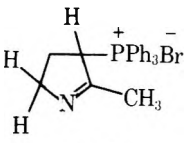
occurred, as predicted by previous work (eq 8),[4c] to give N-alkylated product **18**. Thus, both the 2-pyrrolinyl- and 2-pyrazolinylphosphonium ylides alkylate on nitrogen. When R or R′ is a hydrogen, however, **14′** eliminates triphenylphosphine to produce pyrazoles (eq 9); no alkylation products



14″

(9)

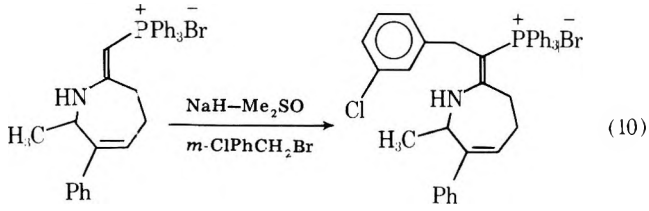
were reported.[4c] Compound **14a**, on the other hand, is apparently more stable to basic conditions. A reasonable rationale for this difference may be found in the mechanism suggested by eq 9. The polarization of the C=N bond in **14‴**



14‴

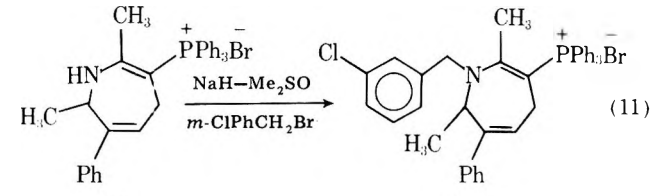
counterbalances the electronegativity of the phosphonium moiety, thus reducing the acidity of the protons on the 5 position, whereas this effect is not present in **14″** and the vinylogous β elimination is relatively easy to accomplish.

Reaction of compound **16b** with *m*-chlorobenzyl bromide in sodium hydride–dimethyl sulfoxide produced compound **19** (eq 10), while reaction of its isomer, compound **17a**, under the same conditions produced compound **20** (eq 11). The former reaction has provided the first instance in this labo-



(10)

16b **19**



(11)

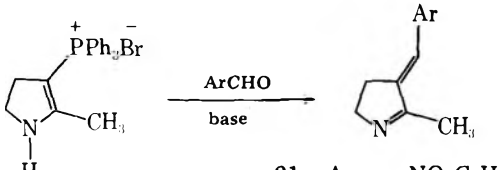
17a **20**

ratory of C alkylation of a β-aminovinylphosphonium salt. It seems likely that the decreased steric hindrance of the carbon next to phosphorus in **16** vs. the same carbon in **14a**, **14′**, or **17** might account for this difference in reactivity.

The ^{13}C NMR spectra of **19** and **20** are reported in Table II. Since no ^{13}C spectra of β-aminovinylphosphonium salts with an α substituent have previously been reported, support for the assigned structures of **19** and **20** was sought by comparison of their ^{13}C NMR spectra with spectra of similar compounds in this work. The ^{13}C spectra of five other such compounds are also presented in Table II. A preliminary inspection of this table shows that the ^{13}C–^{31}P coupling constant for C-2 of the α-substituted compounds is larger than the same coupling constant for compounds without an α substituent

by 4.5–12.2 Hz. Thus, the $J(^{13}C-^{31}P)$ of 19.5 Hz for **19** vs. 12.2 Hz for its precursor **16b** supports the assigned structure for **19**. Also, from Table II one may note that the chemical shifts for C-1 without a substituent range from 54.1 to 59.3 ppm, whereas with a substituent on C-1 they range from 61.8 to 69.7 ppm. Thus, the ^{13}C chemical shift of C-1 in these compounds is displaced an average of 10 ppm to lower field by adding an α substituent. Hence, the value of 69.4 ppm for C-1 in **19** provides additional support for the assigned structure.

Wittig Reactions of 14 and 16. Lastly, the use of these phosphonium salts as Wittig reagents was investigated. Treatment of an ethanolic solution of **14a** and *m*-nitrobenzaldehyde with sodium ethoxide in ethanol produced the pyrroline derivative **21a** (eq 12). Although a similar procedure



(12)

14a

21a, Ar = *m*-$NO_2C_6H_4$; 84%
b, Ar = *o*-$(HO)C_6H_4$; 25%

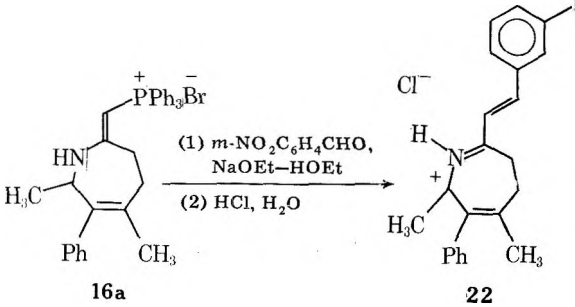
Ar = *m*-$NO_2C_6H_4$, base = NaOEt–HOEt;
Ar = *o*-$(HO)C_6H_4$, base = NaH–Me_2SO

was unsuccessful for the reaction of **14a** and salicylaldehyde, the desired pyrroline, **21b**, was obtained by the use of sodium hydride–dimethyl sulfoxide (eq 12).

The structures of **21** were supported by their ^1H NMR spectra, EI mass spectra, and analytical data. Additionally, an off-resonance decoupling ^1H NMR experiment was performed with **21a**. The ^1H NMR spectrum of this compound exhibits both allylic coupling between the benzylidene proton and the 4 position hydrogens ($J \sim 3$ Hz) and homoallylic coupling between the methyl group and the 5 position hydrogens ($J \sim 1.5$ Hz). Irradiation of the complex multiplet at $\delta \sim 4.3$ (5 position CH_2) changes the resonance at δ 2.33 (CH_3) from a triplet to a singlet and converts the triplet of doublets at δ 3.02 (4 position CH_2) to a doublet. Irradiation of the resonance at δ 3.02 changes the triplet at δ 7.05 (vinyl H) to a singlet, and, finally, irradiation of the δ 2.33 resonance changes the $\delta \sim 4.3$ multiplet to a triplet ($J \simeq 5.7$ Hz).

Again, for reasons similar to those illustrated in eq 9, the resulting pyrrolines, **21**, are stable to the basic reaction conditions, whereas the analogous pyrazolines undergo a base-catalyzed rearrangement to pyrazoles.[4c]

In a similar reaction, treatment of an ethanolic solution of azepine **16a** and *m*-nitrobenzaldehyde with sodium ethoxide in ethanol produced compound **22** (eq 13), isolated as a hydrochloride salt.



(13)

16a **22**

We have demonstrated in this paper that heterocycles bearing phosphorus-containing substituents, namely compounds **14**, **16**, and **17**, may be prepared via the synthesis and rearrangement of [2-(aziridin-1-yl)alkenyl]triphenylphosphonium bromides. These heterocycles may be alkylated or used in a Wittig olefin synthesis.

Experimental Section

Carbon-13 spectra were obtained on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. The ^{13}C data were taken at an operating frequency of 22.63 MHz. The ^{13}C chemical shifts are reported as referenced to Me_4Si. All samples were run in approximately 0.05 M solutions of $CDCl_3$ at 32 °C with broad band ^1H decoupling (except compounds **3a**, **4a**, and **4b**, which were run at approximately −10, −5, and 0 °C, respectively). The proton spectra were obtained on either a Perkin-Elmer R-12 or a Varian A-60A spectrometer and were referenced to Me_4Si. Concentrations used for the proton spectra were similar to those used for the ^{13}C spectra. The ^1H spectra of compound **3a** was taken at −10 °C; all others were taken at normal probe temperatures (~30–40 °C). Infrared spectra were recorded on either a Perkin-Elmer 337 or a Unicam SP1100 spectrometer. FD, CI, and EI mass spectra were all obtained on a duPont CEC 21-110B modified for the respective methods. Melting points were taken with a Mel-Temp apparatus and are uncorrected. Elemental analyses were obtained from Micro Analysis, Inc., Wilmington, Del., Chemalytics, Inc., Tempe, Ariz., and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Aziridines **1b** and **c** were prepared by the method of Hassner et al.[23] and purified by distillation. Aziridines **15** were prepared by the method of Chaabouni et al.[24] and purified by column chromatography (silica gel; petroleum ether (30–60 °C)/ether = 4.1). Aziridines **1a** and **d** were graciously donated to this laboratory by Dr. Harold W. Heine. The (2-propynyl)triphenylphosphonium bromide (**2**),[4f] (1-propynyl)triphenylphosphonium bromide (**5b**),[4f] and (phenylethynyl)triphenylphosphonium bromide (**5a**)[25] were prepared as previously described. All other reagents and solvents were obtained from either Aldrich Chemical. Co., Eastman Organic Chemical Co., or Fisher Scientific Co. *m*-Nitrobenzaldehyde (Eastman) was recrystallized from ethanol, and aniline (Fisher) was distilled before use. Acetonitrile, dimethyl sulfoxide, and chloroform were purified as described in the literature.[26]

[2-(Aziridin-1-yl)-2-propenyl]triphenylphosphonium Bromides (3; eq 1), [2-(Aziridin-1-yl)-1-propenyl]triphenylphosphonium Bromides [4; eq 1 (ii)], and [2-(Aziridin-1-yl)-2-phenylethenyl]triphenylphosphonium Bromide (6). The following general procedure was used for the preparation of **3**, **4**, and **6**. While stirring a slurry of **2** or **5a** in methylene chloride (20 mL/g of **2** or **5a**) at the temperature given in Table I, the appropriate aziridine **1** (1.01 mol/mol of **2** or **5a**) in methylene chloride (20 mL/g of **1**) was added over the time given in Table I. In the preparation of **3** or **6**, the mixture was stirred for an additional 5 min and then poured into anhydrous ethyl ether (70 mL/g of **2** or **5a**). For the preparation of **4**, the mixture was warmed briefly to the temperature given in Table I [eq 1 (ii)] and then poured into anhydrous ethyl ether. After stirring vigorously for several minutes, the precipitate was filtered and dried in a vacuum oven (2–3 mm, 40 °C). In addition to the ^{13}C NMR data for **3a**, **4a**, and **4b** given in Table II and melting point and yield data in Table I, the following data were collected.

[2-(Aziridin-1-yl)-2-propenyl]triphenylphosphonium Bromide (3a): IR (KBr) 3050, 2990, 2870, 2840 (CH), 1630 (C=C), 1580 (phenyl), 1110 (CP), 750, 720, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$ at −10 °C) δ 1.4–2.1 (m, 4, CH_2CH_2), 4.3–5.0 (m, 4, CH_3P and H_2C=), 7.4–8.2 (m, 15, C_6H_5); CIMS (isopentane) *m/e* (relative intensity) 344 (45.76, M^+).

Anal. Calcd for $C_{23}H_{23}BrNP$ (424.309): C, 65.10; H, 5.46. Found: C, 64.96; H, 5.44.

[2-(7-Azabicyclo[4.1.0]hept-7-yl)-2-propenyl]triphenylphosphonium Bromide (3b): IR (KBr) 3050, 2980, 2930, 2850 (CH), 1620 (C=C), 1110 (CP), 750, 710, 690 (phenyl) cm^{-1}; CIMS (isopentane) *m/e* (relative intensity) 398 (100, M^+).

[2-(2-Benzoyl-3-(*p*-nitrophenyl)aziridin-1-yl)-2-propenyl]triphenylphosphonium Bromide (3d): IR (KBr) 1670 (C=O), 1620 (C=C), 1520, 1350 (NO_2), 1110 (CP), 750, 720, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (d, 1, CH, $J_{HH} \simeq 2$ Hz), 3.5C (d, 1, CH, $J_{HH} \simeq 2$ Hz), ~4.5 (brd d, 2, CH_2P, $J_{PH} \simeq 20$ Hz), 4.92 (d, 1, =CH, $J_{HH} \simeq 7$ Hz), 5.12 (d, 1, =CH, $J_{HH} \simeq 7$ Hz), 6.8–8.0 (m, 24, aromatic H's); FDMS *m/e* (relative intensity) 569 (79, M^+), 647 (9.4, M^+ $^{79}Br^-$ − 1), 649 (17, M^+ $^{81}Br^-$ − 1); CIMS (isopentane) *m/e* 569 (6.14, M^+), 279 [100, $(Ph_3PO + 1)^+$].

[2-(Aziridin-1-yl)-1-propenyl]triphenylphosphonium Bromide (4a): IR (KBr) 3050, 3000 (CH), 1580 (phenyl), 1560 (C=C), 1110 (CP), 765, 750, 730, 720, 695 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (s, 3, CH_3), 2.55 (s, 4, CH_2CH_2), 5.31 (d, 1, =C(H)P, $J_{PH} \simeq 16$ Hz), 7.4–8.0 (m, 15, C_6H_5); CIMS (isopentane) *m/e* (relative intensity) 344 (4.19, M^+).

[2-(7-Azabicyclo[4.1.0]hept-7-yl)-1-propenyl]triphenylphos-

phonium Bromide 4b: IR (KBr) 1550 (C=C), 1110 (CP), 750, 720, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.5 (m, 4, $-CH_2CH_2-$), 1.80 (s, 3, CH_3), 1.7–2.1 (m, 4, $-CH_2CCCH_2-$), 3.00 (m, 2, -CHCH-), 5.18 (d, 1, =C(H)P, $J_{PH} \simeq 16$ Hz), 7.5–8.0 (m, 15, C_6H_5); CIMS (isopentane) *m/e* (relative intensity) 398 (40.56, M^+).

[2-(2-Phenylaziridin-1-yl)-1-propenyl]triphenylphosphonium Bromide 4c: IR (KBr) 3050, 2900, 2870 (CH), 1570 (C=C), 1108 (CP), 860, 750, 740, 710, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (d, 3, CH_3, $J_{PH} \simeq 1.2$ Hz), 2.58 (d, 1, H trans to H, $J_{trans} \simeq 4$ Hz), 3.32 (d, 1, H cis to H, $J_{cis} \simeq 7$ Hz), 4.08 (dd, 1, C(H)Ph, $J_1 \simeq 7$ Hz, $J_2 \simeq 4$ Hz), 5.41 (d, 1, =C(H)P, $J_{PH} \simeq 16.8$ Hz), 7.1–7.5 (m, 5, Ph on ring), 7.5–8.1 (m, 15, PPh_3); CIMS (isopentane) *m/e* (relative intensity) 420 (28.29, M^+).

Anal. Calcd for $C_{29}H_{27}BrNP$ (500.409): C, 69.60; H, 5.44. Found: C, 69.35; H, 5.57.

[2-(Aziridin-1-yl)-2-phenylethenyl]triphenylphosphonium Bromide (6): 85%; mp 118–124 °C; IR (KBr) 3050, 3040, 2970 (CH), 1580 (phenyl), 1550 (C=C), 1110 (CP), 765, 753, 740, 730, 720, 705, 685 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 4, CH_2CH_2), 6.13 (d, 1, =C(H)P, $J_{PH} \simeq 14$ Hz), 7.20 (s, 5, PhC=), 7.5–8.2 (m, 15, PPh_3); CIMS (isopentane) *m/e* (relative intensity) 406 (26.01, M^+).

4a and 4b via Equation 1 (i). The corresponding phosphonium salt (**3a** or **3b**) was dissolved in the appropriate solvent (0.236 mmol/mL) and then heated to the temperature and for the time prescribed in Table I. The solution was then added to anhydrous ethyl ether (500 mL/g of phosphonium salt) with vigorous stirring. Filtration and vacuum drying (2–3 mm, 40 °C) provided materials whose spectral data agreed favorably with **4a** and **4b** as prepared above. Due to the highly hygroscopic nature of **4b** produced by this process, an accurate determination of the percent yield could not be made.

[2-(Alkylamino)-1-propenyl]triphenylphosphonium Bromides (7–10). Compounds **7** and **8** were prepared by a procedure similar to that employed in the preparation of **3a**, with the exception that the addition was carried out at room temperature or slightly below. Yields and infrared data are as follows (NMR data are reported elsewhere).[4i]

[2-(Azetidin-1-yl)-1-propenyl]triphenylphosphonium Bromide (7): yield 95%; mp 232–238 °C (from CH_2Cl_2–EtOAc); IR (Nujol mull) 1540 (C=C), 1100 (CP), 750, 720, 685 (phenyl) cm^{-1}; FDMS *m/e* (relative intensity) 358 (100, M^+); CIMS (isopentane) m/e 358 (100, M^+).

[2-(Piperidin-1-yl)-1-propenyl]triphenylphosphonium Bromide (8): yield 94%; mp 233–239 °C (from CH_2Cl_2–EtOAc); IR (Nujol mull) 1540 (C=C), 1100 (CP), 750, 745, 715, 690 (phenyl) cm^{-1}; FDMS *m/e* (relative intensity) 386 (100, M^+); CIMS (isopentane) 386 (92.13, M^+).

Compounds **9** and **10** were prepared by the following general procedure. An aqueous solution of greater than 2 M excess of the amine hydrochloride was made strongly basic with sodium hydroxide. This solution was extracted several times with methylene chloride, and the extracts were dried over anhydrous $MgSO_4$ and then added to a slurry of **2** in methylene chloride in the same manner as for the preparation of **7** and **8**. Addition to anhydrous ethyl ether, filtration, and vacuum drying provided the following yields (NMR data are reported elsewhere).[4i]

[2-(*N,N*-Dimethylamino)-1-propenyl]triphenylphosphonium Bromide (9): yield 82%; mp 208–214 °C (from CH_2Cl_2–EtOAc); IR (Nujol mull) 1560 (C=C), 1100 (CP), 760, 745, 715, 690 (phenyl) cm^{-1}; CIMS (isopentane) *m/e* (relative intensity) 346 (100, M^+).

Anal. Calcd for $C_{23}H_{25}BrNP$ (426.329): C, 64.79; H, 5.91. Found: C, 64.89; H, 5.75.

[2-(*N*-Methylamino)-1-propenyl]triphenylphosphonium Bromide (10): yield 95.6%; mp 270–276 °C (from CH_2Cl_2–EtOAc); IR (Nujol mull) 1560 (C=C), 1110 (CP), 750, 720, 690 (phenyl) cm^{-1}; FDMS *m/e* (relative intensity) 332 (100, M^+).

Alkylation of Aniline with 3 or 4. A mixture of 3a, 4a, or 3b and aniline (molar ratio ~1:25) was stirred magnetically and heated to 70 °C for 15 h. Addition of the resulting red solution to anhydrous ethyl ether (250 mL/mmol of phosphonium salt) with vigorous stirring produced the following respective products.

[2-(2-Anilinoethylamino)-1-propenyl]triphenylphosphonium Bromide (13a): yield 96%; mp 204–214 °C (CH_2Cl_2–heptane); IR (Nujol mull) 3200 (NH), 1600 (phenyl), 1530 (C=C), 1500 (phenyl), 1100 (CP), 760, 750, 740, 715, 685 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (s, 3, CH_3), 3.1–3.8 (m, 4, CH_2CH_2), 3.84 (d, 1, =C(H)P, $J_{PH} \simeq 14$ Hz), 5.75 (brd s, 1, NHPh, exchanges quickly with D_2O), 6.4–7.3 (m, 5, PhN), 7.3–7.9 (m, 15, PPh_3), 8.64 (brd s, 1, NHC=, exchanges slowly with D_2O).

Anal. Calcd for $C_{29}H_{30}BrN_2P$ (517.441): C, 67.31; H, 5.84. Found: C, 67.50; H, 5.54.

[2-(2-Anilinocyclohexylamino)-1-propenyl]triphenylphosphonium Bromide (13b): yield 95%; mp 254–261 °C (CH_2Cl_2–EtOAc); IR (Nujol mull) 3200 (NH), 1590 (phenyl), 1540 (C=C), 1100 (CP), 755, 740, 715, 685 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.3 (m, 8, cyclohexyl ring), 1.68 (s, 3, CH_3), 3.3–3.9 (m, 2, CHCH), 4.09 (d, 1, =C(H)P, $J_{PH} \simeq 15$ Hz), 6.5–7.2 (m, 5, PhN), 7.2–7.9 (m, 15, PPh_3), 8.4 (brd s, 1, NHC=); FDMS *m/e* (relative intensity) 491 (100, M^+).

Anal. Calcd for $C_{33}H_{36}BrN_2P$ (571.53): C, 69.35; H, 6.35. Found: C, 69.86; H, 6.55.

(2-Methyl-2-pyrrolin-3-yl)triphenylphosphonium Bromide (14a). A round-bottom flask fitted with a reflux condenser was charged with 3.00 g (7.08 mmol) of **3a** or **4a**, approximately 0.4 mL of pyridine, and 100 mL of acetonitrile. The mixture was refluxed for 24 h, after which time 300 mL of anhydrous ethyl ether was added. The resulting suspension was stirred vigorously (magnetic) for 15 min and then filtered. The filtrate was poured into 1500 mL of anhydrous ethyl ether. After stirring for 15 min, the mixture was filtered; the filter cake and gummy yellow residue left in the flask were dissolved in 100 mL of methylene chloride. Slow addition of this solution to 1500 mL of anhydrous ethyl ether (with vigorous stirring) produced 1.95 g (65%) of a yellow-white powder which was immediately placed in a vacuum oven (40 °C, 2–3 mm): mp 80–110 °C; IR (KBr) 3150 (H-bonded NH), 2850 (CH), 1550 (C=C), 1110 (CP), 760, 720, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (brd s, 3, CH_3), 2.67 (brd t, 2, CH_2 at 4 position, $J_{HH} \simeq 10$ Hz), 3.85 (brd t, 2, CH_2 at 5 position, $J_{HH} \simeq 10$ Hz), 7.5–8.1 (m, 15, C_6H_5), 8.53 (brd s, 1, NH, D_2O exchangeable); FDMS *m/e* (relative intensity) 344 (100, M^+); CIMS (isopentane) *m/e* 344 (100, M^+).

(2-Phenyl-2-pyrrolin-3-yl)triphenylphosphonium Bromide (14b). In a round-bottom flask fitted with a reflux condenser was placed 1.00 g (2.06 mmol) of **6**, 5 drops of pyridine, and 50 mL of acetonitrile. The mixture was refluxed for approximately 15 h and then cooled and added slowly to 900 mL of anhydrous ethyl ether. The white precipitate which was filtered off, after vacuum oven drying, weighed 0.89 g (89%), mp 212–217 °C dec. After five recrystallizations from methylene chloride–ethyl acetate, the product melted at 234–236 °C: IR (KBr) 3150 (H-bonded NH), 2930, 2850 (CH), 1580 (phenyl), 1550 (C=C), 1110 (CP), 770, 750, 720, 695 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (brd t, 2, CH_2 at 4 position, $J_{HH} \simeq 11$ Hz), 4.10 (brd t, 2, CH_2 at 5 position, $J_{HH} \simeq 11$ Hz), 6.8–7.5 (m, 5, Ph), 7.5–8.4 (m, 16, PPh_3 and NH); FDMS *m/e* (relative intensity) 406 (100, M^+).

Anal. Calcd for $C_{28}H_{25}BrNP$ (486.390): C, 69.14; H, 5.18. Found: C, 68.99; H, 5.76.

Preparation of 16. To a slurry of **2** in methylene chloride (12.5 mL/g of **2**), kept at 0 °C, was added the appropriate 2-vinylaziridine **15** (1.01 mol/mol of **2**) in methylene chloride (12.5 mL/g of **2**) over the period of time specified in Table III. The mixture was allowed to warm to room temperature and was then poured into anhydrous ethyl ether (250 mL/g of **2**) with vigorous stirring. Filtration and vacuum drying (2–3 mm, 40 °C) provided the crude products listed below, which were recrystallized from methylene chloride–ethyl acetate. ^{13}C NMR data are listed in Table II; percent yield and melting point data are listed in Table III.

[(5,7-Dimethyl-6-phenyl-2*H*-1,3,4,7-tetrahydroazepin-2-ylidene)methyl]triphenylphosphonium Bromide (16a): IR (KBr) 3170 (NH), 3070, 3050, 3020, 2960, 2890 (CH), 1580 (C=CH), 1101 (CP), 763, 750, 713, 700, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3, $=CCH_3$), 1.38 (d, 3, CH_3, $J_{HH} \simeq 7.2$ Hz), 1.6–2.0 (m, 2, CH_2), 2.3–2.7 (m, 2, CH_2) 4.3–4.9 (brd m, 1, HCN), 5.44 (d, 1, =C(H)P, $J_{PH} \simeq 16.8$ Hz), 7.0–8.1 (m, 20, C_6H_5), 9.80 (brd d, 1, NH, $J_{HH} \simeq 7.2$ Hz); CIMS (isopentane) *m/e* (relative intensity) 474 (100, M^+).

Anal. Calcd for $C_{33}H_{33}BrNP$ (554.515): C, 71.48; H, 6.00. Found: C, 71.65; H, 5.93.

[(6-Phenyl-7-methyl-2*H*-1,3,4,7-tetrahydroazepin-2-ylidene)methyl]triphenylphosphonium Bromide (16b): IR (KBr) 3230, 3140 (NH), 1640 (C=C), 1600 (C=CN), 1110 (CP), 785, 765, 750, 734, 721, 715, 695, 690 (phenyl) cm^{-1}; H NMR ($CDCl_3$) δ 1.44 (d, 3, CH_3, $J_{HH} \simeq 7$ Hz), 1.6–2.9 (m, 4, CH_2CH_2), 4.6–5.0 (m, 1, CHN), 5.30 (d, 1, =C(H)P, $J_{PH} \simeq 16.2$ Hz), 5.49 (t, 1, =C(H)C, $J_{HH} \simeq 5$ Hz), 7.25 (s, 5, C_6H_5), 7.4–8.1 (m, 15, $P(C_6H_5)_3$), 9.70 (brd d, 1, NH, $J_{HH} \simeq 6$ Hz); FDMS *m/e* (relative intensity) 460 (100, M^+).

Anal. Calcd for $C_{32}H_{31}BrNP$ (540.489): C, 71.11; H, 5.78. Found: C, 71.29; H, 6.04.

[(1*H*-2,3,4,6,7,8,9,9a-Octahydro-1-benzazepin-2-ylidene)-methyl]triphenylphosphonium Bromide (16c): IR (KBr) 3220 (NH), 1595 (NC=C), 1105 (CP), 750, 715, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–3.0 (m, 12, alkyl H's), 3.85–4.35 (m, 1, CHN), ~5.3 (m under =C(H)P, 1, =C(H)C), 5.47 (d, 1, =C(H)P, $J_{PH} \simeq 17$ Hz), 7.5–8.2 (m, 15, C_6H_5), ~9 (brd d 1, NH); FDMS *m/e* (relative inten-

sity) 424 (100, M^+).

Preparation of 17. A mixture of **5**, the appropriate vinylaziridine **15** (1.05 mol/mol of **5**), and acetonitrile (15 mL/g of **5**) was refluxed for the time specified in Table III. After cooling, the mixture was added to anhydrous ethyl ether (250 mL/g of **5**) with stirring. Filtration and vacuum drying (2–3 mm, 40 °C) provided the crude products listed below, which were recrystallized from methylene chloride–ethyl acetate. ^{13}C NMR data are listed in Table II; percent yield and melting point data are listed in Table III.

(2,7-Dimethyl-3-phenyl-1*H*-2,5-dihydroazepin-6-yl)triphenylphosphonium Bromide (17a): IR (KBr) 3220 (NH), 1615 (C=C), 1555 (NC=C), 1101 (CP), 765, 756, 750, 715, 690 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (d, 3, CH_3, $J_{HH} \simeq 7.2$ Hz), 1.81 (s, 3, $=CCH_3$), 2.2–3.2 (m, 2, CH_2), 4.8–5.2 (m, 1, CHN), 5.85 (t, 1, =C(H)C, $J_{HH} \simeq 8.4$ Hz), 7.1–8.0 (m, 20, C_6H_5), 8.86 (dd, 1, NH, $J_1 \simeq 6$ Hz, $J_2 \simeq 5$ Hz); FDMS *m/e* (relative intensity) 460 (100, M^+).

Anal. Calcd for $C_{32}H_{31}BrNP \cdot H_2O$ (558.497): C, 68.82; H, 5.96. Found: C, 69.44; H, 5.98.

(2,4-Dimethyl-3,7-diphenyl-1*H*-2,5-dihydroazepin-6-yl)triphenylphosphonium Bromide (17b): IR (KBr) 3350, 3230 (NH), 3060, 2990, 2840 (CH), 1630 (C=C), 1540, 1510 (NC=C), 1101 (CP), 767, 759, 710, 695 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 3, CH_3, $J_{HH} \simeq 5.4$ Hz), 1.58 (s, 3, CH_3), 2.0–2.9 (m, 2, CH_2), 5.4–5.8 (m, 1, CHN), 6.9–8.5 (m, 26, C_6H_5's and NH).

Anal. Calcd for $C_{38}H_{35}BrNP$ (615.579): C, 74.02; H, 5.72. Found: C, 74.14; H, 5.60.

(2-Methyl-3,7-diphenyl-1*H*-2,5-dihydroazepin-6-yl)triphenylphosphonium Bromide (17c): IR (KBr) 3200 (NH), 3060, 3000, 2940, 2890 (CH), 1630 (C=C), 1525 (NC=C), 1105 (CP), 760, 720, 710, 695 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (d, 3, CH_3, $J_{HH} \simeq 6.6$ Hz), 3.15 (dd, 2, CH_2, $J_{PH} \simeq 12$ Hz, $J_{HH} \simeq 7.8$ Hz), 5.1–5.6 (m, 1, CHN), 6.02 (t, 1, =C(H)C, $J_{HH} \simeq 7.8$ Hz), 6.5–8.2 (m, 26, C_6H_5's and NH); FDMS *m/e* (relative intensity) 522 (100, M^+).

Alkylation of 14, 16, and 17. To a solution of **14**, **16**, or **17** in dimethyl sulfoxide (~0.3 M) under dry nitrogen was added an equimolar amount of sodium hydride (as a 57% mineral oil dispersion). The mixture was stirred for 1 h before adding the appropriate alkylating agent (~3 mol/mol of phosphonium salt). After stirring overnight, the mixture was added to anhydrous ethyl ether (75 mL/mL of Me_2SO) with stirring. A gummy precipitate formed, from which the ethereal supernatant was decanted. The residue was triturated with a few milliliters of methylene chloride and filtered into anhydrous ethyl ether (~50 mL/mL of CH_2Cl_2) with vigorous stirring. Filtration provided the crude product.

Purification of **18** was effected in the following manner. The crude product was dissolved in methylene chloride (~10 mL/g of phosphonium salt) and then added with stirring to ethyl acetate (~500 mL/g). The mixture was filtered, and the filtrate was poured into anhydrous ethyl ether (~1500 mL/g) with stirring. The purified product was filtered.

Purification of **19** or **20** was effected in the following manner. The crude product was dissolved in excess methylene chloride (*n* mL) and added to ethyl acetate (*n* mL). The methylene chloride was removed by boiling until a slight cloudiness appeared. The mixture was allowed to cool, and the supernatant liquid was poured into anhydrous ethyl ether (2*n* mL). Purification provided purified phosphonium salt. ^{13}C NMR data of **19** and **20** are reported in Table II. Other data are as follows.

(1-Benzyl-2-methyl-2-pyrrolin-3-yl)triphenylphosphonium Bromide (18): yield 67 (crude) and 35% (purified); mp 188–204 °C; IR (KBr) 3060 (CH), 1590 (phenyl), 1545 (C=C), 1110 (CP), 760, 720, 695 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (s, 3, CH_3), 2.58 (brd t, 2, CH_2 at 4 position, $J_{HH} \simeq 10$ Hz), 3.75 (brd t, 2, CH_2 at 5 position, $J_{HH} \simeq 10$ Hz), 4.62 (brd s, 2, NCH_2Ph), 7.40 (s, 5, C_6H_5), 7.0–8.2 (m, 15, $P(C_6H_5)_3$); CIMS (isopentane) *m/e* (relative intensity) 434 (54.71, M^+).

[(*m*-Chlorobenzyl)-(6-phenyl-7-methyl-2*H*-1,3,4,7-tetrahydroazepin-2-ylidene)methyl]triphenylphosphonium Bromide (19): yield 64% (crude); mp 140–155 °C dec (purified); IR (KBr) 3200 (NH), 1625 (C=C), 1570 (NC=C), 1101 (CP), 757, 720, 692 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (d, 3, CH_3, $J_{HH} \simeq 7.8$ Hz), 1.4–2.1 (m, 2, CH_2), 2.4–3.0 (m, 2, CH_2), 3.96 (d, 2, CH_2Ar, $J_{PH} \simeq 20.4$ Hz), 5.1–5.7 (m, 2, =C(H)C and CHN), 6.7–8.3 (m, 24, aromatic H's), 8.65 (brd d, 1, NH, $J_{HH} \simeq 6$ Hz); FDMS *m/e* (relative intensity) 584 (100, M^+ from ^{35}Cl), 586 (61, M^+ from ^{37}Cl).

Anal. Calcd for $C_{39}H_{36}BrClNP \cdot H_2O$ (683.066): C, 68.58; H, 5.60. Found: C, 68.49; H, 5.48.

[(1-(*m*-Chlorobenzyl)-2,7-dimethyl-3-phenyl-1*H*-2,5-dihydroazepin-6-yl]triphenylphosphonium Bromide (20): yield 59% (crude); mp 140–160 °C dec (purified); IR (KBr) 3060, 3040, 2940 (CH), 1620 (C=C), 1600 (phenyl), 1530 (NC=C), 1101 (CP), 750, 715, 695 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, 3, CH_3, $J_{HH} \simeq 5.4$ Hz), 1.5–2.2 (m, 2, CH_2), 2.11 (s, 3, CH_3), 3.8 (brd s, 2, CH_2Ar), 4.8–5.2 (m, 1, CHN), 5.5–6.0 (m, 1, =C(H)C), 6.8–8.4 (m, 24, aromatic H's).

Anal. Calcd for $C_{39}H_{36}BrClNP \cdot H_2O$ (683.066): C, 68.58; H, 5.60. Found: C, 68.64; H, 5.40.

2-Methyl-3-(*m*-nitrobenzylidene)-1-pyrroline (21a). In a round-bottom flask fitted with a reflux condenser and an addition funnel was placed 1.00 g (2.36 mmol) of **14a**, 0.45 g (2.98 mmol) of *m*-nitrobenzaldehyde, and 10 mL of absolute ethanol. While stirring magnetically, 0.060 g (2.6 mmol) of sodium dissolved in 20 mL of absolute ethanol was added from the addition funnel over a 1-h period. After stirring at room temperature for 20 h, the volume was reduced (in vacuo) to approximately 2 mL and 100 mL of ethyl ether added. The resulting mixture (including the precipitate) was washed twice with 40 mL of water and then shaken for about 3 min with 50 mL of 10% HCl solution. The aqueous acid layer was washed successively with 50 mL of ethyl ether and 50 mL of ethyl acetate. The aqueous layer was basified with 20% sodium hydroxide solution (aqueous), and the resulting mixture (including the precipitate) was extracted with two 100-mL portions of ethyl ether. The combined ether extracts were dried (anhydrous $MgSO_4$) and filtered, and the ether was removed in vacuo to provide 0.43 g (84%) of crude product: mp 154–157 °C (after four recrystallizations from acetone–water); IR (KBr) 3100, 2920, 2850 (CH), 1600, 1590 (C=N, C=C), 1510, 1350 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (t, 3, CH_3, $J_{HH} \simeq 1.5$ Hz), 3.02 (td, 2, CH_2 at 4 position, $^tJ_{HH} \simeq 5.7$ Hz, $^dJ_{HH} \simeq 3$ Hz), 4.0–4.5 (m, 2, CH_2 at 5 position), 7.05 (t, 1, =C(H)Ar, $J_{HH} \simeq 3$ Hz), 7.7–8.9 (m, 4, $C_6H_4NO_2$); EIMS *m/e* (relative intensity) 216 (100 M^+).

Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.60. Found: C, 66.41; H, 5.49.

2-Methyl-1-(*o*-hydroxybenzylidene)-1-pyrroline (21b). Sodium hydride (57% mineral oil dispersion; 0.10 g, 2.38 mmol) and **14a** (1.00 g, 2.36 mmol) were stirred in 5 mL of dimethyl sulfoxide over nitrogen for 1 h. Salicylaldehyde (0.35 g, 2.87 mmol) was then added in one portion, and the mixture was stirred for approximately one day. The dark red solution was then poured into 100 mL of water and stirred vigorously. The resulting emulsion was extracted thrice with 100 mL of ethyl acetate, the extracts were dried (anhydrous $MgSO_4$), and the solvent was removed in vacuo. The residue was dissolved in a minimum quantity of hot benzene and allowed to cool overnight. Orange-yellow spines (0.11 g, 25%) were recovered by filtration after two recrystallizations from methanol–water: mp 195–198 °C; IR (KBr) 3070 (weak, H-bonded OH), 2940, 2880, 2860 (CH), 2600 (broad, $\geq N^+H$), 1600, 1590, 1575 (C=N, C=C, and phenyl), 1251 (C–O), 750 (phenyl) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.15 (t, 3, CH_3, $J_{HH} \simeq 1.5$ Hz), 2.6–3.0 (m, 2, CH_2 at 4 position), 3.7–4.1 (m, 2, CH_2 at 5 position), 6.7–7.9 (m, 6, =C(H)Ar, phenolic OH, or $\geq N^+H$ and aromatic H's); EIMS *m/e* (relative intensity) 187 (10.81, M^+), 186 (72.68, $M^+ - 1$).

Anal. Calcd for $C_{12}H_{13}NO$ (187.241): C, 76.98; H, 7.00. Found: C, 76.72; H, 7.11.

2,4-Dimethyl-3-phenyl-7-[2-(*m*-nitrophenyl)ethenyl]-2*H*-5,6-dihydroazepinium Chloride (22). A procedure similar to that used for the preparation of **21a** was employed with the following exceptions. After evaporating the ethanol solution to 1–2 mL and adding 50 mL of ethyl ether, the resulting mixture was washed twice with 20 mL of water. The ether layer was then placed in an Erlenmeyer flask with 25 mL of 10% hydrochloric acid, and the mixture was vigorously stirred for at least 15 min. The thick paste which formed was collected and triturated with 10 mL of ethanol. Filtration provided 0.10 g of crude product [29%; from 0.55 g (0.99 mmol) of **16a**, 0.03 g (1.33 mmol) of sodium, and 0.19 g (1.3 mmol) of *m*-nitrobenzaldehyde]. An analytical sample was obtained after three recrystallizations from ethanol–benzene: mp 210–220 °C dec; IR (KBr) 3040, 2960, 2930, 2860 (CH), 2600 (broad, N^+H), 1630 (C=N), 1615 (C=C), 1532, 1352 (NO_2), 832, 810, 795, 769, 738, 710 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$–CF_3CO_2H) δ 1.55 (d, 3, CH_3, $J_{HH} \simeq 7$ Hz), 1.65 (s, 3, CH_3), 2.87 (brd t, 2, CH_2, $J_{HH} \simeq 5.4$ Hz), 3.68 (d, 2, CH_2, $J_{HH} \simeq 5.4$ Hz), 5.1–5.7 (m, 1, CHN), 7.08–8.9 (m, 12, aromatic H's, HC=CH, and N^+H).

Anal. Calcd for $C_{22}H_{23}ClN_2O_2$ (382.889): C, 69.01; H, 6.05. Found: C, 69.14; H, 6.31.

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Registry No.—**1a**, 151-56-4; **1b**, 286-18-0; **1c**, 1499-00-9; **1d**, 51659-22-4; **2**, 2091-46-5; **3a**, 66966-54-9; **3b**, 66966-55-0; **3d**, 67011-18-1; **4a**, 66966-56-1; **4b**, 66966-57-2; **4c**, 66966-58-3; **5a**, 34387-64-9; **5b**, 54599-98-3; **6**, 66966-69-6; **7**, 66966-70-9; **8**, 66966-71-0; **9**,

66966-72-1; **10**, 66966-73-2; **13a**, 66966-74-3; **13b**, 66966-75-4; **14a**, 66966-59-4; **14b**, 66966-60-7; **15a**, 66966-76-5; **15b**, 60073-28-1; **15c**, 57291-16-4; **16a**, 66966-61-8; **16b**, 66966-62-9; **16c**, 66966-63-0; **17a**, 66966-65-2; **17b**, 66966-66-3; **17c**, 66966-67-4; **18**, 66966-77-6; **19**, 66966-64-1; **20**, 66966-68-5; **21a**, 66966-78-7; **21b**, 66966-79-8; **22**, 66966-80-1; azetidine, 503-29-7; piperidine, 110-89-4; dimethylamine HCl, 506-59-2; methylamine HCl, 593-51-1; aniline, 62-53-3; *m*-nitrobenzaldehyde, 99-61-6; salicylaldehyde, 90-02-8.

References and Notes

(1) Taken from the Ph.D. Thesis of M.A.C., University of Delaware, Del., 1978.
(2) D. Redmore, *Chem. Rev.*, **71**, 315 (1971).
(3) E. Zbiral, *Synthesis*, 775 (1974).
(4) (a) E. E. Schweizer, Choong Sup Kim, C. S. Labaw, and W. P. Murray, *J. Chem. Soc., Chem. Commun.*, 7 (1973); (b) E. E. Schweizer and C. S. Labaw, *J. Org. Chem.* **38**, 3069 (1973); (c) E. E. Schweizer and Choong Sup Kim, *ibid.*, **36**, 4033 (1971); (d) *ibid.*, **36**, 4041 (1971); (e) E. E. Schweizer, Choong Sup Kim, and R. A. Jones, *Chem. Commun.*, 39 (1970); (f) E. E. Schweizer, S. D. Goff, and W. P. Murray, *J. Org. Chem.*, **42**, 200 (1977); (g) E. E. Schweizer, unpublished results; (h) T. A. Albright, S. V. DeVoe, W. J. Freeman, and E. E. Schweizer, *J. Org. Chem.*, **40**, 1650 (1975); (i) E. E. Schweizer and M. A. Calcagno, *ibid.*, **42**, 2641 (1977).
(5) G. W. Wood, J. J. McIntosh, and Pui-YanLau, *J. Org. Chem.*, **40**, 636 (1975).
(6) M. A. Baldwin and F. W. McLafferty, *Org. Mass Spectrom.*, **7**, 1353 (1973).
(7) B. Munson and C. Harson, private communication.
(8) J.-Y. Merour, Nguyen Thanh Thuong, P. Chabrier, and M. H. Normant, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **280**, 473 (1975).
(9) H. W. Whitlock, Jr., and G. L. Smith, *J. Am. Chem. Soc.*, **89**, 3600 (1967).
(10) D. A. Archer and B. W. Singer, *J. Chem. Soc., Perkin Trans. 1*, 2484 (1976).
(11) A. Kunar, H. Ila, U. Junjappa, and S. Mhatre, *J. Chem. Soc., Chem. Commun.*, 592 (1976).
(12) (a) M. Neuenschwander and P. Bigler, *Helv. Chim. Acta*, **56**, 959 (1973); A. Neuenschwander, A. Frey, and M. Neuenschwander, *ibid.*, **56**, 944 (1973); W. E. Truce and D. W. Onken, *J. Org. Chem.*, **40**, 3200 (1975); W. E. Truce and L. D. Markley, *ibid.*, **35**, 3275 (1970); L. I. Vereshchagin, R. L. Bol'shedvorskaya, G. A. Pavlova, A. A. Verschchagina, and N. V. Alekseeva, *J. Org. Chem. USSR (Engl. Transl.)*, **11**, 97 (1975); Zh. A. Krasnaya, T. S. Stytsenko, E. P. Prokof'ev, and V. F. Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1959 (1973); A. V. Eremeev, D. A. Tikhomirov, and E. Liepin, *Khim. Geterotsikl. Soedin.*, 207 (1977); *Chem. Abstr.*, **87**, 5737b (1977). (b) W. Scroth and G. Dill, E. Ger. Patent 106 642, 1974; *Chem. Abstr.*, **82**, 170649d (1975); W. Gauss, H. Heitzer, and S. Petersen, *Justus Liebigs Ann. Chem.*, **764**, 131 (1972); H. Nakao, M. Arakawa, T. Makamura, and M. Fukushima, *Chem. Pharm. Bull.*, **20**, 1968 (1972); G. Manecke and H.-J. Kretzschmar, *Makromol. Chem.*, **169**, 15 (1973); A. H. Khan and J. S. Driscoll, *J. Med. Chem.*, **19**, 313 (1976); W. Ried and A. H. Schmidt, *Justus Liebigs Ann. Chem.*, 1863 (1975); H. Huber-Ernden, L. Schibler, H. Jaeger, A. Hiestand, and A. Maeder, (Aba-Geigy, A.-G.), Swiss Patent 511 831 (1971); *Chem. Abstr.*, **76**, 72387y (1972). (c) M. Mihalic, V. Sunjic, P. Mildner, and F. Kajfez, *Croat. Chem. Acta*, **48**, 125 (1976); *Chem. Abstr.*, **86**, 4800j (1977). (d) T. Fukunaga, *J. Am. Chem. Soc.*, **94**, 3242 (1972).
(13) O. C. Dermer and C. E. Ham, "Ethylenimine and Other Aziridines", Academic Press, New York, N.Y., 1969, pp 140, 141.
(14) A. A. Kropacheva, G. I. Derkach, and A. V. Kirsanov, *J. Gen. Chem. USSR (Engl. Transl.)*, **31**, 1489 (1961); G. I. Derkach, L. D. Protsenko, L. P. Zhuravleva, and A. V. Kirsanov, *ibid.*, **32**, 2942 (1962).
(15) H. W. Heine, *Mech. Mol. Mig.*, **3**, 145–176 (1971).
(16) Cf. ref 13, pp 283–289.
(17) S. I. Miller and R. Tanaka, *Sel. Org. Transform.*, **1**, 196 (1970).
(18) N. Gakis, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **57**, 1403 (1974); (b) *ibid.*, **58**, 748 (1975); (c) U. Widner, N. Gakis, B. Arnet, H. Heimgartner, and H. Schmid, *Chimia*, **30**, 453 (1976).
(19) R. Kotani, *J. Org. Chem.*, **30**, 350 (1965).
(20) A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley New York, N.Y., 1972, p 254.
(21) P. Gassman and E. A. Armour, *Tetrahedron Lett.*, 1431 (1971).
(22) (a) P. G. Mente, H. W. Heine, and G. R. Scharoubin, *J. Org. Chem.*, **33**, 4547 (1968); P. C. Mente and H. W. Heine, *ibid.*, **36**, 3076 (1971); P. Scheiner, *ibid.*, **32**, 2628 (1967); A. Sauleau, J. Sauleau, H. Bourget, and J. Huet, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **279**, 473 (1974); (b) E. L. Stogryn and S. J. Brois, *J. Am. Chem. Soc.*, **89**, 605 (1967).
(23) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).
(24) R. Chaabouni and A. Laurent, *Synthesis*, 464 (1975).
(25) H. Hoffmann and H. Forster, *Tetrahedron Lett.*, 983 (1964).
(26) Reference 20, pp 431–433.

Photochemistry of 2-Acetyl-3-phenylnorbornanes: Influence of a β-Phenyl Group on Carbonyl Reactivity in Relation to the Geometry of Both Chromophores

Jacqueline Moron and Georges Roussi*

Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif sur Yvette, France

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The photochemistry of *trans*- and *cis*-2-acetyl-3-phenylnorbornanes *exo*-**3** and **5** and *endo*-**4** and -**6** has been investigated and compared to that of *exo*-acetylnorbornane (**1**) and the endo isomer **2**. The trans, exo compound **3** led exclusively to the Norrish type I photoproducts via the triplet state, while the cis isomer was inert. The endo compounds **4** and **6** underwent the type II photoelimination exclusively from the singlet state, and cyclization from both the singlet and the triplet. It has been shown that deactivation of excited states of carbonyl compounds by the phenyl group in both exo and endo isomers occurs only when the two chromophores are in the cis position.

The photoreactivity of formally nonconjugated phenyl–carbonyl compounds has been the subject of some recent investigations.[1,2] Thus, it was shown by Whitten[2] that β-phenyl ketones with an available γ hydrogen undergo type II photoelimination as the only significant reaction. This author showed that while the triplet state is formed in good yields it returns exclusively to the ground state. The reaction occurs exclusively from the singlet state. The kinetic data obtained with somewhat rigid ketones allowed Whitten to suppose a through-space coupling between the two chromophores. Sauers,[3] studying the two isomeric 2-acetylbenzonorbornanes, reported that the exo isomer undergoes a nonefficient type I cleavage, while the endo isomer is photostable. The author suggested that the proximity of the two chromophores in the latter provides a channel for radiationless decay of the triplet.

It therefore appeared attractive to us to study rigid systems with an available γ hydrogen in order to investigate the influence of the phenyl group on carbonyl reactivity in relation to the relative geometry of both chromophores. Thus, the four isomeric acetylphenylnorbornanes **3**, **4**, **5**, and **6** were synthesized and their photochemical reactivity was compared to the acetylnorbornanes **1** and **2**. The photochemistry of the latter had not been studied before.

We report first that the behavior of the methyl ketones **1** and **2** was entirely different from that of the corresponding aryl ketones.[4] Secondly we show that the phenyl group exerts its influence only in the cis isomers **4** and **6**. Finally, we demonstrate that the Norrish type I reaction was more subject to the influence of the phenyl group than the γ hydrogen abstraction reaction.

Results

I. Product Study. The structures of the products were assigned on the basis of their spectral data and by chemical correlation in the case of ketone **13**.[5]

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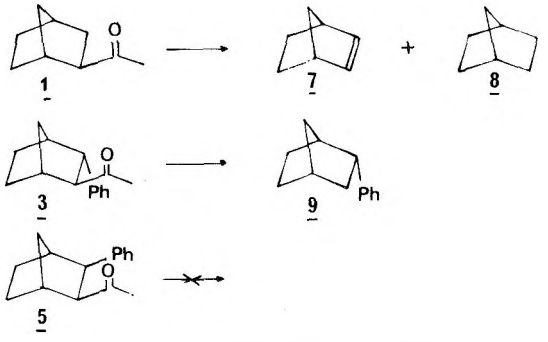
Table I. ^{13}C NMR and ^1H NMR Data Used in the Assignment of the C_4 Stereochemistry in Compounds 11, 14, and 15

	^{13}C NMR, δ		^1H NMR, δ		
	Me	C_4	Me	H_6	H_2
11a	19.5	79.1	1.1	3.1	
11b			1.3	>2.3	
14a	20.1	78.9	1.2	3.2	2.9
14b	27.9	70.6	1.4	2.4	3.3
15	22.3	79.5	0.4	3.3	

The C_4 stereochemistry of the two isomers (a and b) of the alcohol **14** was assigned on the basis of comparison of their ^1H NMR and ^{13}C NMR spectra (Table I). Compound **14a** possesses a methyl group which is more hindered than in **14b**. Its ^{13}C resonance was therefore found at higher field (20.1 ppm) than the similar carbon atom in **14b** (27.9 ppm). The same phenomenon was observed in the ^1H NMR spectrum for the methyl protons (respectively δ 1.2 in **14a** and δ 1.4 in **14b**). In addition, H_6 is more shielded in **14a** (δ 3.2) than in **14b** (δ 2.4)[6] and there was a marked difference in the position of the resonance for the benzylic protons H_2 in the two isomers, these effects being due to the influence of the hydroxylic group.[7] Similar H_6 shifts in the ^1H NMR spectra of **11a**, **14a**, and **15** were observed. The same trend was noted for the methyl group shift in ^{13}C NMR and ^1H NMR spectra.

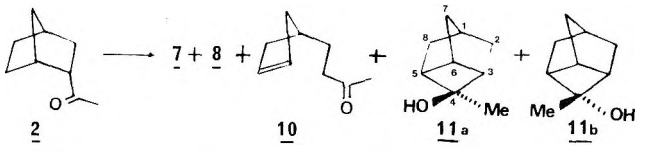
These results show that **11a**, **14a**, and **15**, which are the major isomers formed by irradiation, possess the same C_4 stereochemistry, whereas **11b** and **14b** have the opposite C_4 configuration. It must be noted that the **14b** quaternary carbon C_4 signal in the ^{13}C NMR spectrum was surprisingly deshielded relative to that for **14a**. Contrary to the acyclic β-phenyl ketones described by Whitten,[2] compounds **3**, **4**, **5**, and **6** show fluorescence emission in acetonitrile. The phosphorescence spectra of those ketones taken at 77 K permitted the evaluation of their triplet energy (~ 74 kcal/mol).

A. Photochemistry of the Exo Isomers 1, 3, and 5. In acetonitrile *exo*-1-acetylnorbornane (**1**) was observed to undergo complete conversion to a mixture of norbornene (**7**) and norbornane (**8**). Irradiation of **3** resulted in the formation of



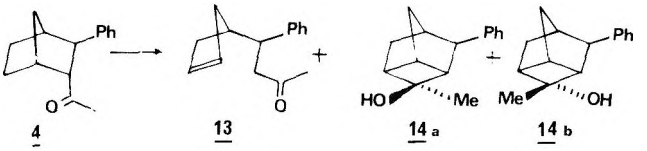
endo-phenylnorbornane (**9**), while the exo,cis isomer **5** proved to be quite stable under irradiation.

B. Photochemistry of the Endo Isomers 2, 4, and 6. *endo*-1-Acetylnorbornane underwent three types of reaction: Norrish type I (NI) (leading to **7** and **8**), Norrish type II (NII) photoelimination (leading to **10**, which disappeared upon

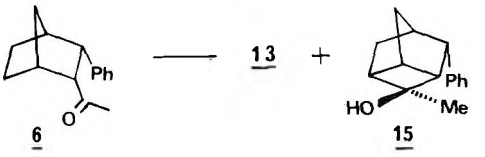


prolonged irradiation), and photocyclization [leading to the two isomers (a and b) of 4-methyltricyclo[3.2.1.0^{3,6}]octan-4-ol (**11**)].

Irradiation of *endo*-2-acetyl-3-phenylnorbornane (**4**) resulted in the formation of the photoelimination product **13** and to the mixture of the two isomers (a and b) of the tricyclic alcohol **14**.



Endo,cis isomer **6** underwent photoelimination (leading to **13**) and photocyclization, which gave only one isomer of the tricyclic alcohol **15**.



II. Mechanistic Studies. Degassed 0.01 M solutions of ketones **1**–**6** contained in UV cells were irradiated by a 313-nm line produced by a monochromator. Light intensities were measured by ferrioxalate actinometry. Product yields were determined by analytical VPC for conversion of <10% in acetonitrile solutions. The quantum yields (Φ) are given in Table II. The reactivity of ketones **1**–**6** was also investigated in the presence of high concentrations (0.2 M) of *cis*-1,3-pentadiene (piperylene), and the quantum yields (Φ_q) were determined. No quenching of the type II elimination process occurred in **2**, **4**, or **6** at concentrations up to 0.6 M.

Linear Stern–Volmer plots for quenching of alcohols **11**, **14**, and **15** could not be obtained owing to the very small value of their quantum yield formation, but were obtained for quenching of norbornane (**8**) from the endo ketone **2** and phenylnorbornane (**9**) from **3**.

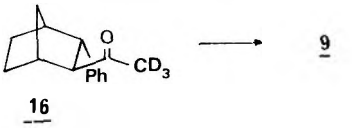
The quantum yields for triplet sensitized cis–trans isomerization of piperylene by the different ketones were measured as a function of diene concentrations. Good correlation of $1/\Phi_{c\rightarrow t}$ vs. 1/[diene] was obtained for every ketone except **1**. From these plots, the triplet lifetimes (τ_T) and intersystem crossing quantum yields (Φ_{isc}) were obtained.[8] In the case of **1** the lack of correlation was possibly due to a consumption of piperylene by ketone.

Quantum yields of sensitized reactions (Φ_{sens}) were determined in acetonitrile–acetone mixture)1 M).[9]

All the results are summarized in Table II.

Discussion

I. Photochemical Behavior of *exo*- and *endo*-Acetylnorbornane (1 and 2). A. *exo*-Acetylnorbornane (1) in Acetonitrile. The exo ketone bearing a γ hydrogen gave **7** and **8** essentially via the ketone triplet state.[12] The formation of this saturated compound was unusual in the NI reaction. However, Sauers[3] obtained this type of compound after irradiation of acetylbenzoylnorbornane. Sauers[3] considered that the hydrogen originates from a radical pair disproportionation, giving the saturated compound and ketene, rather than from the solvent used (cyclohexane). We tested this possibility using the trideuterated ketone **16**. The recovered saturated



product was found to contain no deuterium. We concluded that acetonitrile (a poor hydrogen-donating solvent) was the hydrogen source, this being allowed by the unusually high degree of strain associated with a norbornene double bond

Table II. Quantum Yields and Quenching Data[i]

starting compd	product	Φ	Φ_{sens}	Φ_q	$\Phi_{t\text{-BuOH}}$[a]	Φ_{isc}	τ, s[b]
1	7	0.024 ± 0.005				0.9	2×10^{-9}
	8	0.64 ± 0.1	0.014 ± 0.002	0.014[c] ± 0.003			
3	9	0.28 ± 0.07	0.05 ± 0.005			1	6×10^{-9}
5						0.7	2×10^{-8}
2	7	0.0038 ± 0.0005				0.2	1.8×10^{-8}
	8	0.14 ± 0.01	0	0			
	10	0.096 ± 0.01	0	0.10[d] ± 0.01	0.12 ± 0.01		
	11a,b	0.026 ± 0.001	0.006 ± 0.001	0.020 ± 0.001	0.027 ± 0.002		
4	9					0.3	5×10^{-9}
	13	0.22[e] ± 0.05	0.058 ± 0.005	0.23 ± 0.02			
	14a,b	0.024[f] ± 0.005	0.19[g] ± 0.04	0.007 ± 0.001	0.0079		
6	13	0.059 ± 0.004	0.0034 ± 0.0005	0.055 ± 0.005	0.04	0.2	9×10^{-9}
	15	0.012[h] ± 0.001	0.027 ± 0.005	0.004 ± 0.001	0.01 ± 0.001		

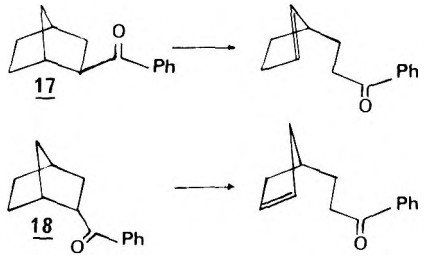
[a] Quantum yields were determined in a 2:1 mixture of acetonitrile–*tert*-butyl alcohol.[10] Added *t*-BuOH had no influence on the results obtained in acetonitrile, due to an insufficient difference in polarity between the two solvents. [b] Calculated from slope of $1/\Phi_{c\to t}$ vs. 1/[diene] taking $k_q(CH_3CN) = 2.9 \times 10^{10}$ L/mol · s.[11] [c] Up to 0.6 M in piperylene. [d] The photolabile ketone **10** was stable in the presence of piperylene, which explains the higher quenched quantum yields observed and results in its preparation in a very good yield. [e] This value is approximate, since **13** was not completely stable under irradiation. [f] The ratio **14a/14b** in acetonitrile (3.2) and in an acetonitrile–acetone mixture (3.2) was determined after purification by column chromatography. [g] This result is incompatible with the intersystem crossing quantum yield. A possible explanation could be that acetone, which is used in large excess, generates important solvent effects. [h] The formation of the single hindered isomer of the alcohol **15** in this reaction was not surprising if one considers that there was a solvation of the biradical intermediate, which prevented the cyclization leading to the *endo*-hydroxyl group isomer. [i] Registry no.: **1**, 824-59-9; **2**, 824-58-8; **3**, 67271-49-2; **4**, 67335-59-5; **5**, 67335-58-4; **6**, 67335-60-8; **7**, 498-66-8; **8**, 279-23-2; **9**, 17989-94-5; **10**, 60443-42-7; **11a**, 67271-50-5; **11b**, 67335-61-9; **13**, 67271-51-6; **14a**, 67271-52-7; **14b**, 67335-62-0; **15**, 67335-63-1.

Table III. Ratios of the Isomeric Alcohols 11 According to the Carbonyl Excited States

	CH_3CN	*t*-BuOH	CH_3CN + piperylene	CH_3 + acetone
11a + 11b	0.026	0.027	0.020	0.006
11a	0.021	0.021	0.017	
11b	0.0056	0.006	0.003	
11a/11b	3.8	3.5	5.1	1.7

formation. As expected, the norbornene quantum yield in benzene (a very poor hydrogen donating solvent) was greater (0.24) than in acetonitrile.[12b]

B. Comparison between *exo*-Acetylnorbornane (1) and *exo*-Benzoylnorbornane (17).[4] The behavior of ketone **1** was different from that of the corresponding aryl ketone (**17**)



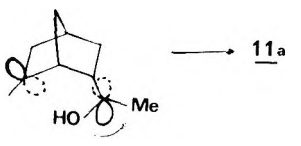
studied by Lewis,[4] which gave exclusively type II photoelimination in benzene.

Lewis showed that NII was much more efficient in the endo isomer **18** than in the exo isomer **17** [k_γ**18**/**17** = 500] and that this reflects conformational or stereoelectronic requirements for γ-hydrogen abstraction. The rigid bicycloalkane structure allows the carbonyl oxygen to come within 1.7 Å of the endo γ-H and more than 2.2 Å in the exo isomer.[4]

The same steric requirements exist in the *exo*-**1** isomer, which follows the NI pathway. We think that this photochemical behavior could be explained through energy considerations. The triplet energy of the excited ketones **1** and **3** (~78 kcal/mol) is located on a chromophore ($-COCH_3$) and is high enough to break the C–C bond. The triplet energy of aromatic ketone is much lower and spread over a larger chromophore (–COPh), which does not allow C–C bond rupture: γ-hydrogen abstraction is then the preferred reaction pathway followed by these ketones.[26] A result favoring this hypothesis was obtained with the exo ketone **3** (triplet energy ~74 kcal/mol). Here again, only the NI reaction was observed, but with a lower efficiency (0.28) than in ketone **1**.

C. Photochemical Behavior of *endo*-Acetylnorbornane (2). Photoelimination and cyclization reactions compete with the Norrish type I due to the favorable conformation for γ-H abstraction. The elimination reaction occurs almost exclusively from the singlet excited state and could not be sensitized by acetone.[9] In the cyclization reaction, however, a slight sensitization by acetone was possible. It must be pointed out that we observed a variation in the ratio of the isomeric alcohols **11**, depending on the carbonyl excited state (1.7 in the triplet state and 5.1 in the singlet state in acetonitrile in the presence of piperylene) (Table III).

The same stereoselectivity originating from the singlet excited state has already been observed by Turro[14] in the photocyclization of 1-adamantylacetone. This observation was consistent with a singlet short-lived biradical undergoing rehybridization on the γ-C resulting in a preferential rotation and closure to **11a**. The absence of stereoselectivity in the



triplet state may be due to the longer triplet biradical lifetime which could attain its preferential conformation before closure (cf. ref 14).

II. Phenyl Group Influence on Carbonyl Reactivity in Correlation with Relative Geometry of Both Chromophores in Ketones 3–6. A. Triplet Deactivation. Ketones **3–6** allow one to compare in the same system the three classical types of intramolecular ketone reactions, i.e., NI, NII, and photocyclization. As shown in Table II, the greatest influence of the β-phenyl group was observed for the type I reaction. Thus, norbornane (**8**) was formed essentially from the triplet either from the *exo*-**1** or *endo*-**2** isomer with good quantum

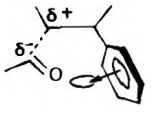
yields (respectively 0.64 and 0.14). For the *trans,exo*-acetylphenylnorbornane (**3**), the reaction was purely triplet but the quantum yield formation of **9** was lower (0.28). As before, we attributed this smaller value to the lower triplet energy level of the β-phenyl ketone relative to **1**. In the trans,endo ketone **4**, the type II and cyclization reactions are favored, since practically no NI product was detected. For the cis isomers neither *exo*-**5** nor *endo*-**6** underwent type I reaction, although their triplet is formed in good yield.

NII elimination occurs mostly via the singlet state, but sensitizing experiments showed that there was a greater participation of the triplet state in the trans isomer **4** (Φ_{sens}/Φ = 0.27) than in the cis isomer **6** (Φ_{sens}/Φ = 0.057).

Quenching experiments showed that photocyclization reactions occurred mostly via the triplet state of excited ketones. As in the NI and NII reactions, we observed a deactivation of those triplets only for the cis isomers (**11**, Φ = 0.026; **14**, Φ = 0.024; **15**, Φ = 0.012).

These results show that a considerable through-space interchromophoric coupling exists which provides a channel for rapid radiationless deactivation of the triplet. Such a coupling has been proposed by Whitten[2] and by Wagner and Sternitz in the β-phenyl aromatic ketones.[1b,c] This coupling could proceed via a *n*-type exciplex as proposed in the case of the benzophenone triplet quenching by aromatic solvents.[15] The radiationless deactivation of this exciplex leads to the ground-state molecule, and the cis geometry of **5** and **6** offers very favorable conditions for its formation. Thus ultraviolet spectra of these compounds showed important perturbations which are not observed in the trans isomers **3** and **4**, for which there is no possibility of such coupling (see Experimental Section). In acyclic β-phenyl ketones there is no important phenyl–carbonyl interactions in the ground state.[1a] However these take place in the excited state, implying preferential conformations for orbital overlap of the two chromophores.

It appears that γ-hydrogen abstraction by excited triplet ketone is not completely prevented by the *cis*-β-phenyl group, contrary to the Norrish I reaction. This fact could be due to a difference in activation energy between the two reactions. An alternate explanation could be that there is considerably more ionic character in the transition state for the NI reaction than for γ-hydrogen abstraction in alkanones, as in the case of aromatic ketones.[16]



The *n*-type exciplex tends to prevent bond breaking and thus disfavors the NI reaction, since the half-filled n orbital of the ketone is directed toward the aromatic electrons.

B. Singlet Deactivation. As shown in Table II, the major reaction pathway observed for the endo isomer occurs in the *singlet state*. Here again, we only observed a quantum yield decrease for the cis isomer (Φ in **2** = 0.096; in **4** = 0.22; in **6** = 0.059). This nonradiative decay from singlets of β-phenyl ketones in the course of the NII elimination has been extensively studied by Whitten in acyclic ketone systems.[2] This author concluded that there is significant through-space coupling between the two chromophores in the singlet state. Our comparative results obtained with endo ketones **4** and **6** agree with this type of coupling as in the triplet manifold.

III. Intersystem Crossing Quantum Yields in Acetylnorbornane Derivatives. Our results showed that there was a striking difference in the Φ_{isc} value between the *exo*-**1** (0.9) and *endo*-**2** (0.2) isomers. The decrease observed could be due to the availability of the γ-H in the endo ketone, which resulted in an increase in chemical reactivity from the singlet state and in radiative or nonradiative decay from this state.[17] The presence of a phenyl group in the cis or trans endo ketones **4** and **6** resulted in no change in the Φ_{isc}. In the exo compounds **3** and **5**, in which γ-H is less available, the low Φ_{isc} value (0.6) observed in the cis compound is due to the proximity of the phenyl group, which offers a different deactivating process from the singlet state (via the *n*-type exciplex).

Summary

The system studied has allowed us to compare the intramolecular influence of a phenyl group on the carbonyl reactivity of the three types of ketone photoreactions: NI, photoelimination, and photocyclization. Nothing was known about the phenyl influence on the latter.

It has been shown that deactivation of both singlet and triplet excited states occurs only when the two chromophores are in the cis position. This geometry favors the *n*-type exciplex formation, which provides a way for rapid radiationless deactivation of excited states. Finally, it has been found that NI is more subject to the presence of the *cis*-phenyl group than photocyclization, the other triplet reaction.

Experimental Section

Infrared spectra (IR) were determined in $CHCl_3$ solutions on a Perkin-Elmer Model 257 spectrometer; ultraviolet (UV) spectra were recorded on a Bausch and Lomb Spectrometric 505, in ethanol as solvent. Nuclear magnetic resonance (NMR) data were obtained from a Varian Model T60 or a Perkin Elmer R12 spectrometer in CCl_4 or $CDCl_3$ solutions. ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a Brucker HFX-90 MHz NMR spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in δ (ppm) from the internal standard Me_4Si. Mass spectra (MS) were recorded on a MS9 spectrometer. Vapor-phase chromatograms (VPC) were obtained from a Girdel 75 model on the following columns: A, 5% OV_1 (300 × 0.6 cm); B, 8% QF_1 (300 × 0.6 cm); C, 20% ββ′-ODPN (300 × 0.6 cm). Relative retention times (t_R) refer to the ratios of retention times of formed products to the corresponding starting product. Analyses were carried out in the Service Central de Microanalyse du CNRS. Melting points were uncorrected. All experiments were carried out under nitrogen.

***exo*-2-Acetylnorbornane (1)** was prepared according to Stockmann.[18] Pure product (4.6 g, 33 mmol, 67%) was obtained after chromatography on silica gel (5% ether in pentane) from 4.6 g of norbornene (49 mmol): UV λ_{max} 280 nm (ε 27); NMR ($CDCl_3$) δ 2.16 (s) in a multiplet between 2.0 and 2.8 (5 H), 1–1.9 (m, 9 H); ^{13}C NMR δ 28.7 (q, Me), 29.0, 29.9 (t, C_5, C_6), 32.5 (t, C_3), 36.0 (t, C_7), 36.2 (d, C_4), 40.0 (d, C_1), 55.0 (d, C_2), 209.0 (s, C=O).

***endo*-2-Acetylnorbornane (2).** *endo*-2-Norbornanecarboxylic acid (2.97 g, 21.2 mmol), prepared according to the literature,[19] was treated with MeLi in anhydrous ether. Workup and chromatography on silica gel (5% ether in pentane) gave 2.1 g (15.2 mmol, 72%) of **2**:[20] UV λ_{max} 280 nm (ε 24); NMR ($CDCl_3$) δ 2.08 (s) in a multiplet between 1.0 and 2.1 (12 H), 2.2–3 (m, 2 H); ^{13}C NMR δ 24.5 (t, C_6), 29.1, 29.7 (t, C_5–C_3), 29.6 (Me), 37.2 (d, C_4), 40.4 (d, C_1), 40.7 (t, C_7), 54.8 (d, C_2), 210.0 (s, C=O).

***exo*-2-Acetyl-*endo*-3-phenylnorbornane (3).** *endo*-3-Phenylnorbornene-2-*exo*-carboxylic acid (4.2 g, 19.8 mmol), prepared according to the literature,[21] was dissolved in 70 mL of anhydrous ether in a three-neck flask equipped with a magnetic stirrer, reflux condenser, and a dropping funnel. Methyllithium (40 mmol) in anhydrous ether was added dropwise. The mixture was stirred for 0.5 h and hydrolyzed by the addition of saturated NH_4Cl solution. Extraction and usual treatments furnish 4 g of crude product which was purified on alumina column chromatography (10% benzene in pentane) to yield 3.1 g (14.4 mmol, 73%) of unsaturated product, *exo*-2-acetyl-*endo*-3-phenylnorbornene: NMR (CCl_4) δ 1.5 (br d, 2 H), 2.1 (s, 3 H), 2.5 (br d, 1 H), 3 (m, 2 H), 3.5 (m, 1 H), 6 (m, 1 H), 6.5 (m, 1 H).

Hydrogenation in MeOH over PtO_2 of 1 g (4.7 mmol) of unsaturated ketone gave 0.94 g (4.39 mmol, 93%) of **3**: UV λ_{max} 258 (ε 250), $\lambda_{n\pi^*}$ 280 nm (ε 53); NMR (CCl_4) δ 1.3 (m, 6 H), 2 (s, 3 H), 2.5 (m, 3 H), 3.4 (m, 1 H), 7.2 (s, 5 H); ^{13}C NMR δ 22.6, 29.9 (t, C_6, C_5), 29.1 (Me), 38.3 (t, C_7), 41.2, 42.7 (C_1, C_4), 48.3, 59.2 (d C_3, C_2), 126.2, 128.2, 128.3, 141.6 (aromatic carbons), 209.1 (s, C=O); MS (*m/e*) 214 (M^+), 171, 147, 43. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.67; O, 7.47. Found: C, 83.90; H, 8.36; O. 7.48.

***endo*-2-Acetyl-*exo*-3-phenylnorbornane (4).** The corresponding carboxylic acid (430 mg, 2 mmol), prepared according to the literature,[21] was treated with $(COCl)_2$ in anhydrous benzene. The resulting

acid chloride was added at −78 °C to an ethereal solution of dimethylcopper reagent prepared according to the literature.[22] Crude product **4** (370 mg) was obtained after hydrolysis at −78 °C and usual chromatographic workup chromatographic over alumina (ether 1% in pentane) gave 274 mg (1.28 mmol, 64%) of pure product **4**: UV λ_{max} 258 (ϵ 246), $\lambda_{n\pi^*}$ 280 nm (ϵ 58); NMR (CCl_4) δ 1.4 (m, 6 H), 2.0 (s, 3 H), 2.6 (m, 3 H), 3.1 (m, 1 H), 7.0 (s, 5 H); ^{13}C NMR δ 23.9, 30.1 (t, C_6, C_5), 29.6 (Me), 38.9 (t, C_7), 41.0, 42.7 (d, C_1, C_4), 46.4, 64.8 (d C_3, C_2), 125.8, 126.9, 128.5, 146.4 (aromatic carbons), 208.7 (s, C=O); MS 214 (M^+), 171, 77, 43. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.67; O, 7.47. Found: C, 83.82; H, 8.50; O, 6.95.

***exo*-2-Acetyl-*exo*-3-phenylnorbornane (5).** Prepared from 127 mg (0.59 mmol) of the corresponding carboxylic acid[21] and treated as described above. Chromatography over alumina (ether 1% in pentane) gave 87 mg (0.41 mmol, 69%) of pure product **5**: UV λ_{max} 260 (ϵ 190), $\lambda_{n\pi^*}$ 280 nm (ϵ 20); NMR (CCl_4) δ 1.3 (s) in a multiplet centered at 1.4 (8 H), 2.3 (m, 3 H), 2.9 (m, 2 H), 7.2 (s, 5 H); ^{13}C NMR δ 28.5, 31.2 (C_5, C_6), 29.4 (Me), 37.1 (t, C_7), 38.5, 43.6 (d, C_1, C_4), 52.7, 62.6 (d, C_3, C_2), 126.5, 128.0, 128.3, 142.5 (aromatic carbons), 209.9 (s, C=O); MS (*m/e*) 214 (M^+), 171, 147, 77, 43. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.67; O, 7.47. Found: C, 83.85; H, 8.49; O, 7.54.

***endo*-2-Acetyl-*endo*-3-phenylnorbornane (6)** was prepared from 600 mg (2.75 mmol) of the corresponding cis carboxylic acid,[21] care being taken of the following steps. MeLi was freshly prepared and titrated in such a way to avoid its excess (negative Gilman's test). Hydrolysis of the reaction mixture was run at −78 °C with theoretical amounts of aqueous 5% H_2SO_4. Chromatography on silica (ether 2% in pentane) gave 380 mg (1.77 mmol, 64%) of 6 containing 4% of trans isomer **3** (VPC column B): UV λ_{max} 260 nm (ϵ 400), $n\pi^*$ disappears in $\pi\pi^*$ absorption; NMR (CCl_4) δ 1.5 in a broad multiplet centered at 1.4 (9 H), 2.4 (m, 2 H), 3 (m, 1 H), 3.7 (m, 1 H), 7.3 (m, 5 H); ^{13}C NMR δ 23.1, 23.3 (br s, C_5, C_6), 30.6 (q, Me), 39.4, 44.4 (d, C_1, C_4), 40.2 (t, C_7), 47.6, 57.8 (d, C_3, C_2), 126.1, 127.2, 127.8, 128.1, 128.6, 140.4 (aromatic carbons), 210.2 (s, C=O); MS (*m/e*) 214 (M^+), 171, 147, 43. Correct elemental analyses could not be obtained with this compound owing to its lability.

***exo*-2-Acetyl-d_3-*endo*-3-phenylnorbornane (16).** Prepared from 138 mg (0.64 mmol) of the corresponding carboxylic acid[21] by action of $(CD_3)_2CuLi$ in the conditions described above. Chromatography on silica gel (ether 2% in pentane) gave 96 mg (0.44 mmol, 69%) of **16**. The NMR spectrum was practically identical with that of **3**, exception being made of the singlet at δ 2 (3 H); MS (*m/e*) 217 (M^+), 171, 46.

4-Cyclopentyl-4-phenyl-2-butanone (12). Anhydrous THF (10 mL) was added to 10 mmol of cyclopentylmagnesium bromide in ether. The solution was added dropwise to a well-stirred mixture of 0.7 g (5 mmol) of *trans*-4-phenyl-3-buten-2-one and 28 mg (0.15 mmol) of CuI in anhydrous THF. After 2 h at room temperature, hydrolysis, and usual treatment, 1 g of crude product was obtained. Chromatography on SilicAR CC-4 (benzene 25% in pentane) gave 352 mg (1.64 mmol, 33%) of pure product: NMR (CCl_4) δ 1.8 (s) in a broad multiplet between 1 and 2 (12 H), 2.6 (m, 3 H), 7.1 (5 H); semicarbazone (EtOH) mp 152–153 °C. Anal. Calcd for $C_{16}H_{23}N_3O$: C, 71.04; H, 8.77; O, 5.57; N, 14.62. Found: C, 70.92; H, 8.68; O, 5.68; N, 14.48.

Photolyses. Preparative irradiations were carried out in a water-cooled immersion apparatus equipped either with a 450-W (Hanovia 450 W, lamp A), or a 100-W medium-pressure mercury arc (Hanau NK 6/20 100 W, lamp B). During irradiations a stream of argon was bubbled through the solutions. In the case of **3**, preparative irradiations were simply carried out in quartz tubes (lamp A) under argon atmosphere.

Irradiation of 1. A solution of 410 mg (2.3 mmol) of **1** in 280 mL of CH_3CN was irradiated for 7 h in a quartz apparatus (lamp B). VPC analysis (column A) showed almost complete disappearance of **1** and formation of two new compounds, **7** and **8**, identified by comparison of their retention times with those of authentic samples on three different VPC column (A, B, and C).

Irradiation of 2. (A) Irradiation in Acetonitrile. A solution of 480 mg (3.47 mmol) of **2** in 400 mL of CH_3CN was irradiated in a quartz apparatus (lamp B). Three photoproducts were detected by VPC (column B, 110 °C) in respective yields of 1 (**11a**, t_R = 0.49), 4 (**11b**, t_R = 0.62), and 21% (**10**, t_R = 1.22) relative to **2**. Chromatography of the crude mixture on silica gel gave 96 mg of volatile starting product **2** (ether 5% in pentane), 81 mg (0.58 mmol, 17%) of the colorless oil **10** (ether 5% in pentane), and 19 mg (0.14 mmol, 4%) of white needles **11a** (ether 30% in pentane). **10**: NMR ($CDCl_3$) δ 2.1 (s) in a broad multiplet between 1 and 3 (12 H), 5.7 (s, 2 H). **11a**: NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.1–1.8 (m, 6 H), 1.9–2.4 (m, 4 H and 3 H after deuteriation), 3.1 (m 1 H); ^{13}C NMR δ 19.5 (q, Me) 34.0 (*t*, C_2, C_8) 36.3, 39.2 (d, C_1, C_6), 38.0 (t, C_7), 45.0 (d, C_3, C_5), 79.1 (s, C_4); mp (sublimated) 94–95 °C. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21; 0, 11.58. Found: C, 77.88; H, 10.34; 0, 11.85.

(B) Irradiation in Acetone. A solution of 526 mg (3.8 mmol) of **2** in 450 mL of acetone was irradiated in a Pyrex apparatus for 16 h. The yields of **11a** and **11b** were respectively 17 and 9% relative to the starting product **2**. Chromatography of the crude mixture on silica gel gave a mixture of starting ketone **2** and unidentified products (ether 5% in hexane), 78 mg of a fraction containing **11b** (ether 10% in hexane), and 68 mg (13%) of **11a** (ether 20% in hexane). Another chromatography gave 6 mg of the very volatile alcohol **11b**: NMR ($CDCl_3$) δ 1.3 (s) in a broad multiplet between 1.1 and 2.4 (14 H); MS (*m/e*) 138 (M^+, low intensity), 120.

Irradiation of 3. A solution of 80 mg (0.37 mmol) of **3** in 10 mL of CH_3CN was irradiated for 16 h in quartz tubes (lamp B). VPC analysis (column A) showed the presence of a single product (t_R = 0.36) with traces of other unidentified products (~2%). Chromatography over SilicAR CC-4 (pentane) gave 22 mg (0.11 mmol, 31%) of **9**; NMR identical with literature description;[23] MS (*m/e*) 172 (M^+).

Another experiment from 150 mg of **3** (0.7 mmol) in acetone as solvent and in a Pyrex tube led to 83 mg (0.48 mmol, 68%) of pure product.

Irradiations of 4. (A) Irradiation in Acetonitrile. A solution of 450 mg (2.10 mmol) of **4** in 450 mL of CH_3CN was irradiated for 4 h (lamp B). Two photoproducts were detected by VPC (column A) in yields of 47 (t_R = 0.8) and 9% (t_R = 1.2) relative to the starting product **4**. Chromatography of the crude mixture on alumina gave 110 mg (25%) of **4**, 172 mg (0.80 mmol, 38%) of **13** (benzene 10% in pentane), and 33 mg (0.15 mmol, 7%) of **14** (ether). **13**: NMR (CCl_4) δ 1.8 (s, 3 H), 1.8–3 (m, 8 H), 5.6 (s, 2 H), 7.1 (s, 5 H); MS (*m/e*) 214 (M^+), 156, 147, 77, 43. Catalytic hydrogenation of **13** over PtO_2 in MeOH gave a compound identical (IR, NMR, VPC) with **12**.

By analytical VPC (column B) it was possible to separate the two isomers of **14** (**14a**/**14b** ~ 3), but they were obtained in pure form only in the case of the irradiation of **4** in acetone as solvent.

(B) Irradiation in Acetone. A solution of 450 mg (2.10 mmol) of **4** in 450 mL of freshly distilled acetone was irradiated for 15 h in a Pyrex reactor (lamp B). Short retention time products coming from irradiated acetone[24] were detected by VPC (column A). The yields of **13** and **14** were respectively 2 and 77% relative to the starting product. Chromatography of the crude mixture on alumina gave unidentified products, **4** (50 mg), **13** (15 mg, 3%) (benzene 75% in pentane), and the mixture **14a** + **14b** (380 mg, 80%) (ether 10% in benzene). VPC (column B) showed **14a**/**14b** ~ 3. Repeated chromatography of this fraction (benzene 75% in pentane) followed by preparative TLC gave 30 mg (7%) of pure **14b**: NMR ($CDCl_3$) δ 1.4 (s) in a multiplet between 1.3 and 1.6 (4 H), 1.7 (m, 2 H, 1 H after deuteriation), 1.9 (m, 1 H), 2.4 (m, 5 H), 3.3 (s, 1 H), 7.2 (m, 5 H); ^{13}C NMR δ 27.9 (Me), 31.7, 33.4 (C_8, C_7), 35.3, 43.9 (C_6, C_1), 45.0 (C_5), 46.6, 50.8 (C_3, C_2), 70.6 (C_4), 125.5, 127.9, 128.0, 145.3 (aromatic carbons); MS (*m/e*) 214 (M^+), 196.

Elution with benzene first gave a fraction containing both **14a** and **14b**, and then pure **14a**: 96 mg (21%); NMR ($CDCl_3$) δ 1.2 (s, 3 H), 1.4 (m, 2 H), 1.7 (m, 2 H), 2–3 (m, 4 H), 2.9 (s, 1 H), 3.2 (br s, 1 H), 7.2 (m, 5 H); ^{13}C NMR δ 20.1 (q, Me) 33.9, 34.0, (t, C_8, C_7), 39.3, 43.7 (d, C_6, C_1), 44.9 (d, C_5), 49.4, 50.6 (d, C_3, C_2), 78.9 (s, C_4), 125.7, 125.8, 128.2, 144.7 (aromatic carbons); MS (*m/e*) 214 (M^+), 196; mp (pentane–ether) 68 °C. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.67; O, 7.47. Found: C, 84.13; H, 8.46; O, 7.65.

Irradiation of 5. Ketone **5** was irradiated in different solvents (CH_3CN, acetone, *t*-BuOH). This compound was quite stable even after a long period of irradiation (20 h, lamp A).

Irradiation of 6. (A) Irradiation in Acetonitrile. A solution of 350 mg (1.6 mmol) of **6** in 300 mL of freshly distilled acetonitrile was irradiated for 16 h in a quartz reactor (lamp B). Two photoproducts were detected by VPC (column A) in yields of 47 (t_R = 0.79) and 20% (t_R = 1.1) relative to the starting product **6**. Chromatography of the crude mixture on silica gel gave 70 mg (20%) of **13** (ether 2% in pentane) and 27 mg (8%) of **15**, which crystallized into two forms (pentane–ether): NMR ($CDCl_3$) δ 0.4 (s, 3 H), 1.5 (m, 2 H), 2.2 (m, 4 H, 3 H after deuteriation), 2.8 (m, 2 H), 3.2 (m, 2 H), 7.2 (s, 5 H); ^{13}C NMR δ 22.3 (q, Me), 31.0 (t, C_8), 37.4 (t, C_7), 38.1, 41.6 (C_6, C_1), 45.6 (d, C_5), 47.8, 50.2 (d, C_3, C_2), 79.5 (s, C_4), 125.4, 127.5, 128.1, 141.7 (aromatic carbons); MS (*m/e*) 214 (M^+), 196; mp 80 and 90 °C. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.67; O, 7.47. Found: C, 83.82; H, 8.35; O, 7.65.

(B) Irradiation in Acetone. A solution of 175 mg of **6** (0.82 mmol) in 320 mL of acetone was irradiated for 19 h in a Pyrex reactor (lamp B). The yields of **13** and **15** determined by VPC (column A) were respectively 4 and 50% relative to the starting product. A first chro-

matography of the crude mixture on silica gel gave 54 mg of 6 and 73 mg (42%) of 15. A second chromatography (ether 5% in benzene) gave 49 mg (28%) of pure 15.

Quantum Yield Determinations. Solutions of different ketones 1–6 ($\sim 10^{-2}$ M) in spectrograde acetonitrile or in a 1 M solution of acetone in acetonitrile were subjected to three freeze–pump–thaw cycles and sealed at 10^{-4} mm in 10-mm o.d. quartz cells. Irradiations were carried out using a 313-nm line produced by a Bausch and Lomb monochromator. Light intensities were measured by ferrioxalate actinometry. Photolyses were run to <10% conversion, and the resulting solutions were analyzed by VPC.

Quenching Studies. Sample preparations and irradiations were the same as for the quantum yield determinations except that varying amounts of *cis*-1,3-pentadiene (10^{-3} to 0.6 M) were added to the solutions. Percentages of isomerization of *cis*-pentadiene were determined on column C (room temperature).

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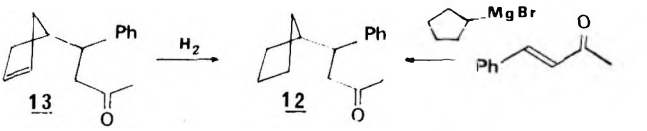
Registry No.—12, 67271-53-8; 12 semicarbazone, 67271-56-11; **16**, 67271-54-9; *endo*-2-norbornanecarboxylic acid, 934-28-1; *endo*-3-phenylnorbornane-2-*exo*-carboxylic acid, 59286-05-4; *endo*-2-carboxy-*exo*-3-phenylnorbornene, 58800-36-5; *exo*-2-carboxy-*exo*-3-phenylnorbornane, 59286-12-3; cyclopentyl bromide, 137-43-9; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; *exo*-2-acetyl-*endo*-3-phenylnorbornene, 67271-55-0; 2-*endo*-carboxy-3-*endo*-phenylnorbornene, 59286-09-8.

References and Notes

(1) (a) D. G. Whitten and W. E. Punch, *Mol. Photochem.*, **2**, 77 (1970); (b) P. J. Wagner, P. A. Kelso, A. E. Kemppainen, A. Haug, and D. R. Graber, *ibid.*, **2**, 81 (1970); (c) F. R. Stermitz, D. E. Nicodem, V. P. Muralidharan, and C. M. O'Donnell, *ibid.*, **2**, 87 (1970).
(2) G. L. B. Carlson, F. H. Quina, B. M. Zarnegar, and D. G. Whitten, *J. Am. Chem. Soc.*, **97**, 347 (1975).
(3) R. S. Sauers and A. M. De Paolis, *J. Org. Chem.*, **38**, 639 (1973).
(4) F. D. Lewis, R. W. Johnson, and R. A. Ruden, *J. Am. Chem. Soc.*, **94**, 4292 (1972).
(5) Hydrogenation of **13** over PtO_2 gave **12**, having spectral properties and VPC retention times of the synthetic sample prepared according to the following scheme.



(6) M. Geisel, C. A. Grob, W. Santi, and W. Tschudi, *Helv. Chim. Acta*, **56**, 1046 (1973).
(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, England 1969, p 81.
(8) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965). All of the plots obtained were treated by the least-squares method.
(9) I. Fleming and W. E. Long, *J. Chem. Soc., Perkin Trans. 2*, 14 (1976).
(10) P. J. Wagner, *Tetrahedron Lett.*, 1753 (1967).
(11) S. L. Murov "Handbook of Photochemistry", Marcel Dekker, New York, N.Y., 1973, p 55.
(12) (a) Traces of other unidentified products were detected by VPC, but we never attempted to isolate them. Among them, there are certainly type II and cyclization products and CH_2CN adducts on the norbornene double bond.[13] (b) A preliminary experiment in benzene showed that the NI reaction quantum yield is lower than in acetonitrile (7, $\Phi = 0.24$; **8**, $\Phi = 0.15$) and that a compound ($\Phi = 0.12$) appeared having retention time which could correspond to an NII reaction product.
(13) S. H. Schroeter, *Justus Liebigs Ann. Chem.*, 1890 (1974).
(14) R. B. Gagosian, J. C. Dalton, and N. J. Turro, *J. Am. Chem. Soc.*, **97**, 5189 (1975).
(15) M. W. Wolf, R. E. Brown, and L. A. Singer, *J. Am. Chem. Soc.*, **99**, 526 (1977), and references cited herein.
(16) F. D. Lewis, R. T. Lauterbach, H. G. Heine, W. Hartmann, and H. Rudolph, *J. Am. Chem. Soc.*, **97**, 1519 (1975). A result in favor of this hypothesis is that the NI quantum yield is greater in acetonitrile (0.65) than in nondissociative benzene (0.4).[12b]
(17) N. C. Yang, S. P. Elliott, and B. Kim, *J. Am. Chem. Soc.*, **91**, 7551 (1969).
(18) H. Stockmann, *J. Org. Chem.*, **29**, 245 (1964).
(19) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1959).
(20) J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959).
(21) K. Alder and W. Günzl, *Chem. Ber.*, **93**, 809 (1960).
(22) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).
(23) F. A. Carey and H. S. Tremper, *J. Org. Chem.*, **34**, 4 (1969).
(24) J. T. Przybytek, S. P. Singh, and J. Kagan, *Chem. Commun.*, 1224 (1969).
(25) H. Sakuragi, M. Yoshida, H. Kinoshita, K. Utena, K. Tokumaru, and M. Hoshino, *Tetrahedron Lett.*, 1529 (1978).
(26) Just after submission of our manuscript, H. Sakuragi[25] has shown that the reactivity of the triplet states of the *O*-acyl oximes are correlated with their triplet energies.

Marine Natural Products: Sesquiterpene Alcohols and Ethers from the Sea Hare *Aplysia dactylomela*

Francis J. Schmitz,* Francis J. McDonald, and David J. Vanderah[1]

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019

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Three isomeric sesquiterpene ethers, dactyloxene-A, -B, and -C, as well as a related alcohol, dactylenol, and its acetate were isolated from the sea hare *Aplysia dactylomela*. Structure determinations involved ^{13}C NMR, ^{1}H NMR in the presence of shift reagent, and chemical degradation. All of the compounds have a common rearranged monocyclofarnesyl skeleton. Dactyloxene-B and -C are stereoisomers, each having a tetrahydrofuran ring spiro-fused on a substituted cylohexene ring. Dactyloxene-A possesses an oxadecalin skeleton. Dactylenol was converted by acid treatment to a mixture containing dactyloxene-A and -C.

Earlier we described[2] the isolation of dactyloxene-B (**5**), a sesquiterpene ether having a rearranged monocyclofarnesyl skeleton, from the sea hare *Aplysia dactylomela*. Since then, other investigators studying marine red algae have discovered two alcohols[3] having the same carbon skeleton as **5** as well as two monobromo alcohols[4] and a related ether,[5] each having an unrearranged monocyclofarnesyl skeleton. One of the bromo alcohols has been synthesized by a biomimetic route utilizing bromonium ion induced cyclization of a farnesyl derivative.[6] In this paper we report the isolation and structure determination of four new monocyclofarnesyl sesquiterpenoids from *A. dactylomela*, all of which have the rearranged skeleton of dactyloxene-B (**5**). Two of these compounds are ethers, dactyloxene-A (**12**) and -C (**10**). The remaining compounds are an alcohol, dactylenol (**1**), and its acetate **4**. In addition to these sesquiterpenoids, extracts of *A. dactylomela* have also yielded a new bicyclic sesquiterpene alcohol, dactylol,[7] and two halogenated straight-chain acetylenic ethers,[8] one of which has shown interesting central nervous system activity.[9]

The sesquiterpene ethers **5**, **10**, and **12**, the related alcohol **1**, and the acetate **4** were isolated from hexane extracts of whole dried animals or dichloromethane solubles of an alcohol extract of fresh digestive glands of the sea hare. Chromatography of the hexane extracts over Florisil using hexane as eluent provided fractions containing dactyloxene-A, -B, and -C.

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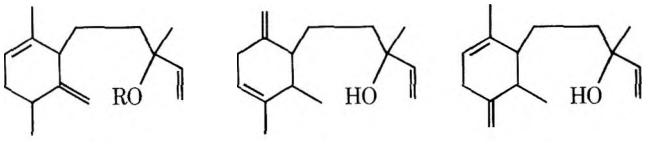
Repeated preparative layer chromatography (silica gel) of these fractions yielded the pure sesquiterpene ethers. Dactylenol (1) and its acetate (4) were eluted from the Florisil column with hexane–benzene in fractions that also contained dactylyne,[8a] isodactylyne,[8b] and dactylol.[7] Dactylenol (1) was isolated from these fractions by repeated silica gel chromatography followed by silver nitrate–silica gel preparative layer chromatography. Dactylenol acetate (4) was partially purified by silica gel chromatography, but final purification of this compound could be accomplished only by preparative gas chromatography.

Dactylenol (1) was obtained as a colorless oil: $[\alpha]_C$ +204°; $C_{15}H_{24}O$. Absorption in the infrared spectrum at 3400 cm^{-1} and the absence of signals in the ^1H NMR spectrum in the δ 3.0–4.5 region indicated that dactylenol was a tertiary alcohol.

The ^1H NMR spectrum revealed the presence of three methyl groups in 1: a quaternary methyl most likely bonded to the carbinol carbon [δ 1.14 (s)], a secondary methyl [δ 1.08 (d)], and an olefinic methyl group [δ 1.68 (brd s)] on a trisubstituted double bond. The olefinic region possessed the following signals: a broad one-proton multiplet at δ 5.36 coupled to the olefinic methyl signal, a two-proton doublet at δ 4.73 (J = 2 Hz) corresponding to an exocyclic methylene group, and three one-proton signals that formed a clear AMX pattern [δ 5.06 (J = 10 and 2 Hz), 5.20 (J = 18 and 2 Hz), and 5.94 (J = 18 and 10 Hz)]. The last signals are indicative of a vinyl group attached to a quaternary center. Assuming that this group is attached to the quaternary carbinol carbon leads to formulation of the partial structure $-C(OH)(CH_3)-CH{=}CH_2$.

Three possible structures for dactylenol, 1, 2, and 3, could be envisaged from the spectrally deduced structural fragments, the inclusion of a ring to account for the final degree of unsaturation required by the molecular formula, and consideration of the isoprene rule. Structure 1 was confirmed for dactylenol by extensive decoupling of the europium shifted ^1H NMR spectrum (0.45 mol ratio for Eu(fod)$_3$/dactylenol). Under these conditions the signal for each of the nonequivalent protons or sets of protons in dactylenol was distinctly resolved. The increments in chemical shifts for the quaternary methyl signal (δ 1.14→8.75) and the lowest field signal from the vinyl group (δ 5.94→12.5) confirmed that these groups are attached to the carbinol carbon. The methylene chain attached to the carbinol carbon was identified by the occurrence of a pair of one-proton doubled triplets at δ 9.27 and 9.63 (J = 13 and 4 Hz) coupled to another pair of one-proton signals at δ 6.82 (tt, J = 13 and 4 Hz) and 6.26 (ddt, J = 13, 10, and 4 Hz). The latter signals were further coupled only to a one-proton, broadened doublet at δ 4.36 (brd d, J = 10 Hz, small). Irradiation of this δ 4.36 signal revealed that it was coupled only to the two methylene protons in the side chain and slightly with one of the exocyclic methylene protons (δ 5.68), thus supporting structure 1. Further decoupling showed that



1, R = H
4, R = Ac

2 3

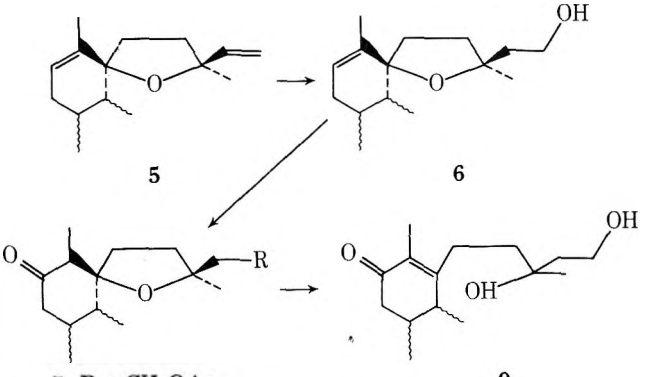
the methine proton signal at δ 3.66 (poorly resolved septet?), which was coupled to the secondary methyl group at δ 1.34, was coupled further only to two one-proton multiplets (δ 2.02 and 2.63). Both of the last signals were coupled to the olefinic proton (δ 5.80) of the trisubstituted double bond. This confirms all of the proton sequences in structure 1 and unambiguously confirms it as the structure for dactylenol.

Dactylenol acetate (4), an oil, $[\alpha]_D$ +168°, $C_{17}H_{26}O_2$, was correlated with dactylenol (1) by reductive removal of the acetate using lithium aluminum hydride. Conversely, dactylenol (1) was converted to the acetate 4 in approximately 10% yield (GC analysis) by reaction with acetic anhydride–pyridine at 50 °C for 8 h.

Dactyloxene-B (5), an oil, $[\alpha]_D$ +106°, $C_{15}H_{24}O$, exhibited infrared absorption indicative of double bonds [3080, 1640, 910 (vinyl) and 810 (trisubstituted double bonds) cm^{-1}] and an ether group (990 cm^{-1}), while being devoid of hydroxyl and carbonyl absorption. Only end absorption was noted in the UV spectrum. The ^{13}C NMR spectrum possessed singlet signals for two carbons attached to oxygen (δ 83.2 and 86.1), and this established the ditertiary ether nature of dactyloxene-B. The ^{13}C NMR spectrum further showed signals for only four unsaturated carbons, all sp^2: δ 145.6 (d), 136.9 (s), 124.2 (d), and 110.7 (t). Hence, dactyloxene-B must be bicyclic.

The ^1H NMR spectrum of dactyloxene-B exhibited signals for four methyl groups: δ 0.97 and 1.06 (doublets, secondary methyls), 1.34 (s, $-C(CH_3)-O-$), and 1.70 (olefinic methyl). Decoupling of the secondary methyl signals by irradiation at δ 1.77 and 1.52, respectively, demonstrated that the secondary methyl groups are attached to separate carbons and are not part of an isopropyl group. The olefinic region of the spectrum contained a broad multiplet at δ 5.44 that was reduced to a triplet upon irradiation at δ 1.70 (vinyl methyl position), thus indicating the partial structure $-CH_2CH{=}C(CH_3)-$. The remaining signals in the olefinic region were a set of three one-proton signals that formed a clear AMX pattern [δ 4.97 (J = 11 and 2 Hz), 5.12 (J = 17 and 2 Hz), and 6.09 (J = 17 and 11 Hz) indicative of a vinyl group attached to a quaternary center as in 1.

By analogy with structure 1, the above structural units are readily incorporated into formula 5 as a possible structure for dactyloxene-B. Compelling support for this formula was obtained from the mass spectral fragmentation pattern which contained a sizeable peak at m/e 164 (calcd for $C_{11}H_{16}$, 164.1201; found, 164.1199), corresponding to a facile loss of C_4H_8 in a retro-Diels–Alder fragmentation.



7, R = CH_2OAc
8, R = CO_2H

9

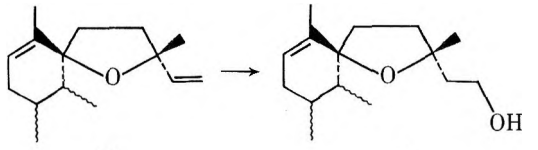
Additional confirmation for structure 5 was obtained by the conversions outlined below. Hydroboration of dactyloxene-B (5) with a hindered borane followed by oxidation yielded the alcohol 6, which showed the same facile loss of C_4H_8 in its mass spectrum as did 5. The acetate of 6 upon hydroboration followed by oxidation with chromic acid[10] afforded two products: keto acetate 7 and keto acid 8. The keto acid 8 showed carbonyl absorption only at 1700 cm^{-1}, corresponding to both carboxyl and cyclohexanone carbonyl groups, thus confirming the carbocyclic ring size in dactyloxene-B (5). The keto acetate 7 upon treatment with sodium methoxide in methanol at room temperature underwent a facile elimination to give the α,β-unsaturated keto diol 9 (IR 1660 and 1650 cm^{-1}). The ^1H NMR spectrum of 9 possessed a signal for an olefinic methyl

Table I. Europium ^{1}H NMR Shift Data for Alcohols 6 and 11

	6				11			
	Eu(fod)$_3$/alcohol mole ratio (±5%)				Eu(fod)$_3$/alcohol mole ratio (±5%)			
protons	0	0.57	1.26	Δδ	0	0.57	1.26	Δδ
secondary Me	0.97	1.52	1.75	0.78	0.97	1.10	1.10	0.13
secondary Me	1.04	2.34	3.05	2.01	1.00	2.40	3.60	2.60
$CH_3C\lessdot O$	1.30	3.50	4.90	3.60	1.36	2.92	4.60	3.24
$-C=C(CH_3)-$	1.74	3.80	4.70	2.96	1.74	2.46	3.18	1.44
$-CH_2CH_2OH$	3.7	4.70	5.72		3.7	3.4	5.17	
		7.00	9.85			5.96	9.90	
		11.65	15.85			9.00	14.40	
		12.80	17.65			10.10	16.93	
$-CH=C-$	5.85	6.10	6.45	1.10	5.35	5.6	5.80	0.45

group (δ 1.78), but it clearly lacked any olefinic proton signals. This ring opening confirmed that one of the ether links is β to the carbonyl group in **7**, and hence allylic to the ring double bond as proposed in **5**. Thus, the overall structure for dactyloxene-B, disregarding stereochemistry, is given by **5**.

Dactyloxene-C (**10**), a colorless oil, $[\alpha]_D$ +45.8°, $C_{15}H_{24}O$, possessed the same diagnostic spectral features in its IR, ^{1}H NMR, ^{13}C NMR, and mass spectra as dactyloxene-B (**5**), and hence the two were judged to be stereoisomers. Both dactyloxene-C (**10**) and the derived alcohol **11** (selective hydroboration/oxidation) showed a facile loss of C_4H_8 in their mass spectra, corresponding to a retro-Diels–Alder loss of butene as observed for **5**. In the ^{1}H NMR spectrum of dactyloxene-C (**10**), the two secondary methyl resonances are superimposed to give a single doublet at δ 0.93 in carbon tetrachloride, but in benzene-*d* two doublets are observed. The stereochemical relationships of **5** and **10** are discussed below.

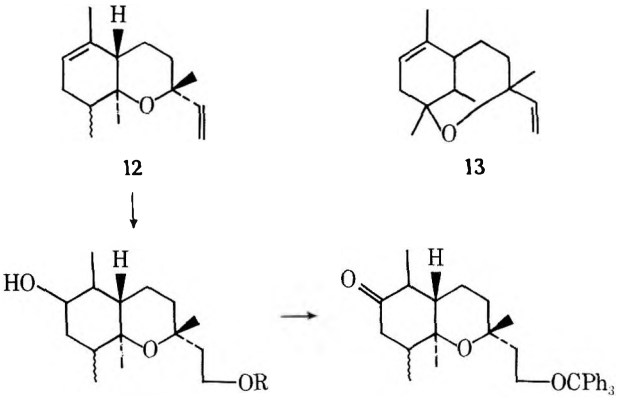


10 **11**

Dactyloxene-A (**12**), a colorless oil, $C_{15}H_{24}O$, exhibits a small negative rotation, $[\alpha]_D$ −5.9°, in contrast to the positive rotations found for the isomeric ethers. The infrared spectrum of **12** shows absorption for unsaturation (1630, 910, and 790 cm^{-1}) and an ether (990 cm^{-1}). The ^{13}C NMR spectrum contained signals corresponding to two quaternary carbons attached to oxygen [(δ 75.7 and 72.0) and four sp^2 carbons (144.2, 135.4, 118.7, and 109.7 (t)], thus characterizing dactyloxene-A also as a bicyclic ditertiary ether.

The ^{1}H NMR spectrum of dactyloxene-A (**12**) was significantly different from those of **5** and **10** in the methyl region. Two quaternary methyl groups were indicated in **12** (δ 1.04 and 1.23) and only one secondary methyl group (δ 0.97), in addition to one olefinic methyl (δ 1.68). The olefinic region exhibited signals for one proton on a trisubstituted double bond of the type $-CH_2CH=C(CH_3)-$ (δ 5.20) and three distinct multiplets corresponding to a vinyl group attached to a quaternary center (δ 4.94, 4.95, and 6.10).

Using compounds **1**, **5**, and **10** as models, the structures **12** and **13** were formulated as likely ones for dactyloxene-A based on the spectral data. The large peak in the mass spectrum corresponding to a reverse Diels–Alder fragmentation, prominent in the spectra of dactyloxene-B (**5**) and C (**10**), was completely absent in the spectrum of dactyloxene-A. A decision in favor of formula **12** was made on the basis of the chemical conversions outlined below. Hydroboration of dactyloxene-A with excess diborane followed by hydrogen peroxide oxidation afforded the diol **14**, which was selectively tritylated to give the ether alcohol **15**. Oxidation of **15** with chromium trioxide–pyridine complex[11] afforded in quantitative yield the keto trityl ether **16**, which showed carbonyl absorption at 1712 cm^{-1} in agreement with the postulated cyclohexene structure for dactyloxene-A. Treatment of the ketone **16** with sodium methoxide–methanol did not bring about the elimination and ether ring opening that would be expected for a ketone derived from structure **13** (cf. the ready opening observed for the keto acetate **7** derived from dactyloxene-B). Thus, the overall structure **12** is proposed for dactyloxene-A.



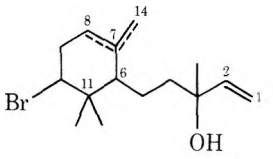
12 **13**

14, R = H
15, R = CPh_3

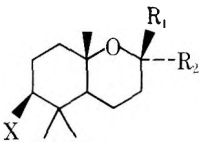
16

A tentative partial assignment of the relative stereochemistry of **5** and **10** was derived from analysis of the europium induced chemical shifts of the methyl group signals in the respective derived alcohols **6** and **11** (see Table I). The chemical shift changes in the protons of the hydroxyethyl side chain provide a convenient internal standard to show that comparable complexing with Eu(fod)$_3$ occurred with both alcohols. The signal for the olefinic methyl group in **6** was shifted downfield more than twice as much as the corresponding signal in **11**. Calculations using a graphical method[12] and assuming that the principal magnetic axis falls approximately parallel to and near the plane of the tetrahydrofuran ring predict a significantly larger shift for the vinyl methyl signal when that group and the hydroxyethyl side chain are cis oriented on the tetrahydrofuran ring. This leads to the conclusion that **5** and **10** differ in configurations at the tertiary ether carbons as shown.

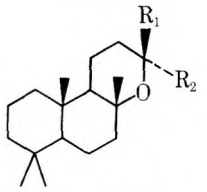
The partial relative stereochemistry shown for **12** is also based on ^{1}H NMR data. The chemical shifts for the quaternary methyl groups in **12** (δ 1.04 and 1.23) are very similar to those for the analogous methyl groups in 3β-bromo-8-*epi*-caparrapi oxide (**19**) (δ 1.12 and 1.14),[5] (+)-8-*epi*-caparrapi oxide (**21**) (δ 1.14 and 1.22),[13] and epimanoyl oxide (**23**) (δ 1.08 and 1.17)[14] all of which have the cis 1,3-diaxial quaternary methyl/vinyl group arrangement as proposed for **12**. On the other hand, in those cases where the two quaternary methyl groups are cis 1,3-diaxially oriented, i.e., caparrapi oxide (**20**)[13] and manoyl oxide (**22**),[14] the quaternary methyl group



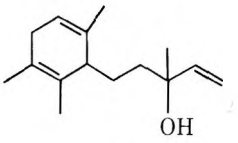
17, Δ^7
18, $\Delta^{7,14}$



19, X = Br; R_1 = CH=CH_2; R_2 = CH_3
20, X = H; R_1 = CH_3; R_2 = CH=CH_2
21, X = H; R_1 = CH_3; R_2 = CH=CH_2



22, R_1 = CH_3; R_2 = CH=CH_2
23, R_1 = CH=CH_2; R_2 = CH_3



24

chemical shifts differ by only 0.02 ppm or less. The signal for the -CH=CH_2 proton in **12** occurs at δ 6.10, close to where the corresponding protons in (+)-8-*epi*-caparrapi oxide (**21**) and epimanoyl oxide (**23**) absorb (δ 6.08 and 6.04, respectively). The trans ring juncture with the axial vinyl group in **12** is also supported by the fact that the -C**H**=CH_2 proton experiences long range coupling (~1 Hz). The W arrangement[15] of bonds between this proton and one of the ring methylene protons that is conducive to such coupling is best accommodated when the vinyl group is axial.

Treatment of **1** with toluenesulfonic acid or BF_3 etherate in ether afforded a complex mixture of products (at least 22 components) which contained **5** as one of the major components and **12** as a minor one. No attempts were made to optimize conditions for this conversion or to identify the remainder of the products. It is interesting to note that under these conditions the tetrahydrofuran derivative **5** is formed to a greater extent than the tetrahydropyran isomer **12**, even though formation of **5** requires isomerization of **1** prior to cyclization.

Dactylenol (**1**), its acetate **4**, and the ethers **5**, **10**, and **12** are closely related structurally to α- and β-snyderol (**17** and **18**),[4] 3β-bromo-8-*epi*-caparrapi oxide (**19**),[5] and nidifidienol (**24**),[3] all of which have been isolated from marine red algae. Three of these terpenoids, **17**, **18**, and **19**, retain an unrearranged monocyclofarnesyl skeleton, while the fourth, **24**, has the same rearranged skeleton that **1**, **4**, **5**, **10**, and **12** have. The biogenesis proposed for this group of compounds involves bromonium ion induced cyclization of farnesol.[16] Solvolytic loss of bromine from **17** followed by a methyl migration would produce an intermediate that could readily give rise to **1**, **4**, **5**, **10**, **12**, and **24**.

Experimental Section[17]

Isolation of Dactylenol (1), Dactylenol Acetate (4), and Dactyloxene-A (12), -B (5), and -C (10). Sea hares were collected and extracted as described previously.[8b] A portion (5.0 g) of the fourth hexane fraction (10.63 g) from the Florisil chromatography described earlier was chromatographed on a column using 40 g of silica gel H. The column was eluted with a benzene–hexane (15:85) mixture. An elution volume of 50–320 mL yielded a red oil (2.88 g, fraction A). The next 75 mL of eluate, fraction B, contained 0.51 g of a mixture consisting primarily of dactyloxene-A and -B with small amounts of dactyloxene-C. Further elution, 15-mL cuts, yielded four additional fractions containing sesquiterpene ether mixtures, fractions C (0.25 g), D (0.20 g), E (0.14 g), and F (0.10 g).

Pure dactyloxene-A (**12**) could be obtained from fraction B by thick-layer chromatography on silica gel–9% silver nitrate plates, 20 × 20 cm, 2 mm thick. A 100-mg amount of fraction B on a single plate eluted twice with ethyl acetate–diethyl ether–hexane (4:8:88) gave 25 mg of pure dactyloxene-A. (Bands were visualized by spraying the edges and a center strip with 2′,7′-dichlorofluorescein.) Alternatively, pure dactyloxene-A could be obtained by repeated chromatography of fractions enriched in this isomer over TLC mesh silica gel using a hexane–ether (98:2) mixture as eluent.

Dactyloxene-B and -C were each purified by repeated chromatography of fractions C–F over TLC mesh silica gel using a hexane–ether (98:2) mixture as eluent.

The combined yield of the dactyloxene-A, -B, and -C mixture from the original hexane extract was approximately 0.4%.

The sesquiterpene ethers were obtained from the alcohol extracts of freshly collected digestive glands somewhat more conveniently in the following manner. The concentrated alcohol extract was suspended in water and extracted with dichloromethane for 24 h. The dichloromethane solubles were dissolved in a methanol–water (9:1) mixture and extracted three times with hexane. A 33-g portion of the hexane extract was distilled at 53–67 °C and 5 μm of pressure to yield an orange distillate (9.58 g). Chromatography of this distillate over silicic acid (Bio-Sil A, 80 g; Bio-Rad Laboratories, Richmond, Calif.) with a hexane–benzene mixture (1:1) gave fractions containing dactyloxene-A, -B, and -C, quite free of other contaminants, and some fractions were nearly homogeneous with respect to individual isomers.

Dactyloxene-A (12): Colorless oil; $[\alpha]_D$ −5.9° (*c* 1.4, $CHCl_3$); n^{24}_D 1.4912; IR (film) 3090, 1630 (w), 1450, 1375, 990 (ether), 910 (vinyl), 790 cm^{-1}; UV, only end absorption; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 (3 H, d, *J* = 6 Hz), 1.04 and 1.23 (3 H each, s), 1.68 (3 H, m, vinyl methyl), 1.3–2.4 (8 H, m), 4.94 (1 H, dd, *J* = 11 and 1.5 Hz), 4.95 (1 H, d, *J* = 18 and 1.5 Hz), 5.20 (1 H, m), 6.10 (1 H, ddd, *J* = 18, 11, and 1.0 Hz). ^{13}C NMR ($CDCl_3$) (off-resonance mult): sp^2 δ 144.3 (d), 135.4 (s), 118.7 (d), 109.7 (t); sp^3 δ 75.7 (s), 72.0 (s), 47.4 (d), 33.3 (t), 32.3 (t), 31.5 (q), 28.3 (d), 22.4 (t), 21.4 (q), 20.8 (q), 14.3 (q). Mass spectrum, *m/e* 220.1838 (M^+; calcd for $C_{15}H_{24}O$, 220.1827), (70 eV) (relative intensity) 220 (M^+, 3), 202 (14), 187 (7), 177 (3), 173 (6), 159 (6), 152 (10), 145 (10), 133 (50), 121 (100), 120 (50), 109 (43), 105 (43), 91 (27).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.91; H, 10.99.

Dactyloxene-B (5): colorless oil; $[\alpha]_D$ +110.2° (c 0.74, $CHCl_3$); n^{25}_D 1.4925; IR (film) 3080, 1640, 990 (ether), 910 (vinyl), 810 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$), see text and ref 2. ^{13}C NMR ($CDCl_3$) (off-resonance mult): sp^2 δ 145.6 (d), 136.9 (d), 124.2 (d), 110.7 (t); sp^3 δ 86.1 (s), 83.2 (s), 45.6 (d), 38.0 (t), 34.9 (t), 32.6 (t), 32.1 (d), 27.8 (q), 20.9 (q), 20.0 (q), 15.0 (q). Mass spectrum, *m/e* 220.1814 (M^+; calcd for $C_{15}H_{24}O$, 220.1827), (70 eV) 220 (M^+, 1), 202 (78), 187 (41), 173 (61), 164 (19), 164.1199 (calcd for $C_{11}H_{16}O$, 164.1201), 145 (47), 133 (100), 132 (87), 121 (53), 119 (59), 105 (50), 91 (47), 79 (23), 77 (27), 54.0466 (calcd for C_4H_8, 54.0469).

Anal. Calcd for $C_{15}H_{24}O$; C, 81.76; H, 10.98. Found: C, 81.94; H, 11.04.

Dactyloxene-C (10): colorless oil; $[\alpha]_D$ +45.8° (*c* 0.9, $CHCl_3$); n_D 1.4941; IR (film) 3080, 1640, 1460, 1375, 1015 (ether), 910 (vinyl), 780 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.93 (6 H, d, *J* = 6 Hz, coincident methyl d), 1.40 (3 H, s, -$C(CH_3)$-O-), 1.80 (3 H, m, olefinic methyl), 5.0 (1 H, dd, *J* = 10 and 2 Hz, -CH=C**H**$_2$, cis H), 5.17 (1 H, dd, *J* = 17 and 2 Hz, -CH=C**H**$_2$, trans H), 5.41, (1 H, m, -CH=C(CH_3)-), 6.13 (1 H, dd, *J* = 17 and 10 Hz, -C**H**=CH_2); ^1H NMR (C_6D_6) δ 0.89 and 0.94 (3 H each, d, *J* = 7 Hz), 1.33 (3 H, s), 1.74 (3 H, m); ^1H NMR (decoupling in C_6D_6) irr δ 1.56 (collapse δ 0.89) and irr δ 1.78 (collapse δ 0.94). ^{13}C NMR ($CDCl_3$) (off-resonance mult): sp^2 δ 145.3 (d), 139.2 (s), 123.9 (d), 110.7 (t); sp^3 δ 89.2 (s), 83.8 (s), 45.7 (d), 37.9 (t), 34.9 (t), 32.9 (q), 31.5 (t), 28.7 (q), 20.1 (q), 19.9 (d), 13.3 (q). Mass spectrum, *m/e* 205.1586 (M^+ − 15; calcd for $C_{14}H_{21}O$, 205.1592), (70 eV) (relative intensity) 202 (M^+ − 18, 100), 137 (52), 173 (51), 164 (35), 164.1194 (calcd for $C_{11}H_{16}O$, 164.1201), 159 (20), 145 (61), 133 (95), 119 (75), 105 (57), 91 (39), 84 (56), 77 (27).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.91; H, 10.99.

Isolation of Dactylenol (1) and Dactylenol Acetate (4). A portion (2.62 g) of the material obtained in combined fractions 9–11 from the Florisil chromatography described earlier[8b] was chromatographed on TLC mesh silica gel (40 g) using benzene–hexane (1:1) as solvent. After initially collecting 31 15-mL fractions, many of which contained dactylyne,[8a] three 100-mL fractions were collected. The first of these contained predominantly (80–90%) dactylenol acetate (**4**) (61 mg).

Attempts to obtain pure **4** by further chromatography on silica gel or 9% silver nitrate impregnated silica gel were unsuccessful. Preparative gas chromatography on a 6 ft × 0.25 in 20% FFAP column at 169 °C yielded 4 as a colorless oil: $[\alpha]_D$ +168° (*c* 2.46, $CHCl_3$); bp (Kugelrohr) 75 °C yielded 4 as a colorless oil: $[\alpha]_D$ +168° (c 2.46, $CHCl_3$); bp (Kugelrohr) 75 °C (1 Torr); IR (neat) 3090, 2970, 2945, 2885, 2835, 1740, 1645, 1455, 1370, 1245, 1090, 915, 885 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.08 (3 H, d, *J* = 6 Hz), 1.48 (3 H, s, $CH_3CO_2C(CH_3)$–), 1.65 (3 H, brd s, –CH=C(CH_3)–, 1.95 (3 H, s, acetate), 2.6–~1.12 (8 H, m), 4.68 (2 H, brd d, *J* = 2 Hz, C=CH_2), 5.05 (1 H, dd, *J* = 10 and 2 Hz, –CH=CH_2, cis H), 5.08 (1 H, dd, *J* = 17 and 2 Hz, –CH=CH_2, trans H), 5.23 (1 H, brd t, *J* = 6 and <1 Hz, –C**H**=C(CH_3)–), 5.91 (1 H, dd, *J* = 17 and 10 Hz, –C**H**=CH_2); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion observed) 202 (M^+ − 60, 35), 187 (17), 173 (16), 159 (15), 145 (11), 134 (97), 121 (100), 105 (12), 81 (42).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.72; H, 9.95.

Chromatography of the material (6.3 g) obtained from the combined fractions 15–18 described earlier[8b] on 60 g of TLC mesh silica gel using benzene–hexane (7:3) as solvent and collecting 50-mL fractions yielded, in fractions 17–20 and a 100-mL 100% benzene flush, ~1.8 g of dactylenol (**1**), homogeneous by TLC analysis. Gas chromatographic analysis of this material on a 5 ft × ⅛ in 10% FFAP column indicated that this material was a mixture of at least five components. Pure **1** was obtained by chromatography on 9% $AgNO_3$ impregnated silica gel thick-layer plates (20 × 20 cm, 2 mm thick) employing ethyl acetate–cyclohexane (4:6) for development. From a 100-mg sample applied on a single plate, 40–50 mg of pure dactylenol was obtained.

Pure dactylenol (**1**) was a colorless oil: $[\alpha]_D$ +203.8°; IR (neat) 3400 (broad), 3080, 1640, 1150, 1100, 985, 910, 880, 800, 775 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.60–1.0 (8 H, m), see text for remainder; ^1H NMR (100 MHz, CCl_4, 0.45 mol ratio of Eu(fod)$_3$/dactylenol) (signals not discussed in text) δ 2.29 (3 H, m, vinyl methyl), 5.30 (1 H, d, *J* = 2 Hz), 7.81 (1 H, dd, *J* = 10 and 1 Hz, –CH=CH_2, cis H), 10.75 (1 H, dd, *J* = 18 and 1 Hz, –CH=CH_2, trans H); mass spectrum (70 eV), *m/e* (relative intensity) 220 (M^+, 3), 202 (13), 187 (12), 173 (10), 159 (8), 145 (8), 134 (100), 132 (23), 121 (80), 119 (32), 105 (12), 71 (10).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.94; H, 11.14.

Dactylenol (1) from Dactylenol Acetate (4). To a 25-mL round-bottom flask containing 57.3 mg of **4** and a magnetic stirring bar was added ~10 mL of dry ether (distilled directly from lithium aluminum hydride) and then 20 mg of lithium aluminum hydride ($LiAlH_4$). After the reaction mixture had stirred at room temperature for 30 min, excess $LiAlH_4$ was destroyed by the addition of ethyl acetate followed by water. The water layer was extracted twice with ethyl acetate and twice with ether. The organic layers were combined, dried (Na_2SO_4), and evaporated under reduced pressure, leaving 49.5 mg of a colorless oil. The reaction product was chromatographed on 10 g of thin-layer mesh silica gel using ether–hexane (1:9) as solvent and collecting 7-mL fractions. Fractions 14–17 contained a single compound (TLC, GC) which was identical with naturally occurring **1** based on the following criteria: $[\alpha]_D$ +204° (*c* 0.25, $CHCl_3$); IR, ^1H NMR (60 MHz), and mass (chemical ionization using methane and isobutane) spectra and gas chromatographic retention time (5 ft × ⅛ in 10% FFAP column).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.93; H, 10.91.

Acetylation of Dactylenol (1). A mixture of 25 mg of **1**, 1.0 mL of pyridine (dried over molecular sieves), and 1.0 mL of acetic anhydride was heated under nitrogen at 50 °C for 8 h. The solvent was removed in vacuo to yield a semisolid residue that was only partially soluble in hexane. Gas chromatographic analysis of the hexane solubles on a 5 ft × ⅛ in 10% FFAP column showed a peak with a retention time identical with that of **4**, which corresponded to an approximately 10% conversion of alcohol to acetate.

Hydroboration of Dactyloxene-B (5). Dactyloxene-B (200 mg) was added to 3 mL of 9-borabicyclo[3.3.1]nonane–THF solution (0.5 M), and the mixture was stirred at room temperature for 3 h. The solution was cooled in an ice bath, treated with 2.5 mL of 3 N NaOH and then 2.5 mL of 30% hydrogen peroxide, and stirred overnight at room temperature. The solution was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The ether solution was washed with water, dried ($MgSO_4$), and evaporated to give 250 mg of a colorless oil. This oil was chromatographed on 12 g of silica gel (TLC mesh) using chloroform as eluent to give 160 mg of the alcohol **6**: IR (neat) 3450 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.99 and 1.03 (6 H, overlapping d, *J* = 6 Hz, secondary methyls), 1.30 (3 H, s, tertiary methyl), 1.74 (3 H, brd s, vinyl methyl), 3.44–3.96 (2 H, m, –CH_2CH_2OH), 5.34 (1 H, m, olefinic H); MS (70 eV) *m/e* (relative intensity) 182 (M^+ − 56, 8, –C_4H_8), 149 (3), 135 (7), 121 (9), 109 (20), 91 (19), 82 (17), 79 (17), 77 (14), 69 (13), 67 (18), 56 (42), 43 (75), 41 (100).

Acetylation of Alcohol 6. A 64-mg amount of alcohol **6** was acetylated using 0.3 mL of pyridine and 0.3 mL of acetic anhydride at room temperature for 72 h. The reaction mixture was hydrolyzed by adding a 10% $NaHCO_3$ solution and stirring for 3 h. The solution was diluted further with water and extracted with ether (2 × 10 mL). The combined ether layers were washed with a 5% $NaHCO_3$ solution, 1 N HCl, and water and then dried and evaporated to give 60 mg of a colorless oil that was essentially pure as judged by TLC: ^1H NMR (60 MHz, $CDCl_3$) δ 1.00 (6 H, overlapping d, secondary methyls), 1.32 (3 H, s, tertiary methyl), 2.1 (3 H, s, vinyl methyl), 4.22 (2 H, t, –CH_2CH_2OH), 5.38 (1 H, m, vinyl H).

Preparation of the Keto Acetate 7 and Keto Acid 8. According to the procedure of Brown and Garg,[10] the acetate of **6** (60 mg) and lithium borohydride (9.9 mg) in 1 mL of ether were treated with boron trifluoride etherate (20 mg) dissolved in ether (1 mL). The reaction mixture was stirred at room temperature for 2 h, and then water (9.1 mL) and an oxidizing solution (220 mg of $Na_2Cr_2O_7$, 9.16 mL of concentrated H_2SO_4, and 0.9 mL of H_2O) were added and the mixture was heated at 40 °C (reflux condenser) for 2 h. The reaction mixture was cooled to room temperature, the layers were separated, and the water layer was extracted further with ether. The combined ether layers were dried and evaporated to give a colorless oil, 60 mg.

The crude product was chromatographed on 12 g of silica gel. Elution with chloroform–methanol (99:1) yielded 30 mg of the keto acetate **7**. Subsequent elution with chloroform–methanol (95:5) afforded 17 mg of the keto acid **8**: mp 134–145 °C; IR (KBr) 3300–2500 (brd), 1700 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.05, 1.08, and 1.12 (3 H each, d, secondary methyls), 1.27 (3 H, s, tertiary methyl), 2.07 (AB q, –CH_2CO_2H), 6.3 (1 H, brd, exchangeable, –CO_2H); MS (70 eV) *m/e* (relative intensity) 268 (M^+, 11), 223 (2), 212 (25), 197 (77), 170 (19), 149 (30), 109 (41), 83 (43), 67 (68), 60 (44), 55 (62), 44 (55), 43 (93), 41 (100).

Treatment of the Keto Acetate 7 with Base. The keto acetate **7** was dissolved in a few milliliters of methanol in which a small piece of sodium had been dissolved. The mixture was stirred at room temperature overnight and then diluted with water. The product was isolated by extraction with ether and chromatographed on silica gel as described above for the keto acetate/keto acid mixture to give the α,β-unsaturated keto alcohol **9**: IR (film) 3400 (OH), 1660, 1650 cm^{-1}; UV (95% EtOH) λ_{max} 249 nm (ε 16 100); ^1H NMR (100 MHz, $CDCl_3$) δ 1.02 and 1.25 (3 H each, d, secondary methyls), 1.32 (3 H, s, tertiary methyl), 1.78 (3 H, s, vinyl methyl), 3.94 (2 H, t, –CH_2CH_2OH); MS (70 eV) *m/e* (relative intensity) 236 (M^+ −18, 10), 218 (12), 206 (11), 203 (12), 190 (15), 163 (28), 149 (60), 135 (46), 123 (28), 121 (38), 107 (65), 91 (45), 81 (53), 77 (47), 67 (60), 55 (65), 43 (55), 41 (100).

Hydroboration of Dactyloxene-A (12). To 80 mg of **12** in 2 mL of tetrahydrofuran freshly distilled from lithium aluminum hydride was added 16 mg (0.73 mmol) of lithium borohydride. The solution was cooled in an ice bath, and 0.6 mL of a THF solution containing 0.24 mg of boron trifluoride etherate was added over a 25-min period. The ice bath was removed and the mixture stirred overnight. Then 0.1 mL of 3 N NaOH and 0.1 mL of 30% hydrogen peroxide were added, and stirring was continued for 1.25 h at 35–50 °C. Potassium carbonate (0.5 g) was added to cause separation of the water and THF layers, and the water layer was extracted twice more with 10-mL portions of THF. The combined organic layers were dried ($MgSO_4$), the solvent was evaporated, and the product was filtered through a short column of silica gel (0.4 g, 100–200 mesh). Elution with benzene (10 mL) removed a milky oil, and further elution with two 10-mL portions of benzene–methanol (85:15 and then 70:30) yielded 77 mg of the diol **14**: IR ($CHCl_3$) 3600 (w), 3420 (brd s), 1450, 1370, 1090, 1050, 1030 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.90 and 1.03 (overlapping methyl d, *J* = 6 Hz), 1.23 and 1.36 (3 H each, s), 3.2–4.0 (3 H, brd overlapping mult, –CH_2OH and –CH(OH)–).

Dactyloxene-A Diol Monotrityl Ether 15. To 39 mg of the diol **14** dissolved in 2.5 mL of dry pyridine was added 150 mg of trityl chloride. The reaction mixture, protected by a drying tube, was heated on a steam bath for 1.25 h and then cooled to room temperature and diluted with 20 mL of dichloromethane and 15 mL of water. The layers were separated, and the water layer was extracted again with dichloromethane. The combined organic layers were washed with water (3 × 10 mL) and 10% HCl (3 × 10 mL), followed by single washes with water, 10% $NaHCO_3$, and water again. The organic layer was dried (Na_2SO_4) and evaporated. The crude product (89 mg) was chromatographed on 4 g of 100–200 mesh silica gel. The triphenylcarbinol was eluted with benzene–hexane mixtures and pure benzene.

Elution with benzene–methanol (98:2) afforded 23 mg of the monotrityl ether **15**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.83 and 0.90 (overlapping methyl d, J = 6 Hz), 1.13 and 1.20 (3 H each, s), 3.28 (2 H, t, J = 7 Hz, $-CH_2-O-CPh_3$), 3.4–4.0 (1 H, m, $-CH(OH)-$), 7.4 (15 H, m); MS (70 eV) *m/e* (relative intensity) 498 (M^+, 2), 424 (4), 259 (4), 243 (100, Ph_3C^+), 237 (14), $M^+ - 18$, $-Ph_3C^+$), 211 (25), 193 (10), 165 (46), 135 (10), 121 (7), 105 (21), 91 (6), 77 (13), 69 (10), 55 (17), 43 (31).

Preparation of Keto Trityl Ether 16. The trityl ether **15** dissolved in 3 mL of dichloromethane was added at room temperature to 0.8 mg of a chromium trioxide–pyridine–dichloromethane solution,[11] which was being stirred rapidly. A black precipitate formed immediately. Stirring was continued for 25 min, and then the dichloromethane was decanted off and the insoluble precipitate washed twice with 8-mL portions of ether. The combined organic layers were washed with 5% NaOH (3 × 8 mL), 5% HCl (8 mL), and 5% $NaHCO_3$ and then dried (Na_2SO_4). Evaporation of the solvent gave a quantitative yield of the keto trityl ether **16**: IR (CCl_4) 1712, 1100, 1080, 1058, 1030 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.75 and 0.85 (overlapping methyl d), 1.17 and 1.28 (3 H each, s), 3.20 (2 H, t, J = 6 Hz), 7.30 (15 H, m); ^{1}H NMR (C_6D_6) δ 0.63 and 0.98 (methyl d), 0.93 and 1.13 (3 H each, s), 3.41 (2 H, t, J = 7 Hz, $-CH_2-O-CPh_3$), 7.15 and 7.60 (15 H, m, $-CCPh_3$).

Treatment of the Keto Trityl Ether 16 with Base. The crude keto trityl ether **16** (16 mg) in methanol (0.7 mL) was added to 1.5 mL of dry methanol in which a small chip of sodium metal had been dissolved. The reaction mixture was degassed (vacuum), placed under a nitrogen atmosphere, and allowed to stand at room temperature overnight. The reaction mixture was diluted with a few milliliters of water and then extracted with dichloromethane (3 × 8 mL) and benzene (3 × 8 mL). The combined organic layers were washed with water and brine and dried (Na_2SO_4). Evaporation afforded 4 mg of a colorless oil which showed carbonyl absorption (strong) only at 1712 cm^{-1}. The still cloudy basic aqueous methanol layer was acidified with a few drops of 5% HCl and then extracted with dichloromethane (3 × 8 mL). Workup of the organic layer as above yielded an additional 9 mg of product that showed carbonyl absorption (strong) only at 1712 cm^{-1}; ^{1}H NMR (100 MHz, C_6D_6) δ 0.60 and 0.67 (3 H, overlapping d, J = 7 Hz), 0.90 (3 H, s), 0.93 (methyl d), 1.05 and 1.09 (each a singlet, combined area equivalent to 3 H), 3.28 (2 H, t, J = 7 Hz), 7.1 and 7.55 (15 H, m). (The doubling of methyl signals indicates that some epimerization has occurred adjacent to the ketone.)

Hydroboration of Dactyloxene-C (10). Dactyloxene-C (55 mg) was hydroborated using 1.5 mL of 9-borabicyclo[3.3.1]nonane–THF solution (0.5 M) as described above for the hydroboration of **5**. After oxidation, extraction, and chromatography, 40 mg of pure alcohol **11** was obtained: oil; IR (neat) 3400, 1450, 1370, 1100, 1045, 1005 cm^{-1}; ^{1}H NMR (100 MHz, CCl_4) δ 0.98 and 1.00 (overlapping methyl d, J = 6 Hz), 1.36 (3 H, s, $-C(CH_3)-O-$), 1.74 (3 H, m, olefinic methyl), 3.46–4.0 (2 H, complex m, $-CH_2OH$), 5.33 (1 H, m, $-CH=C(CH_3)-$).

Acid Treatment of Dactylenol (1) with Acid. A mixture of 19 mg of **1** in 5 mL of ether containing a few crystals of *p*-toluenesulfonic acid monohydrate was allowed to stand at room temperature for a few hours. The ether solution was then washed with water, dried, and concentrated. The products were analyzed on a 100-ft support coated open tubular (S.C.O.T.) FFAP column. Dactyloxene-A (**12**), a minor component, and dactyloxene-B (**5**), a major component, were identified by peak enhancement. Cyclization catalyzed by BF_3 etherate in ether at 0 °C with warming to room temperature gave similar results.

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Registry No.—**1**, 58542-82-8; **4**, 58071-43-5; **5**, 54928-03-9; **6**, 54706-65-9; **6** acetate, 67360-86-5; **7**, 67360-87-6; **8**, 54706-68-2; **9**, 67360-88-7; **10**, 54990-55-5; **12**, 54990-54-4; **14**, 67360-89-8; **15**, 67360-90-1; **16**, 67360-91-2; trityl chloride, 76-83-5.

References and Notes

(1) (a) Taken in part from the Ph.D. Dissertation of D. J. Vanderah, University of Oklahoma, Norman, Okla., June 1975. (b) Part of these results have been reported earlier: F. J. McDonald, D. J. Vanderah, and F. J. Schmitz, Abstracts, 30th Southwest Regional American Chemical Society Meeting, Houston, Tex., 1974; F. J. Schmitz, D. C. Campbell, K. H. Hollenbeak, D. J. Vanderah, L. S. Ciereszko, P. Steudler, J. D. Ekstrand, D. van der Helm, P. N. Kaul, and S. Kulkarni in "Marine Natural Products", D. J. Faulkner and W. H. Fenical, Ed., Plenum Press, New York, N.Y., 1977, p 292. (c) This research was supported by National Cancer Institute Grants CA 17256 and 12530.
(2) F. J. Schmitz and F. J. McDonald, *Tetrahedron Lett.*, 2541 (1974).
(3) H. H. Sun, S. M. Waraszkiewicz, and K. L. Erickson, *Tetrahedron Lett.*, 585 (1976).
(4) W. Fenical and B. M. Howard, *Tetrahedron Lett.*, **41** (1976).
(5) D. J. Faulkner, *Phytochemistry*, **15**, 1992 (1976).
(6) A. G. González, J. D. Martin, C. Perez, and M. A. Ramirez, *Tetrahedron Lett.*, 137 (1976).
(7) F. J. Schmitz, K. H. Hollenbeak, and D. J. Vanderah, *Tetrahedron*, in press.
(8) (a) F. J. McDonald, D. C. Campbell, D. J. Vanderah, F. J. Schmitz, D. M. Washecheck, J. E. Burks, and D. Van der Helm, *J. Org. Chem.*, **40**, 665 (1975); (b) D. J. Vanderah and F. J. Schmitz, *ibid.*, **41**, 3480 (1976).
(9) P. N. Kaul, S. K. Kulkarni, F. J. Schmitz, and K. H. Hollenbeak in "Drugs and Food from the Sea–Myth or Reality", P. N. Kaul and C. J. Sindermann, Ed., The University of Oklahoma Press, Norman, Okla., 1978, p 99.
(10) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).
(11) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 35, 4000 (1970).
(12) R. M. Wing, T. A. Early, and J. J. Uebel, *Tetrahedron Lett.*, 4153 (1972).
(13) R. C. Cookson and P. Lombardi, *Gazz. Chim. Ital.*, **105**, 621 (1975).
(14) E. Wenkert and P. Beak, *Chem. Ind. (London)*, 1574 (1961); J. A. Giles, J. N. Schumacher, S. S. Mims, and E. Bernasek, *Tetrahedron*, **18**, 169 (1962).
(15) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy In Organic Chemistry", 2nd ed, Pergamon Press, London, 1969, p 334ff.
(16) (a) A. G. Gonzáles, J. M. Aguiar, J. D. Martin, and M. Norte, *Tetrahedron Lett.*, 2499 (1975); (b) W. Fenical, *J. Phycol.*, **11**, 245 (1975).
(17) Melting points are uncorrected. Infrared spectra were taken on Beckman IR-8 or Acculab 3 spectrophotometers. NMR spectra were acquired on Varian T-60 or XL-100 instruments in the solvents specified; signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on Hitachi RMU-7, Finnegan 3000 D, and CEC (Dupont, Monrovia, Calif.) 110 mass spectrometers. A Perkin-Elmer 141 or Gaertner polarimeter was used for obtaining optical rotations. Microanalyses were obtained from Mr. E. Meier, Department of Chemistry, Stanford University, Stanford, Calif. Chromatographic adsorbents used were Florisil (Fisher, 100–200 mesh) and silicic acid (Mallinckrodt, SilicAR CC-7; Brinkman TLC mesh). The 9-borabicyclo[3.3.1]nonane solution, 0.5 M in tetrahydrofuran, was purchased from Aldrich Chemical Co., Milwaukee, Wis.

Nitroxides Derived from 3,4-Dihydro-2,5-dimethyl-2*H*-pyrrole 1-Oxide: A New Series of Minimum Steric Perturbation Lipid Spin Labels

Terry D. Lee and John F. W. Keana*[1]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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The synthesis and stereochemical assignments of a series of *cis*- and *trans*-2,5-dialkyl-2,5-dimethylpyrrolidine (azethoxyl) nitroxides are described. A significant reduction in steric bulk compared to other nitroxide labeled lipids results from integration of the nitrogen atom and two of the pyrrolidine ring carbon atoms into the lipid chain. Models suggest the cis isomers resemble the geometry about a cis carbon–carbon double bond, while the trans isomers are reasonably good analogues of a saturated chain. In the synthetic route, nitrone **1** was converted (**1** → **2** → **3** → **8** + **9**) into a mixture of nitroxide alcohols **8** and **9**. These were separated as diacetates **6** and **7** (trans/cis, 75:25). The isomer ratio in the series could be altered by the choice of reaction pathways. Thus, nitrone **13** was converted via **14** and **15** into a mixture of **8** and **9** (trans/cis, 35:65). Cis,trans structure assignments were made as follows. The isomer identities of nitroxides **16** and **17** (prepared from nitrone **2**) were established by ^{19}F NMR spectroscopy of (+)-methoxy(trifluoromethyl)phenylacetate derivatives **20** and **21**. The two series were linked by converting **9** to cis nitroxide **17** via **12** and **11**. In another series of experiments a mixture of **8** and **9** was converted to separable isomeric iodides **10** and **11**, which were then converted separately into azethoxyl acids **25** and **26** via **23** and **24**. Phospholipid **31** was prepared by coupling **25** to lysophosphatidylcholine.

Nitroxide[2] labeled lipids and phospholipids have been used extensively in ESR studies[3] of the structure and function of biological membranes. Despite the proven usefulness of the technique, key studies are sometimes precluded by the unavailability of labels having suitable spectral, physical, and/or chemical properties. For example, nitroxide spin label studies in certain systems are plagued by ESR signal loss due to in situ reduction[2] of the nitroxide. Spin labeled analogues of bent chain fatty acids such as those which contain a cis double bond or a cyclopropane ring have not been readily available. Finally, there is the constant concern that the spin labeled molecule does not accurately reflect the behavior of its naturally occurring analogue owing to the steric bulk of the nitroxide moiety.

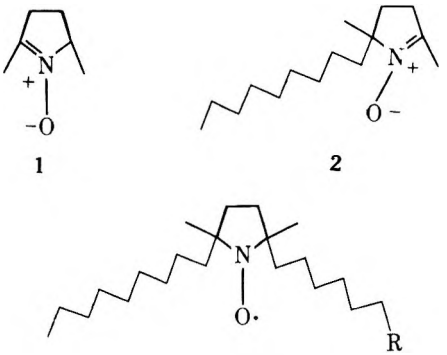
In a recent communication[4] we described a new series of minimum steric perturbation nitroxide lipid spin labels with unique features making them especially attractive probes for the study of biological membranes. These nitroxides are derivatives of the pyrrolidine ring system in which the alkyl side chains are attached to the C_2 and C_5 ring atoms. Thus, the nitroxide moiety is an integral part of the hydrocarbon chain, significantly reducing the steric bulk over that found in other classes of nitroxide labels. The existence of cis and trans isomers, moreover, provides for a series of either bent or straight chain structures. These labels show resistance to reduction by sodium ascorbate superior to that of proxyl and doxyl nitroxides.[2,4] For convenience, we have called these spin labels azethoxyl[5] nitroxides in order to distinguish them from the chemically similar but structurally different proxyl nitroxides.[6]

We now describe in detail the synthesis and stereochemical assignments of the *cis*- and *trans*-azethoxyl nitroxides. The ESR spectral characteristics of these labels in a number of systems will be the subject of a subsequent paper.[7]

Results and Discussion

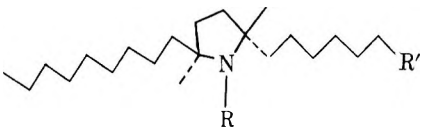
The method of synthesis of the azethoxyl nitroxides takes advantage of much of the chemistry developed in the synthesis of the proxyl nitroxides.[6] Starting with nitrone **1**[8] (Chart I), two successive Grignard addition–air oxidation sequences (e.g., **1** → **2** → **3**) would yield a nitroxide with side chains attached at positions 2 and 5 of the pyrrolidine ring. In order that the cis isomer would resemble naturally occuring oleic acid, it was decided to build a nitroxide in which the pyrrolidine ring was near the center of the chain, roughly at the 9,10 position. Thus, nonylmagnesium bromide was added to nitrone **1**.[8] The intermediate *N*-hydroxy compound was oxidized to give in 45% yield nitrone **2**. The addition of the Grignard reagent derived from the tetrahydropyranyl ether of 6-chlorohexanol followed by Cu^{2+}-catalyzed air oxidation[9] gave nitroxide **3**. Although the yield for this reaction is low (~20%), much of the starting nitrone could easily be recovered for reuse. A major side reaction thus appeared to be the generation of the anion of the nitrone which yields the starting nitrone upon aqueous workup. The yield of **3** could be improved by doing the Grignard addition in refluxing THF.

Chart I

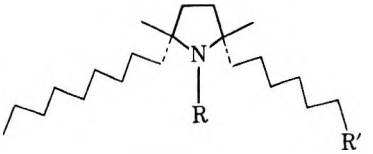


1 **2**

3, R = OTHP
4, R = OH
5, R = OSO_2CH_3



6, R = OAc; R′ = OAc
8, R = O·; R′ = OH
10, R = O·; R′ = I



7, R = OAc; R′ = OAc
9, R = O·; R′ = OH
11, R = O·; R′ = I
12, R = O·; R′ = OSO_2CH_3

0022-3263/78/1943-4226$01.00/0

Chart II

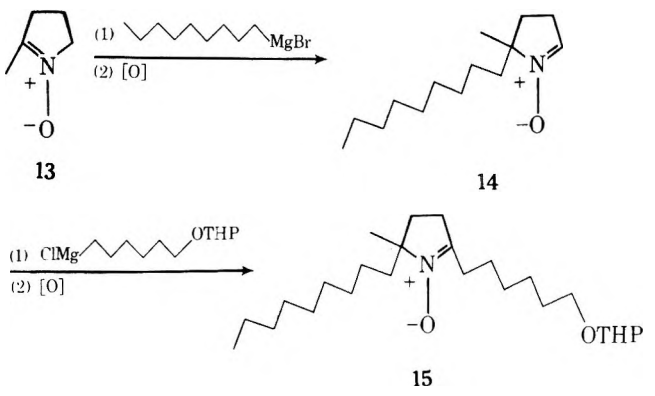
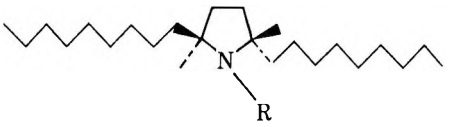
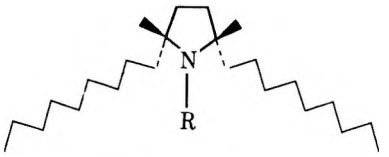


Chart III



16, R = O·
18, R = OAc
20, R = $O_2CC(OCH_3)(CF_3)C_6H_5$



17, R = O·
19, R = OAc
21, R = $O_2CC(OCH_3)(CF_3)C_6H_5$
22, R = $OCH_2CH_2CH_3$

However, the purification of **3** was complicated by the formation of several higher molecular weight nitroxides formed under these conditions, presumably via self-condensation of the nitrone.

Cleavage of the THP protecting group with *p*-toluenesulfonic acid in methanol gave the nitroxide alcohol **4** as a mixture of cis,trans isomers. It was not possible to separate the two alcohol isomers, probably because the hydroxyl group, which governs the behavior during chromatography, is remote from that portion of the molecule which gives rise to the different isomers. However, when the nitroxides were reduced (Pd/C, H_2) to the corresponding *N*-hydroxy compounds and then converted to the diacetates **6** and **7**, it was possible to separate these latter isomers by simple column chromatography on silica gel.

Since it was expected that the Grignard reagent would prefer to attack nitrone **2** from the less hindered side, the major isomer **6** (75%) was assigned the trans geometry and the minor isomer **7** (25%) the cis geometry. These assignments later proved to be correct based on the work described below. One would also expect that the addition of methyllithium to a nitrone in which the two long chain alkyl groups are already in place should give a product mixture that favors the cis isomer. This proved to be correct. Nitrone **13**[10] (Chart II) was treated with nonylmagnesium bromide followed by copper-catalyzed air oxidation to give nitrone **14.** The Grignard reagent derived from 6-chlorohexanol tetrahydropyranyl ether was then added to nitrone **14** followed by copper-catalyzed air oxidation to give nitrone **15.** Methyllithium addition to nitrone **15** and subsequent copper-catalyzed air oxidation gave a cis,trans mixture of nitroxide **3.** Conversion to the diacetates **6** and **7** followed by chromatographic separation gave a

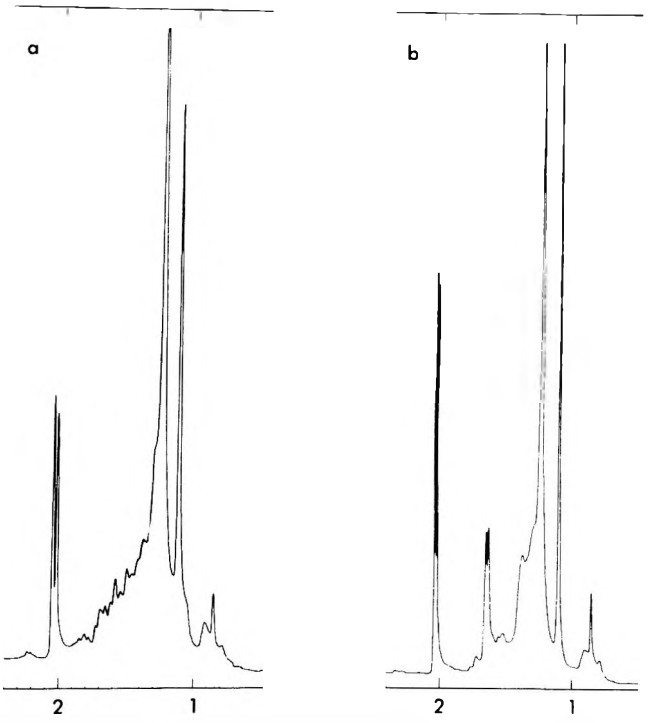


Figure 1. 100 MHz NMR spectra ($CDCl_3$) of (a) trans diacetate **6** and (b) cis diacetate **7.**

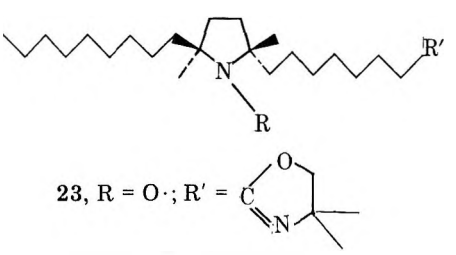
trans/cis ratio of 35:65. Thus, it is possible to control the isomer ratio by appropriate choice of reaction pathways.

Since the essentially quantitative catalytic reduction and acetylation of the nitroxide function yields diamagnetic compounds, this procedure constitutes a useful alternative to the in situ phenylhydrazine reduction of nitroxides[11] for obtaining NMR spectral information. The *N*-acetoxy derivatives have the advantage that they can be stored indefinitely, although some conversion to the nitroxide is observed when they are chromatographed on silica gel. NMR spectra of **6** and **7** are shown in Figure 1. Note the characteristic pattern at δ 1.6–1.75 for the cis isomer which is absent in the spectrum for the trans compound. These patterns were observed for every cis–trans combination that has thus far been examined.

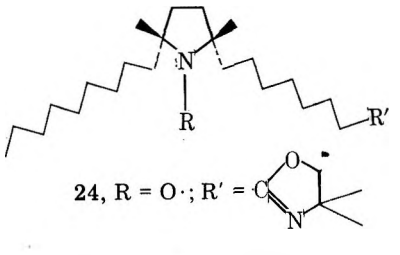
Alkaline hydrolysis of diacetates **6** and **7** with concurrent air oxidation gave the nitroxide alcohols **8** and **9.** The identity of the two geometrical isomers was established as follows. Nitroxides **16** and **17** (Chart III) were synthesized by the reaction of nonylmagnesium bromide with nitrone **2** followed by air oxidation. In this instance, where the primary absorption site is located in the same portion of the molecule that gives rise to the different isomers, the isomers were readily separated by silica gel chromatography using $CHCl_3$ (cis/trans ratio, 20:80). The nitroxides were then in turn converted to the acetates **18** and **19.** The hope was that the trans isomer would show two different acetate absorptions in the NMR spectrum when complexed with an optically active NMR shift reagent[12] while the cis isomer (a meso compound) would show only one. However, even with a large excess of tris[(3-trifluoromethyl)hydroxymethylene-*d*-camphorato]europium(III) in CCl_4, only minor differences in the chemical shift values were observed, and there was no evidence of two acetate absorptions for either isomer.

Turning to another approach, catalytic reduction of both **16** and **17** followed by reaction of the resulting N–OH compounds with (+)-methoxy(trifluoromethyl)phenylacetyl chloride (MTPACl)[13] using the procedure of Mosher[13] gave the corresponding MTPA esters **20** and **21** in ~60% yield. The reaction of the trans isomer with an optically active acid chloride must give rise to two diasteriomeric esters, whereas the cis isomer can only yield one compound. The ^{19}F NMR

Chart IV



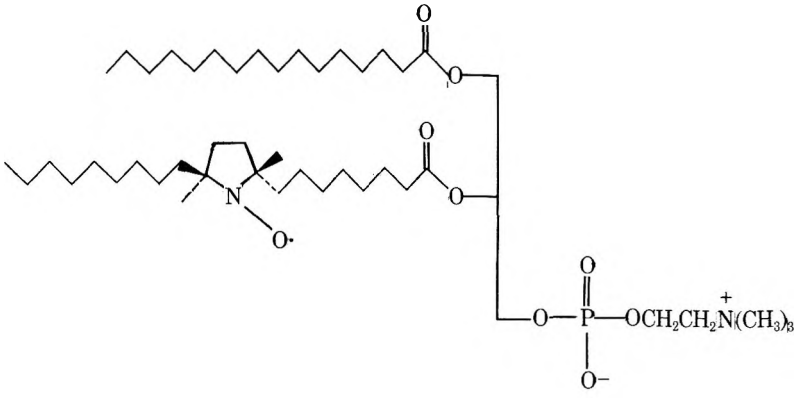
23, R = O·; R′ =



24, R = O·; R′ =

25, R = O·; R′ = CO_2H
27, R = O·; R′ = CO_2CH_3
29, R = OAc; R′ = $COCH_3$

26, R = O·; R′ = CO_2H
28, R = O·; R′ = CO_2CH_3
30, R = OAc; R′ = CO_2CH_3



31

spectrum for **20** showed two absorptions (see Experimental Section). By contrast, the ^{19}F NMR spectrum for **21** showed only one.

To complete the isomer assignment of nitroxide alcohols **8** and **9**, **9** was converted to iodide **11** by way of mesylate **12**. The coupling of **11** with propylmagnesium chloride was readily accomplished using Li_2CuCl_4[14] as a catalyst. The nitroxide moiety was reduced to the N–OH compound under the conditions of the reaction and had to be reoxidized, affording **17**. There was also a sizable amount of the O-alkylated product **22** isolated. The nitroxide obtained from the coupling reaction was identical chromatographically to cis nitroxide **17**. Upon reduction followed by acetylation, both nitroxides gave the same acetate (by NMR).

The presence of a hydroxyl group at the end of the *cis*- and *trans*-azethoxyl nitroxides made possible their conversion into spin labeled analogues of the biologically important fatty acids. The method chosen for this transformation was that of Meyers et al.,[15] in which an alkyl halide is converted into a carboxylic acid having a chain two carbons longer.

Fortuitously, when the cis,trans mixture of alcohols **4** was converted to the mixture of mesylates **5** and thence to iodides **10** and **11**, it was found that these latter isomers could be readily separated by silica gel chromatography. Thus, it was no longer necessary to separate the isomers as the diacetates **6** and **7**. The minor (18%) isomer **11** was identical with that obtained from nitroxide alcohol **9**. Iodides **10** and **11** were separetely converted to the corresponding acids **25** and **26** via the oxazoline derivatives **23** and **24** (Chart IV). The acids could be esterified with diazomethane to give **27** and **28**. Catalytic reduction of these latter substances followed by acetylation as described above gave esters **29** and **30**. The NMR spectra of **29** and **30** showed the pattern at δ 1.6–1.8 which was characteristic of other cis,trans pairs (see above).

A representative phospholipid containing an azethoxyl nitroxide was synthesized by coupling *trans*-10-azethoxyleicosanoic acid (**25**) with lysopalmitoylglycerolphosphatidylcholine using carbonyldiimidazole[16,17] to give the spin labeled phosphatidylcholine derivative **31**.[18]

The synthetic route to azethoxyl labeled lipids and phospholipids is sufficiently straightforward that these nitroxides should prove useful in spin labeling studies. Experiments are currently underway to determine their value in probing biological membranes.

Experimental Section[19]

3,4-Dihydro-2,5-dimethyl-2-nonyl-2*H*-pyrrole 1-Oxide (2). To 100 mL of a 1.0 M nonylmagnesium bromide solution in ether was added with stirring 5.65 g (50.0 mmol) of nitrone **1**[8] in 30 mL of ether at a rate sufficient to maintain gentle reflux. The solution was stirred for an additional 30 min at 21 °C and then treated with an amount of saturated aqueous NH_4Cl sufficient to collect the precipitated aqueous salts in a mass at the bottom of the flask. The ether layer was decanted and combined with two ether washings of the aqueous residue. The solvent was evaporated to yield a yellow oil which was taken up in 50 mL of CH_3OH and 5 mL of concentrated aqueous NH_4OH and stirred with 1 g of $Cu(OAc)_2 \cdot H_2O$ under O_2 until the solution developed a deep blue color. The solution was diluted with ether and H_2O. The usual workup gave a brown oil which was distilled to give 5.43 g (45%) of **2**: bp 100–109 °C (0.005 mm); IR (CCl_4) 1595 cm^{-1} (C=N); NMR δ 0.88 (3 H, m, term Me), 1.38 (3 H, s, ring Me), 2.02 (3 H, t, J = 2 Hz, N=CMe), 2.57 (2 H, m, N=CCH_2); MS *m/e* 239.223 (31) (calcd for $C_{15}H_{29}NO$, 239.225), 222 (34), 113 (68), 96 (75), 73 (27), 55 (28), 45 (53), 43 (100), 41 (36).

2,5-Dimethyl-5-nonyl-2-(6′-tetrahydropyranyloxyhexyl)tetrahydropyrrole-1-oxyl (3) (Mixture of Cis and Trans Isomers). To 25 mL of a 1 M THF solution of the Grignard reagent derived from the tetrahydropyranyl ether of 6-chlorohexanol was added at 21 °C with stirring over a period of 15 min 10 mL of a THF solution of 2.39 g (0.010 mmol) of nitrone **2**. After the addition was complete (~15 min), saturated aqueous NH_4Cl was added. The ether was decanted and combined with an ether washing of the residue. The ether was evaporated, the residue was taken up in 100 mL of CH_3OH and stirred vigorously with 30 mg of $Cu(OAc)_2 \cdot H_2O$ for 30 min, and the solvent was then evaporated. Silica gel chromatography of the residue ($CHCl_3$ elution) gave 0.929 g (22%) of **3** as a yellow oil sufficiently pure for the next reaction. An analytical sample was prepared by preparative TLC (ether, R_f 0.7): MS *m/e* 424.380 (6) (calcd for $C_{26}H_{50}NO_3$, 424.379),

352 (6), 340 (10), 282 (22), 240 (100), 224 (68), 214 (66), 198 (22), 85 (100), 73 (20), 69 (26), 57 (24), 55 (33), 43 (26), 41 (30).

2,5-Dimethyl-5-nonyl-2-(6'-hydroxyhexyl)tetrahydropyrrole-1-oxyl (4) (Mixture of Cis and Trans Isomers). To a 50 mL CH_3OH solution of 0.929 g (2.19 mmol) of **3** was added 70 mg of *p*-toluenesulfonic acid monohydrate. The solution was allowed to stand for 2 h at 21 °C and then was diluted with ether and H_2O. The ether phase was washed with H_2O and brine, dried over Na_2SO_4, filtered, and then evaporated to give a yellow oil. This was taken up in $CHCl_3$ and put on a 2 × 20 cm dry silica gel column. The column was eluted with 200 mL of $CHCl_3$ followed by 200 mL of ether. The ether portion was evaporated to give 0.569 g (76%) of **4** as a mixture of the cis and trans isomers which was pure by TLC (ether, R_f 0.4).

Trans Diacetate 6 and Cis Diacetate 7. The mixture of cis and trans nitroxide alcohols **4** (121 mg, 0.355 mmol) in 3 mL of dry THF was hydrogenated in a Brown microhydrogenator[20] using 10 mg of 10% Pd/C catalyst. The hydrogen uptake stopped cleanly at 0.5 mol equiv of H_2. The mixture was filtered directly into a N_2-flushed flask and cooled to 0 °C under N_2. To the stirred solution was added 0.2 mL of Et_3N followed by 0.1 mL of acetyl chloride. The mixture was warmed to 21 °C, diluted with a four-fold volume of cyclohexane, and filtered, and the solvent was evaporated. The residue was put on a 2 × 35 cm silica gel column which was eluted with CH_2Cl_2. A total of 200 6-mL fractions were collected with the aid of a fraction collector. Fractions 30–50 gave 2.2 mg (14%) of the cis isomer **7**: single spot by TLC ($CHCl_3$, R_f 0.5); IR (CCl_4) 1770 (NOC=O), 1740 (COC=O) cm^{-1}; NMR δ 0.88 (3 H, m, term Me), 1.12 (6 H, s, ring Me), 1.66 (4 H, m, ring Me), 2.03 (3 H, s, acetate), 2.05 (3 H, s, acetate), 4.06 (2 H, t, J = 6.5 Hz, CH_2O); MS *m/e* 425.352 (2) (calcd for $C_{25}H_{47}NO_4$, 425.350), 410 (3), 383 (20), 368 (11), 298 (43), 282 (49), 256 (81), 240 (100), 224 (22), 55 (12), 43 (16). Fractions 60–120 gave 65.7 mg (44%) of the trans isomer **6**: single spot by TLC ($CHCl_4$, R_f 0.4); IR (CCl_4) 1770, 1740 cm^{-1}; NMR δ 0.88 (3 H, m, term Me), 1.14 (6 H, s, ring Me), 2.04 (3 H, s, acetate), 2.06 (3 H, s, acetate), 4.06 (2 H, t, J = 6.5 Hz, CH_2O); MS *m/e* 425.349 (3) (calcd for $C_{25}H_{47}NO_4$, 425.350), 410 (3), 383 (15), 368 (7), 298 (34), 256 (75), 240 (67), 220 (36), 205 (66), 61 (86), 57 (45), 55 (44), 43 (100). Later fractions off the column gave nitroxide-containing material. It was found that if pure **6** or **7** was subjected to silica gel chromatography, a certain amount of it was converted to the nitroxide, indicating that slow hydrolysis of the acetyl group and subsequent oxidation occurred during the chromatography.

3,4-Dihydro-2-methyl-2-nonyl-2*H*-pyrrole 1-Oxide (14). Following the procedure for the synthesis of **2**, nitrone **14** was obtained from nitrone **13**[10] and nonylmagnesium bromide in 20% yield as a yellow oil: bp 90–100 °C (0.005 mm); NMR δ 0.89 (3 H, m, term Me), 1.42 (3 H, s, ring Me), 1.6–1.9 (2 H, m, CH_2–C–N), 1.9–2.3 (2 H, m, ring CH_2), 2.4–2.7 (2 H, m, CH_2C=NO), 6.80 (1 H, t, J = 3 Hz, CH=N).

3,4-Dihydro-2-methyl-2-nonyl-5-(6'-tetrahydropyranyloxyhexyl)-2*H*-pyrrole 1-Oxide (15). To a solution of 612 mg (2.54 mmol) of **14** in 1 mL of THF was added 2.6 mL of a 1.0 M THF solution of the Grignard reagent derived from the tetrahydropyranyl ether of 6-chlorohexanol. After a 15-min stir at 21 °C, the solution was diluted with ether, saturated aqueous NH_4Cl was added, and the ether was decanted and evaporated. The residue was taken up in 25 mL of CH_3OH and 1 mL of concentrated aqueous NH_4OH, and then 336 mg of $Cu(OAc)_2 \cdot H_2O$ was added. The solution was stirred under air for 30 min. The solvent volume was reduced by half, and then ether was added. The ether layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over K_2CO_3, and evaporated to give a yellow oil. Chromatography on a silica gel column eluting with acetone gave 403 mg (39%) of the nitrone **15** as a yellow oil: single spot by TLC (acetone, R_f 0.3); NMR δ 0.88 (3 H, m, term Me), 1.38 (3 H, s, ring Me), 2.3–2.7 (4 H, m, CH_2C=N), 3.2–4.0 (6 H, m, CH_2O), 4.58 (1 H, m, O–CH–O); MS *m/e* 409.353 (0.6) (calcd for $C_{25}H_{47}NO_3$, 409.356), 325 (30), 308 (28), 252 (24), 239 (27), 198 (27), 182 (28), 114 (100), 85 (49), 55 (29), 41 (35).

Diacetates 6 and 7 via Methyllithium Addition to Nitrone 15. To a solution of 181 mg (0;22 mmol) of **15** in 6 mL of dry ether was added dropwise with stirring under N_2 1.0 mL of a 1.6 M ether solution of methyllithium. The solution was treated with saturated aqueous NH_4Cl 2 min after the addition was complete. The ether phase was washed with H_2O and brine and evaporated, and the residue was taken up in CH_3OH and stirred with 10 mg of $Cu(OAc)_2 \cdot H_2O$ under air for 15 min. The solvent was evaporated and the resulting green oil chromatographed on a silica gel column ($CHCl_3$ elution) to yield 61.4 mg (34%) of **3** as a mixture of cis and trans isomers. Hydrolysis of the THP ether, hydrogenation, acylation, and chromatography as described above gave 19.0 mg (29% from **3**) of **7** and 10.6 mg (16.4% from **3**) of **6**.

Base Hydrolysis of Trans and Cis Diacetates 6 and 7 to Trans and Cis Alcohol Nitroxides 8 and 9. A solution of 40 mg of KOH in 5 mL of CH_3OH was added to a solution of 65 mg (0.15 mmol) of **6** and 2 mg of $Cu(OAc)_2 \cdot H_2O$ in 5 mL of CH_3OH, and the mixture was stirred under air at 21 °C for 6 h. The solution was diluted with ether, washed with H_2O and brine, and evaporated to give a yellow oil which after silica gel chromatography gave 45.5 mg (88%) of **8** as a yellow oil: single spot by TLC (ether, R_f 0.4); IR (CCl_4) 3200–3600 cm^{-1} (OH); MS *m/e* 340.321 (8) (calcd for $C_{21}H_{42}NO_2$, 340.320), 326 (7), 310 (6), 240 (100), 224 (37), 214 (86), 198 (49), 69 (20), 55 (41), 43 (17), 41 (20). Anal. Calcd for $C_{21}H_{42}NO_2$: C, 74.06; H, 12.43; N, 4.11. Found: C, 73.81; H, 12.48; N, 3.78.

In an analogous fashion, **9** was obtained from **7** (76%) as a yellow oil: single spot by TLC (ether, R_f 0.4); IR (CCl_4) 3200–3600 cm^{-1} (OH); MS *m/e* 340 (12), 326 (7), 310 (3), 240 (100), 224 (14), 214 (89), 198 (16), 55 (23), 43 (10), 41 (11). Anal. Calcd for $C_{21}H_{42}NO_2$: C, 74.06; H, 12.43; N, 4.11. Found: C, 73.58; H, 12.03; N, 4.32.

***trans*-2,5-Dimethyl-2,5-dinonyltetrahydropyrrole-1-oxyl (16) and *cis*-2,5-Dimethyl-2,5-dinonyltetrahydropyrrole-1-oxyl (17).** Following the procedure for the preparation of **3**, treatment of 122 mg (0.51 mmol) of **2** with nonylmagnesium bromide followed by $Cu(OAc)_2 \cdot H_2O$ gave a mixture of **16** and **17** which was chromatographed on a dry silica gel column using $CHCl_3$ to yield 26 mg of **16** (14.2%) as a yellow waxy solid [single spot by TLC ($CHCl_3$, R_f 0.4); MS *m/e* 366.372 (6) (calcd for $C_{24}H_{48}NO$, 366.374), 352 (2), 350 (3), 336 (4), 240 (100), 224 (61), 55 (21), 43 (20), 41 (18)]. Anal. Calcd for $C_{24}H_{48}NO$: C, 78.62; H, 13.19; N, 3.82. Found: C, 78.74; N, 13.31; N, 3.66. Also obtained was 6.2 mg of **17** (3.4%) as a yellow oil [single spot by TLC ($CHCl_3$, R_f 0.3); MS *m/e* 366 (8), 352 (3), 350 (2), 336 (2), 240 (100), 224 (35), 69 (15), 55 (15), 43 (22), 41 (10)]. Anal. Calcd for $C_{24}H_{48}NO$: C, 78.62; H, 13.19; N, 3.82. Found: C, 78.14; H, 13.05; N, 3.29.

Trans Acetate 18 and Cis Acetate 19. Nitroxide **16** (10 mg, 0.027 mmol) in 2 mL of dry THF was hydrogenated in a Brown microhydrogenator[20] using 5 mg of 10% Pd/C catalyst. The mixture was filtered directly into a N_2-flushed flask and cooled to 0 °C under N_2. To the stirred solution was added 50 mg of Et_3N followed by 35 mg of acetyl chloride. The stirred mixture was allowed to warm to room temperature, diluted with cyclohexane, and filtered. The solvent was evaporated to give 9.8 mg (89%) of acetate **18** as a yellow waxy solid: single spot by TLC (CH_2Cl_2, R_f 0.7); IR (CCl_4) 1770 (NOC=O), 1200 (C–O) cm^{-1}; MS *m/e* 409.391 (0.5) (calcd for $C_{26}H_{51}NO_2$, 409.392), 282 (50), 240 (100), 224 (25), 55 (11), 43 (12), 41 (9); NMR δ 0.88 (6 H, m, term Me), 1.15 (6 H, s, ring Me), 2.08 (3 H, s, acetate).

Similarly prepared was 4.2 mg of acetate **19** from 4.3 mg (0.012 mmol) of **17** as a yellow oil: single spot by TLC (CH_2Cl_2, R_f 0.8); IR (CCl_4) 1770 (NOC=O), 1200 (C–O) cm^{-1}; MS *m/e* 409.391 (1) (calcd for $C_{26}H_{51}NO_2$, 409.392), 367 (7), 352 (6), 282 (75), 240 (100), 224 (10), 71 (15), 69 (14), 57 (20), 55 (18), 43 (24), 41 (14); NMR δ 0.89 (6 H, m, term Me), 1.14 (6 H, s, ring Me), 1.68 (4 H, m, ring CH_2), 2.08 (3 H, s, acetate).

(+)-Methoxy(trifluoromethyl)phenylacetate Esters of 16 and 17. A solution of 16.8 mg (0.0458 mmol) of **16** in 3 mL of THF was hydrogenated in a Brown microhydrogenator using 5 mg of 10% Pd/C; 0.0226 mmol of H_2 was absorbed. The mixture was filtered into a N_2-flushed flask, and the solvent was evaporated with a slow stream of N_2. Following the procedure of Mosher,[13] a solution of 32.3 mg (0.127 mmol) of (+)-methoxy(trifluoromethyl)phenylacetyl chloride[13] in 0.1 mL of CCl_4 was added followed by 0.1 mL of dry pyridine. After an 18-h stir at 21 °C, 1 mL of H_2O and 20 mL of ether were added. The ether phase was separated, washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and then dried over $MgSO_4$. Evaporation of the solvent and chromatography on silica gel gave 16.4 mg (61%) of **20** as a colorless oil: single spot by TLC (CH_2Cl_2, R_f 0.8); IR (CCl_4) 1775 (NOC=O), 1190 (C–O) cm^{-1}; MS *m/e* 583.419 (0.4) (calcd for $C_{34}H_{56}NO_3F_3$, 583.421), 456 (100), 366 (23), 254 (30), 240 (23), 224 (27), 189 (36); NMR δ 0.88 (6 H, m, term Me), 1.10 (3 H, s, ring Me), 1.12 (3 H, s, ring Me), 3.58 (3 H, m, OCH_3).

Similarly prepared using the above procedure was **21** as a colorless oil: single spot by TLC (CH_2Cl_2, R_f 0.8); IR (CCl_4) 1775 (NOC=O), 1190 (C–O) cm^{-1}; MS *m/e* 583.420 (0.2) (calcd for $C_{34}H_{56}NO_3F_3$, 583.421), 456 (36), 366 (11), 316 (43), 308 (13), 254 (24), 240 (13), 224 (100), 189 (25); NMR δ 0.88 (6 H, m, term Me), 1.00 (3 H, s, ring Me), 1.07 (3 H, s, ring Me), 1.68 (4 H, m, ring CH_2), 3.57 (3 H, m, OCH_3).

Fluorine-19 NMR spectra (proton decoupled) were determined in $CHCl_3$ with 3% CF_3CO_2H as an internal standard. Compound **20** gave two peaks 538.8 and 530.3 Hz downfield from CF_3CO_2H. Compound **21** gave one peak, 524.3 Hz downfield from CF_3CO_2H.

***cis*-2,5-Dimethyl-5-nonyl-2-(6'-iodohexyl)tetrahydropyr-**

role-1-oxyl (11). To a stirred solution of 9.9 mg (0.029 mmol) of **9** and 6.1 mg (0.06 mmol) of Et_3N in 1 mL of dry CH_2Cl_2 at −20 °C (dry ice–CCl_4) was added 5.7 mg (0.05 mmol) of methanesulfonyl chloride. The mixture was allowed to warm to 21 °C, 8 mL of cyclohexane was added, the mixture was filtered, and the solvent was then evaporated to give crude **12** as an orange oil. This was taken up in 1 mL of methyl ethyl ketone along with 27 mg (0.18 mmol) of NaI and stirred at reflux for 30 min. The mixture was diluted with cyclohexane and filtered, and the solvent was evaporated. Preparative TLC ($CHCl_3$) of the resulting yellow oil gave 11.6 mg (88%) of cis iodide **11**: single spot by TLC ($CHCl_3$, R_f 0.3); MS *m/e* 450.221 (23) (calcd for $C_{21}H_{41}NOI$, 450.223), 324 (99), 308 (21), 294 (10), 254 (41), 240 (100), 223 (82), 198 (33), 196 (36), 182 (56), 127 (24), 96 (21), 85 (35), 71 (56), 69 (35), 55 (46), 43 (44), 41 (36). Anal. Calcd for $C_{21}H_{41}NOI$: C, 55.99; H, 9.17; N, 3.11. Found: C, 55.69; H, 9.06; N, 2.71.

***cis*-2,5-Dimethyl-2,5-dinonyltetrahydropyrrole-1-oxyl (17) via (11).** To a stirred solution of 11.6 mg (0.026 mmol) of **11** in 0.1 mL THF at 0 °C under N_2 was added 0.13 mL of a 1.0 M solution of propylmagnesium chloride in THF followed immediately with 0.01 mL of a 0.1 M THF solution of Li_2CuCl_4.[14] After 2 min, saturated aqueous NH_4Cl was added. The mixture was diluted with ether, and the ether was decanted and combined with an ether washing of the residue. The solvent was evaporated, and the residue was taken up in CH_3OH and stirred with 5 mg of $Cu(OAc)_2 \cdot H_2O$ for 30 min. Evaporation of the solvent and silica gel chromatography of the residue gave 3.7 mg (35%) of *O*-propyl derivative **22** as a colorless oil [NMR δ 0.8–1.0 (9 H, m, term Me), 1.09 (6 H, s, ring Me), 1.51 (4 H, m, ring CH_2), 3.66 (2 H, t, J = 7 Hz, CH_2O); MS *m/e* 409.430 (calcd for $C_{27}H_{55}NO$, 409.428)] and 4.3 mg (46%) of **17**, which by TLC was identical with that obtained from nonylmagnesium bromide addition to nitrone **2**. Catalytic reduction and acetylation gave **19**, identical by NMR with that obtained as described above.

***trans*-2,5-Dimethyl-5-nonyl-2-(6′-iodohexyl)tetrahydropyrrole-1-oxyl (10) and *cis*-2,5-Dimethyl-5-nonyl-2-(6′-iodohexyl)tetrahydropyrrole-1-oxyl (11).** Using the procedure for the preparation of **11** as described above, the mixture (394 mg, 0.94 mmol) of cis and trans nitroxide alcohols **4** was converted to a mixture of the cis and trans mesylates **5**: IR (CCl_4) 1370 (S=O), 1180 (S–O) cm^{-1}; MS *m/e* 418.300 (6) (calcd for $C_{22}H_{44}NO_4S$, 418.299), 292 (50), 276 (23), 240 (100), 234 (42), 224 (47), 126 (25), 113 (29), 108 (25), 96 (62), 69 (22), 55 (31), 41 (21).

The mixture of **5** was then converted to the mixture of nitroxide iodides **10** and **11** (381 mg, 90% from **4**). The isomers were separated by dry column silica gel chromatography eluting with $CHCl_3$ to give **10** (82%) as a yellow waxy solid: single spot by TLC ($CHCl_3$, R_f 0.4); MS *m/e* 450.221 (9) (calcd for $C_{21}H_{41}NOI$, 450.223), 324 (100), 308 (12), 240 (100), 224 (26), 196 (27), 96 (20), 69 (43), 57 (47), 55 (61), 43 (33), 41 (56). Anal. Calcd for $C_{21}H_{41}NOI \cdot H_2O$: N, 2.99. Found: N, 2.64. Isomer **11**, identical with that obtained previously from **9**, was also obtained (18% yield).

Trans Oxazoline Nitroxide 23 and Cis Oxazoline Nitroxide 24. The procedure used was that of Meyers.[15] To a stirred solution of 340 mg (3.00 mmol) of 2,4,4-trimethyloxazoline in 2 mL of THF at −78 °C (dry ice–acetone) under N_2 was added 1.6 mL of a 1.6 M solution of butyllithium in hexane. After 3 min, the iodide **10** (290.9 mg, 0.646 mmol) in 1.0 mL of THF was added. A white precipitate formed after 1 min, and the mixture was stirred for an additional 20 min at −78 °C before the bath was removed and the mixture allowed to warm to 0 °C, during which time the precipitate dissolved. The solution was treated with saturated aqueous NH_4Cl, diluted with ether, washed with H_2O and brine, dried over K_2CO_3, and evaporated to give a yellow oil which was chromatographed on silica gel to give 202.2 mg (72%) of **23** as a yellow waxy solid: single spot by TLC (ether, R_f 0.4); MS *m/e* 436 (72), 435 (68), 422 (9), 421 (8), 405 (17), 309 (75), 293 (66), 240 (100), 224 (68), 196 (34), 126 (40), 113 (68), 96 (18), 69 (16), 55 (25), 43 (12), 41 (16).

Similar treatment of **11** gave **24** (59%) as a yellow oil: single spot by TLC (ether, R_f 0.4); MS *m/e* 436 (32), 435.396 (33) (calcd for $C_{27}H_{51}N_2O_2$, 435.395), 422 (5), 421 (6), 405 (7), 309 (64), 293 (21), 240 (100), 224 (27), 196 (30), 126 (44), 113 (56), 96 (29), 69 (38), 55 (77), 43 (39), 41 (53).

trans-2,5-Dimethyl-5-nonyl-2-(8′-carboxyoctyl)tetrahydropyrrole-1-oxyl (25) and *cis*-2,5-Dimethyl-5-nonyl-2-(8′-carboxyoctyl)tetrahydropyrrole-1-oxyl (26). Using the procedure of Meyers,[15] a solution of 196.8 mg (0.45 mmol) of **23** in 3 mL of methyl iodide was allowed to stand in the dark at 21 °C for 14 h. The methyl iodide was evaporated and the residue stirred with 8 mL of CH_3OH and 2 mL of 4 N NaOH for 20 h. The solution was acidified with cold 1 N aqueous HCl and washed with ether. The ether solution was washed with H_2O and brine, dried over $MgSO_4$, and evaporated to give a yellow oil. Silica gel chromatography gave 145.7 mg (84%) of **25** as a yellow waxy solid: single spot by TLC (ether/0.5% HOAc, R_f 0.7); IR (CCl_4) 2800–3400 (OH), 1710 (acid carbonyl) cm^{-1}; MS *m/e* 382.332 (12) (calcd for $C_{23}H_{44}NO_3$, 382.332), 368 (2), 352 (2), 256 (71), 240 (100), 224 (10), 113 (10), 81 (10), 69 (10), 55 (19), 43 (11), 41 (13). Anal. Calcd for $C_{23}H_{44}NO_3$: C, 72.20; H, 11.59; N, 3.66. Found: C, 71.77; H, 11.76; N, 3.47.

Similarly prepared from 23 mg of **24** was *cis*-azethoxyleicosanoic acid **26** (73%) as a yellow waxy solid: single spot by TLC (ether/0.5% HOAc, R_f 0.7); IR (CCl_4) 2800–3400 (OH), 1710 (acid carbonyl) cm^{-1}; MS *m/e* 382.330 (21) (calcd for $C_{23}H_{44}NO_3$, 382.332), 368 (4), 352 (3), 256 (81), 240 (100), 224 (17), 113 (5), 96 (8), 69 (10), 55 (13), 43 (10), 41 (14). Anal. Calcd for $C_{23}H_{44}NO_3 \cdot 0.25H_2O$: C, 71.36; H, 11.59; N, 3.62. Found: C, 71.55, H, 11.07; N, 3.21.

Acetate Esters 29 and 30. Treatment of 7.0 mg (0.18 mmol) of **25** in 0.5 mL of ether with 0.2 mL of a 0.5 M ether solution of diazomethane followed by silica gel TLC (ether, R_f 0.8) gave the corresponding methyl ester **27**: IR (CCl_4) 1745 cm^{-1} (ester carbonyl). Using the procedure described for acetate **6**, **27** was converted to acetate ester **29**: IR (CCl_4) 1770 (N—O—C=O), 1745 (CH_3OC=O) cm^{-1}; NMR δ 0.89 (3 H, m, term Me), 1.14 (6 H, s, ring Me), 2.08 (3 H, s, acetate), 2.33 (2 H, t, J = 7 Hz, CH_2C=O), 3.69 (3 H, s, CH_3O).

Similarly prepared from **26** was acetate ester **30**: IR (CCl_4) 1770 (N—O—C=O), 1745 (CH_3OC=O) cm^{-1}; NMR δ 0.88 (3 H, m, term Me), 1.12 (6 H, s, ring Me), 1.66 (4 H, m, ring CH_2), 2.06 (3 H, s, acetate), 2.31 (2 H, t, J = 7 Hz, CH_2C=O), 3.68 (3 H, s, OCH_3).

1-Palmitoyl-2-(10′-aza-9′,11′-dimethyl-9′,11′-ethano-*N*-oxyleicosanoyl)-*sn*-glycerol-3-phosphatidylcholine (31). The procedure followed was patterned after that of Boss.[17] To a solution of 47.7 mg (0.122 mmol) of **25** in 0.4 mL of dry $CHCl_3$ was added 22.3 mg (0.137 mmol) of carbonyldiimidazole. After stirring for 20 min at 21 °C, 35.2 mg (0.071 mmol) of lysopalmitoylglycerolphosphatidylcholine (Sigma) in 0.2 mL of $CHCl_3$ was added and the mixture was heated under N_2 to 50–55 °C for 5 days, during which time most of the solvent had evaporated. The reaction was quenched with H_2O and taken up in $CHCl_3$. Azeotropic removal of the H_2O by several evaporations from $CHCl_3$ gave a yellow foam which was put on a silica gel column prewashed with a 50:50 mixture of $CH_3OH/CHCl_3$ and then $CHCl_3$ only. The starting nitroxide acid and imidazole were eluted with $CHCl_3/CH_3OH$ (85:15). Crude **31** was eluted with $CHCl_3/CH_3OH$ (50:50). Final purification on an 18 × 1650 cm Sephadex LH-20 column eluting with 95% EtOH gave 37.3 mg (61%) of **31** as a yellow solid. Anal. Calcd for $C_{47}H_{92}N_2O_9P \cdot 3H_2O$: C, 62.84; H, 10.10; N, 3.12. Found: C, 63.07; H, 10.44; N, 3.47.

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Registry No.—**1**, 67408-72-4; **2**, 67408-73-5; *cis*-**3**, 67462-27-5; *trans*-**3**, 67462-28-6; *cis*-**4**, 67408-74-6; *trans*-**4**, 67408-75-7; *cis*-**5**, 67408-76-8; *trans*-**5**, 67408-77-9; **6**, 67408-78-0; **7**, 67408-79-1; **8**, 67408-75-7; **9**, 67408-74-6; **10**, 67408-80-4; **11**, 67408-81-5; **12**, 67408-76-8; **13**, 6931-10-8; **14**, 67408-82-6; **15**, 67408-83-7; **16**, 67408-84-8; **17**, 67408-85-9; **18**, 67408-86-0; **19**, 67408-87-1; **20** (isomer 1), 67408-88-2; **20** (isomer 2), 67408-89-3; **21**, 67462-29-1; **22**, 67425-69-8; **23**, 67408-90-6; **24**, 67408-91-7; **25**, 67408-92-8; **26**, 67408-93-9; **27**, 67408-94-0; **28**, 67408-95-1; **29**, 67408-96-2; **30**, 67408-97-3; **31**, 67408-98-4; nonyl bromide, 693-58-3; tetrahydropyranyl 6-chlorohexyl ether, 2009-84-9; (+)-methoxy(trifluoromethyl)phenylacetyl chloride, 20445-33-4; methanesulfonyl chloride, 124-63-0; propyl chloride, 540-54-5; 2,4,4-trimethyloxazoline, 1772-43-6; diazomethane, 334-88-3; lysopalmitoylglycerolphosphatidylcholine, 17364-16-8.

References and Notes

(1) Alfred P. Sloan Foundation Fellow; Recipient of an NIH Research Career Development Award.
(2) For a review of nitroxide spin label chemistry, see J. F. W. Keana, *Chem. Rev.*, **78**, 37 (1978).
(3) For a review, see "Spin Labeling: Theory and Applications", L. J. Berliner, Ed., Academic Press, New York, N.Y., 1976.
(4) T. D. Lee, G. B. Birrell, and J. F. W. Keana, *J. Am. Chem. Soc.*, **100**, 1618 (1978).
(5) It is convenient to name spin labeled lipids as derivatives of their naturally occurring analogues. Thus, compound **8** can be named *trans*-8-aza-7,9-dimethyl-7,9-ethano-1-octadecanol-*N*-oxyl, which is shortened to *trans*-8-azethoxyloctadecanol. This system has the advantage in that it immediately locates the position of the label.
(6) J. F. W. Keana, T. D. Lee, and E. M. Bernard, *J. Am. Chem. Soc.*, **98**, 3052 (1976).
(7) T. D. Lee, G. B. Birrell, P. Bjorkman, and J. F. W. Keana, *Biochim. Biophys.*

Acta, in press.
(8) J. F. Elsworth and M. Lamchen, *J. S. Afr. Chem. Inst.*, **24**, 196 (1971); *Chem. Abstr.*, **75**, 151083d (1971).
(9) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).
(10) H. A. Brandman and R. T. Conley, *J. Org. Chem.*, **38**, 2236 (1973).
(11) T. D. Lee and J. F. W. Keana, *J. Org. Chem.*, **40**, 3145 (1975).
(12) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974).
(13) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
(14) M. Tamura and J. Kochi, *Synthesis*, 303 (1971).
(15) A. I. Meyers, D. L. Temple, R. L. Nolen, and E. O. Mihelich, *J. Org. Chem.*, **39**, 2778 (1974).
(16) H. A. Staab, *Angew. Chem. Int. Ed. Engl.*, **1**, 351 (1962).
(17) W. F. Boss, C. J. Kelley, and F. R. Landsberger, *Anal. Biochem.*, **64**, 289 (1975).
(18) Acyl migration in lysophosphatidylcholine is known to occur; see B. Serdarevich, *J. Am. Oil Chem. Soc.*, **44**, 381 (1967). The extent to which acyl migration might have occurred in our experiment has not been determined.
(19) Infrared spectra were recorded with either a Beckman IR-5 or IR-7 spectrophotometer. NMR spectra were recorded on a Varian XL-100 high-resolution spectrometer in $CDCl_3$, and only the characteristic peaks are reported. Chemical shifts are reported in parts per million (δ) downfield from internal Me_4Si. Mass spectra (70 eV) (*m/e*) are given followed by the relative peak height in parentheses and were determined on a CEC 110-2B double-focusing mass spectrometer equipped with a direct inlet. Elemental analyses were performed at the University of Oregon by Dr. R. Wielesek. Ultraviolet spectra were determined on a Cary 15 UV spectrometer. Unless otherwise noted, all silica gel column chromatography was done with Baker 60–200 mesh silica gel packed dry and eluted in the usual fashion. Preparative thin-layer chromatography (TLC) was done on Analtech 1000 silica gel plates with the fluorescent indicator. Analytical TLC used EM silica gel F-254 plates. Solvents were routinely distilled. Commercial reagents were used as received.
(20) C. A. Brown, *Anal. Chem.*, **39**, 1882 (1967).

Notes

Synthesis of 3-Carboethoxyoxindoles

Arthur G. Schultz* and William K. Hagmann

Department of Chemistry, Cornell University, Ithaca, New York 14853

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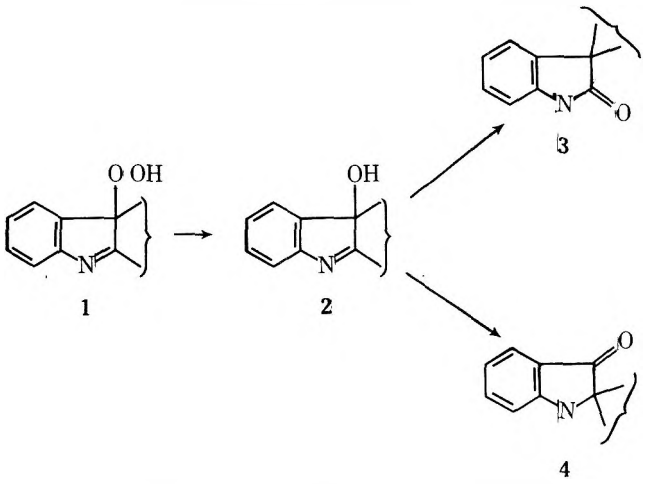
Indoles have been converted to 3-hydroperoxyindolenines **1** on autoxidation or peracid oxidation. Selective reduction of the hydroperoxy group in **1** gives 3-hydroxyindolenines **2**, which can rearrange to either oxindole **3**[1] or indoxyl **4**[2] de-

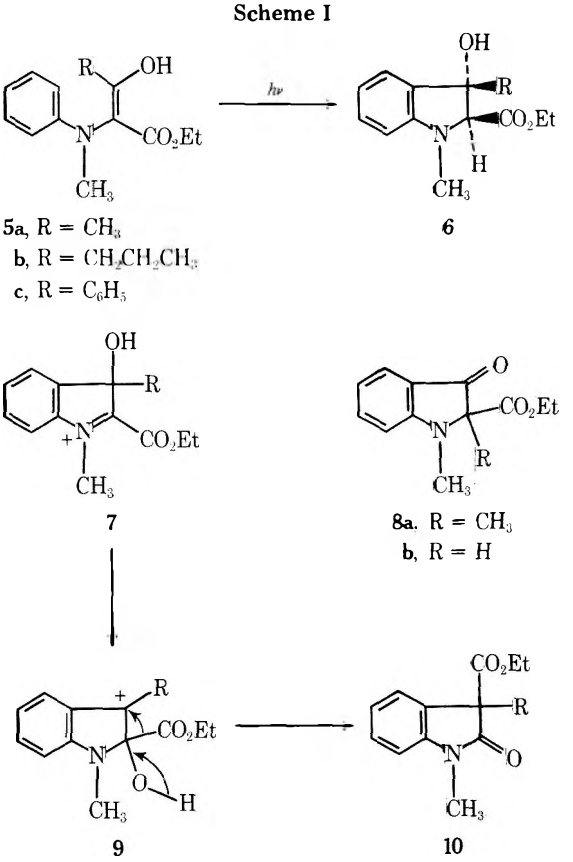


rivatives. Unfortunately, peracid oxidation can often be troublesome as a result of competitive N-oxide formation.[3] Other methods that circumvent this problem involve reaction of indoles with *tert*-butyl hypochlorite[4] or *N*-bromosuccinimide[5] to give 3-haloindolenines, and these can be converted to oxindoles. However, halogenation of the indole benzene ring[5] can sometimes be competitive with 3-haloindolenine formation (vide infra). In this paper, we present a new, high-yield method for oxindole preparation, which is based on the photosynthesis of 3-hydroxyindolines **6** and their oxidative rearrangement to oxindoles **9**.

We have reported that *N*-methyl-3-hydroxyindolines can be prepared in excellent yield by photocyclization–rearrangement of 2-(*N*-methylanilino)acetoacetates.[6] For example, irradiation of **5a** in *n*-pentane in the presence of suspended sodium carbonate gives 3-hydroxyindoline **6a** in quantitative yield. In similar fashion, indolines **6b** and **6c** also are prepared. Treatment of these 3-hydroxyindolines **6a–c** with lead tetraacetate (1.1 equiv) and pyridine (1.1 equiv) in benzene solution at room temperature results in a high-yield conversion to oxindoles **10a–c** (Table I).

In order to unambiguously establish the structure of the lead tetraacetate oxidation product, we attempted to prepare **10a** by treatment of *N*-methyl-2-carboethoxy-3-methylindole with *tert*-butyl hypochlorite using literature procedures.[4] Under these conditions, products resulting from chlorination of the benzene ring as well as the C(3) methyl substituent in the indole were obtained. Oxindole **10a** was eventually pre-

Scheme I



* Direct corresponcence to this author at the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181.

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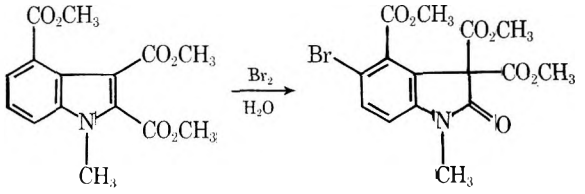
Table I. Oxidation–Rearrangement of 3-Hydroxyindolines 6 to Oxindoles 10

compd	R	yield, %[a]	Mp, °C
10a	CH_3	80	67.5–68.5
10b	$CH_2CH_2CH_3$	76	83–84
10c	C_6H_5	70	109–110

[a] Isolated yield of crystallized product based on the two-step sequence from 5.

pared in low yield by reaction of *N*-methyloxindole with lithium diisopropylamide–ethyl chloroformate in THF followed by alkylation with sodium ethoxide–methyl iodide in ethanol. The material thus obtained was found to be identical with that isolated from oxidative rearrangement of **6a**. Indoxyl **8a** was prepared from previously reported **8b**[7] by alkylation with sodium hydride–methyl iodide in THF. The absence of **8a** from reaction mixtures of **6a** with lead tetraacetate was confirmed by comparison of appropriate ^1H NMR spectral data.

A reasonable mechanism for oxidative rearrangement of **6** requires lead tetraacetate oxidation to iminium ion **7**, from which rearrangement to carbonium ion **9** occurs. A 1,2 shift of the ethoxycarbonyl group in **9** with loss of a proton gives the oxindole **10**. Migration of an alkoxycarbonyl group to an electron deficient carbon is well-documented,[8] and we note the relevant rearrangement of **11** to **12** reported by Acheson and coworkers.[9]



11 12

As a result of our study of substituents compatible with photocyclization of 2-anilino keto acetates,[6,10] we feel confident that oxindoles with a variety of substituents in the benzene ring will be available by utilization of the methodology reported here.

Experimental Section

General. ^1H NMR spectra were obtained on a Varian A-60A or EM-390 NMR spectrometer (tetramethylsilane standard, deuteriochloroform solvent). Infrared spectra were recorded on a Perkin-Elmer 137B infrared spectrometer and melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet spectra were taken on a Cary 14 spectrometer. The light source for irradiation was a 450-W Ace-Hanovia medium pressure, mercury vapor lamp. Mass spectra were obtained on a Finnigan 3300 gas chromatograph–mass spectrometer.

Ethyl 2-(*N*-methylanilino)acetoacctate (5a). A solution of ethyl 2-bromoacetoacetate (36.34 g, 0.173 mol) and *N*-methylaniline (37.24 g, 0.348 mol) in 95% ethanol (85 mL) was refluxed for 5.5 h. After cooling, the solvent was removed in vacuo and the residue dissolved in ether (300 ml) which was washed successively with 1 N hydrochloric acid (4 × 75 mL), 1 N sodium bicarbonate solution (1 × 50 mL), and water (3 × 100 mL) and dried over anhydrous magnesium sulfate. Removal of solvent in vacuo and distillation gave **5a** (31.05 g, 76%, bp 93–95 °C at 0.03 mm): IR ($CHCl_3$) 6.05, 6.25, 6.70 μm; ^1H NMR δ 1.10 (3 H, triplet, J = 7.5 Hz), 1.97 (3 H, singlet), 3.04 (3 H, singlet), 4.11 (2 H, quartet, J = 7.5 Hz), 6.50–7.38 (5 H, multiplet), 12.28 (1 H, singlet); UV (benzene) λ_{max} 295 nm (ε 2940); electron impact mass spectrum, *m/e* 235, 189, 161, 118.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.34; H, 7.32.

Ethyl 2-(*N*-methylanilino)butyroylacetate (5b). Prepared from ethyl 2-chlorobutyroylacetate and *N*-methylaniline by the method described for **5a** (52%, bp 100–102 °C at 0.04 mm): IR (neat) 6.05, 6.25, 6.70 μm; ^1H NMR δ 0.90 (3 H, triplet, J = 7.5 Hz), 1.09 (3 H, triplet, J = 7.0 Hz), 1.61 (2 H, sextet, J = 7.5 Hz), 2.32 (2 H, triplet, J = 7.5 Hz), 3.02 (3 H, singlet), 4.11 (2 H, quartet, J = 7.0 Hz), 6.58–6.80 (3 H, multiplet), 7.10–7.31 (2 H, multiplet), 12.40 (1 H, singlet).

Ethyl 2-(*N*-methylanilino)benzoylacetate (5c). Prepared from ethyl 2-chlorobenzoylacetate and *N*-methylaniline by the method described for **5a**; purified by medium-pressure liquid chromatography on silica gel using benzene/hexane (1:1) as eluent (50% yield): IR ($CHCl_3$) 6.09, 6.25, 6.70 μm; ^1H NMR δ 1.07 (3 H, triplet, J = 7.5 Hz), 2.91 (3 H, singlet), 4.14 (2 H, quartet, J = 7.5 Hz), 6.55–6.86 (3 H, multiplet), 7.03–7.40 (5 H, multiplet), 7.62–7.84 (2 H, multiplet).

Ethyl 1,3-Dimethyloxindole-3-carboxylate (10a). A solution of **5a** (4.01 g, 17.1 mmol) and sodium carbonate (18 mg, 0.17 mmol) in dry pentane (300 mL) was purged with argon for 30 min and irradiated with Uranyl glass-filtered light, while a slow stream of argon was bubbled through the solution. After 5.3 h, the solution was filtered and solvent removed in vacuo at room temperature to give ethyl 1,3-dimethyl-3-hydroxyindoline-2-carboxylate (**6a**) as a colorless oil: IR (neat) 2.90, 5.75, 6.20 μm; ^1H NMR δ 1.30 (3 H, triplet, J = 7.5 Hz), 1.44 (3 H, singlet), 2.78 (3 H, singlet), 2.7 (1 H, broad singlet, disappears upon addition of deuterium oxide), 3.97 (1 H, singlet), 4.28 (2 H, quartet, J = 7.5 Hz), 6.40–7.35 (4 H, multiplet).

A solution of **6a** in dry benzene (18 mL, 18.5 mmol) was cooled to 5 °C and lead tetraacetate (8.35 g, 18.5 mmol) was added in portions. After stirring for 4.5 h, water (10 mL) was added and the solution extracted with ether (3 × 30 mL). The combined ether extracts were washed successively with 1 N sodium hydroxide (5 × 20 mL), 1 N hydrochloric acid (3 × 29 mL), and water (3 × 20 mL) and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent and recrystallization from ether/hexane gave **10a** (3.17 g, 80%, mp 67.5–68.5 °C): IR ($CHCl_3$) 5.75, 5.83, 6.18, 6.70, 6.80, 7.25 μm; ^1H NMR δ 1.14 (3 H, triplet, J = 7.0 Hz), 1.63 (3 H, singlet), 3.24 (3 H, singlet), 4.12 (2 H, quartet, J = 7.0 Hz), 6.80–7.46 (4 H, multiplet); electron impact mass spectrum *m/e* 233 (16), 161 (25), 160 (100).

Anal. Calcd for $C_{13}H_{15}NO_3$; C, 66.94; H, 6.48. Found: C, 67.01; H, 6.43.

Alternate Preparation of 10a. Ethyl 1-methyloxindole-3-carboxylate was prepared by adding a solution of 1-methyloxindole (95 mg, 0.72 mmol) in THF (0.3 mL) to a stirred solution of lithium diisopropylamide (0.72 mmol from *n*-BuLi and diisopropylamine) in THF (0.5 mL) at −78 °C. After stirring for 30 min at −78 °C, ethyl chloroformate (0.07 mL, 79 mg, 0.73 mmol) was added and the solution was stirred at −78 °C for an additional 4 h. Ether (25 mL) and 1 N hydrochloric acid (0.5 mL) were added and the resulting solution was washed successively with 1 N hydrochloric acid (3 × 5 mL) and water (3 × 5 mL) and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent and recrystallization from hot petroleum ether gave ethyl 1-methyloxindole-3-carboxylate (23 mg, 15%, mp 96–97 °C): IR (neat) 5.72, 5.80, 6.06, 6.15 μm; ^1H NMR δ 1.26 (3 H, triplet, J = 7.5 Hz), 3.24 (3 H, singlet), 4.25 (2 H, quartet, J = 7.5 Hz), 4.42 (1 H, singlet), 6.70–7.40 (4 H, multiplet).

A solution of ethyl 1-methyloxindole-2-carboxylate (23 mg, 0.11 mmol), methyl iodide (20 mg, 0.14 mmol), and sodium ethoxide (11 mg, 0.14 mmol) in absolute ethanol (0.2 ml) was heated to reflux temperature for 4 h. After cooling, water (1.0 mL) was added and the solution was extracted with ether (3 × 10 mL). The combined ether extracts were washed successively with 1 N sodium hydroxide (3 × 5 mL) and water (3 × 5 mL) and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent gave **10a** (11 mg, 43%, mp 68 °C).

Ethyl 1-Methyl-3-*n*-propyloxindole-3-carboxylate (10b). 10b was prepared from **5b** by the method described for **10a**, purified by column chromatography on silica gel using methylene chloride as eluent, and recrystallized from ethyl acetate/hexane (76%, mp 83–84 °C): IR ($CHCl_3$) 5.75, 5.85, 6.19, 6.70, 6.81, 7.30, 7.44 μm; ^1H NMR δ 0.83 (5 H, multiplet), 1.14 (3 H, triplet, J = 7.0 Hz), 2.11–2.34 (2 H, multiplet), 3.24 (3 H, singlet), 4.13 (2 H, quartet, J = 7.0 Hz), 6.80–7.48 (4 H, multiplet).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.89; H. 7.24.

Ethyl 1-Methyl-3-phenyloxindole-3-carboxylate (10c). 10c was prepared from **5c** by the method described for **10a**. Recrystallization from hexane gave **10c** (70%, mp 109–110 °C); IR ($CHCl_3$) 5.72, 5.81, 6.19, 6.70, 6.80, 7.30, 7.41 μm; ^1H NMR δ 1.19 (3 H, triplet, J = 7.0 Hz), 3.22 (3 H, singlet), 4.22 (2 H, quartet, J = 7.0 Hz), 6.88–7.57 (4 H, multiplet), 7.34 (5 H, singlet).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80. Found: C, 73.06; H, 5.69.

Ethyl 1,2-Dimethylindoxyl-2-carboxylate (8a). A solution of ethyl 1-methylindoxyl-2-carboxylate[7] (1.21 g, 5.5 mmol) and sodium

hydride (132 mg, 5.5 mmol) in tetrahydrofuran (8 mL) was stirred at room temperature for 2 h. Methyl iodide (0.44 mL, 1.00 g, 7.1 mmol) was added and the solution refluxed for 2 h. After cooling, ether (30 mL) was added and the solution was washed with 1 N sodium hydroxide (3 × 10 mL) and water (3 × 10 mL) and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was separated by preparative thick layer chromatography on silica gel using ether/methylene chloride (1:9) as eluent to give **8a** (0.87 g, 68%, mp 63–64 °C): IR (neat) 5.74, 5.88, 6.18 μm; ^{1}H NMR δ 1.20 (3 H, triplet, J = 7.5 Hz), 1.55 (3 H, singlet), 2.96 (3 H, singlet), 4.17 (2 H, quartet, J = 7.5 Hz), 6.70–6.88 (2 H, 3 singlets), 7.36–7.70 (2 H, multiplet).

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. DA 01552-2).

Registry No.—**5a,** 67271-23-2; **5b,** 67271-24-3; **5c,** 67271-25-4; **6a,** 61838-88-8; **6b,** 67271-26-5; **6c,** 67271-27-6; **8a,** 67271-28-7; **10a,** 67271-29-8; **10b,** 67271-30-1; **10c,** 67271-31-2; *N*-methylaniline, 100-61-8; ethyl 2-bromoacetoacetate, 609-13-2; ethyl 2-chlorobutyroylacetate, 67271-32-3; ethyl 2-chlorobenzoylacetate, 41381-97-9; 1-methyloxindole, 61-70-1; ethyl chloroformate, 541-41-3; ethyl 1-methyloxindole-3-carboxylate, 39478-72-3; ethyl 1-methylindoxyl-2-carboxylate, 67271-33-4.

References and Notes

(1) B. Witkop, *Bull. Soc. Chim. Fr.*, 423 (1954).
(2) R. J. S. Beer, T. Donavanik, and A. Robertson, *J. Chem. Soc.*, 4139 (1954).
(3) See ref 4 and especially footnote 6 in ref 4.
(4) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84,** 3871 (1962).
(5) W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26,** 263 (1961); T. Kobayashi and N. Inokuchi, *Tetrahedron*, **20,** 2055 (1964); R. J. Bass, *ibid.*, **27,** 3263 (1971).
(6) A. G. Schultz and W. K. Hagmann, *Chem. Commun.*, 726 (1976).
(7) G. Durrant, P. D. Edwards, and L. N. Owen, *J. Chem. Soc., Perkin Trans. 1*, 1271 (1973).
(8) R. M. Acheson, *Acc. Chem. Res.*, **4,** 177 (1971); J. N. Marx, J. C. Argyle, L. R. Norman, *J. Am. Chem. Soc.*, **96,** 2121 (1974); P. J. Abbott, R. M. Acheson, R. F. Flowerday, and G. W. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1177 (1974); T. H. Phan and H. Dahn, *Helv. Chim. Acta*, **59,** 335 (1976).
(9) R. M. Acheson, R. W. Snaith, and J. M. Vernon, *J. Chem. Soc.*, 3229 (1964).
(10) A. G. Schultz and W. K. Hagmann, *J. Org. Chem.*, **43,** 3391 (1978).

Condensation Reactions of Carbanions and Ylides Derived from α-Halo Sulfoximines

H. G. Corkins, Lois Veenstra, and Carl R. Johnson*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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The homologation of aldehydes and ketones is a classic problem in organic chemistry with many practical solutions. The limitations and disadvantages of the known methods are sufficient to warrant development of new methods. We have recently described the first preparations of α-halo sulfoximines[1] and we envisioned in their chemistry a carbonyl homologation scheme (Scheme I).

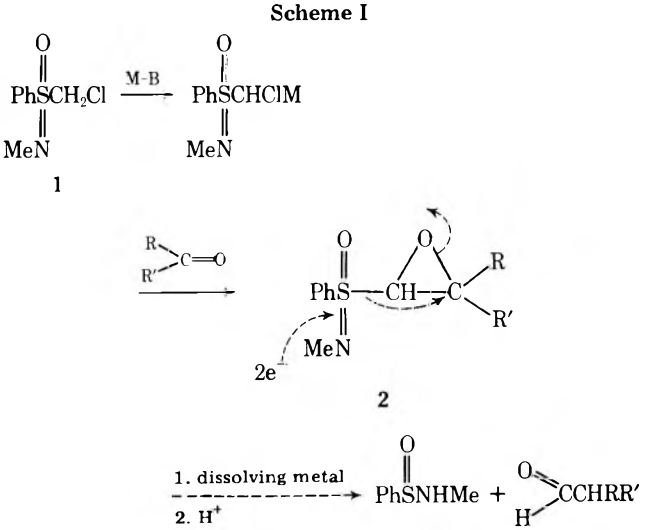
After considerable experimentation, the most effective condition which we found for the condensation of **1** with carbonyl compounds involved potassium *tert*-butoxide in a mixture of dimethyl sulfoxide (Me_2SO) and tetrahydrofuran (THF) at 0 °C to room temperature. Table I lists the epoxy sulfoximines produced in this manner. The use of symmetrical ketones simplified product analysis by restricting the diastereomers to two in each case. Chromatography on basic alumina was found to be acceptable for the isolation of the epoxy sulfoximines. Attempts to condense **1** with *p*-nitrobenzaldehyde and 2-propenal under the above conditions were unsuccessful. The diastereomeric alcohols **3** and **4** were obtained in good yield by using sodium hydride in THF at 0 °C. All four diastereomeric α-chloro-β-hydroxy sulfoximines (**3**) were separated and characterized by NMR spectroscopy. All attempts to effect ring closure of **3** and **4** to epoxy sulfoximines have been unsuccessful.

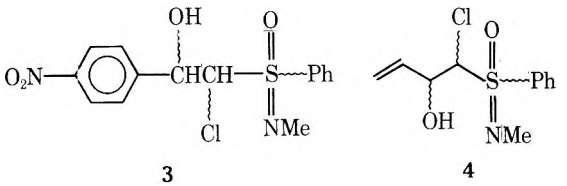
Table I. Condensation of 1 with Carbonyl Compounds

carbonyl compound	registry no.	product	R	R′	yield, %	diastereomeric ratio[a]
acetone	67-64-1	**2a**	CH_3	CH_3	81	29/72
cyclohexanone	108-94-1	**2b**	$-(CH_2)_5-$		75	32/68
4-*tert*-butylcyclohexane	98-53-3	**2c**	$-(CH_2)_2-CH(t\text{-Bu})-(CH_2)_2-$		50	*b*
benzaldehyde	100-52-7	**2d**	H	Ph	75	44/56

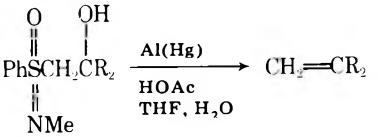
[a] Diastereomers due to contiguous chiral centers at S and the α-C. [b] Mixture of four diastereomers due to chiral centers at S and the α-C plus cis–trans ring isomers. The diastereomers with the *tert*-butyl and oxide cis accounted for 90% of the product.

Scheme I





Aluminum amalgam in the presence of acetic acid in aqueous THF has been found effective for the reductive elimination of β-hydroxy sulfoximines to yield alkenes (eq 1).[2]



(1)

When the epoxy sulfoximines **2a** and **2b** were treated under the above conditions no isobutyraldehyde or cyclohexanecarboxaldehyde could be detected by gas chromatography. Thin-layer chromatography indicated rapid loss of the starting material. From the reaction of **2b,** cyclohexylmethanol was isolated. In the absence of acetic acid **2b** is slowly reduced to **5** (eq 2). Although the above experiments are not exhaustive we have concluded that Scheme I is not likely to provide a practical method for homologation of aldehydes and ketones.

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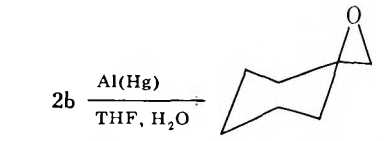
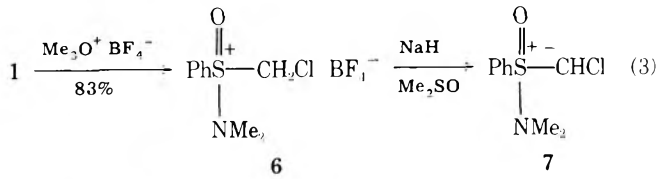


(2)

Epoxy sulfoximines may be interesting substrates for other types of reactions.

The use of sulfoximine derivatives as nucleophilic alkylidene transfer reagents has been described earlier.[3] To test the feasibility of chloromethylene transfer to Michael acceptors the reactions shown in eq 3–5 were examined.



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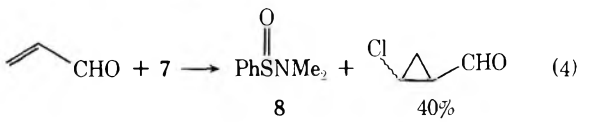

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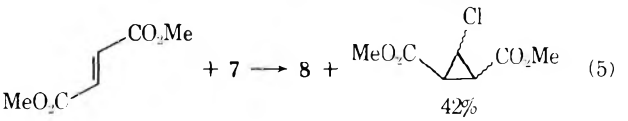

(5)

In the examples shown, the corresponding chlorocyclopropane derivatives were obtained in moderate yields. The isomeric 2-chlorocyclopropyl-1-carboxaldehydes (**9**) were isolated as dinitrophenylhydrazones.

Experimental Section

2,2-Dimethyl-3-(*N*-methylphenylsulfonimidoyl)oxirane (2a). Under a dry nitrogen atmosphere, a solution of 1.06 g (5.2 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine in 15 mL of THF–Me_2SO (1:2 by volume) was cooled in an ice bath. Addition of 0.66 g (5.9 mmol) of potassium *tert*-butoxide (MSA Research Corp.) produced a red solution. With continuous stirring 1.15 mL (3 equiv) of acetone was added via syringe. The solution was stirred at 0 °C for 3 h and at room temperature for an additional 4 h. The reaction mixture was poured into an equal volume of saturated ammonium chloride and extracted three times with equal volumes of ether. The ether extracts were washed with several portions of water, dried (Na_2SO_4), and concentrated by rotary evaporation to give 0.95 g (81%) of crude oil. The NMR spectrum of this oil indicated a 28:72 mixture of diastereomeric epoxy sulfoximines. Chromatography (silica gel/ether) and fractional crystallization (ether–pentane) resulted in 0.3 g of one diastereomer as a white crystalline solid, mp 79.5–80.5 °C.

2-(*N*-Methylphenylsulfonimidoyl)-1-oxaspiro[2.5]octane (2b). Under a nitrogen atmosphere, 4.06 g (19.6 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine was dissolved in a mixture of 5 mL of THF (distilled from Na) and 17 mL of Me_2SO (distilled from CaH_2). The solution was cooled in an ice bath. Addition of 2.26 g (20.0 mmol) of potassium *tert*-butoxide resulted in a red-brown solution. After the addition of 4.1 mL (2 equiv) of freshly distilled cyclohexanone the reaction mixture was treated as described for **2a** to give 4 g (75%) of crude brown oil. The NMR spectrum of this oil showed the presence of both diastereomeric epoxy sulfoximines. Approximately 1 g of the oil was dissolved in ether (5 mL) and cooled to −78 °C. Scratching induced crystallization. Recrystallization (pentane–ether) resulted in the isolation of one diastereomer as a white crystalline solid, mp 95–95.5 °C.

6-*tert*-Butyl-2-(*N*-methylphenylsulfonimidoyl)-1-oxaspiro-[2.5]octane (2c). Under a nitrogen atmosphere 4.02 g (17.4 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine was dissolved in a mixture of 7 mL of THF (distilled from Na) and 15 mL of Me_2SO (distilled from CaH_2). The solution was cooled in an ice bath. Addition of 2.36 g (21.0 mmol) of potassium *tert*-butoxide resulted in a red-brown solution. With continuous stirring 6.11 g (40.0 mmol) of 4-*tert*-butylcyclohexanone dissolved in 3 mL of THF and 5 mL of Me_2SO was added via syringe. After stirring 2 h at 0 °C the ice bath was removed and stirring was continued 16 h. The workup followed that described for **2a**. The crude oil was subjected to fractional sublimation and steam distillation to remove unreacted ketone to give 2.79 g of a red-brown oil which was finally subjected to column chromatography. A total of 2.0 g of impure epoxy sulfoximine was obtained. The NMR indicated the presence of diastereomers.

***trans*-1-(*N*-Methylphenylsulfonimidoyl)-2-phenyloxirane (2d).** Under a nitrogen atmosphere 1.4 g (7 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine was dissolved in 3.0 mL of THF (distilled from Na) and 8.0 mL of Me_2SO (distilled from CaH_2). The solution was cooled to 0 °C in an ice bath. Addition of 0.79 g (7 mmol) of potassium *tert*-butoxide resulted in a red-brown solution. With continuous stirring 1.72 mL (2 equiv) of benzaldehyde was added. After stirring for 30 min at 0 °C the ice bath was removed and stirring was continued for 3 h. Workup as for **2a** gave a crude oil. The oil was dissolved in carbon tetrachloride (50 mL) and concentrated again to give 0.907 g (75%) of oil. Column chromatography (silica gel/ether) gave 0.24 g of a mixture (44:56) of diastereomeric epoxy sulfoximines. Pure *N*-methylbenzenesulfinamide was also isolated from the chromatography and identified by IR and NMR.

2-Chloro-2-(*N*-methylphenylsulfonimidoyl)-1-(4-nitrophenyl)ethanol (3). To a cold (−78 °C) solution of 1.63 g (8.0 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine in 8 mL of dry THF was added 3.90 mL (8.0 mmol) of 2.05 M butyllithium. A yellow solution resulted. Addition of 1.69 g (12.0 mmol) of 4-nitrobenzaldehyde in 5 mL of THF was made in one portion. After stirring for 45 min the dark red solution was poured into an equal volume of saturated ammonium chloride and extracted twice with 100-mL portions of ether. The extracts were washed with 10% aqueous sodium hydrogen sulfite and then water. Drying over sodium sulfate and concentrating by rotary evaporation gave 2.26 g of a crude yellow solid. This material was found to be a mixture of four diastereomers. By a combination of fractional crystallization and thick-layer chromatography each of the four diastereomers was isolated in high enough purity that the proton resonance for each could be measured. Spectal data for diastereomers A, B, C, and D have been included in the microfilm edition.

1-Chloro-1-(*N*-methylphenylsulfonimidoyl)-3-buten-2-ol (4). A solution of 0.622 g (3.06 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine in 10.0 mL of THF (distilled from Na) was cooled to −78 °C and 1.51 mL of 2.05 M *n*-butyllithium was added. A pale yellow solution was obtained. After stirring 5 min at −78 °C 0.21 mL (3.1 mmol) of 2-propenal (freshly distilled) was added in one portion. The reaction flask was stoppered, wrapped with Parafilm, and placed in the freezer (−38 °C) for 11.5 h. The yellow solution was poured into an equal volume of saturated ammonium chloride and extracted with two equal volumes of ether. The extracts were washed with 10% aqueous sodium hydrogen sulfite and water. Drying (Na_2SO_4) and concentrating resulted in 0.726 g of slightly yellow oil. The α-chloro-β-hydroxy sulfoximine was further purified by thick-layer chromatography to give 0.29 g of **4** (36%).

Reduction of 2c with Aluminum Amalgam in Aqueous THF. A total of 0.53 g (~1.6 mmol) of the diastereomeric epoxy sulfoximine (**2c**) contaminated with ~10–20% 4-*tert*-butylcyclohexanone was dissolved in 30 mL of 10% aqueous THF. After adding 0.94 g (16.0 g-atom) of aluminum amalgam, the mixture was stirred at room temperature for 48 h and then filtered. Addition of 20 mL of water was followed by extraction with ether. The extracts were dried (Na_2SO_4) and concentrated via rotary evaporation to give 0.28 g of pale yellow oil. Column chromatography (basic Al_2O_3/ether) gave 0.107 g of a mixture of isomeric 6-*tert*-butyl-1-oxaspiro[2.5]octanes. The ratio of cis (*tert*-butyl and oxide) to trans isomers was found to be 90:10 by NMR (by comparison of the NMR spectrum to those of authentic samples).

(Chloromethyl)[(dimethylamino)phenyl]oxosulfonium Fluoroborate (6). To 1.020 g (5.02 mmol) of *S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine in 25 mL of dichloromethane was added in one portion 0.773 g (5.23 mmol) of trimethyloxonium fluoroborate. A heterogenous mixture was obtained that became homogeneous after 15 min. After stirring for 30 min diethyl ether was added to precipitate the fluoroborate salt (1.264 g, 82.9%). Recrystallization from methanol gave fine white needles, mp 159.5–160.5 °C.

Reaction of (Dimethylamino)phenyloxosulfonium Chloromethylide with Dimethyl Fumarate. In a flamed out flask purged with dry nitrogen was added 0.056 g (1.3 mmol) of sodium hydride (57% oil dispersion). The oil was removed by washing with pentane. The last traces of pentane were blown off in a stream of nitrogen. The sodium hydride was slurried in 1.0 mL of THF (distilled from Na) and 2.0 mL of Me_2SO (distilled from CaH_2) and cooled in an ice bath. A total of 0.4 g (1.3 mmol) of **6** in 2.0 mL of Me_2SO was added dropwise. After 5 min hydrogen ceased evolving and a yellow solution was obtained. While stirring at 0 °C, 0.189 g (1.3 mmol) of dimethyl fumarate

in 1.8 mL of THF was added in one portion. The ice bath was removed and the solution was stirred at room temperature for 12 h. The brown solution was poured into an equal volume of cold aqueous ammonium chloride and extracted with two equal volumes of ether. The extracts were backwashed with water, dried ($MgSO_4$), and concentrated by rotary evaporation to give 0.36 g of a brown semisolid. Column chromatography (silica gel/30% ether–cyclohexane) resulted in 0.11 g (42%) of a diastereomeric mixture of 1,2-bis(carbomethoxy)-3-chlorocyclopropane and 0.13 g (60%) of *N,N*-dimethylbenzenesulfinamide.

Reaction of 7 with 2-Propenal. The reaction was carried out in the manner described above. The extraction was done with pentane. Some product codistilled with pentane, but the residue after concentration and treatment with 2,4-dinitrophenylhydrazine yielded 40% of 2-chlorocyclopropanecarboxaldehyde as its 2,4-dinitrophenylhydrazone, mp 160–161 °C. In a separate run, *N,N*-dimethylbenzenesulfinamide was found to be produced in 81% yield.

Acknowledgment. This research was supported by the National Science Foundation.

Registry No.—**1**, 67069-79-8; **2a** isomer 1, 67069-67-4; **2a** isomer 2, 67069-68-5; **2b** isomer 1, 67069-69-6; **2b** isomer 2, 67069-70-9; **2c**, 67069-71-0; **2d** isomer, 67112-77-0; **2d** isomer 2, 67069-63-0; **3** isomer 1, 67112-78-1; **3** isomer 2, 67112-76-9; **3** isomer 3, 67069-62-9; **3** isomer 4, 67145-49-7; **4**, 67069-72-1; **6**, 67069-74-3; **7**, 67069-75-4; **8**, 5539-54-8; **9** isomer 1, 67069-76-5; **9** isomer 2, 67069-77-6; *cis*-6-*tert*-butyl-1-oxaspiro[2.5]octane, 7787-78-2; *trans*-6-*tert*-butyl-1-oxaspira[2.5]-octane, 18881-26-0; 1,2-bis(carbomethoxy)-3-chlorocyclopropane, 67069-78-7; 4-nitrobenzaldehyde, 555-16-8; 2-propenal, 107-02-8; dimethyl fumarate, 624-49-7.

Supplementary Material Available: Analytical and spectral data of the compounds discussed in this paper (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) C. R. Johnson and H. G. Corkins, *J. Org. Chem.*, companion paper in this issue.
(2) C. R. Johnson, J. R. Shanklin, and R. A. Kirchhoff, *J. Am. Chem. Soc.*, **95**, 6462 (1973).
(3) C. R. Johnson, *Acc. Chem. Res.*, **6**, 341 (1973).

Temperature-Dependent Rearrangement of 2-(2-Furyl)-2-lithio-1,3-dithiane

Michael J. Taschner and George A. Kraus*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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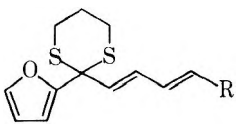
In the course of our work directed in the area of the Diels–Alder reaction, we required the preparation of compounds such as **1**. It was thought the use of 2-(2-furyl)-1,3-dithiane

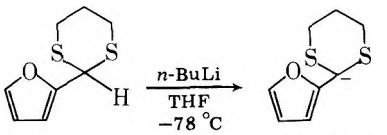


1

(**2**) as a nucleophilic acylating agent would provide an efficient entry into such a system. The use of lithiated 1,3-dithianes is well known and is the subject of two excellent reviews by Seebach.[1,2] Interestingly, the synthesis and use of compound **2** had not previously been recorded in the literature. We wish to report the preparation of **2** and the temperature dependent rearrangement of the anion produced from **2**.

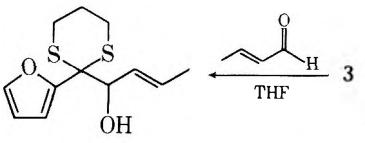
Results and Discussion

Preparation and Metalation of 2-(2-Furyl)-1,3-dithiane. The preparation of dithiane **2** was accomplished in



2 **3**

75% yield from furfural using the method of Corey and Seebach.[3] Metalation of **2** is complete within 10 min at −78 °C (method A). Reaction of anion **3** at −78 °C with crotonaldehyde and ethyl formate led to the isolation of alcohol **4** and aldehyde **5** in 95 and 60% yields, respectively.



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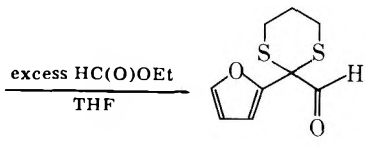

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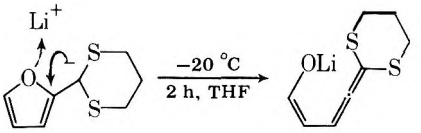
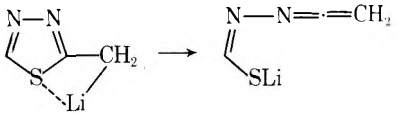
Temperature-Dependent Rearrangement of 3. When metalation was attempted using the method of Corey and Seebach[3] (method B), anion **3** underwent a novel rearrangement resulting in the formation of **6**. Analogy for such a re-

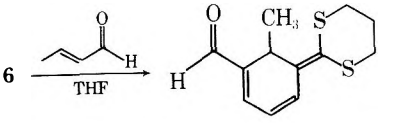


3 **6**

arrangement has previously been reported in the literature.[4] The rearrangement of 2-lithiomethylthiadiazoles reported by Meyers was also shown to be temperature dependent.[4a]



Compound **6** is postulated to account for the unexpected formation of ketene thioacetal **7**, the result of quenching the anion produced by method B with crotonaldehyde at −78 °C. Structural assignment **7** is based on the spectral characterization data (Experimental Section). The formation of **7** could be envisioned by one of two possible mechanisms. Compound **7** could arise from a 1,4 addition to crotonaldehyde at the γ

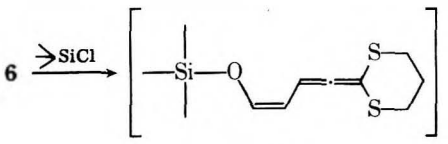


7

position of dienolate **6**, followed by cyclization and subsequent loss of H_2O. The other possibility is a Diels–Alder addition of **6** with crotonaldehyde followed by elimination of water after acidification.[5]

Further insight into the rearrangement was gained by quenching **6** with trimethylchlorosilane. Aqueous workup of the reaction furnished the cis unsaturated aldehyde **9** in quantitative yield. The structure is based on spectral data and the conversion of **9** to *n*-pentyl alcohol by successive treatment with $NaBH_4$ and Raney-Nickel.[6] The coupling constant of 7.5 Hz between H_2 and H_3 is indicative of a cis double bond when compared to *trans*-2-penten-4-ynal, a known trans-α,β-un-

saturated aldehyde, which has a coupling constant of 16 Hz.[7] Nonaqueous workup led to an extremely unstable product. This product exhibited no absorptions indicative of an aldehyde in the IR or NMR. This is consistent with O-silylation rather than C-silylation and suggests the possible intermediacy of allene 8. Although no direct evidence for 8 can be given, it seems to be most consistent with the results.



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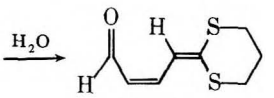
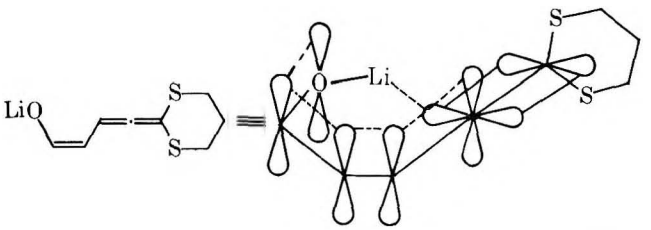


9

Reaction of 6 with D_2O led to the quantitative isolation of 9 with incorporation of deuterium in the γ position. In the NMR spectrum of the deuterated sample, a doublet at δ 6.63 in the spectrum of 9 was absent. Formation of the enol-OD followed by a 1,5-suprafacial shift of D would account for the position of the deuterium and the cis configuration about the double bond.[8] Anion 6 might best be depicted as shown below.



Attempts to quench 6 with other electrophiles (CH_3I, PhCOCl, and Ac_2O) led to unidentifiable products.

Experimental Section

All melting points were taken on a Fisher-Johns Mel-Temp apparatus and are uncorrected. IR spectra were obtained on a Beckman IR 4250 spectrometer. NMR spectra were recorded using a Varian A-60 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. An AEI-MS902 mass spectrometer was used for mass spectral data. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Visible spectra were recorded on a Cary-14 spectrometer. All organic solutions were dried over sodium sulfate.

2-(2-Furyl)-1,3-dithiane (2). A solution of 50 mmol of 1,3-propanedithiol and 50 mmol of furfural in 50 mL of CH_2Cl_2 was stirred at 0 °C for 30 min under an atmosphere of N_2. Then 5 mmol of BF_3-Et_2O were added and the reaction was slowly warmed to room temperature. The solution was stirred overnight at room temperature. It was then washed with $NaHCO_3$ solution, dried, filtered, and concentrated. The residue was recrystallized from hexane/benzene solution yielding 7.0 g (75%) analytically pure 2 (mp 43 °C): NMR ($CDCl_3$) 2.1 (m, 2 H), 3.0 (m, 4 H), 5.31 (s, 1 H), 6.49 (m, 2 H), 7.5 (m, 1 H).

Anal. Calcd for $C_8H_{10}OS_2$: C, 51.57; H, 5.41. Found C, 51.7; H, 5.62.

Method A: General Procedure for Expected Adducts. A 0.10 M solution of dithiane 2 in THF was cooled to −78 °C. To this was added an equivalent amount of *n*-butyllithium. The reaction was stirred at −78 °C for 10 min. During this time the solution turns deep red. This was followed by addition of a 2 M THF solution of the appropriate electrophile. The reaction was stirred at −78 °C for 15 min. It was then slowly warmed to room temperature. The solution was poured into ether and washed with a buffered (pH 7) NH_4Cl/NH_4OH solution. The organic solution was dried, filtered, and concentrated. The residue was chromatographed on silica gel using ether/hexane.

2-(2-Furyl)-2-(1-hydroxy-2-butenyl)-1,3-dithiane (4): 95% yield; IR (film) 3435 cm^{-1}; NMR ($CDCl_3$) 1.70 (d, J = 4.0 Hz, 3 H), 2.00 (m, 2 H), 2.77 (m, 4 H), 4.37 (d, J = 4.0 Hz, 1 H), 5.55 (m, 2 H), 6.37 (m, 1 H), 6.60 (m, 1 H), 7.50 (m, 1 H). High resolution mass spectrum *m/e* 256.0600 ($C_{12}H_{16}O_2S_2$ requires 256.05918).

2-Formyl-2-(2-furyl)-1,3-dithiane (5). A fourfold excess of ethyl formate was used to quench the anion. The compound after chromatography was recrystallized from hexane/CH_2Cl_2: 60% yield; white crystals (mp 72 °C); IR ($CHCl_3$) 1730, 2705, and 2820 cm^{-1}; NMR ($CDCl_3$) 2.14 (m, 2 H), 3.05 (m, 4 H), 6.60 (m, 2 H), 7.10 (m, 1 H), 9.40 (s, 1 H). High resolution mass spectrum *m/e* 213.9939 ($C_9H_{10}O_2S_2$ requires 214.0122).

Method B: General Procedure for Rearrangement of 2-(2-Furyl)-1,3-dithiane. A solution of 40 mL of anhydrous THF and 10 mmol of dithiane 2 was cooled to −40 °C. To this solution was added 10 mmol of *n*-butyllithium. The reaction was warmed to −20 °C and stirred at this temperature for 2 h. The resulting dark red solution was cooled to −78 °C. This was followed by addition of 10 mmol of the appropriate electrophile. The reaction was slowly warmed to 0 °C, poured into ether, and washed with a buffered (pH 7) NH_4Cl/NH_4OH solution. The organic solution was dried, filtered, and concentrated. The residue was chromatographed on silica gel using ether/hexane.

2-(5-Formyl-6-methyl-2,4-cyclohexadien-1-ylidene)-1,3-dithiane (7): red oil; 15% yield; IR (film) 2800, 2709, 1650 cm^{-1}; NMR ($CDCl_3$) 1.0 (d, J = 4.0 Hz, 3 H), 2.28 (m, 2 H), 3.05 (m, 4 H), 4.20 (q, J = 4.0 Hz, 1 H), 6.14 (dd, J_{32} = 3.0 Hz, J_{34} = 4.8 Hz, 1 H), 6.98 (d, J_{23} = 3.0 Hz, 1 H), 7.19 (d, J_{43} = 4.8 Hz, 1 H), and 9.65 (s, 1 H). High-resolution mass spectrum *m/e* 238.0434 ($C_{12}H_{14}OS_2$ requires 238.0486). Visible spectra (CH_3OH) 441 nm.

2-(3-Formyl-(*Z*)-2-propen-1-ylidene)-1,3-dithiane (9): red oil; 100% yield; IR (film) 2800, 2710, 1655 cm^{-1}; NMR ($CDCl_3$) 2.28 (m, 2 H), 3.10 (m, 4 H), 6.10 (dd, J_{32} = 7.5 Hz, J_{34} = 4.2 Hz, 1 H), 6.63 (d, J_{12} = 6.0 Hz, 1 H), 7.68 (dd, J_{21} = 6.0 Hz, J_{23} = 7.5 Hz, 1 H), and 9.78 (d, J_{43} = 4.2 Hz, 1 H). High-resolution mass spectrum *m/e* 186.0154 ($C_6H_{10}OS_2$ requires 186.0173). Visible spectra (CH_3OH) 365 nm.

2-(4-Hydroxy-(*Z*)-2-buten-1-ylidene)-1,3-dithiane. To a solution of 4 mL of CH_3OH and 2 mmol of 9 was added 0.55 mmol of $NaBH_4$. The reaction was stirred at room temperature for 30 min. It was diluted with 30 mL of Et_2O and washed with saturated NaCl solution. The Et_2O was dried and concentrated: yield 0.30 g (8); IR (film) 3434 cm^{-1}; NMR ($CDCl_3$) 2.20 (m, 2 H), 3.10 (m, 4 H), 4.20 (d, J = 5.0 Hz, 2 H), 5.85 (m, 1 H), 6.50 (m, 2 H).

***n*-Pentyl Alcohol.** A solution of 0.53 mmol of 2-(4-hydroxy-(*Z*)-2-buten-1-ylidene)-1,3-dithiane and 1 g of W-4 Ra-Ni in 25 mL of EtOH was refluxed for 1 h. Analysis by GLC proved the product to be *n*-pentyl alcohol.

Registry No.—2, 67421-75-4; 4, 67421-76-5; 5, 67421-77-6; 7, 67421-78-7; 9, 67421-79-8; 1,3-propanedithiol, 109-80-8; furfural, 98-01-1; 2-(4-hydroxy-(*Z*)-2-buten-1-ylidene)-1,3-dithiane, 67421-80-1; pentanol, 71-41-0; 2-(2-furyl)-2-lithio-1,3-dithiane, 67421-81-2.

References and Notes

(1) D. Seebach, *Synthesis*, 17 (1969).
(2) D. Seebach, *Synthesis*, 357 (1977).
(3) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(4) (a) A. I. Meyers and G. N. Knaus, *J. Am. Chem. Soc.*, **95**, 3408 (1973); (b) A. Suzuki, N. Miyaura, and M. Itoh, *Tetrahedron*, **27**, 2775 (1971); and (c) S. Gronowitz and T. Frejd, *Acta. Chem. Scand., Ser. B*, **29**, 818 (1975).
(5) We would like to thank a referee for helpful suggestions.
(6) I. Ernest, *Collect. Czech. Chem. Commun.*, **21**, 1468 (1956).
(7) Personal communication from Professor W. S. Trahanovsky.
(8) C. W. Jefford, A. F. Boschung, and C. G. Rimbault, *Tetrahedron Lett.*, 3387 (1974).

Tri-*tert*-butylmethylsilane

R. J. Wroczynski, Linda D. Iroff, and Kurt Mislow*

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received May 23, 1978

In connection with our studies of internal conformational dynamics in systems of the type t-Bu_3MX,[1] it became of interest to prepare tri-*tert*-butylmethylsilane (1, t-Bu_3SiCH_3). This compound had resisted a prior attempt at preparation by a copper-catalyzed methylene insertion into tri-*tert*-but-

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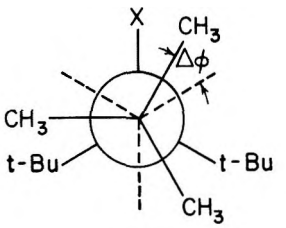
Table I. Calculated Structural Parameters for *t*-Bu_3SiX (X = CH_3 and H)



	X = CH_3 (1)	X = H (2)
$r(Si–C_q{}^a)$, Å	1.925	1.916
r(Si–X), Å	1.878	1.483
$r(C_q–C)$, Å	1.535	1.533
$\theta(C_q–Si–C_q)$, deg	113.5	114.7
$\theta(C–C_q–C)$, deg	106.9	107.8
$\Delta\phi^b$	15.3	14.4

[a] C_q = quaternary carbon atom. [b] $\Delta\phi$ = average angle of twist from the staggered conformation. See structure above.

ylsilane (**2**).[2] We have succeeded in obtaining **1** by *n*-Bu_3SnH reduction of *t*-Bu_3SiCH_2Br (**3**), which was prepared by bromocarbene insertion into **2**.[3]

Full relaxation empirical force field calculations[4] show that **1**, like **2**,[1] has C_3 symmetry in the ground state. Each *tert*-butyl group is twisted ca. 15° from a staggered conformation, thus rendering the three methyls in each group diastereotopic. The silyl methyl group is twisted by 11° in the same sense as the *tert*-butyls. The mutual repulsion of the bulky *tert*-butyl groups is the dominant structural feature of **1** (Table I). This is reflected in the long C_q–Si bonds and in the wide C_q–Si–C_q angles (113.5°). Replacement of the silyl CH_3 by H (**2**) allows the *tert*-butyl groups to move farther apart [θ(C–Si–C) = 114.7°] with a concomitant relaxation of other structural parameters. It is noteworthy that this angle in **2** is essentially the same as the C–Si–C angle calculated for trimesitylsilane (114.9°);[6] in analogous *t*-Bu_3MX and $(mesityl)_3MX$ systems, the C–M–C angles are also closely comparable for M = C, X = H (116.0[7] and 115.9°,[8] respectively)[9] and for M = P, X = lone pair (109.9[12] and 109.7°,[13] respectively). Evidently, *tert*-butyl and mesityl groups have similar steric demands in the C_3 ground states of these congested systems.

Hindered rotation about the Si–C bond in tri-*tert*-butylhalosilanes (*t*-Bu_3SiX) has been reported,[2a] with $\Delta G^{\ddagger}$ values of 8.2, 7.8, and 7.6 kcal/mol for X = I, Br, and Cl, respectively.[14] We have observed an analogous process in the variable temperature 100 MHz ^1H NMR spectra of **1**. At −117 °C, the *tert*-butyl methyl singlet splits into two peaks in a 2:1 ratio,[15] with $\Delta\nu$ = 16.5 Hz. The calculated value of $\Delta G^{\ddagger}_c$ = 7.9 ± 0.3 kcal/mol lies within the narrow range of barriers for the halosilanes, suggesting that the steric requirements for CH_3, Cl, Br, and I are similar in these systems. The significantly lower barrier for parent compound **2** ($\Delta G^{\ddagger}_{-140}$ = 6.1 kcal/mol[1]) indicates that **2** suffers less intramolecular crowding in the transition state.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Phenyl(dibromomethyl)mercury[16] and tri-*tert*-butylsilane[17] were prepared using reported procedures. Chlorobenzene was washed with concentrated H_2SO_4 and then aqueous $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and distilled from P_2O_5 onto type 3Å molecular sieves. Tri-*n*-butyltin hydride was used as purchased from Alfa-Ventron Corp., Danvers, Mass. Melting points were taken on a Thomas-Hoover apparatus and are corrected. Ambient temperature ^1H NMR spectra were recorded on a Varian A-60A instrument. All GLC analyses were carried out on a FM Research Chromatograph 810 with a 6 ft × 0.25 in SE-30 (20% on Chromosorb W) column. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y.

DNMR Measurements. All variable temperature ^1H NMR spectra were recorded at 100 MHz in the Fourier transform mode on a Varian XL-100. The spectrometer was locked on ^{19}F present in the CF_2Cl_2 solvent. Temperature measurements were made with a copper–constantan thermocouple inserted directly into the 10 mm o.d. sample tube at coil height. Temperatures are considered to be accurate to ±2 °C, although within a given series smaller differences (ca. ±0.5 °C) were considered significant. Activation parameters were obtained by a least-squares fit of the rate data obtained by lineshape analysis using the Saunders program[18] and the Eyring equation.

Preparation of Tri-*tert*-butyl(bromomethyl)silane (3). Compound **2** (9.0 g, 0.045 mol), $PhHgCHBr_2$ (9.3 g, 0.021 mol), and 15 mL of chlorobenzene were placed in a 100-mL two-neck flask equipped with a nitrogen inlet, magnetic stirrer, and condenser. The mixture was then heated at reflux for a period of 96 h. The dark red liquid was cooled to room temperature, and the PhHgBr precipitate was filtered and washed with *n*-pentane. Vacuum distillation of the combined filtrates allowed removal of the remaining solvent and recovery of the excess of unreacted **2**. Consecutive sublimations of the resulting pot residue at 90 °C (0.5 Torr) gave 2.5 g (41%) of **3** as a white waxy solid: mp 189–195 °C; ^1H NMR ($CDCl_3$) δ 1.18 (s, CH_3), 2.73 (s, CH_2Br). Anal. Calcd for $C_{13}H_{29}BrSi$: C, 53.22; H, 9.96; Br, 27.24. Found: C, 53.65; H, 9.98; br, 27.04.

Preparation of Tri-*tert*-butylmethylsilane (1). Compound **3** (0.90 g, 0.0031 mol) and 20 mL of heptane were placed in a 25-mL three-neck flask equipped with a condenser, nitrogen inlet, and magnetic stirrer. The reaction vessel was flushed with nitrogen, *n*-Bu_3SnH (0.89 mL, 0.0034 mol) was added by syringe, and the reaction mixture was refluxed for 24 h. The solvent was removed by vacuum distillation. Preparative GLC of the resulting pot residue gave 0.29 g (44%) of **1**: mp (sealed tube) 141–145 °C; ^1H NMR ($CDCl_3$) δ −0.06 (s, Si–CH_3), 1.04 (s, CH_3). Anal. Calcd for $C_{13}H_{30}Si$: C, 72.80; H, 14.10; Si, 13.10. Found: C, 72.88; H, 14.10; Si, 12.96.

Acknowledgment. We thank the National Science Foundation (CHE 77-07665) for support of this work and Ms. Mary Baum for technical assistance.

Registry No.—**1**, 67382-52-9; **2**, 18159-55-2; **3**, 67382-53-0; $PhHgCHBr_2$, 1124-50-1.

References and Notes

(1) W. D. Hounshell, L. D. Iroff, R. J. Wroczynski, and K. Mislow, *J. Am. Chem. Soc.*, **100**, 5212 (1978).
(2) (a) M. Weidenbruch, W. Peter, and C. Pierrard, *Angew. Chem., Int. Ed. Engl.*, **15**, 43 (1976); (b) M. Weidenbruch, H. Pesel, W. Peter, and R. Steichen, *J. Organomet. Chem.*, **141**, 9 (1977).
(3) For the insertion of dihalocarbenes into **2**, see ref 2.
(4) These calculations were performed using program BIGSTRN (QCPE No. 348) and the Allinger 1971 force field parameters.[5] input structures were relaxed using a modified version of the pattern search minimization technique, with an energy criterion of 0.005 kcal/mol over one iteration.
(5) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93**, 1637 (1971); M. T. Tribble and N. L. Allinger, *Tetrahedron*, **28**, 2147 (1972).
(6) J. P. Hummel, E. P. Zurbach, E. N. DiCarlo, and K. Mislow, *J. Am. Chem. Soc.*, **98**, 7480 (1976).
(7) H. B. Burgi and L. S. Bartell, *J. Am. Chem. Soc.*, **94**, 5236 (1972).
(8) J. F. Blount and K. Mislow, *Tetrahedron Lett.*, 909 (1975).
(9) Force field calculations also give close agreement for this angle in *t*-Bu_3CH (117.8°)[10] and $(mesityl)_3CH$ (117.7°).[11]
(10) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(11) J. D. Andose and K. Mislow, *J. Am. Chem. Soc.*, **96**, 2168 (1974).
(12) H. Oberhammer, R. Schmutzler, and O. Stelzer, *Inorg. Chem.*, **17**, 1254 (1978).
(13) J. F. Blount, C. A. Maryanoff, and K. Mislow, *Tetrahedron Lett.*, 913 (1975).
(14) M. Weidenbruch, private communication.
(15) The observation of two methyl resonances (rather than the expected three) at slow exchange may be due to a (nonobserved) low-energy process which averages two of the three sites, resulting in an average C_{3v} symmetry. Such a low-energy process in which all three groups go through a staggered position has been calculated for **2**.[1] Alternatively, the possibility of accidental isochrony cannot be excluded.
(16) D. Seyferth and R. L. Lambert, Jr., *J. Organomet. Chem.*, **16**, 21 (1969).
(17) For a preparation of **2**, see ref 2b and references cited therein.
(18) The computer program used was adapted from one developed by M. Saunders; see M. Saunders in "Magnetic Resonance in Biological Systems", A. Ehrenberg, B. G. Malmström, and T. Vänngård, Eds., Pergamon Press, New York, N.Y., 1967, p 85.

Ochtodene and Ochtodiol: Novel Polyhalogenated Cyclic Monoterpenes from the Red Seaweed *Ochtodes secundiramea*[1]

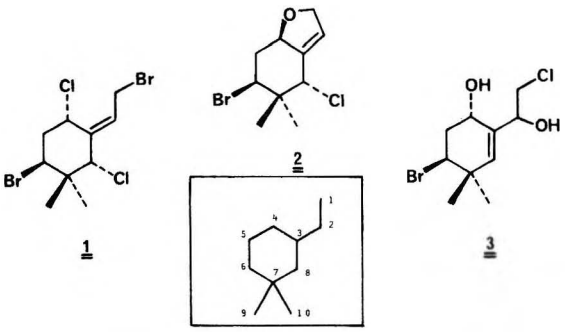
Oliver J. McConnell and William Fenical*

Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla, California 92093

Received April 11, 1978

Although a diverse array of halogenated terpenoids have been isolated from marine red algae (Rhodophyta),[2] cyclic halogenated monoterpenes have been found only in the red algae *Chondrococcus hornemanni* (Mertens) Schmitz[3a,b] and several species of the genus *Plocamium*.[4a,b] From *Ochtodes secundiramea* (Montagne) Howe,[5] a Caribbean red alga which is related to *C. hornemanni* (order, Gigartinales; family, Rhizophyllidaceae), we have isolated and fully characterized two new halogenated cyclic monoterpenes. Interestingly, and contrary to *Chondrococcus* and *Plocamium* species, *O. secundiramea* does not produce substantial amounts (<0.5% of the extract) of acyclic halogenated monoterpenes.

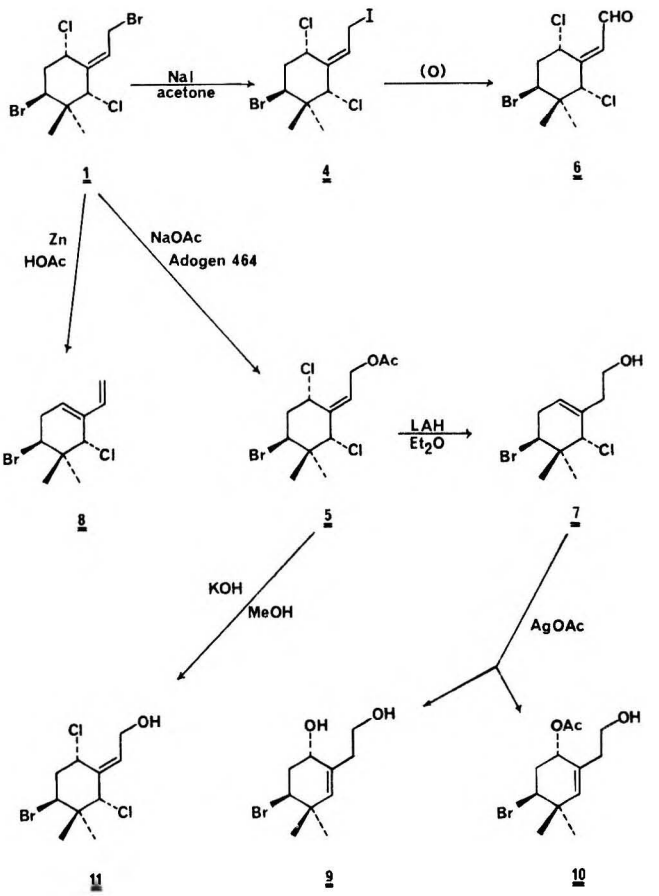
A small collection of *O. secundiramea* was made in April 1977 near Water Key along the Belizean barrier reef. The fresh algae were stored in 2-propanol and subsequently repeatedly extracted with chloroform. Silica gel column chromatography of the combined and concentrated extracts gave first the major nonpolar component **1**, next the known compound chondrocole A (**2**),[6] and later minor amounts of the diol **3**. We suggest



the trivial names ochtodene (**1**) and ochtodiol (**3**) for these new compounds.

Ochtodene (**1**) (ca. 50% of the organic extract), mp 60–62 °C, $[\alpha]^{22}_D$ +179° (c 12, $CHCl_3$), was determined to have the molecular formula $C_{10}H_{14}Br_2Cl_2$ from the high-resolution mass measurement of the $M^+ - Br$ fragment ion and from the low intensity low-resolution mass spectral isotopic clusters for the parent ion at *m/e* 362. One of the two requisite degrees of unsaturation in this formula was accounted for by a trisubstituted olefin deduced from the ^{13}C NMR absorptions at δ 137.7 (s) and 131.9 (d). The additional degree of unsaturation was determined to be a cyclohexane ring from the remaining NMR data. The ^1H NMR spectrum of ochtodene exhibited a lone olefinic proton at δ 5.96, which was shown by spin decoupling to be coupled (J = 7 and 10 Hz) to two geminally coupled protons attached to a halogen-bearing primary carbon [δ 4.05 (1 H, J = 7 and 12.5 Hz) and 4.20 (1 H, J = 10 and 12.5 Hz)]. A gem dimethyl moiety was recognized to exist in ochtodene from the classical NMR (^1H singlets at δ 1.03 and 1.30 and ^{13}C off-resonance quartets at δ 20.4 and 28.5 and singlet at δ 41.3) and infrared (doublet absorptions at 1360 and 1380 cm^{-1}) characteristics. Three halogen-bearing secondary carbons were also observed in the ^{13}C NMR spectrum as off-resonance doublets at δ 70.0, 52.7, and 50.4. The ^1H NMR spectrum of **1** contains bands characteristic of an allylic –CHX– group (singlet at δ 4.40) and an isolated –CHX–CH_2–CHX'– constellation: δ 4.99 (1 H, dd, J = 1.8 and 4.8 Hz), 4.85 (1 H, dd, J = 4.5 and 12.5 Hz), 2.71 (1 H, ddd, J = 1.8, 4.5, and 15 Hz), 2.55 (1 H, ddd, J = 4.8, 12.5, and 15 Hz). Interpretation of the coupling constants for the latter constellation and of spin decoupling experiments led us to assign the δ 4.99 proton absorption to an equatorial α-halogen proton and the δ 4.85 band to an axial α-halogen proton.

Scheme I



The combined spectral features for ochtodene were readily interpreted to yield the gross structure as in **1**. However, neither the locations and stereochemistry of the halogens nor the geometry of the double bond could be rigorously defined. Problems analogous to these have recently manifested themselves in the incorrect structure assignments of chondrocole A[3a,b] and violacene.[4b,c] Thus, it was deemed necessary to selectively degrade **1** to resolve these ambiguities.

Treatment of ochtodene with sodium iodide in acetone provided the primary iodide **4** but no 1,4-dehalogenation products. Since a simple S_N2 reaction transpired, introduction of an oxygen functionality in the primary position was conceived and the positions of the halogens were subsequently determined by the chemical transformations[7] shown in Scheme I.

The primary halogen in **1** was shown to be bromine. Treatment of ochtodene under phase-transfer conditions with sodium acetate resulted in the primary acetate **5** in high yield (96%). The spectral data of **5** clearly established the product as the primary acetate. The mass spectrum of **5** illustrated a facile loss of halogen to provide fragment ions with bromine and/or chlorine but none with three halogens or two of the same. Elemental analysis of **5**, however, confirmed the presence of two chlorines and one bromine. Also, slight heating of the primary iodide **4** followed by exposure to the air resulted in a modest yield of the α,β-unsaturated aldehyde **6**, which possessed a parent ion in the mass spectrum (*m/e* 298) with characteristic isotopic components for Cl_2Br.

The axial halogen which was part of the isolated –CHX–CH_2–CHX'– system in **1** was shown to be an allylic chlorine

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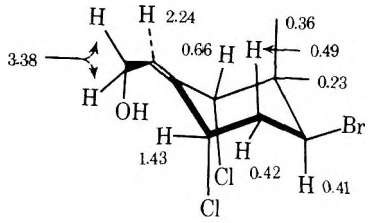
Chart I. Changes ($\Delta\delta$) in Chemical Shifts of 11 after the Addition of 1 Equivalent of Eu(fod)$_3$



11

since reaction of **5** with lithium aluminum hydride in diethyl ether at 0 °C reduced not only the acetate but also displaced this chlorine to yield the cyclohexene **7**. The mass spectrum of **7** revealed a $M^+ - H_2O$ fragment ion at *m/e* 248 for $C_{10}H_{14}BrCl$. The resultant endocyclic olefin proton, appearing in the ^1H NMR spectrum at δ 5.49, was shown by spin decoupling not to be coupled to the primary α-hydroxyl protons [δ 3.76 (t, J = 6.2 Hz)], thus establishing that the proposed reduction had occurred. An allylic –CHX– singlet remained (δ 4.29) for the C-8 methine, as well as a pseudoaxial halogen-bearing methine proton at δ 4.51 (dd, J = 6.1 and 10.0 Hz). The 1,4-dehalogenation product **8**, resulting from reaction of **1** with zinc in acetic acid at room temperature, also showed the loss of one bromine and one chlorine by the molecular ion in the mass spectrum at *m/e* 248 ($C_{10}H_{14}BrCl$) and thus corroborated these two halogen assignments in **1**. Upfield shifts of the C-6 axial proton in **7** and **8** relative to **1** reveal that the deshielding effect of one 1,3-diaxial proton–halogen interaction in the ^1H NMR spectrum is approximately 0.3 ppm.

Finally, the isolated allylic halogen in **1** was shown to be chlorine. Treatment of **7** with silver acetate in aqueous acetic acid containing tetrahydrofuran yielded the allylic alcohol **9** and allylic acetate **10** in a 4:1 ratio. The structure of the acetate **10** was confirmed by $LiAlH_4$ reduction to yield **9**. Both **9** and **10** contained only one bromine atom. Interestingly, the carbonium ion which is generated from the loss of the allylic and neopentyl chlorine is trapped regio- and stereospecifically without methyl migration. In **9** and **10**, the olefin proton is observed in the ^1H NMR spectrum as a singlet and the C-6 pseudoaxial methine proton remains intact as a doublet of doublets.

The geometry of the olefin in **1** was determined by an Eu(fod)$_3$-induced shift study[8] of the primary allylic alcohol **11**, which was obtained by saponification of the primary acetate **5**. The induced shifts of the protons in **11** indicated that the alcohol has the stereochemistry as shown in Chart I. The geometry of the olefin was clearly established as *E*, and the isolated C-8 methine proton was shown to be equatorial.[9]

Ochtodiol (**3**) was isolated in trace amounts (0.1% of the extract) after repeated silica gel and Florisil chromatography. Acetylation (Ac_2O/pyridine/room temperature) gave the diacetate **12**, which was established to have the molecular formula $C_{14}H_{19}O_4BrCl$ by high-resolution mass measurements of the $M^+ - HOAc$ and $M^+ - HCl$ fragments. The ^1H NMR similarities between ochtodiol, its diacetate, and the two silver acetate reaction products **9** and **10** greatly facilitated the structure assignment of this diol.[9]

The C-6 halogen in **3** was assigned as a pseudoequatorial bromine based upon a comparison of the ^1H NMR band for the C-6 methine proton at δ 4.43 (dd, J = 4.8 and 11.2 Hz) with that from 8 [δ 4.44 (dd, J = 6.6 and 9.7 Hz)], and also the C-6 methine proton of **9** [δ 4.23 (dd, J = 5 and 12 Hz)] with that of **11** [δ 4.27 (dd, J = 5.8 and 11.0 Hz)]. All of these protons illustrated pseudoaxial–pseudoaxial and pseudoaxial–pseudoequatorial coupling constants. The C-6 methine proton was further determined by spin decoupling to be in an isolated CHX–CH_2–CHY constellation where Y is hydroxyl. The C-4 methine proton was observed as a multiplet at δ 4.32 and was coupled to a two-proton multiplet at δ 2.30. The C-8 olefin proton appeared as a singlet at δ 5.69 and the two methyl groups as singlets at δ 1.19 and 1.07. The remaining protons at C-1 and C-2 were also related by spin decoupling and appeared at δ 4.32 (C-2 proton) and 3.62 (C-1 methylene pair). Two D_2O exhangeable protons were also observed at δ 2.95 and 3.10. They were replaced by two 3 H singlets at δ 2.07 in the spectrum of the diacetate **12**. Also observable in the spectrum of the diacetate was the C-4 methine proton at δ 5.39. The coupling constants for this proton (dd, J = 2.7 and 3.6 Hz) clearly established it to be pseudoequatorial.

Ochtodes secundiramea, although relatively sparse, was one of the few collectable red algal representatives to be found in the Caribbean waters along the coast of Belize. This alga is also quite unique in its bright red-blue fluorescent appearance, which is the result of refractance from large lipid-like bodies dispersed along the cortex of the thallus of the alga. Studies of similar bodies in *Laurencia* and *Plocamium* species have shown that these bodies are the sites of storage of the products of halogen metabolism.[10] The very large concentrations of ochtodene in *O. secundiramea* (50% of the organic extract) and the sensitivity of this compound toward nucleophiles suggest that it may be stored in these refractile bodies. Indeed, when fresh plants were briefly dipped in cool ethanol, the refractile bodies were destroyed, and by TLC the ethanol extract contained ochtodene. Finally, the production of halogenated monoterpenes may result in decreased predation of this alga in an ecosystem with many rapacious herbivores. In this regard, ochtodene is physiologically active against microorganisms showing strong antibacterial activity (agar plate method, 20 mm inhibition at a 0.5 mg disc load) against *Staphylococcus aureus*.

Experimental Section

^1H NMR spectra were recorded on a Varian HR-220 spectrometer with computerized Fourier transform and spin-decoupling capabilities. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer. Chemical shifts are expressed as δ values in ppm relative to Me_4Si = 0. Infrared spectra were obtained on a Perkin-Elmer 137 sodium chloride spectrophotometer, UV spectra were recorded on a Perkin-Elmer 124 spectrophotometer, and optical rotations were measured on a Perkin-Elmer 1410 polarimeter. Low-resolution mass spectra and high-resolution mass measurements were supplied by the Analytical Facility at the California Institute of Technology. Low-resolution GC–MS were obtained using a Hewlett-Packard 5930A mass spectrometer interfaced with a Hewlett-Packard 5910 gas chromatograph. Elemental analyses were supplied by Galbraith Laboratories, Inc., Tenn. All high pressure liquid chromatography separations were obtained using a Waters 6000 LC with 2 × 1 ft μ-porasil as the support. Melting points were measured on a Fisher-Johns apparatus and are reported uncorrected.

Collection and Extraction. *Ochtodes secundiramea* (Montagne) Howe was collected in the shallow lagoon area between the reef crest and the coral rubble on the east side of Water Key, 12 miles off the coast of Stann Creek, Belize, in April 1977.[5] The algae were stored fresh in 2-propanol. Subsequent pentane extraction of the decanted 2-propanol solution yielded 0.6 g of extract. This pentane extract was obtained to examine for highly volatile components; none were found. The algae were then homogenized and extracted with IPA/$CHCl_3$ (1:2) to yield an additional 0.47 g of extract. The total organic extract was 1.95% of the dried extracted weight of the algae.

Ochtodene (1). The crude extract (1.0 g) was applied to a silica gel column (2.5 × 45 cm) prepared with 100% petroleum ether. Ochtodene (**1**; 0.50 g, 0.9% of the dried extracted weight) was eluted pure with 10% diethyl ether in petroleum ether. Compound **1**: mp 60–62 °C; $[\alpha]^{23}_D$ +179° (*c* 12.0, $CHCl_3$); high-resolution mass measurement of $M^+ -$ Br, observed *m/e* 282.969 ($C_{10}H_{14}{}^{79}Br^{35}Cl_2$ requires *m/e* 282.966); low-resolution mass spectrum (50 eV), *m/e* (halogen composition, relative intensity) 362 ($^{79}Br_2{}^{35}Cl_2$, 1.3), 327 (Br_2Cl, 7.7), 283 ($BrCl_2$, 26.0), 247 (ClBr, 18.0), 211 (Br, 23.3), 203 (Cl_2, 50.7), 167 (Cl, 100.0), 91 (86.7); ^1H NMR [$CDCl_3$ (benzene-d_6)] δ 1.03 (0.59) (3 H, s), 1.30 (1.16) (3 H, s), 2.55 (2.01) (1 H, ddd, J = 4.8, 12.5, and 15.0 Hz), 2.71 (2.40) (1 H, ddd, J = 1.8, 4.5, and 15.0 Hz), 4.05 (3.24) (1 H, dd, J =

7.0 and 12.5 Hz), 4.20 (3.48) (1 H, dd, J = 10.0 and 12.5 Hz), 4.40 (3.79) (1 H, s), 4.85 (4.85) (1 H, dd, J = 4.5 and 12.5 Hz), 4.99 (4.28) (1 H, dd, J = 1.8 and 4.8 Hz), 5.96 (5.22) (1 H, dd, J = 7.0 and 10.0 Hz); ^{13}C NMR [$CDCl_3$ (benzene-d_6)] δ 20.4 (20.2) (q), 28.5 (28.5) (q), 37.6 (37.6) (t), 41.32 (41.3) (t), 41.32 (41.6) (s), 50.41 (50.5) (d), 52.7 (53.2) (d), 69.95 (69.9) (d), 131.9 (132.0) (d), 137.7 (137.3) (s); IR (CCl_4) 2960, 2870, 1380, 1360, 897 cm^{-1}.

An epimer or double-bond isomer **1b** and a trichlorobromo analogue **1a** of ochtodene (**1**) were also detected in fractions containing mixtures from silica gel chromatography (10% diethyl ether in petroleum ether). The low-resolution GC–MS of **1a** provided the following: m/e 318 (M^+, $C_{10}H_{14}{}^{35}Cl_3{}^{79}Br$, 2.6), 283 ($Cl_2Br$, 17.8), 239 ($Cl_3$, 15.8), 203 ($Cl_2$, 79.5), 187 ($Cl_2$, 23.6), 167 (Cl, 100.0), 131 (47.9), 91 (75.3).

The low-resolution GC–MS of **1b** was quite similar to **1** in ion fragments: m/e 362 (M^+, $C_{10}H_{14}{}^{79}Br_2{}^{35}Cl_2$, 1), 327 ($Br_2Cl$, 5.6), 283 ($BrCl_2$, 37.3), 247 (BrCl, 20.9), 211 (Br, 20.2), 203 (Cl_2, 39.6), 167 (Cl, 94.0), 91 (100.0).

Retention times using temperature programming (160–250 °C, 2-min delay, 16 °C/min) on a 2 M 3% SP-2401 column (He flow, 60 mL/min) were 5.0 min for **1**, 4.1 min for **1b**, and 3.45 min for **1a**.

Chondrocole A (2). Elution of pure chondrocole A (**2**) (0.04 g) was facilitated by silica gel chromatography using 25% diethyl ether in petroleum ether. The NMR and mass spectra and optical rotation of **2** were identical with those of an authentic sample of chondrocole A obtained from the red alga *Chondrococcus hornemanni* (Mertens) Schmitz collected in Hawaii.[6]

Aldehyde 6. Sodium iodide (0.05 g, 0.33 mmol) was added with stirring to an ice-cooled solution of **1** (0.06 g, 0.165 mmol) in 15 mL of acetone. After 5 min, the ice bath was removed and the solution was stirred for an additional 15 min. To the acetone solution was added 15 mL of saturated NaCl solution, and the aqueous phase was extracted with 3 × 35 mL of diethyl ether. The combined organic phases were washed twice with 15 mL of saturated NaCl solution, dried ($MgSO_4$), and reduced in volume in vacuo to yield 60 mg of an oily residue. ^1H NMR (benzene-d_6) revealed a 1:2 mixture of **1** and the primary allylic iodide (**4**): δ 0.61 (3 H, s), 1.16 (3 H, s), 2.09 (1 H, ddd, J = 5, 12.5, and 15.0 Hz), 2.41 (1 H, ddd, J = 1.8, 4.5, and 15.0 Hz), 2.95 (1 H, dd, J = 7.5 and 10.0 Hz), 3.25 (1 H, dd, J = 10.0 and 10.5 Hz), 3.79 (1 H, s), 4.38 (1 H, dd, J = 1.8 and 5.0 Hz), 4.86 (1 H, dd, J = 4.5 and 12.5 Hz), 5.23 (1 H, dd, J = 7.5 and 10.5 Hz)

Simply removing the benzene-d_6 under vacuum followed by exposure to air caused extensive decomposition. From this dark violet oily material, the aldehyde **6** was obtained (10 mg) by repeated LC purification using 25% diethyl ether in hexane as the solvent system. Compound **6**: ^1H NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.30 (3 H, s), 2.50 (1 H, ddd, J = 4, 10, and 15 Hz), 2.71 (1 H, ddd, J = 2, 5, and 15 Hz), 4.33 (1 H, s), 4.77 (1 H, dd, J = 5 and 10 Hz), 5.51 (1 H, dd, J = 2 and 4 Hz), 6.01 (1 H, d, J = 7 Hz), 9.94 (1 H, d, J = 7 Hz); IR ($CHCl_3$) ($\nu_{C=O}$) 1683 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 298 (M^+, $BrCl_2$, 0.3), 283 ($BrCl_2$, 1.4), 263 (BrCl, 2.5), 247 (BrCl, 2.1), 227 (Br, 9.3), 183 (Cl, 10.0).

Acetate 5. Ochtodene (**1**; 0.0159 g, 0.044 mmol) was added to 2 mL of CCl_4 and 1 mL of H_2O. $NaOAc{\cdot}3H_2O$ (0.009 g, 0.066 mmol) was then added with stirring. After the sodium acetate had dissolved, 1 drop of Adogen 464 (Aldrich Chemical Co.) was added. The mixture was refluxed for 3 h. Saturated NaCl solution (10 mL) was added, and the aqueous phase was extracted with 3 × 30 mL of diethyl ether. The combined ether layers were then dried ($MgSO_4$) and reduced in vacuo. Purification by LC using 10% diethyl ether in hexane provided 16.3 mg (96%) of the acetate **5**: ^1H NMR ($CDCl_3$) δ 1.00 (3 H, s), 1.30 (3 H, s), 2.09 (3 H, s), 2.55 (1 H, ddd, J = 5, 13, and 14 Hz), 2.70 (1 H, ddd, J = 2, 5, and 14 Hz), 4.39 (1 H, s), 4.56 (1 H, dd, J = 5 and 14 Hz), 4.83 (1 H, dd, J = 5 and 13 Hz), 5.07 (1 H, dd, J = 2 and 5 Hz), 5.84 (1 H, dd, J = 5 and 8 Hz); IR (CCl_4) ($\nu_{C=O}$) 1725 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 307 (BrCl, 31.3), 271 (Br, 4.7), 247 (BrCl, 21.9), 229 (Br, 25.0), 167 (Cl, 50.0). Elemental analysis: 19.71% Br (calcd, 26.5%).

$LiAlH_4$ Reduction. Cyclohexenol 7. Excess $LiAlH_4$ (ca. 6 mg) was added to a well-stirred and ice-cooled solution of **5** (0.021 g, 0.0544 mmol) in 10 mL of anhydrous diethyl ether under argon. The mixture was stirred for 0.5 h at 0 °C and then quenched by adding H_2O dropwise until no further reaction occurred. A pinch of $MgSO_4$ was added with stirring. The reaction mixture was then filtered, and the filtrate was washed with 30 mL of diethyl ether. After reducing the ether solution under vacuum, the residue was chromatographed by preparative silica gel thin-layer chromatography (diethyl ether/benzene (1:1), 0.2 mm sheets; R_f 0.32–0.50) to yield 9 mg of pure alcohol **7**: ^1H NMR ($CDCl_3$) δ 1.11 (3 H, s), 1.27 (3 H, s), 2.39 (2 H, mult), 2.64 (1 H, mult), 2.85 (1 H, mult), 3.76 (2 H, t, J = 6.2 Hz), 4.29 (1 H, s), 4.51 (1 H, dd, J = 6.1 and 10.0 Hz), 5.49 (1 H, mult); IR (CCl_4) (ν_{OH}) 3600 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 248 (BrCl, 20.0), 213 (Br, 16.7), 169 (Cl, 40.0), 133 (80.0), 91 (100.0).

Diene 8. Zinc dust (0.025 g, 0.385 mmol) was added with stirring to **1** (0.025 g, 0.069 mmol) in 2 mL of dry acetic acid at room temperature. After stirring for 1 h, 10 mL of diethyl ether was added, the mixture was filtered, and the filtrate was washed with ether. The solvent was then removed in vacuo. After repeated purification by LC using 5% diethyl ether in hexane and then 100% 2,2,5-trimethylpentane, 5 mg of the diene **8** was isolated: ^1H NMR ($CDCl_3$) δ 1.08 (3 H, s), 1.33 (3 H, s), 2.73 (1 H, mult), 2.93 (1 H, mult), 4.51 (1 H, s), 4.59 (1 H, dd, J = 6.1 and 12.0 Hz), 5.14 (1 H, d, J = 11.2 Hz), 5.33 (1 H, d, J = 17.5 Hz), 5.65 (1 H, dd, J = 2 and 7 Hz), 6.24 (1 H, dd, J = 11.2 and 17.5 Hz); UV λ_{max} (MeOH) 232–233 nm (ϵ 15 400); low-resolution mass spectrum (75 eV), m/e 248 (M^+, BrCl, 16.7), 213 (Br, 7.7), 169 (Cl, 96.7), 130 (100.0), 91 (43.3).

Silver Acetate Reaction. Cyclohexenediol 9 and Cyclohexenol Acetate 10. Compound **7** (0.011 g, 0.042 mmol) was dissolved in 2 mL of tetrahydrofuran, 1 mL of acetic acid, and 1 mL of water. Silver acetate (0.010 g, 0.060 mmol) was added with stirring, and the mixture was refluxed for 2 h. Brine (15 mL) was added, and the aqueous phase was extracted with 3 × 25 mL of diethyl ether. The combined ether layers were washed with 4 × 10 mL of saturated $NaHCO_3$, 10 mL of 5% HCl, and 2 × 10 mL of brine, dried ($MgSO_4$), and reduced in vacuo. The diol (4 mg) was isolated by silica gel column chromatography (1 × 30 cm) by elution with 100% diethyl ether. Compound **9**: ^1H NMR ($CDCl_3$) δ 1.08 (3 H, s), 1.24 (3 H, s), 2.23–2.32 (4 H, m), 3.65 (1 H, ddd, J = 4, 9, and 10 Hz), 3.65 (1 H, brd s; D_2O exchangeable), 3.87 (1 H, ddd, J = 5, 9, and 10 Hz), 4.05 (1 H, dd, J = 3 and 5 Hz), 4.44 (1 H, dd, J = 6.6 and 9.7 Hz), 5.45 (1 H, s); low-resolution mass spectrum (75 eV), m/e 248 (M^+, Br, 5.6), 217 (Br, 8.9), 169 (40.7).

The acetate **10** (1 mg) was also isolated by column chromatography: ^1H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.25 (3 H, s), 2.07 (3 H, s), 2.20 (2 H, mult), 2.34 (2 H, mult), 3.66 (2 H, t, J = 5 Hz), 4.23 (1 H, dd, J = 5 and 12 Hz), 5.23 (1 H, dd, J = 3 and 6 Hz), 5.57 (1 H, s). The structure of the acetate **10** was confirmed by $LiAlH_4$ reduction to provide material identical (NMR and mass spectra) with the diol **9**.

Allylic Alcohol 11. A 5% solution of KOH (0.4 mL) in anhydrous methanol was added with stirring to an ice-cooled solution of the acetate **5** (0.019 g, 0.049 mmol) in 5 mL of MeOH. Stirring was continued for 5 h at 0 °C. A 5% HCl solution (aqueous, 1 mL) was then added, the excess methanol was removed under vacuum, and the residue was taken up in 50 mL of diethyl ether. The organic solution was washed twice with 2 × 10 mL of saturated NaCl solution, dried ($MgSO_4$), and reduced in vacuo. Preparative silica gel thick-layer chromatography (diethyl ether/benzene (1:1), 1.5 mm plates; R_f 0.2–0.4) yielded 10 mg of the alcohol **11**: ^1H NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.31 (3 H, s), 2.52 (1 H, ddd, J = 5, 12, and 15 Hz), 2.68 (1 H, ddd, J = 2, 5, and 15 Hz), 4.35 (2 H, d, J = 6 Hz), 4.42 (1 H, s), 4.86 (1 H, dd, J = 5 and 15 Hz), 5.00 (1 H, d, J = 2 and 5 Hz), 5.93 (1 H, t, J = 6 Hz); IR ($CDCl_4$) (ν_{O-H}) 3500 cm^{-1}; low-resolution mass spectrum (50 eV), m/e 265 (BrCl, 12.9), 229 (BrCl, 4.8), 203 (Br, 11.3).

Lanthanide Shift Study of 11. Aliquots of $Eu(fod)_3$ in $CDCl_3$ were added to compound **11** in $CDCl_3$, and the 220 MHz ^1H NMR spectrum was recorded. A plot of chemical shift (δ) vs. $[Eu(fod)_3]/[11]$ was constructed, and a least-squares fit of the slopes normalized to 1 molar equiv of shift reagent was obtained for each absorption using the following formula: slope $(\Delta\delta) = [n(\Sigma xy) - (\Sigma x)(\Sigma y)]/[n(\Sigma x^2) - (\Sigma x)^2]$, where $x = [Eu(fod)_3]/[11]$ and y = chemical shift (δ).[8] Assuming that the principal magnetic axis of $Eu(fod)_3$ was collinear with the europium–oxygen bond in solution, the simplified form of the general dipolar (pseudocontact) contribution equation, $\Delta\delta = \kappa(3\cos^2\theta - 1)/r^3$, was used for calculations. Distances and angles were measured using a Dreiding model of **11** after fixing the europium–oxygen bond distance at 2.7 Å and the carbon–oxygen–europium bond angle at ca. 120°. The methyl protons were treated as a single proton with a bond length of 1.94 Å from the quaternary ring carbon. Positioning the europium atom such that the resultant constants κ for each respective proton deviated minimally provided the data in Table I.

Ochtodiol (3) and the Diacetate 12. Ochtodiol (**3**) was eluted as a mixture during silica gel chromatography with 100% diethyl ether. It was separated from pigments by elution from a Florisil column on chromatography (0.5 × 10 cm) with 100% diethyl ether. **3** (5 mg) was finally obtained pure after two successive silica gel column chromatographies using increasing percentages of diethyl ether in petroleum ether: 220 MHz ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.19 (s, 3 H), 2.28–2.32 (2 H, m), 2.95 (1 H, brd s; D_2O exchangeable), 3.1 (1 H, brd s; D_2O exchangeable), 3.62 (2 H, m), 4.32 (2 H, m), 4.43 (1 H, dd, J = 4.8 and 11.2 Hz), 5.69 (s).

Acetylation of **3** was effected by treatment with excess pyridine and acetic anhydride at room temperature for 2 h and removal of the ex-

Table I

δ	Δδ	r_{measd}, Å	θ	r_{calcd}, Å	% r
4.35	3.376				
5.93	2.236	4.4	36	4.20	4.5
5.00	1.429	5.8	23	5.71	1.6
4.42	0.663	6.7	35	6.51	2.8
2.52	0.497	7.8	28	7.74	0.8
4.86	0.415	8.7	18	8.92	2.5
2.68	0.442	8.4	21	8.70	3.4
1.02	0.363	8.0	34	7.96	0.5
1.30	0.227	9.6	31	9.70	1.0

cess reagent in vacuo to yield 6 mg of the diacetate **12**: $[\alpha]^{23}_D$ −37.0° (*c* 0.33, $CHCl_3$); high-resolution mass measurement of $M^+ - HCl$ (obsd, *m/e* 330.044; calcd, *m/e* 330.047) and $M^+ - HOAC$ (obsd, *m/e* 307.014; calcd, *m/e* 307.010); ^1H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.18 (3 H, s), 2.07 (6 H, s), 2.35 (2 H, m), 3.64 (2 H, m), 4.27 (1 H, dd, *J* = 5.8 and 11.0 Hz), 5.31 (1 H, dd, *J* = 5.8 and 7.2 Hz), 5.39 (1 H, dd, *J* = 2.7 and 3.6 Hz), 5.91 (1 H, s).

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Registry No.—**1**, 67237-02-9; **3**, 67237-01-8; **4**, 67237-03-0; **5**, 67237-04-1; **6**, 67237-05-2; **7**, 67237-06-3; **8**, 67237-07-4; **9**, 67237-08-5; **10**, 67237-09-6; **11**, 67237-10-9; **12**, 67237-11-0.

References and Notes

(1) Inshore Marine Shallow Water Ecosystem project (IMSWE) contribution No. 39. We thank Dr. Klaus Ruetzler, Smithsonian Institution, for the kind invitation to participate in this project.
(2) W. Fenical, *J. Phycology*, **11**, 245 (1975).
(3) (a) B. J. Burreson, F. X. Woolard, and R. E. Moore, *Tetrahedron Lett.*, 2155 (1975); (b) *Chem. Lett.*, 1111 (1975).
(4) (a) D. J. Faulkner, *Tetrahedron*, **33**, 1421 (1977); (b) M. D. Higgs, D. J. Vanderah, and D. J. Faulkner, *ibid.*, **33**, 2775 (1977); (c) D. V. Engen, J. Clardy, E. Kho-Wiseman, P. Crews, M. D. Higgs, and D. J. Faulkner, *Tetrahedron Lett.*, 29 (1978).
(5) We wish to thank Dr. James Norris, Smithsonian Institution, for aid in the collection and identification of *O. secundiramea*. A voucher specimen has been deposited in the U.S. National Herbarium, Washington, D.C.
(6) We gratefully acknowledge F. X. Woolard and R. E. Moore for providing new structural information and a sample of authentic chondrocole A.[3a] The depiction of **2** with the halogens transposed relative to the published structure is due to a recent revision of structure based upon X-ray studies.
(7) The trisubstituted olefin in ochtodene could not be oxidatively cleaved under a variety of conditions: (a) O_3/CH_2Cl_2 or EtOAc, −78 °C to room temperature; (b) $KMnO_4$, 18-crown-6, benzene, room temperature, 20 h; (c) $RuO_2/NaIO_4$, CH_2Cl_2/H_2O, room temperature, 12 h; (d) $KMnO_4$, $MgSO_4$, H_2O/acetone, −78 °C to room temperature, 1 h.
(8) R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, N.Y., 1973.
(9) It should be pointed out that the absolute stereochemistries of **1** and **3** have not been determined in this study.
(10) D. Young, B. M. Howard, and W. Fenical, work in progress.

α,α-Dichlorocyclopropanols. Attenuation of Cyclopropyl Rearrangement Processes in the 3-Bicyclo[4.1.0]heptene System. A Novel Regiospecific 2-Chlorotropone Synthesis

T. L. Macdonald

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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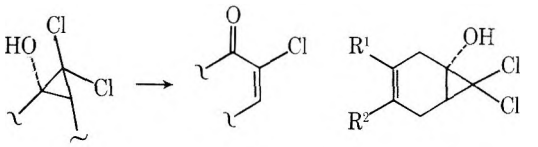
α,α-Dichlorocyclopropanols **1** rearrange with facility to α-chloroenones **2**, illustrating a transformation that has been synthetically employed in one-carbon ring expanding[1-3] or chain homologating[3,4] sequences. Indeed, these compounds are believed to thermally rearrange rapidly upon their in situ generation. However, we have recently uncovered a class of bicyclic, tertiary α,α-dichlorocyclopropanols which possess unusual thermal stability.[1,6b] The stable α,α-dichlorocyclopropanols were incorporated in the norcar-3-en-1-ol structure **3** and suggested an investigation of dichlorocyclopropanol stability with respect to olefin regioposition in the norcarene bicyclic system. We now report the results of these studies. In addition, we describe some chemistry of the compounds encountered in these studies, including a regiospecific cyclohexenone to α-chlorotropone conversion.



1 **2** **3**

The three isomeric 7,7-dichloronorcaren-1-ol compounds desired for our studies have structures **4a**, **5a**, and **6a**. Facile entry into these materials was provided by sodium trichloroacetate mediated and regiospecific dichlorocyclopropanation of the corresponding dienol silyl ethers **4c**, **5c**, and **6c**.[1,5] In this fashion, we have prepared the silyl ethers corresponding to the desired norcarenol olefin isomers **4b** and **5b** and to an alkylated derivative **7b**. In addition, the saturated parent trimethylsilyl 7,7-dichloronorcaran-1-yl ether **8b**, previously synthesized by Conia et al. as the dibromo derivative (Cl = Br),[3] was prepared. Methanolic acid-catalyzed hydrolysis of the trialkylsilyl ether is thought to release the desired dichlorocyclopropanol structures **4a**, **5a**, **7a**, and **8a**. Under these reaction conditions (vide infra), only dichloronorcarenol **4a** possesses stability. The products **9** and **10** (from **5b**) and **11** (from **7b**) of the isomeric silyl norcarenyl ether compounds **5b** and **7b** are exclusively ring-expanded α-chlorocycloheptenones, which arise by way of the intermediate α,α-dichlorocyclopropanols **5a** and **7a** via rearrangement. Such a sequence has been implied for the trimethylsilyl 7,7-norcaran-1-yl ether **8b** (Cl = Br) to 2-bromocycloheptenone **12** (Cl = Br) conversion.[3]

Our studies could not detect chemical intermediates in the silyl ether hydrolysis–hydroxy cyclopropyl ring expansion transformation of compounds **5b**, **7b**, or **8b** (TLC) [room temperature, pH adjusted methanolic aqueous hydrochloric acid]. In these instances, formation of α-chloroenone products appeared coincident with norcarenyl silyl ether hydrolysis. In contrast, the isolated α,α-dichlorocyclopropanol **4a** was stable (85% recovery, no detectable UV absorption by TLC) to refluxing acidic aqueous 2-propanol for 20 h and could be purified via Kugelrohr distillation at 145 °C (0.1 mm). Two studies on alternate catalytic methodology to facilitate the rearrangement of **4a** deserve mention. Mildly basic treatment of cyclopropanol **4a** [methanolic $NaHCO_3$ or $Ba(OH)_2$] or base assisted hydrolysis of silyl ethers **5b**, **7b**, or **8b** generated carboxylic acid compounds directly (no detectable intermediates), presumably via the corresponding α-chlorodienone, which is rapidly consumed in a Favorski ring contraction sequence. Attempted catalysis of chloride ionization with monovalent silver ion had little effect on **4a** with moderate substrate to Ag^+ ratios (3.0 equiv of $AgClO_4$ in refluxing methanol, 12 h) and converted **4a** directly to tropone with high ratios (1:15), albeit in low yield (~20%).[6]

The stability afforded the α,α-dichlorocyclopropanol function in **4a** by the appositely positioned carbon–carbon unsaturation is dramatic. However, stabilization of the cyclopropane moiety embraced in the Δ^3-norcarene system is not unique. In fact, such stabilization appears to be generally

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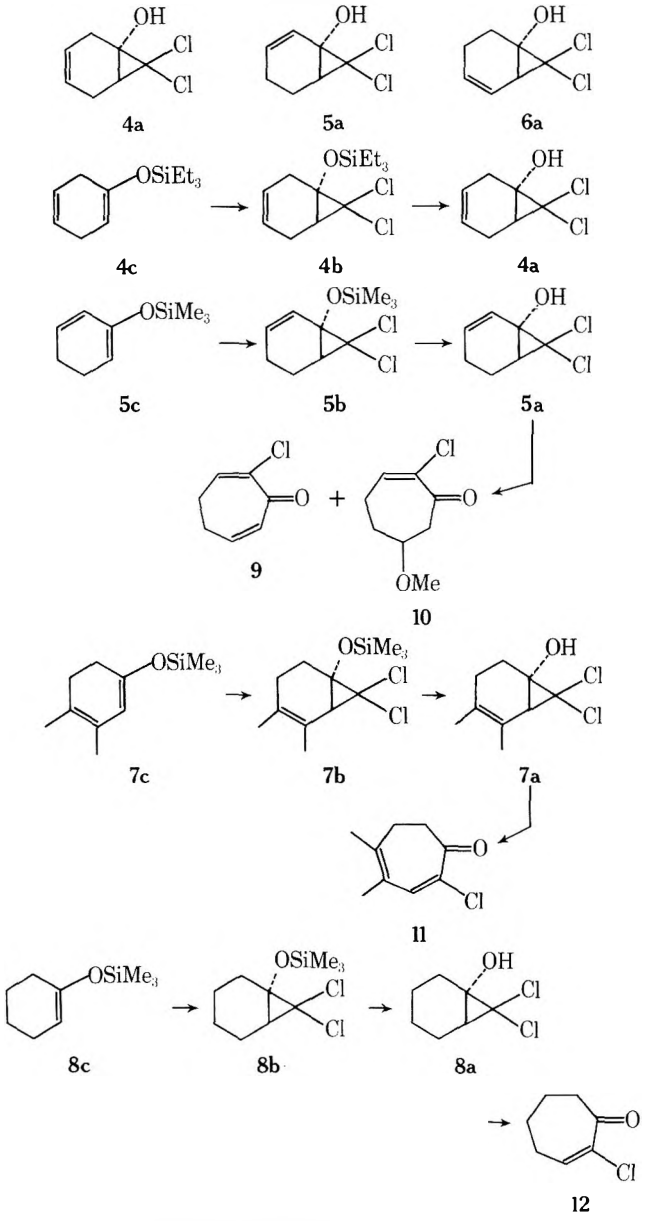
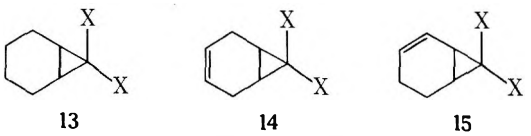
Scheme I

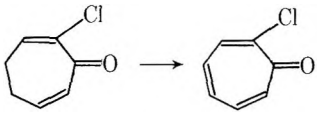


observed in cyclopropane rearrangement processes of bicyclo[4.1.0]hept-3-ene systems relative to their isomeric Δ^2-unsaturated or saturated counterparts. For example, "unusual thermal stability"[7a] of the parent Δ^3-unsaturated hydrocarbon and of 3-carene[7b] has been noted and the facility of ring expansion for the Δ^2-[9a] and saturated[9b,c] 7,7-dihalonorcarane systems relative to the Δ^3 skeleton has been described. Furthermore, the corresponding Δ^2- and Δ^3-carane oxides exhibit a pronounced difference in ease of cyclopropane (and epoxide) rearrangement.[8] Taken together,[9] studies on the rearrangement of 7,7-dihalonorcarane (-2- or -3-ene) systems would suggest the "cyclopropane rearrangement ease" relationship to be **15** > **13** ≫ **14**.

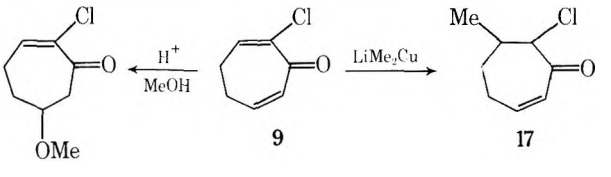


The underlying rationale for this "site specific olefin" stabilizing effect inherent in the bicyclo[4.1.0]heptane system is not clear. Allylic stabilization of the transition state incipient carbocation generated during thermal ring expansion of **15** has been suggested to facilitate its rearrangement (relative to **13** and **14**).[9a] Postulated allylic cationic stabilization may well play a role in isomeric norcarene rearrangements, although such effects are probably minimal in the molecules examined here due to distortion of the incipient charge distribution resulting from strong nucleophilic oxygen participation in the activated complex for ring expansion (cf. no discernible difference under our conditions in the rate of rearrangement of **5a**, **7a**, and **8a**). It is relevant to note the findings of Ledlie et al.[9c] on the rate parameters for cyclopropane rearrangement of the bicyclic dibromides **13** and **14** (X = Br). The Ledlie group found *entropic factors* to be the primary source of k_{13}–k_{14} rate difference in silver ion assisted solvolysis. Apparently, subtle geometric factors occur in the isomeric norcarene-norcarane structures which have substantial impact on activation entropies for cyclopropane rearrangement. However, despite lack of understanding of the source of such 3-norcarene "stabilization factor(s)", the 3-norcarene system represents a structural device which may have general mechanistic utility in attenuating rearrangement processes of reactive cyclopropanes.

Apart from their mechanistic interest, the 2-chlorocycloheptadienone systems prepared in the course of these studies have considerable synthetic value. The present work describes new, regiospecific syntheses of 2,6-cycloheptadienones[10] and 2,4-cycloheptadienones[11] for which few preparations are currently available. The synthetic utility of the regiospecifically generated 2-chloro-2,6-cycloheptadienone system can be illustrated by its facile dehydrogenation into the 2-chlorotropone system. Thus, chlorodienone **9** can be converted into chlorotropone **16** with dichlorodicyanoquinone.[10c] This regiospecific conversion of cyclohexenones into α-chlorotropones complements our reported phenol to α-chlorotropone transform.[1] In contrast to the facile dehydrogenation of chlorodienone **9** with DDQ, 2-chloro-2,4-cycloheptadienone **11** yields a one to one adduct, presumably a cycloaddition product. We are currently elucidating the structure of this adduct.



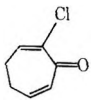
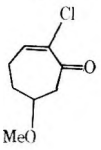
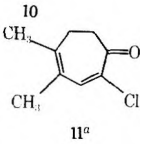
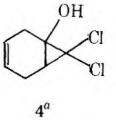
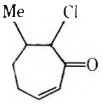
In addition, 2-chlorocycloheptadienone **9** serves as a useful probe into chloro-substituent perturbation on cyclic α-enone reactivity. Thus, **9** under acidic methanolysis adds methanol exclusively to the more electron rich olefin forming 2-chloro-6-methoxycycloheptadienone **11**. In contrast, nucleophilic lithium dimethylcuprate addition occurs exclusively across the chlorodienone system in **9** to give chlorodienone **17** (configuration based on NMR analysis).



Experimental Section

General. Melting points were taken with a Thomas-Hoover apparatus using open capillaries and are uncorrected. Proton magnetic resonance spectra were recorded at 100 MHz with a Joel JNM-MH-100 spectrometer employing tetramethylsilane as an internal standard. Low resolution mass spectra were obtained by direct insertion with an LKB 9000 spectrometer at 70 eV. The parent ion and the most intense peaks (2–4) are reported. Infrared spectra were obtained on a Perkin-Elmer 727 infrared spectrometer. Elemental analyses on all used compounds were performed by Galbraith Laboratories, Inc., Knoxville, Tenn; results were within acceptable limits.

Table I. Physical Data for Products from Silyloxy Diene Dichlorocyclopropanation–Aqueous Hydrolysis

compd	registry no.	bp (mm) or mp, °C	IR (neat), cm^{-1}	NMR ($CDCl_3$, Me_4Si), δ	MS m/e rel abundance
 9[a]	67382-58-5	thermally labile mp ≃ 8–11	1655 (stg) 1635 (med) 790 (stg)	2.5 (t, J = 4.0 Hz, 4 H) 6.20 (d, J = 12.5 Hz, 1 H) 6.72 (m of d, J = 12.5 Hz, 1 H) 7.12 (m, 1 H)	142 (51) 125 (35) 107 (79) 79 (100)
 10	67382-59-6	thermally labile	1695 (stg) 1625 (med) 725 (st)	2.00 (qt, J = 7.5 Hz, 2 H) 2.60 (m, 2 H) 2.95 (d, J = 10.5 Hz, 2 H) 3.60 (s, 3 H) 3.87 (aquint, J = 10.5 Hz, 1 H) 7.20 (t, J = 11.0 Hz)	174 (12) 142 (24) 79 (100)
 11[a]	67382-60-9	160 (0.1 mm)	1660 (stg) 1620 (m) 1595 (w)	2.12 (s, 6 H) 2.52 (s, 4 H) 6.08 (s, 1 H)	170 (72) 155 (68) 107 (100) 90 (75)
 4[a]	67382-61-0	145 (0.1 mm)	3375 (stg) 820 (stg)	1.82 (d,d, J = 8.0 Hz, 1 H) 2.20–2.80 (m centered at 2.60, 4 H) 5.60 (s, 2 H) 2.2 (s, 1 H(OH))	178 (8) 143 (100) 115 (45)
 17	67382-62-1			1.08 (d, J = 6.0 Hz, 3 H) 1.89 (m, 2 H) 2.2 (brm, 3 H) 7.58 (d, J = 3.5 Hz, 1 H) 6.05 (d, J = 12.5 Hz, 1 H) 6.60 (d,d,d, J = 12.5, 4.0, 6.5 Hz, 1 H)	158 (37) 123 (72) 95 (100)

[a] Satisfactory elemental analysis was obtained (C, H = ±0.3%).

For all column chromatography, E. Merck (type 60) silica gel and short column techniques were utilized and for TLC analysis, E. Merck Silica Gel 60, F-254 precoated (0.25 mm) plates were employed. Magnesium sulfate was used as drying agent throughout and all experimental procedures were performed under an atmosphere of dry nitrogen.

Trialkylsilyl Cyclohexadienyl Ethers 4c, 5c, and 7c. (a) Triethylsilyloxy-1,4-cyclohexadiene (4c). This dihydroaromatic ether was prepared as described in ref 1. Treatment of triethylsilyl phenyl ether (2.420 g, 12.0 mmol) in anhydrous THF (55 mL), *tert*-butyl alcohol (10 mL), and ammonia (120 mL) at −33 °C with lithium wire (75.0 mmol) for 45 min, followed by ammonium chloride (4.0 g) quench and rapid pentane (300 mL) saturated aqueous ammonium chloride (200 mL) partitioning, gave crude (>90% pure by NMR) **4c** (2.112 g, 87%). The sole impurity was unreduced (and noninterfering) starting material and the product was consequently utilized without further purification: NMR δ 1.10–0.40 (m, 15 H), 2.68 (s, 4 H), 4.88 (s, 1 H), 5.65 (s, 2 H); IR 1605 and 1240 cm^{-1}.

(b) Cyclohexadienyl Trimethylsilyl Ethers 5c and 7c. These compounds were prepared according to Rubottom and Gruber.[5] Ether **5c** is described therein, although data for **7c** are not presented. Silyloxy diene **7c**: bp 65–72 °C (0.1 mm); NMR δ 0.30 (s, 9 H), 1.58 (s, 6 H), 2.08 (s, 4 H), 4.90 (s, 1 H); IR 1655 and 1250 cm^{-1}.

General Procedures for Sequential Dichlorocyclopropanation–Hydrolysis of 4c, 5c, 7c, and 8c. (a) Dichlorocyclopropanation. The requisite trialkylsilyl cyclohexadienyl ether (4.00 mmol) was dissolved in freshly distilled tetrachloroethylene (5 mL) and anhydrous dimethoxyethane (5 mL). Anhydrous sodium trichloroacetate (1.20 g, 6.00 mmol) was introduced and the suspension refluxed for 1.5 h. The solution was then cooled, poured into pentane (150 mL), and washed rapidly twice with water and then brine and the organic layer dried. Solvent removal in vacuo afforded the crude siloxy norcarene compounds: **4b, 5b, 7b,** and **8b.** These materials were somewhat unstable to distillation;[3] however, for comparative rate study, partial purification (>80%) could be effected via rapid (<5 min) silica gel chromatography (20 g) using pentane as eluent giving **4b** (~65%), **5b** (~80%), **7b** (~70%), and **8b** (~65%) in the noted approximate yields. These compounds did not give satisfactory elemental analysis.

(b) Methanolic Aqueous Hydrochloric Acid Hydrolysis. The crude product silyloxy norcanene **4b, 5b, 7b,** and **8b** was dissolved in a solution of methanol (80 mL) and 10% (by volume) aqueous hydrochloric acid (25 mL) then stirred at room temperature for 2.0 h. The mixture was partitioned between ether (300 mL) and water (200 mL) and the ethereal layer was washed once with water and then brine and dried. Chromatography (ethyl acetate/petroleum ether) afforded the described compounds in the noted yields. The principle recovered by-product in all cases was the unreacted (or hydrolyzed) cyclohexenone derivative. See Table I for the physical constants of reported compounds.

From triethylsilyl cyclohexadienyl ether (**4b**) was obtained 7,7-dichloro-3-norcaren-1-ol (**4a**) (59% based on starting trimethylsilyl phenyl ether; 73% mass material balance based on starting phenylsilyl ether).

From trimethylsilyl cyclohexadienyl ether (**5b**) was obtained 2-chloro-2,5-cycloheptadienone (**9**) (73%) and 2-chloro-5-methoxy-2-cycloheptenone (**10**) (8%). A mass balance (total material derived from **5b**) of 89% was obtained.

From trimethylsilyl dimethylcyclohexadienyl ether (**7b**) was obtained 2-chloro-4,5-dimethyl-2,4-cycloheptadienone (**11**) (72%). A mass balance of 88% was obtained.

From trimethylsilyl cyclohexenyl ether (**8b**) was obtained 2-chloro-2-cycloheptenone **12** (62%) (reported for the α-bromo compound 90%;[3] mass balance 77%).

2-Chlorotropone (16). 2-Chlorocycloheptadienone **9** (0.210 g, 1.5 mmol), dichlorodicyanoquinone (0.450 g, 2.0 mmol), and *p*-toluenesulfonic acid (~15 mg) was refluxed in benzene (10 mL) for 6.5 h. The reaction mixture was cooled and the bulk of the solvent removed in vacuo. The residue was then chromatographed [ethyl acetate (30%)/pentane] affording 2-chlorotropone (**16**) (0.165 g, 78%) identical in spectral and physical characteristics with an authentic sample (prepared from α-tropolone and thionyl chloride[12]).

Methyl Chloroenone (17). Lithium dimethylcuprate (1.5 mmol) was generated by methyllithium (1.5 mL of a 2.0 M ethereal solution, 3.0 mmol) addition to a cold (−10 °C) suspension of cuprous iodide (0.288 g, 1.5 mmol) in anhydrous ether (10 mL). The solution was stirred for 10 min then cooled to −40 °C and 2-chlorocycloheptadienone **9** (0.178 g, 1.25 mmol) in ether (3 mL) was added dropwise. After 30 min, the reaction was poured into saturated aqueous ammonium chloride overlayered with pentane. The layers were separated and the organic phase dried. The solvent was removed in vacuo and the residue chromatographed [ethyl acetate (10%)/pentane] affording chloroenone **17** (0.181 g, 91%).

Acknowledgment. The author is grateful for the financial assistance of the Vanderbilt University Natural Sciences Committee and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**4b,** 67382-63-2; **4c,** 67382-64-3; **5b,** 67382-65-4; **5c,** 54781-19-0; **7b,** 67382-66-5; **7c,** 67382-67-6; **8b,** 67382-68-7; **8c,** 6651-36-1; **12,** 67382-69-8; **16,** 3839-48-3; triethylsilyl phenyl ether, 5888-66-4; tetrachloroethylene, 127-18-4.

References and Notes

(1) T. L. Macdonald, *J. Org. Chem.*, in press.
(2) Gilbert Stork and T. L. Macdonald, *J. Am. Chem. Soc.*, **97,** 1264 (1975).
(3) P. Amice, L. Blanco, and J. M. Conia, *Synthesis*, 196 (1976).
(4) E. Yoshii, T. Koizumi, and T. Kawazoe, *Chem. Pharm. Bull.*, **24,** 1957 (1976).
(5) G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **42,** 1051 (1977).
(6) See for example: (a) A. J. Birch and R. Keeton, *J. Chem. Soc. C*, 109 (1967); (b) A. J. Birch and R. Keeton, *Aust. J. Chem.*, **24,** 1673 (1971).
(7) (a) V. A. Mironov, A. A. Akrem et al., *Izv. Acad. Sci., USSR, Atmos. Oceanic Phys. (Engl. Transl.)* **883** (1967); (b) W. Cocker, D. P. Hanna and R. V. P. Shannon, *J. Chem. Soc. C*, 489 (1968); (c) K. Gollnick and G. Schade, *Tetrahedron*, **22,** 123 (1966); (d) see also B. A. Arbvzov and Z. G. Isaeva, *Russ. Chem. Rev. (Engl. Transl.)*, **45,** 673 (1976).
(8) K. Arata, J. O. Bledsoe, and K. Tanabe, *J. Org. Chem.*, **43,** 1660 (1978).
(9) (a) O. G. Lindsay and C. B. Reese, *Tetrahedron*, **21,** 1673 (1965); (b) D. B. Ledlie, W. Barber, and F. Switzer, *Tetrahedron Lett.*, 607 (1977); (c) D. B. Ledlie, T. Swan, J. Pile, and L. Bowers, *J. Org. Chem.*, **41,** 419 (1976); (d) G. W. Klump and J. J. Vrielink, *Tetrahedron Lett.*, 539 (1972).
(10) (a) H. Takaya, Y. Hayakawa, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100,** 1778 (1978); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *ibid.*, **97,** 5434 (1975); (c) K. Takenchri, K. Yasuda, and K. Okamoto, *Chem. Lett.*, 715 (1976); (d) E. Garbish, *J. Org. Chem.*, **20,** 2109 (1965); (e) A. J. Birch, G. M. Iskander, B. I. Magbord, and F. Stansfield, *J. Chem. Soc. C*, 358 (1967).
(11) (a) K. E. Hine and R. F. Childs, *Can. J. Chem.*, **54,** 12 (1976), and references therein; (b) A. Eisenstadt, *J. Organomet. Chem.*, **97,** 443 (1975); **113,** 147 (1976); (c) P. F. Ranken, B. J. Harty, L. Kapicak, and M. A. Battisle, *Synth. Commun.*, **3,** 311 (1973).
(12) See T. Nozoe, T. Asas, E. Takahashi, and K. Takahashi, *J. Chem. Soc. Jpn.*, 39, 1310 (1966), and references therein.
(13) After submission of this manuscript, Torii et al. reported the isolation of dichloronorcaranol **8a** via cold methanolysis of the precursor silyl ether **8b.** Although thermal unstability was not noted, their subsequent employment of this substance required low temperatures (−10 °C): S. Torii, T. Okamoto, and N. Ueno, *J. Chem. Soc., Chem. Commun.*, 293 (1978).

Solvolysis of Virescenol B 19-Tosylate

Paolo Ceccherelli* and Massimo Curini

Istituto di Chimica Organica della Facolta di Farmacia, Università degli Studi, Perugia, Italy

Roberto Pellicciari

Istituto di Chimica Farmaceutica e Tossicologica, Università degli Studi, Perugia, Italy

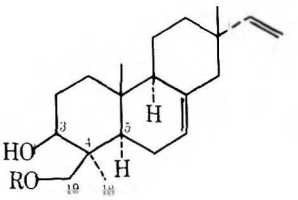
G. Vernon Baddeley, Muppala S. Raju, and Ernest Wenkert*

Department of Chemistry, Rice University, Houston, Texas 77001

Received March 21, 1978

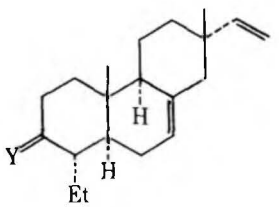
In continuation of a study of the chemistry of virescenol B (**1a**),[1] the aglycon of several of the fungal, virescenoside metabolites,[3] the solvolysis of the 19-tosylate (**1b**)[4] in dimethyl sulfoxide was investigated. It produced two carbonyl-containing substances whose structures are the subject of this note.

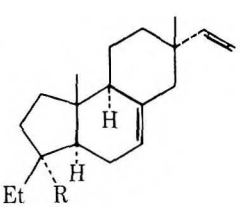
One of the products could be shown to be ketone **2a** on the basis of the following facts. Its infrared absorption at 1708 cm^{-1} revealed it to be a cyclohexanone. The disappearance of the oxymethine, oxymethylene, and 4-methyl ^1H NMR signals normally associated with the C(3) and C(4) substitution pattern of the virescenol B skeleton and the exhibition of a methyl triplet (J = 6 Hz) in the ^1H NMR spectrum of the product suggested the latter to be an α-ethyl ketone. Finally,



1a, R = H
b, R = Ts

its ^{13}C NMR spectra confirmed the structural changes at C(3) and C(4), showed rings B and C of virescenol B (**1a**)[5] to be affected only minimally, and ring A reminiscent of a 3-ketosteroid.[6] Sodium borohydride reduction of the ketone yielded a ca. 2:1 mixture of alcohols, whose ^1H NMR spectra indicated them to be equatorial and axial isomers, respectively. The low equatorial–axial isomer ratio, in contrast to the high ratio resulting from the hydride reduction of a 3-ketosteroid,[7] was in accord with the presence of a 4α-ethyl-3-keto system whose ethyl group offered resistance to the normal α attack by borohydride. The ^{13}C NMR spectra of the alcohols confirmed fully structures **2b** and **2c** for the reduction products.

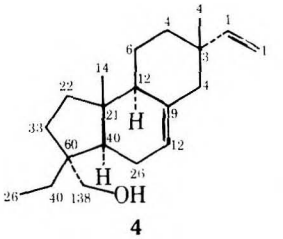




2a, Y = O
b, Y = α-H, β-OH
c, Y = α-OH, β-H

3a, R = CHO
b, R = CH_2OH

The minor product of the solvolysis of **1b** was shown by its infrared absorption bands of 2670 and 1722 cm^{-1} to be an aldehyde and by its ^1H NMR spectrum to have its carboxaldehyde unit in an equatorial orientation[8] next to a nonprotonated carbon center. Once again the structural change at C(3) and C(4) was revealed not only by the new carbonyl group, but also by a methyl triplet (J = 5 Hz) indicative of the presence of an ethyl group. Sodium borohydride reduction of the aldehyde yielded an alcohol whose ^1H NMR spectral characteristics revealed the presence of an equatorial hydroxymethyl group[8,9] next to a nonprotonated carbon and an ethyl group. The ^{13}C NMR spectra of the alcohol exhibited virescenol B-like ring B and C carbon signals and a homoneopentyl carbon signal customary for a methyl group on an ethyl function terminating on a nonprotonated carbon site. A Yb(DPM)$_3$ shift study (cf. $\Delta\delta$ values on formula **4**) permit-



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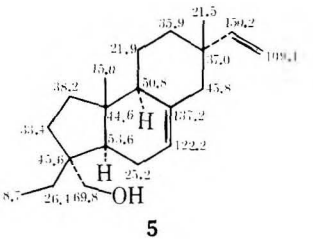

5

ted a carbon signal assignment and structure analysis as depicted by formula **5** (**3b**), thus showing the aldehyde to possess structure **3a.**

The simplest explanation for the production of the two carbonyl compounds, **2a** and **3a,** on solvolysis of tosylate **1b** involves the migration of the 4α-methyl group to the site of the departing tosylate group with concommitant O–C(4) bond formation by the neighboring 3β-hydroxy group. Hydride migration from C(3) to C(4) of the resultant conjugate acid of a 3β,4β-epoxide (**6**) leads to an O-protonated 4β-ethyl 3-

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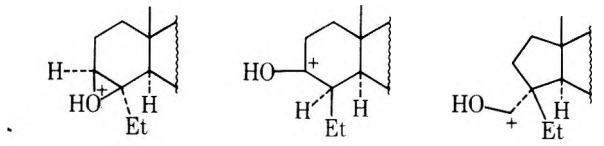
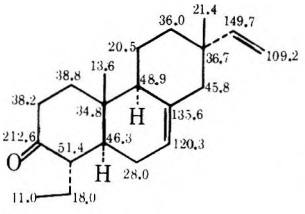


6 7 8

ketone (7), whose enolization and reketonization gives ketone **2a**, whereas C(2)–C(3) bond migration to C(4) of **6** yields the conjugate acid (8) of aldehyde **3a**.

The carbon shifts of ketone **2a** are outlined on formula **9**. The similarity of the C(2) shift of 38.2 ppm with that of 5α-androstan-3-one (38.1 ppm)[6] shows the ethyl group to be equatorial and hence 4α oriented. The assignment of the chemical shifts of the alcohols **2b** and **2c** is portrayed on formulas **10** and **11**, respectively.



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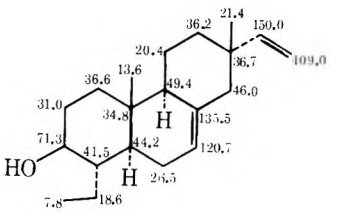

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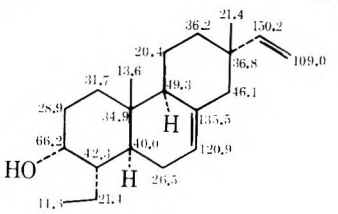

11

The migration of C(18) from C(4) to C(19) in the solvolysis of virescenol B 19-tosylate (**1b**) may be of biogenetic significance. Whereas many one-carbon rearrangements abound in the pimaranic diterpene field, none of the aforementioned type has been observed heretofore. Nevertheless, an ethano unit attachment to C(4) of diterpene rings A, such as in ketone **2a**, appears in the form of a furan ring in some constituents of the coffee bean.[10]

Experimental Section

Melting points were determined on a Reichert micro-hotstage and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 167 spectrophotometer. ^1H NMR spectra (Me_4Si, $\delta = 0$) were recorded on a Jeol H-60 spectrometer and the ^{13}C NMR spectra were produced on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode.

Solvolysis of Virescenol B Tosylate (1b). A solution of 600 mg of tosylate **1b** in 7 mL of dimethyl sulfoxide was heated at 95 °C under nitrogen with stirring for 7 h. After the addition of 50 mL of saturated brine solution the mixture was extracted thoroughly with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated under vacuum. Chromatography of the residual oil, 330 mg, on silica gel and elution with benzene yielded 60 mg (16%) of liquid aldehyde **3a**: IR (CCl_4) 2670 (CHO), 1722 (C=O) cm^{-1}; NMR (C_6D_6) δ 0.68, 0.86 (s, 3 each, Me_2), 0.73 (t, 3, J = 6 Hz, Me of Et), 8.96 (s, 1, CHO).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.70; H, 10.72.

Elution with 20:1 benzene–ethyl acetate gave 185 mg (50%) of solid whose crystallization from pentane led to crystalline ketone **2a**: mp 92–94 °C; IR (CCl_4) 1708 cm^{-1} (C=O); NMR (C_6D_6) δ 0.76, 0.90 (s, 3 each, Me_2), 0.96 (t, 3, J = 6 Hz, Me of Et).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.92; H, 10.54.

Alcohols 2b and 2c. A solution of 60 mg of sodium borohydride in 5 mL of ethanol was added dropwise to a stirring solution of 600 mg of ketone **2a** in 15 mL of ethanol at 0 °C. The mixture then was stirred at room temperature for 1 h and poured into ice water. It was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated. Chromatography of the oily residue, 550 mg, on silica gel and elution with 20:1 benzene–ethyl acetate afforded 180 mg (30%) of semisolid alcohol **2c**: IR (CCl_4) 3625 cm^{-1}(OH); NMR (CCl_4) δ 3.86 (m, 1 OCH).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.42; H, 11.02.

Further elution with the same solvent pair gave 310 mg (51%) of solid whose crystallization from pentane–benzene yielded crystalline alcohol **2b**: mp 120–125 °C; IR (CCl_4) 3620 cm^{-1}(OH); NMR (CCl_4) δ 3.20 (m, 1, OCH).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.38; H, 11.00.

Alcohol 3b. A solution of 15 mg of sodium borohydride in 5 mL of ethanol was added dropwise to a stirring solution of 50 mg of aldehyde **3a** in 3 mL of ethanol at 0 °C. The mixture then was stirred at room temperature for 1 h. Workup as above, chromatography of the curde product, 40 mg, on silica gel, and elution with 30:1 benzene–ethyl acetate led to 35 mg (80%) of semisolid alcohol **3b**: NMR δ 3.25, 3.45 (AB dd, 2, J = 11 Hz, OCH_2).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.05; H, 11.31.

Acknowledgment. P.C. and M.C. acknowledge with thanks financial support by the Consiglio Nazionale delle Ricerche (C.N.R.). The authors are grateful to Professor N. Cagnoli-Bellavita for her interest in this study.

Registry No.—**1b**, 67393-59-3; **2a**, 67393-60-6; **2b**, 67393-61-7; **2c**, 67393-62-8; **3a**, 67393-63-9; **3b**, 67393-64-0.

References and Notes

(1) P. Ceccherelli, M. Curini, R. Pellicciari, M. S. Raju, and E. Wenkert, *J. Org. Chem.*, **42**, 3438 (1977).[2]
(2) References 7 and 8, inadvertently omitted therefrom, were E. Wenkert and B. L. Buckwalter, *J. Am. Chem. Soc.*, **94**, 4367 (1972), and J. Polonsky, Z. Baskevitch, N. Cagnoli-Bellavita, P. Ceccherelli, B. L. Buckwalter, and E. Wenkert, *ibid.*, **94**, 4369 (1972).
(3) N. Cagnoli-Bellavita, P. Ceccherelli, M. Ribaldi, J. Polonsky, and Z. Baskevitch, *Gazz. Chim. Ital.*, **99**, 1354 (1969); P. Ceccherelli, N. Cagnoli-Bellavita, J. Polonsky, and Z. Baskevitch, *Tetrahedron*, **29**, 449 (1973); N. Cagnoli-Bellavita, P. Ceccherelli, M. Ribaldi, J. Polonsky, Z. Baskevitch-Varon, and J. Varenne, *J. Chem. Soc., Perkin Trans. 1*, 351 (1977); P. Ceccherelli, N. Cagnoli-Bellavita, J. Polonsky, Z. Baskevitch, and M. Ribaldi, *Gazz. Chim. Ital.*, **107**, 51 (1977).
(4) J. Polonsky, Z. Baskevitch, N. Cagnoli-Bellavita, and P. Ceccherelli, *Bull. Soc. Chim. Fr.*, 1912 (1970).
(5) Second citation in ref 2.
(6) J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.*, **9**, 439 (1977).
(7) Cf. A. H. Soloway, A. S. Deutsch, and T. F. Gallagher, *J. Am. Chem. Soc.*, **75**, 2356 (1953); O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *ibid.*, **75**, 1286 (1953).
(8) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, J. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).
(9) A. Gaudemer, J. Polonsky, and E. Wenkert, *Bull. Soc. Chim. Fr.*, 407 (1964).
(10) A. Ducrux, C. Pascard-Billy, M. Hammoniere, and J. Poisson, *J. Chem. Soc., Chem. Commun.*, 396 (1975), and references cited therein.

Novel Applications of the Potassium Chlorate–Osmium Tetroxide Oxidizing System. Synthesis of α-Dicarbonyl Derivatives from Acetylenic Compounds. Synthesis of a 2,3-Dihydroxy-1,4-dione from a 2,5-Dialkylfuran

Luciano Bassignani, Alberto Brandt, Valerio Caciagli, and Luciano Re*

Snamprogetti S.p.A., L.P.M., 00015 Monterotondo (Rome), Italy

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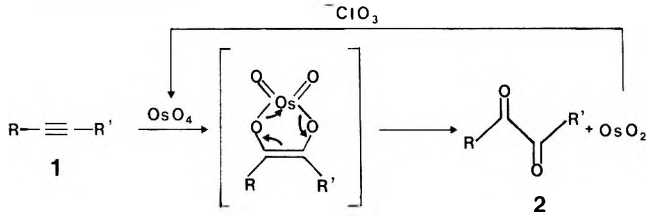
The cis hydroxylation of olefins to α-diols by metal chlorates in aqueous solution containing catalytic amounts of osmium tetroxide has found wide use.[1] This method is especially useful when the oxidation of other organic functions present in the substrate has to be avoided; most of these functions are, in fact, unaffected by the said oxidizing system. The reaction of acetylenic compounds with this oxidizing

mixture has, however, never been reported previously in the literature. Being interested in the preparation of some α-dicarbonyl compounds, we speculated that the said oxidation may afford the desired derivatives in one step from the corresponding acetylenic precursors. A plausible mechanism for this reaction is, in fact, as follows.[2]



a: R = Me ; R' = OMe

b: R = Et ; R' = OMe

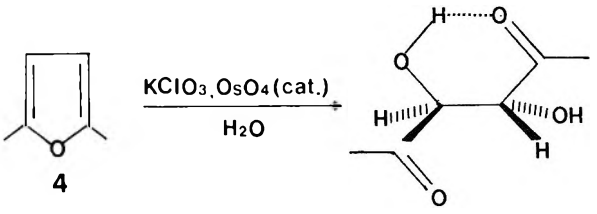
c: R = i-Pr ; R' = OMe

d: R = R' = $CH_3CH(OH)$

The present paper reports the successful application of this reaction (potassium chlorate was used for the in situ osmium tetroxide regeneration) for the preparation of α-keto acid methyl esters **2a–c** and 2,5-dihydroxyhexane-3,4-dione (**2d**; existing only as the polymeric form[3]) from 1-methoxy-1-alkynes **1a–c** and 3-hexyne-2,5-diol (**1d**), respectively. Our interest for these synthesis relyed in the fact that α-keto esters can be converted[4] to optically active α-amino acids by asymmetric synthesis and that **2c** affords,[3] by acid-catalyzed cyclization, 2,5-dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (furaneol), a flavor principle of pineapple and strawberry whose preparation has become of substantial practical interest.[5]

In the reaction of the acetylenic derivatives 1 with the aqueous potassium chlorate–osmium tetroxide mixture, the development of slight acidity (final pH, ~3.5–5.0) from side reactions occurred and caused with substrates of type **1a–c**, but not with **1d**, competitive acid-catalyzed hydratation of the triple bond.[6] As a result, when in preliminary experiments these reactions were carried out in water at "free" pH, the α-keto ester yields fell quite low, while the yield for **2d** was high (~85%). On the other hand, when the reaction on type **1a–c** substrates was carried out at higher pH values (with **1a** and **1c** a series of experiments at constant pH 5.4, 5.9, 6.4, or 6.8 was performed[7]), the rate of oxidation to α-keto ester decreased so much as to allow the addition of hypochlorous acid to the triple bond[8] to become the predominant reaction. Finally, when the reaction was performed in a water–ether mixture at "free" pH, satisfactory yields of α-keto esters **2a–c** from **1a–c** could be achieved (48, 69, and 80%, respectively). In such a system, in fact, due to the low solubility of the acetylenic ethers **1a–c** in the aqueous phase, the addition of water, as well as that of hypochlorous acid, to the triple bond is depressed considerably, while the reaction between substrate and osmium tetroxide can take place in the ether phase, where both of the latter are freely soluble.

Another known direct precursor of furaneol (base-catalyzed cyclization) is *erythro*-3,4-dihydroxyhexane-2,5-dione[9] (**5**), which has been prepared previously by bromination of 2,5-dimethylfuran (**4**) in methanol solution to 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (**3**) (60% yield),[10] followed by oxidation of the latter with potassium chlorate and a catalytic amount of osmium tetroxide in aqueous tetrahydrofuran (~100% yield of crude **5**).[9] It occurred to us, however, that this system might oxidize **4** directly to the dihydroxyhexanedione level. In fact, we have now found that this synthesis too can be realized and that the product of the reaction, carried out in water, is the erythro isomer **5** (61% yield).



To our knowledge this reaction represents the first example of oxidation with a metal chlorate–osmium tetroxide mixture of a 2,5-dialkylfuran to a 2,3-dihydroxy-1,4-dione.

Experimental Section

Materials. Osmium tetroxide was from Merck, and 3-hexyne-2,5-diol and 2,5-dimethylfuran were purchased from Fluka. The 1-methoxy-1-alkynes (RC≡COMe) were prepared according to Nooi and Arens[11] from the corresponding aldehydes (RCH_2CHO). The latter and all other materials were obtained from Carlo Erba.

Spectra. The IR spectra were taken with a Perkin-Elmer 457 spectrometer and the 60 MHz ^1H NMR spectra with a Varian T-60 instrument using tetramethylsilane as an internal standard.

General Procedure for the Preparation of α-Keto Esters 2a–c. A mixture of 0.15 mol of 1-methoxy-1-alkyne (**1a–c**), 36.76 g (0.30 mol) of $KClO_3$, 1.52 g (6 mmol) of OsO_4 (*caution: vapor is poisonous!*), 200 mL of water, and 300 mL of ether was stirred at room temperature until the black coloring of the mixture disappeared. The organic phase was separated and the aqueous phase extracted with ether in a continuous extractor (~4 h). The combined ether solutions were dried (Na_2SO_4), the solvent was evaporated, together with the OsO_4, at 0 °C on a rotary evaporator, and the α-keto ester (**2a–c**) was distilled from the residue under vacuum through a Vigreux fractionating column.

2-Oxopropanoic Acid Methyl Ester (2a): reaction time, 4 h; bp 50–53 °C (15 mm) [lit.[12] bp 53 °C (15 mm)]; yield 48%; IR and ^1H NMR spectra were identical with those reported for **2a**.[13,14]

2-Oxobutanoic Acid Methyl Ester (2b): reaction time, ~16 h (overnight); bp 72–74 °C (27 mm) [lit.[15] bp 72–74 °C (27 mm)]; yield 69%; IR (film) 1730 cm^{-1}; ^1H NMR (C_6D_6) δ 0.90 (3 H, t, J = 6 Hz, CH_3C), 2.57 (2 H, q, J = 6 Hz, CH_2), 3.53 (3 H, s, $COOCH_3$).

3-Methyl-2-oxobutanoic Acid Methyl Ester (2c): reaction time, ~16 h (overnight); bp 64–68 °C (23 mm); yield 80%; IR (film) 1730 cm^{-1}; ^1H NMR (C_6D_6) δ 1.08 (6 H, d, J = 6 Hz, $(CH_3)_2C$), 3.15 (1 H, m, J = 6 Hz, CH), 3.42 (3 H, s, $COOCH_3$).

2,5-Dihydroxyhexane-3,4-dione (2d). A mixture of 1.14 g (10.0 mmol) of **1d**, 2.80 g (22.8 mmol) of $KClO_3$, and 0.050 g (0.197 mmol) of OsO_4 (*caution: vapor is poisonous!*) in 15 mL of water was stirred at room temperature for 18 h. The water was removed, together with the OsO_4, under vacuum (1 mm) at room temperature, and the residue was extracted at room temperature and under stirring with four successive 30-mL portions of acetone. The combined filtered extracts were dried (Na_2SO_4) and rotary evaporated at room temperature (until constant weight) to a yellow viscous residue of 1.23 g (84.5%) of **2d** (polymeric form[3]); IR and ^1H NMR spectra and TLC and VPC behavior were in accord with those reported in the literature for **2d**.[3] Cyclization of the above unpurified **2d** by a literature procedure[3] gave furaneol (50% overall yield from **1d**).

***erythro*-3,4-Dihydroxyhexane-2,5-dione (5).** The oxidation of 0.96 g (10.0 mmol) of 4 and workup were carried out as for substrate **1d**, the only differences being that ethyl acetate (4 × 30 mL) was used instead of acetone to extract the first residue and that the final residue was crystalline. The latter was recrystallized from chloroform–petroleum ether to give 0.89 g (61%) of pure **5**: mp 60–62 °C (lit.[9] mp 59–61 °C); IR, ^1H NMR, and mass spectra were identical with those reported in the literature for **5**.[9]

Registry No.—**1a**, 13169-01-2; **1b**, 13279-94-2; **1c**, 55755-14-1; **1d**, 3031-66-1; **2a**, 600-22-6; **2b**, 3952-66-7; **2c**, 3952-67-8; **4**, 625-86-5; **5**,

36871-95-1; potassium chlorate, 3811-04-9; osmium tetroxide, 20816-12-0.

References and Notes

(1) For a review on the uses of osmium tetroxide as an oxidation catalyst, see P. N. Rylander, *Org. Chem. (N.Y.)*, **28**, 121–133 (1973).
(2) A mechanism entailing as intermediate the symmetrical adduct between one molecule of **1** and two molecules of osmium tetroxide is less plausible due to the low concentration of the osmium tetroxide with respect to that of the substrate.
(3) L. Re, B. Maurer, and G. Ohloff, *Helv. Chim. Acta*, **56**, 1882 (1973).
(4) See, for example, B. W. Bycroft and G. R. Lee, *J. Chem. Soc., Chem. Commun.*, 988 (1975), and references cited therein.
(5) G. A. M. van den Ouweland and S. B. Tjan, *Recl. Trav. Chim. Pay-Bas*, **93**, 312 (1974), and references cited therein.
(6) T. L. Jacobs and S. Scarles, Jr., *J. Am. Chem. Soc.*, **66**, 686 (1944).
(7) The pH was kept constant by the use of an automatic titrator charged with 1 N KOH.
(8) For an analogous side reaction occurring in the hydroxylation of olefins with the chlorate–osmium tetroxide mixture, i.e., the addition of hypochlorous acid to the double bond, see ref 1.
(9) G. Büchi, E. Demole, and A. F. Thomas, *J. Org. Chem.*, **38**, 123 (1973).
(10) J. Levisalles, *Bull. Soc. Chim. Fr.*, 997 (1957).
(11) J. R. Nooi and J. F. Arens, *Recl. Trav. Chim. Pay-Bas*, **78**, 284 (1959).
(12) S. Piaux, *Bull. Soc. Chim. Biol.*, **6**, 416 (1924).
(13) C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Inc., Milwaukee, Wis., 1970, p 304.
(14) (a) C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Vol. 3, Aldrich Chemical Co., Inc., Milwaukee, Wis., 1974, p 61.
(15) H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1372 (1947).

Aleuritic Acid, an Abundant Source of Prostanoid Synthons

James M. Reuter and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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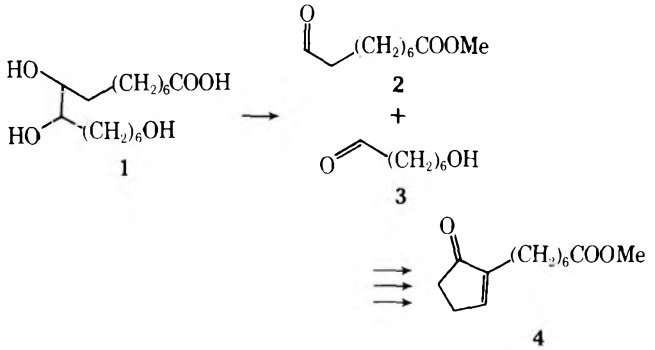
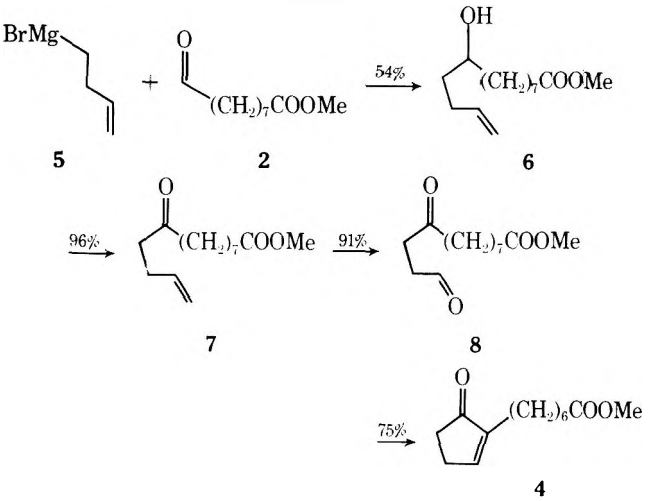
An attractive strategy for the construction of valuable prostanoids exploits readily available synthons derived from natural products.[1] Aleuritic acid (**1**) is a major component of shellac.[2,3] Crude lac resin contains up to 30% of **1**, which is



isolated by a simple extraction with base.[4] Oxidative cleavage of **1** with metaperiodate affords methyl azealdehydate (**2**) and 7-hydroxyheptanal (**3**).[5] A synthesis of the synthon **4**, a popular intermediate for prostaglandin syntheses,[6] has been achieved from cyclopentanone and the hydroxyaldehyde **3**.[5] Since azealdehydic acid is a byproduct of this synthesis, we examined the possibility that **2** might also be a synthon for prostaglandins. The present report demonstrates the feasibility of a complementary synthesis of **4** from **2** (see Scheme I).

Completion of the carbon skeleton of **4** is achieved by chemoselective reaction at −45 °C of the Grignard reagent **5** with the aldehydic carbonyl group in **2**. Chromic acid oxidation[7] of the hydroxyl in **6** to a carbonyl group and oxidative cleavage[8] of the olefin **7** affords γ-keto aldehyde **8**. Cyclodehydration of **8** gives methyl 7-(5-oxocyclopentenyl)heptanoate (**4**) in 35% overall yield from **2**.[9,10]

Scheme I



Experimental Section

Methyl Azealdehydate (2). A solution of potassium periodate (6.0 g) in 1 N H_2SO_4 (300 mL) at 20 °C was added rapidly to a vigorously stirred solution of trihydroxypalmitic acid (8.0 g) in a methanol–water solution (200 mL:200 mL) at 40 °C. After 10 min, the mixture was cooled to 15 °C in a methanol–ice bath and the solution was extracted immediately with ether (2 × 400 mL). The combined organic layers were extracted with saturated $NaHCO_3$ (2 × 100 mL), and the combined aqueous layers were acidified with concentrated HCl. The acidic aqueous solution was then extracted with ether (2 × 100 mL), and the combined ether layers were washed with brine (2 × 100 mL) and dried ($MgSO_4$). Removal of the solvent yielded 3.9 g (93%) of 95% pure product. The acid was then esterified with diazomethane (94%): bp 86–92 °C (0.2 mm);[11] NMR (CCl_4) δ 1.02–1.90 (10 H, m, $5CH_2$), 1.94–2.52 (4 H, m, $2CH_2$), 3.60 (3 H, s, CO_2CH_3), 8.70 (1 H, t, J = 2.4 Hz, CHO).

3-Butenyl-1-magnesium Bromide. Magnesium turnings (1.52 g), THF (5 mL; freshly distilled from benzophenone potassium ketyl), and 1-bromo-3-butene (1 mL of 5.1 mL total, 6.75 g, 0.05 mol) were placed in a flame-dried three-neck flask fitted with a reflux condenser, addition funnel, mechanical stirrer, and nitrogen inlet tube. When the reaction between the magnesium and bromide began, the remainder of the bromide in THF (45 mL) was added dropwise with stirring under nitrogen over a period of 1 h. After stirring at room temperature overnight, titration indicated an 83% yield.

Methyl 9-Hydroxy-12-tridecenoate (6). Methyl azealdehydate (70 g, 0.374 mol) and THF (500 mL; freshly distilled from benzophenone potassium ketyl) were added to a flame-dried three-neck flask fitted with a nitrogen inlet, addition funnel, low-temperature thermometer, and mechanical stirrer. The mixture was stirred under nitrogen and cooled to −45 °C, and the Grignard reagent from 3-butenyl bromide (200 mL of a 0.88 M solution) was added dropwise over a period of 1 h. The temperature of −45 °C was maintained throughout the addition. The mixture was stirred for 3 h at −40 °C, quenched by the dropwise addition of saturated NH_4Cl (100 mL), and allowed to warm to room temperature. Additional saturated NH_4Cl (200 mL) was added, and the mixture was extracted with ether (3 × 100 mL). The combined organic fractions were washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). Distillation gave 42.0 g of recovered starting material **2** and 19.8 g (54%) of **6**: bp 115–120 °C (0.2 mm); ^1H NMR (CCl_4) δ 1.08–1.89 (12 H, broad m, $6CH_2$), 1.90–2.50 (6 H, m, $3CH_2$), 2.70 (1 H, broad s, OH), 3.61 (3 H, s, CO_2CH_3), 3.60–3.70 (1 H, m, CH), 4.73–5.21 (2 H, m, vinyl CH_2), 5.47–6.08 (1 H, m, vinyl CH).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.37; H, 10.81. Found: C, 69.32; H, 11.09.

Methyl 9-Oxo-12-tridecenoate (7). An aqueous chromic acid solution prepared from sodium dichromate dihydrate (5.0 g, 16.8 mmol) and 96% sulfuric acid (3.75 mL, 67 mmol diluted to 25 mL) was added dropwise to a stirred solution of **1** (9.5 g, 40.1 mmol) and ether (25 mL) in a 100-mL three-neck flask fitted with an addition funnel, reflux condenser, and magnetic stirring bar. Addition was performed over a 15-min period and the temperature maintained at 25 °C

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(cooling with an ice bath was required). After 2 h, the upper layer was separated and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded 9.0 g (96%) of **7**: NMR (CCl_4) δ 1.05–1.85 (12 H, broad m, $6CH_2$), 2.06–2.50 (6 H, m, $3CH_2$), 3.60 (3 H, s, CO_2CH_3), 4.72–5.18 (2 H, m, vinyl CH_2), 5.45–6.12 (1 H, m, vinyl CH).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.24; H, 10.23.

Methyl 9-Oxo-12-dodecanaloate (8). A three-neck round-bottom flask fitted with a mechanical stirrer was charged with *tert*-butyl alcohol (60 mL), water (20 mL), **5** (4.32 g, 17.8 mmol), and osmium tetroxide (45.2 mg, 0.17 mmol in *tert*-butyl alcohol). The resulting solution was stirred for 5 min. A temperature of 24–26 °C was maintained with ice bath cooling during the addition of sodium metaperiodate (8.24 g, finely divided) in small portions over a period of 30 min. The tan-colored slurry was stirred at ambient temperature for an additional 4 h. At the end of this period the precipitate was white. The reaction mixture was extracted thoroughly with ether (3 × 100 mL), and the combined organic layers were washed with saturated sodium sulfite, saturated $NaHCO_3$, and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded 3.9 g (91%) of product: NMR (CCl_4) δ 1.04–1.83 (10 H, broad m, $5CH_2$), 2.10–2.55 (4 H, m, $2CH_2$), 2.61 (4 H, s, $COCH_2CH_2CO$), 3.61 (3 H, s, CO_2CH_3), 9.60 (1 H, s, CHO).[10]

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Registry No.—**1**, 533-87-9; **2**, 1931-63-1; **4**, 34546-57-1; **6**, 67237-57-4; **7**, 67237-58-5; **8**, 50266-44-9; 1-bromo-3-butene, 5162-44-7.

References and Notes

(1) The prostanoid synthon **4** is readily obtained from traumatic acid. However, this natural product is expensive: (a) P. D. Gokhale, V. S. Dalavoy, A. S. C. Prakasa Rao, U. Nayak, and S. Dev, *Synthesis*, 718 (1974); (b) A. S. C. Prakasa Rao and U. R. Nayak, *ibid.*, 608 (1975).
(2) F. Endeman, *Angew. Chem.*, **22**, 676 (1909).
(3) W. Nagel, *Chem. Ber.*, **60**, 605 (1927).
(4) W. Nagel and W. Mertens, *Chem. Ber.*, **74**, 976 (1941).
(5) M. Caton, E. Coffee, and G. Watkins, *Tetrahedron Lett.*, 585 (1974).
(6) For example, see (a) C. J. Sih, R. G. Salomon, P. Price, G. Peruzzotti, and R. Sood, *J. Chem. Soc., Chem. Commun.*, 240 (1972); (b) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Am. Chem. Soc.*, **94**, 3643 (1972); (c) C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *Tetrahedron Lett.*, 2435 (1972); (d) C. J. Sih, J. B. Heather, G. Peruzzotti, P. Price, R. Sood, and L. F. H. Lee, *J. Am. Chem. Soc.*, **95**, 1676 (1973); (e) J. B. Heather, R. Sood, P. Price, G. Peruzzotti, S. S. Lee, L. F. H. Lee, and C. J. Sih, *Tetrahedron Lett.*, 2313 (1973); (f) R. Pappo and P. W. Collins, *ibid.*, 2627 (1972); (g) F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.*, **94**, 7823 (1972); (h) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972); (i) E. J. Corey and D. J. Beams, *ibid.*, **94**, 7210 (1972); (j) K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972); (k) J. F. Bagli and T. Bogri, *ibid.*, 5 (1967); 1639 (1969); 3815 (1972); *J. Org. Chem.*, **37**, 2132 (1972); (l) J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966); (m) O. Attanasi, G. Baccolini, L. Caglioti, and G. Rosini, *Gazz. Chim. Ital.*, **103**, 31 (1973); (n) L. Novak and C. Szantay, *Synthesis*, 353 (1974); (o) E. Hardegger, H. P. Schenk, and E. Borger, *Helv. Chim. Acta*, **50**, 2501 (1967); (p) R. Klok, H. J. J. Pabon, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **87**, 813 (1968); **89**, 1043 (1970); (q) K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972); (r) R. F. Schaub and M. J. Weiss, *ibid.*, 129 (1973); (s) C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *J. Am. Chem. Soc.*, **97**, 857 (1975); (t) F. S. Alvarez and D. Wren, *Tetrahedron Lett.*, 569 (1973); (u) S. B. Thakur, K. S. Jadav, and S. C. Bhattacharyya, *Indian J. Chem.*, **12**, 893 (1974); (v) S. Kurozomi, T. Torn, and S. Ishimoto, *Tetrahedron Lett.*, 4959 (1973); (w) G. Piancatelli and A. Scettri, *ibid.*, 1131 (1977); (x) P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413 (1973); (y) C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *J. Am. Chem. Soc.*, **97**, 865 (1975).
(7) H. C. Brown and C. P. Gara, *J. Am. Chem. Soc.*, **83**, 2952 (1961).
(8) R. Pappo, D. Allen, Jr., R. Lemieux, and W. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
(9) A conceptually related synthesis of **6** from monomethyl azelate was reported recently: P. Bakuzis and M. L. F. Bakuzis, *J. Org. Chem.*, **42**, 2362 (1977).
(10) E. Wenkert, B. L. Buckwalter, A. A. Craveira, E. L. Sanchez, and S. S. Sathe, *J. Am. Chem. Soc.*, **100**, 1267 (1978).
(11) E. Pryde, D. Anders, H. Teeter, and J. Cowan, *J. Org. Chem.*, **25**, 618 (1960).

An Efficient Conversion of Ketones to α,β-Unsaturated Ketones

Riaz F. Abdulla* and Kenneth H. Fuhr

Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, Indiana 46140

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The C-alkylation of a terminal carbon in conjugated enamino ketones may be achieved through reaction with alkyl halides in the presence of *n*-butyllithium,[1] hydroxymethylation of acylated enamines with formaldehyde and an alkyllithium,[2] or through use of enamino ketones as nucleophilic acylating agents.[3,4]

We have now found that the reaction of structurally related β-acylenamines with alkyllithium reagents follows an alternative course to yield α,β-unsaturated carbonyl compounds. The problems associated with the synthesis of such compounds have been documented[5,6] and some particularly efficient methods have been developed for their preparation.[7] The work reported herein affords a practical, efficient route to α,β-unsaturated ketones in 60–85% yield based on starting ketone.

Condensation of ketones **1–7** with *N,N*-dimethylformamide dimethyl acetal at 110 °C for 12 h under nitrogen gave enamino ketones **8–14**, respectively.[8] When the enamino ketones were treated with 1.1 equiv of *n*-butyllithium in anhydrous tetrahydrofuran at −30 to 0 °C and then allowed to warm to room temperature, the corresponding α,β-unsaturated ketones **15–24** were obtained (Table I).

In order to demonstrate the versatility of this synthetic method, we have applied the sequence to prepare several natural products of which dihydrojasmone (**26**) and perillaketone (**30**), originally isolated from *Perilla frutescens* Brit.,[13] are representative examples.

The conversion of *N,N*-dimethylatropaldehyde (**31**)[12] to the unsaturated aldehyde (**32**) in 70% yield without any concomitant carbinol formation would serve to indicate that the course of these reactions is not sterically determined. Furthermore, the absence of any additional attack on the α,β-unsaturated carbonyl compounds by alkyllithium is believed due to the intervention of intermediates such as **33** which have no propensity for additional attack by nucleophiles.

The generality of the process is demonstrated by successful extension to methyllithium and *tert*-butyllithium reagents

Scheme I. A Total Synthesis of Dihydrojasmone

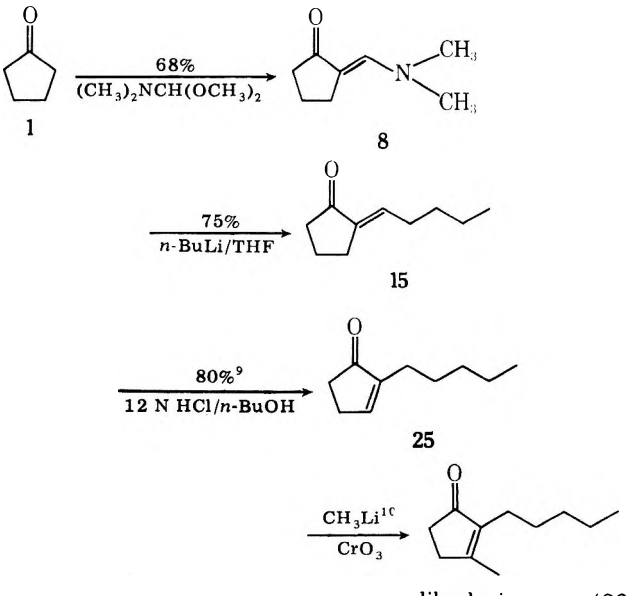

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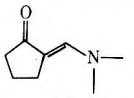
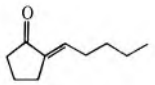
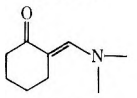
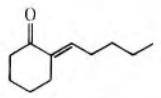
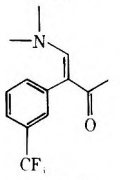
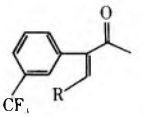
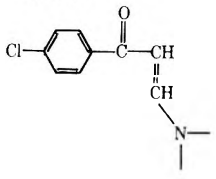
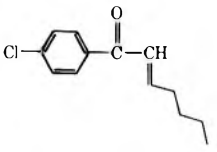
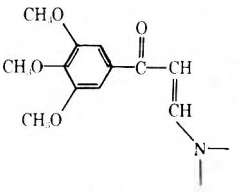
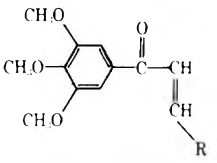
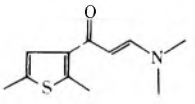
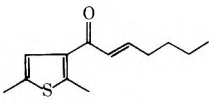
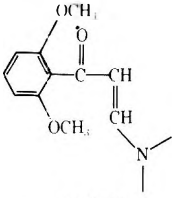
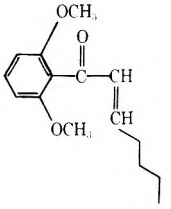
Table I. Two-Step Conversion of Ketones to α,β-Unsaturated Ketones

ketones	registry no.	enamines (yield, %)[a]	registry no.	α,β-unsaturated ketones (yield, %)	registry no.
cyclopentanone (1)	120-92-3	 8 (68%)	67382-33-6	 15 (75%)	67382-39-2
cyclohexanone (2)	108-94-1	 9 (66%)	28467-36-9	 16 (73%)	67382-40-5
m-trifluoromethylphenylacetone (3)	349-76-8	 10 (83%)	67382-34-7	 17, R = *n*-C_4H_9 (65%) 18, R = *t*-C_4H_9 (55%) 19, R = CH_3 (75%)	67382-41-6 67382-42-7 67382-43-8
p-chloroacetophenone (4)	99-91-2	 11 (85%)	67382-35-8	 20 (68%)	67382-44-9
3,4,5-trimethoxyacetophenone (5)	1136-86-3	 12 (89%)	67382-36-9	 21, R = *n*-C_4H_9 (60%) 22, R = CH_3 (64%)	67382-45-0 67382-46-1
3-acetyl-2,5-dimethylthiophene (6)	2530-10-1	 13 (81%)	67382-37-0	 23 (60%)	67382-47-2
2,6-dimethoxyacetophenone (7)	2040-04-2	 14 (95%)	67382-38-1	 24 (68%)	67382-48-3

[a] These refer to isolated yields of chromatographically homogeneous materials. All intermediates and products were characterized by IR, NMR, and mass spectroscopy and afforded satisfactory combustion analyses.

(Table I), and the data show that these conversions are comparable in efficiency.

In view of the capriciousness of 1,4 vs. 1,2 addition of organometallic reagents[14] to unsaturated carbonyl compounds, the consistency of our results provides a useful route to substituted, conjugated enones.

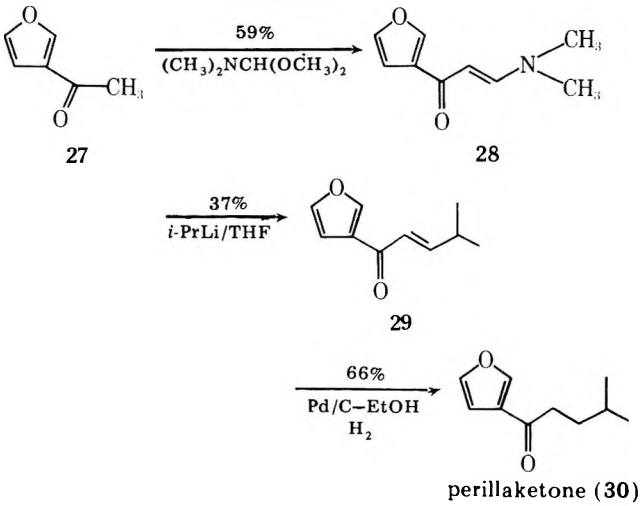
Experimental Section

2-[(Dimethylamino)methylene]cyclopentanone (8). To 8.4 g (0.1 mol) of cyclopentanone was added 11.9 g (0.1 mol) of *N,N*-dimethylformamide dimethyl acetal and the mixture was refluxed under nitrogen at 110 °C for 12 h. The resulting mixture was stripped of methanol and distilled in a Kugelrohr apparatus at 90 °C/30 μm to afford 12.2 g (88%) of the title compound as an amber oil which was used without further purification [n^{25}D 1.5795; $\bar{\nu}_{CO}$ 1685 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 1.5–3.0 (m, 6 H, cyclopentanone ring protons), 3.08 (s, 6 H, $N(CH_3)_2$), 7.1 (t, J = 0.75 Hz, =CH; M$^+$ *m/e* 139).

2-Pentylidenecyclopentanone (15). To 11.12 g of 8 in 350 mL of tetrahydrofuran at −30 °C (N_2) was added 57.2 mL (1.1 equiv) of 1.6 M *n*-butyllithium reagent, dropwise over 30 min. The reaction mixture was stirred to room temperature over 2 h. The excess *n*-butyllithium was destroyed with water (5.0 mL) and the solvent was removed in vacuo. The oily residue was treated with 100 mL of water and extracted five times with 100-mL portions of ether. The ether was washed with water, dried ($MgSO_4$), and evaporated in vacuo (40 °C (10 mm)) to give 9.4 g (75%) of the title compound **15**: bp 100–102 °C (8 mm); n^{25}D 1.4756, lit.[7c] n^{20}D 1.4743; $\bar{\nu}_{CO}$ = 1660, 1730 cm^{-1} (lit.[9] 1653, 1709 cm^{-1}); NMR ($CDCl_3$, Me_4Si) δ 0.50–1.33 (m, 15 H), 6.30–6.73 (m, 1 H, vinyl). Anal. Calcd: 78.95; H, 10.53. Found: C, 78.73; H, 10.49.

2-Pentyl-2-cyclopenten-1-one (25). To 1.0 g of **15** dissolved in 10.0 mL of *n*-butyl alcohol was added 2.0 mL of 12 N hydrochloric acid and the mixture was stirred at 100 °C for 1 h.[9] The mixture was poured into water and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and stripped to give 0.8 g (80%) of **25** as a mobile, colorless, fragrant liquid whose obtention comprises a synthesis of dihydrojasmone[10] (**26**): n^{25}D 1.4687; $\bar{\nu}_{CO}$ 1715, 1638; NMR ($CDCl_3$, Me_4Si) δ 0.33–3.00 (m, 15 H), 7.26–7.5 (m, 1 H, vinyl). Anal. Calcd: C, 78.90; H, 10.59. Found: C, 78.65; H, 10.44.

Scheme II. A Total Synthesis of Perillaketone



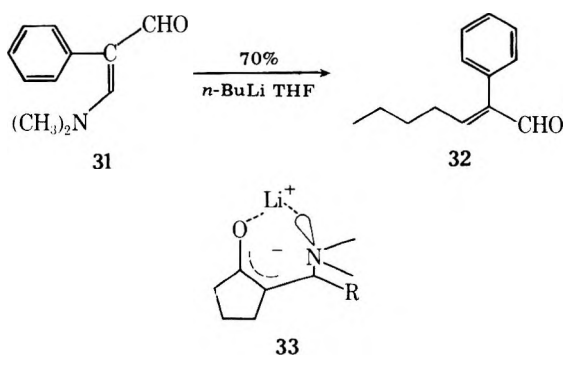
***trans*-3-[3-(Dimethylamino)acryloyl]furan (28).** A mixture of 3.30 g (0.03 mol) of 3-acetylfuran (27) and 25.0 mL of *N,N*-dimethylformamide dimethyl acetal was heated under reflux for 12 h. The mixture was evaporated in vacuo and the residue was crystallized under pentane. Recrystallization from diisopropyl ether/dichloromethane gave 2.9 g (59%) of *trans*-3-[3-(dimethylamino)acryloyl]-furan (28): mp 103–105 °C; NMR ($CDCl_3$, Me_4Si) δ 2.95 (s, 6 H, $N(CH_3)_2$), 5.42 (d, 1 H), 7.68 (d, 1 H, J = 13.5 Hz, *trans*-vinyl), 6.68, 7.41, 8.0 (m, 3 H, furan). Anal. Calcd: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.55; H, 6.42; N, 8.63.

***trans*-3-Furyl 3-Methyl-1-butenyl Ketone (29).** To 1.65 g (0.01 mol) of the *trans*-enamino ketone (28) in 100 mL of dry (Linde 4A Sieves) tetrahydrofuran under nitrogen was added 5.5 mL of 1.85 M isopropyllithium reagent in pentane. After stirring at −30 °C for 0.5 h, the solution was stirred to room temperature and 5.0 mL of water was added. The solution was stripped dry, and the residue was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo to give an oil which was purified by chromatography (325 g of silica gel, gradient elution with dichloromethane and ethyl acetate/dichloromethane) to give 0.6 g (37%) of the trans-α,β-unsaturated ketone (29): NMR ($CDCl_3$, Me_4Si) δ 1.13 [d, 6 H, J = 6.2 Hz, $(CH_3)_2C$], 2.55 (m, 1 H, CH(C)(C)), 6.4 (d, 1 H, J = 14 Hz, *trans*-vinyl), 7.0 (m, 1 H, vinyl), 7.0 (m, 1 H, vinyl), 8.0, 7.4, 6.8 (m, 3 H, furan). Anal. Calcd: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.14.

Synthesis of Perillaketone (30). To a solution of 0.6 g of 29 in 100 mL of ethanol was added 60 mg of 5% palladium on carbon and the mixture was hydrogenated for 1 h. The solution was filtered through celite and evaporated in vacuo to give 0.4 g (66%) of perillaketone (30) identical with authentic material: NMR ($CDCl_3$, Me_4Si) δ 2.71 (t, 2 H, J = 8 Hz, $-COCH_2-$), 0.7–2 (m, 7 H, aliphatic), 6.7–8.1 (m, 3 H, furan).

2-Phenyl-*trans*-2-heptenal (32). To 3.5 g of *N,N*-dimethylatropaldehyde (31)[12] was added 150 mL of dry tetrahydrofuran (Linde 4A Sieves) and the solution was cooled to −30 °C. Under nitrogen was added 9.0 mL of 2.4 M *n*-BuLi reagent in 2 min and the reaction mixture was stirred to room temperature over 2 h. To the solution was added 100 mL of 1 N HCl followed by 500 mL of ether. The ether extract was dried (magnesium sulfate) and removed in vacuo to give 1.3 g (35%) of 32 as an amber oil. The analytical sample was obtained by column chromatography over 45 g of silica gel (Woelm Act. 1) using dichloromethane as the eluant: NMR ($CDCl_3$, Me_4Si) δ 0.6–1.65 (m, 7 H, $CH_3(CH_2)_2$), 2.33 (q, 2 H, J = 8 Hz, $-CH_2C{=}C-$), 6.67 (t, 1 H, J = 8 Hz, $-CH{=}C<$), 6.85–7.5 (m, 5 H, aromatic), 9.50 (s, 1 H, CH=O); M^+ *m/e* 188; n^{25}_D 1.5247.

Scheme III



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References and Notes

(1) M. Yoshimoto, N. Ishida, and T. Hiraoka, *Tetrahedron Lett.*, 39 (1973).
(2) B. Ganem, *J. Am. Chem. Soc.*, **98,** 244 (1976).
(3) R. R. Schmidt and J. Talbiersky, *Angew. Chem., Int. Ed. Engl.*, **15,** 171 (1976).
(4) C. Wlaux-Zamar, J.-P. Dejonghe, L. Ghosez, J. F. Normant, and J. Villieras, *Angew. Chem., Int. Ed. Engl.*, **15,** 371 (1976).
(5) L. Birkofer, S. M. Kim, and H. E. Engels, *Chem. Ber.*, **95,** 1495 (1962).
(6) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28,** 6 (1963).
(7) (a) D. Seebach, M. Kolb, and B. T. Gröbel, *Tetrahedron Lett.*, 3171 (1974); (b) R. A. J. Smith and T. A. Spencer, *J. Org. Chem.*, **35,** 3220 (1970); (c) M. F. Ansell and J. W. Ducker, *J. Chem. Soc.*, 329 (1959); (d) N. Katsin and R. Ikan, *Synth. Commun.*, **7,** 185 (1977).
(8) *E* stereochemistry is assigned to the enamino ketones by analogy with 1-dimethylamino-2-benzoylethylene derived from acetophenone, in which $J_{H_\alpha H_\beta}$ = 11.5 Hz. *E* stereochemistry is assigned on the same basis to the α,β-unsaturated ketones. See H. Meerwein, W. Florian, G. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641,** 1 (1961), for use of DMF acetals as formylating agents.
(9) M. P. L. Caton, E. C. J. Coffee, and G. L. Watkins, *Tetrahedron Lett.*, 773 (1972).
(10) T. L. Ho, *Synth. Commun.*, **4,** 265 (1974).
(11) K. Kondo and M. Matsumoto, *Tetrahedron Lett.*, 4363 (1976).
(12) Z. Arnold, *Collect. Czech. Chem. Commun.*, **26,** 3051 (1961).
(13) R. Goto, *J. Pharm. Soc. Jpn.*, **57,** 77 (1937).
(14) (a) G. H. Posner, *Org. React.*, **19,** 1 (1972); (b) J. V. Greenhill, *Chem. Soc. Rev.*, **6,** 277 (1977); (c) A. I. Meyers and S. Singh, *Tetrahedron Lett.*, 5319 (1967).

Annelation of Ethyl Propiolate with Ethyl Pipecolate

Peter Walter and Thomas M. Harris*

Department of Chemistry Vanderbilt University, Nashville, Tennessee 37235

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In conjunction with studies of the alkaloid slaframine[1] we undertook a search for routes to Δ^2 derivatives of 1-oxooctahydroindolizines. The cycloaddition of ethyl propiolate to ethyl pipecolate (1) was formally attractive for this purpose although an earlier attempt by Winterfeldt and Dillinger to effect a similar condensation of dimethyl acetylenedicarboxylate with methyl ethylaminoacetate had met with failure, only an uncyclized Michael adduct being obtained.[2,3] Nevertheless, we were encouraged by molecular model studies which suggested that the geometry of the zwitterionic intermediate resulting from addition of 1 to the acetylenic ester would be particularly conducive to annelation.

Treatment of ethyl pipecolate with ethyl propiolate in refluxing ethanol gave Michael adduct 2 in yield >90%. Examination of the NMR spectrum of the crude reaction mixture revealed no more than a trace of a signal that might represent the vinyl proton of the desired 1-oxohexahydroindolizine 3 but when the reaction was repeated in hexane at ambient

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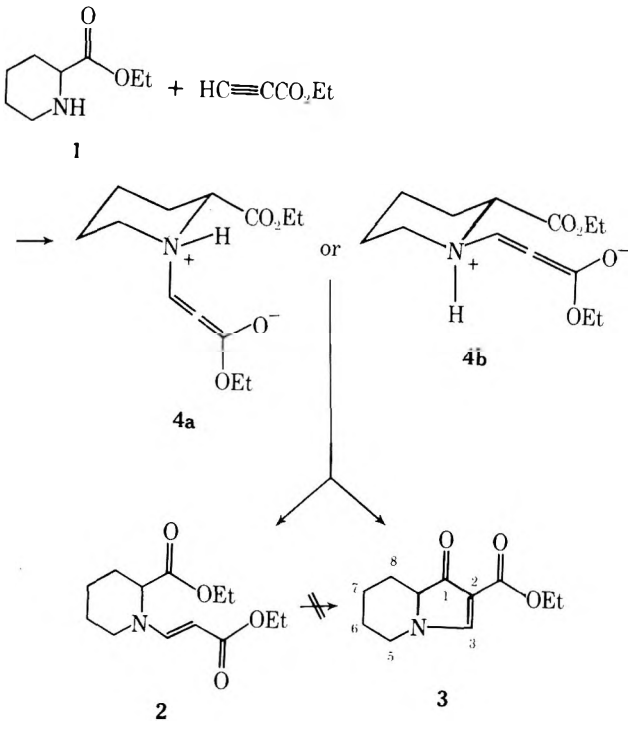
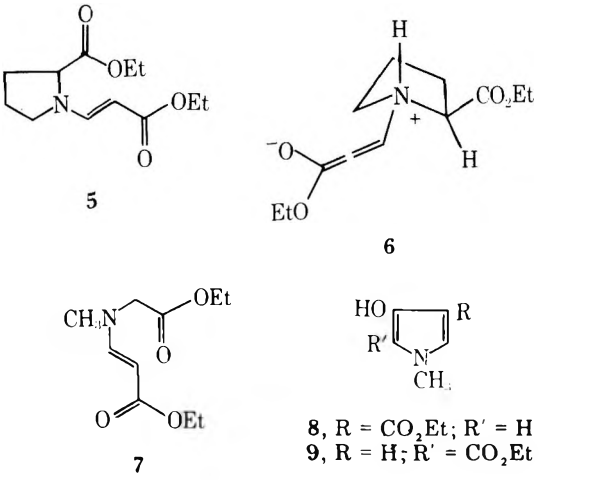
Scheme I



temperature, the NMR spectrum showed, in addition to **2**, a substantial amount of a second product having a vinyl proton singlet at 6.75 ppm. Integration indicated the molar ratio of **2** and the new compound in the product mixture to be 63:37. When refuxing hexane (~70 °C) was employed as the solvent, the latter compound represented 54% of the product mixture; with refluxing heptane (~100 °C) it reached 74%. GLC showed only the two products being formed and these compounds were separated by preparative GLC although substantial losses, particularly of **3**, were experienced during the process due to air-oxidation and thermal degradation. The new compound was identified as **3** on the basis of spectral data and elemental analyses. Compounds **2** and **3** are both formed by pathways which are irreversible under the reaction conditions, the relative yields being independent of reaction times. Moreover, **2** when resubmitted to refluxing heptane was not converted into **3**, proving that it is not a precursor of **3** in the condensation reaction.

Attack of ethyl propiolate on ethyl pipecolate probably occurs axially to give cis zwitterion **4a** having the two substituents on the same face of the piperidine ring, although trans zwitterion **4b** arising by equatorial attack would also be capable of cyclization. In ethanol, proton transfer from solvent intercepts **4** before intramolecular acylation can occur but in hydrocarbon solvents, where the zwitterion is the only source of protons, acylation competes effectively with inter- and intramolecular proton transfer.

The structure of the zwitterionic intermediate appears to be crucial to this annelation reaction. Only Michael adduct **5** was obtained from the condensation of ethyl propiolate with the ethyl ester of proline, probably because eclipsing interactions hinder cis attack of ethyl propiolate on the proline ester. Trans zwitterion **6**, which forms instead, is structurally incapable of cyclization and consequently undergoes a proton transfer to give **5**. Cyclization is unlikely with zwitterionic intermediates which are conformationally mobile. Although the condensation of methyl ethylaminoacetate with dimethyl acetylenedicarboxylate was carried out by Winterfeldt and Dillinger in *tert*-butyl alcohol which precluded cyclization, we have obtained a similar result from the condensation of ethyl methylaminoacetate with ethyl propiolate in refluxing



heptane. The latter reaction gave predominantly Michael adduct **7**; a trace of a second component, possibly pyrrole **8** or **9**, was obtained but the compound was unstable and was not fully characterized.

Experimental Section

NMR spectra were obtained with a JEOL MH-100 100 MHz spectrometer operating in the external lock mode. Spectra were obtained in dilute solution in $CDCl_3$ or CCl_4. Mass spectra (70 eV) were obtained with an LKB-9000 spectrometer using the direct inlet. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Condensations of Ethyl Propiolate with Esters of Amino Acids. Ethyl Pipecolate. A solution of ethyl propiolate (0.4 g, 4.1 mmol) in 2 mL of heptane was added dropwise to 0.64 g (4.1 mmol) of ethyl pipecolate in refluxing heptane (10 mL) under N_2. After 15 min, a sample was removed and added to $CDCl_3$; the NMR spectrum showed the reaction was essentially complete and had given a 24:76 mixture of **2** and **3**. Heptane was removed under a stream of N_2 and the residue was partitioned by GLC on a column of 3% OV-17 (Chromosorb W) at 240 °C. Compound **3**, ethyl 1-oxo-1,5,6,7,8,8a-hexahydroindolizine-2-carboxylate, eluted first: NMR δ 1.3 (t) and 4.3 (q, C_2H_5), 6.75 (s, not exchangeable with D_2O, 3-CH), the remaining protons appeared in unresolved multiplets at 3.9, 2.7, and 2.0–1.6; MS *m/e* 209 (parent), 163, 135, 107. The compound was sensitive to oxygen and had to be stored under N_2 at −10 °C.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.16; H, 7.18,; N, 6.70. Found: C, 62.93; H, 7.11; N, 6.63.

Compound **2** was retained 35% longer than **3**: NMR δ 1.3 (2 × t) and 4.3 (2 × q, 2 × C_2H_5), 4.61 (d, J = 13 Hz, -CH=CHCO-), 7.68 (d, J = 13 Hz, -CH=CHCO-), the remaining protons appeared in unresolved multiplets at 3.18, 2.22, 2.12, and 1.9–1.5 (the proton at 4.61 underwent exchange ($t_{1/2}$ ~ 20 min) with D_2O; the doublet at 7.68 collapsed simultaneously to a singlet.); MS *m/e* 255 (parent). The compound was sensitive to oxygen and was stored under N_2 at −10 °C.

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.18; H, 8.24; N, 5.49. Found: C, 61.31; H, 8.12; N, 5.44.

Proline Ethyl Ester. Similar treatment of the ethyl ester of proline gave exclusively Michael adduct **5**: NMR δ 1.25 (2 × t) and 4.15 (2 × q, 2 × C_2H_5), 4.61 (d, J = 13 Hz, -CH=CHCO-), 7.65 (d, J = 13 Hz, -CH=CHCO-), the remaining protons appeared in unresolved multiplets at 3.7–3.2 and 2.3–1.8; MS *m/e* 241 (parent). The compound was air sensitive.

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.75; H, 7.88. Found: C, 59.49; H, 7.80.

Ethyl Methylaminoacetate. Similar treatment of the ethyl ester of methylaminoacetic acid gave 90% of Michael adduct **7**: NMR δ 1.27 (2 × t) and 4.19 (2 × q, 2 × C_2H_5), 2.96 (s, NCH_3), 3.89 (s, CH_2), 4.64 (d, J = 13 Hz, -CH=CHCO-), 7.43 (d, J = 13 Hz, -CH=CHCO-); MS *m/e* 215 (parent).

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.91. Found: C, 55.62; H, 7.81.

A more volatile component was obtained from the reaction in very low yield and is provisionally assigned as cycloadduct **8** or **9**: NMR δ 1.3 (t) and 4.3 (q, C_2H_5), 3.6 (s, NCH_3), 6.2 (d) and 6.9 (d, ring CH's, J = 2.8 Hz); MS *m/e* 169 (parent). The compound was highly air sensitive and was not characterized further.

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Registry No.—**1**, 15862-72-3; **2**, 67425-79-0; **3**, 67425-80-3; **5**, 67425-81-4; **7**, 67425-82-5; **8**, 65172-11-4; **9**, 65171-90-6; ethyl propiolate, 623-47-2; proline ethyl ester, 5817-26-5; methylaminoacetic acid ethyl ester, 13200-60-7.

References and Notes

(1) For a review on this alkaloid, see F. P. Guengerich and H. P. Broquist in "A Survey of Contemporary Bioorganic Chemistry", Vol II, E. E. van Tamelen, Ed., Academic Press, New York, N.Y., 1976.
(2) E. Winterfeldt and H. J. Dillinger, *Chem. Ber.*, **99**, 1558 (1966). These workers converted the Michael adduct into a pyrrole derivative by treatment with potassium metal in toluene; the Dieckmann ring closure involved nucleophilic attack on the maleate terminal carbonyl group rather than on the carbonyl group of the acetate fragment. Winterfeldt and Dillinger also achieved a one-step condensation–cyclization involving the acetate carbonyl group by employing methyl diethylaminoacetate with dimethyl acetylenedicarboxylate.
(3) For a review of related reactions of acetylene compounds with amino acids, see M. V. George, S. K. Khetan, and R. K. Gupta, *Adv. Heterocycl. Chem.*, **19**, 279 (1976).

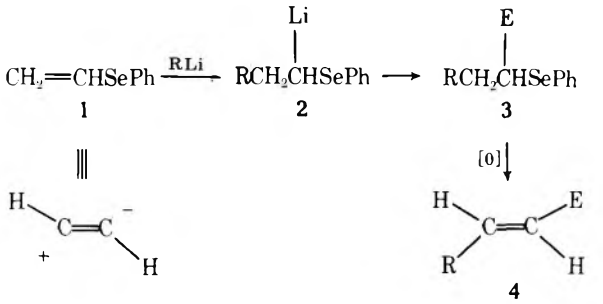
Communications

Vinyl Phenyl Selenide: A $^{+}CH{=}CH^{-}$ Synthon[1]

Summary: Vinyl phenyl selenide (**1**) may be utilized as a $^{+}CH{=}CH^{-}$ synthon by reaction with alkyllithiums, trapping of the resulting α-lithioalkyl phenyl selenides **2** with electrophiles to give **3**, and oxidative elimination of phenylselenenic acid to produce the disubstituted alkenes **4**.

Sir: The use of a variety of synthons for the formation of new carbon to carbon bonds is a well-established strategy in synthetic organic chemistry. In this communication we wish to report the use of vinyl phenyl selenide (**1**) as a $^{+}CH{=}CH^{-}$ synthon (Scheme I).[2]

Scheme I



The addition of alkyllithiums to a number of vinyl derivatives of second-row elements in their lower oxidation states has been reported.[3] We felt that such additions to vinyl phenyl selenides would be particularly useful for the following reasons: (1) the ability of a phenylseleno group to stabilize an adjacent carbanion and the reaction of these carbanions with a variety of electrophiles has been demonstrated;[4] (2) subsequent to performing its function, the phenylseleno group may be easily removed via oxidative elimination of phenylselenenic acid to generate alkenes, often regio- and stereospecifically;[5] and (3) the requisite vinyl phenyl selenides are readily available.[6]

Although vinyl phenyl selenide (**1**) is unreactive toward both *n*-Bu_2CuLi and *n*-BuMgBr, alkyllithiums readily add to **1**[7] in dimethoxymethane or diethyl ether at 0 °C to give the α-lithioalkyl phenyl selenides **2**, which may be trapped by electrophiles to give the substituted alkyl phenyl selenides **3**; oxidative elimination of phenylselenenic acid for instances in which the regiospecificity is unambiguous (e.g., E = > C=O or >COH) leads to the formation of the *E*-disubstituted alkenes **4** in good overall yield (Table I).[8]

Since the reaction of alkyllithiums with **1** can also lead to α-deprotonation[9] or carbon–selenium bond cleavage,[10] the proper choice of reaction conditions is essential for the success of the desired addition reaction (Scheme II). In particular,

Table I. Alkyllithium Addition–Electrophile Trapping with Vinyl Phenyl Selenide[a]

entry	RLi	electrophile	E	% yield 3	% yield 4
a	*n*-BuLi	D_2O	D–	97	
b	*n*-BuLi	CH_3I[b]	CH_3–	95	
c	*n*-BuLi	*n*-$C_{10}H_{11}Br$[b]	*n*-$C_{10}H_{21}$–	80	
d	*n*-BuLi	PhSeBr	PhSe–	84	*c*
e	*n*-BuLi	$(CH_3)_3SiCl$	$(CH_3)_3Si$–	90	*d*
f	*n*-BuLi	PhCHO	PhCH(OH)–	71	75[h]
g	*n*-BuLi	CH_3COCH_3	$(CH_3)_2C(OH)$–	60	83[h]
h	*n*-BuLi	$PhCOCH_3$	$PhC(CH_3)(OH)$–	*e*	50[f,h]
i	*n*-BuLi	PhCN	PhCO–	*e,g*	61[f,h]
j	*i*-PrLi	D_2O	D–	92	
k	*i*-PrLi	CH_3COCH_3	$(CH_3)_2C(OH)$–	72	81[h]
l	*i*-PrLi	$(CH_3)_3SiCl$	$(CH_3)_3Si$–	86	*d*
m	*t*-BuLi	D_2O	D–	85	

[a] Yields refer to isolated, purified products. See ref 8. All reactions utilize 1.2 equiv of alkyllithium and 1.2–1.5 equiv of electrophile (except D_2O quenches). Reactions with *n*-BuLi were run in dimethoxymethane; reactions with *i*-PrLi and *t*-BuLi were run in diethyl ether. [b] 1 equiv of HMPA was added with the electrophile. [c] Bis(phenylseleno) acetals may be hydrolyzed to the corresponding aldehydes; thus, **1** is also a $^{+}CH_2CHO$ synthon. [d] Oxidation of (α-trimethylsilyl)alkyl phenyl selenides affords the corresponding aldehydes: K. Sachdev and H. S. Sachdev, *Tetrahedron Lett.*, 4223 (1976). [e] Intermediate not isolated. [f] Overall yield from **1**. [g] Hydrolyzed with 5% HCl (75 °C, 15 min) prior to oxidation–elimination. [h] Only the *E* isomer was produced.

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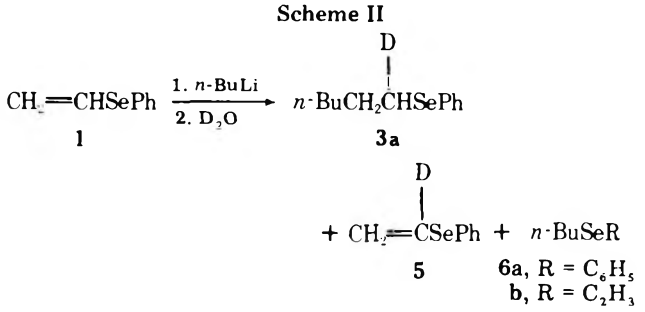
Table II. Solvent–Temperature Effects for the Reaction of n-BuLi with 1[a]

solvent	temp, °C	% products[b] 3a	5[c]	6
$(CH_3O)_2CH_2$	0	97	3	0
Et_2O	0	90	10	0
Et_2O	−78	55	15[d]	0
THF	0	70	20	10
THF	−78	5	15	80

[a] All reactions were 0.1 M in 1 and utilized 1.2 equiv of *n*-BuLi; after 1 h the reactions were quenched with excess D_2O. [b] Determined by VPC on 5 ft × ¼ in. 1.5% OV 101 on 100/120 Chromosorb G column. In all cases, mass balance was >80%. [c] Deuterium incorporation verified by NMR. [d] Amount of 5 estimated by NMR; unreacted 1 accounted for the remainder of the mass.

Scheme II



solvent and temperature effects are crucial, with dimethoxymethane or diethyl ether at 0 °C providing the best results in preliminary studies involving the addition of *n*-BuLi to 1 followed by quenching with D_2O (Table II). Related solvent effects have been previously observed for the reaction of alkyllithiums with alkenes, and, although complex, may be related to the state of aggregation of the alkyllithium reagent.[11]

We are currently investigating the use of vinyl phenyl selenides as synthons in a number of other reactions; these results will be reported in due course.

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References and Notes

(1) Organoselenium Chemistry. 5. Presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, Calif., March, 1978. For previous papers in this series see: S. Raucher and G. A. Koolpe, *J. Org. Chem.*, **43**, 3794 (1978).

(2) (a) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967); (b) D. Lednicer, *Adv. Org. Chem.*, **8**, 179 (1972). (c) For the use of HC≡CH as a $^+CH{=}CH^-$ equivalent via addition of cuprates and trapping by electrophiles see: A. Alexakis, J. Normant, and J. Villieras, *Tetrahedron Lett.*, 3461 (1976). It is noteworthy that this procedure yields (*Z*)-alkenes, thus making it complementary to the selenoxide elimination, which produces (*E*)-alkenes.

(3) For the addition of *n*-BuLi to vinyl phenyl sulfide see: (a) W. E. Parham and R. F. Motter, *J. Am. Chem. Soc.*, **81**, 2146 (1959); (b) W. E. Parham, M. A. Kalnins, and D. R. Theissen, *J. Org. Chem.*, **27**, 2698 (1962). For addition of *n*-BuLi to vinyldiphenylphosphine see: (c) D. J. Peterson, *J. Org. Chem.*, **31**, 950 (1966). For addition of *n*-BuLi to vinyltriphenylsilane see: (d) L. F. Cason and H. G. Brook, *J. Am. Chem. Soc.*, **74**, 4852 (1952); (e) L. F. Cason and H. G. Brook, *J. Org. Chem.*, **19**, 1278 (1954); (f) A. G. Brook, J. M. Duff, and D. G. Anderson, *Can. J. Chem.*, **48**, 561 (1970). For Michael additions to vinyl sulfoxides, see: (g) G. Tsuchihashi, S. Mitramura, S. Inoue, and K. Ogura, *Tetrahedron Lett.*, 323 (1973); (h) G. Tsuchihashi, S. Mitramura, and K. Ogura, *ibid.*, 855 (1976); (i) G. A. Koppel and M. D. Kinnick, *J. Chem. Soc., Chem. Commun.*, 473 (1975).

(4) (a) For recent reviews see: D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978); E. Block and M. Haake, *Org. Compd. Sulphur, Selenium, Tellurium*, **4**, 102–105 (1977); (b) D. Seebach and N. Peleties, *Angew. Chem., Int. Ed. Engl.*, **8**, 450 (1969); (c) D. Seebach and N. Peleties, *Chem. Ber.*, **105**, 511 (1972); (d) R. H. Mitchell, *J. Chem. Soc., Chem. Commun.*, 990 (1974); (e) D. Seebach and A. K. Beck *Angew. Chem., Int. Ed. Engl.*, **13**, 806 (1974); (f) W. Dumont, P. Bayet, and A. Krief, *ibid.*, **13**, 804 (1974); (g) H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **97**, 3250 (1975); (h) H. J. Reich and F. Chow, *J. Chem. Soc., Chem. Commun.*, 790 (1975); (i) H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); (j) A. Anciaux, A. Eman, W. Dumont, and A. Krief, *Tetrahedron Lett.*, 1617 (1975).

(5) (a) Review: K. B. Sharpless, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A**, 9 (1975); (b) D. N. Jones, D. Mundy, and R. D. Whitehouse, *Chem. Commun.*, 86 (1970); (c) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973); (d) H. J. Reich, I. L. Reich, and J. M. Renga, *ibid.*, **95**, 5813 (1973); (e) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, **39**, 2133 (1974); (f) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973); (g) ref 4g.

(6) (a) Vinyl phenyl selenide (**1**) is readily prepared by dehydrohalogenation (1.2 equiv of *t*-BuOK in THF, 25 °C) of 2-chloroethyl phenyl selenide, prepared by reaction of $PhSe^-$ (PhSeSePh, $NaBH_4$, EtOH) with excess 1,2-dichloroethane (50 equiv), in 95% overall yield from PhSeSePh. (b) Substituted vinyl phenyl selenides are available from the corresponding alkenes: S. Raucher, *J. Org. Chem.*, **42**, 2950 (1977).

(7) (a) Reaction of vinyl phenyl selenoxide with *n*-BuLi or *n*-Bu_2CuLi led to products resulting from carbon–selenium bond cleavage. (b) We have been unable to effect addition of methyllithium to **1**.

(8) (a) All new compounds were fully characterized by spectroscopic methods. Yields are given for chromatographically pure, isolated products. (b) A typical experimental procedure for the preparation of (*E*)-2-methyl-3-octen-2-ol (**4g**) follows. A solution of vinyl phenyl selenide (**1**) (305 mg, 1.67 mmol) in freshly dried (CaH_2) dimethoxymethane (1.5 mL) was added over 10 min to a solution of *n*-BuLi (2.4 M in hexane, 0.83 mL, 2.0 mmol) in dimethoxymethane (5.0 mL) at 0 °C under an atmosphere of argon. The clear solution was stirred at 0 °C for 1 h, cooled to −78 °C, and a solution of acetone (145 mg, 2.5 mmol) in THF (2.0 mL) was added over 10 s, and stirring was continued at −78 °C for 1 h. The reaction mixture was quenched with aqueous NH_4Cl, extracted with ether, and dried ($MgSO_4$), and the solvents were removed in vacuo to give crude 2-methyl-3-phenylseleno-2-octanol (**3g**), which was dissolved in CH_2Cl_2 (15 mL), cooled to −78 °C, and ozonized[5e] for 5 min. Diisopropylamine (1 mL)[4g] and CCl_4 (25 mL) were added, the mixture was refluxed for 30 min, the solvents were removed in vacuo, and the residue was purified on silica gel (20 g) with hexane–ether to give (*E*)-2-methyl-3-octen-2-ol as a clear liquid (117 mg, 50% overall from **1**): ^1H NMR (CCl_4) δ 0.70–2.20 (m) and 1.25 (s) [total 15 H], 2.75 (bs. 1 H, OH), 5.58 (m, 2 H). (c) Additional ^1H NMR data (CCl_4): **3a** δ 0.70–1.90 (m, 12 H), 2.85 (t, *J* = 6 Hz, 1 H), 7.10–7.60 (m, 5 H); **3b** δ 0.70–1.90 (m) and 1.34 (d, *J* = 7 Hz) [total 14 H], 3.20 (m, 1 H), 7.05–7.80 (m, 5 H); **3d** δ 0.70–2.10 (m, 11 H), 4.41 (t, *J* = 6 Hz, 1 H, –CH(SePh)$_2$), 7.10–7.70 (m, 10 H); **3e** δ 0.08 (s, 9 H), 0.67–1.75 (m, 11 H), 2.30 (t, *J* = 6 Hz, 1 H, –CH(SePh)$SiMe_3$), 7.00–7.60 (m, 5 H); **3f** δ 0.68–1.80 (m, 11 H), 3.30 (m) and 3.51 (bs) [total 2 H], 4.51 (d, *J* = 8 Hz, 1 H, PhCH(OH)CH<), 7.15–7.70 (m, 10 H); **3g** δ 0.70–2.00 (m), 1.28 (s) and 1.44 (s) [total 17 H], 2.80 (bs, 1 H), 3.18 (m, 1 H), 7.20–7.80 (m, 5 H); **3j** δ 0.92 (d, *J* = 7 Hz, 6 H), 1.12–1.98 (m, 4 H), 2.87 (t, *J* = 7 Hz, 1 H), 7.10–7.62 (m, 5 H); **3k** δ 0.75 (d, *J* = 7 Hz), 0.97 (d, *J* = 7 Hz), 1.21 (s), 1.33 (s), and 1.40–2.00 (m) [total 14 H], 2.72 (bs, 1 H), 3.15 (m, 1 H), 7.06–7.74 (m, 5 H); **3m** δ 0.88 (s, 9 H), 1.50 (m, 2 H), 2.83 (t, *J* = 9 Hz), 7.10–7.58 (m, 5 H); **4f** δ 0.70–1.65 (m, 7 H), 2.06 (m, 2 H), 2.88 (bs, 1 H), 5.04 (m, 1 H), 5.61 (m, 2 H), 7.20–7.42 (m, 5 H); **4h** δ 0.70–1.65 (m) and 1.57 (s) [total 9 H], 2.00 (m, 2 H), 5.47 (d of t, *J* = 14 and 5 Hz), 5.68 (d, *J* = 14 Hz) [total 2 H], 7.16–7.60 (m, 5 H); **4i** δ 0.70–1.80 (m, 7 H), 2.38 (m, 2 H), 6.95 (m, 2 H), 7.32–8.10 (m, 5 H); **4j** δ 0.98 (d, *J* = 7 Hz, 6 H), 1.26 (s, 6 H), 1.91 (m, 1 H), 2.42 (bs, 1 H), 5.53 (m, 2 H).

(9) (a) For the α-deprotonation of vinyl phenyl selenides see: S. Raucher and G. A. Koolpe, *J. Org. Chem.*, in press. (b) Vinyl sulfides undergo α-deprotonation with *s*-BuLi in THF–HMPA: K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 2694 (1973).

(10) (a) H. Gilman and F. J. Webb, *J. Am. Chem. Soc.*, **71**, 4062 (1949); (b) ref 4.

(11) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Oxford, 1974, chapter 7, and references cited therein.

Stanley Raucher,* Gary A. Koolpe

Department of Chemistry, University of Washington Seattle, Washington 98195

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Template Synthesis of Macromolecules. Selective Functionalization of an Organic Polymer

Summary: Hydrolysis of a copolymer of divinylbenzene and bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate liberates polymer-bound benzyl alcohol groups; rebinding studies and chemical transformations of the benzyl alcohol groups suggest that the functional groups are capable of retaining some stereochemical information originally present in the cyclobutane diester.

Sir: The ability to selectively introduce organic functionality in fixed geometrical relationships has remained a longstanding challenge to chemists. A variety of ingenious approaches have been employed to accomplish this goal.[1] A technique recently developed by Wulff and co-workers[2] strikes us as having the

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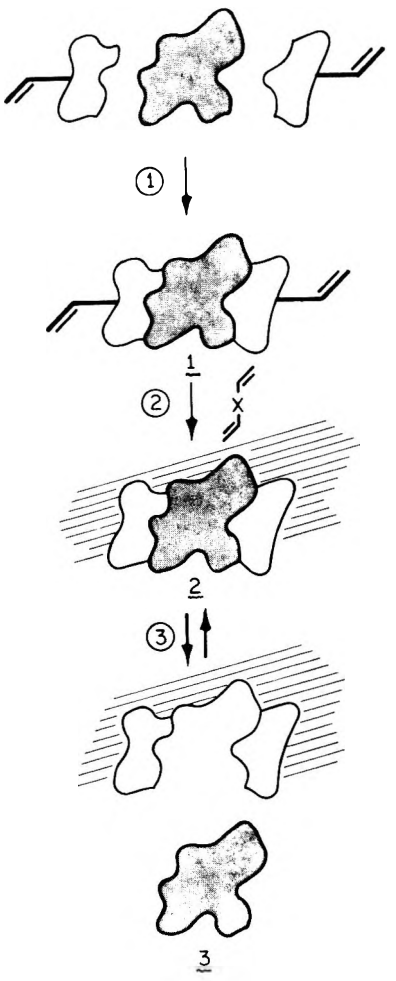
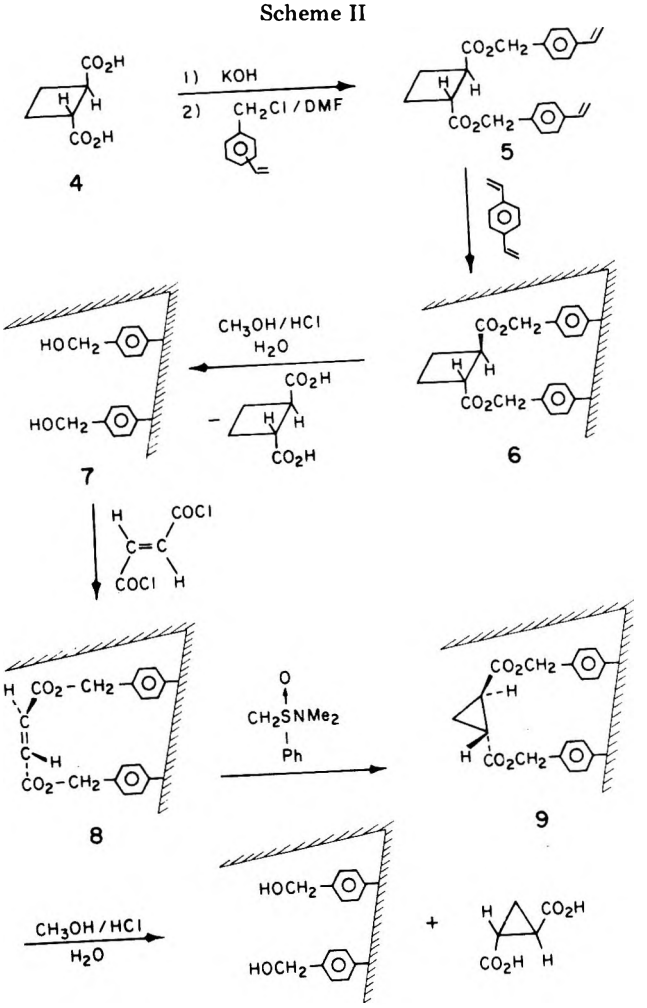
Scheme I



Scheme II



potential to be one of the more general methods for the controlled introduction of multiple organic functionality in organic polymers. The technique, which we term the template synthesis method, is illustrated in Scheme I. A template assembly (1), synthesized from three difunctional subunits (step 1), is copolymerized with a large excess of cross-linking monomer (step 2). Polymerization results in the formation of a three-dimensional polymeric matrix interspaced by an occasional template assembly (2). Hydrolysis of accessible template assemblies (step 3) liberates the incipient functionality to produce regions of multiple functionality on the macromolecule (3). Provided that the hydrolysis (step 3) does not introduce gross structural deformations in the macromolecule, the hydrolyzed polymer can exhibit a "memory" for the original template molecule (T).

We wish to describe a sequence of experiments that employs the template synthesis method to introduce masked organic functionality in a macromolecular solid. Conditions have been developed that permit the liberation of these functional groups and in subsequent reactions this functionality is utilized to covalently bind an organic substrate molecule to the macromolecular solid. Further chemical transformations on the covalently bound substrate molecule provide an opportunity to probe the local environment of the functionality. The overall series of reactions is illustrated in Scheme II.

Bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate (**5**), prepared from the dipotassium salt of *trans*-1,2-cyclobutanedicarboxylic acid and vinylbenzyl chloride (mixture of meta and para isomers), is copolymerized under free-radical conditions with divinylbenzene (technical, 55% para, meta isomers) in acetonitrile (0.05:0.49:0.46, w/w/w)[3]. The resulting solid (**6**) is crushed and sized (75–250 μm), extracted with CH_3OH (to remove unreacted monomer), and dried in vacuo. The IR of this polymer exhibits the expected superimposition of the spectra of the diester $\bar{\nu}_{C=O}$ 1736 cm^{-1}) over that of poly(divinylbenzene). A variety of conditions were examined to effect the hydrolysis of dicarboxylic acid (**4**) from the polymer; optimum yields were obtained by refluxing in methanol–HCl (1:1) under a nitrogen atmosphere. After 8 h approximately 30% of the total template assemblies had undergone hydrolysis. Prolonged exposure to the reaction conditions did not appreciably increase this yield. The hydrolyzed polymer (**7**) contains 0.064 mequiv of sites/g; each site contains two polymer-bound benzyl alcohol groups. The presence of these functional groups is verified by treatment of **7** with trifluoroacetic anhydride; the resulting polymer exhibits a new IR absorption at 1788 cm^{-1} (trifluoromethylacetate group); control reactions with unhydrolyzed polymer did not produce this new absorption.[4]

Reaction of hydrolyzed polymer with difunctional reagents of similar geometry to the original template molecule can lead to two-point rebinding. Treatment of **7** with fumaryl chloride results in covalent attachment of the fumarate group to the polymer. The rebinding occurs by formation of new ester linkages between the polymer and the fumarate group. This rebinding can be monitored by examining the change in intensity in the carbonyl region of the polymer before and after exposure to fumaryl chloride. The individual carbonyl absorptions of polymer-bound fumaric and cyclobutanedicarboxylic acid esters are not resolved; nevertheless, upon treatment of **7** with fumaryl chloride the expected increase in carbonyl intensity is observed. That fumaric acid is *covalently bound* to the polymer is established by the finding that the acid can only be liberated by a second hydrolysis

(CH_3OH–HCl); the quantity of fumaric acid recovered indicates that 80% of the available sites in **7** have covalently bound the new template molecule.[5]

The sequence of transformations serves to illustrate several important points. The fractional recovery of template molecules (30%), even after prolonged hydrolysis, establishes that a significant number of template assemblies occupy inaccessible regions of the polymer. Unlike Merrifield polymers which, at least in their swollen state, undergo reaction throughout the polymer network,[6] hydrolysis occurs largely in the region that may be loosely defined as the surface of a solid polymer particle. This finding is undoubtedly a consequence of the higher degree of cross-linking in poly(divinylbenzene). Second, the uptake of fumaryl chloride is approximately equal to the theoretical number of *difunctional* sites and suggests that, at least in a significant number of cases, rebinding can occur in a manner similar to that which was found in the original polymer (two site).

The region in which the hydrolysis and rebinding occur is rather poorly defined. The area is at the interface between solvent phase and the highly cross-linked "nucleus" of the solid poly(divinylbenzene). Located in this region are pendant polymer and vinyl groups, template assemblies, rebinding sites, and more lightly cross-linked segments of the polymer.[7] If the hydrolyzed polymer is to exhibit a "memory" for the template molecule (T), the template assembly must "imprint" stereochemical information at the polymerization stage. Our first test for this "memory" is illustrated in Scheme II. The sequence involves at the penultimate step a methylene transfer to a prochiral alkene (fumaric acid) covalently bound to the macromolecule. When racemic template (**5**) is used for the polymer synthesis, racemic cyclopropanedicarboxylic acid would be the product from the methylenation step; however, when a chiral template is used for the polymer synthesis the "memory" can take the form of local asymmetry in the region of the functional groups; this asymmetry may induce formation of a chiral product in the methylenation step. The polymer-bound fumaric ester (**8**) was reacted with methylene transfer reagents to form 1,2-cyclopropanedicarboxylic acid ester (**9**). This transformation was successfully executed using (dimethylamino)phenyloxosulfonium methylide as the nucleophilic methylene transfer reagent.[8] Synthetic cyclopropanedicarboxylic acid is liberated by hydrolysis in 34% overall yield based upon available sites of the hydrolyzed polymer (**7**).

The preceding sequence was repeated using (−)-*trans*-1,2-cyclobutanedicarboxylic acid ($[\alpha]^{25}_D$ −158.7° (CH_3OH)) as the template.[9] After hydrolysis, rebinding of fumaryl chloride, cyclopropanation, and hydrolysis, *trans*-1,2-cyclopropanedicarboxylic acid was recovered as the dimethyl ester by preparative VPC. The diester exhibited a specific rotation, $[\alpha]^{21}_D$ 0.1°, which corresponds to a 0.05% enantiomeric excess.[10] The slight enantiomeric excess arises in the methylene transfer step and is the result of a chiral environment (of some unspecified nature) surrounding the reaction zone. Considering the severity of the hydrolysis conditions, the observed asymmetric induction is encouraging. Work is continuing in an effort to understand those factors which will influence the magnitude of asymmetric induction and to define the degree of stereochemical control available by the template synthesis approach.

Acknowledgment. We thank the donors of the Research Corporation and the National Institutes of Health for generous support of this work.

References and Notes

(1) See references cited in review articles such as: (a) R. Breslow, *Chem. Soc. Rev.*, **1**, 553 (1972); (b) D. W. Griffiths and M. L. Bender, *Adv. Catal.*, **23**, 209 (1973); V. A. Kabanov in "Advances in Polymer Science", Z. A. Rogovin, Ed., Wiley, New York, N.Y., 1974, p 263; (d) T. Kunitake and Y. Okahata, *Fortschr. Hochpolym.-Forsch.*, **20**, 159 (1976); (e) T. Shimidzu, *ibid.*, **23**, 56 (1977); (f) M. L. Bender and M. Komiyama *Bioorg. Chem.*, **1**, 19 (1977); (g) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., (1975); (h) E. Tsuchida and H. Nishide, *Fortschr. Hochpolym.-Forsch.*, **24**, 1 (1977).

(2) (a) G. Wulff, A. Sarhan, and K. Zabrocki, *Tetrahedron Lett.*, 4329 (1973); (b) G. Wulff, W. Vesper, R. Grobe-Einsler, and A. Sarhan, *Makromol. Chem.*, **178**, 2799, 2817 (1977).

(3) The polymerization conditions result in the formation of an insoluble, highly porous (macroreticular) polymer with an average surface area of 200 m^2/g.

(4) Development of analytical procedures and detection of nonspecific reactions with the polymer was facilitated by a parallel series of reactions performed with a "blank" polymer; that is, one prepared in an identical manner only without template assemblies.

(5) In our idealized representation (Scheme II) we have assumed that two-point rebinding reconnects two functional groups that were previously connected by a template assembly (intersite) as opposed to two "unrelated" functional groups (intrasite). At present we have no evidence to confirm this assumption. Additional studies are underway to distinguish between these possibilities.

(6) (a) G. R. Stark, "Biochemical Aspects of Reactions on Solid Supports", Academic Press, New York, N.Y., 1971; (b) W. Heitz, *Fortschr. Hochpolym.-Forsch.*, **23**, 1 (1977).

(7) Characterization of the surface of solid organic polymers continues to be a very active area of investigation. For recent studies of the generation, characterization, and functionalization of the surface of a solid polymer, see J. R. Rasmussen, E. R. Stedronsky, and G. M. Whitesides, *J. Am. Chem. Soc.*, **99**, 4736 (1977), and references cited therein.

(8) C. R. Johnson, E. R. Janiga, and M. Haake, *J. Am. Chem. Soc.*, **90**, 3890 (1968).

(9) This material is assumed to be optically pure; Y. Inouye, S. Sawada, M. Ohno, and H. M. Walborsky, *Tetrahedron*, **23**, 3237 (1967).

(10) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).

Kenneth J. Shea,* Evan A. Thompson
Department of Chemistry
University of California, Irvine
Irvine, California 92717
Received June 27, 1978

Lithiation of Ethyl 2,4,6-Triisopropylbenzoate Adjacent to Oxygen: The α-Lithioalkyl Alcohol Synthon

Summary: Metalation of ethyl 2,4,6-triisopropylbenzoate (**1**) with *sec*-butyllithium/tetramethylethylenediamine in tetrahydrofuran provides α-lithioethyl 2,4,6-triisopropylbenzoate (**2**). Reaction of **2** with carbonyl and halide electrophiles provides the expected products **3a–g**. Reduction of typical products with lithium aluminum hydride gives the corresponding alcohols. Overall this sequence provides the α-lithioalkyl alcohol synthon from a primary alcohol.

Sir: The formation and use of α-heteroatom carbanions has been widely explored and exploited in recent years. In conjunction with our studies of prospectively dipole-stabilized carbanions, we have reported metalations adjacent to the heteroatom of methyl 2,4,6-triisopropylbenzoate, methyl and ethyl 2,4,6-trialkylthiobenzoates, and methyl- and ethyl-2,4,6-triisopropylbenzamides.[1,2] The metalations of the ester and thioesters have been shown to be key steps in providing the α-lithiomethyl alcohol and the α-lithiomethyl and α-lithioethyl thiol synthons, respectively. More recently Seebach et al. have observed similar metalations of 2,4,6-trialkylbenzoate derivatives and also have shown that dimethyltriphenylacetamide provides the (α-lithiomethyl)alkylamine synthon.[3] We now wish to report that ethyl 2,4,6-triisopropylbenzoate can be metalated adjacent to oxygen and to suggest that this approach will provide α-lithioalkyl alcohol synthons for the corresponding primary alcohols.

Reaction of ethyl 2,4,6-triisopropylbenzoate (**1**) with 2–4 equiv of *sec*-butyllithium/tetramethylethylenediamine (*s*-BuLi/TMEDA) in tetrahydrofuran (THF) at −78 °C for 3–6

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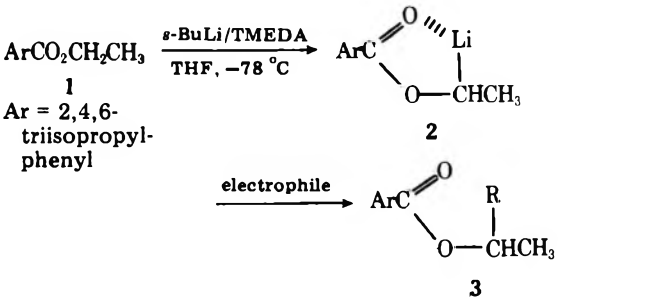
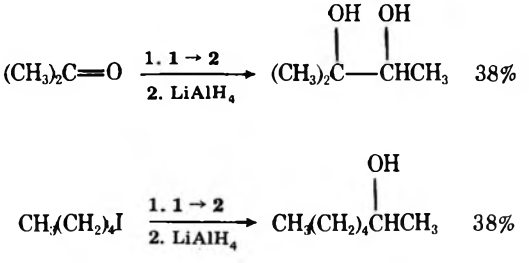
Scheme I



a, R = $HOC(CH_3)_2$ 41% (64%)
b, R = $HOC(CH_2)_5$ 31% (50%)
c, R = $CH_2CH{=}CH_2$ 42% (79%)
d, R = $Si(CH_3)_3$ 64% (94%)
e, R = $Sn(C_4H_9)_3$ 53% (85%)
f, R = $HOC(CD_3)_2$
g, R = D

Scheme II



h gives **2**, which can be trapped by addition of acetone, cyclohexanone, allyl bromide, trimethylsilyl chloride, and tri-*n*-butyltin chloride to give the expected products, **3a–e**, in the purified (and crude) yields indicated in Scheme I.[5] When hexadeuterioacetone is used as the electrophile and the composition of the products determined by NMR, the product **3f** is obtained in 67% yield, while the ethyl ester is observed to be 58% deuterated material, **3g**. This result, as well as the 85% crude yield of **3e**, suggests that metalation is satisfactorily complete under these conditions and that the relatively low yields obtained with the ketones are due to competing enolizations.

On a preparative scale the metalation can be a key step in the preparation of the α-lithioethyl alcohol synthon. Thus formation of **2** from **1** on a several gram scale, followed by addition of hexamethylphosphoric triamide (HMPA) just prior to addition of the electrophile followed by reduction with lithium aluminum hydride in THF or dimethoxyethane, yields the substituted alcohols as shown in Scheme II. The isolated yields are based on **1**.

It is reasonable that corresponding α-lithio derivatives of other primary alcohols will be available by metalation of the esters of 2,4,6-trisubstituted benzoates or closely related compounds.[6] For some situations the presence of excess *s*-BuLi/TMEDA or unmetalated ester may be inconvenient. In that case the tin compound **3d** can be reacted with methyllithium to provide **2** in high yields; subsequent additions of deuteriomethanol, methyl iodide, and methyl benzoate give the expected products in 80–100% crude yield. An imaginative alternative route to α-lithioalkyl alcohol synthons by stannylation of the corresponding aldehydes has recently been reported by Still.[7]

Activation by the benzoate carbonyl has now been shown to facilitate direct metalative preparation of primary and secondary organolithiums adjacent to oxygen, sulfur, and nitrogen.[1-3] While such organometallics can be considered dipole-stabilized carbanions, further information on that point, as well as development of the synthetic potential of these species, is being studied.

Procedure. To a solution of 1:1 *s*-BuLi/TMEDA (25.3 mmol) in THF stirring at −78 °C under nitrogen was added a solution of 3.98 g (14.4 mmol) of ethyl 2,4,6-triisopropylbenzoate (**1**) in THF. After the reaction mixture was allowed to stir at −78 °C for 6 h, 4 mL of HMPA was added, followed by 20 mL of 1-iodopentane. The reaction mixture was allowed to stir at −78 °C for 20 min, and then allowed to warm to room temperature. Ether was added and the organic phase was washed with aqueous saturated NH_4Cl, concentrated, dissolved in ether, and washed with aqueous 10% HCl and 10% NaOH. The organic layer was dried ($CaSO_4$) and concentrated under vacuum to give 4.8 g of a clear, orange oil. This material and 5.0 g (0.13 mol) of $LiAlH_4$ in 75 mL of dimethoxyethane (DME) were heated at reflux for 2.5 h. The heterogeneous reaction mixture was cooled to room temperature and treated with a minimal amount of H_2O. The insoluble salts were removed by filtration and washed with ether. The filtrates were combined, dried ($MgSO_4$), and concentrated under vacuum to give a clear, yellow oil which was distilled at atmospheric pressure to afford 0.64 g (5.51 mmol, 38%) of 2-heptanol.

Acknowledgment. We are grateful to the National Institutes of Health—Institute of General Medicine for support of this work.

References and Notes

(1) (a) P. Beak and B. G. McKinnie, *J. Am. Chem. Soc.*, **99**, 5213 (1977); (b) D. B. Reitz, P. Beak, R. F. Farney, and L. S. Helmick, *ibid.*, **100**, 5428 (1978); (c) P. Beak, B. G. McKinnie, and D. B. Reitz, *Tetrahedron Lett.*, 1839 (1977).
(2) P. Beak and D. B. Reitz, *Chem. Rev.*, **78**, 275 (1978).
(3) R. Schecker, D. Seebach, and W. Lubosch, *Helv. Chim. Acta*, **61**, 512 (1978).
(4) Prepared from the corresponding acid chloride and ethanol: R. C. Fuson and E. C. Horning, *J. Am. Chem. Soc.*, **62**, 2962 (1940). An alternative route from 2,4,6-triisopropylphenyllithium and diethyl carbonate is also useful.
(5) All new compounds were characterized by IR, NMR, and satisfactory combustion analysis except for **3b**, which was 0.5% low for hydrogen. Previously known compounds were identified by comparison of NMR and IR spectra with published data.
(6) For example, metalation of *n*-octyl 2,4,6-triisopropylbenzoate under similar conditions followed by separate reactions with deuteriomethanol, acetone, or allyl bromide gives the expected products in crude yields of 90, 45, and 95%, respectively.
(7) W. C. Still, *J. Am. Chem. Soc.*, **100**, 1481 (1978).

Peter Beak,* Maurice Baillargeon, Linda G. Carter
Roger Adams Laboratory, University of Illinois
Urbana, Illinois 61801
Received July 10, 1978

Photochemical Transformations of Chalcone Oxides

Summary: Close examination of the photobehavior of several chalcone oxides has demonstrated that aryl ring substituents control whether the C_α–O or C_α–C_β bond of the oxirane ring will be cleaved.

Sir: Photochemical rearrangements of α,β-epoxy ketones have received extensive study and have been the subject of several reviews.[1-4] These compounds generally display two types of photobehavior: (a) photoisomerization of arylcyclopentenone oxides to pyrylium oxides,[5,6] and (b) photoisomerization of α,β-epoxy ketones to β-diketones.[8-10] Although much data have been accumulated to show that C_α–O bond cleavage is the predominant mode of photofragmentation in α,β-epoxy ketones, Muzart and Pète[11] have demonstrated that cleavage of the oxirane C_α–C_β bond also can occur in certain optically active derivatives. Interestingly, epoxynaphthoquinones have been shown to undergo two types of photocycloaddition reactions with olefins arising either from n,π* excited-state addition of the carbonyl group to form oxetanes, or from C–C bond fission of the oxirane ring followed by 1,3-dipolar addi-

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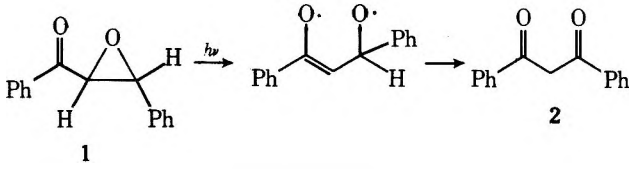
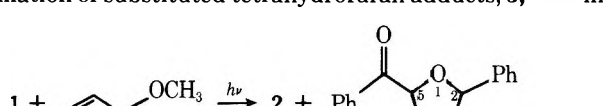
tion to the olefin forming substituted tetrahydrofurans.[12] Because of our interest in the photochemical generation of carbonyl ylides from aryloxiranes[13,14] we have reexamined the photobehavior of chalcone oxides[8,15] to see if carbonyl ylides might also be intermediates in rearrangements of these compounds.

Irradiation[16] of *trans*-chalcone oxide (**1**) in acetonitrile with 313-nm radiation led to the formation of dibenzoylmethane (**2**) as the major product (Φ = 0.019) accompanied by an unidentified isomer[17] (Φ = 0.009). The formation of **2** from **1** was first described by Bodforss in 1918[8] and is assumed to arise from cleavage of the C_α–O bond of the oxirane followed by a 1,2 shift of the β-hydrogen to the α position.[10]

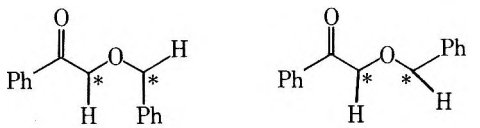


1 **2**

However, irradiation of **1** in the presence of a sixfold excess of methyl acrylate, an efficient dipolarophile,[13,18,19] led to the formation of substituted tetrahydrofuran adducts, **3**,[17b,20] in addition to dibenzoylmethane. The configuration of the THF adducts **3** suggests that at least 83% of the intermediate carbonyl ylide precursors were formed by a disrotatory cleavage of the oxirane C_α–C_β bond,[21] producing the trans ylide A, which was subsequently trapped by methyl acrylate. These



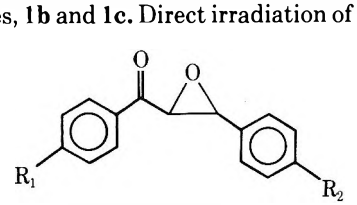
3



A B

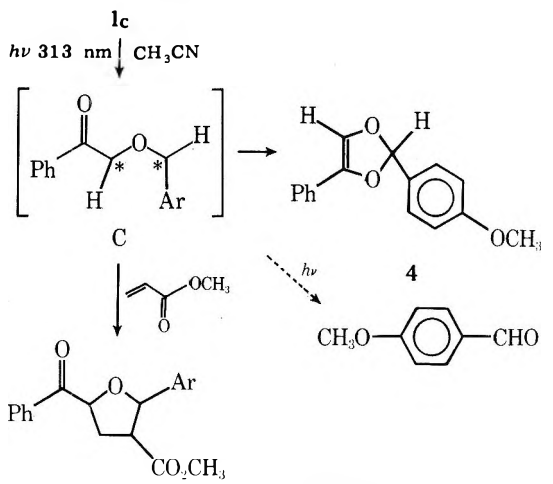
results are consonant with Woodward and Hoffmann's predictions of disrotatory electrocyclic ring opening in four-electron systems,[21] but the formation of adducts derived from the cis ylide B is an anomaly, similar to that previously observed by us[13] and by Huisgen.[14b] In attempting to determine the nature of the excited states responsible for these rearrangements, we have observed that the reaction is not quenched by 0.3 M piperylene, but is apparently sensitized by acetophenone (E_t = 74 kcal/mol) and by xanthone (E_t = 74 kcal/mol). Under conditions where both sensitizers absorbed >95% of the light, the same distribution of products was obtained. These data suggest that both C_α–O and C_α–C_β bond cleavages occur from a triplet excited state of **1** which is so short-lived that it cannot be quenched by energy transfer to piperylene.

Since substituents on the oxirane ring should affect the stability of the photogenerated carbonyl ylides,[12,14b,c] we have examined the photochemistry of the methoxy-substituted chalcone oxides, **1b** and **1c**. Direct irradiation of a 0.03 M solution of **1b** in acetonitrile led cleanly to the formation of a single product (Φ = 0.024), isolated and identified as 1-(4-methoxyphenyl)-3-phenyl-1,3-propanedione (**2b**).[22] Irradiation of **1b** with a sixfold excess of methyl acrylate decreased the efficiency of **2b** formation (Φ = 0.011), but did not lead to detectable amounts of adducts, similar to those observed from **1a.** The quantitative mass balance obtained in both of the above experiments suggests that **1b** undergoes photoreaction exclusively by C_α–O bond cleavage.



1a, $R_1 = R_2 = H$
b, $R_1 = OCH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = OCH_3$

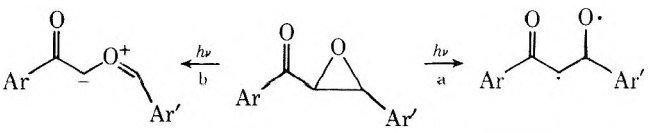
In contrast to the clean C–O bond fragmentation obtained from **1b,** direct irradiation of 4-methoxychalcone oxide (**1c**) led to rapid formation (Φ = 0.27) of 2-(4-methoxyphenyl)-4-phenyl-1,3-dioxole[24] (**4**) along with a small amount (Φ = 0.03) of anisaldehyde. The formation of dioxole **4** can be rationalized by C_α–C_β bond fission to form the stabilized ylide C, which then predominantly undergoes ring closure to **4** or can suffer further photodegradation to form anisaldehyde.[26]



Ar = 4-methoxyphenyl-

We have been unable to detect any 1,3-diketone **2b,** which would have arisen by C_α–O bond cleavage. Irradiation of **1c** in acetonitrile containing a 15 molar excess of methyl acrylate gave a reduced yield of **4** and gave rise to the formation of THF adducts (Φ = 0.05),[27] **5.** Isolation and stereochemical analysis of **5** indicates that they primarily (>90%) derive from disrotatory C–C oxirane ring cleavage of **1c** (forming carbonyl ylide C), followed by 1,3-cycloaddition to methyl acrylate. Attempts to trap ylide C with other olefins, such as norbornene, have been unsuccessful. The apparent necessity of electron-deficient olefins to trap carbonyl ylides has been noted previously[5-7,13,14b] and is consistent with Houk's suggestion that alkyl and conjugated carbonyl ylides should undergo HOMO (dipole) controlled 1,3-dipolar cycloaddition reactions.[18,28]

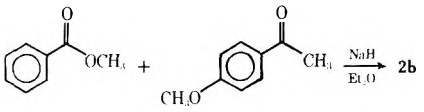
These preliminary results illustrate the importance which substituents can play in controlling whether C_α–O or C_α–C_β bond cleavage occurs from photoexcited chalcone oxides, and suggests a new synthetic route for preparing unstable substituted dioxoles. Further work is now underway to determine the photochemical consequences of other substituents and of starting material geometry in related α,β-epoxy ketones to provide a clearer and unified mechanistic understanding of these reactions.



References and Notes

(1) N. R. Bertoniere and G. W. Griffin, "Organic Photochemistry", Vol. III, O. L. Chapman, Ed., Marcel Dekker, New York, N.Y., 1973, Chapter 2.
(2) G. W. Griffin and A. Padwa, "Photochemistry of Heterocyclic Compounds", O. Buchardt, Ed., Wiley-Interscience, New York, N.Y., 1976, Chapter 2.

(3) A. Padwa, ref 1, Vol. 1, 1967, p 91.
(4) A. Padwa, *Acc. Chem. Res.*, **4**, 48 (1971).
(5) E. F. Ullman, *J. Am. Chem. Soc.*, **85**, 3529 (1963).
(6) E. F. Ullman and J. E. Milks, *J. Am. Chem. Soc.*, **86**, 3529 (1964).
(7) H. E. Zimmerman and R. D. Simkin, *Tetrahedron Lett.*, 1847 (1964).
(8) S. Bodforss, *Ber. Dtsch. Chem. Ges.*, **51**, 214 (1918).
(9) C. K. Johnson, B. Dominy, and W. Reusch, *J. Am. Chem. Soc.*, **85**, 3894 (1963).
(10) O. Jeger, K. Schaffner, and H. Wehrli, *Pure Appl. Chem.*, **9**, 555 (1964).
(11) J. Muzart and J. P. Pète, *Tetrahedron Lett.*, 303, 307 (1977).
(12) S. Arakawa, *J. Org. Chem.*, **42**, 3800 (1977).
(13) G. A. Lee, *J. Org. Chem.* **41**, 2656 (1976).
(14) For examples of related work, see also (a) I. J. Lev, K. Ishikawa, N. S. Bhacca, and G. W. Griffin, *J. Org. Chem.*, **41**, 2654 (1976); (b) V. Markowski and R. Huisgen, *Tetrahedron Lett.*, 4643 (1976); (c) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **16**, 572 (1977), and references contained therein.
(15) Previous studies on the parent chalcone oxide had failed to find any evidence for the intermediacy of carbonyl ylides; (a) A. Padwa and W. Eisenhardt, *J. Am. Chem. Soc.*, **93**, 1400 (1971); (b) D. J. Dewar and R. G. Sutherland, *J. Chem. Soc., Perkin Trans. 2*, 1522 (1977).
(16) All irradiations carried out *on* $\sim 4 \times 10^{-2}$ M solutions of the respective chalcone oxides in various solvents contained in 15 × 150 mm Pyrex test tubes. Samples were deaerated at 0 °C with argon, capped with a rubber septum and irradiated on a merry-go-round apparatus with 8-3130 Å or 8-3660 Å low-pressure Hg vapor lamps in a Srinivasan–Griffin reactor.
(17) (a) Due to the relative instability of this unknown, we have as yet been unable to adequately characterize its structure. (b) Irradiation of **1** in the presence of methyl acrylate significantly reduced the yield of this unknown.
(18) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973).
(19) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963); *J. Org. Chem.*, **41**, 403 (1976).
(20) The structure and stereochemistry of the adducts (**3** and **5**) are based upon spectroscopic data (^{1}H NMR, IR, *m/e*) and upon base-catalyzed (NaOMe/MeOH) epimerization of the C_3 center to give the thermodynamically favored trans orientation to the C_2–C_3 substituents.
(21) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965); cf. ref 12 and 13b.
(22) Spectral characteristics (^{1}H NMR, IR, *m/e*) and melting point (129–130 °C) of isolated **2b** identical with an independently prepared sample. Lit.[23] mp 132 °C.



(23) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 59 (1954).
(24) The structure of **4** is based upon ^{1}H NMR, IR (no C=O, 1308, 1312, 1020, 1038, and 1096 cm^{-1}, attributed to cyclic acetal[25]), and *m/e* (254 parent, 105 base) analysis and upon quantitative chemical degradation to anisaldehyde and phenacyl acetate upon treatment with AcOH/Ac_2O/*p*-toluenesulfonic acid.
(25) A. Robert and B. Moisan, *J. Chem. Soc., Chem. Commun.*, 337 (1972), and references cited therein.
(26) G. W. Griffin, K. Ishikawa, and I. J. Lev, *J. Am. Chem. Soc.*, **98**, 5697 (1976).
(27) At higher concentrations of methyl acrylate (90 molar excess) the ratio of **5/4** = 60:40.
(28) A similar interpretation has been presented by R. Sustmann [*Tetrahedron Lett.*, 2717, 2721 (1971)] and by N. D. Epiotis [*J. Am. Chem. Soc.*, **94**, 1924, 1935, 1941, 1946 (1972)].

George A. Lee
Dow Chemical USA
Central Research—New England Laboratory
Wayland, Massachusetts 01778
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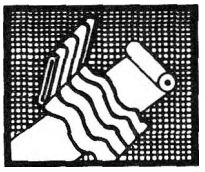

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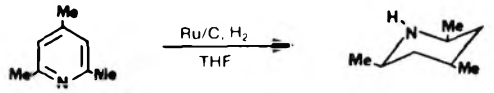
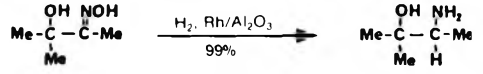
For the hydrogenation of alkylpyridines, **ruthenium on carbon** (or **rhodium on carbon**) is more selective than Raney nickel. For example, the following reaction proceeds at 150°C in a yield of 86%.[1]



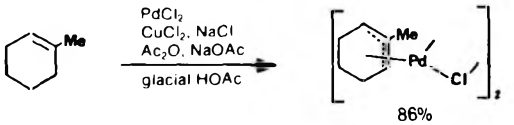
In fact, the most active catalyst known for the reduction of aromatic rings under mild conditions (minimal reduction of substituents) is supported **rhodium**.[2]

The versatility of **rhodium on alumina** is demonstrated by the high-yield reduction of 2-hydroxy oximes to α-hydroxy amines, such as that shown below.[3]

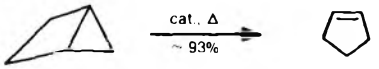


Similarly, zerovalent palladium, produced by the action of **sodium borohydride** on $PdCl_2$ in methanol,[4] can be used to hydrogenate selectively C=C, N=N, and N=O bonds without affecting C=O and C=N groups.

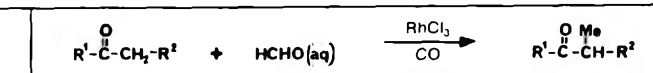
Recently, specifically controlled natural product syntheses[5] have been carried out using π-allyl palladium intermediates; the preparation of these intermediates can be characterized by the general method represented below:[6]



An interesting variety of precious metal salts is effective in isomerizations such as that shown below; these include $[Rh(CO)_2Cl]_2$,[7] $RhCl_3$, $IrCl_3$, $RuCl_3$, $(Ph_3P)_2RhCl$ and Na_2PtCl_6.[8]



In the above reaction, and in the following,[9] a complex metal-hydride intermediate is postulated.



Catalytic activity of a different sort has been exhibited by the less commonly used **rhodium(II) acetate** dimer in the addition of dimethyl diazomalonate to thiophene;[10] this type of rhodium catalyst, listed below, frequently seems to work when others such as Cu_2Cl_2, silver acetate, or $(Ph_3P)CuI$ fail.

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1) R. Schubart, H. Ziemann, and D. Wendisch, *Synthesis*, 220 (1973).
2) P.N. Rylander, "Catalytic Hydrogenation Over Platinum Metals," Academic Press, New York, N.Y., 1967; P.N. Rylander, "Organic Syntheses with Noble Metal Catalysts," Academic Press, New York, N.Y., 1973.
3) M.S. Newman and V. Lee, *J. Org. Chem.*, **40**, 381 (1975).
4) T.W. Russell and D.M. Duncan, *J. Org. Chem.*, **39**, 3050 (1974).
5) B.M. Trost and T.R. Verhoeven, *J. Am. Chem. Soc.*, **100**, 3435 (1978).
6) B.M. Trost and P.E. Strege, *Tetrahedron Lett.*, 2603 (1974).
7) P.G. Gassman, T.J. Atkins, and J.T. Lumb, *J. Am. Chem. Soc.*, **94**, 7757 (1972).
8) K.B. Wiberg and K.C. Bishop III, *Tetrahedron Lett.*, 2727 (1973).
9) Y. Watanabe, Y. Shimizu, K. Takatsuki, and Y. Takegami, *Chem. Lett.*, 215 (1978).
10) R.J. Gillespie, J. Murray-Rust, P. Murray-Rust, and A.E.A. Porter, *Chem. Commun.*, 83 (1978).

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