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NOTES

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One-Flask Phosphorylative Coupling of Two Alcohols by Means of Aryl Cyclic Enediol Phosphates. Phenoxide Ion Catalysis of Phosphorylations in Aprotic Solvents

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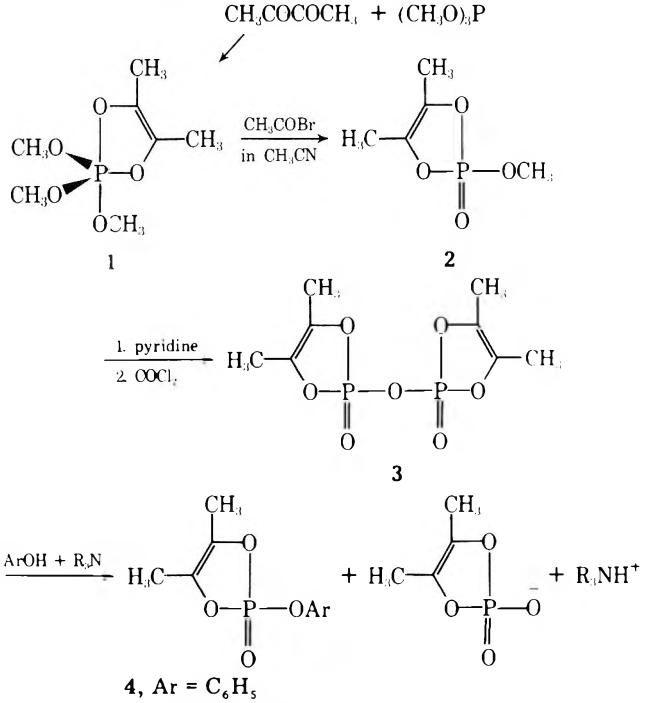
Received July 7, 1976

Aryl cyclic enediol phosphates, 2-*p*-nitrophenoxy- and 2-pentafluorophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide, are efficient reagents for the *one-flask* conversion of two different alcohols, R^1OH and R^2OH, into dialky(1-methylacetonyl) phosphates, $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$, which are readily hydrolyzed to unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$. The synthesis is made possible by the effective phenoxide ion catalysis of the phosphorylation of alcohols by alkyl cyclic enediol phosphates in aprotic solvents. Mechanisms which involve penta- and hexacoordinate phosphorus intermediates are suggested for the reactions. The phenoxide catalysis of the phosphorylations in aprotic solvents may have a bearing on enzymatic phosphorylations where the hydrophobic active site of the enzyme has tyrosine and lysine, arginine, or histidine residues.

This paper gives full details[2] of a new procedure to convert two different alcohols into a dialkyl(1-methylacetonyl) phosphate, $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$, without isolation of intermediates ("one-flask" reaction), using as reagent an aryl cyclic enediol phosphate, 2-*p*-nitrophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide (**6**), or its pentafluorophenyl analogue (**7**). The 1-methylacetonyl group can be easily removed from the triesters, and the procedure constitutes a two-stage synthesis of unsymmetrical phosphodiesters, $(R^1O)(R^2O)P(O)OH$, from the alcohols. The X=P(O)Ar[3] reagents, **6** and **7**, are made from the phenol and di(1,2-dimethylethenylene) pyrophosphate[4] (**3**), which is readily available from biacetyl and trimethyl phosphite via the oxyphosphorane[5] (**1**) and 2-methoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide (**2**).



4, Ar = C_6H_5
5, Ar = *p*-FC_6H_4
6, Ar = *p*-$NO_2C_6H_4$
7, Ar = C_6F_5

A second "one-flask" synthesis of dialkyl(1-methylacetonyl) phosphates from two alcohols utilizes the pyrophosphate **3** as reagent.[6] These alternate procedures are desirable in view of the complexity of many biological phosphodiesters, e.g., the phospholipids of biological membranes and the polynucleotides. These substances, $(R^XO)(R^YO)P(O)OH$, are derived from two polyfunctional alcohol moieties, R^XOH and R^YOH, and can, in principle, be synthesized following the sequence $R^1OH = R^XOH$, $R^2OH = R^YOH$, or the sequence $R^1OH = R^YOH$, $R^2OH = R^XOH$, where R^1 and R^2 refer to the order in which the alcohols are phosphorylated. A choice of reagents widens the scope of these syntheses by making it possible to utilize different protective groups on the polyfunctional alcohols, and different phosphorylation sequences.[7]

Results

Preparation of 2-Aryloxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxides (4–7). Phenols react with the pyrophosphate **3** by displacement at phosphorus with ring retention.[4] It has now been found that tertiary amines, which are used to neutralize the acidic by-product of this reaction, X=P(O)OH, exert also a catalytic effect. The approximate half-time for the reaction of equimolar amounts of C_6H_5OH with **3**, in 0.2 M $CDCl_3$ (25°C), is reduced from 17 min to about 0.5 min upon addition of 1 molar equiv of pyridine; the reac-

Table I. Elemental Analyses and Spectral Data[a] of Aryl(1,2-dimethylethenylene) Phosphates, Dialkyl(1-methylacetonyl) Phosphates, and Dialkyl Phosphates

Compd	Substituents	Mp or bp, °C (mm)	Molecular formula	Calcd, %			Found, %			^{1}H NMR, τ, ppm (J, Hz)
	Ar			C	H	P	C	H	P	CH_3C
			X=P(O)OAr[b]							
4	C_6H_5	100 (0.1)[c]	[d]							8.20
5	p-FC_6H_4	105 (0.15)	$C_{10}H_{10}O_4PF$	49.2	4.1	12.7	49.4	4.3	12.5[e]	8.10
6	p-$NO_2C_6H_4$	102–104[f]	[d]							8.10 (0.6)
7	C_6F_5	54–56[g]	$C_{10}H_6O_4PF_5$	38.0	1.9	9.8	37.8	2.0	9.6[h]	7.98
	R^1; R^2		$(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$[i]							CH_3CO; CH_3CH[j]
15	$(CH_3)_3CCH_2$; $(CH_3)_2CHCH_2$	90 (0.1)	$C_{13}H_{27}O_5P$	53.1	9.3	10.5	53.2	9.4	10.5	7.75; 8.60 (7.0)
10	c-C_5H_9; CH_2=$C(CH_3)CH_2CH_2$	110 (0.1)	$C_{14}H_{25}O_5P$	55.2	8.3	10.2	55.1	8.3	10.1	7.75; 8.55 (7.0)
16	c-C_5H_9; $BrCH_2CH_2$	105 (0.1)	$C_{11}H_{20}O_5PBr$	38.5	5.9	9.0	38.7	5.9	9.0[k]	7.76; 8.53 (6.5)
13	c-C_6H_{11}; CH_3CH_2	95 (0.1)	$C_{12}H_{23}O_5P$	51.8	8.3	11.1	52.0	8.3	11.1	7.71; 8.53 (6.8)
11	$(CH_3CH_2)_2CH$; $(CH_3)_3CCH_2$	95 (0.15)	$C_{14}H_{29}O_5P$	54.5	9.5	10.1	54.3	9.6	9.9	7.74; 8.52 (6.9)
12	$(CH_3CH_2)_2CH$; $(CH_3CH_2)_2CH$	95 (0.15)	$C_{14}H_{29}O_5P$	54.5	9.5	10.1	54.3	9.3	10.0	7.75; 8.54 (6.9)
14	$[(CH_3)_2CH]_2CH$; $(CH_3)_2CHCH_2$	100 (0.15)	$C_{15}H_{31}O_5P$	55.9	9.7	9.6	55.9	9.8	9.6	7.65; 8.46 (7.0)
18	c-C_5H_9; C_6H_5		$C_{15}H_{21}O_5P$	57.7	6.8	9.9	57.7	6.9	10.1	7.78,[l] 8.47 (7.0) 7.82; 8.53 (7.0)
19	$[(CH_3)_2CH]_2CH$; C_6H_5		$C_{17}H_{27}O_5P$	58.2	8.2	9.4	58.3	8.1	9.2	7.78,[l] 8.52 (6.8) 7.90; 8.64 (6.8)
	R^1; R^2		$(R^1O)(R^2O)P(O)(OM)$[m]							Main signals of R^1 and R^2
20a	$(CH_3)_3CCH_2$; $(CH_3)_2CHCH_2$	186–188[n]	$C_{21}H_{44}O_4PN$	62.2	10.9	7.6	62.0	10.9	7.7	6.50; 7.07; 8.35; 9.06; 9.13 (7.0)
21a	c-C_5H_9; CH_2=$C(CH_3)CH_2CH_2$	158–159[o]	$C_{22}H_{42}O_4PN$	63.6	10.2	7.5	63.4	10.2	7.6	5.30; 6.10 (7.0) 7.10; 7.70 (7.0); 8.28
22a	c-C_5H_9; $BrCH_2CH_2$	111–112[p]	$C_{13}H_{27}O_4PNBr$	41.9	7.3		43.2	7.6		5.37; 5.90; 6.50 (6.0); 8.35
23a	c-C_6H_{11}; CH_3CH_2	135–137[n]	$C_{20}H_{40}O_4PN$	61.7	10.4	8.0	61.7	10.4	7.8	5.95; 6.13 (7.2); 8.76 (7.2)
24a	$(CH_3CH_2)_2CH$; $(CH_3)_3CCH_2$	181–183[n]	$C_{22}H_{46}O_4PN$	63.0	11.1	7.4	62.9	11.1	7.2	5.95; 6.50 (4.8); 8.39 (7.3); 9.06; 9.11 (7.3)
25a	$(CH_3CH_2)_2CH$; $(CH_3CH_2)_2CH$	149–150[n]	$C_{22}H_{46}O_4PN$	63.0	11.1	7.4	62.9	11.0	7.4	5.94; 8.36 (7.3); 9.10 (7.3)
26a	$[(CH_3)_2CH]_2CH$; $(CH_3)_2CHCH_2$	155–156[n]	$C_{23}H_{48}O_4PN$	63.7	11.2	7.1	63.6	11.1	7.0	6.38 (6.3); 9.02 (6.8); 9.11 (6.3)

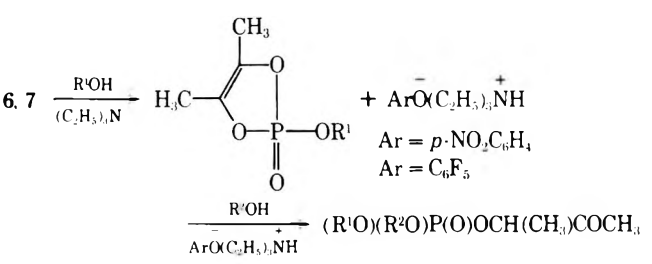
[a] NMR spectra in $CDCl_3$; ^{1}H shifts in parts per million vs. Me_4Si (τ 10), ^{31}P shifts in parts per million vs. H_3PO_4 = O; coupling constants, J, in hertz. ^{1}H integrations agree with the proposed structures. [b] δ ^{31}P—6.2 (C_6H_5); —6.3 (p-FC_6H_4); —6.4 (p-$NO_2C_6H_4$); —8.0 ppm (C_6F_5). [c] Bath temperature in molecular distillation, in all cases. [d] Reference 4. [e] F: calcd, 7.8; found, 7.5. [f] From dichloromethane-hexane. [g] After molecular distillation at 75 °C (0.1 mm). [h] F: calcd, 30.0; found, 30.0. [i] δ ^{31}P of acyclic triesters, and of diesters and their salts, fall within 0 and +3.5 ppm. [j] Multiplet at τ 5.2–5.4 ppm due to methine ^{1}H of 1-methylacetonyl, and corresponding signals for R^1 and R^2 groups also present. [k] Br: calcd, 23.3; found, 23.0. [l] Two diastereomers are detectable. [m] M = $(C_6H_{11})_2NH_2^+$ in compounds 20a, 21a, 23a–26a; M = $C_6H_{11}NH_3^+$ in 22a. [n] From ethyl acetate. [o] The salt crystallized from ethyl acetate upon addition of the amine to the acid; recrystallized from cyclohexane. [p] Prepared in ether–hexane; recrystallized from cyclohexane.

tion is too fast to measure in the presence of triethylamine.

Two of the aryl cyclic triesters (**4**, **6**) have been described,[4] while compounds **5** and **7** are new; all have ^{31}P NMR shifts in the range −5 to −8 ppm. A small ($J \simeq 0.6$ Hz) long-range coupling, **H**–C–C–O–**P**, can be detected in the signal from the methyl groups.

One-Flask Phosphorylative Coupling of Two Alcohols. The p-nitrophenyl and the pentafluorophenyl cyclic phosphates, **6** and **7**, are excellent reagents for the conversion of two alcohols into a dialkyl(1-methylacetonyl) phosphate. The synthesis involves two steps, which are carried out in one laboratory operation according to the directions given in the Experimental Section.

The first step involves the reaction of the aryl cyclic triester, **6** or **7**, with alcohol R^1OH, and is carried out in the presence



of triethylamine. The reaction is autocatalytic, since the phenoxide ion that is generated as a by-product has a pronounced accelerating effect on the phosphorylation of the alcohol by the reagent, **6** or **7**, as shown below. The product of this step is an alkyl cyclic triester, X=P(O)OR^1, which results from a displacement at phosphorus with ring retention.

Table II. One-Flask Synthesis of Dialkyl(1-methylacetonyl) Phosphates from Alcohols R^1OH and R^2OH by Aryl(1,2-dimethylethenylene) Phosphates

Compd	R^1	R^2	Yield, %[a]
	$X=P(O)OC_6H_4NO_2$-*p*		
8	c-C_5H_9	$(CH_3)_2CHCH_2$	93[b]
9	c-C_5H_9	$C_6H_5CH_2$	91[b]
10	c-C_5H_9	$CH_2=C(CH_3)$-CH_2CH_2	93
11	$(CH_3CH_2)_2CH$	$(CH_3)_3CCH_2$	88[c]
12	$(CH_3CH_2)_2CH$	$(CH_3CH_2)_2CH$	90
13	c-C_6H_{11}	CH_3CH_2	90
14	$[(CH_3)_2CH]_2CH$	$(CH_3)_2CHCH_2$	90
	$X=P(O)OC_6F_5$		
15	$(CH_3)_3CCH_2$	$(CH_3)_2CHCH_2$	98
8	c-C_5H_9	$(CH_3)_2CHCH_2$	90[b]
16	c-C_5H_9	$BrCH_2CH_2$	97
17	(±)-3-*p*-Menthanyl	$C_6H_5CH_2$	95[b]

[a] Crude triester based on R^1OH; purity >98% according to ^1H NMR and the yield of diester after hydrolysis. [b] Triester first synthesized by another procedure; cf. ref 4, 6. [c] Yield after molecular distillation.

The second step is the reaction of the alkyl cyclic triester with alcohol R^2OH, and is also effectively catalyzed by phenoxide ion.[8] The product is the dialkyl(1-methylacetonyl) phosphate, which results from an attack at phosphorus with ring opening. Several examples of the synthesis are listed in Table II; the analytical data for the new compounds are summarized in Table I. The "first alcohols", R^1OH, in Table II range from relatively hindered primary alcohols to acyclic and alicyclic secondary alcohols. The "second alcohols", R^2OH, are mostly primary. Such combinations produce less than 2% of undesirable symmetrical dialkyl(1-methylacetonyl) phosphates.

The acyclic triesters, **8–17**, are converted into the unsymmetrical dialkyl phosphates by the procedures given in the Experimental Section. In these examples, less than 2% of alkyl(1-methylacetonyl) phosphates are generated during the hydrolysis. The new dialkyl phosphates are listed in Table I.

$$(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3 \xrightarrow{H_2O} (R^1O)(R^2O)P(O)OH + HOCH(CH_3)COCH_3$$

The optimum experimental conditions for the acyclic triester synthesis were deduced from independent studies of the four sets of reactions shown in Tables III–VI. From these results it is concluded that alcohol R^1OH reacts much faster with the reagent $X=P(O)OAr$ than with the product $X=P(O)OR^1$, and, therefore, the symmetrical phosphates are not formed to any appreciable extent according to eq 1:

$$R^1OH + X=P(O)OR^1 \rightarrow (R^1O)_2P(O)OCH(CH_3)COCH_3 \quad (1)$$

Phenols, in particular those with electron-withdrawing substituents, are much less reactive than alcohols toward $X=P(O)OR^1$ and $X=P(O)OAr$, and, hence, aryl phosphates are not generated by reactions 2 and 3, under the conditions of the synthesis:

$$ArOH + X=P(O)OR^1 \rightarrow (R^1O)(ArO)P(O)OCH(CH_3)COCH_3 \quad (2)$$

$$ArOH + X=P(O)OAr \rightarrow (ArO)_2P(O)OCH(CH_3)COCH_3 \quad (3)$$

Table III. Half-Times of the Reaction of Alcohols with Aryl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] $R^1OH + X=P(O)OAr \rightarrow X=P(O)OR^1 + ArOH$

R^1	Catalyst	$t_{1/2}$
	$X=P(O)OC_6F_5$	
$(CH_3)_2CHCH_2$	None	15 s
$(CH_3)_2CHCH_2$	$(C_2H_5)_3N$[b]	2 s
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	2 s
c-C_5H_9	None	45 s
c-C_5H_9	$(C_2H_5)_3N$	2 s
c-C_5H_9	$C_6F_5O^-(C_2H_5)_3NH^+$	2 s
$[(CH_3)_2CH]_2CH$	None	2.5 h
$[(CH_3)_2CH]_2CH$	$(C_2H_5)_3N$	2 h
$[(CH_3)_2CH]_2CH$	$C_6F_5O^-(C_2H_5)_3NH^+$	2 h
$(CH_3)_3C$	None	2 h
$(CH_3)_3C$	$(C_2H_5)_3N$	1.75 h
$(CH_3)_3C$	$C_6F_5O^-(C_2H_5)_3NH^+$	1.75 h
	$X=P(O)OC_6H_4NO_2$-*p*	
$(CH_3)_2CHCH_2$	None	10 min
$(CH_3)_2CHCH_2$	$(C_2H_5)_3N$	30 s
$(CH_3)_2CHCH_2$	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 s
c-C_5H_9	None	20 min
c-C_5H_9	$(C_2H_5)_3N$	1 min
c-C_5H_9	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 s
$[(CH_3)_2CH]_2CH$	None	22 h
$[(CH_3)_2CH]_2CH$	$(C_2H_5)_3N$	4 h
$[(CH_3)_2CH]_2CH$	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	45 min
$(CH_3)_3C$	None	30 h
$(CH_3)_3C$	$(C_2H_5)_3N$	3 h
$(CH_3)_3C$	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	45 min
	$X=P(O)OC_6H_4F$-*p*	
$(CH_3)_2CHCH_2$	None	20 min
$(CH_3)_2CHCH_2$	Et_3N	1 min
$(CH_3)_2CHCH_2$	*p*-$FC_6H_4O^-(C_2H_5)_3NH^+$	30 s
c-C_5H_9	None	2.5 h
c-C_5H_9	Et_3N	20 min
c-C_5H_9	*p*-$FC_6H_4O^-(C_2H_5)_3NH^+$	[c]

[a] Equimolar amounts of reagents and catalyst; $t_{1/2}$ from ^1H NMR spectra. [b] The reaction is autocatalytic in the presence of $(C_2H_5)_3N$; $t_{1/2}$ is the time at which [X=P(O)OAr] = [X=P(O)OR]. [c] Products of ring opening are observed.

Table III shows that in reaction $R^1OH + X=P(O)OAr$, the order of reactivity is Ar = C_6F_5 > *p*-$NO_2C_6H_4$, in the absence of catalyst. This sequence corresponds to the acidities of C_6F_5OH > *p*-$NO_2C_6H_4OH$, pK_a = 5.5 and 7.2, respectively;[9,10] hence, the effect may result from the greater leaving group ability, or the higher reagent electrophilicity, or both, in $X=P(O)OC_6F_5$ vs. $X=P(O)OC_6H_4NO_2$-*p*. In contrast, if the corresponding salt, $ArO^-(C_2H_5)_3NH^+$, is initially introduced into the reaction, the relative reactivities become $X=P(O)OC_6H_4NO_2$-*p* > $X=P(O)OC_6F_5$, which is consistent with the higher nucleophilicity of *p*-$NO_2C_6H_4O^-$ vs. $C_6F_5O^-$ in their role as catalysts. It is noteworthy that the catalytic effect of $C_6F_5O^-$ in the reactions of $X=P(OC)OC_6F_5$ (but not of *p*-$NO_2C_6H_4O^-$, in the reactions of $X=P(O)OC_6H_4NO_2$-*p*) vanishes in the case of the two bulkiest alcohols, R^1OH, included in Table III, which suggests that additional steric considerations are involved.

Table IV discloses the effective phenoxide ion catalysis of the reaction $R^2OH + X=P(O)OR^1$, and shows that *p*-$NO_2C_6H_4O^-$ is more efficient than $C_6F_5O^-$ for all combinations of alkyl groups. $C_6F_5O^-$ does not accelerate the reaction when $R^1 = [(CH_3)_2CH]_2CH$ and R^2 = c-C_5H_9, or when $R^1 = (CH_3)_3C$ and $R^2 = (CH_3)_2CHCH_2$. The free phenol has no significant effect on the reaction rate. The pure $X=P(O)OR^1$ used for the study summarized in Table IV was prepared from

Table IV. Phenoxide Ion Catalysis of the Reaction of Alcohols with Alkyl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] $R^2OH + X{=}P(O)OR^1 \rightarrow (R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

R^2	Catalyst	$t_{1/2}$
	$X{=}P(O)OCH_2CH(CH_3)_2$	
$(CH_3)_2CHCH_2$	None	4 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	25 min
	$X{=}P(O)OCH_2CH_2Br$	
$(CH_3)_2CHCH_2$	None[b]	25 min
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	0.5 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	3 min
	$X{=}P(O)OCH(CH_3)(CCl)_3$	
$(CH_3)_2CHCH_2$	None	10 min
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	0.5 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	4 min
	$X{=}P(O)O$-c-C_5H_9	
$(CH_3)_2CHCH_2$	None[c]	7.5 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	3 min
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4OH$	9.5 h
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	1 h
$(CH_3)_2CHCH_2$	C_6F_5OH	10 h
$C_6H_5CH_2$	None	2.5 h
$C_6H_5CH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 min
$C_6H_5CH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	30 min
c-C_5H_9	None	28 h
c-C_5H_9	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	15 min
c-C_5H_9	$C_6F_5O^-(C_2H_5)_3NH^+$	6 h
$(CH_3CH_2)(CH_3)CH$	None	34 h
$(CH_3CH_2)(CH_3)CH$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	35 min
$(CH_3CH_2)(CH_3)CH$	$C_6F_5O^-(C_2H_5)_3NH^+$	12 h
	$X{=}P(O)OCH[CH(CH_3)_2]_2$	
$(CH_3)_2CHCH_2$	None	22 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	25 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	9.5 h
c-C_5H_9	None	70 h
c-C_5H_9	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2.5 h
c-C_5H_9	$C_6F_5O^-(C_2H_5)_3NH^+$	78 h
	$X{=}P(O)C(CH_3)_3$	
$(CH_3)_2CHCH_2$	None	45 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	1.5 h
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	46 h

[a] Equimolar amounts of reagents and catalyst; $t_{1/2}$ from ^1H NMR spectra. [b] Small amounts (3–4%) of symmetrical triester detected in all cases. [c] Addition of 1 molar equiv of $X{=}P(O)O^-(C_2H_5)_3NH^+$ to the mixture of 2-butanol and $X{=}P(O)O$-c-C_5H_9 had no significant effect.

the reaction of the alcohol R^1OH with the pyrophosphate[4,6] 3. The reaction $R^1OH + X{=}P(O)OAr$ is not a practical method to make pure $X{=}P(O)OR^1$.

The data in Tables III and IV suggest an interplay of electronic and steric factors associated with the aryl and alkyl groups in the *phenoxide catalyzed* reactions $R^1OH + X{=}P(O)OAr$ and $R^2OH + X{=}P(O)OR^1$. Similar phenomena have been observed[6] in the *tertiary amine catalyzed* reaction $R^2OH + X{=}P(O)OR^1$ in $CDCl_3$ solution. Triethylamine is an effective catalyst when R^2OH is a primary alcohol and R^1 is a primary or secondary alkyl group; however, the rate enhancement decreases as the steric requirements of R^1 increase, e.g., when $R^1 = [(CH_3)_2CH]_2CH$, and the catalysis vanishes when $R^1 = (CH_3)_3C$. Triethylamine does not increase the rate of the reaction of secondary alcohols (R^2OH) with esters $X{=}P(O)OR^1$, even if R^1 is primary. On the other hand, the less hindered quinuclidine is an effective catalyst when R^2OH is a primary or a secondary alcohol, and R^1 is primary, secondary, or tertiary.

Table V. Half-Times of the Reaction of Phenols with Alkyl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] $ArOH + X{=}P(O)OR^1 \rightarrow (R^1O)(ArO)P(O)$-$OCH(CH_3)COCH_3$

Catalyst[b]	$t_{1/2}$
$C_6H_5OH + X{=}P(O)OCH_2CH(CH_3)_2$[c]	
None	No reaction[d]
$[(CH_3)_2N]_2C{=}NH$	1.5 min
$(i$-$C_3H_7)_2(C_2H_5)N$	4
$(C_2H_5)_3N$	2 h
Imidazole	3 h
γ-Collidine	No reaction
$C_6H_5OH + X{=}P(O)O$-c-C_5H_9	
None	No reaction
$[(CH_3)_2N]_2C{=}NH$	2 min
$(i$-$C_3H_7)_2(C_2H_5)N$	45 min
Quinuclidine	2 h
$(C_2H_5)_3N$	3 h
Imidazole	4 h
γ-Collidine	No reaction
C_5H_5N	No reaction
$C_6H_5OH + X{=}P(O)OCH[CH(CH_3)_2]_2$	
None	No reaction
$(i$-$C_3H_7)_2(C_2H_5)N$	70 h
$(C_2H_5)_3N$	70 h
Imidazole	30 h
p-$NO_2C_6H_4OH + X{=}P(O)O$-c-C_5H_9	
None	No reaction
$(i$-$C_3H_7)_2(C_2H_5)N$	~7 days
$(C_2H_5)_3N$	~8 days
Imidazole	~10 days

[a] Equimolar amounts of reagents; $t_{1/2}$ from ^1H NMR spectra. [b] pK_B of amines: tetramethylguanidine, 0.4; diisopropylethylamine, 2.0; quinuclidine, 2.9; triethylamine, 3.0; imidazole, 6.9; γ-collidine, 6.7; pyridine, 8.7 (ref 11). [c] Small amounts of symmetrical phosphotriesters observed in this particular system. [d] Within 3 days, in all cases.

Table V shows that phenols are quite unreactive toward $X{=}P(O)OR^1$ in the absence of amines. Amines accelerate the reaction, and their effectiveness correlates mainly with their basicity,[11] except in the case of imidazole, which is more efficient than it would be expected from its basicity. γ-Collidine, which is slightly more basic than imidazole, but more hindered around the nitrogen, is inactive. It appears that amines can exert their catalytic action in two ways: by converting the phenol into the more nucleophilic phenoxide ion, and by activating the $X{-}P(O)OR^1$ reagent. As expected, p-nitrophenoxide is less reactive than the more nucleophilic unsubstituted phenoxide toward a given $X{=}P(O)OR^1$, in the presence of the same amine. Two new arylalkyl (1-methyl

Table VI. Half-Times of the reaction of Phenols with Aryl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] ArOH + X=P(O)OAr → $(ArO)_2P(O)OCH(CH_3)$-$COCH_3$

Catalyst	$t_{1/2}$
C_6H_5OH + X=P(O)OC_6H_5	
None	No reaction[b]
$[(CH_3)_2CH]_2C$=NH	2 min
$(i\text{-}C_3H_7)_2(C_2H_5)N$	35 min
$(C_2H_5)_3N$	45 min
Imidazole	1.5 h
γ-Collidine	36 h
C_5H_5N	No reaction
p-$NO_2C_6H_4OH$ + X=P(O)$OC_6H_4NO_2$-*p*	
None	No reaction
$(i\text{-}C_3H_7)_2(C_2H_5)N$	45 h
Imidazole	80 h
C_5H_5N	No reaction

[a] Equimolar amounts of reagents. The structures of the diaryl(1-methylacetonyl) phosphates are based on ^1H and ^{31}P NMR spectra; the compounds were not isolated in pure state. [b] Within 3 days in all cases.

acetonyl) phosphates, **18** and **19**, made by this reaction are described in Table I.

Table VI shows some analogy with Table V, since both refer to reactions of phenols; however, the higher reactivity of X=P(O)OAr vs. X=P(O)OR^1 is reflected in the catalysis by γ-collidine shown in Table VI. The weakest base, pyridine, is ineffective in the reaction of the phenols with X=P(O)OAr. From an analysis of the data in Tables III–VI it can be seen that there is no difficulty in making unsymmetrical dialkyl(1-methylacetonyl) phosphates free from aryl-containing triesters, and from symmetrical by-products resulting from the first step (eq 1, above). To verify these points consider the $t_{1/2}$ values for reactions such as c-C_5H_9OH and *p*-$NO_2C_6H_4OH$ with X=F(O)$OC_6H_4NO_2$-*p* vs. X=P(O)OR^2, including R^2 = c-C_5H_9, in the presence of $ArO^-R_3NH^+$ or R_3N, as appropriate.

Symmetrical dialkyl(1-methylacetonyl) phosphates can, in principle, be produced during the second step of the synthesis, as shown in eq 4, which is a displacement at phosphorus with ring retention:

$$R^2OH + X{=}P(O)OR^1 \rightarrow X{=}P(O)OR^2 + R^1OH \quad (4)$$

This transesterification would be followed by the reaction of eq 1, and by that of eq 5:

$$R^2OH + X{=}P(O)OR^2 \rightarrow (R^2O)_2P(O)OCH(CH_3)COCH_3 \quad (5)$$

It has been found that the relative amounts of unsymmetrical vs. symmetrical triesters vary according to the sequence in which the two alcohols are submitted to the phosphorylative coupling, *in the absence of catalyst*. This is shown by a study of reactions R^2OH + X=P(O)OR^1 and R^1OH + X=P(O)-OR^2. Symmetrical triester formation is minimized if the smaller alcohol is added to the cyclic triester containing the bulkier alkyl group, or if a more electronegative alcohol is added to the triester with the less electronegative alkyl group; cf. Table II.

The formation of the symmetrical triester by-product in a particular uncatalyzed reaction is significantly reduced by the presence of the *p*-nitrophenoxide ion, and the synthetic procedure is practicable even if the uncatalyzed reaction R^2OH + X=P(O)OR^1 yields ca. 6–8% of symmetrical triester, since this value becomes <2% in the presence of phenoxide ion. This effect is best studied in the system $(CH_3)_2CHCH_2OH$ + X=P(O)OCH_3, where the proportion of unsymmetrical vs. symmetrical triesters varies from 54:46% to 75:25%, in the absence and in the presence of *p*-$NO_2C_6H_4O^-(C_2H_5)_3{}^+NH$, respectively.

Discussion

To our knowledge, the phenoxide ion catalysis of the phosphorylation of alcohols in aprotic solvents, or in aqueous solution, has not been previously described. We have reported imidazole,[6] tertiary amine,[6] and carboxylate ion[12] catalysis of the reaction R^2OH + X=P(O)OR^1 in aprotic solvents. Westheimer and co-workers[13] observed imidazole catalysis of the solvolysis of tetrabenzyl pyrophosphate in 1-propanol. Van Boom, Reese, et al.[14] noted 5-chloro-1-methylimidazole catalysis of the reaction of alcohols with diphenylphosphorochloridate in acetonitrile. The role played by imidazole, tertiary amines, carboxylate ions, and other nucleophiles in the reactions of phosphotriesters, phosphodiesters, and related compounds, *in aqueous solutions*, has been extensively investigated, in particular by Jencks,[15] Kirby,[16] Benkovic,[17] Westheimer,[18] Haake,[19] and Simons.[20] It has been generally accepted[15-20,21-23] that in those types of compounds, the catalysis is exerted by conversion of the P(4)[24] into a more reactive P(4)′ intermediate via a P(5)[24] intermediate, e.g.[35]

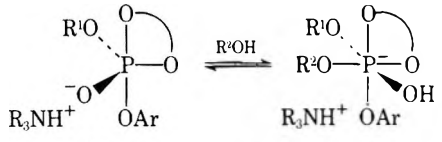
$$Nu + \rangle P(O)X \longrightarrow \rangle P(O)(X)(Nu) \longrightarrow \rangle P(O)Nu + X$$

$$ROH + \rangle P(O)Nu \longrightarrow \rangle P(O)OR + Nu + H^+$$

(with the appropriate charge distribution depending on the type of nucleophile and leaving group).

The phosphorylations in aprotic solvents described in this and in the previous papers[4,6,12] are difficult to explain except under the assumption that the nucleophilic catalyst converts the phosphate into a P(5) intermediate, and that the reagent being phosphorylated then transforms the P(5) into a P(6)[24] intermediate. The products are obtained from the subsequent transformations: P(6) → P(5)′ → P(4)″. The underlying assumptions, as well as the literature references in support of these hypotheses, have been given.[4,6] These hypotheses can be applied to the observations reported in the present paper. The significant findings are (1) the phenoxide ion catalysis of the reaction R^2OH + X=P(O)OR^1 without incorporation of the phenoxide into the product or into any detectable P(4) intermediate; (2) the amine catalysis of the reaction ArOH + X=P(O)OR^1 with incorporation of the phenoxide into the product; (3) the variation of the proportion of unsymmetrical vs. symmetrical dialkyl(1-methylacetonyl) phosphate with the order in which the two alcohols are phosphorylated, in the absence of catalyst; (4) the decrease in the amount of symmetrical triester, in any given order of phosphorylation, in the presence of phenoxide ion.

In the oxyphosphorane-intermediate hypothesis, the first step of the phenoxide-catalyzed reaction of alcohol R^2OH with X=P(O)OR^1 involves the formation of the P(5) **27**. The second step is the conversion of **27** into the P(6) **28**. The latter, **28**, can collapse[25] to one or to both isomeric P(5)′, **29** or **30**, which are also interconvertible by an intramolecular permutational isomerization, possibly by the TR mechanism[26] with the ring as ligand pair.[27] Isomer **29** is generated, directly, by apical addition of R^2OH to X=P(O)OR^1, in the uncatalyzed reaction. If isomer **29** is formed exclusively, and if it collapses by ring opening before it equilibrates with **30**, the unsymmetrical acyclic triester is exclusively formed in the uncatalyzed reaction. If equilibration **29** ⇌ **30** takes place, and there is apical departure of R^1O ligand from **30**, the new X=P(O)OR^2 is produced and eventually there is formation of symmetrical

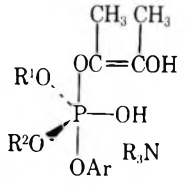


27 28

29 30

acyclic triesters by eq 1 and 5. The variation in the relative amounts of unsymmetrical vs. symmetrical triesters with the order in which the two alcohols are allowed to react implies that ring opening is competitive with the equilibration of isomers **29** and **30** by permutational isomerization.

A possible explanation for the decrease in the amount of symmetrical triesters in the phenoxide-catalyzed couplings is that ring opening may occur at the P(6) intermediate stage, **28**; the resulting acyclic P(5)′ **31** yields the unsymmetrical triester by loss of ArO^-. This interpretation has been advanced to account for a similar effect in the imidazole- and triethylamine-catalyzed reactions.[6] It is also speculated that the catalysis results from a higher nucleophilicity of the phenoxide anion vs. neutral alcohol, R^2OH. The P(4) ⇌ P(5) step is assumed to be relatively rapid in this particular case.[28] The various ways in which the P(5) and P(6) intermediates can collapse and the possibility of a permutational isomerization of P(5) provide for product control in this and in the other related reactions of Tables III–VI.



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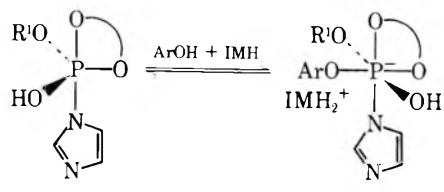
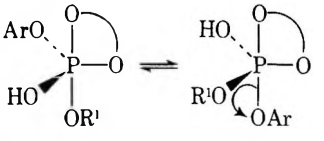
The P(5) intermediate **27** accounts for part of the effect of the amine, R_3N, on the reaction $ArOH + X{=}P(O)OR^1$ (Table V); i.e., dissociation, $ArOH + R_3N \rightleftharpoons ArO^-R_3NH^+$, followed by addition of ArO^- to P(4) to give **27**. In the absence of alcohol, **27** eventually collapses to the observed arylalkyl(1-methylacetonyl) phosphate by ring opening. The second effect of the amine is probably related to the amine catalysis[6] of the reaction $R^2OH + X{=}P(O)OR^1$. Imidazole can add to P(4) to give the P(5) **32**, and the latter is converted into the P(6) **33** by the phenol in the presence of imidazole. The loss of imidazole from **33** generates a P(5) analogous to **27** which eventually collapses to the arylalkyl triester.



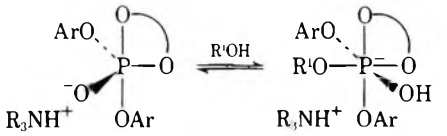
32 33

The reaction $R^1OH + X{=}P(O)OAr$, which results in ring retention, and the reaction $ArOH + X{=}P(O)OAr$, which results in ring opening, can be rationalized as follows. The uncatalyzed reactions of the alcohols (Table III) are relatively rapid and can be viewed as involving the formation of the P(5) **34**, *followed by a relatively rapid permutational isomerization* to **35**, which places the apicophilic[26] ArO^- at the apical position, from which it can depart to give the observed product $X{=}P(O)OR^1$.



34 35

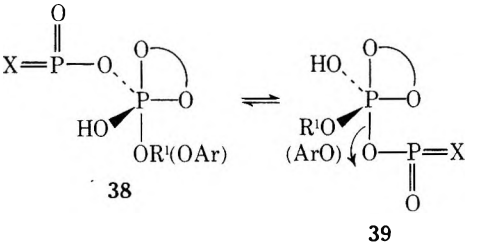
The phenoxide ion catalysis of $R^1OH + X{=}P(O)OAr$ would involve the P(5) intermediate **36**, which adds R^1OH to give the P(6) intermediate **37**. The latter collapses to a P(5) intermediate analogous to **35**. The P(5) intermediate **36** also accounts for the product of the reaction $ArOH + X{=}P(O)OAr + R_3N$ (Table VI), which results from ring opening of **36**.



36 37

The loss of catalysis by $C_6F_5O^-$ in some of the reactions $R^1OH + X{=}P(O)OC_6F_5$, when R^1OH is relatively bulky (entries 8, 9, 11, 12 in Table III), could result from an inability of the alcohol to add to P(5), **36**, and form P(6), **37**. Since the catalysis is retained in the comparable reactions involving the *p*-nitrophenyl analogues (entries 20, 21, 23, 24 in Table III), this rationale implies a lower degree of steric hindrance in the transformation **36** + $R^1OH \rightarrow$ **37** in the latter case.[29]

The mechanism of the reaction of alcohols and phenols with the pyrophosphate **3** has already been discussed.[4,6] These reactions proceed with ring retention and can be explained by the P(5) intermediates **38** and **39**. The amine catalysis of the phenol reaction may simply result from the generation of the more nucleophilic phenoxide ion.



38 39

The experimental results, and the hypotheses offered to explain them, may be related to some of the mechanisms operating in enzymes which are involved in biological phosphoryl group transfers.[30-32] It is apparent that phenoxide ion is capable of exerting a strong phosphate activation *in aprotic solvents of low polarity*. Tyrosine residues have been implicated in the catalytic activity of enzymes such as fructose 1,6-diphosphatase[33] and ATP-creatine phosphotransferase,[34] in the latter case, in conjunction with lysine and histidine residues. The possible involvement of hexacoordinate as well as pentacoordinate phosphorus species in the hydrophobic active sites of these enzymes is an attractive hypothesis.

Experimental Section

The physical properties of new compounds are given in Table I. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Compounds with the X=P(O)– group are very sensitive to moisture. Solvents were purified, and were stored over molecular sieves. A dry N_2 atmosphere is advisable in all reactions.

2-*p*-Nitrophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxide (6). Yields of 6 higher than those reported[4] were obtained by the following procedure. A solution of *p*-nitrophenol (8.76 g, 63 mmol) in anhydrous ether (60 ml) was added dropwise in 20 min to a stirred solution of the pyrophosphate (**3**, 17.75 g, 63 mmol) in dichloro-

methane (200 ml), containing nicotinamide (8 g, slight excess over 63 mmol) in suspension, at 25 °C. After 4.5 h at 25 °C, the nicotinamide salt of 2-hydroxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide was filtered off and washed with dichloromethane (100 ml). The combined washing and filtrate were concentrated to ca. 40 ml and diluted with ether (150 ml) to induce the crystallization of the product. The mixture was concentrated to ca. 30 ml, and X=P(O)$OC_6H_4NO_2$-*p* (**6**) was filtered off, washed with a small volume of ether, and dried under vacuum. Yield of first crop: 15.5 g (90%); the chilled filtrate gave 0.2 g (2%) of additional **6**. Both materials had mp 102–104 °C, as reported.[4]

2-Pentafluorophenoxy- and 2-*p*-Fluorophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxides (7 and 5). A dichloromethane solution (50 ml) containing pentafluorophenol (6.95 g, 37.8 mmol) and γ-collidine (4.57 g, 37.8 mmol) was added over a 30-min period to a dichloromethane solution (100 ml) of the pyrophosphate (**3**, 10.66 g, 37.8 mmol), at 0 °C. The mixture was stirred at 0 °C for 30 min, and at 20 °C for 2 h. The solution was evaporated, and the residue was extracted with anhydrous ether (4 × 75 ml). The extract was filtered and evaporated, leaving a residue which was purified by molecular distillation (Table I) to give X=P(O)OC_6F_5 (**7**) in 90% of the theory.

The same procedure yielded X=P(O)OC_6H_4F-*p* (**5**) in 82% of the theory.

Procedure 1. One-Flask Synthesis of Dialkyl(1-methylacetonyl) Phosphates by X=P(O)$OC_6H_4NO_2$-*p* (6). A dichloromethane solution containing R^1OH (1 molar equiv) and triethylamine (1 molar equiv) is added dropwise (5 min) to a stirred dichloromethane solution of **6** (1 molar equiv, 0.6–0.8 M) at 25 °C. After 15–60 min, 1 molar equiv of R^2OH is added dropwise (5 min) in the same solvent. The solution (0.4–0.6 M) is stirred at 25 °C for periods which depend on the structures of R^1 and R^2 (1–12 h; see Table IV), and is then diluted with dichloromethane (0.1–0.2 M) and repeatedly extracted with dilute, aqueous alkali (Na_2CO_3 or NaOH) to remove *p*-nitrophenol. The dichloromethane solution is dried over Na_2SO_4 and evaporated under vacuum to give the dialkyl(1-methylacetonyl) phosphate, which was then hydrolyzed to the dialkyl phosphate, before or after purification by short-path distillation. The crude acyclic triester may have a slight yellow color owing to traces of *p*-nitrophenol, but the contamination is insignificant (<0.5% by ^1H NMR), and it does not affect the quality of the final dialkyl phosphate.

Procedure 2. One-Flask Synthesis of Dialkyl(1-methylacetonyl) Phosphates by X=P(O)OC_6F_5 (7). Analogous to procedure 1. Alternatively, the pentafluorophenol by-product can be removed by short-path vacuum distillation, after evaporation of the original dichloromethane solution, instead of by alkaline extraction, if the dialkyl(1-methylacetonyl) phosphate has alkali-sensitive substituents.

Hydrolysis of Dialkyl(1-methylacetonyl) Phosphates. Procedure A. With Triethylamine. The crude or distilled acyclic triester is dissolved in a 2:1 v/v mixture of water and acetonitrile (0.1 M solution) containing 2 molar equiv of triethylamine or of diisopropylethylamine. The mixture is stirred for 10 h at 70 °C; triesters with the bulkiest substituents, e.g., compounds **12** and **14**, Table II, require longer times, 70–100 h at 70 °C. The acetonitrile is evaporated at 40 °C (30 mm) and the aqueous residue is diluted with water to a volume that is convenient for ether extraction to remove neutral contaminants. The aqueous phase, after ether extraction, is acidified with 5% hydrochloric acid, and is extracted with dichloromethane. The organic extract is dried (Na_2SO_4), and is evaporated to yield the crude dialkyl phosphate, $(R^1O)(R^2O)P(O)OH$, analyzed by ^1H NMR spectrometry (Table I); less than 2% of by-product monoalkyl(1-methylacetonyl) phosphate is found in the examples given in Table II. The dialkyl phosphates are converted into crystalline salts as indicated in Table I. The salts are isolated in about 75% of the theoretical yield based on the first alcohol, R^1OH.

Procedure B. With Sodium Carbonate. If the alkyl groups in the dialkyl(1-methylacetonyl) phosphate are sensitive to the tertiary amine, the hydrolysis is carried out as in procedure A, except that the amine is replaced by 2 molar equiv of Na_2CO_3. This procedure is indicated for the synthesis of 2-bromoethylalkyl phosphates, e.g., **22a**; in this example, a relatively large (ca. 7%) amount of alkyl(1-methylacetonyl) phosphate by-product is formed in the hydrolysis.

Synthesis of Cyclopentylisobutyl Phosphate by X=P(O)$OC_6H_4NO_2$-*p* (6) in the Absence of Triethylamine. Cyclopentanol was added to **6** as in procedure 1, *but without triethylamine*. In this case, 4.5 h was required for the preparation of the intermediate X=P(O)O-c-C_5H_9, as monitored by ^1H NMR spectrometry. An equimolar mixture of 2-butanol and triethylamine was introduced at this point, and the cyclopentylisobutyl(1-methylacetonyl) phosphate (**8**) was obtained in ca. 45 min (90% yield); total reaction time 6 h vs. 1.5 h by procedure 1. The corresponding salt of the dialkyl phosphate was isolated in 75% yield based on cyclopentanol.

Isolation of 2-Alkoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxides. A. From Pyrophosphate 3. The pure X=P(O)OR^1 for the experiments in Tables IV and V was made as described.[4,6]

B. From X=P(O)OC_6F_5 (7). Cyclopentanol (0.74 g, 8.6 mmol) in dichloromethane solution (10 ml) was added in 15 min to X=P(O)OC_6F_5 (**7**, 2.71 g, 8.6 mmol) in the same solvent (30 ml) at 0 °C. The solution was kept at 0 °C for 30 min, and at 25 °C overnight. The solution was evaporated at 0.15 mm, first at 45 °C, then at 90 °C (15 min) to remove pentafluorophenol, leaving X=P(O)O-c-C_5H_9 (1.85 g, 92% of the theory) as the residue. The ^1H NMR of the latter (in $CDCl_3$) was identical with that of the distilled product,[4] bp 102–104 °C (0.2 mm).

Registry No.—**3**, 55894-94-5; **4**, 55895-03-9; **5**, 61010-62-6; **6**, 55895-04-0; **7**, 57204-50-9; **10**, 57204-53-2; **11**, 61010-63-7; **12**, 61010-64-8; **13**, 61010-65-9; **14**, 61010-66-0; **15**, 57204-55-4; **16**, 57204-54-3; **18** isomer A, 61010-67-1; **18** isomer B, 61010-68-2; **19** isomer A, 61010-69-3; **19** isomer B, 61010-70-6; **20a**, 61010-72-8; **21a**, 61010-74-0; **22a**, 61010-76-2; **23a**, 61010-77-3; **24a**, 61010-79-5; **25a**, 61010-81-9; **26a**, 61010-83-1; R^1OH (R^1 = c-C_5H_9), 96-41-3; R^1OH (R^1 = $(CH_3CH_2)_2CH$), 584-02-1; R^1OH (R^1 = c-C_6H_{11}), 108-93-0; R^1OH (R^1 = $[(CH_3)_2CH]_2CH$), 600-36-2; R^1OH (R^1 = $(CH_3)_3CCH_2$), 75-84-3; R^1OH ((±)-3-*p*-menthanyl), 15356-70-4; R^1OH (R^1 = $(CH_3)_3C$), 75-65-0; R^2OH (R^2 = $(CH_3)_2CHCH_2$), 78-83-1; R^2OH (R^2 = $C_6H_5CH_2$), 100-51-6; R^2OH (R^2 = $CH_2{=}C(CH_3)CH_2CH_2$), 763-32-6; R^2OH (R^2 = CH_3CH_2), 64-17-5; R^2OH (R^2 = $BrCH_2CH_2$), 540-51-2; R^2OH (R^2 = $(CH_3CH_2)(CH_3)CH$), 78-92-2; R^2OH (R^2 = C_6H_5), 108-95-2; X=P(O)$OCH_2CH(CH_3)_2$, 16764-09-3; X=P(O)-OCH_2CH_2Br, 55894-97-8; X=P(O)$OCH(CH_3)(CCl_3)$, 55894-01-7; X=P(O)O-c-C_5H_9, 55894-98-9; X=P(O)$OCH[CH(CH_3)_2]_2$, 60807-32-1; X=P(O)$OC(CH_3)_3$, 55895-02-8; *p*-nitrophenol, 100-02-7; pentafluorophenol, 771-61-9.

References and Notes

(1) Research supported by Grant GM-20672 from the National Institute of General Medical Sciences. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support.
(2) Preliminary communication: F. Ramirez and J. F. Marecek, *J. Org. Chem.*, **40**, 2849 (1975).
(3) X is the 1,2-dimethylethenylenedioxy group. Pyrophosphate **3** is $[X{=}P(O)]_2O$ or oxybis(1,2-dimethylethenylenedioxyphosphoryl).
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(24) P(4), P(5), P(6) = tetra-, penta-, and hexacoordinate phosphorus compound.
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(35) **Note Added in Proof.** This mechanism—P(4) → P(5) → P(4)′ → P(5)′ → P(4)″—is inconsistent with the following data: $t_{1/2} \sim 15$ h for the reaction R^2OH + (ArO)(R^1O)P(O)OCH(CH_3)$COCH_3$ + R_3N → (R^2O)(R^1O)P(O)OCH(CH_3)$COCH_3$ + $ArO^-R_3NH^+$, at 25 °C in 0.2 M $CDCl_3$, while $t_{1/2}$ = 3 min for R^2OH + X=P(O)OR^1 → (R^2O)(R^1O)P(O)OCH(CH_3)$COCH_3$, under comparable conditions (Table IV), when R^2 = $(CH_3)_2CHCH_2$, R^1 = c-C_5H_9, Ar = p-$NO_2C_6H_4$, R = C_2H_5. It is clear that the acyclic P(4)′ intermediate, that should have been formed from the cyclic triester according to this mechanism, reacts at a much slower rate (~15 h) than the cyclic triester itself (~3 min). Hence the latter reaction must proceed by a different mechanism, possibly that postulated here: P(4) → P(5) ≡ **27** → P(6) ≡ **28** → P(5)′ ≡ **31** → P(4)″. Moreover, the reaction ROH + (ArO)P(O)(OC_6H_5)$_2$ → (RO)P(O)(OC_6H_5)$_2$ + ArOH is *effectively catalyzed* by $ArOR_3NH^+$, as well as by $ArO^-R_4N^+$, in either $CDCl_3$ or CD_3CN (0.2 M, 25 °C), although it is evident that in this case the intermediate P(4)′ postulated by the mechanism P(4) → P(5) → P(4)′ → P(5)′ → P(4)″ is identical with the starting triester, P(4), and therefore the catalysis must be exerted via a different mechanism (F. Ramirez and J. Marecek, *Tetrahedron Lett.*, submitted for publication).

Synthesis, Structure Analysis, and Stereochemistry of Some Reactions of *cis*- and *trans*-2,2,5-Trimethyl-3-phenyl-1,3-oxaphospholane

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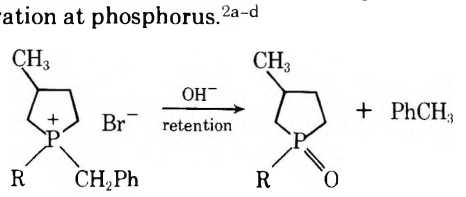
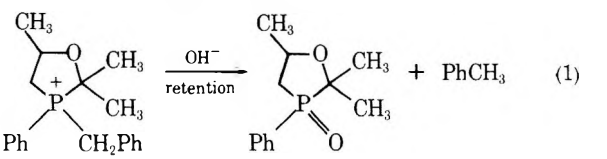
The syntheses of *cis*- and *trans*-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane are reported and a detailed analysis of the NMR spectra given from which stereochemical assignments were made and conformational structure suggested. Hydroxide cleavage of *cis*- and *trans*-3-benzyl-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholanium bromide occurred stereospecifically with retention of configuration at phosphorus to yield the corresponding diastereomers of 2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane 3-oxide.

Stereochemistry of nucleophilic displacement at a phosphonium phosphorus atom confined to a five-membered ring (phospholanium salts) has been the subject of a number of investigations which are briefly summarized in a recent paper.[1] One of the most significant findings in this system is the hydroxide-induced displacement of benzyl from both the cis and trans isomers of **1** and **2** with complete retention of configuration at phosphorus.[2a-d]



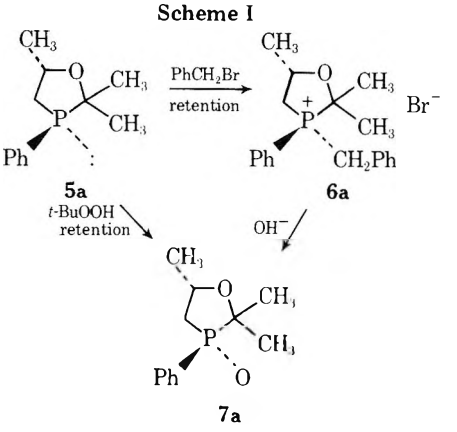
1, R = CH_3 **3**
2, R = Ph

The possible influence of any "element effect" of a second heteroatom on the stereochemistry of this reaction has prompted us to synthesize the cis and trans isomers of 3-benzyl-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholanium bromide (**4**). The 1,3-oxaphospholane system is a newly synthesized one,[3a] and its chemistry has been essentially limited to a few NMR studies.[4-6] Also no pure geometric isomers have been isolated until this report. With this appropriately substituted 1,3-oxaphospholane system in hand, chosen especially for its relatively simple NMR spectra, we have now discovered that the presence of oxygen in the ring provokes no stereochemical change. Indeed, **4** behaves precisely as **1** and **2** toward base cleavage, which again occurs with complete retention of configuration. The stereochemistry for eq 1 was demonstrated by completion of the stereochemical cycle shown in Scheme I for which the stereochemistry of reduction[2,7] and oxidation[8]



4 (1)

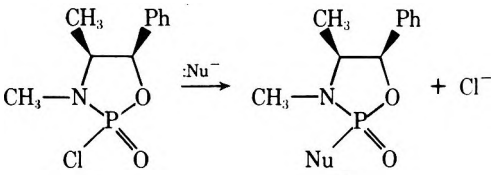
Scheme I



is known. Stereospecific oxidation of **5a** produces the same isomer as cleavage of **6a**. Although racemic mixtures of both cis and trans isomers were used, the cycle is illustrated with one enantiomer of the trans phosphine **5a**.

Since the completion of this work, Cooper and others[9] have

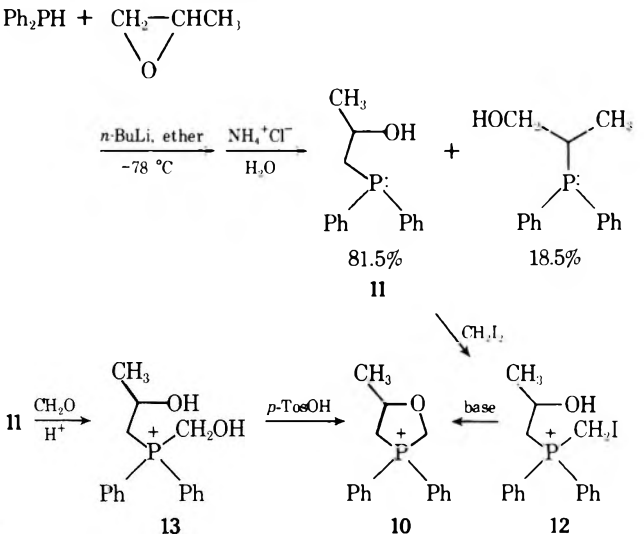
reported that for the two isomers of **8**, epimeric at phosphorus, retention accompanies displacement of chloride by methoxide or phenoxide to give **9**. Retention of configuration at phos-



8 **9**

phorus resulting from nucleophilic displacement of leaving groups for the cis and trans isomers **1**, **2**, **4**, and **8** is presently best explained by apical attack at phosphorus by the nucleophile to produce a trigonal bipyramidal intermediate with one ring bond and the nucleophile occupying apical positions in order to minimize ring strain. The leaving group is then expelled following one Berry pseudorotation.[1] We are now investigating the effect of incorporation of larger heteroatoms in place of oxygen in structures similar to **4**. This could conceivably lead to some inversion of configuration at phosphorus if the larger atom alleviates some ring strain during the course of nucleophilic substitution.[10]

Synthesis of Cis and Trans Isomers of 2,2,5-Trimethyl-3-phenyl-1,3-oxaphospholane (15). A preliminary attempt was made to synthesize **10**, by the route shown.



11 **13** **10** **12**

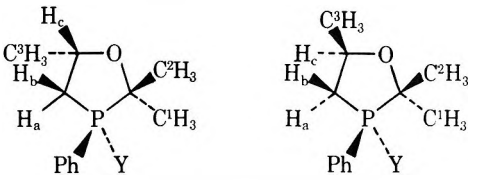
However, difficulty was experienced in the ring closure steps.

It was proposed that **10** could be cleaved by base[2c] to 5-methyl-3-phenyl-1,3-oxaphospholane 3-oxide which could in turn be reduced[7] to 5-methyl-3-phenyl-1,3-oxaphospholane, the immediate precursor for the oxa analogue of **2**. However, protonation of **13** is evidently retarded by the presence of the positively charged phosphonium atom since only unreacted phosphonium salt was recovered from acid treatment of **13**. No exhaustive study was made to cyclize **12**. The use of Me_2SO[11] or 2,4,6-collidine also failed to effect ring closure of **13** or **12**, respectively.

By modification of Oehme's procedure,[3a] in order to enable the use of a volatile ketone such as acetone, it was possible to prepare a mixture of the cis and trans isomers of **5** in yields surpassing literature reports for the use of ketones in such cyclizations.

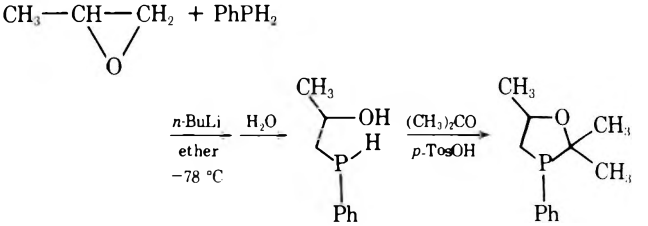
The mixture of isomeric cyclic phosphines **15** was subjected to fractionation on a spinning band column and the lower boiling isomer of bp 95 °C (3.5 mm) was obtained pure. This isomer was assigned a trans configuration (**5a**) based upon its NMR spectrum as discussed below. The tail fraction of bp 97 °C (3.0 mm) was found to be a mixture consisting of 80% cis isomer and 20% trans isomer. These two fractions were separately subjected to the reactions illustrated in Scheme I. It was possible to show that the isomeric composition of the phosphonium salt and phosphine oxide derived from the phosphine mixture was identical within experimental error with that of the original phosphine mixture.

Table I. Chemical Shifts and Coupling Constants for *trans*- and *cis*-2,2,5-Trimethyl-3-phenyl-1,3-oxaphospholane and the Corresponding Oxides[a]



	5a[b] (Y = lone pair)	**7a**[c] (Y = O)	**5b**[d] (Y = lone pair)	**7b**[e] (Y = O)
Chemical Shift (δ, ppm from Me_4Si)				
δH_a	2.50	2.42	1.91	2.12
δH_b	1.89	2.04	2.43	2.72
δC^1H_3	1.37	1.57	1.53	1.56
δC^2H_3	1.03	1.07	1.02	1.00
δC^3H_3	1.51	1.47	1.36	1.49
δC_6H_5	7.44		7.44	
δH_c	4.10	4.47	4.45	4.34
Coupling Constant, Hz				
$J_{H_aCH_b}$	14.2	14.9	14.4	15.2
$J_{H_aCCH_c}$	6.9	6.3	9.6	9.9
$J_{H_bCCH_c}$	8.3	8.7	5.6	6.0
$J_{C^3H_3CH_c}$	6.3	6.2	6.0	5.9
J_{PCH_a}	24.4	14.9	19.5	19.0
J_{PCH_b}	6.2	9.9	2.7	6.0
J_{PCCH_c}		1.4		2.8
$J_{PCC^1H_3}$	17.6	10.9	18.2	11.0
$J_{PCC^2H_3}$	7.6	13.5	6.4	13.6
$J_{PCCC^3H_3}$		1.8		1.8

[a] Determined at ambient temperature using a 100-MHz Varian Associates Model XL-100-15 spectrometer. Chemical shifts were measured from tetramethylsilane as an internal standard in a neat sample for the phosphines and in $CDCl_3$ for the oxides. [b] Registry no., 61009-58-3. [c] Registry no., 61009-59-4. [d] Registry no., 61009-60-7. [e] Registry no., 61009-61-8.

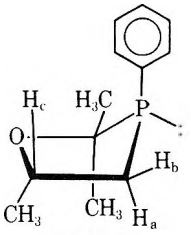


14 **15**

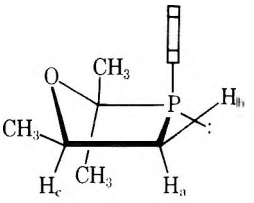
Assignment of Cis, Trans Structure to 5. The ^1H NMR spectra obtained for the phosphines were completely analyzed and the analysis verified using the computer program LAOCOON III.[12] The chemical shifts and coupling constants are presented in Table I. Data supporting configurational assignments are summarized as follows:

1. H_c would be expected to be found further downfield than either H_a or H_b because of deshielding by oxygen.[2d] The protons of the methyl group to which H_c is coupled resonate

at 1.51 ppm for one isomer and at 1.36 ppm for the other. The methyl group is designated as C^3H_3 in each case. Where C^3H_3 is cis to phenyl, an upfield shift would be expected because of the shielding effect of the aromatic ring. Where C^3H_3 is cis to the lone pair on phosphorus (trans isomer) a downfield shift[4,13] would be expected for the methyl group. Thus the lower boiling isomer having δC^3H_3 1.51 ppm is assigned the structure **5a.** The isomer of δC^3H_3 1.36 ppm is given the structure **5b.**



5a



5b

2. H_a in each structure should exhibit a larger coupling constant than H_b because of the cis relationship of H_a with the lone pair on phosphorus.[13] Once identified, H_a is seen to be trans to H_c in **5a** and cis to H_c in **5b.** These spatial relationships are borne out by the values of the coupling constants for $J_{H_aCCH_c}$ and $J_{H_bCCH_c}$ for the two isomers; e.g., the Karplus equation would predict a larger value for $J_{H_aCCH_c}$ for the cis isomer than for the trans. This is indeed the case as shown in Table I. The values for $J_{H_aCCH_c}$ and $J_{H_bCCH_c}$ for the two isomers suggest dihedral angles consistent for phosphorus at the flap of an envelope for **5a** and with oxygen at the flap position in **5b** in the principal conformers. In both conformations Courtauld models show *cis*-1,3-dimethyl and *cis*-1,2-methylphenyl interactions to be optimized and the lone pair on phosphorus oriented pseudoequatorially.[14] These models also strongly suggest a highly rigid system for both **5a** and **5b** around the phosphorus atom. For **5b** H_b is downfield with respect to the same proton in **5a,** possibly owing to the conformational preference of the phenyl group as shown in **5b** which minimizes interaction with the two cis methyl substituents. Of course, unequivocal assignment of H_a and ring conformation await x-ray analysis which we have planned.

The spectra of the corresponding oxides **7a** and **7b** are also given in Table I. The ring geometry for the oxides, as indicated by the coupling constants $J_{H_aCCH_c}$ and $J_{H_bCCH_c}$, has evidently not changed significantly as a result of oxidation of the phosphines **5a** and **5b.** The values of $J_{H_aCH_b}$ for both the phosphines and the phosphine oxides indicate a nearly normal tetrahedral angle and thus considerable ring puckering.

Table II gives NMR data for the diastereomeric phosphonium salts **6a** and **6b.** It is interesting to note that the benzyl protons are nonequivalent owing to the adjacency of the benzyl methylene to an asymmetric phosphorus atom in each case. This is in marked contrast to the behavior of benzyl protons in the isomers of **1** and **2** which appear as one set of doublets.[2a-c]

Experimental Section

2-Hydroxypropyldiphenylphosphine (11). To 42.6 g (0.23 mol) of diphenylphosphine dissolved in 1 l. of anhydrous ether was added dropwise with stirring 159 ml of 1.45 M butyllithium. The reaction was conducted at 0 °C under nitrogen. The yellow reaction mixture was cooled to −78 °C using a dry ice–acetone bath and an equimolar amount of a 0.25 M solution of propylene oxide[15] in ether was added with stirring. After addition, the mixture was allowed to come to room temperature and 107 ml of 4 M ammonium chloride solution was added whereupon the earlier formed precipitate dissolved and the solution became colorless. The ether layer was removed and the aqueous layer was extracted twice with two portions of 200 ml of ether. The ether layer and extracts were combined. The residue, after concentration of the ether solution, was fractionally distilled and two principal fractions were obtained. The first fraction of bp 147 °C (0.05 mm) accounted for 51% of the product and was identified as **11.**

Anal. Calcd for $C_{15}H_{17}OP$: C, 73.76; H, 7.01; P, 12.68. Found: C, 73.76; H, 7.11; P, 12.54. NMR (neat) δ 1.27 (d, 3 H, J = 6 Hz, CCH_3), 2.29 (d of d, 2 H, PCH_2), 3.54–4.00 (m, 1 H, CHOH), 7.1–7.6 (m, 5 H, C_6H_5), 3.70 (s, 1 H, OH).

The infrared spectrum of a neat sample of **11** showed an intermolecular hydrogen bonded band at 3325 cm^{-1} which disappeared on dilution with chloroform. No appearance of a distinctive free OH stretching vibration could be observed upon dilution, but a band appeared at 3150 cm^{-1} which may be attributed to intramolecular association between phosphorus and the hydroxyl hydrogen.

A second fraction (13.4% yield) distilling at 153–154 °C (0.07 mm) was found to be enriched in $Ph_2PCH(CH_3)CH_2OH$: NMR (neat) δ 0.95 (d, 3 H, J = 6 Hz, $CHCH_3$), 4.23 (d, 2 H, J = 5 Hz, CH_2OH).

Anal. Calcd for $C_{15}H_{17}OP$: C, 73.76; H, 7.01; P 12.68. Found: C, 73.48; H, 7.12; P, 12.96.

NMR analysis of the reaction product prior to fractional distillation showed 81.5% of the hydroxyphosphine product to be **11** and 18.5% its isomer, $Ph_2PCH(CH_3)CH_2OH$.

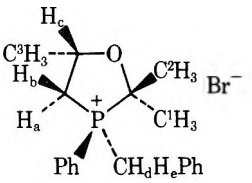
Preparation of 2-Hydroxypropyliodomethyldiphenylphosphonium Iodide (12). A benzene solution (50 ml) containing 1.2 g of **11** was treated with 2.8 g of methylene diiodide to yield 1.34 g of pure **12** after recrystallization from ethanol, mp 200.5–201 °C.

Anal. Calcd for $C_{16}H_{19}I_2OP$: C, 37.52; H, 3.74. Found: C, 37.57; H, 3.88.

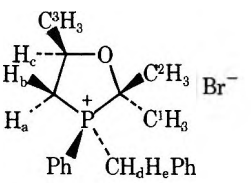
Attempted ring closure reactions with **12** using 2,4,6-trimethylpyridine failed to bring about cyclization and resulted in recovery of starting materials.

Hydroxymethyl-2-hydroxypropyldiphenylphosphonium Chloride (13). Equimolar amounts of **11** and 37% formaldehyde were allowed to react in concentrated hydrochloric acid at 0 °C. After 1 h the solution was extracted continuously for a period of 3 days with chloroform. The resulting glassy product was recrystallized from ethanol–ethyl acetate to give a 60% yield of **13** of mp 130.5–132.5 °C. Equivalent weight: calcd for $C_{16}H_{20}ClO_2P$, 310.7; found, 312.7.

Table II. NMR Data for Diastereoisomeric 3-Benzyl-3-phenyl-2,2,5-trimethyl-1,3-oxaphospholanium Bromides[a]



6a[c]



6b[d]

	6a	6b
Chemical Shifts (δ, ppm from Me_4Si)		
C^1H_3	2.06 (d)	2.03 (d)
C^2H_3	1.48 (d)	1.30 (d)
C^3H_3	1.56 (d)	1.53 (d)
H_a	2.34 (d of d)	*b*
H_b	2.46 (pent)	*b*
H_c	4.04 (pent)	3.98 (m)
H_d	5.00 (t)	4.88 (t)
H_e	5.50 (t)	5.41 (q)
Coupling Constants, Hz		
$J_{PCC^1H_3}$	13.7	14.7
$J_{PCC^2H_3}$	15.9	14.1
$J_{H_2CC^3H_3}$	7.11	6.74
$J_{H_aCH_b}$	14.0	*b*
$J_{H_bCCH_c}$	7.33	*b*
$J_{H_dCH_e}$	14.7	13.3
J_{PCH_a}	4.3	*b*
J_{PCH_b}	8.2	*b*
J_{PCH_d}	15.0	15.3
J_{PCH_e}	14.7	19.3

[a] Data measured at ambient temperature using a 60-MHz Perkin-Elmer R12-B spectrometer with Me_4Si as an internal standard in $CDCl_3$ solution. [b] The spectrum of **6b** could not be completely analyzed. [c] Registry no., 61009-62-9. [d] Registry no., 61009-63-0.

Anal. Calcd for $C_{16}H_{20}ClO_2P$: C, 61.79; H, 6.44; Cl, 11.41; P, 9.98. Found: C 61.57; H, 6.72; Cl, 11.44; P, 9.80. NMR ($CDCl_3$) δ 1.5 (unresolved d, 3 H, J = 6 Hz, CCH_3), 3.5 (m, 3 H, $CHCH_3$ and PCH_2OH), 5.25 (d of d, 2 H, PCH_2), 6.26 (s, 1 H, OH), 7.75 (m, 5 H, C_6H_5).

Attempted cyclization of **13** with catalytic quantities of *p*-toluenesulfonic acid, dimethyl sulfoxide,[11] or cyclohexylcarbodiimide were unsuccessful.

2-Hydroxypropylphenylphosphine (14). Phenylphosphine (41.1 g, 0.374 mol) was made to react with 260 ml of 1.45 M *n*-butyllithium in the manner described above for the preparation of **11**. The resulting solution was treated with 22.0 g of propylene oxide and the product worked up as for **11** to yield 70% of **14**: bp 103 °C (0.5 mm); NMR (neat) δ 1.25 (d, 3 H, J = 6 Hz, CCH_3), 1.66–2.66 (m, 2 H, CH_2), 3.56–4.16 (m, 1 H, CH), 4.62 (s, OH), 5.8–6.2 (d, 1 H, J = 216 Hz, PH), 6.93–7.66 (m, 5 H, C_6H_5). There was no NMR evidence for the formation of appreciable amounts of $PhPHCH(CH_3)CH_2OH$. Compound **14** was further characterized by reaction with cyclopentanone following the procedure for the synthesis of **5** given below to yield 50% of 5-methyl-3-phenyl-2,2-tetramethylene-1,3-oxaphospholane, bp 174 °C (0.4 mm).

Anal. Calcd for $C_{14}H_{19}OP$: C, 71.77; H, 8.17. Found: C, 72.0; H, 8.26.

***cis*- and *trans*-3-Phenyl-2,2,5-trimethyl-1,3-oxaphospholane (5).** 2-Hydroxypropylphenylphosphine (**14**, 11.3 g, 0.0673 mol), dissolved in approximately 350 ml of benzene, was mixed with 100 ml of acetone and 0.2 g of *p*-toluenesulfonic acid added as a catalyst. The reaction mixture was refluxed for 16 h and condensed vapors were passed through a Soxhlet extractor thimble filled with Linde 3A molecular sieves which had been dried at 140 °C for 60 h previous to use. At this point an additional 100 ml of acetone was added and the reaction mixture allowed to reflux in like manner for 6 h longer. The resulting solution was treated with sodium to precipitate unreacted phosphine as the sodium salt, and the precipitate was removed by filtration. After removal of the solvent, vacuum distillation of the residue yielded 9.80 g (70%) of product [bp 91 °C (1 mm)]. By NMR analysis, the product was shown to consist of 70% **5a** and 30% **5b** (Table I).

Fractionation of *cis*- and *trans*-2,2,5-Trimethyl-3-phenyl-1,3-oxaphospholane (15). A mixture of phosphines **5a** and **5b** (19.0 g) was subjected to fractional distillation on a spinning band column. The fraction boiling at 95 °C (3.5 mm) and consisting of 3.2 g was collected and shown by NMR to be isomerically pure. Based upon its NMR spectrum, this isomer is assigned the structure *r*-3-phenyl-2,2,*t*-5-trimethyl-1,3-oxaphospholane (**5a**).

***r*-3-Phenyl-2,2,*t*-5-trimethyl-1,3-oxaphospholane 3-Oxide (7a).** The pure isomeric oxaphospholane (**5a**) was oxidized with *tert*-butyl hydroperoxide in accordance with a literature procedure[8] to yield the corresponding oxide (**7a**) of bp 115 °C (0.07 mm) (Kugelrohr), mp 78–80 °C.

Anal. Calcd for $C_{12}H_{17}O_2P$: C, 64.27; H, 7.64. Found: C, 64.18; H, 7.88. NMR data are presented in Table I.

Cleavage of 3-Benzyl-*r*-3-phenyl-2,2,*t*-5-trimethyl-1,3-oxaphospholanium Bromide (6a). This salt (0.715 g) was cleaved with 1 N sodium hydroxide under previously described conditions except that the reaction time was limited to 1 h. GLC analysis of the cleavage product showed the formation of toluene to the exclusion of any benzene. The oxide **7a** was obtained in 93% yield and was identical in every respect with that prepared by *tert*-butyl hydroperoxide oxidation of **5a**. The NMR spectrum of the product, mp 78–80 °C, showed no trace of **7b**. The spectrum of **7b** was determined by *tert*-butyl hydroperoxide oxidation of a 60:40 mixture (trans:cis) of the isomeric oxaphospholanes and subtraction of the spectrum of **7a**.

Cleavage of 3-Benzyl-*r*-3-phenyl-2,2,*c*-5-trimethyl-1,3-oxaphospholanium Bromide (6b). A salt mixture consisting of 38% of **6b** and 62% of **6a** as determined by NMR analysis was treated with 1 N sodium hydroxide as described above for **6a**. Upon workup, a mixture of oxides consisting of 42% **7b** and 58% **7a** of bp 120 °C (0.2 mm) (Kugelrohr) was obtained in 93% yield. The composition of reactants and products is consistent with complete retention of configuration within the limits of error of NMR integration.

Anal. Calcd for $C_{12}H_{17}O_2P$: C, 69.21; H, 8.23. Found: C, 69.29; H, 8.31. NMR spectrum (see Table I).

All higher boiling fractions were combined and carefully redistilled. The final fraction (1.90 g) of bp 97 °C (3 mm) was collected and shown to consist of 80% of *r*-3-phenyl-2,2,*c*-5-trimethyl-1,3-oxaphospholane (**5b**) and 20% of the corresponding trans isomer (**5a**). Further separation was not achieved. The NMR spectrum of **5b** was obtained by difference (Table I).

Anal. Calcd for $C_{12}H_{17}OP$: C, 69.21; H, 8.23. Found: C, 69.30; H, 8.18.

3-Benzyl-*r*-3-phenyl-2,2,*t*-5-trimethyl-1,3-oxaphospholanium Bromide (6a). The pure phosphine **5a** (1.4 g, 0.0067 mol) was treated with 2.3 g of benzyl bromide in 50 ml of benzene. After 1 week at room temperature the resulting crystals were removed and recrystallized from ethanol–ethyl acetate to give 1.9 g of **6a**, mp 208–209 °C. For NMR spectrum see Table II.

Anal. Calcd for $C_{19}H_{24}OPBr$: C, 60.17; H, 6.38. Found: C, 59.91; H, 6.58.

Mixtures Enriched in 3-Benzyl-*r*-3-phenyl-2,2,*c*-5-trimethyl-1,3-oxaphospholanium Bromide (6b). A mixture consisting of 80% **5b** and 20% **5a** (1.19 g), dissolved in 50 ml of benzene, was treated with 1.96 g of benzyl bromide and, after 2 days, 1.855 g of crude product recovered. The crude material was recrystallized from ethyl acetate–ethanol to give a product of mp 200–202 °C.

Anal. Calcd for $C_{19}H_{24}OPBr{\cdot}C_2H_5OH$: C, 59.30; H, 7.11. Found: C, 59.41; H, 7.09. The NMR spectrum indicated the presence of 1 mol of ethanol per mole of phosphonium salt.

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Registry No.—**11**, 2652-63-3; **12**, 61009-64-1; **13**, 61047-25-4; **14**, 2328-18-9; diphenylphosphine, 829-85-6; propylene oxide, 75-56-9; $Ph_2PCH(CH_3)CH_2OH$, 61009-65-2; formaldehyde, 50-00-0; phenylphosphine, 638-21-1; cyclopentanone, 120-92-3; 5-methyl-3-phenyl-2,2-tetramethylene-1,3-oxaphospholane, 61047-24-3.

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A Stereochemical Study of the Reactions of Trisubstituted Phosphites with *N*-Chlorodialkylamines[1]

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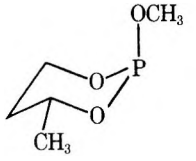
The cyclic phosphites 1 and 2 have been allowed to react with *N*-chlorodialkylamines. Mixtures of geometric isomers of cyclic phosphoramidates result. The loss of stereochemistry is consistent with a mechanism in which there is initial insertion by the phosphorus into the N–Cl bond to give a phosphorane which can pseudorotate in competition with ionization. The results do not eliminate a competing ionic reaction; however, a total ionic process would have been expected to be stereospecific. Rate studies on trivalent phosphorus compounds of varying nucleophilicity show that the rates of the reactions do not follow a straight nucleophilicity order. These results also support the insertion mechanism.

Evidence has been provided that trivalent phosphorus compounds can react with substances containing weak σ bonds to give phosphoranes which are products of insertion into the σ bond. When these products are found in a concerted process, the reaction has been called a "biphilic insertion reaction".[2] The formation of phosphoranes does not in itself yield any information concerning the mechanism of their formation.

In some reactions phosphoranes are formed as unstable intermediates and these decompose under conditions that do not allow for their detection. In these cases indirect methods are required to infer the formation of pentacoordinate intermediates. Two of the more powerful methods for accomplishing this task are stereochemical studies and kinetic investigations.[3]

The stereochemistries of reactions of the two isomeric phosphites 1 and 2 have often been used as a mechanistic



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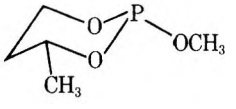

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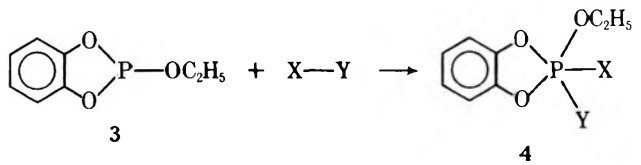
probe. Stereochemically homogeneous reactions have been observed in a number of cases. These results combined with other studies have led to the conclusion that stereochemically pure nonradical reactions follow ionic pathways. They involve as the first step displacement by phosphorus, which is functioning as a nucleophile, to give an ion pair which collapses by attack of the anion of the ion pair on the methyl group carbon. Thus 1 and 2 react stereospecifically with chlorine to give two isomeric phosphorochloridates.[4] Similarly benzenesulfenyl chloride reacts stereospecifically with 1 and 2.[5] These results have been rationalized in terms of ionic reaction mechanisms. Unfortunately, these results cannot be generalized for all phosphorus containing nucleophiles. For example, it has been recently shown that ethyl catechol phosphite (3) reacts at low



3 4

X = Y = Cl

X = C_6H_5S; Y = Cl

temperatures with both chlorine and benzenesulfenyl chloride to give phosphoranes. These substances were detected by low temperature ^{31}P NMR measurements.[6] These findings do not eliminate a series of ionic steps for the formation of the phosphoranes; however, direct insertion becomes a viable possibility.

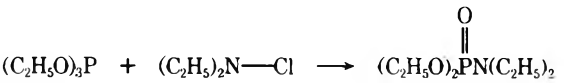
Benzoyl peroxide reacts with 1 and 2 with some loss of stereochemistry.[7] Other work has shown that this is most probably an ionic reaction and that the loss of stereochemistry most likely occurs after the initial displacement.

The reactions of 1 and 2 with neopentyl hypochlorite have been interpreted as involving the formation of pentacoordinate intermediates which undergo permutational isomerization in competition with ionization.[8]

Interpretation of loss of stereochemistry in reactions of 1 and 2 must be done with considerable care. The thermodynamic equilibrium mixture of 1 and 2 is 95:5. Conversion of 2 into the equilibrium mixture is extremely facile and it is catalyzed by traces of acid. Isomerization can compete with the desired reaction and lead to loss of stereochemistry by this pathway.[9] The least stable isomer, 2, is considerably more nucleophilic than 1 and it is conceivable that the two isomers might react with the same substrate by different reaction mechanisms.

It was the purpose of this work to study the stereochemistries of the reactions of 1 and 2 with various *N*-chlorodialkylamines. At the same time competitive kinetic experiments between various trivalent phosphorus compound were conducted. This was done to assess the response of the rates of the reactions toward variations in the nucleophilicity of the trivalent phosphorus compounds.

Petrov and Sokolskii[10] have studied the reaction of triethyl phosphite with *N*-chlorodiethylamine (5). They found that the phosphoramidate, 6, was the product. More recently

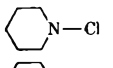
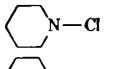
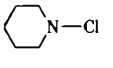


5 6

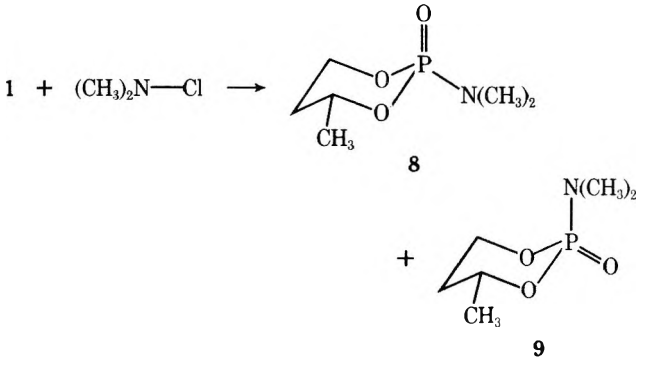
phosphoranes have been isolated from the reactions of *N*-chlorohexafluorodimethylamine with various trivalent phosphorus compounds.[11,12]

There have been two reports of the reactions of 1 and 2 with *N*-chlorodimethylamine (7). Mosbo and Verkade[13] allowed 1 to react with 7 in refluxing benzene. They obtained a 2:1 mixture of 8:9. Stec and Mikotajczyk[4] allowed 1 to react with 7 in methylene chloride and they obtained a 91:9 mixture of 8 and 9. When 2 was allowed to react with 7 a 65:35 mixture of 8 to 9 resulted. The results of these two studies show that the reactions have different stereochemistries and that the stereochemistries are affected by the reaction conditions, i.e., solvent and temperature.

Table I. Reactions of 1 and 2 with *N*-Chlorodialkylamines[a]

Isomer composition, %	R_2NCl	Product composition, %	Solvent	Temp, °C
1:2	$(C_2H_5)_2NCl$	11:12		
95:5	$(C_2H_5)_2NCl$	43:57	Hexane	25
95:5	$(C_2H_5)_2NCl$	65:35	Benzene	25
95:5	$(C_2H_5)_2NCl$	80:20	Benzene	78
95:5	$(C_2H_5)_2NCl$	83:17	Benzene	78
95:5	$(C_2H_5)_2NCl$	22:78	CH_2Cl_2	25
15:85	$(C_2H_5)_2NCl$	80:20	Hexane[b]	25
15:85	$(C_2H_5)_2NCl$	86:14	Benzene	25
15:85	$(C_2H_5)_2NCl$	89:11	Benzene	78
30:70	$(C_2H_5)_2NCl$	84:16	CH_2Cl_2	25
5:95	$(C_2H_5)_2NCl$	95:5	CH_2Cl_2	−70 to 25
1:2	$(CH_3)_2NCl$	8:9		
95:5	$(CH_3)_2NCl$	64:35	CH_2Cl_2	25
5:95	$(CH_3)_2NCl$	48:52	CH_2Cl_2	−78 to 25
5:95	$(CH_3)_2NCl$	45:55	CH_2Cl_2	−78 to 25
5:95	$(CH_3)_2NCl$	49:51	CH_2Cl_2	−78 to 25
95:5	$(CH_3)_2NCl$	40:60	Hexane	25 $t/2$ = 5 h
5:95	$(CH_3)_2NCl$	84:16	Hexane	25 (1 h)
1:2		13:14		
95:5		40:60	CH_2Cl_2	25
10:90		68:32	CH_2Cl	0 to 25

[a] The reactions of the *N*-chlorodiethylamines with 1 and 2, in general, gave the corresponding phosphoramidates in greater than 80% yield. In the reactions of *N*-chlorodimethylamine and *N*-chloropiperidine with 1 and 2, the isomeric phosphoramidates were obtained in 90–95% yield. All isomeric phosphoramidates were identified by ^{31}P NMR peak enhancements with authentic samples prepared via an independent route and by other spectral information. The ratios of the isomers were determined by integration of the ^{31}P NMR spectra on expanded sweep width. In the reactions of *N*-chlorodiethylamine with 1 and 2, the isomer ratios were also determined by the areas obtained by GLC analysis. [b] Run in presence of calcium hydride.



Other reactions of *N*-halo compounds with trivalent phosphorus compounds have been recently reviewed.[14]

Results and Discussion

The percentages of the products of the reactions of 1 and 2 with 7, *N*-chlorodiethylamine (5), and *N*-chloropiperidine (10) are collected in Table I. The products 8 and 9 had been previously characterized.[4,13] The products of the reactions of 5 are 11 and 12 with the same stereochemistries as 8 and 9, respectively. These materials were prepared by an independent route as were 13 and 14, the products of the reaction of 10. The structures of these materials have been assigned on the basis of ^1H and ^{31}P NMR spectroscopy, and on the basis of the effect of a lanthanide shift reagent on the ^1H NMR spectra of these materials. This latter technique has been used previously by Bentrude and Tan[15] and Mosbo and Verkade[13] for similar compounds. The infrared spectra of these compounds followed the pattern observed for similar pairs of isomers.[13,15]

A control experiment was conducted to determine if isomerization of 2 → 1 was important during the reaction of 7 with a 22:78 mixture of 1:2 in methylene chloride. The mixture (2 mmol) was allowed to react with 0.8 mmol of 7. The composition of the remaining starting material after the reaction was 1, 38.5, and 2, 61.5. This change in ratio is due to the greater concentration and reactivity of 2. If rapid isomerization had occurred the ratio would have been 1, 95, and 2, 5. Isomerization is usually fast and complete when it occurs.

The stability of the products was investigated by allowing 1 and 2 to react with 10 in the presence of 14, the least stable isomer. Analysis of the reaction mixture after the reaction showed that the ratio of 13 to 14 was just that which would have been predicted if no isomerization of 14 had occurred.

When *N*-chlorodiisopropylamine (15) was allowed to react with 1 and 2 at 25°C for 2 weeks, there was essentially no reaction. Similarly trimethyl phosphite did not react with 15 over a 2-week period at 25 °C.

The reactions of $(C_2H_5O)_3P$ (16), $C_6H_5P(OC_2H_5)_2$ (17), $(C_6H_5)_2POC_2H_5$ (18), $(C_6H_5)_3P$ (19), methyl ethylene phosphite (20), and methyl catechol phosphite (21) were conducted with pairs of reactants and *N*-chlorodiethylamine. The ratio of products was determined. In each case there was no change in the nature of the products from those obtained from each reactant and *N*-chlorodiethylamine, and also there was no change in the remaining starting materials after the competitive rate studies were completed. The relative rates for the reactions in methylene chloride were found to be $(C_6H_5)_3P$, 3.5; $(C_6H_5)_2POC_2H_5$, 4.5; $C_6H_5P(OC_2H_5)_2$, 3.8; and $(C_2H_5O)_3P$, 1.0. Triethyl phosphite was found to react to the exclusion of 20 which in turn reacted to the exclusion of 21. In hexane the relative rates were $(C_6H_5)_3P$, 2.3; $(C_6H_5)_2POC_2H_5$, 2.1; $C_6H_5P(OC_2H_5)_2$, 2.3; $(C_2H_5O)_3P$, 1.0; 20, 1.0; and 21, 0.11.

The stereochemical results of the reactions of 1 and 2 with the various *N*-chlorodialkylamines show quite clearly that varying amounts of loss of stereochemistry occur during the reactions. The results therefore are suggestive of the formation of phosphoranes as intermediates in the reactions. They do not of course rule out competing ionic reactions and perhaps even changes in mechanism with changes in reaction conditions and reactants. An ionic pathway with 1 as an example and considering displacement on nitrogen as being most likely[14] would be stereospecific as illustrated below.

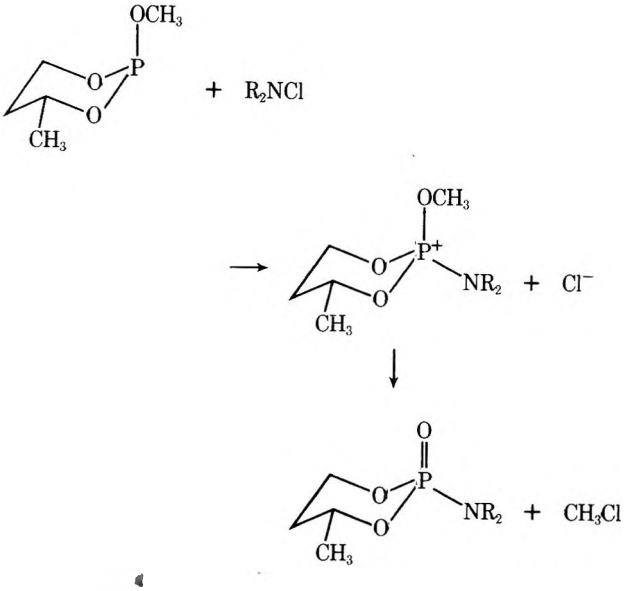


Table II. Spectral Data for 1,3,2-Dioxaphosphorinanes

Registry no.	Compd	R_1	R_2	$\delta^{31}P$, ppm	δCH_3	δNCH_2	$\delta NCCH_3$	J_{CHCH_3}	J_{PNCH_2}	$J_{NCH_2CH_3}$	J_{POCCH_3}	IR, cm^{-1} $\nu_{P=O}$ ($CHCl_3$)
54515-66-1		Lone pair	NEt_2	−144	1.22	3.1	1.05	6.5	9.5	7		
54515-67-2		NEt_2	Lone pair	−135	1.28			6.5				
	11	O	NEt_2	−7	1.29	3.08	1.07	6.5	12	7	2.5	1231
	12	NEt_2	O	−3.5	1.38	3.03	1.09	6.5	11	7	1.5	1242
41252-67-9		Lone pair		−139.5	1.22	2.7–3.3		6.5				
61062-26-8			Lone pair	−134.5								
	13	O		−4.5	1.28	2.73–3.3		6.5			2.5	1238
	14		O	−2.5	1.37	2.78–3.32		6.5			2.0	1242

Mosbo and Verkade[13] have provided evidence that the most thermodynamically stable isomers of the pair **8** and **9** is **8**, the compound in which the dialkylamino groups is in an equatorial position. The data in Table I show that there is a trend toward this type of product in most cases, the notable exception being the reaction **1**, 95, and **2**, 5, with *N*-chlorodiethylamine in which the opposite was observed. This result was reproducible.

Another anomaly is that Stec and Mikotajczyk[4] found that **1**, 95, and **2**, 5, with **7** gave 91% **8** and 9% **9**. Their results were not duplicated in this study. No apparent reason for these different results can be offered at this time.

The relative rate data suggest that the initial reaction involves insertion into the nitrogen–chlorine bond; however there is an apparent nucleophilic component which renders **20** and **21** less reactive than triethyl phosphite. The opposite reactivity order, i.e., **21** > **20** > **16**, was found for the reaction of diethyl peroxide with these substances.[16] The small rate change with changes in structure in the series **16**–**19** mimics that found for the diethyl peroxide reaction.[17] It has been shown that in S_N2 displacement reactions the rate increases through the series with triphenylphosphine being the most reactive.[18] Clearly it is not possible to conclude that the stereochemical and kinetic data require the direct insertion mechanism; they do, however, favor it.

Experimental Section

Instrumentation. ^1H NMR spectra were recorded on a Varian T-60 spectrometer. Chemical shifts are reported in parts per million relative to internal tetramethylsilane. Phosphorus NMR spectra were recorded on a Varian HA-100 spectrometer operating at 40.5 MHz and chemical shifts are reported in parts per million relative to external 85% phosphoric acid. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrometer. GLC analyses were performed on a F and M Model 700 gas chromatograph using a 20 ft × 0.125 in. 5% silicone gum nitrile column, XE-60.

Materials. The trivalent phosphorus compounds were either obtained commercially or prepared by known procedures unless otherwise stated. *N*-Chlorodialkylamines were prepared in hexane, benzene, and methylene chloride by previously reported procedures[19] and they were dried over sodium sulfate. The chloroamine solutions were standardized by iodometric titration. All reactions involving trivalent phosphorus compounds were carried out under an atmosphere of dry nitrogen. The solvents were anhydrous and deoxygenated by a dry nitrogen flush. NMR samples of phosphorus compounds were deoxygenated with a stream of nitrogen. All spectral data are tabulated in Tables II and III.

Preparation of 2-Diethylamino-4-methyl-1,3-dioxaphosphorinane. To a cold (0 °C) solution of 2.93 g (40 mmol) of diethylamine in 50 ml of anhydrous ether was added dropwise with stirring a solution of 3.08 g (20 mmol) of freshly prepared 2-chloro-4-methyl-1,3,2-dioxaphosphorinane in 20 ml of ether. After stirring for 2 h at 0–5 °C the reaction mixture was filtered through a filter stick under nitrogen. The white solid was washed with two 50-ml portions of ether. The combined ether solutions were concentrated to give a colorless oil which gave absorptions at −135 and −144 ppm with approximately equal intensities in the ^{31}P NMR spectrum. Distillation of the mixture at 47–48 °C (0.2 Torr) gave a colorless liquid. Its ^{31}P NMR spectrum showed one absorption at −144 ppm. Upon standing for 5 days, the crude mixture gave one major absorption at −144 ppm (~95%) in the ^{31}P NMR spectrum. This material was assigned the cis configuration.[20]

The ^1H NMR spectrum of a 50:50 mixture of the cis and trans isomers showed two doublets, δ 1.22 (J = 6.5 Hz) and 1.28 (J = 6.5 Hz), for the hydrogens of the ring methyl groups.

Preparation of 2-Diethylamino-4-methyl-2-oxo-1,3,2-dioxaphosphorinane (11). To a chilled solution of 1.91 g (10 mmol) of distilled 2-diethylamino-4-methyl-1,3,2-dioxaphosphorinane in 5 ml of methylene chloride there was added dropwise a saturated solution of N_2O_4 in methylene chloride until a permanent green end point was reached. The excess N_2O_4 and the solvent were removed in vacuo to give 1.8 g (87%) of a yellow liquid, whose ^{31}P NMR shifts were −7 (>95%) and −3.5 ppm (<5%). GLC analysis showed two components in a ratio of 94:6 with retention times of 29 and 46 min. Since the oxidation with N_2O_4 is known to proceed with retention of configuration

this product is assigned the structure **11**. Distillation at 98 °C (0.2 Torr) gave pure **11**.

A mixture of cis and trans isomers (50:50) was oxidized as described above with N_2O_4. The ^{31}P NMR spectrum showed two signals at −7 and −3.5 ppm with approximately equal intensities. GLC analysis showed two components in a ratio of 45:55. Addition of **11** augmented the lower boiling component in GLC analysis and the signal at −7 ppm in the ^{31}P NMR spectrum. The structure of the higher boiling component is assigned as **12**.

Preparation of 2-Piperidinyl-4-methyl-1,3,2-dioxaphosphorinane. This compound was prepared in a manner similar to the methods described above. From 7.7 g (0.05 mol) of 2-chloro-4-methyl-1,3,2-dioxaphosphorinane and 9.4 g (0.11 mol) of piperidine in ether, there was obtained after the usual isolation a colorless liquid. Its ^{31}P NMR spectrum showed two signals at −139.5 (91%) and −134.5 ppm (9%). Distillation at 95–96 °C (1.5 Torr) gave 8.6 g (78%) of a mixture of the cis and trans isomers (91:9).

Preparation of *cis*-2-Piperidinyl-4-methyl-2-oxo-1,3,2-dioxaphosphorinane. The cis isomer was prepared by oxidation of *cis*-2-piperidinyl-4-methyl-1,3,2-dioxaphosphorinane (90:10) with N_2O_4 as described above. Its ^{31}P NMR spectrum showed two signals at −5 (90%) and −2.5 ppm (10%).

Preparation of *trans*-2-Piperidinyl-4-methyl-2-oxo-1,3,2-dioxaphosphorinane (14). A solution of 3.0 g (0.176 mol) of *cis*-2-chloro-4-methyl-2-oxo-1,3,2-dioxaphosphorinane in 30 ml of benzene was added dropwise to a solution of 3.0 g (0.353 mol) of piperidine in 30 ml of benzene with stirring and cooling (5 °C). After the addition, the mixture was stirred at room temperature for 2 h, and the piperidine hydrochloride was removed by filtration. The filtrate was extracted with 50 ml of 1 N hydrochloric acid; it was washed with water and dried over sodium sulfate. Evaporation of the solvent in vacuo gave a light yellow oil which solidified upon standing. Recrystallization of the crude solid from cyclohexane gave 2.5 g (66%) of white, crystalline **14**, mp 59–61 °C.

Reaction of 1 or 2 with *N*-Chlorodialkylamine. A solution of 1.5 g (10 mmol) of **1** or **2** in 10 ml of the chosen solvent was mixed with 8 ml of 1.25 M *N*-chlorodialkylamine in the same solvent at −78 °C. After the mixture was warmed to room temperature, an aliquot was removed for NMR studies which were in turn used to monitor the course of the reaction. After the reaction was completed (less than 0.5 h for **2**, 6 h for **1**), the mixture was concentrated in vacuo and the product distribution was determined by ^{31}P NMR spectroscopy and/or GLC. All components were identified by peak augmentation with an authentic sample. The non-phosphorus-containing byproduct, methyl chloride, was identified by ^1H NMR spectroscopy.

Two control experiments were performed as follows.

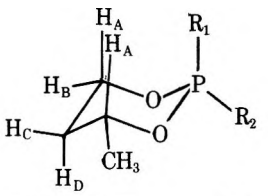
(1) A mixture of 2 mmol of **1** and **2** (22:78) was allowed to react with 0.8 mmol of *N*-chlorodimethylamine. The final mixture contained **1** (0.46 mmol), **2** (0.74 mmol), **8** (0.48 mmol), and **9** (0.35 mmol). The molar ratio of **1** to **2** after reaction is in complete agreement with the calculated based on the assumption that **2** reacts faster than **1** and reacts exclusively with the limiting *N*-chlorodimethylamine. The molar ratio of **8** and **9** was in close agreement with those found in the reaction of **2** with *N*-chlorodimethylamine.

(2) A mixture of 2 mmol of **2** and **1** (73:27) was allowed to react with 1 mmol of *N*-chloropiperidine in the presence of 0.39 mmol of **14**. The final reaction mixture contained nonreacted **2** and **1** in a molar ratio of 42:58 and product **14** and **13** in a molar ratio of 53:47 (0.69 mmol to 0.61 mmol), in addition to 15% of phosphates. After subtracting the amount of **14** present before the reaction, the product ratio of **14** to **13** is 68:32 which is consistent with those found in the reaction of **2** with *N*-chloropiperidine.

Competition Reactions of P(III) Compounds with *N*-Chlorodialkylamines. A solution of 5 mmol of the P(III) compound in 5 ml of solvent (CH_2Cl_2 or hexane) was treated with a solution of 5 mmol of *N*-chlorodiethylamine dropwise at −78 °C with stirring. Usually, there was no reaction at −78 °C; the mixture was then warmed to room temperature and stirred for at least 30 min. ^1H and ^{31}P NMR spectra were recorded before and after the mixture was concentrated.

In competitive rate studies, a solution of *N*-chlorodiethylamine was added dropwise to a solution of a mixture of the two P(III) compounds in a molar ratio of 1:1:1. The product distribution was analyzed by ^{31}P NMR spectroscopy (peak height measurement) and ^1H NMR spectroscopy when feasible.

Table III. Lanthanide[a] Shift Behavior of Selected Protons in 11–14



Compd	Molar[b] ratio	Δδ H_A[c]	Δδ H_B[c]	Δδ $H_{C,D}$[c]
11	0.1	0.23	0.23	0.06
	0.25	1.33	0.8	0.04
	0.5	2.53	0.93	0.9
12	0.1	0.16	0.16	0.28
	0.25	0.40	0.40	0.55
13	0.08	0.44	0.44	0.30
	0.12	1.20	0.20	0.43
	0.19	1.68	0.28	0.58
	0.25	2.10	0.58	0.72,[d] 1.02[e]
14	0.08	0.10	0.10	0.22
	0.12	0.30	0.30	0.25
	0.19	0.41	0.41	0.44
	0.25	0.70	0.70	0.71

[a] Eu(fod)$_3$-d_{30}: tris(1,1,1,2,2,3,3-heptafluoro-4,6-octanedione)europium III-d_{30}. [b] Molar ratio of Eu/P (0.2 M). [c] The downfield shifts in parts per million were obtained by comparing spectra of 0.2 M solution of the phosphorus compounds in $CDCl_3$ with and without added shift reagent. [d] Proton C. [e] Proton D.

Registry No.—**1**, 7735-81-1; **2**, 7735-85-5; **8**, 41158-20-7; **9**, 41158-21-8; **11**, 61062-22-4; **12**, 61062-23-5; **13**, 61062-24-6; **14**, 61062-25-7; chlorodiethylamine, 5775-33-7; chlorodimethylamine, 1585-74-6; *N*-chloropiperidine, 2156-71-0; 2-chloro-4-methyl-1,3,2-dioxaphosphorinane, 6362-87-4; *cis*-2-chloro-4-methyl-2-oxo-1,3,2-dioxaphosphorinane, 38302-69-1.

References and Notes

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A Stereoselective Route to the Prostaglandin Intermediate from Norbornadiene

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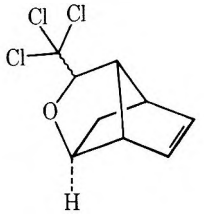
Tricyclic compound **2** which was prepared from norbornadiene (**1**) was shown to be an excellent starting material for the preparation of prostaglandins. **2** was transformed reductively into the bicyclic ketene dichloride **3** with zinc and acetic acid which on tosylation followed by solvolysis afforded the epimeric tricyclic acetate **5**. Hydrolysis, followed by Jones oxidation, of **5** afforded the tricyclic ketone **9** in an excellent yield. The cyclopropane ring of **9** was cleaved regio- and stereoselectively with hydrobromic acid to give the bromo ketone **11** which upon the Baeyer–Villiger oxidation, followed by heating with ethanol, provided the monocyclic ester **13**. **13** was treated with mercuric acetate or silver perchlorate under the solvolytic condition to form the lactone **16** stereoselectively. The Corey prostaglandin aldehyde (**18**) was prepared in two steps by acylation with 4-phenylbenzoyl chloride and subsequent ozonolysis.

Corey's group[1] and Sutherland's group[2] have independently described the synthesis of the synthon for all the primary prostaglandins from norbornadiene (**1**). We wish to report here an alternative synthesis of the synthon **18**[3] from norbornadiene (**1**) by a stereoselective sequence which would allow a practical production of the prostaglandins. Special practical values of this synthesis are mild reaction conditions employed, dispensability of chromatographic purifications, and a good overall conversion. Further, this approach would be applied to the synthesis of the Fried prostaglandin synthon (**20**),[4] since the key intermediate (**16**) of the synthon **18** possessed a potential acetylenic function at the right position as a ketene dichloride group.[5]

1



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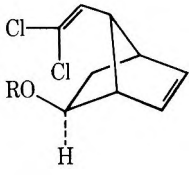
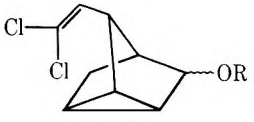
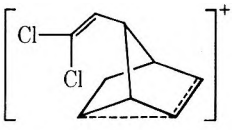


3, R = H
4, R = *p*-tosyl



5, R = Ac
6, R = H



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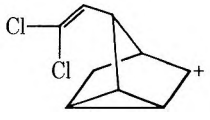

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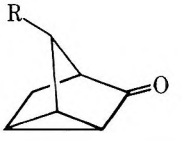
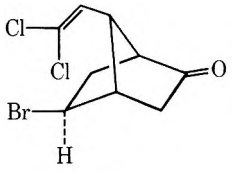


9, R = CH=CCl$_2$
10, R = CO$_2$H



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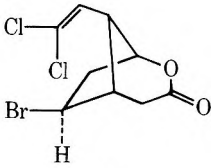

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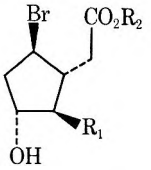
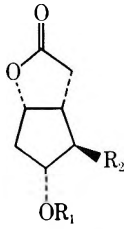


13, R$_1$ = CH=CCl$_2$; R$_2$ = Et
14, R$_1$ = CO$_2$H; R$_2$ = H



15, R$_1$ = H; R$_2$ = CO$_2$H
16, R$_1$ = H; R$_2$ = CH=CCl$_2$
17, R$_1$ = PB; R$_2$ = CH=CCl$_2$
18, R$_1$ = PB; R$_2$ = CHO
19, R$_1$ = PB; R$_2$ = CH$_2$OH
20, R$_1$ = H; R$_2$ = CH=CH—C(OH)(H)—*n*-C$_5$H$_{11}$

PB = *p*-phenylbenzoyl

The tricyclic compound **2**, prepared by following Fritz et al.,[6] from norbornadiene (**1**) and chloral in the presence of aluminum chloride, was treated with zinc and acetic acid to give the bicyclic ketene dichloride **3** in a 74.2% yield. This was tosylated with *p*-toluenesulfonyl chloride in pyridine affording the tosylate **4**, which on treatment with potassium acetate in acetic acid at 50–52 °C gave the tricyclic acetate **5** as an 1:1 epimeric mixture in an excellent overall yield. In the solvolysis a bulky dichloroketene group would control the regioselectivity leading to the exclusive formation of a localized carbonium ion (**8**) through a nonclassical carbonium ion (**7**) and the stability of the ion **8** would allow the nonstereoselective nucleophilic attack from both endo and exo sides to form an epimeric mixture of the acetates (**5**). However, the nonstereoselectivity was not an important problem from the synthetic point of view, since the epimeric center was lost in the later stage. Hydrolysis of this mixture with ethanolic potassium carbonate afforded an epimeric mixture of the alcohols (**6**), quantitatively, which on oxidation by means of the Jones reagent gave rise to the tricyclic ketone **9** as a sole product in a 95.8% yield. The structure and stereochemistry of the products was established by transforming **6** into the known keto acid **10**[1,2] through a two-stage oxidation by ozonolysis, followed by Jones oxidation. Electrophilic regio- and stereochemical ring opening of the cyclopropyl ketone system in **9** was accomplished cleanly to give an 87.6% yield of the bicyclic bromo ketone **11** by hydrobromic acid in hot acetic acid which has been successfully applied to the keto acid **10** by Sutherland's

group.[2] By use of 1.2 molar equiv of *m*-chloroperbenzoic acid in chloroform or methylene chloride at room temperature, the bromo ketone **11** was oxidized chemo- and regioselectively to yield the δ-lactone **12** as a sole product. Susceptibility of the lactone **12** to the alcoholic solvent made us isolate the product as the monocyclic ethyl ester **13** after a brief heating of the reaction mixture with ethanol in the presence of *p*-toluenesulfonic acid. Since intramolecular lactonization catalyzed by hydroxide ion, which has been successfully employed to convert the similar compounds (**14**[1] and **14**[2], Br = Cl) into the lactone **15**, was ineffective to our compound (**13**), an alternative method was developed. Initially we selected mercuric acetate as a catalyst to convert **13** into the lactone **16** under the solvolytic condition. This choice was based on the observation by McKillop and Ford[7] that mercuric salts catalyzed the solvolytic nucleophilic substitution of aliphatic halides. The bromo ester **13** was treated with 1 molar equiv of mercuric acetate in the presence of perchloric acid in aqueous dimethoxyethane at room temperature to yield the lactone **16** in a 79.0% yield. A substitution of poisonous mercuric acetate was simply achieved by using silver salt instead. Thus, the treating of the bromo ester **13** with 1 molar equiv of silver perchlorate under the same condition as the mercuric salt gave rise to **16** in an 82.8% yield with a precipitation of a recoverable solid silver by-product. The conversion of the lactone **16** into the prostaglandin synthon (the Corey aldehyde) (**18**) was completed by a two-step sequence by acylating with *p*-phenylbenzoyl chloride, followed by ozonolysis in an excellent overall yield. The unstable aldehyde **18** was reduced with sodium borohydride to give the known alcohol **19** which was completely identical with the authentic material. Conversion of the lactone **16** into the Fried prostaglandin synthon **20** is now under investigation.

Experimental Section[8]

7-(2,2-Dichlorovinyl)-5-hydroxy-2-norbornene (3). To a stirred suspension of 5-trichloromethyl-4-oxatricyclo[4.3.0.0^{3,7}]non-8-ene (**2**,[6] 11.98 g, 50 mmol) and zinc powder (22.88 g, 0.35 g-atom) in ether (300 ml) was added a solution of acetic acid (50 ml) in ether (200 ml) at 0 °C and the mixture was stirred for 8 h at room temperature. The organic layer was filtered and the insoluble material was washed thoroughly with ether. The combined ethereal solution was washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left crude **3** (9.43 g), which on crystallization from petroleum ether yielded pure **3** (7.6 g, 74.2%) as colorless needles: mp 35–37 °C; ν_{max} (neat) 3300, 3050, 1605, 1570, 1050 cm^{-1}; δ 1.65 (2 H, m), 1.76 (1 H, s, disappeared with D_2O), 2.80 (3 H, br s), 3.96 (1 H, m), 6.16 (1 H, m), 6.00 (1 H, m), 6.44 (1 H, d, J = 9.5 Hz); *m/e* 208, 206, 204, 160 (100). Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91; Cl, 34.57. Found: C, 52.45; H, 4.80; Cl, 34.35.

3-Acetoxy-7-(2,2-dichlorovinyl)tricyclo[2.2.1.0^{2,6}]heptane (5). A solution of **3** (2.05 g, 10 mmol) in dry pyridine (20 ml) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (6.30 g, 33 mmol) with stirring under nitrogen for 2 h. After 24 h at room temperature, the reaction mixture was diluted with water and extracted with benzene. The organic layer was washed with 10% HCl and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a practically pure oily tosylate (**4**, 3.55 g, 98.9%) which was used without further purification: ν_{max} (neat) 3050, 1605, 1595, 1570, 1355, 1185, 1170 cm^{-1}; δ 1.72 (2 H, m), 2.44 (3 H, s), 2.82 (3 H, m), 4.56 (1 H, m), 6.00 (2 H, m), 6.06 (1 H, d, J = 9.5 Hz), 7.32 (2 H, d, J = 8.5 Hz), 7.79 (2 H, d, J = 8.5 Hz).

Crude **4** (3.59 g, 10 mmol) and fused potassium acetate (1.96 g, 20 mmol) were dissolved into acetic acid (80 ml) and the mixture was heated at 50–52 °C for 42 h with stirring under nitrogen. After cooling, the reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a practically pure oily **5** (2.47 g, 87.1%) as a 1:1 epimeric mixture, which was used without further purification. A preparative GLC (10% SE-30, 1-m column) purification afforded an analytically pure endo isomer: ν_{max} (neat) 1730, 1605, 1235 cm^{-1}; δ 1.43 (6 H, m), 2.07 (3 H, s), 2.67 (1 H, d, J = 6.0 Hz), 4.72 (1 H, br s), 5.65 (1 H, d, J = 6.0 Hz); *m/e* 250, 248, 246, 43 (100). Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.89. Found: C, 53.65; H, 5.09. Exo isomer: ν_{max} (neat) 1730, 1605, 1235 cm^{-1}; δ 1.43 (6 H, m), 2.09 (3 H, s), 3.11 (1 H, d, J = 6.0 Hz), 4.75 (1 H, br s), 5.81 (1 H, d, J = 6.0 Hz); *m/e* 250, 248, 246, 43 (100). Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.89. Found: C, 53.70; H, 5.12.

7-(2,2-Dichlorovinyl)-3-hydroxytricyclo[2.2.1.0^{2,6}]heptane (6). A solution of an epimeric mixture of **5** (1.65 g, 6.68 mmol) in ethanol (120 ml) was treated with anhydrous potassium carbonate (1.26 g, 7.35 mmol) and stirred under nitrogen for 3.5 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was extracted with methylene chloride. The extract was washed with 10% HCl and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a practically pure oily **6** (1.37 g, 100%) as a 1:1 epimeric mixture, which was used without further purification. A preparative TLC (silica gel) purification afforded an analytically pure endo isomer: ν_{max} (neat) 3275, 3050, 1608, 1065 cm^{-1}; δ 1.25 (3 H, br s), 1.73 (3 H, m), 2.50 (1 H, br d, J = 9.0 Hz), 3.09 (1 H, s, disappeared with D_2O), 3.78 (1 H, br s), 5.63 (1 H, d, J = 9.0 Hz); *m/e* 208, 206, 204, 66 (100). Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 53.04; H, 5.11. Exo isomer: ν_{max} (neat) 3275, 3050, 1608, 1068 cm^{-1}; δ 1.30 (5 H, br d), 1.81 (1 H, br s), 2.94 (1 H, s, disappeared with D_2O), 3.11 (1 H, br d J = 9.0 Hz), 3.86 (1 H, br s), 5.74 (1 H, d, J = 9.0 Hz); *m/e* 208, 206, 204, 66 (100). Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 52.73; H, 5.26.

7-(2,2-Dichlorovinyl)tricyclo[2.2.1.0^{2,6}]hept-3-one (9). A solution of an epimeric mixture of **6** (4.10 g, 20 mmol) in acetone (21 ml) was added to the Jones reagent, prepared by mixing CrO_3 (2.2 g, 22 mmol) in H_2O (21 ml) with 98% H_2SO_4 (2.51 ml) at 0 °C, with stirring at 0 °C and the mixture was kept stirring for 2.5 h at room temperature. The reaction was quenched by addition of isopropyl alcohol (ca. 1 ml) and the reaction mixture was extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to leave a crystalline residue, which was recrystallized from petroleum ether to give **9** (3.89 g, 95.81%) as colorless needles: mp 29–30 °C; ν_{max} (neat) 3020, 1750, 1608 cm^{-1}; δ (CCl_4) 1.36 (1 H, t, J = 6.5 Hz), 1.91 (3 H, br s), 2.15 (2 H, br d, J = 6.5 Hz), 3.07 (1 H, d, J = 9.0 Hz), 5.78 (1 H, d, J = 9.0 Hz); *m/e* 206, 204, 202, 103 (100). Anal. Calcd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97. Found: C, 53.29; H, 4.32.

7-Carboxytricyclo[2.2.1.0^{2,6}]hept-3-one (10) from 6. An epimeric mixture of **6** (1.18 g, 5.76 mmol) in acetone (60 ml) was treated with ozone at −78 °C with stirring until the reaction mixture became blue. After excess ozone was bubbled out with nitrogen, the Jones reagent, prepared by mixing CrO_3 (6.3 g, 63 mmol) in H_2O (60 ml) with 98% H_2SO_4 (7.2 ml) at 0 °C, was added to the reaction mixture and the stirring was continued for 2 h at room temperature. The reaction was quenched by addition of isopropyl alcohol (ca. 2 ml) and the reaction mixture was extracted with ether. The ethereal layer was extracted with saturated $NaHCO_3$ and the aqueous layer was reextracted with ether after acidification with 10% HCl. The ethereal extract was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a crystalline residue, which was recrystallized from a mixture of *n*-hexane and benzene to give **10** (0.65 g, 74.3%) as colorless needles: mp 142–143 °C (lit.[9] 143–144 °C); ν_{max} (Nujol) 3300–2500, 1730–1710 cm^{-1}; δ ($CDCl_3$ + CF_3CO_2H) 1.58 (1 H, m), 2.01 (2 H, br s), 2.39 (3 H, m), 3.08 (1 H, br s); *m/e* 152, 79 (100). Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.26; H, 5.22.

5-Bromo-7-(2,2-dichlorovinyl)norbornan-2-one (11). A solution of **9** (3.78 g, 18.6 mmol) in a mixture of 47% HBr (3.53 g, 20.5 mmol) and acetic acid (74.5 ml) was refluxed for 2 h under nitrogen. The reaction mixture was poured into ice–water (ca. 200 ml) and extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to leave a crystalline residue, which was recrystallized from *n*-hexane to give **11** (4.63 g, 87.55%) as pale yellow needles: mp 66–67 °C; ν_{max} (Nujol) 1745, 1610 cm^{-1}; δ 2.03 (2 H, m), 2.49 (3 H, m), 2.94 (1 H, br s), 3.05 (1 H, br d, J = 9.0 Hz), 4.05 (1 H, br t, J = 4.0 Hz), 6.44 (1 H, d, J = 9.0 Hz); *m/e* 288, 286, 284, 282, 139 (100). Anal. Calcd for $C_9H_9BrCl_2O$: C, 38.07; H, 3.19. Found: C, 38.04; H, 3.10.

6-Bromo-8-(2,2-dichlorovinyl)-2-oxabicyclo[3.2.1]oct-3-one (12). A solution of **11** (0.284 g, 1 mmol) in methylene chloride (10 ml) was stirred with 70% *m*-chloroperbenzoic acid (0.296 g, 1.2 mmol) at room temperature for 24 h. The reaction mixture was washed with 2% $Na_2S_2O_4$, saturated $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a crystalline residue, which on recrystallization from *n*-hexane gave **12** (0.267 g, 89.0%) as colorless needles: mp 80–81 °C; ν_{max} (Nujol) 3030, 1730, 1607, 1150 cm^{-1}; δ 2.80 (5 H, m), 3.22 (1 H, br d, J = 9.0 Hz), 4.29 (1 H, m), 4.70 (1 H, m), 6.24 (1 H, d, J = 9.0 Hz); *m/e* 304, 302, 300, 298, 113 (100). Anal. Calcd for $C_9H_9BrCl_2O_2$: C, 36.03; H, 3.02. Found: C, 36.03; H, 3.03.

Ethyl 5β-Bromo-3α-hydroxy-2β-(2,2-dichlorovinyl)cy-

clopentane-1α-acetate (13). A solution of **11** (2.84 g, 10 mmol) in chloroform (30 ml) was stirred with 70% *m*-chloroperbenzoic acid (2.96 g, 12 mmol) at room temperature for 24 h. To the reaction mixture ethanol (5 ml) was added, the mixture was refluxed for 4 h, and the solvent was removed in vacuo. The residue was extracted with methylene chloride and the extract was washed with 2% $Na_2S_2O_4$, saturated $NaHCO_3$, and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left practically pure **13** (3.46 g, 100%) as a pale yellow oil, which was used without further purification. A preparative TLC (silica gel) purification afforded analytically pure **13** as pale yellow oil: ν_{max} (neat) 3400, 1720, 1608, 1170, 1030 cm^{-1}; δ (CCl_4) 1.31 (3 H, t, J = 7.5 Hz), 2.56 (6 H, m), 3.14 (1 H, br s, disappeared with D_2O), 4.18 (2 H, q, J = 7.5 Hz), 4.32 (2 H, m), 5.79 (1 H, d, J = 9.0 Hz); *m/e* 350, 348, 346, 344, 173 (100). Anal. Calcd for $C_{11}H_{15}BrCl_2O_3$: C, 38.18; H, 4.37. Found: C, 38.82; H, 4.25.

3α,5α-Dihydroxy-2β-(2,2-dichlorovinyl)cyclopentane-1α-acetic Acid γ-Lactone (16). A. $Hg(OAc)_2$-Catalyzed Reaction. A solution of **13** (2.955 g, 8.54 mmol) in 1,2-dimethoxyethane (10 ml) was added to a mixture of 98.5% $Hg(OAc)_2$ (2.763 g, 8.54 mmol), 70% $HClO_4$ (2.14 ml), water (1.71 ml), and 1,2-dimethoxyethane (15.6 ml) with stirring at room temperature under nitrogen. After stirring for 2 h, the reaction mixture was evaporated in vacuo and the residue was extracted with methylene chloride. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to leave a crystalline residue, which was recrystallized from a mixture of *n*-hexane and benzene to give **16** (1.61 g, 79%) as colorless needles: mp 106–107 °C; ν_{max} (Nujol) 3450, 1755, 1615, 1200, 1080 cm^{-1}; δ 2.30 (3 H, m), 2.76 (3 H, m), 3.21 (1 H, br s, disappeared with D_2O), 4.16 (1 H, m), 5.03 (1 H, br s), 5.68 (1 H, d, J = 9.0 Hz); *m/e* 240, 238, 236, 115 (100). Anal. Calcd for $C_9H_{10}Cl_2O_3$: C, 45.60; H, 4.25; Cl, 29.91. Found: C, 45.79; H, 4.21; Cl, 29.77.

B. $AgClO_4$-Catalyzed Reaction. A solution of **13** (2.46 g, 7.11 mmol) in 1,2-dimethoxyethane (15 ml) was added to a mixture of $AgClO_4$ (1.55 g, 7.11 mmol), water (1.5 ml), and 1,2-dimethoxyethane (10 ml) with stirring at room temperature under nitrogen. After stirring for 30 min, insoluble precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was extracted with methylene chloride and the extract was washed with saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a crystalline residue, which on recrystallization from a mixture of *n*-hexane and benzene gave **16** (1.41 g, 82.84%).

2β-(2,2-Dichlorovinyl)-5α-hydroxy-3-(4-phenylbenzoyloxy)cyclopentane-1α-acetic Acid γ-Lactone (17). A solution of **16** (0.237 g, 1 mmol) in a mixture of ether (10 ml) and methylene chloride (10 ml) was mixed with a solution of 4-phenylbenzoyl chloride (0.473 g, 1.1 mmol) in ether (10 ml) in the presence of triethylamine (0.2 ml) under stirring at room temperature. After stirring for 24 h, separating triethylamine hydrochloride was filtered off and the filtrate was evaporated in vacuo. The residue was extracted with methylene chloride and the extract was washed with 5% HCl, saturated $NaHCO_3$, and saturated NaCl and dried over Na_2SO_4. Removal of solvent in vacuo left a crystalline residue, which on recrystallization from a mixture of *n*-hexane and benzene afforded **17** (0.36 g, 86.12%) as colorless needles: mp 133–134 °C; ν_{max} (Nujol) 1755, 1705, 1610, 1600, 1270, 745, 690 cm^{-1}; δ 2.18–3.36 (6 H, m), 5.09 (1 H, br s), 5.32 (1 H, m), 5.78 (1 H, d, J = 9.0 Hz), 7.33–7.68 (7 H, m), 8.07 (2 H, d, J = 8.0 Hz); *m/e* 420, 418, 416, 181 (100). Anal. Calcd for $C_{22}H_{18}Cl_2O_4$: C, 63.32; H, 4.35; Cl, 16.99. Found: C, 63.57; H, 4.50; Cl, 16.76.

2β-Formyl-5α-hydroxy-3α-(4-phenylbenzoyloxy)cyclopentane-1α-acetic Acid γ-Lactone (18). To a stirring solution of **17** (0.105 g, 0.25 mmol) in a mixture of methanol (20 ml) and methylene chloride (10 ml) was bubbled ozone at −20 to −15 °C until the no starting material was detected by TLC. After an excess of ozone was bubbled out by means of nitrogen, NaI (0.083 g, 0.55 mmol) and acetic acid (0.15 ml) was added and the stirring was continued for 30 min at room temperature; during the reaction 10% $Na_2S_2O_3$ was added dropwise to remove liberating iodine. The reaction mixture was extracted with methylene chloride and the extract was washed with saturated $NaHCO_3$, 10% $Na_2S_2O_3$, and saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to yield practically pure **18** (0.087 g, 98.86%) as a colorless foam, which was used without further purification: ν_{max} ($CHCl_3$) 1770, 1720, 1610 cm^{-1}; δ 2.03–3.29 (6 H, m), 5.14 (1 H, br s), 5.79 (1 H, m), 7.33–7.80 (7 H, m), 8.07 (2 H, d, J = 8.0 Hz), 9.85 (1 H, s); *m/e* 350, 198 (100). In order to confirm its structure, unstable **18** was reduced with sodium borohydride in methanol to yield the stable alcohol **19**:[10] mp 123–124 °C (from *n*-hexane–CH_2Cl_2) (lit.[3,11] 130–131 °C); ν_{max} ($CHCl_3$) 3650, 3500, 1770, 1710, 1610, 1280 cm^{-1}; δ 2.08 (1 H, s, disappeared with D_2O), 2.18–3.04 (6 H, m), 3.71 (2 H, d, J = 6.0 Hz), 5.08 (1 H, br s-), 5.41 (1 H, m), 7.34–7.72 (7 H, m), 8.04 (2 H, d, J = 8.0 Hz); *m/e* 352, 181 (100).

5α-Hydroxy-2β-hydroxymethyl-3α-(4-phenylbenzoyloxy)-cyclopentane-1α-acetic Acid γ-Lactone (19) from 17. To a stirring solution of **17** (0.105 g, 0.25 mmol) in a mixture of methanol (20 ml) and methylene chloride (10 ml) was bubbled ozone at −20 to −15 °C until no starting material was detected by TLC. After an excess of ozone was bubbled out by means of nitrogen, sodium borohydride (ca. 1 g) was added dividedly into the reaction mixture and the stirring was continued for 1 h at room temperature. The reaction mixture was extracted with methylene chloride and the extract was washed with saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to leave a crystalline residue which was recrystallized from a mixture of *n*-hexane and methylene chloride to yield **19** (0.065 g, 73.86%) as colorless needles, mp 123–124 °C.

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Registry No.—**2**, 61046-12-6; **3**, 61009-51-6; **4**, 61009-52-7; **5** isomer A, 61091-84-7; **5** isomer B, 61047-20-9; **6** isomer A, 61047-21-0; **6** isomer B, 61091-83-6; **9**, 61047-22-1; **10**, 52730-40-2; **11**, 61009-53-8; **12**, 61009-54-9; **13**, 61009-55-0; **16**, 61009-56-1; **17**, 61009-57-2; **18**, 38754-71-1; **19**, 31752-99-5; *p*-toluenesulfonyl chloride, 98-59-9; HBr, 10035-10-6; 4-phenylbenzoyl chloride, 14002-51-8.

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(11) Recorded with optically active sample.

Additivity Relationships in Carbon-13 Nuclear Magnetic Resonance Spectra of Dihydroxy Steroids

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The ^{13}C NMR spectra of 26 dihydroxy steroids and 10 acetylated derivatives have been obtained and assigned. It was found that only for compounds with 1,2- or 1,3-dihydroxy groups are there significant differences between the observed chemical shifts and those calculated assuming additivity of the substituent effects found for the monosubstituted compounds. When there is steric interaction between the functionalities the deviation from additivity can be rationalized by considering the nature of the steric interactions which are introduced. It is demonstrated that in many cases the effect of OH–OH interactions can be approximated by the magnitude and direction of analogous OH–C or C–C interactions. Significant deviations from additivity were also found for a few compounds with no steric interaction between the substituents (1,3-trans and 1,2-diaxial diols). An upfield 1,3-syn-diaxial δ substituent effect is reported.

In connection with our artificial intelligence project directed toward the computerized identification of unknown steroids from their ^{13}C NMR spectra, we have undertaken a systematic study of the effects of various substituents on such spectra. In particular, we have studied the influence of those substituents most commonly found in steroids of biological interest, and in previous papers we reported on the spectra of monoketo[2] and monohydroxy[3,4] steroids. In these papers, the effects of the functional groups were quantified by empirical rules which are of value for both interpretative and predictive applications. However, since most steroids of biological interest are polyfunctional, it is necessary to understand the effect which the interaction of substituents has on the ^{13}C NMR spectra of polyfunctional molecules. We now present the ^{13}C NMR spectra of 26 dihydroxy steroids and examine them in light of the previously determined[3] empirical rules. Furthermore, the chemical shifts predicted assuming additivity of the substituent effects observed for monohydroxy steroids are compared to experimental values in order to determine the extent to which this assumption is valid for polysubstituted steroids. The observed deviations from additivity are discussed.

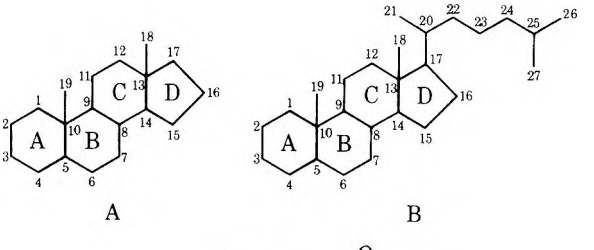
Experimental Section

A number of the dihydroxy steroids used in this investigation are from the authors' collections and have been described previously. Those remaining are all known compounds and were prepared by the following methods: **4** by treatment with lithium in ammonia[5] of 5α-cholestan-3β-ol-11-one; **5** by Jones oxidation of **4** followed by lithium aluminum hydride reduction; **8** and **9** by epoxidation[6] of 5α-cholest-1-en-3-one[7] with hydrogen peroxide followed by lithium aluminum hydride reduction;[6] **16** by hydroboration–oxidation[8,9] of cholest-4-en-3-one;[10] **18** by epimerization[11] of cholesterol followed by epoxidation with hydrogen peroxide and reduction with lithium aluminum hydride;[6] and **20** by treatment of cholest-4-ene with osmium tetroxide.[12] The acetoxy steroids were prepared by reaction of the alcohols with acetic anhydride in pyridine. The spectra were recorded as $CDCl_3$ solutions under the same conditions and with the same instruments as described previously.[3]

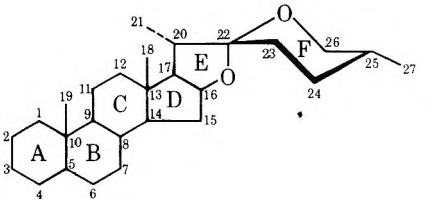
Results

Based on the previously published data for monohydroxy steroids,[3,4] the substituent-induced shifts caused by the presence of one hydroxyl group were obtained for each hydroxyl position by subtracting the chemical shift of each carbon atom in the parent hydrocarbon[2,3,13] from the chemical shift of the corresponding carbon atom in the appropriate hydroxy steroid. For each of the dihydroxy steroids studied in the present investigation, the chemical shift of each carbon atom was then calculated by adding the substituent-induced shifts obtained above for each of the two hydroxyl positions to the chemical shift of the parent hydrocarbon. It is necessary to use a complete table of substituent effects instead of only the effects at α, β, and γ carbon atoms summarized previously.[3] Substituent effects at δ carbons and at carbon atoms farther removed become nonnegligible when adding the effects of two hydroxyl groups. The calculated chemical shifts agree with those observed within 0.4 ppm at every carbon atom (0.8 ppm for carbinol carbon atoms, owing to their greater dependence on sample concentration) for the following compounds of the present study: (1) 5α-androstane-3β,6β-diol, (2) 5α-androstane-3β,7α-diol, (3) 5α-androstane-3β,7β-diol, (4) 5α-androstane-3β,11α-diol, (5) 5α-androstane-3β,11β-diol, (6) 5α-androstane-11α,17β-diol.

This is also the case for 5α-cholestane-3β,6α-diol, 5α-cholestane-3β,6β-diol, 5α-androstane-3β,17β-diol, and 5α-androstane-3α,17β-diol previously reported.[14,15] For those compounds where the difference at one or more carbon atoms is outside this limit, the chemical shifts are given in Table I together with the deviation from the calculated values. Table I also includes for comparison the previously assigned[2,13] chemical shifts for the parent hydrocarbons, 5α-androstane (A), 5α-cholestane (B), and (25*R*)-5α-spirostane (C).



A B



C

The ^{13}C NMR spectra of the 26 dihydroxy steroids studied were assigned by a combination of techniques as described previously.[3] In this study, however, the shift reagent Eu(fod)$_3$ was used only to differentiate the signals of carbon atoms close to a hydroxyl group from those of carbons further removed. Table II lists the assigned chemical shifts of the acetylated dihydroxy steroids which were studied for assignment purposes.

The ^{13}C NMR data for certain polyhydroxy steroids have

Table I. ^{13}C Chemical Shifts in Dihydroxy Steroids[a]

	Compd	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A	5α-Androstane	38.8	22.3	26.9	29.2	47.1	29.2	32.6	36.0	55.1	36.4	20.9	39.0	40.8	54.7	25.5	20.5	40.5	17.6	12.3
B	5α-Cholestane	38.8	22.3	26.9	29.2	47.1	29.2	32.2	35.6	54.9	36.3	20.9	40.2	42.6	56.7	24.2	28.3	56.4	12.2	12.2
C	(25*R*)-5α-Spirostane	38.7	22.2	26.8	29.0	47.1	29.0	32.4	35.2	54.8	36.3	20.7	40.2	40.6	56.5	31.8	80.8	62.3	16.5	12.3
7	5α-Cholestane-1α,2β-diol	74.3 (−3.5)	72.3 (−2.2)	29.0 (+1.8)	23.7 (+0.5)	39.6	28.5	31.7	34.7	48.1	39.6	20.5	39.9	42.6	56.4	24.2	28.2	56.4	12.1	12.4 (−3.0)
8	5α-Cholestane-1α,3α-diol	72.7 (+7.8)	36.2 (+0.5)	67.8 (+8.0)	33.6* (−1.6)	32.2* (+1.2)	28.4	31.7	35.4	46.8	40.3	20.2	39.7	42.6	56.3	24.2	28.2	56.3	12.1	12.3
9	5α-Cholestane-1α,3β-diol	73.2 (+3.5)	38.3* (+1.2)	66.7 (+2.0)	38.1* (+0.6)	37.4 (+0.6)	28.6	31.7	35.5	46.9	39.8 (+0.5)	20.7	39.8	42.6	56.4	24.3	28.2	56.2	12.1	13.0
10	(25*R*)-5α-Spirostane-2α,3α-diol	40.9 (−0.8)	69.0* (−5.7)	69.1* (−6.8)	34.3	38.1	27.6	32.0	34.4	54.2	37.0	20.7	40.0	40.6	56.2	31.7	80.7	62.2	16.5	12.4
11	(25*R*)-5α-Spirostane-2α,3β-diol	45.1* (−1.3)	73.0 (−4.2)	76.4 (−4.1)	35.6 (−1.0)	44.9* (+0.7)	27.9	32.1	34.5	54.3	37.6 (+0.9)	21.2	40.0	40.6	56.1	31.8	80.7	62.2	16.5	13.5
12	(25*R*)-5α-Spirostane-2β,3α-diol	40.1 (+1.6)	71.7 (−3.1)	70.6 (−2.9)	31.8 (+1.3)	39.0	28.2	32.1	34.6	55.2	35.9	20.8	40.1	40.6	56.3	31.8	80.7	62.2	16.5	14.4 (+0.7)
13	5α-Cholestane-3α,4α-diol	31.5*	27.1	69.5 (−6.3)	72.0 (−5.0)	45.8	22.8 (+0.7)	31.7*	35.3	54.4	37.1	21.0	40.1	42.6	56.6	24.2	28.3	56.4	12.2	12.7
14	5α-Cholestane-3α,4β-diol	31.7	24.6 (+0.8)	70.3 (−3.1)	76.1 (−3.0)	44.0 (+2.0)	25.2	32.4	35.6	55.2	35.9	20.3	40.0	42.6	56.6	24.3	28.3	56.3	12.2	14.3 (+0.6)
15	(25*R*)-5α-Spirostane-3α,4β-diol	31.7	24.6 (+0.7)	70.2 (−3.3)	76.0 (−2.9)	43.8 (+1.8)	25.0	32.5	35.1	55.1	35.9	20.0	39.9	40.5	56.3	31.6	80.7	62.1	16.5	14.4 (+0.5)
16	5α-Cholestane-3β,4α-diol	36.2	28.3 (−1.3)	76.4 (−4.3)	75.6 (−3.7)	50.8 (−1.0)	22.7	31.5	35.0	54.4	37.3 (+0.6)	21.0	40.0	42.5	56.3	24.2	28.3	56.3	12.1	13.6
17	5α-Cholestane-3β,4β-diol	37.0	26.0	72.2 (−6.1)	74.8 (−6.6)	48.9 (+1.1)	26.0	32.4	35.6*	55.3	35.4*	20.6	40.0	42.6	56.6	24.2	28.2	56.3	12.1	14.7
18	5α-Cholestane-3α,5α-diol	25.5* (+0.5)	29.0 (+1.3)	67.5 (+7.2)	39.4 (−1.7)	75.0 (+9.9)	34.0	26.5*	34.8	45.7	—	21.0	40.0	42.7	56.2	24.1	28.2	56.2	12.2	15.8 (+0.7)
19	5α-Androstane-3β,5α-diol	31.0 (+1.2)	31.0 (+0.9)	67.2 (+2.0)	44.0 (+0.6)	75.2 (+4.3)	34.5	26.3	35.1	46.2	38.9	21.4	38.9	40.9	54.3	25.4	20.5	40.4	17.6	16.3
20	5α-Cholestane-4α,5α-diol	30.5	19.5 (+0.5)	30.0	71.3 (−4.2)	75.1 (−4.9)	28.4	26.0	34.5	45.9	40.2	20.9	40.0	42.5	56.2	24.1	28.3	56.2	12.1	15.5 (−1.9)
21	5α-Cholestane-5α,6α-diol	31.8	20.7*	20.4*	28.5 (+0.5)	75.0 (−4.8)	70.9 (−4.5)	35.8	33.6	45.0 (−0.5)	39.6	20.7	39.9	42.6	56.0	24.1	28.2	56.2	12.1	15.3 (−1.9)
22	5α-Cholestane-6α,7α-diol	38.6	21.8	26.2	22.8 (+0.5)	45.3* (−0.6)	72.2 (−5.4)	71.3 (−6.4)	38.4	45.4*	36.7	20.6	39.5	42.5	50.2	23.6	28.2	56.0	11.8	12.3
23	5α-Cholestane-6β,7α-diol	40.3	22.0	27.0	25.5	43.3 (+1.4)	76.5 (−3.6)	71.9 (−3.7)	34.6	45.7 (−0.6)	36.2	20.4	39.6	42.7	50.1	23.6	28.1	56.2	11.8	15.3 (+0.6)
24	5α-Cholestane-12β,15α-diol	38.8	22.1	26.7	28.9	46.8	28.9	32.0	34.5	53.5	36.4	29.8	79.1 (−1.0)	46.6 (−0.6)	60.3	75.3	33.0	36.0	13.0	12.2
25	5α-Androstane-15β,17β-diol	38.8	22.2	26.9	29.1	47.4	28.9	31.5	31.5	55.5	36.6	20.4	38.5	42.4 (−0.5)	56.1	69.4 (−1.0)	43.1 (−1.0)	81.4 (−0.6)	13.9	12.3
26	5α-Androstane-16β,17β-diol	38.7	22.2	26.8	29.0*	47.1	28.9*	31.9	35.0	55.1	36.4	20.2	37.5	42.5	47.6 (−0.5)	35.0	70.1 (−11.9)	80.9 (−15.0)	12.0 (−0.7)	12.3

[a] In parts per million relative to Me_4Si. Values in parentheses give the deviation from additivity ($\delta^{obsd} - \delta^{calcd}$). Assignments of close-lying peaks marked with an asterisk may be interchanged. Chemical shifts for the side chain carbon atoms are all unchanged relative to the parent compounds and are not included. Dash (—) indicates peak not observed.

Table II. ^{13}C Chemical Shifts in Acetylated Diols[a]

Compd[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	CH_3[b]	C=O	CH_3[b]	C=O
5α Cholestane 2β,3α diol 3α-acetate	10.0	68.6	73.0	28.7	10.5	28.2	31.9	34.9	55.1	35.4	20.9	40.0	42.6	56.5	24.1	28.2	56.3	12.1	14.2	21.4	170.3		
5α-Cholestane-3α,4β-diol 4β-acetate	31.5	24.8	67.0	77.0	42.7	25.0	32.2	35.5	55.1	35.9	20.5	40.0	42.6	56.6	24.2	28.3	56.3	12.1	13.7	21.1	170.3		
5α-Cholestane 3α,4β-diacetate	32.0	22.3	69.6	73.3	44.1	24.7	32.0	35.4	55.0	35.6	20.4	40.0	42.5	56.5	24.2	28.2	56.3	12.1	13.6	21.2	169.3	21.2	169.4
(25*R*)-5α-Spirostane 3α,4β-diacetate	32.0	22.2	69.4	73.2	44.0	24.6	32.0	34.9	54.9	35.6	20.2	39.8	40.4	56.2	31.7	80.6	62.2	16.4	13.7	21.1	169.3	20.9	169.2
5α-Cholestane 3β,4α-diacetate	35.8	26.0	75.4*	74.0*	49.3	22.9	31.3	35.0	54.2	37.3	21.0	40.0	42.5	56.2	24.1	28.2	56.2	12.1	13.4	21.0	170.5	21.0	170.3
5α-Cholestane-3α,5α-diol 3α-acetate	25.6*	25.6*	70.8	37.5	73.0	33.6	26.8*	34.9	45.2	—	20.9	40.1	42.7	56.2	24.0	28.3	56.2	12.1	15.9	21.4	168.8		
5α-Cholestane-3β,6β-diol 6β-acetate	38.3	31.3	71.3	35.0	46.4	73.6	36.5	31.1	54.0	35.5	21.1	39.9	42.7	56.1*	24.2	28.2	56.3*	12.2	15.3	21.4	170.5		
5α-Cholestane 3β,6β-diacetate	38.0	27.3	73.3	31.0	46.2	73.3	36.4	31.0	53.8	35.5	21.0	39.8	42.6	56.0	24.2	28.0	56.2	12.1	15.1	21.3	170.1	21.3	170.1
5α-Cholestane-3β,7α-diol 3β-acetate	36.9	27.4	73.5	33.6	36.1	36.5	67.7	39.5	45.7	35.5	21.0	39.5	42.6	50.5	23.6	28.2	56.1	11.8	11.1	21.3	170.2		
5α-Cholestane-4α,5α-diol 4α-acetate	30.4	19.4	26.3	75.2	74.2	29.2	25.9	34.5	45.4	40.7	20.9	40.0	42.5	56.2	24.1	28.3	56.2	12.1	15.4	20.9	169.9		

[a] See footnote *a*, Table I. [b] Acetoxy methyl group. [c] Registry no. are, respectively, 61010-51-3, 61010-52-4, 20834-79-1, 61010-53-5, 21157-50-6, 17305-80-6, 26358-65-6, 3514-29-2, 40823-41-4, 5748-95-8.

been reported previously.[14-23] Of these, the data for cholestane-3β,5α-diol and cholestane-3β,5α,6α-triol 3β-acetates[18] and 5α-cholestane-3β,6β-diol[14,15] were used in the assignments for compounds **19, 21,** and **1**, respectively.

Discussion

In a previous paper[3] we suggested an empirical correlation relating the α and β substituent effects to the type and number of specific steric interactions of the hydroxyl group in monosubstituted cyclic compounds. Thus, when a hydroxyl group is situated γ-gauche to a carbon atom, not only the γ-gauche carbon experiences the well-known upfield shift, but the hydroxyl substituent parameters for α and β carbons in the path of the γ-gauche interaction are modified by −3.5 and −2.4 ppm, respectively, for each interaction of this kind. It is a consequence of these rules that whenever the substituents of polyhydroxy steroids give rise to steric interactions which are not present or are different from those in the monosubstituted derivatives, deviation from additivity of substituent effects is expected. Inspection of Table I reveals that with one exception (**24**), only compounds with 1,2- or 1,3-dihydroxy groups give rise to deviations of more than 0.4 ppm (0.8 ppm, respectively, see above) between the experimental chemical shifts and those calculated by assuming additivity of the substituent effects observed in the monosubstituted compounds.

The 1,2 (vicinal) diols can be separated into three categories according to the stereochemistry of the hydroxyl groups: diequatorial, equatorial–axial, and diaxial. In the diequatorial cases (compounds **11** and **16**) the chemical shifts of both carbinol (α) carbon atoms in each compound deviate from the calculated values by −4.0 ppm (±0.3 ppm). In this arrangement each hydroxyl group experiences an additional γ-gauche interaction (with the other OH group) which is not accounted for when adding the individual substituent effects. The difference, then, can be considered to be the result of the mutual interaction of the two hydroxyl groups, and it is close to the value of −3.5 ppm found for the analogous carbon atoms in systems with hydroxyl–carbon[3] and carbon–carbon[24,25] γ-gauche interactions. Hence, the equation which for cyclic monohydroxy compounds relates the substituent effects of a hydroxyl group to its steric interactions also predicts the correct value (within the limit given) for the carbinol carbons in the diequatorial diols.

The vicinal hydroxyl groups in the axial–equatorial cases (compounds **10, 13, 17, 20,** and **21**) also experience an additional γ-gauche interaction relative to the monosubstituted compounds. In this arrangement, however, the deviation from additivity at the α carbons is larger (see Table III). This increase probably reflects a greater steric interaction between an axial and an equatorial OH group, vis-à-vis two equatorial OH groups, caused by a smaller dihedral angle between the two HO–C bonds. It is known that the six-membered rings in the steroid skeleton are slightly flattened compared to a perfect chair form.[26] As a consequence of this, the dihedral angle ϕ between two vicinal bonds is decreased in the case of axial–equatorial bonds (ϕ_{ae}) but increased in the case of two equatorial vicinal bonds (ϕ_{ee}) relative to the ideal value of 60°. Furthermore, if the axial vicinal bond carries a substituent, ϕ_{ae} is expected to be further decreased by deformations introduced to relieve the steric interactions of the axial substituent. X-ray data for 3α- and 3β-hydroxyandrostan-17-one[27,28] illustrate this point. The above is consistent with the finding that the intramolecular hydrogen bonds are stronger for axial–equatorial than for equatorial–equatorial 1,2-diols.[29,30] The deviations from additivity for the carbinol carbon atoms in the 4α,5α- and 5α,6α-diols (**20** and **21**) are smaller (ca. −4.6 ppm) than in the other axial–equatorial 1,2-diols (ca. −6.0 ppm). In spite of the large number of 1,3-

Table III. Deviations from Additivity (ppm) for Proximate Diols[a]

			α carbons[b]		β carbons[b]		
1,2 Diequatorial	11	2α, 3β	−4.2 (2)	−4.1 (3)	−1.3 (1)		−1.0 (4)
	16	3β, 4α	−4.3 (3)	−3.7 (4)	−1.3 (2)		−1.0 (5)
1,2 Axial–equatorial	10	2α, 3α	−6.8 (3)	−5.7 (2)	— (4)		−0.8 (1)
	13	3α, 4α	−6.3 (3)	−5.0 (4)	— (2)		— (5)
	17	3β, 4β	−6.6 (4)	−6.1 (3)	+1.1 (5)		— (2)
	20	4α, 5α	−4.9 (5)	−4.2 (4)	— (6)		— (3)
					— (10)		
	21	5α, 6α	−4.8 (5)	−4.5 (6)	+0.5 (4)		
					— (10)		— (7)
	22	6α, 7α	−6.4 (7)	−5.4 (6)	— (8)		−0.6 (5)
1,2 Trans-diaxial	7	1α, 2β	−3.5 (1)	−2.2 (2)	+1.8 (3)		— (10)
	12	2β, 3α	−3.1 (2)	−2.9 (3)	+1.6 (1)		+1.3 (4)
	14, 15	3α, 4β	−3.2 (3)	−3.0 (4)	+0.8 (2)		+1.9 (5)
	23	6β, 7α	−3.6 (6)	−3.7 (7)	+1.4 (5)		— (8)
1,2-Cis, ring D	26	16β, 17β	−11.9 (16)	−15.0 (17)	— (15)		— (13)
1,3-Syn-diaxial	8	1α, 3α	+7.8 (1)	+8.0 (3)	— (10)	+0.5 (2)	−1.6 (4)
	18	3α, 5α	+7.2 (3)	+9.9 (5)	+1.3 (2)	−1.7 (4)	— (6)
	25	15β, 17β	−1.0 (15)	−0.6 (17)	−0.5 (13)	— (14)	−1.0 (16)
1,3-Trans	9	1α, 3β	+3.5 (1)	+2.0 (3)	— (10)	+1.2 (2)	+0.6 (4)
	19	3β, 5α	+2.0 (3)	+4.3 (5)	+0.9 (2)	+0.6 (4)	— (10)

[a] Values given are the difference between observed and predicted shieldings assuming additivity of substituent effects. A dash indicates negligible deviation from additivity (≤0.4 ppm). [b] Carbon atom number given in parentheses.

diaxial interactions, the decrease in the dihedral angle ϕ_{ae} is much less pronounced in **20** and **21** owing to the rigid trans fusion at the site of substitution, resulting in a smaller steric interaction between the hydroxyl groups than in the other cases. In each of these compounds, the deviation from additivity is greater for the axially substituted carbon than for the equatorially substituted one (Table III).

The hydroxyl groups are trans diaxial in compounds **7, 12, 14,** and **23.** In this arrangement the substituents are spatially remote from one another to the extent that no additional steric interactions are expected to be introduced beyond those already encountered in the two corresponding monohydroxy compounds. The chemical shifts of the hydroxyl-bearing carbons, however, are all 3.0 ppm (±0.8 ppm) upfield from the values calculated assuming additivity of substituent effects. The chemical shifts of the remaining carbon atoms do not provide any evidence to suggest that the vicinal diaxial substitution causes appreciable distortions of the molecule relative to the corresponding monosubstituted compounds. Such distortions should affect the chemical shifts of all (or most) carbon atoms whose environment is sterically perturbed by the hydroxyl groups. However, deviations from additivity in this class of compounds are in most cases restricted to the hydroxylated (α) carbon atoms and the adjacent (β) carbon atoms. Stothers et al.[31-33] have recently studied the interactions of hydroxyl and methyl groups in a series of methylnorbornanols and bicyclo[2.2.2]octane derivatives. They concluded that when vicinal methyl and hydroxyl groups are well separated, the observed shieldings agree well with values predicted assuming additivity of the substituent effects. However, the dihedral angles relating the methyl and hydroxyl groups were all in the 0–120° range, with no examples of vicinal diaxial groups. If the ^{13}C NMR data[15] for 10-methyl-*trans*-1α-decalol are analyzed in light of the data for the mono- and unsubstituted decalins, it becomes apparent that also in this case the CH_3–OH vicinal diaxial arrangement gives rise to shifts upfield from those calculated for the carbons bearing the substituents.

It has been suggested[34] that anti-periplanar arrangements involving O, N, or F atoms give rise to a hyperconjugative interaction of free electron pairs of the heteroatom with the C–C bond. This transmission of electronic effects has been invoked to explain the upfield shift observed in the resonance signal of a carbon atom situated γ-trans to the heteroatom (O, N, F). It is possible that a similar electronic effect causes the upfield shifts observed in the anti-periplanar arrangement of two hydroxyl groups by interaction of free electron pairs on both oxygen atoms with the intervening C–C bond, increasing the electron density on those carbon atoms. It is worth noting that for compounds **7, 12, 14,** and **23** the carbon atoms adjacent to the sites of substitution (β carbons, see Table III) appear to be deshielded compared to the predicted chemical shifts, thus suggesting an alternating (electronic) effect.

In compound **25** the hydroxyl groups are cis on a five-membered ring and probably more closely eclipsed than gauche. (The corresponding dihedral angle in 16β,17β-dibromo-5α-androstane is 30°).[35] The steric interactions between the vicinal hydroxyl groups are therefore expected to be very strong and the deviations from additivity for C-16 and C-17 in **25** are the largest (−12 and −15 ppm) among the compounds studied, although the chemical shifts of all the remaining carbons in this compound may be predicted within 0.7 ppm employing additivity parameters.

From the above it is clear that the mutual interaction of vicinally situated hydroxyl groups, as reflected in the deviation between observed and predicted carbon chemical shifts, varies as a function of the dihedral angle between the two C–OH bonds. When the dihedral angle is small the signals of the carbon atoms bearing the substituents are shifted considerably upfield from the predicted positions, while increasing the dihedral angle results in progressively smaller deviations. The smallest deviation measured (~−3 ppm) occurs in the trans-diaxial cases; however, our set of compounds does not include samples with a dihedral angle around 120°, for which almost complete substituent effect additivity has been found[31-33] for vicinal hydroxyl–methyl substituents.

The hydroxyl groups are 1,3 syn-diaxial in compounds 8 and 18 and the deviations from additivity at the hydroxyl-bearing carbons are large (7–10 ppm downfield, Table III). This is not surprising as 1,3 syn-diaxial substituted compounds possess steric interactions which are not present in the monosubstituted analogues, namely the OH–OH skew pentane interaction. Furthermore, where these interactions appear, they replace a hydroxyl γ-gauche interaction present in the corresponding monosubstituted compounds. On the basis of our study of monohydroxy steroids[3] both these changes are (for methyl or hydroxyl substitution) expected to result in downfield carbinol carbon shifts, totaling approximately 7

ppm. This value is very close to that actually observed (Table III), showing again that the OH–OH interactions can be approximated by the OH–CH_3 interactions observed previously, although the present data indicate a somewhat larger parameter value (~+4.5 ppm instead of +3.5 ppm, cf. ref 3) associated with the OH–OH skew pentane interaction. The chemical shifts of carbons 15 and 17 of compound **25** agree well with the predicted values (Table III). Although this is a 1,3 syn arrangement of the hydroxyl groups, both are on the five-membered ring D and hence oriented away from one another, making the total change in steric interactions for the diol compared to the two corresponding monohydroxy compounds small.

There are no apparent steric interactions between the hydroxyl groups in the 1,3-trans diols **9** and **19**, but there are nonetheless significant deviations from additivity at the α carbon atoms. The resonances of the equatorially and the axially substituted carbons are respectively 2 and 4 ppm downfield from the predicted values. The same pattern in deviations from additivity of substituent effects is observed for 1,3-trans methyl–hydroxyl substituents (equatorial hydroxyl, axial methyl) in monohydroxy steroids,[3] *trans-anti-trans*-perhydrophenanthrene,[25] and various trans decalins.[15] Upfield hydroxyl-induced γ-trans shifts have been reported to be general,[34] but in all the above mentioned 1,3-trans-substituted compounds, downfield rather than upfield γ-trans shifts are encountered at the axially substituted carbons, all of which are γ-trans to the equatorial hydroxyl group. These observations show that the γ-trans shifts caused by second row heteroatoms[34] in anti-periplanar geometries are also dependent on the presence and steric environment of atoms removed from the γ-trans fragment. This is emphasized by considering that γ-trans shifts on methyl groups are downfield for a hydroxyl substituent[3,4] but become large upfield shifts (~−6 ppm) when the oxygen atom is part of a cyclic ether.[13,34]

The deviations from additivity for β carbons (one bond removed from the nearest hydroxylated site) in the vicinal diols are all less than 2 ppm. In general the deviation for a β carbon next to an equatorial hydroxyl group is negligibly small or negative, whereas for a β carbon next to an axial hydroxyl group it is negligible or positive (see Table III). Interestingly, these effects are largest for the diequatorial diols (**11** and **16**) and the trans-diaxial cases (**7, 12, 14,** and **22**). In the 1,3 diols, the deviations from additivity for all β carbons are also in the range of ±2 ppm, although most are negligible. No patterns or trends could be discerned.

The chemical shifts for γ carbon atoms are with few exceptions predicted well (to within 1 ppm) employing additivity parameters. However the C-19 methyl resonance is off by −1.9 ppm in compounds **20** and **21** and by −3.0 ppm in **7**. In all of these compounds, one of the hydroxyl groups of a vicinal pair is γ-trans to C-19. In compound **7** the two hydroxyl groups and the C-19 methyl group form an extended anti-periplanar arrangement, as there are three consecutive carbon atoms axially substituted. An upfield shift of 3 ppm relative to the predicted value is also found at C-19 in 5α,6β-diols (using ^{13}C NMR data from ref 17 and 18) where the same extended anti-periplanar geometry occurs. Clearly, the γ-trans hydroxyl substituent effect (see above) is varied by introduction of a vicinal hydroxyl group when this hydroxyl group and the C-19 methyl group are syn-diaxial (as in **7**). This may cause the hydroxyl syn-diaxial δ substituent effect to become upfield,[18] in direct contrast to what has previously been found.[3,15,31-33]

For the other vicinal diaxial cases (**12, 14, 15,** and **23**) the hydroxyl 1,3-syn-diaxial δ substituent effects become slightly larger (0.6–0.7 ppm) than in the monosubstituted compound.

To summarize, additivity of substituent effects adequately approximates the chemical shifts of most carbon atoms in dihydroxy steroids, except for positions at which the interaction of the substituents perturbs the steric or electronic environment. Since the effects of these interactions on the chemical shifts are regular, knowledge of them will be quite useful for both the interpretation and prediction of ^{13}C NMR spectra of polyfunctional molecules.

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Registry No.—A, 438-22-2; B, 481-21-0; C, 5012-14-6; **7,** 20834-84-8; **8,** 571-01-7; **9,** 571-00-6; **10,** 61046-17-1; **11,** 511-96-6; **12,** 61046-18-2; **13,** 20834-98-4; **14,** 20834-88-2; **15,** 61010-49-9; **16,** 20835-09-0; **17,** 20834-99-5; **18,** 570-96-7; **19,** 5223-92-7; **20,** 19536-21-1; **21,** 566-30-3; **22,** 20835-05-6; **23,** 20834-91-7; **24,** 61010-50-2; **25,** 13864-58-9; **26,** 32810-91-6.

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Difunctionalized Brendanes via Thallium Triacetate Cleavage of the Cyclopropyl Ring of Triaxane

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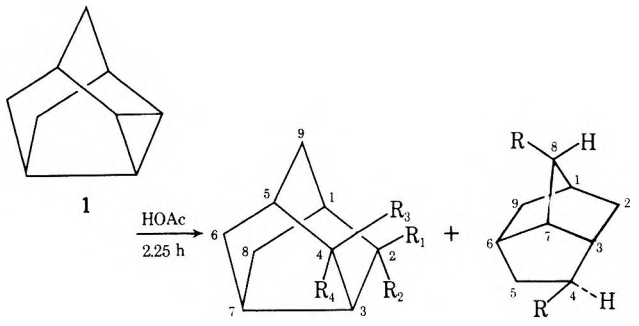
The reaction of triaxane with thallium triacetate in acetic acid gave a 90% yield of a diacetate mixture which contained 2-(a)-acetoxy-4-(e)-acetoxynoradamantane, 2,4-di-(e)-diacetoxynoradamantane, and 4-*exo*-acetoxy-8-*anti*-acetoxybrendane in the ratio 3:15:82. The preponderant diacetate was isolated from the mixture in 43% yield. This reaction provides a simple synthetic route to previously unreported C-8 functionalized brendane derivatives. A structure proof for the brendyl diacetate is presented together with analytical and spectroscopic evidence for the two noradamantyl diacetates. The lead tetraacetate cleavage of triaxane was also investigated and found by GLC analysis to produce 2-acetoxytriaxane, an unidentified component, 2-acetoxynoradamantane, 2-(a)-acetoxy-4-(e)-acetoxynoradamantane, 2,4-di-(e)-diacetoxynoradamantane, and 4-*exo*-acetoxy-8-*anti*-acetoxybrendane in the ratio of 72:1:8:<1:2:17.

The reaction of cyclopropanes with thallium triacetate has been reported to lead predominantly to ring-opened diacetates.[1] Our interest in bridged molecules for mechanistic studies led us to explore the applicability of this reaction for the preparation of difunctionalized systems, which are useful for selective multiple deuterium labeling. We wish to report that cleavage of the cyclopropyl ring of triaxane (1)[2] with thallium triacetate is largely accompanied by a rearrangement that provides a simple, stereospecific route to a C-4, C-8 difunctionalized brendane. Functionalization of the brendane system at C-8 has not been previously reported. Our treatment of 1 with thallium triacetate in refluxing acetic acid gave in



	R_1	R_2	R_3	R_4
2	OAc	H	H	OAc
3	H	OAc	H	OAc
4	OH	H	H	OH
5	H	OH	H	OH

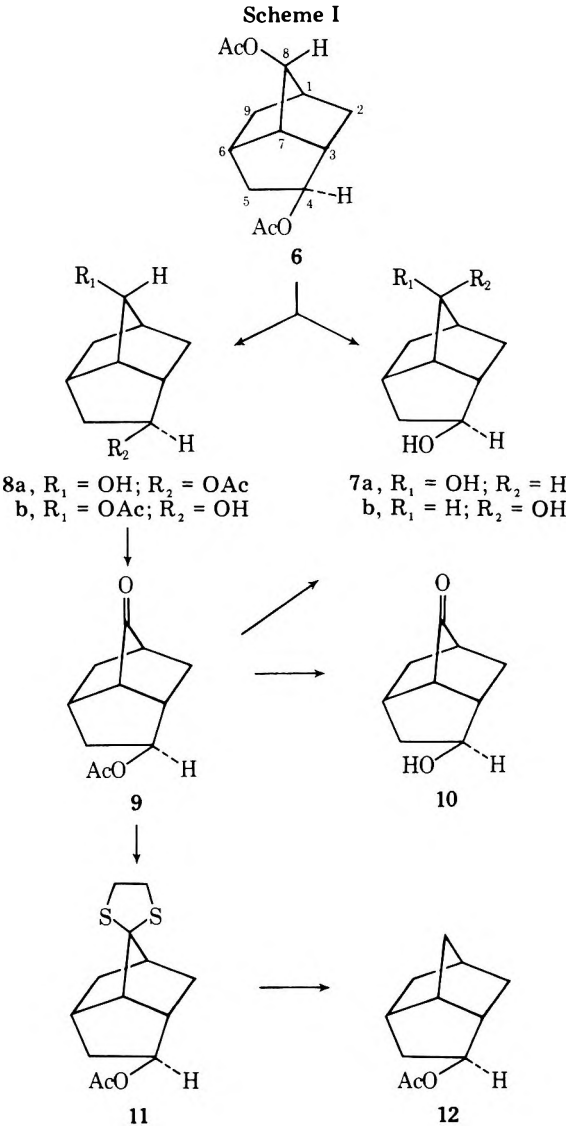
90% yield a diacetate mixture that consisted of three components: 2-(a)-acetoxy-4-(e)-acetoxynoradamantane (**2**), 3%; 2,4-di-(e)-diacetoxynoradamantane (**3**), 15%; and 4-*exo*-acetoxy-8-*anti*-acetoxybrendane (**6**), 82%. Because **3** and **6** were unresolved on preparative GLC columns, we saponified the mixed diacetates to the diol mixture **4, 5,** and **7a.** Diol **7a** was isolated by preparative GLC and was acetylated to **6** with Ac_2O/Py. Diols **4** and **5** were unresolved on GLC but acetylation followed by preparative GLC gave the individual acetates **2** and **3.** Thus yields of separated **2, 3,** and **6** were ca. 0.5, 5, and 43%, respectively.

Structure Proof for Diacetate 6. Conversion of **6** to the known *exo*-4-acetoxybrendane (**12**)[3] by the route shown in Scheme I established the skeletal structure as well as the position and stereochemistry of the acetate group at C-4.

Partial saponification of **6** in aqueous methanol gave a mixture of five compounds in the following relative amounts and eluted on GLC in this order: diacetate **6,** 6%; 4-*exo*-hydroxy-8-*anti*-acetoxybrendane (**8b**), 9%; 4-*exo*-acetoxy-8-*anti*-hydroxybrendane (**8a**), 52%; an unidentified component, 2%; and diol **7a,** 31%. A combination of column chromatography and preparative GLC gave pure hydroxy acetates **8b** and **8a** in yields of 4 and 39%, respectively. Acetylation of **8a** and **8b** reverted each to diacetate **6.**

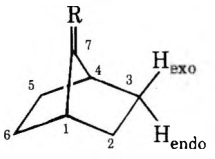
Hydroxy acetate **8a** was oxidized with Jones reagent[4] to 4-*exo*-acetoxybrendan-8-one (**9**). To ensure that no rearrangement occurred during the oxidation, **9** was reduced with

Scheme I



lithium aluminum hydride to a ca 1:1 mixture of 4-*exo*-hydroxy-8-*anti*- and -*syn*-hydroxybrendanes (**7a** and **7b**) as assayed by ^{1}H NMR. The mixture was not separated and analytical and spectroscopic data were not recorded for the pure diol **7b**. We also prepared 4-*exo*-hydroxybrendan-8-one (**10**) by saponification of keto acetate **9** with methanolic potassium hydroxide.

The ethylene dithioketal **11** was obtained by treatment of **9** with ethanedithiol in acetic acid and boron trifluoride etherate.[5] Spectroscopic data, but no elemental analyses, were recorded on a crystalline sample (mp 87.5–89 °C) of **11**. Desulfurization of **11** with Raney nickel[6] gave the known 4-*exo*-acetoxybrendane (**12**) in 67% yield based on starting keto acetate **9**. That no skeletal rearrangement occurred during the formation of ethylene dithioketal **11** was concluded from IR and NMR evidence. An unusually high frequency ketone vibration (1779 cm^{-1}) in keto acetate **9** is consistent with its location at C-8 in a brendane ring system. [cf. norbornan-7-one (**13**) absorbs at 1773 cm^{-1}].[7] Except for compounds that

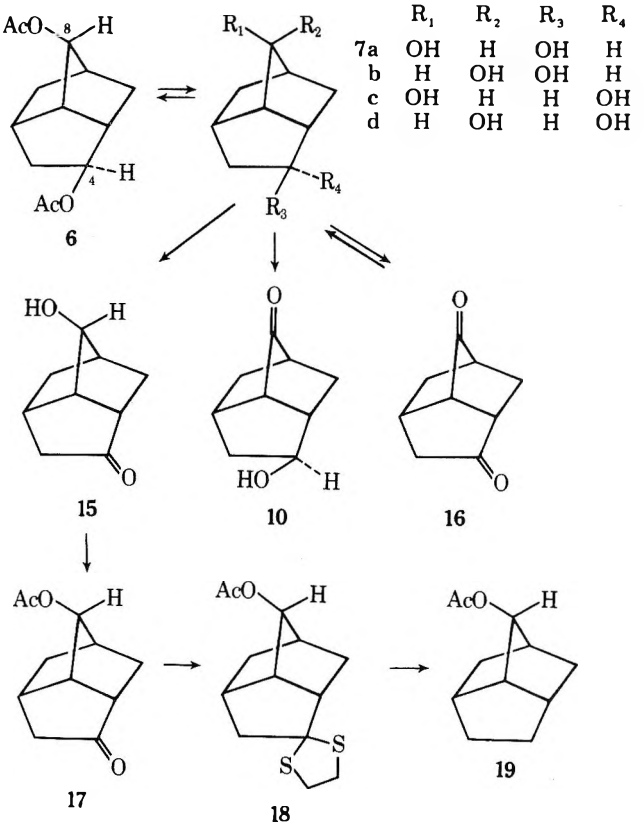


13, R = O
14, R = H, H

contain an endo hydroxyl group at C-4, the NMR spectra of all brendane derivatives in this study had two high-field protons which we have assigned as the C-2 and C-9 endo protons. Tori et al.[8] have reported that the endo and exo protons of norbornane (**14**) are at δ (CCl_4) 1.18 and 1.49, respectively. Pretsch et al.[9] report that the introduction of an endo methyl group at C-2 in **14** shifts the C-3 endo proton upfield to δ ($CDCl_3$) 0.55 and the C-3 exo proton downfield to δ 1.79. Foster and McIvor[10] have postulated that the upfield shifts of endo protons are caused by the diamagnetic anisotropy of the endo C–C bond of the neighboring substituent. Thus the C-4, C-5 bridge of the brendane system might be expected to shift the C-2 and C-9 endo protons upfield relative to the endo protons of norbornane. The reported[11] ^{1}H NMR (CCl_4) of brendane does indeed show a two-proton broad doublet at δ 0.79 (J_{gem} = 11 Hz) which we assign as the chemically equivalent C-2 and C-9 endo protons. The endo protons at C-2 and C-9 in ethylene dithioketal **11** appear as overlapped doublets at δ 1.18–0.84. Interestingly, the four protons of the ethylene dithioketal group appear as a sharp singlet at δ 3.17 ($W_{1/2} \sim 1$ Hz). That these protons do not split each other probably reflects their quasi-symmetrical local environment in **11**.

To establish the position of the second acetate group of diacetate **6** we proceeded as outlined in Scheme II. Diol **7a** was partially oxidized with Jones reagent at 0 °C. Gas chromatographic analysis of the crude product showed four components in the following relative amounts: brendane-4,8-dione (**16**), 8%; hydroxy ketone **10**, 7%; 8-*anti*-hydroxybrendan-4-one (**15**), 75%; and starting diol **7a**, 10%. Hydroxy ketone **15** was isolated in 56% yield by preparative GLC. Dione **16** could be obtained as the major product by oxidation at 25 °C. Acetylation of **15** gave 8-*anti*-acetoxybrendan-4-one (**17**), which produced 4-*endo*-hydroxy-8-*anti*-hydroxybrendane (**7c**) on reduction with lithium aluminum hydride. Although GLC of **7c** showed only one peak, the ^{1}H NMR revealed that ~2% of diol **7a** was present. The high stereoselectivity of this reduction was expected since similar reduction of brendan-4-one was reported to give 4-*endo*-hydroxybrendane with ca. 99.5% stereoselectivity.[12] Lithium aluminum hydride reduction of dione **16** led, as expected, to a mixture of the four stereoisomeric diols **7a–d**. The diol mixture was unresolved by GLC, but ^{1}H NMR showed that the stereoisomeric pair **7a** and **7b** (ca. 1:1) comprised ca. 15–20% of the mixture and the stereoisomeric pair **7c** and **7d** (ca. 1:1) comprised 80–85% of the mixture. Diol **7d** was never isolated pure and characterized.

Scheme II

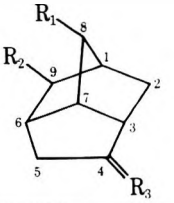


	R_1	R_2	R_3	R_4
7a	OH	H	OH	H
b	H	OH	OH	H
c	OH	H	H	OH
d	H	OH	H	OH

Keto acetate **17** was converted to its crystalline ethylene dithioketal **18** and directly desulfurized to give the previously unreported 8-acetoxybrendane (**19**) in 61% yield. The brendane skeleton in **19** was established as described earlier in Scheme I. The ^{1}H NMR of **19** had the expected high-field C-2 and C-9 endo protons at δ 0.83, the acetate methyl at δ 1.93, and the C-8 proton at δ 4.78. In the brendyl skeleton secondary acetates are possible only at C-2 (or equivalent C-9), C-4 (or equivalent C-5), and C-8. The endo and exo acetates at C-2[12] and C-4[3,13] are all known compounds. Our acetate **19** was spectroscopically (IR and NMR) different from all of these known brendyl secondary acetates; thus it must be the C-8 acetate.

The anti configuration of the C-8 acetate group relative to the C-4 functional group in **6** was assigned on the basis of the long-range "W" coupling $J_{9\text{-endo},8\text{-syn}}$ in the ^{1}H NMR spectrum of keto acetate **17**. Similar "W" couplings of 1.3–2.6 Hz have been reported in heterocyclic brendane derivatives[14] and couplings of ~3–4 Hz have been reported for norbornane derivatives.[15] To eliminate as a possible structure the C-8 epimer, 8-*syn*-acetoxybrendan-4-one, whose NMR would be expected to show a $J_{2\text{-endo},8\text{-anti}}$ long-range "W" coupling, we first established unambiguously our individual assignments for the C-2 and C-9 endo protons of **17**. Comparison of **19** with **20** (Table I) shows that the acetate group at C-8 has little effect on the position of either endo proton. Likewise an acetate group at C-9 has little effect on the C-2 endo proton (cf. **21** with **20**). In contrast a carbonyl group at C-4 causes a pronounced downfield shift for the C-2 endo proton (cf. **22** and **21**). Thus in keto acetate **17** the resonances at δ 1.34 and 1.01 can be assigned to the C-2 and C-9 endo protons, respectively. Spin–spin decoupling by irradiation of the C-8 proton of **17** caused a change in the splitting pattern of the C-9 endo proton

Table I. Chemical Shifts (CCl_4) for the C-2 and C-9 Endo Protons of Brendane and Its Derivatives



				2-Endo		9-Endo		
Compd	R_1	R_2	R_3	δ	Δδ[a]	δ	Δδ[a]	Ref
20	H	H	H, H	0.79		0.79		11
19	OAc	H	H, H	0.83	−0.04	0.83	−0.04	This work
21	H	OAc	H, H	0.70	+0.09	4.06	−3.27	13
22	H	OAc	O	1.25	−0.46	4.13	−3.34	18
23	H	H	O	1.58	−0.79	0.91	−0.12	11
17	OAc	H	O	1.34	−0.55	1.01	−0.22	This work

[a] $\delta_{brendane}$ (20) minus δ_{compd}.

but the pattern for the C-2 endo proton was unchanged. This decoupling result establishes the stereochemistry of the OAc group in 17 and, thereby, the anti configuration at C-8 in diacetate 6.

Spectroscopic Evidence for Diacetate Structures 2 and 3. As expected for symmetrical diacetate 3 its ^1H NMR showed equivalent acetate methyl groups at δ 1.93 (6 H) and equivalent α-acetoxy protons at δ 4.79 (2 H, $W_{1/2} \sim 3$ Hz), broadened as expected for axial protons in noradamantyl systems.[16] That the equivalence of the acetate methyls was not accidental was supported by use of the shift reagent, $Eu(fod)_3$.[17] Additions of as much as 1.65 molar equiv of shift reagent failed to alter the equivalence of the acetate groups. The shift reagent also revealed the existence of four nonequivalent protons (H_3, H_7, H_{9syn}, and H_{9anti}) and three additional pairs of equivalent protons (H_1 and H_5, H_{6e} and H_{8e}, and H_{6a} and H_{8a}) as expected for structure 3. At molar ratios of shift reagent larger than 0.44 one proton was shifted farther downfield than the α-acetoxy protons (δ 11.37 vs. 10.85 at mole ratio 0.44). This large shift would be expected for the C-3 proton of diacetate 3 because of its unique, proximate position between the C-2 and C-4 acetate groups. At a molar ratio of shift reagent of 0.12 the assigned C-3 bridgehead proton appeared as a multiplet at δ 4.74 which was coupled to an apparent quartet ($J \sim 6$ Hz) at δ 2.84. Irradiation at δ 4.74 collapsed the apparent quartet to a triplet ($J \sim 6$ Hz). The C-7 bridgehead proton of diacetate 3 would be expected to appear as a doublet of overlapping triplets or as an apparent quartet, if $J_{7,6e(8e)} \simeq J_{7,3}$, which may be broadened or slightly split by long-range "W" couplings. Irradiation of the C-3 proton would collapse the C-7 proton to a triplet and thus this decoupling experiment can be explained by a diacetate of structure 3. We feel that this preponderance of NMR evidence strongly supports our assigned structure for diacetate 3.

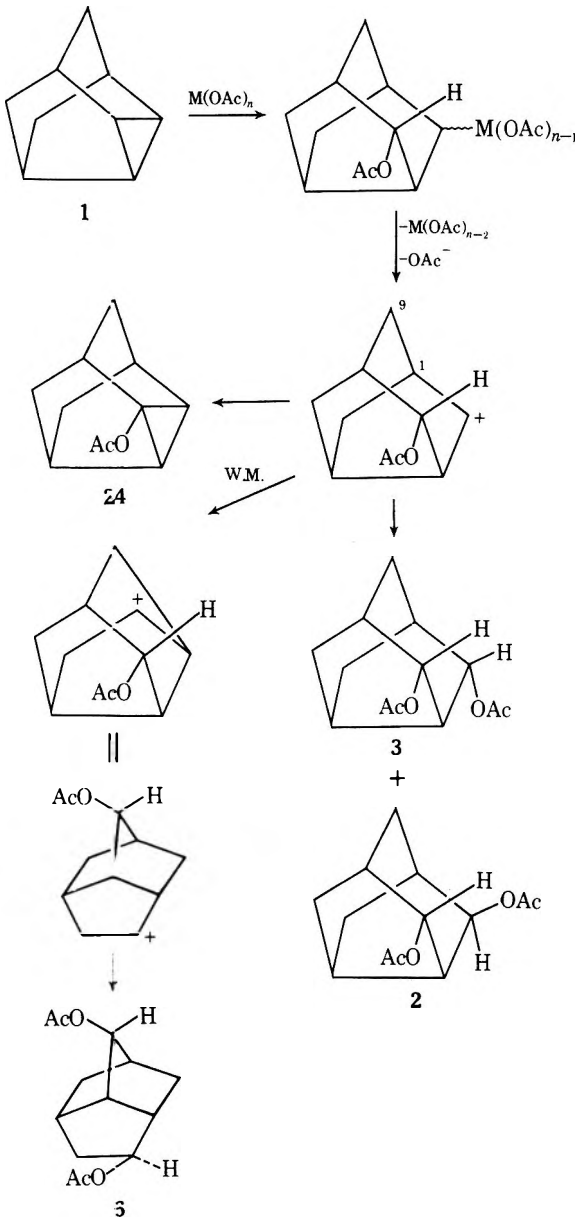
The assignment of structure for diacetate 2 is considered to be tentative and is based solely on a partial analysis of the ^1H NMR. The methyl protons of the two acetate groups appear at δ 2.11 and 1.97. One α-acetoxy proton appeared as a singlet at δ 5.30 ($W_{1/2} \sim 3$ Hz) and the other appeared as a multiplet (J = 1.5, 3.5, 7 Hz) at δ 4.95 as expected for an axial and equatorial proton, respectively, in a noradamantyl system.

Comparison of Thallium Triacetate and Lead Tetraacetate Cleavage of Triaxane. A lead tetraacetate oxidation of triaxane was carried out under essentially the same conditions as those used for the thallium triacetate oxidation, and the products were examined by GLC. This analysis revealed six components: 2-acetoxytriaxane (24),[19] 72%; 2-acetoxynoradamantane[16] (configurational homogeneity unknown) and an unidentified peak, 9%; diacetate 2, <1%; diacetate 3, 2%; and diacetate 6, 17%. These results are not unexpected since different product distributions from the oxidation of the same cyclopropanes by these reagents have been reported.[1,20] The formation of cyclopropyl acetates by lead tetraacetate oxidation of cyclopropanes has also been reported.[21] Scheme III [$M(OAc)_n$ = thallium triacetate or lead tetraacetate] shows one simple mechanistic pathway to rationalize the products of oxidations by both reagents. The formation of 2-acetoxynoradamantane is not shown in this scheme because we presume that it arises trivially from opening of triaxane with acetic acid; and our use of simple cationic intermediates does not imply any preference for stepwise over concerted bonding processes.

Experimental Section

General. Melting points were determined on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Proton magnetic resonance spectra were recorded on a Varian Associates Model HA-100 spectrometer equipped with a Hewlett-Packard Model 522 B electronic counter and Model 200 ABR audio oscillator for spin–spin decoupling. Chemical shifts are given in δ units (ppm) downfield from tetramethylsilane internal standard. The multiplicity is identified by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or b (broad); and coupling constants (J) are reported in hertz. Subscripts n and x indicate endo and exo, respectively. Infrared spectra were recorded on a Perkin-Elmer Model 457 A double-beam spectrometer equipped with a grating. Characteristic bands are listed in units of reciprocal centimeters. The letters sh, w, m, s, and br represent shoulder, weak, medium, strong, and broad bands, respectively. Full NMR and IR spectra are reproduced in the Ph.D. Dissertation of D. F. Covey, the Johns Hopkins University, 1973. Analytical gas–liquid phase chromatography (GLC) was performed on a Perkin-Elmer Model 900 analytical gas chromatograph with a flame ionization detector and a Honeywell Model 16 recorder equipped with a disk integrator. The carrier gas was helium. All integrations reported are approximate since detector response variation was not calibrated for each compound. Components are listed in order of increasing retention time. Analytical columns and conditions used were Golay R 150 ft, 0.01 in. i.d. with polypropylene glycol liquid phase (UCON oil LB-550-X), 140 °C, 50 psi (conditions 1); and 9 ft, 0.125 in. o.d., 10% Carbowax 20M on Chromosorb W 80/100, 200 °C, 50 psi (conditions 2). Preparative GLC was done on a Varian Aerograph Autoprep Model A-700 chromatograph (carrier gas, helium) equipped with a thermal conductivity detector and a Honeywell recorder. Columns used were 4 ft, 0.25 in. o.d., 20% Carbowax 20M on Anakrom ABS 80/90 (column 1); 12 ft, 0.25 in. o.d., 5% Carbowax 20M on Chromosorb W 60/80 (column 2); and 6 ft, 0.25 in. o.d., 20% Carbowax 20M on Anakrom ABS 80/90 (column 3). A saturated solution of sodium chloride or sodium bicarbonate is referred to as "brine" or "bicarbonate". Solvents were removed on a rotary evaporator under aspirator vacuum unless otherwise stated. Sublimations and bulb to bulb distillations were done at 136 °C, ca. 0.2 mm, in a Kugelrohr apparatus. Solvents and other chemicals were reagent grade. Pyridine was distilled from

Scheme III



calcium hydride. Acetone was distilled from potassium permanganate. Magnesium sulfate was used as a drying agent. Elemental analyses were performed by either Mr. Joseph Walter of this department or by M-H-W Laboratories, Garden City, Mich. The europium shift reagent Eu(fod)$_3$ and thallium oxide were purchased from Ventron Corp., Alfa Products Division. Silica gel for column chromatography was 0.05–0.2 mm manufactured by EM Reagents Division, Brinkmann Instruments, Inc. Raney nickel catalyst powder no. 2813 was purchased from W R. Grace and Co.

Cleavage of Triaxane (1) with Thallium Triacetate. Thallium triacetate (9.613 g, 25.2 mmol) prepared from thallium oxide[22a] was refluxed with triaxane (**1**, 1.445 g, 12.0 mmol) in acetic acid (50 ml) for 2.25 h. The solution was cooled, added to water (500 ml), and extracted with ether (5 × 100 ml). The extracts were washed with water (3 × 100 ml) and bicarbonate (1 × 100 ml) and dried. GLC (condition 1) indicated no starting material and three products in the relative ratio of 3 (**2**):15 (**3**):82 (**6**). Bulb to bulb distillation gave a colorless liquid (2.58 g, 90%). Although diacetate **2** could be purified by preparative GLC, diacetates **3** and **6** were unresolved by all our preparative GLC columns. Pure samples of **3** and **6** were obtained by esterification of the corresponding diols as obtained by sensitive preparative GLC.

4-*exo*-Hydroxy-8-*anti*-hydroxybrendane (7a). The diacetate mixture (1.003 g, 4.21 mmol) was saponified with methanolic potassium hydroxide (0.347 g, 6.20 mmol, in 20 ml) at 25 °C for 2.5 h. After removal of methanol, ether (50 ml) and water (2 ml) were added and the two-phase mixture was dried. GLC (condition 2) showed predominantly (>98%) two components in the ratio of 82 (**7a**):18 (unresolved **4** and **5**). Solvent removal (ca. 55 °C, ca. 0.2 mm) left a white solid (0.61 g, 94%). Typically diol **7a** was isolated in 50% yield by preparative GLC (column 1, 180 °C, 30 psi): white solid, mp 110–112 °C; 99% pure (condition 2); IR (KBr) 3322 cm^{-1} (b, bonded **OH**); NMR (pyridine-d_5) δ 5.91 (s, 2, $W_{1/2} \sim 23$ Hz, **CHOH**, C-4, C-8), 4.45 (s, 1, $W_{1/2} \sim 4$ Hz, syn **CHOH**, C-8), 4.34 (d of d, 1, $J_{4n,5x} = 3$, $J_{4n,5n} = 6$ Hz, endo **CHOH**, C-4), 3.00–1.64 (m, 8), 0.90 (superimposed d of m, 2, J_{gem} of each d ~ 12 Hz, endo **HCH**, C-2 and C-9).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.09; H, 9.26.

4-*exo*-Acetoxy-8-*anti*-acetoxybrendane (6). Diol **7a** (43 mg, 0.39 mmol) was stirred in pyridine (1 ml) and acetic anhydride (2 ml) at 25 °C for ca. 21 h. Water (10 ml) was added and the solution was made basic with solid sodium bicarbonate, extracted with ether (4 × 10 ml), and dried. The pale yellow liquid (65 mg) was distilled bulb to bulb (130 °C, ca. 0.2 mm) to give the diacetate as a colorless liquid (60 mg, 91%): ca. >99% pure (condition 1); IR (neat) 1746 (s, ester C=O), 1245 cm^{-1} (s); NMR ($CDCl_3$) δ 5.02–4.86 (d of d, 1, endo **CHOAc**, C-4; overlapped by s, 1, syn **CHOAc**, C-8), 2.68–1.65 (m, 8), 2.01 (s, 3, $OCOCH_3$), 1.97 (s, 3, $OCOCH_3$), 1.12–0.78 (d of d, 1, endo **HCH**, C-2; overlapped by d of m, 1, endo **HCH**, C-9).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.63; H, 7.61. Found: C, 65.51; H, 7.53

2,4-Di-(e)-diacetoxynoradamantane (3). Unresolved diols **4** and **5** were typically isolated in 8% yield by preparative GLC (column 1, 180 °C, 30 psi) of the saponified diacetate mixture. A sublimed (138 °C, ca. 0.2 mm) mixture of diols **4** and **5** (56 mg) was acetylated by the procedure used to prepare diacetate **7a** to give a colorless liquid (81 mg), which GLC (condition 2) showed to be a 11:89 mixture of diacetates **2** and **3**. The diacetates were separated by preparative GLC (column 2, 162 °C, 40 psi). Diacetate **3** was initially obtained as a colorless liquid (60 mg) which crystallized when shaken with pentane. Recrystallization from pentane gave white crystals (53 mg): mp 71.5–72.5 °C, >99% pure (condition 1); IR (CCl_4) 1758 (s, ester C=O), 1250 cm^{-1} (s); NMR (CCl_4) δ 4.79 (s, 2, $W_{1/2} \sim 3$ Hz, axial **CHOAc**, C-2, C-4), 2.42 (m, 2), 2.28–1.86 (m, 4), 1.93 (s, 6, $OCOCH_3$, C-2, C-4), 1.59 (t, 2, $J = 3$ Hz, $CHCH_2CH$, C-9), 1.47 (d, 2, $J_{gem} = 11$ Hz, axial **HCH**, C-6, C-8).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.61; H, 7.60.

2-(a)-Acetoxy-4-(e)-acetoxynoradamantane (2). Diacetate **2** was obtained by preparative GLC along with diacetate **3** by the procedure described for the isolation of **3**. Bulb to bulb distillation (136 °C, ca. 0.2 mm) gave **2** as a colorless liquid (7 mg): ca. 99% pure (condition 1); IR (CCl_4) 1751 (s, ester C=O), 1248 cm^{-1} (s); NMR (CCl_4) δ 5.30 (s, 1, axial **CHOAc**, C-2), 4.95 (m, 1, $J = 1.5, 3.5, 7$ Hz, equatorial **CHOAc**, C-4), 2.66–1.38 (m, 10), 2.11 (s, 3, $OCOCH_3$), 1.97 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.63; H, 7.39.

2,4-Di-(e)-dihydroxynoradamantane (5). Diacetate **3** (48 mg, 0.02 mmol, mp 71.5–72.5 °C) was saponified with methanolic potassium hydroxide (38 mg, 0.68 mmol, in 10 ml) at 25 °C for 1 h. Workup as previously reported for the preparation of diol **7a** afforded white crystals (30 mg). Sublimation (136 °C, ca. 0.2 mm) gave diol **5** (26 mg, 84%): mp 256–257.5 °C (sealed capillary); IR (KBr) 3310 cm^{-1} (b, bonded OH); NMR (pyridine-d_5) δ 5.95 (s, 2, $W_{1/2} \sim 6$ Hz, **CHOH**, C-2, C-4), 4.25 (s, 2, $W_{1/2} \sim 4$ Hz, axial **CHOH**, C-2, C-4), 2.92–2.42 (m, 4), 2.30–2.06 (br s, 2, $W_{1/2} \sim 8$ Hz, CH, C-1, C-5), 1.76–1.24 (m, 4).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.39; H, 8.89.

4-*exo*-Acetoxy-8-*anti*-hydroxybrendane (8a). Diacetate **6** (463 mg, 1.95 mmol, >99% pure, condition 1) was dissolved in stirred 50% aqueous methanol (10 ml). Potassium hydroxide (66 mg, 1.18 mmol) in 50% aqueous methanol (4 × 1 ml) was added with a 10-min interval after addition of each 1 ml. The solvent was removed (25 °C, ca. 0.2 mm), ether (50 ml) was added, and the solution was dried. GLC (condition 2) showed five components in the following relative ratios: diacetate **6** (6%), hydroxy acetate **8b** (9%), hydroxy acetate **8a** (52%), an unidentified component (2%), and diol **7a** (31%). The components were partially separated by column chromatography on silica gel (10 g, column o.d. 14 mm) with 3:7 ether/pentane (12 × 40 ml) followed by methanol (1 × 200 ml). Fractions 1–3 contained diacetate **6** (27 mg). Hydroxy acetate **8a** and the unidentified component (161 mg) were eluted together in fractions 4–8. Fractions 9–12 contained **8a** and **8b** and the unknown component (42 mg). The methanol fraction contained diol **7a** (149 mg). Pure **8a** was obtained by preparative GLC (column 3, 175 °C, 29 psi) of fractions 4–8 as a colorless liquid (149 mg, 39%): ca. >99% pure (condition 2); IR (neat, 3430 (b, bonded OH),

1745 (s, ester C=O), 1725 (sh), 1253 cm^{-1} (s); NMR ($CDCl_3$) δ 4.91 (d of d, 1, $J_{4n,5x}$ = 3, $J_{4n,5n}$ = 7 Hz, endo CHOAc, C-4), 4.17 (s, 1, $W_{1/2}$ ~ 4 Hz, syn CHOH, C-8), 2.69–1.64 (m, 8), 2.51 (s, 1, CHOH, C-8), 1.97 (s, 3, $OCOCH_3$), C-4), 0.97 (overlapped d of m, l, J_{gem} = 12 Hz, endo HCH, C-2 or C-9), 0.88 (overlapped br d, 1, J_{gem} ~ 12 Hz, endo HCH, C-2 or C-9).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.29; H, 8.58.

4-*exo*-Hydroxy-8-*anti*-acetoxybrendane (8b). Hydroxy acetate **8b** was isolated as a colorless liquid in 4% yield by the identical procedure reported for the preparation of hydroxy acetate **8a**: ca. >99% pure (condition 2); IR (neat) 3420 (b, bonded OH), 1746 (s, ester C=O), 1252 cm^{-1} (s); NMR ($CDCl_3$) 4.93 (m, 1, $W_{1/2}$ ~ 5 Hz, syn CHOAc, C-8), 4.15 (d of d, 1, $J_{4n,5x}$ = 2, $J_{4n,5n}$ = 7 Hz, endo CHOH, C-4), 2.76–1.52 (m, 8), 2.01 (s, 3, $OCOCH_3$, C-8), 1.83 (s, 1, CHOH, C-4), 1.02–0.74 (overlapped d of m, 2, endo HCH, C-2 and C-9).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.31.

Brendane-4,8-dione (16). The diol mixture (340 mg, 1.97 mmol) obtained by saponification of the unseparated diacetates from the thallium triacetate reaction was oxidized with Jones reagent[4] (5 ml added dropwise over 4 min) in acetone (20 ml) at 25 °C for 3 h. Methanol (6 ml) was added to destroy the excess of oxidant. Solid potassium carbonate was added to neutralize any acid present, and the solution was dried. GLC (condition 2) showed three components: dione **16** (94%), an unidentified product, and some unoxidized diol (6% total for both components). The crude product (273 mg) was purified by column chromatography on silica gel (10 g, column o.d. 14 mm). The column was eluted successively with 1:9 ether/pentane (5 × 40 ml), 2:8 ether/pentane (6 × 40 ml), and 3:7 ether/pentane (8 × 40 ml). The dione was eluted in fractions 13–18. Sublimation (136 °C, ca. 0.2 mm) gave the diketone as a white solid (109 mg, 37%): mp 159–161 °C; >99% pure (condition 2); IR (CCl_4) 1794 (s, C=O), 1763 cm^{-1} (s, C=O); NMR (CCl_4) δ 3.03–1.92 (m, 8), 1.51 (d of d, 1, $J_{2n,3}$ = 2, J_{gem} = 13 Hz, endo HCH, C-2), 1.23 (d of d, 1, $J_{9n,6}$ = 2, J_{gem} = 13 Hz, endo HCH, C-9).

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.71; H, 6.52.

8-*anti*-Hydroxybrendan-4-one (15). Diol **7a** (158 mg, 1.03 mmol, ca. 98% pure, condition 2) was dissolved in acetone (20 ml) and cooled to 0 °C. Jones reagent[4] was added dropwise until a yellowish-green color, characteristic of unreduced oxidant, persisted for ca. 5 min. Methanol (5 drops) was added and the solution was filtered through a sintered glass funnel. GLC (condition 2) showed four components in the following ratios: dione **16** (8%), hydroxy ketone **10** (7%), hydroxy ketone **15** (75%), and diol **7a** (10%). Hydroxy ketone **15** was isolated by preparative GLC (column 1, 180 °C, 30 psi) from the crude product (155 mg) as a white solid (88 mg, 56%): mp 166.5–167.5 °C; ca. 98.5% pure (condition 2); IR ($CHCl_3$) 3622 (w, OH), 3452 (b, bonded OH), 1739 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.25 (s, 1, $W_{1/2}$ ~ 5 Hz, syn CHOH, C-8), 3.17 (s, 1, $W_{1/2}$ ~ 10 Hz, CHOH, C-8), 2.83–1.76 (m, 8), 1.32 (d of m, 1, J_{gem} = 12 Hz, endo HCH, C-2 or C-9), 1.00 (d of d, 1, J_{gem} = 12 Hz, endo HCH, C-9 or C-2).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.71; H, 8.00.

8-*anti*-Acetoxybrendane-4-one (17). Hydroxy ketone **15** (89 mg, 0.59 mmol, ca. 98.5% pure, condition 2) was stirred with acetic anhydride (2 ml) and pyridine (1 ml) at 25 °C for 22 h. Brine (10 ml) was added and the solution was extracted with ether (3 × 10 ml). The extracts were washed with aqueous 5% HCl (2 × 10 ml), water (2 × 10 ml), and bicarbonate (10 ml) and dried. Recrystallization of the crude product (92 mg) from pentane gave white crystals (81 mg, 71%): mp 59–60 °C; >99% pure (condition 2); IR (CCl_4) 1754 (s, C=O and ester C=O), 1245 cm^{-1} (s); NMR (CCl_4) δ 4.87 (m, 1, $W_{1/2}$ ~ 4 Hz, syn CHOAc, C-8), 2.89–2.57 (m, 2), 2.47–1.85 (m, 6), 1.99 (s, 3, anti $OCOCH_3$, C-8), 1.34 (d of d, 1, $J_{2n,3}$ = 2, J_{gem} = 12 Hz, endo HCH, C-2), 1.01 (d of m, 1, J_{gem} = 12 Hz, endo HCH, C-9).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.90; H, 7.47.

8-*anti*-Acetoxybrendan-4-one Ethylene Dithioketal (18). Boron trifluoride etherate (1.5 ml) was added to a solution of keto acetate **17** (30 mg, 0.15 mmol, >99% pure, condition 2) and ethanedithiol (2 ml), and stirred at 25 °C for 16 h. The solution was poured over ice (40 g), water (50 ml) was added, and the mixture was extracted with ether (4 × 30 ml). The extracts were washed with aqueous 10% sodium hydroxide (3 × 20 ml) and brine (1 × 30 ml) and dried. Removal of solvent left a pale yellow oil. Recrystallization from pentane (twice) gave white crystals (16 mg, 38%): mp 86.5–87.5 °C; IR (CCl_4) 1751 (s, ester C=O), 1249 cm^{-1} (s); NMR (CCl_4) δ 4.86 (s, 1, $W_{1/2}$ ~ 4 Hz, syn CHOAc, C-8), 3.40–2.94 (m, 4, SCH_2CH_2S, C-4), 2.86–1.70 (m, 8), 1.92 (s, 3, $OCOCH_3$, C-8), 1.40 (d of d, 1, $J_{2n,3}$ = 3, J_{gem} = 13 Hz, endo HCH, C-2), 1.05 (bd, 1, J_{gem} = 11 Hz, endo HCH, C-9).

8-Acetoxybrendane (19). Ethylene dithioketal **18** (34 mg, combined crystals and mother liquor residue) and activated Raney nickel[22b] were refluxed in ethanol (13 ml) for 1.5 h. The mixture was filtered through Celite, and water (65 ml) was added. The solution was extracted with ether (3 × 30 ml), washed with brine (30 ml), and dried. GLC (condition 2) showed three components: two unidentified products (3% total) and acetate **19** (97%). Preparative GLC (column 2, 110 °C, 30 psi) gave **19** as a colorless liquid (17 mg, 61% based on starting keto acetate **18**: >99% pure, condition 2 (temperature lowered to 140 °C); IR (CCl_4) 1748 (s, ester C=O), 1255 cm^{-1} (s); NMR (CCl_4) δ 4.78 (s, 1, $W_{1/2}$ ~ 4 Hz, CHOAc, C-8), 2.52–1.37 (m, 10), 1.93 (s, 3, $OCOCH_3$, C-8), 0.83 (superimposed d of m, 2, J_{gem} each d ~ 12 Hz, endo HCH, C-2 and C-9).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 9.07.

4-*exo*-Acetoxybrendan-8-one (9). Hydroxy acetate **8a** (149 mg, 0.76 mmol, 99% pure, condition 2) was oxidized with Jones reagent[4] (0.5 ml) in acetone (10 ml) at 25 °C for 2 h. Methanol (10 drops) was added to destroy the excess of oxidant. The solution was filtered and solvent was removed. Ether (30 ml) and bicarbonate (1 ml) were added, and the two-phase mixture was dried. GLC (condition 2) showed a single component. Bulb to bulb distillation (136 °C, ca. 0.2 mm) gave the keto acetate **9** as a colorless liquid (140 ml, 95%): IR (neat) 1779 (s, C=O), 1749 (s, ester C=O), 1251 cm^{-1} (s); NMR ($CDCl_3$) δ 5.12 (d of d, 1, $J_{4n,5x}$ = 3, $J_{4n,5n}$ = 6 Hz, endo CHOAc, C-4), 2.80–1.84 (m, 8), 1.99 (s, 3, $OCOCH_3$, C-4), 1.26 (overlapped d of d, 1, J = 2, J_{gem} = 13 Hz, endo HCH, C-2 or C-9), 1.11 (overlapped d of d, 1, J = 2, J_{gem} = 13 Hz, endo HCH, C-2 or C-9).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.06; H, 7.21.

4-*exo*-Acetoxybrendan-8-one Ethylene Dithioketal (11). Keto acetate **9** (32 mg, 0.16 mmol, >99% pure, condition 2) was converted to its ethylenedithioketal **11** by the identical procedure used to convert keto acetate **17** to ethylene dithioketal **18**. Recrystallization from pentane (twice) gave white crystals (17 mg, 38%): mp 87.5–89 °C; IR (CCl_4) 1745 (s, ester C=O), 1250 cm^{-1} (s); NMR (CCl_4) δ 4.94 (d of d, 1, $J_{4n,5x}$ = 3, $J_{4n,5n}$ = 7 Hz, endo CHOAc, C-4), 3.17 (s, 4, $W_{1/2}$ ~ 1 Hz, SCH_2CH_2S, C-8), 2.63–1.62 (m, 8), 1.90 (s, 3, $OCOCH_3$, C-4), 1.18–0.84 (overlapping d of d, 2, endo HCH, C-2, and C-9).

4-*exo*-Acetoxybrendane (12). Desulfurization of **11** (61 mg) was by the procedure used on ethylene dithioketal **18**. The product was isolated by preparative GLC (column 2, 115 °C, 30 psi) as a colorless liquid (20 mg, 67% based on starting keto acetate **9**): >99.5% pure, condition 2 (temperature lowered to 140 °C). The IR and NMR of this product were identical with those of an authentic sample of **12**.[3]

4-*exo*-Hydroxybrendan-8-one (10). Keto acetate **9** (237 mg, 1.22 mmol, 88% pure by NMR, containing 12% of 4-(e)-acetoxynoradamantan-2-one) prepared by Jones oxidation of a 88:12 mixture (determined by NMR) of unresolved hydroxy acetates **8a** and 2-(e)-hydroxy-4-(e)-acetoxynoradamantane (identified in a similar mixture by hydrolysis to diol **5** and esterification to diacetate **3**) was stirred with potassium hydroxide (35 mg, 0.62 mmol) in methanol (12 ml) for 15 min at 25 °C. The methanol was removed under aspirator vacuum at 40 °C. Ether (50 ml) and water (20 drops) were added to the residue and the solution was dried. GLC (condition 2) showed three components: the unresolved hydroxy ketones (97.5%) and two other unidentified components (2.5% total). The unresolved hydroxy ketones were isolated by preparative GLC (column 1, 180 °C, 30 psi) as a white solid (129 mg, 69%). This solid was extremely hygroscopic and liquefied during an attempt to transfer it from the GLC collector to a vial. The solid was recovered by sublimation (136 °C, ca. 0.2 mm) and analyzed by GLC (condition 2) and NMR. GLC indicated the purity of the unresolved hydroxy acetates as 98%. NMR integration of the CHOH protons indicated <5% of noradamantyl hydroxy ketone in hydroxy ketone **10**: mp unrecorded owing to extreme hygroscopic properties; IR ($CHCl_3$) 3638 (m, free OH), 3472 (b, bonded OH), 1774 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.31 (d of d, 1, $J_{4n,5x}$ = 2, $J_{4n,5n}$ = 6 Hz, endo CHOH, C-4), 3.01 (s, 1, $W_{1/2}$ ~ 4 Hz, CHOH, C-4), 2.80–1.52 (m, 8), 1.08 (superimposed doublets, 2, J_{gem} ~ 12 Hz, endo HCH, C-2 and C-9).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.86; H, 8.04.

4-*endo*-Hydroxy-8-*anti*-hydroxybrendane (7c). Keto acetate **17** (41 mg, 0.21 mmol, >99% pure, condition 2) was added dropwise in ether (5 ml) to a stirred slurry of lithium aluminum hydride (43 mg, 1.13 mmol) in ether (10 ml) at 25 °C. After 11 h the reaction mixture was worked up by the method of Micovic and Mihailovic[23] to give a white solid (31 mg). Preparative GLC (column 3, 185 °C, 30 psi) gave

>98% stereoisomerically pure (determined by NMR) diol **7c** (25 mg, 76%): mp 212.5–213.5 °C; IR (KBr) 3346 cm^{-1} (b, bonded OH); NMR (pyridine-d_5) δ 5.95 (s, 2, $W_{1/2}$ ~ 26 Hz, CHOH, C-4 and C-8), 4.60 (m, 1, $J_{4x,3}$ = 5, $J_{ex,5n}$ = 5, $J_{4x,5x}$ = 9 Hz, exo CHOH, C-4), 4.47 (s, 1, $W_{1/2}$ ~ 5 Hz, syn CHOH, C-8), 2.96–2.24 (m, 5), 2.24–1.94 (m, 2), 1.90–1.42 (m, 2), 1.25 (d, 1, J_{gem} = 10 Hz, endo HCH, C-9).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.25.

Lithium Aluminum Hydride Reduction of Keto Acetate 9. Keto acetate **9** (41 mg, 0.21 mmol, >99% pure, condition 2) was reduced with lithium aluminum hydride (45 mg, 1.21 mmol) by the procedure used for keto acetate **17**. The crude, oily product (37 mg) was purified by preparative GLC (column 3, 185 °C, 30 psi) to give a white solid (24 mg, 73%) shown by NMR to be a ca. 1:1 mixture of diols **7a** and **7b**. Some assigned signals from **7b** that were superimposed on, and therefore masked by, the previously described signals of diol **7a** follow: NMR (pyridine-d_5) 4.52 (overlapping d of d, $J_{4n,5x}$ ~ 4, $J_{4n,5n}$ ~ 4 Hz, endo CHOH, C-4), 4.40 (s, anti CHOH, C-8), ca. 1.01 (d of d, $J_{2n,3}$ = 2, J_{gem} ~ 10 Hz, endo HCH, C-2), ca. 0.77 (d of d, $J_{9n,6}$ = 1, J_{gem} ~ 10 Hz, endo HCH, C-9).

Lithium Aluminum Hydride Reduction of Dione 16. Dione **16** (109 mg, 0.73 mmol, >99% condition 2) was reduced with lithium aluminum hydride (70 mg, 1.84 mmol) by the procedure used for keto acetate **17**. Part (61 mg) of the crude solid product (89 mg) was purified by preparative GLC (column 3, 185 °C, 30 psi) to give a white solid (43 mg) whose NMR showed the presence of all four stereoisomeric diols **7a–d**. The stereoisomeric pair **7a** and **7b** (ca. 1:1) comprised ca. 15–20% of the mixture and the stereoisomeric pair **7c** and **7d** (ca. 1:1) comprised 80–85% of the mixture. Some assigned signals from diol **7d** that were superimposed on the previously described signals of the other stereoisomers follow: NMR (pyridine-d_5) 4.66 (m, $J_{4x,3}$ ~ 6, $J_{4x,5n}$ ~ 6, $J_{4x,5x}$ ~ 10 Hz, exo CHOH, C-4), 4.50 (s, anti CHOH, C-8), 1.09 (d, J_{gem} = 10 Hz, endo HCH, C-9).

Cleavage of Triaxane with Lead Tetraacetate. Triaxane (50 mg, 0.42 mmol, ca. 98% pure) and lead tetraacetate (390 mg) were refluxed in acetic acid for 2 h. Water (20 ml) was added to the cooled solution, and it was extracted with ether (3 × 20 ml). The extracts were washed with water (2 × 10 ml) and bicarbonate (10 ml) and dried. GLC (condition 1) of the liquid (71 mg) showed six peaks: 2-acetoxytriaxane (**24**, 72%), 2-acetoxynoradamantane and an unidentified peak (9%), diacetate **2** (<1%), diacetate **3** (2%), and diacetate **6** (17%). Our GLC conditions are known[12] not to resolve the epimers of 2-acetoxynoradamantane.

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Registry No.—**1**, 20454-87-9; **2**, 61009-83-4; **3**, 61046-13-7; **4**, 61009-84-5; **5**, 61046-14-8; **6**, 61009-85-6; **7a**, 61091-82-5; **7b**, 61009-86-7; **7c**, 61046-15-9; **7d**, 61046-16-0; **8a**, 61009-87-8; **8b**, 61009-88-9; **9**, 61009-89-0; **10**, 61009-90-3; **11**, 61009-91-4; **15**, 61009-92-5; **16**, 61009-93-6; **17**, 61009-94-7; **18**, 61009-95-8; **19**, 61009-96-9; thallium triacetate, 2570-63-0; lead tetraacetate, 546-67-8; ethanedithiol, 540-63-6; acetic anhydride, 108-24-7.

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Stereoselectivity of Proton Loss for "E1-Like" 1,3-Eliminations in Tertiary, Benzylic Systems

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Our objective was to learn whether γ-proton loss from a carbocation to form a cyclopropane ring prefers the semi-W or semi-U pathway. We examined two rigid, tricyclic systems in which the intermediate carbocation in the overall 1,3-elimination is tertiary and carries a *p*-anisyl group. One substrate, 2-chloro-2-*p*-anisylnoradamantane, was synthesized from 2-noradamantanone by action of *p*-anisyllithium, to give the tertiary alcohol, followed by treatment with dry HCl in pentane. The other substrate, 2-chloro-2-*p*-anisylbrendane, was obtained by a similar sequence from 2-brendanone. When heated in hexane, these tertiary chlorides underwent net 1,3-elimination to produce their respective cyclopropyl products, 2-*p*-anisyltriaxane and 2-*p*-anisyldeltacyclane. To elucidate stereochemistry of the proton loss, we synthesized the corresponding 4-axial-*d*- and 4-equatorial-*d* analogues in the noradamantyl series and the corresponding 9-exo-*d* analogues in the brendyl series. The deuterium losses in the 1,3-eliminations were determined mass spectrally. After correction for an isotope effect (k_H/k_D) of 2.04 in the noradamantyl series, the stereoselectivity for γ-proton loss was 7.4/1 in favor of equatorial over axial (i.e., semi-W over semi-U). In the brendyl skeleton loss of the exo proton (i.e., semi-W) was favored over loss of the endo proton (i.e., semi-U) by a factor of ca. 27/1. Our findings with these two tertiary skeletons are contrasted with those reported for secondary norbornyl systems.

Stereochemistry of cyclopropane ring formation via 1,3-elimination has been explored in several cyclic and open-chain systems; and recent publications summarize developments in the field.[2] Such eliminations involve configurational changes at two centers, and most of the common reactions fall into three broad categories, according to whether one or both centers become stereorandomized before closure of the ring.

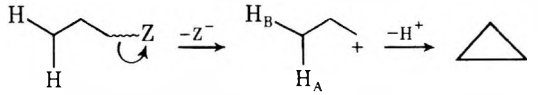
In the first category the initial geometry at *both* centers is maintained until the ring bond is formed. This category would include all concerted 1,3-eliminations, as well as stepwise processes via ions or radicals that preserve stereochemical integrity; and there are four distinct geometric arrangements for the ring-forming transition state. These have been termed W, U, exo-Sickle, and endo-Sickle,[4] and examples of the first three types in this category have been described.[2,5,6]

The second category comprises stepwise 1,3-eliminations via a carbanion that destroys configuration at the *electrofugal* center prior to the ring-forming event. (An analogous pathway in 1,2-elimination is often termed ElcB.)[3] Almost invariably in these cases the cyclopropyl bond forms by inversion at the nucleofugal center, and so a semi-W transition state is highly favored in this category[7] (eq 1).

(1)

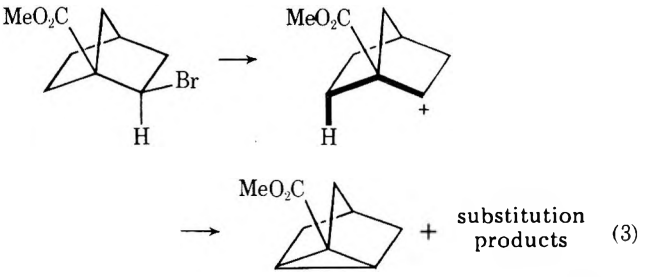
semi-W

The third category is made up of stepwise 1,3-eliminations involving an initial carbocation that destroys configuration at the *nucleofugal* center before ring closure. A typical situation in 1,3-elimination of HZ would be ionization to a configurationless cation followed by loss of a γ proton (eq 2).[8] In



(2)

brief stereochemical notation loss of H_A would be termed semi-U and loss of H_B is named semi-W.[4] This third category has received very little attention stereochemically.[9] A pertinent study is that by Werstiuk, who solvolyzed a deuterated analogue of 1-carbomethoxy-2-exo-norbornyl bromide at 112 °C in 20% H_2O–EtOH with NaOAc buffer (eq 3).[10] In the cyclopropyl product he found a preference of at least 15:1 for loss of the 6-endo proton (i.e., semi-U path) after adjustment for an isotope effect k_H/k_D of 1.6. Whether the $COOCH_3$ unit or

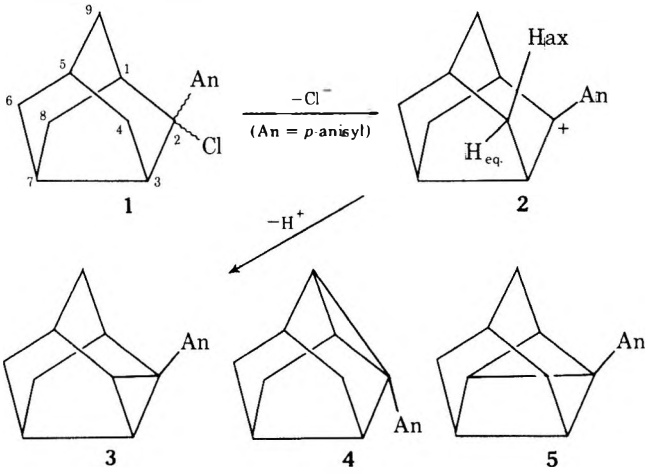


(3)

the peculiarities of norbornyl cations in any way influence this stereoselectivity is not known, although Lenoir reported that a CO_2CH_3 at C-1 does slow the solvolysis rate of *exo*-norbornyl bromide by a factor of ca. 1.6×10^4.[11]

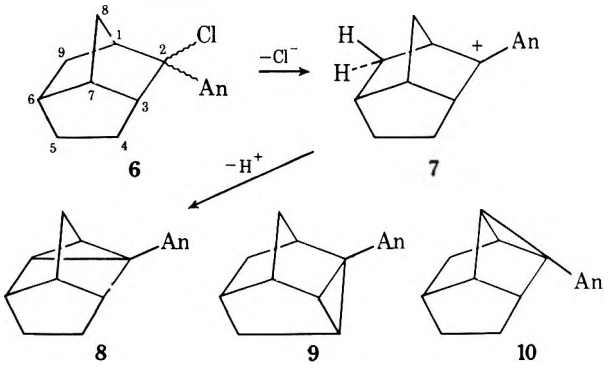
We present here a stereochemical study of HCl loss in a 1,3-elimination that belongs to category three (eq 2). To ensure formation of a carbocation intermediate we examined chlorides that are tertiary and that also contain a *p*-anisyl group, to provide exceptionally powerful driving forces for an "E1-like" process.[12] Noradamantane and brendane were selected as template skeletons for our study. These rigid tricyclic systems possess appropriately oriented C–H bonds that are γ to the nucleofugal center. In each skeleton the stabilized carbocation (see **2** and **7**) is flanked by bridgehead carbons, and so competitive 1,2-eliminations to produce olefins are precluded.

In a tertiary, noradamantyl chloride functionalized at C-2 (**1**, An = *p*-anisyl) the derived cation **2** can lose a γ hydrogen



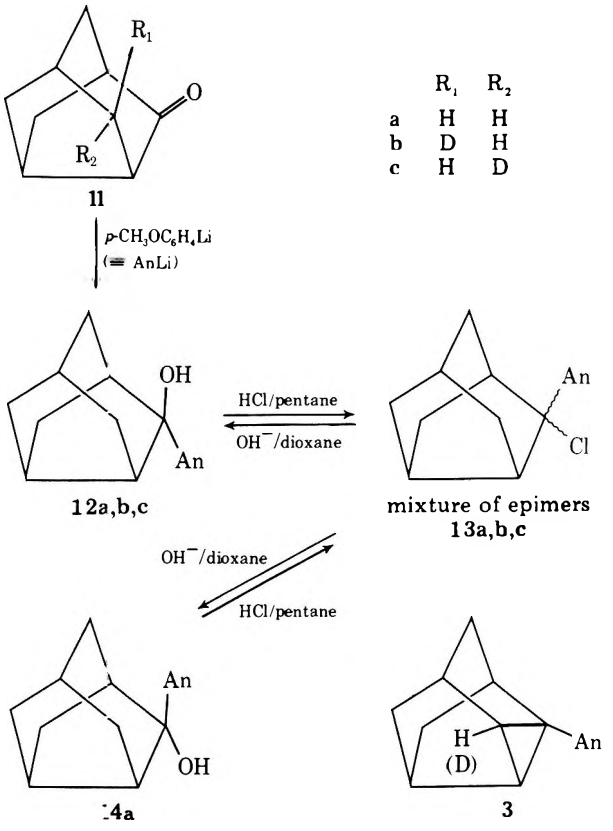
from C-4, C-9, or C-8, to produce respectively the three cyclopropyl products, **3**, **4**, and **5**. The parent skeletons in **3**[13] and **4**[14] are readily accessible tetracyclic systems, and molecular models suggest that **3** should be the least strained of the three hydrocarbons. [Our present study with C-4 deuterium labeled substrates establishes that the major 1,3-elimination product is, in fact, 2-*p*-anisyltriaxane (**3**).] A principal objective was to synthesize tertiary chloride **1** suitably monodeuterated at C-4 and to learn whether there is any preference for loss of the axial (i.e., semi-U) or equatorial (semi-W) hydrogen in the formation of **3**.

In the brendane system the cation **7** derived from the tertiary chloride **6** can, in principle, lead to three cyclopropyl



products, **8**, **9**, and **10**, corresponding to removal of a γ proton from C-9, C-4, and C-8, respectively. Our present work with deuterium labeling shows that the least strained product **8** (2-*p*-anisyldeltacyclane[14,15]) is formed predominantly. We undertook to synthesize tertiary chloride **6** and, with a deuterated analogue, to determine exo–endo selectivity in loss of a C-9 hydrogen.

Syntheses of Noradamantyl Substrates. Treatment of noradamantan-2-one[15] (**11a**) with *p*-anisyllithium followed



	R_1	R_2
a	H	H
b	D	H
c	H	D

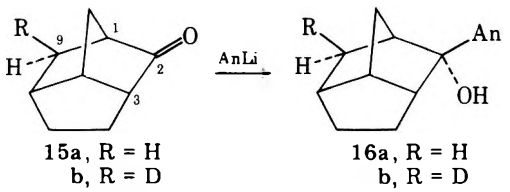
by nonacidic workup affords as principal product the corresponding tertiary alcohol **12a** (mp 69.5–70 °C). The axial configuration for the OH group is not certain but is expected if we presume approach of the aryllithium from the more accessible equatorial face of the carbonyl group. (This view is supported by the known reduction of the same ketone with lithium aluminum hydride, which produces axial alcohol almost exclusively.[15]) The analytical and spectral data and the chemical transformations of **12a** are compatible with its expected structure. For example, ^{1}H NMR shows no low-field carbinyl hydrogen characteristic of secondary alcohols, and treatment with Brown's reagent ($Na_2Cr_2O_7$, H_2SO_4, H_2O) does not oxidize the alcohol but, because of the acidity, only isomerizes it partially to the epimer **14a** (mp 77–78 °C), which we isolated by preparative TLC and characterized analytically and spectrally. Mixtures of the two epimers are readily assayed by gas chromatography.

The alcohol **12a** was converted to the solid tertiary chloride **13a** ($C_{16}H_{19}OCl$) by mild treatment with dry HCl in pentane at 0 °C according to conditions developed by Brown and Rei[16] for tertiary alcohols. In accord with its tertiary structure, the ^{1}H NMR spectrum of chloride **13a** showed no low-field proton typical of secondary halides and gave an instantaneous precipitate with alcoholic silver nitrate. This chloride seems to be a mixture of epimers, but because of the lability of the halogen we were unable to confirm this positively. For example, the chloride melted over a 2–5 °C range, and samples from different runs had melting points that fell between 72 and 87 °C. In the ^{1}H NMR, the CH_3O appeared as two singlets, too closely spaced to be integrated separately for intensity. The chloride decomposed on attempted gas chromatography to give 2-*p*-anisyltriaxane together with an unidentified product. The lability of the chlorine in **13a** was also evident on attempted thin layer chromatography, because substantial hydrolysis to alcohols occurred on the TLC plates. With KOH in dioxane chloride **13a** was converted completely to an 85:15 mixture of alcohols **12a** and **14a**. When this alcohol mixture was treated with HCl in pentane, it reverted to chloride **13a**. The hydrolysis of **13a** is surely of S_N1 type and, interestingly, the capture of OH is not highly stereoselective. This behavior of tertiary, benzylic carbocations contrasts with that of secondary 2-noradamantyl cations, which capture nucleophiles virtually exclusively from the equatorial (i.e., exo) direction.[17]

Chloride **13a** underwent elimination of HCl when heated neat at 205 °C and produced largely 2-*p*-anisyltriaxane (**3**). This hydrocarbon (mp 97–98 °C) was chromatographically separated from minor by-products and showed a cyclopropyl C–H stretch vibration at 3045 cm^{-1}. Its ^{1}H NMR spectrum exhibited the expected aromatic and OCH_3 peaks, and no olefinic C–H. That this cyclopropyl product has structure **3** rather than one of the other two possibilities (**4** or **5**) is supported most directly by results with deuterated precursors to be described.

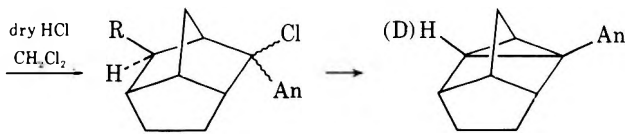
Our synthesis of labeled chlorides **13b** and **13c** began with the authentic epimeric 4-*d*-noradamantan-2-ones, which were prepared by stereoselective homoketonization routes recently developed.[18] 4-(a)-*d*-Noradamantan-2-one (**11b**), with the label >98% configurationally axial, was converted to the corresponding tertiary alcohol **12b** and then to chloride mixture **13b** by the same procedures that were used for the nonlabeled analogues. The 4-equatorial-*d* ketone **11c** was similarly converted to the corresponding tertiary alcohol **12c** and tertiary chloride **13c**.[19] The deuterium in **11c** is only 85% configurationally equatorial[18] and, accordingly, our 1,3-elimination results had to be corrected for the presence of 15% axial-*d*. This correction turns out to be virtually nonconsequential (see later).

Synthesis of Brendyl Substrates. Addition of *p*-anisyllithium to brendan-2-one (**15a**)[14] produced the corresponding tertiary alcohol **16a** (mp 55.5–57 °C), whose ^{1}H NMR showed no carbinyl proton characteristic of a secondary alcohol. The



15a, R = H
b, R = D

16a, R = H
b, R = D



17a, R = H
b, R = D

8

OH configuration is provisionally thought to be endo based on the known preference of lithium aluminum hydride to reduce brendan-2-one almost exclusively to *endo*-brendan-2-ol.[20] Treatment with dry HCl in methylene chloride at room temperature converted **16a** to the tertiary chloride **17a** (mp 93–95 °C), which gave an instantaneous positive silver nitrate test and whose ^{1}H NMR showed no low-field absorption typical of secondary halides. Even though this chloride appeared homogeneous, its ^{1}H NMR shows the CH_3O as two extremely closely spaced singlets, so we suspect an epimer mixture. When chloride **17a** was heated neat at 205 °C, the major product was 2-*p*-anisyldeltacyclane (**8**, mp 58.5–59.5 °C) whose IR showed cyclopropyl C–H stretch at 3055 cm^{-1}. Its ^{1}H NMR indicated no olefinic protons and had the expected aromatic and OCH_3 absorptions. That this 1,3-elimination product is **8** and not either of the other possible cyclopropyl structures (**9** or **10**) becomes evident later from our deuterium studies.

The only *d*-labeled precursor synthetically accessible in the brendane series was 9-*exo*-*d*-brendan-2-one (**15b**) containing 4% d_0, 82% d_1, and 14% d_2, which we prepared as reported.[18] The deuterium at C-9 is virtually entirely exo (>95%), and the d_2 species are known to have the second deuterium at C-3.[18,21] This second deuterium presents no complication since it is not involved in the 1,3-elimination of **17b** → **8**. In fact it provides an additional way to compute, mass spectrally, the *d* loss in the elimination. The labeled ketone **15b** was converted to the tertiary alcohol **16b** and to the tertiary chloride **17b** (5% d_0, 83% d_1, 12% d_2) by the procedures developed for the natural abundance material.

1,3-Elimination Results. Because of the extreme ease of ionization of the C–Cl bond in our tertiary substrates, we had hoped to effect stepwise 1,3-dehydrochlorination in several neutral and alkaline solvents. Unfortunately, however, substitution products predominated overwhelmingly in various media and were not accompanied by significant quantities of cyclopropyl product. However, we found that 1,3-elimination occurred in diluted hexane at ca. 225 °C (sealed tube), and so our stereochemical study was necessarily restricted to this single solvent. The ease with which our chlorides were prepared from the alcohols with dry HCl in pentane showed that even in nonpolar media these highly stabilized carbocations are readily formed. As a further check that our halides would ionize in hexane, we heated a dilute solution of chloride **13a** in hexane containing a small amount (ca. 2.5%) of acetic acid. From the resulting mixture of acetates and starting chlorides, we were able to separate **12a acetate**, which had the expected spectral properties and whose structure was confirmed by saponification to authentic **12a**. The epimeric acetate (i.e., **14a acetate**) was also formed, but we were unable to separate it in pure form from the mixture. Similar replacement of chlorine by OAc occurred when we heated chloride **13a** in hexane containing suspended tetrabutylammonium acetate.

In the noradamantyl series, chloride **13a** at 225 °C in hexane gave 2-*p*-anisyltriaxane **3** (ca. 70%) plus two minor by-products (12 and 18%) which were not identified. Hydrocarbon **3** was separated and purified chromatographically, and controls were run to show that none of the cyclopropyl product was produced during chromatography. Identical treatment of deuterated analogues **13b** and **13c** gave labeled 2-*p*-anisyltriaxane, whose mass spectrum revealed the deuterium content and hence the stereoselectivity in the proton loss. At this temperature the release of HCl (and DCl) is evidently irreversible because no dideuterated cyclopropyl species were observed from our monolabeled noradamantyl chlorides. [Reversibility would produce some dideuterated species because 2-*p*-anisyltriaxane (**3**) has a symmetry plane, and a ring bond that is reopened by DCl need not be the one that already carries a labeled carbon.] In the brendyl series similar dehydrochlorination of 2-*p*-anisylbrendyl chloride (**17a** and labeled analogue **17b**) gave almost exclusively (97%) 2-*p*-anisyldeltacyclane (**8**), which was purified chromatographically and, for the labeled case, analyzed for deuterium.

Table I. Mass Spectral Deuterium Assay of 2-*p*-Anisyltriaxane from Dehydrochlorination of 4-*d*-2-Chloro-2-*p*-anisylnoradamantane at 225 °C in Hexane[a]

Run	Substrate[b]	Cyclopropyl product 3 % d_0	Cyclopropyl product 3 % d_1	% D lost	Fractional % D lost
1	Axial-*d* (**13b**)[c]	17	83	6	6.7
2	Axial-*d* (**13b**)[c]	16	84	5	5.6
3	Equat-*d* (**13c**)[d]	70	30	61	77.8[e]
4	Equat-*d* (**13c**)[d]	71	29	62	79.1[e]

[a] All mass spectral numbers are estimated to be ±1–2%. [b] Concentration ca. 2.5 × 10^{-2} M. [c] The axial-*d* chloride had 11% d_0, 89% d_1. [d] The equatorial-*d* chloride had 9% d_0, 91% d_1. [e] Corrected for 15% configurational inhomogeneity (see footnote 22).

Table I summarizes the mass spectral results for 2-*p*-anisyltriaxane obtained from duplicate runs on each labeled chloride **13b** and **13c**. The axial-*d* substrate **13b** lost 6.2 fractional % of its deuterium (average of runs 1 and 2) in the 1,3-elimination, and the equatorial-*d* substrate **13c** lost 78.5% (average of runs 3 and 4). This last value is corrected for the 15% configurational inhomogeneity in **13c**.[22] From these data the computed isotope effect (k_H/k_D) is 2.04 if we assume, reasonably, that k_H/k_D is the same for cleavage of an axial or an equatorial C–H bond.[23] This value may be compared with one reported earlier (k_H/k_D = 2.1) for 1,3-proton abstraction in acetolysis of *exo*-norbornyl brosylate to form nortricyclane[5a] and with Werstiuk's value of 1.6 in the 1-carbomethoxynorbornyl systems described above.[10] When the isotope effect of 2.04 in our present study is taken into account, the inherent preference for equatorial-H loss over axial-H loss (i.e., semi-W vs. semi-U) is 7.4/1 in this *p*-anisylnoradamantyl system. How much (if any) of this preference for semi-W is attributable to steric as opposed to stereoelectronic factors cannot presently be assessed; but note that the equatorial and axial hydrogens at C-4 in cation **2** have rather similar steric environments.

Table II summarizes relevant data for duplicate dehydrochlorinations on deuterated tertiary brendyl chloride **17b**. The presence of 12% d_2 species in the substrate is immaterial because the second deuterium is at C-3[18] where it plays no relevant role in the 1,3-elimination. However, it does permit the *d* loss to be calculated from the $d_1 \rightarrow d_0$ change as well as from the $d_2 \rightarrow d_1$ change. The d_1–d_0 mass spectral measurements are probably the more accurate because larger numbers are involved; nevertheless, both methods agreed well, cf. average values of 93.5 vs. 92 (Table II and footnotes *b* and *c*) for fractional % D lost. Clearly, this exo-*d* substrate loses most of its

Table II. Mass Spectral Deuterium Assay of 2-*p*-Anisyldeltacyclane from Dehydrochlorination of 9-*exo*-*d*-2-Chloro-2-*p*-anisylbrendane[a] at 225 °C in Hexane

Run	Cyclopropyl product % d_0	% d_1	% d_2	% D lost[b]	Fractional % D lost[b,c]
1	31	18	1	76	92
2	34	15	1	79	95

[a] The substrate had 5% d_0, 83% d_1, 12% d_2. The deuterium at C-9 is virtually entirely exo (>95%).[18] [b] Computed from the amount of a_1 species that became d_0. [c] When computed from the change $d_2 \rightarrow d_1$, the % D lost is 11 (run 1) and 11 (run 2). The corresponding fractional % D lost are 92 and 92.

deuterium. Because only one *d* epimer was available for study, an isotope effect cannot be calculated. However, if we adopt the same value for k_H/k_D (2.04) found with the noradamantyl substrates, we compute the inherent preference for loss of exo H (i.e., semi-W) over endo H (semi-U) to be 27/1. Thus the inclination for semi-W is even higher in the brendyl skeleton than it was in the noradamantyl system (cf. 7.4/1). Steric accessibility of the exo H may be of added importance in the brendyl case because the endo H has extra hindrance due to the ethano bridge.

The preference for semi-W in our two substrates contrasts with the bias for semi-U observed by Werstiuk for secondary halides in the norbornyl series.[10] Because his solvent was aqueous ethanol whereas ours was hexane (where ion pairing should be more pronounced), the different stereoselectivities may be dictated by the media. However, if solvent alone is not responsible for the differences, and if the three skeletons examined to date are representative, it appears that stereochemistry of γ-hydrogen loss from a carbocation may not be subject to overriding stereoelectronic control.

Experimental Section

General. Except where noted otherwise the following information applies. Melting points were taken in open capillary tubes in a Thomas-Hoover apparatus. They are corrected and are rounded to the nearest 0.5 °C. Infrared spectra were recorded in carbon tetrachloride solution on a Perkin-Elmer Model 337 or 457 grating infrared spectrophotometer. A Perkin-Elmer Model 900 analytical gas chromatograph with a hydrogen flame ionization detector was used. Nuclear magnetic resonance spectra were run on a Varian Associates HA-100 or A-60 instrument with tetramethylsilane as the internal reference. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 single-focusing instrument. Spectra used in the identification of new compounds were run at 70 eV; spectra of deuterated samples were recorded at 15 eV. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and Galbraith Laboratories, Inc. Anhydrous sodium sulfate or magnesium sulfate was the drying agent unless specified.

We purified technical grade pentane (Eastman) by stirring it over concentrated sulfuric acid, washing with 10% aqueous sodium bicarbonate, drying, filtering, and distilling. A mixture of hexanes was dried by distillation from sodium; the dried solvent was stored over 4A molecular sieves. The term "hexane" refers to this dried and distilled mixture. Ten percent silver nitrate/silica gel for column chromatography was prepared by addition of a solution of silver nitrate (4.99 g) in 7 ml of water to 50.13 g of silica gel.

Analytical and preparative (20 × 20) thin layer chromatography (TLC) was performed on silica gel plates. Silica gel with 2% silver nitrate was made from 1.5 g of silver nitrate in 170 ml of water and 75 g of silica gel. High-pressure liquid chromatography (HPLC) was done on a Perkin-Elmer Model 1220 with a UV detector (254 nm) and a Xil-X-1 column, 2.6 × 50 mm; mobile phase 20% chloroform/80% hexane; flow rate 1 ml/min; ambient temperature. These solvents were previously distilled and degassed.

2-(a)(?)-Hydroxy-2-*p*-anisylnoradamantane. Noradamantan-2-one[15] (0.50 g, 3.68 mmol) in 10 ml of ether was added dropwise to *p*-anisyllithium[24] (prepared from 36.8 mmol of *p*-bromoanisole and 36.8 mmol of *n*-butyllithium) at 0 °C in 5 min. The mixture was stirred at room temperature for 1 h and poured onto ice. Workup of the ether layer left a yellow oil, which was chromatographed on silica gel with pentane and ether to give 2-*p*-anisylnoradamantan-2-ol (needles from ligroin, mp 69.5–70 °C, 86% yield, >97% pure by GLC): IR 3595 (O–H stretch), 2920, 2835 (methoxyl C–H), 1615, 1505, 1300, 1250, 1185, 1040 cm^{-1}; δ ($CDCl_3$) 7.38–6.76 (m, 4 H, aromatic), 3.72 (s, 3 H, CH_3O), 2.76–1.11 (complex multiplets, 12 H), 1.68 (sharp singlet projecting out of multiplets, 1 H, OH). Prominent mass spectral peaks are at *m/e* 244, 226, 185, 163, 150, 135 (base), 121, 77, and 55.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.87; H, 8.41.

In other runs with 1.2 equiv each of *n*-butyllithium and *p*-bromoanisole and 1.0 equiv of ketone, we obtained lower yields (e.g., 70%), but the alcohol was pure after one recrystallization from pentane *without* any column chromatography. It showed only one peak on two different GLC columns (t_R 10 min on 1.5% SE-30, 9 ft × 0.125 in., 230 °C; t_R 8 min on 5% XE-60, 2% Carbowax 20M on Chromosorb W, 4 ft × 0.125 in., 190 °C) and only one spot on analytical TLC (30% ethyl acetate in hexane).

2-(e)(?)-Hydroxy-2-*p*-anisylnoradamantane. The tertiary alcohol **12a** (470 mg) in ether (25 ml) was stirred with Brown's reagent[25] (1.5 ml) for 15 min. The crude product after workup was chromatographed on preparative TLC plates (30% ethyl acetate in hexane) and gave two major components. The faster moving one (R_f 0.5) was identified by IR and NMR as the starting alcohol (166 mg, mp 68–69 °C). The slower (R_f 0.4) component had mp 71.5–73 °C (88 mg) after one recrystallization from pentane, and showed one peak on GLC (t_R 6 min on 5% XE-60 2% Carbowax 20M on Chromosorb W, 4 ft × 0.125 in., 190 °C): IR 3600, 2935, 2875, 2835, 1610, 1510, 1465, 1330, 1250, 1180, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 7.28–6.65 (m, 4 H, aromatic), 3.74 (s, 3 H, methoxyl CH), 2.7–1.1 (complex multiplets, 13 H with the OH singlet evident at 1.48; in $CDCl_3$ this OH shifted to 2.14 and was a sharp singlet). The analytical sample had mp 77–78 °C (from pentane).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.54; H, 8.40.

Generation of Anhydrous Hydrogen Chloride. The Brown chlorination apparatus[16] was modified to preclude a pressure-controlled reaction. An ordinary glass buret filled with concentrated hydrochloric acid was inserted through a rubber stopper at the top of a suction flask containing well-stirred concentrated sulfuric acid. The flask was connected by Tygon tubing and a vacuum adapter to the reaction vessel, which was equipped with a stirrer, a rubber septum for introduction of the sample by syringe, and a vacuum adapter leading to an aqueous sodium hydroxide trap. This apparatus permitted manual control of the generation of anhydrous hydrogen chloride.

2-Chloro-2-*p*-anisylnoradamantane. The modified chlorination set-up was assembled and purged with dry hydrogen chloride. 2-(a)-Hydroxy-2-*p*-anisylnoradamantane (**12a**, 0.274 g) in 18 ml of pentane was chlorinated at 0 °C for 70 min (6.0 ml of concentrated hydrochloric acid used). The reaction mixture was aspirated gently and then vacuum was applied at 0 °C for 2 h. 2-Chloro-2-*p*-anisylnoradamantane (0.274 g, 93% yield) solidified and was recrystallized from ligroin to flat, rectangular plates, mp 73–75 °C. The chloride gave an immediate positive test with alcoholic silver nitrate solution: ν 2945, 2870, 2840 (methoxyl C–H), 1615, 1520, 1470, 1320, 1260, 1185, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.44–6.78 (m, 4 H, aromatic), 3.82 (s, with a sharp spike on the high field side, 3 H, CH_3O), 2.93–1.32 (complex multiplets, 12 H). Prominent mass spectral peaks are at *m/e* 262, 227, 226, 186, 185 (base), 172, 170, 153, 121, 115, and 77.

Anal. Calcd for $C_{16}H_{19}OCl$: C, 73.13; H, 7.29. Found: C, 73.29; H, 7.11.

In other runs the IR of various chloride mixtures were quite similar, with differences only in relative band intensities. A run conducted for 20 min gave 84% of chloride, mp 79–82 °C after one recrystallization from pentane. GLC (on 5% XE-60 2% Carbowax 20M on Chromosorb W, 4 ft × 0.125 in., 190 °C) decomposed the chloride to give two overlapping peaks with t_R 5 and 7 min, respectively. In attempts to isolate the two decomposition products, we combined several batches of chloride **13a** for preparative GLC at 190 °C and 30 psi on a column 6 ft × 0.25 in. made from 5% XE-60, 2% Carbowax 20M on ABS 80/100. The major component (t_R 12 min) was collected (98% pure) and identified as 2-*p*-anisyltriaxane by comparison of ^1H NMR and IR spectra with those of authentic material. The other product (t_R 16 min) could not be obtained pure and remains unidentified.

Hydrolysis of Chloride Mixture. The chloride (mp 79–82 °C from above, 130 mg) and sodium hydroxide (40 mg) in dioxane (10 ml) and water (10 ml) was heated overnight at 80 °C. The solvent was removed in vacuo, water (10 ml) was added, and the mixture was extracted with pentane (3 × 30 ml), washed with brine (100 ml), and dried. Solvent

removal left 110 mg of crude product, mp 67–69 °C after one recrystallization from pentane, 90 mg (75%). A $AgNO_3$ test was negative, and TLC showed two components with R_f values corresponding to those of alcohols **12a** and **14a**. GLC showed appropriate t_R of 6 and 8 min and a ratio of 85:15, which was confirmed by two ^1H NMR (CCl_4) singlets at δ 3.70 and 3.72 (CH_3O) in the same ratio.

Conversion of Alcohol Mixture to Chloride Mixture. Treatment of the 85:15 mixture of **12a** and **14a** (50 mg) with dry HCl (generated from 1.0 ml of concentrated hydrochloric acid) for 10 min gave a chloride mixture, mp 81–83 °C (32 mg, 60%). The IR was very similar to that of the chloride **13a** obtained from alcohol **12a**.

2-*p*-Anisyltriaxane. 2-Chloro-2-*p*-anisylnoradamantane (65 mg) was heated neat at 205 ± 5 °C for 45 min and vacuum distilled. Analytical GLC of the crude product (44 mg, mp 65–77 °C) showed two peaks (96 and 4%). Column chromatography of the mixture on 10% silver nitrate/silica gel with pentane gave pure 2-*p*-anisyltriaxane (mp 97–98 °C, one peak on GLC): IR 3045 (cyclopropyl C–H), 2945, 2855, 2840 (methoxyl C–H), 1620, 1515, 1470, 1295, 1240, 1175, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 6.99–6.58 (doublet of doublets, 4 H, aromatic), 3.68 (s, 3 H, CH_3O), 2.68 (broad doublet, 3 H, bridgeheads), 2.33 (broad singlet, 2 H, cyclopropyl), 2.03–1.54 (complex multiplet, 3 H, equatorial methylene), 1.34 (d, 3 H, axial methylene).[13] Principal mass spectral peaks are at *m/e* 226, 186, 185 (base), 172, 170, 153, 141, 128, 115, and 77.

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.76; H, 7.96.

2-*p*-Anisylbrendan-2-ol. Brendan-2-one[14,15] (2.6 g, 19 mmol) in 40 ml of ether was added slowly to *p*-anisyllithium[24] (from 144 mmol of *p*-bromoanisole) at 0 °C. The mixture was stirred at room temperature for 90 min, poured onto ice, and worked up to leave a yellow oil. Column chromatography on silica gel with pentane and ether gave >99% pure (by GLC) 2-*p*-anisylbrendan-2-ol (needles from ligroin, mp 55.5–57 °C, 75% yield): IR 3595 (O–H stretch), 2945, 2835 (methoxyl C–H), 1610, 1505, 1470, 1255, 1180, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–6.77 (m, 4 H, aromatic), 3.72 (s, 3 H, CH_3O), 2.54–1.25 (complex multiplets, 12 H), 1.46 (sharp singlet superimposed on multiplets, 1 H, OH).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.91; H, 8.48.

2-Chloro-2-*p*-anisylbrendane. The modified chlorination setup was flushed with dry hydrogen chloride, and 2-*p*-anisylbrendan-2-ol (0.050 g) in 5 ml of methylene chloride was injected. The alcohol was treated at room temperature with anhydrous hydrogen chloride, generated for 1.5 h from 7.0 ml of concentrated hydrochloric acid. The solution was dried, filtered, and evaporated to an oil, which instantaneously gave a positive test with alcoholic silver nitrate solution. The 2-chloro-2-*p*-anisylbrendane was recrystallized from ligroin to flat plates: mp 93–95 °C; IR 2945, 2870, 2840 (methoxyl C–H), 1620, 1515, 1470, 1320, 1255, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.35–6.66 (m, 4 H, aromatic), 3.71 (two very closely spaced singlets, 3 H, CH_3O), 3.08–0.84 (complex multiplets, 12 H). Prominent mass spectral peaks are at *m/e* 262, 227, 226 (base), 211, 198, 197, 186, 185, 159, 153, 141, 128, 121, 117, 115, 91, and 77.

Anal. Calcd for $C_{16}H_{19}OCl$: C, 73.13; H, 7.29. Found: C, 72.94; H, 7.10.

2-*p*-Anisyldeltacyclane. 2-Chloro-2-*p*-anisylbrendane was heated neat at 205 ± 5 °C for 1 h and vacuum distilled. Column chromatography of the crude product (ca. 25% yield) on 10% silver nitrate/silica gel with pentane eluted an oil (99% pure by GLC), which solidified when scratched (mp 58.5–59.5 °C): IR 3055 (cyclopropyl C–H), 2945, 2870, 2840 (methoxyl C–H), 1620, 1515, 1475, 1295, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 6.92–6.58 (doublet of doublets, 4 H, aromatic), 3.67 (s, 3 H, CH_3O), 2.21 (s, 1 H, bridgehead), 2.08 (s, 1 H, bridgehead), 1.82 (s, 1 H, bridgehead), 1.76–1.47 (complex multiplet, 6 H, methylene), 1.20 (s, 2 H, cyclopropyl). Principal mass peaks appeared at *m/e* 226 (base), 211, 198, 197, 185, 159, 153, 141, 121, 115, 91, and 77.

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.83; H, 7.83.

Dehydrochlorination of 2-Chloro-2-*p*-anisylnoradamantane in Hexane. 2-Chloro-2-*p*-anisylnoradamantane (26 mg) and 4 ml of dry hexane in a sealed tube were heated at 225 ± 5 °C for 4 h. Analysis of the contents by GLC (at 150 °C, 50 psi on 5% SE-30 on silanized 60/80 Chromosorb W) indicated three peaks in the ratio of 12, 70, and 18%. Column chromatography of the mixture on 10% silver nitrate/silica gel gave 2-*p*-anisyltriaxane (the major component of the crude mixture) in 99% purity. An infrared spectrum was identical with that of authentic 2-*p*-anisyltriaxane described earlier.

Dehydrochlorination of 2-Chloro-2-*p*-anisylbrendane in Hexane. 2-Chloro-2-*p*-anisylbrendane (30 mg) and 4 ml of dry hexane in a sealed tube were heated at 225 ± 5 °C for 4 h. GLC analysis (as immediately above) showed 97% 2-*p*-anisyldeltacyclane and a 3% impurity. The crude product was chromatographed on 10% silver nitrate/silica gel to provide a solid (99% pure by GLC) whose GLC retention time and infrared spectrum were identical with those of authentic 2-*p*-anisyldeltacyclane.

Controls in Chromatographic Workup. Column chromatography of 2-chloro-2-*p*-anisylnoradamantane on 2% silver nitrate/silica gel with pentane eluted no chlorides or 2-*p*-anisyltriaxane in the pentane fractions. Alcohols produced by hydrolysis on the column were eluted only in the ether fractions. Thus, after dehydrochlorination experiments any residual starting chlorides are trapped on the column as alcohols in our isolation procedure and do not undergo 1,3-elimination on the column.

Ionization of 2-Chloro-2-*p*-anisylnoradamantane in Hexane. Method I. A solution of the chloride **13a** (100 mg) in hexane (20 ml) containing glacial acetic acid (0.5 ml with 1% acetic anhydride) was refluxed for 2 days. The cooled solution was washed consecutively with 10% $NaHCO_3$ (50 ml), water (50 ml), and brine (50 ml), dried and evaporated to leave a liquid (87 mg). Analytical high-pressure liquid chromatography showed two peaks corresponding to alcohols **12a** and **14a**, followed by a broad, unsymmetrical peak. (Separately we showed that HPLC of the original chloride gives two peaks whose retention times are identical with those shown by authentic alcohols **12a** and **14a**.) For separation the total crude product from this experiment was chromatographed on preparative TLC plates (20 × 20 cm, 1.5 mm, silica gel with 2% silver nitrate) with 30% ethyl acetate in hexane. Three bands were obtained.

The fastest band (R_f 0.75) gave 40 mg of liquid acetate, which showed only one spot on analytical TLC: ^1H NMR (CCl_4) δ 7.32–6.65 (m, 4 H, aromatic), 3.75 (s, 3 H, OCH_3), 3.55–3.25 (broad triplet, 1 H), 1.90 (s, $COCH_3$), 2.6–1.0 (m, 14 H); IR 2910, 1740, 1610, 1370, 1240, 1180, 1140 cm^{-1}. Saponification of this acetate (30 mg) in refluxing methanolic KOH under nitrogen for 4 h gave, on conventional workup with ether, 25 mg, mp 69–70 °C (after one recrystallization from pentane). This alcohol showed only one spot on TLC (silica gel, 20% ethyl acetate in benzene), and the IR was identical with that of authentic 2-(a)(?)-hydroxy-2-*p*-anisylnoradamantane (**12a**).

The second TLC band was very close to the first and gave 20 mg of product whose IR, etc., suggested that it was a mixture of the alcohol **12a** and the acetate of **14a**.

The third TLC band gave 20 mg of crude alcohol whose IR was virtually identical with that of the alcohol **14a**.

Method II. 2-Chloro-2-*p*-anisylnoradamantane (**13a**, 130 mg) in hexane (40 ml, previously distilled from molecular sieve 4A) containing suspended tetrabutylammonium acetate (900 mg, dried in vacuo overnight at 78 °C) was heated at reflux overnight. Undissolved salt was separated and the solution was evaporated in vacuo. Preparative TLC (silica gel, 20% ethyl acetate in hexane) gave two principal bands and some minor ones. The fastest band (R_f 0.7) gave 7 mg of liquid whose IR was virtually identical with that of **12a acetate** obtained by method I. The slower band (R_f 0.4) gave 110 mg shown to be a 14:86 mixture on GLC. After recrystallization from pentane the product had mp 71–73 °C and its IR closely resembled that of authentic epimeric alcohol **14a**.

Deuterated Ketones.[18] Homoketonization of 2-acetoxytriaxane in sodium methoxide–methanol-*O*-d_1 as reported provided 4-*d*-noradamantan-2-one (9% d_0, 91% d_1), with the deuterium 85 relative percent equatorial and 15 relative percent axial. Homoketonization in methanol-*O*-d_1 containing sulfuric acid-d_2 gave the deuterated ketone (9% d_0, 91% d_1) with the deuterium >98% axial.

Alkaline homoketonization of 2-acetoxydeltacyclane as reported gave exclusively deuterated brendan-2-one (4% d_0, 82% d_1, 14% d_2) with one deuterium at the 9-exo position (no detectable endo epimer); and the 14% d_2 species has the second deuterium at the C-3 bridgehead.[18,21] Acid homoketonization is known to give a mixture of brexan-2-one and brendan-2-one; the C-9 deuterium in the latter ketone is also entirely exo.[18]

Deuterated Substrates. Deuterium-labeled alcohols were prepared from the corresponding deuterated ketones exactly as we described for the unlabeled ketones. Also, the deuterated chlorides were prepared from the deuterated alcohols by the same procedures used in the analogous natural abundance compounds. The 1,3-eliminations were conducted as before and the mass spectral results are in Tables I and II in the text. Spectral data on the deuterium labeled compounds are summarized below.

4-(e)-*d*-2-(a)-Hydroxy-2-*p*-anisylnoradamantane (12c): mp 71.5–72 °C; ν 3593 (O–H stretch), 2940, 2860, 2835 (methoxyl C–H), 2180 (C–D stretch), 1615, 1515, 1475, 1305, 1250, 1180, 1070, 1040, 1020 cm^{-1}; ^1H NMR (CCl_4) δ 7.36–6.67 (doublet of doublets, 4 H, aromatic), 3.72 (s, 3 H, CH_3O), 2.72–1.05 (complex multiplets, 12 H,

with a sharp singlet at 1.33 (OH) standing out).

4-(a)-*d*-2-(a)-Hydroxy-2-*p*-anisylnoradamantane (12b): mp 70–71.5 °C ν 3595 (O–H stretch), 2940, 2880, 2840, (methoxyl C–H), 2225 (C–D stretch), 1620, 1515, 1475, 1310, 1250, 1180, 1070, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 7.82–6.64 (doublet of doublets, 4 H, aromatic), 3.70 (s, 3 H, CH_3O), 2.68–1.05 (complex multiplets, 12 H).

4-(e)-*d*-2-Chloro-2-*p*-anisylnoradamantane (13c, 9% d_0, 91% d_1): mp 68–70 °C; ν 2940, 2870, 2835 (methoxyl C–H), 2175 (C–D stretch), 1615, 1510, 1310, 1255, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.31–6.65 (complex multiplet, 4 H, aromatic), 3.74 (s with spike, 3 H, CH_3O), 3.20–1.26 (complex multiplets, 11 H).

4-(a)-*d*-2-Chloro-2-*p*-anisylnoradamantane (13b, 11% d_0, 89% d_1): mp 81–83.5 °C; ν 2940, 2870, 2835 (methoxyl C–H), 2225 (C–D stretch), 1620, 1515, 1470, 1320, 1255, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.35–6.67 (complex multiplet, 4 H, aromatic), 3.75 (s with spike, 3 H, CH_3O), 3.19–1.31 (complex multiplets, 11 H).

9-*exo*-*d*-2-*p*-Anisylbrendan-2-ol: mp 55–55.5 °C; ν 3595 (O–H stretch), 2950, 2865, 2835 (methoxyl C–H), 2185 (C–D stretch), 1615, 1510, 1470, 1355, 1300, 1250, 1185, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.34–6.65 (doublet of doublets, 4 H, aromatic), 3.71 (s, 3 H, CH_3O), 2.54–1.18 (complex multiplets, 11 H), 1.13 (s, 1 H, OH).

9-*exo*-*d*-2-Chloro-2-*p*-anisylbrendane (5% d_0, 83% d_1, 12% d_2): ν 2950, 2870, 2835 (methoxyl C–H), 2175 (C–D stretch), 1615, 1510, 1470 1300, 1255, 1185, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.38–6.65 (complex multiplet, 4 H, aromatic), 3.74 (two very closely spaced singlets, 3 H, CH_3O), 3.10–0.90 (complex multiplets, 11 H).

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Registry No.—**3**, 61062-27-9; **8**, 61062-28-0; **11a**, 17931-67-8; **11b**, 61062-31-5; **11c**, 61116-69-6; **12a**, 61062-29-1; **12a** acetate, 61062-32-6; **12b**, 61062-30-4; **12c**, 61116-70-9; **13a** isomer 1, 61062-33-7; **13a** isomer 2, 61116-71-0; **13b** isomer 1, 61062-34-8; **13b** isomer 2, 61116-72-1; **13c** isomer 1, 61116-73-2; **13c** isomer 2, 61116-74-3; **14a**, 61116-75-4; **15a**, 1521-92-2; **15b**, 61092-31-7; **16a**, 61062-35-9; **16b**, 61062-36-0; **17a** isomer 1, 61062-37-1; **17a** isomer 2, 61116-76-5; **17b** isomer 1, 61062-38-2; **17b** isomer 2, 61116-77-6; *p*-anisyllithium, 14774-77-7; *p*-bromoanisole, 104-92-7.

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(8) If the ring arises from radical intermediates, the terms nucleofugal and electrofugal may not be appropriate without further definition.
(9) A (less common) fourth category can be envisaged wherein stereochemistry is lost at both centers if they are converted to a configurationless pair of radicals or ions prior to ring closure. A Favorskii rearrangement that produces a discrete cyclopropanone from a dipolar ion may belong to this category. For discussions, see F. G. Bordwell and M. D. Wolfinger, *J. Org. Chem.*, **39**, 2521 (1974); H. O. House and H. W. Thompson, *ibid.*, **28**, 164 (1963); E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Am. Chem. Soc.*, **88**, 334 (1966).
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(11) (a) D. Lenoir, *Tetrahedron Lett.*, 1563 (1974); (b) D. Lenoir, *Chem. Ber.*, **108**, 2055 (1975).
(12) Studies in the norbornyl series have established that tertiary substrates solvolyze via classical (i.e., nonbridged) cations and that phenyl and *p*-anisyl groups accelerate the rates tremendously. For example, in methanol at 25 °C 2-phenyl-*exo*-norbornyl chloride solvolyzes ca. 10^8 faster than does *exo*-norbornyl chloride. In several tertiary systems *p*-anisyl was found to be still more powerful than phenyl by factors of 10^3–10^4. (a) H. C. Brown, F. J. Chloupek, and M-H. Rei, *J. Am. Chem. Soc.*, **86**, 1246 (1964); (b) H. C. Brown and M-H. Rei, *ibid.*, **86**, 5008 (1964); (c) H. C. Brown and K. Takeuchi, *ibid.*, **90**, 2691, 2693 (1968); (d) H. C. Brown and K-T. Liu, *ibid.*, **91**, 5909 (1969); (e) H. C. Brown, S. Ikegama, and K-T. Liu, *ibid.*, **91**, 5911 (1969); (f) E. N. Peters and H. C. Brown, *ibid.*, **95**, 2397 (1973).
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(19) Interestingly, the axial C–D stretch in alcohol **12b** (2225 cm^{-1}) and that in chloride **13b** (2225 cm^{-1}) are at higher frequencies than the equatorial C–D stretch in **12c** (2180 cm^{-1}) and **13c** (2175 cm^{-1}). This situation is the opposite of that normally observed for axial and equatorial C–D bonds in cyclohexyl rings [E. J. Corey, M. Howell, A. Boston, R. Young, and R. Sneen, *J. Am. Chem. Soc.*, **8**, 5036 (1956); F. Y. Edamura and A. Nickon, *J. Org. Chem.*, **35**, 1509 (1970)]. Ketones **11b** (2180, 2155 shoulder cm^{-1}) and **11c** (2178 cm^{-1}) show less distinction in their C–D band positions.[18]
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(21) A. Nickon, D. F. Covey, F. Huang, and Y-N. Kuo, *J. Am. Chem. Soc.*, **97**, 904 (1975).
(22) Illustrative calculation (run 3). Of the total % *d* loss (61%), the amount that came from the 15% axial-*d* component is 0.8% (i.e., 6.2 × 15 × 91). Therefore the amount lost from the equatorial-*d* component is 60.2% (i.e., 61 − 0.8). The corrected fractional % *d* loss is 60.2/85 × 91 = 77.8. For run 4 this corrected value comes to 79.1.
(23) Let P = inherent preference for loss of equatorial H vs. axial H; let Y = isotope effect (k_H/k_D) for cleavage of C–H (equatorial or axial). For the axial-*d* substrate:

$$\frac{\text{fractional \% equat H lost}}{\text{fractional \% axial D lost}} = P \times Y$$

For the equatorial-*d* substrate:

$$\frac{\text{fractional \% equat D lost}}{\text{fractional \% axial D lost}} = \frac{P}{Y}$$

Substitution of the appropriate average percentages from Table I and solving the two equations simultaneously gives $Y = 2.04$ and $P = 7.4$.
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Cationic Cyclizations of Labda-8(17),12- and Labda-8(17),13(16)-dien-14-ol[1]

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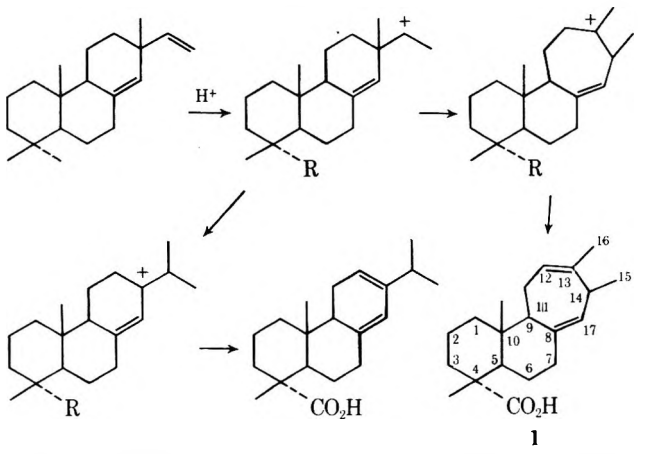
Syntheses of the labda-8(17),13-dien-12-ols (**6**) from sclareol and of the labda-8(17),12- (**16**) and labda-8(17),13(16)-dien-14-ols (**29**) from manool are described. On treatment with Collins reagent, the secondary allylic alcohols **6** and **16** undergo an oxidative rearrangement to α-epoxy ketones later found characteristic of tertiary allylic alcohols. Cationic cyclizations of **16, 29,** and **29** acetate did not result in the hoped-for biogenetic-type strobane synthesis, but yielded tricyclic systems containing five- or six-membered rings (**28** from **16, 32** and **36a** from **29,** and **29** acetate, respectively) as well as a phyllocladane **37** (from **29** acetate). A simple, high-yield preparation of **22** from manool is described.

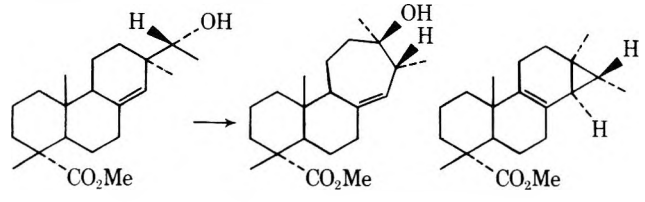
Strobic acid (**1**) and its congeners[2] are representatives of a diterpene group whose biogenesis may involve a variant of the scheme previously[3] proposed for biogenesis of the abietanes. This is shown in Scheme I. (In this and subsequent schemes representation of formulas in the form of discrete carbonium ions is done for convenience only and implies no judgment as to concertedness or lack thereof.)

Scheme I



1

The postulated rearrangement–ring expansion sequence was realized in our laboratory some time ago.[4] Treatment of the hydroxy ester **2** with tosyl chloride–pyridine resulted in genesis of the stroban derivative **3** and the cyclopropane resin acid **4**, apparently by way of a stereospecific homoallylic–cyclopropylcarbinyl–homoallylic pathway. Since the stereochemistry of the C-14 methyl group was opposite of that found in strobic acid, the C-15 epimer of **2** might be expected to

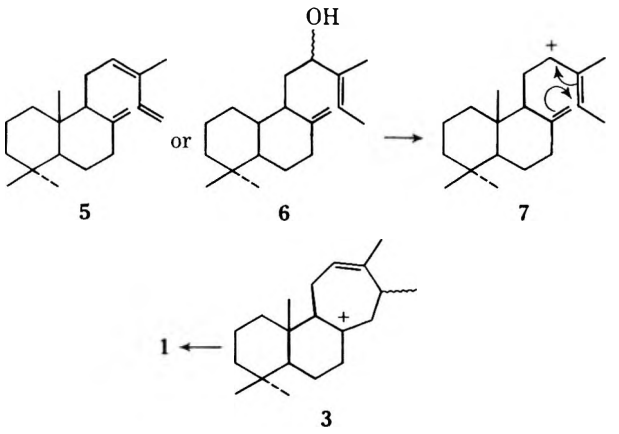


2 3 4

furnish a product with proper C-14 orientation. However, at the time the work was carried out, it proved impossible to separate the 1:1 mixture of C-14 alcohols produced by $NaBH_4$ reduction of the corresponding ketone.

An alternative biogenetic pathway to the strobanes is cyclization (arrows) of the bicyclic ion **7** theoretically derivable from *cis*-biformene (**5**) or the alcohol **6** (Scheme II).[4,5] In the present communication we describe attempts to duplicate this route and variants thereof in the laboratory. Although there are precedents for the formation of seven-membered rings by

Scheme II



5 6 7

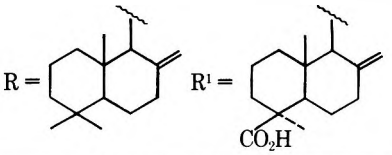
cationically induced cyclization,[6-11] the hoped-for ring closures either did not take place in the desired manner or proceeded beyond the strobane stage.

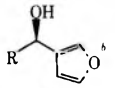
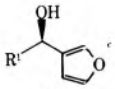
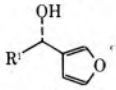
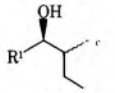
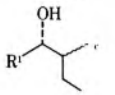
Results and Discussion

Synthesis of Alcohols 6 and 16. The proposed approach required the synthesis of alcohol **6**, which, as depicted in Scheme II, is a mixture of epimers. One possible starting point for the synthesis of this material was lactone **8** from sclareol.[12] $LiAlH_4$ reduction of **8** gave the diol **9a.** The corresponding monoacetate **9b** on dehydration with $POCl_3$–pyridine afforded a mixture of olefinic acetates **10a, 11,** and **12** in the ratio 5:4:1 which was separated by chromatography over silver nitrate–alumina. The structures were established by NMR spectroscopy, **10a** exhibiting two broadened vinylic singlets at 4.65 and 4.85 ppm, **11** a vinyl methyl resonance at 1.69 ppm and no vinylic protons, and **12** a vinyl methyl at 1.72 ppm and a vinyl proton multiplet at 5.05 ppm. Removal of the acetate protecting group by reduction of **10a** with $LiAlH_4$ and oxidation of the resulting alcohol **10b** with either Collins reagent[13] or Ag_2CO_3 on Celite[14] led to aldehyde **13** which exhibited the requisite spectral properties (NMR two broadened vinylic singlets at 4.40 and 4.83 ppm, aldehyde triplet at 9.7 ppm, two-proton doublet at 2.46 ppm, $J_{11,12}$ = 1 Hz).

Addition of *cis*-2-butenyllithium (THF, −78 °C) to **13** gave a 50% yield of alcohols **6a** and **6b** which were separated chromatographically. The NMR spectra of the two products were very similar except for the chemical shifts of H-12 [broadened doublet at 4.60 ($J \sim 10$ Hz) and triplet at 4.73 ppm (J = 6 Hz)], H-14 (broadened quartets due to allylic coupling at 5.24 and 5.37 ppm, J = 6 and 7 Hz), and H-17 (two broadened singlets at 4.40, 4.77 and at 4.73, 4.87 ppm). A comparison of the chemical shifts of H-17 with those reported for other 12-hydroxylabdanes[15,16] indicates (see Table I) that the isomer

Table I. H-17 Resonances of 12-Hydroxylabdanes[a]



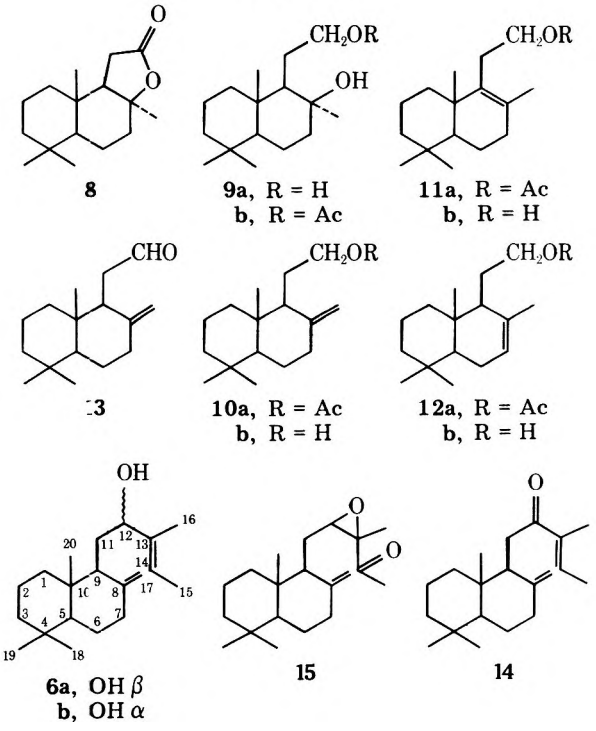
Compd	H-17a	H-17b
6a	4.40	4.77
6b	4.73	4.87
	4.47	4.85
	4.48	4.86
	4.72	4.88
	4.40	4.83
	4.72	4.88

[a] In $CDCl_3$. [b] Taken from ref 16. [c] Taken from ref 15.

with H-17 resonances at 4.73 and 4.87 ppm is **6b** [(*E*)-labda-8(17),13-dien-(12*S*)-ol].

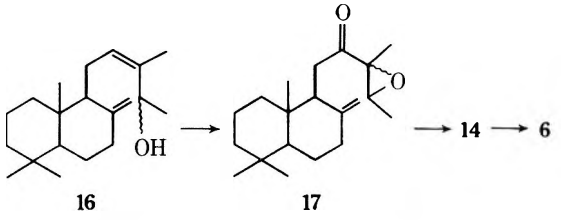
Oxidation of **6a** and **6b** with active MnO_2 to the ketone **14** failed. Oxidation of **6b** with Collins reagent quite unexpectedly gave a substance $C_{20}H_{32}O_2$ which had the properties of an α-epoxy ketone **15** [IR bands at 1705 and 1640 cm^{-1}, significant signals in the NMR spectrum at 1.41 (singlet of methyl on carbon attached to oxygen), 1.97 (methyl ketone), 3.00 (multiplet of H-12), 4.35 and 4.85 ppm (broad singlets of H-17)]. The observation of this unusual oxidative transformation prompted a more extended study[17] which has demonstrated that formation of rearranged α-epoxy aldehydes is a general

Scheme III



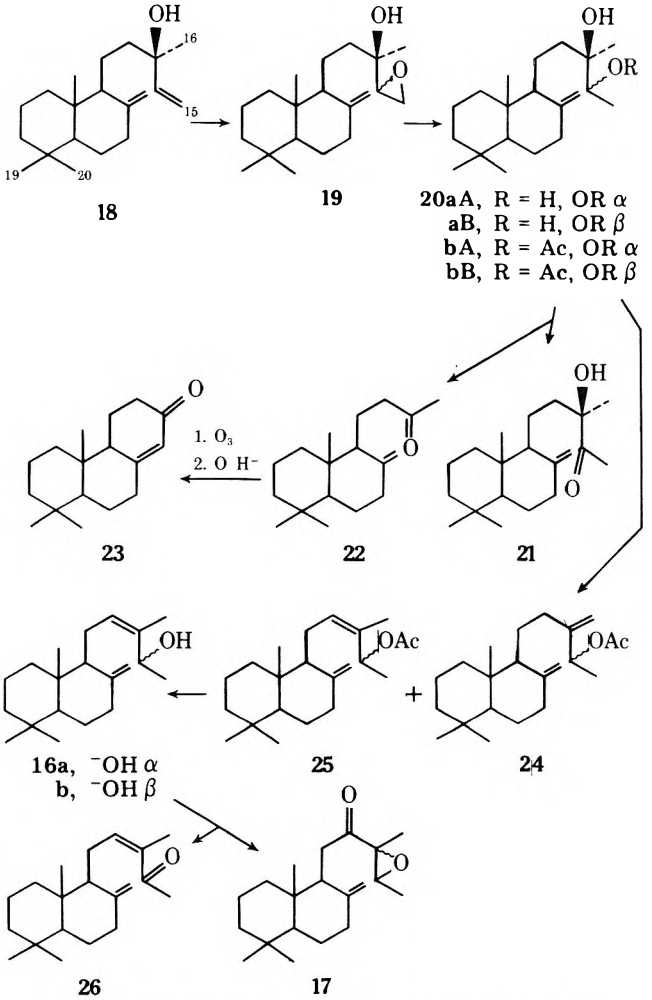
phenomenon when tertiary allylic alcohols are oxidized with Collins reagent. Apparently, certain secondary allylic alcohols are also subject to this rearrangement (see also below). In accordance with the results of this parallel investigation,[17] C-12 of **15** retains the configuration of the precursor alcohol, but the configuration at C-13 is unknown.

The overall yield of alcohols **6** was rather low, owing to the need of separating **10a** from **11** and **12**, and the lithium reagent needed for the last step was difficult to handle. These problems and the interesting oxidative rearrangement of **6b** discussed in the preceding paragraph suggested a different approach to **6**. It was hoped that oxidation of the allylic alcohol **16** with Collins reagent might also be accompanied by rearrangement and lead to epoxy ketone **17** which after reduction with chromous chloride to **14** and further reduction with hydride would yield **6**.



The point of departure for synthesis of **16** was manool (**18**, Scheme IV). Epoxidation with vanadyl acetylacetonate and *tert*-butyl hydroperoxide[18] resulted in selective attack on the

Scheme IV



terminal double bond. The resulting epoxide mixture **19** was reduced with $LiAlH_4$ to **20a** which was a mixture of epimers.[19]

The original plan for converting **20a** to **16** involved oxida-

Table II. Oxidation of 20a with Various Oxidizing Agents

Reagent	Yield, % 21	22
Jones reagent	15	65
Collins reagent	20	76
Pyridinium chlorochromate	15	59
Ag_2CO_3–Celite	28	68
Active MnO_2	5	95

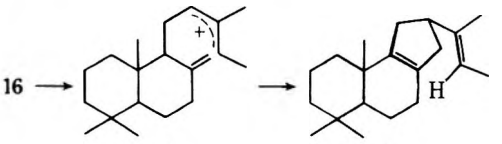
tion to **21** (thus removing the center of asymmetry giving rise to the diastereomeric mixture), dehydration to labda-8(17),12-diene-14-one, and lithium aluminum hydride reduction of the latter. However, exposure of **20a** to a variety of oxidizing agents invariably produced **21** only as a minor product (5–28%, depending on reagent, see Table II). The major product (59–95%) was the well-known ketone **22** which is usually made directly from manool by oxidation with $KMnO_4$.[20]

The formation of ketone **22**, particularly in the high yield shown in the last entry of Table II, while not unprecedented from the chemical point of view,[21] is very interesting because it is an intermediate in the synthesis of **23**, a substance which has proved to be a "versatile starting material" [21] for diterpene synthesis.[23] The maximum yield of **22**, when prepared directly from manool, is about 65%,[20] but this requires work on a relatively small scale and extensive chromatography over $AgNO_3$-impregnated silica gel. The method described here, while involving three steps **18** → **19** → **20** → **21**, seems at least comparable, if not superior. Since each step yields only one product, the operations can be carried through on a large scale without purification of intermediates. In this manner we have achieved overall yields of 90–95% from manool.

Because the yield of **21** was low regardless of the choice of oxidizing agent, the approach to **16** was modified. Dehydration of the monoacetate mixture **20b** ($POCl_3$–pyridine) gave a 1:2 mixture of olefinic acetates **24** and **25** which were separated by preparative TLC. $LiAlH_4$ reduction of **25** then gave the required alcohol **16** as an inseparable mixture of epimers **16a** and **16b**. Subsequently, it was discovered that one of the epimers **20b** could be crystallized from hexane. This isomer (mp 105 °C) was converted in the same way to one of the components of mixture **16** which was needed for another study.[17] Application of Horeau's method[24] showed that the pure substance was labda-8(17),12-dien-(14*S*)-ol (**16b**); consequently the isomer of mp 105 °C was **20bB**.

As hoped for, the epimeric mixture **16** underwent at least partial oxidative rearrangement with Collins reagent to a mixture of the epimeric α-keto epoxides **17** and the α,β-unsaturated ketone **26** which was separated by high-pressure liquid chromatography. Both fractions exhibited the requisite spectral properties; **17** had methyl singlets at 0.75, 0.83, 0.90, and 1.41 ppm, a methyl doublet at 1.38 ppm due to CH_3CHO, the hydrogen of which appeared as a quartet at 3.16 ppm, and an IR band at 1700 cm^{-1}; whereas **26** exhibited methyl singlets at 0.75, 0.80, 0.90, and 2.20 ppm, the triplet of H-12 at 6.61 ppm, and IR bands at 1675 and 1640 cm^{-1}. Unfortunately the attempted reduction of **17** with chromous chloride for eventual conversion to **6** resulted only in quantitative recovery of starting material.

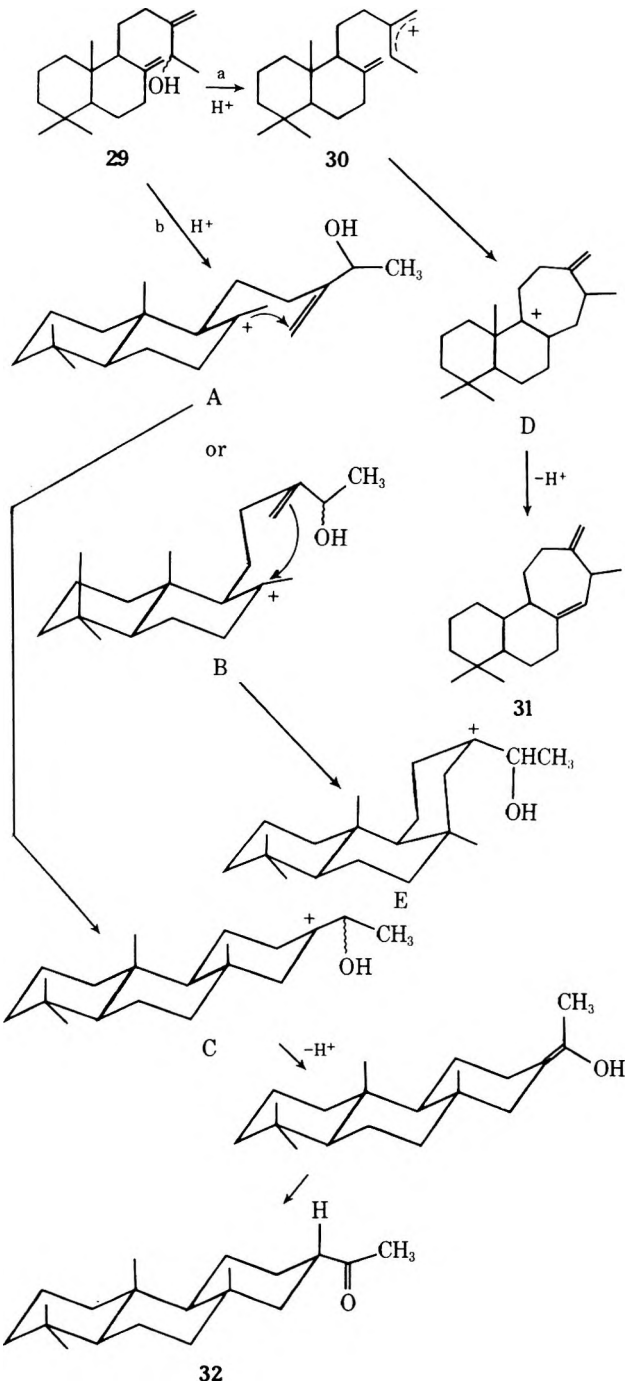
Cyclization Studies. Failure to obtain **6** in reasonable yield prompted a study of the cationic cyclization of alcohol **16** as a possible biogenetic-type route to strobanes since either **6** or **16** could serve as a precursor of the requisite allylic cation **27**. Attempted cyclization of **16** with $SnCl_4$ in CH_2Cl_2 or CH_3NO_2 gave a complex hydrocarbon mixture which could not be separated satisfactorily. Cyclization using formic acid furnished the formate of **16**, and a small amount of a hydrocarbon **28**. The structure assignment was based on the absence of functional groups evidenced by the IR spectrum and the NMR spectrum which showed the presence of a vinylic methyl singlet with fine splitting, a vinylic methyl doublet and a downfield quartet corresponding to one proton, coupling to which was responsible for the fine splitting of the vinyl methyl singlet, as well as three singlets of the three methyl groups attached to ring A. Formation of this hydrocarbon suggests that ion **27**, if formed, undergoes preferential cyclization to a five- instead of a seven-membered ring.



27 28

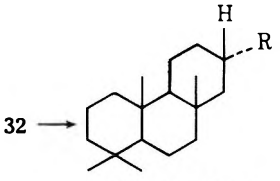
Attention was therefore turned to the cyclization of the

Scheme V

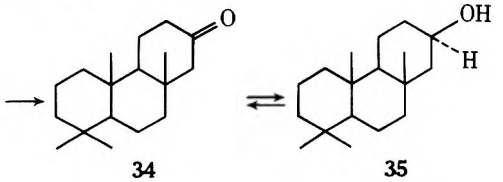


isomeric alcohol **29**, which it was hoped might undergo cyclization to strobane derivative **31** by path a of Scheme V via allylic carbonium ion **30**. Its synthesis was accomplished by $LiAlH_4$ reduction of **24**, a by-product in the preparation of **16**. However, cyclization of **29** with $SnCl_4$–CH_2Cl_2 at −78 °C or $SnCl_4$-nitromethane at 0 °C led in 60% yield to a tricyclic methyl ketone **32** by path b of Scheme V, i.e., by initial protonation at C-17, in a manner reminiscent of the acid-catalyzed cyclizations of labda-8,13-dienes.[23] The IR spectrum of the product had a carbonyl band at 1725 cm^{-1}, but lacked the frequency at 1640 cm^{-1} characteristic of the olefinic methylene group attached to C-8 of the precursor. The NMR spectrum displayed four methyl singlets in the range 0.7–1.0 ppm, a fifth methyl singlet at 2.06 ppm (acetyl methyl), and no downfield signals characteristic of vinylic protons. The absence of unsaturation was confirmed by the ^{13}C NMR spectrum. The stereochemistry of the new angular methyl group at C-8 was assumed to be β since models indicate that attack of the C-13 methylene group on C-8 should occur from the bottom face (ion A) rather than from the top face (ion B) due to steric interactions in ion B between the axial methyl group on -10 and the side chain. The acetyl group attached to C-13 of the product was expected to be equatorial (see Scheme V).

Structure and stereochemistry of **32** were confirmed by the following transformations. Baeyer–Villiger oxidation of **32** gave ester **33a** which was reduced to alcohol **33b** with loss of two carbon atoms. Oxidation of **33b** (Jones reagent) furnished a cyclohexanone **34** (IR band at 1720 cm^{-1}). Reduction of **34** with lithium tri-*tert*-butoxyaluminum hydride afforded a new alcohol **35**. Since the reagent reduces cyclohexanones to axial alcohols, the hydroxyl group of **33b**, and hence the side chain of **32**, must be equatorial. Furthermore, comparison of the NMR spectra of **33a** and **35** revealed that in **35** one of the methyl singlets is downfield as compared with **33a** due to deshielding by the hydroxyl group. This can occur only if the C-8 methyl group is axial to ring C, which would be true of either trans-anti-trans alcohol **35** deived from **32** or a trans-anti-cis alcohol (C-8 methyl α, C-13 hydroxyl α) derived from ion E, Scheme V.



33a, R = OAc
b, R = OH



34 **35**

That formulas **32–35** are indeed correct is evident from the CD curve of ketone **34**. As a *trans*-decalone derivative of the *t*3, *t*2 type,[26] it should exhibit a reasonably strong *positive* Cotton effect ($\Delta\epsilon \sim 1$ or larger), whereas a trans-anti-cis ketone resulting from degradation of E (Scheme V) would be *c*3′ *eq*, *t*4′[26] and should exhibit a relatively weak negative Cotton effect.[27] In fact, $[\theta]_{287}$ of ketone **34** (methanol solution) was +3280 ($\Delta\epsilon \sim 1$) which shows that it and its relatives **32**, **33**, and **35** are *trans-anti-trans*-perhydrophenanthrene derivatives.

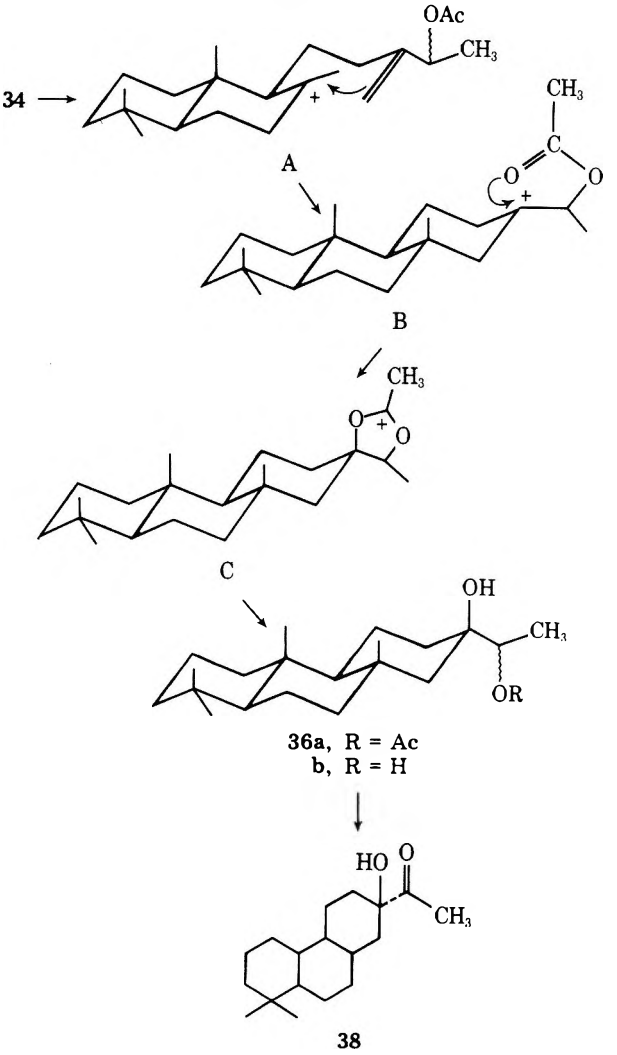
Cyclization of acetate **24** ($SnCl_4$–CH_2Cl_2, −78 °C) proceeded by two competing pathways to yield a mixture of tricyclic hydroxy acetates $C_{22}H_{38}O_3$ (**36a**, Scheme VI) and a tetracyclic substance $C_{20}H_{33}Cl$ (**37**, Scheme VII). The structure of the more polar product **36a** was established as follows. $LiAlH_4$ reduction furnished a diol (**36b**) which was oxidized (Ag_2CO_3–Celite, benzene) to a hydroxy ketone **38** exhibiting a $CH_3C{=}O$ singlet at 2.16 ppm. Further oxidation of **38** with Jones reagent yielded the previously encountered ketone **34** whose formation was not particularly surprising since the reagent is known to cleave 1,2-diols, especially if one of the hydroxyl groups is tertiary.[21] The axial orientation of the

Table III. ^{13}C NMR Spectrum of 37 [a]

Carbon	Chemical shifts	Carbon	Chemical shifts
C-1	41.8 t	C-11	19.5 t[b]
C-2	18.3 t[b]	C-12	32.5 t
C-3	39.7 t	C-13	75.5
C-4	33.1	C-14	38.7 t[c]
C-5	56.3 d	C-15	35.3 t
C-6	21.0 t	C-16	46.4 d
C-7	39.2 t[c]	C-17	6.9 q
C-8	45.1	C-18	33.6 q
C-9	53.9	C-19	21.8 q
C-10	37.3	C-20	15.1 q

[a] Run in $CDCl_3$ at 67.905 MHz, using Me_4Si as internal standard. Assignments are based on predicted shifts and comparison with spectra of kaurenoids: J. R. Hanson, M. Siverns, F. Piozzi, and G. Savona, *J. Chem. Soc., Perkin Trans. 1*, 114 (1976). Unmarked signals are singlets. [b,c] Assignments may be interchanged.

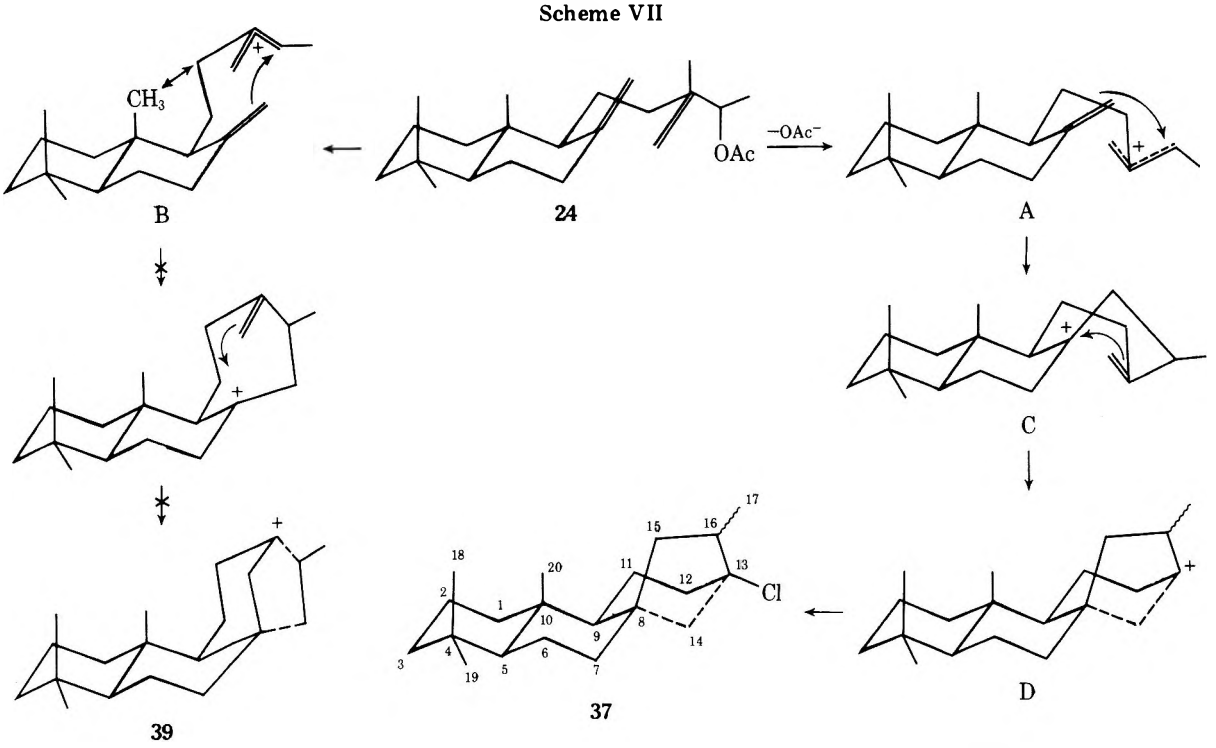
Scheme VI



36a, R = Ac
b, R = H

38

Scheme VII



tertiary hydroxyl group of **36a** was deduced by comparing the chemical shift of the C-8 methyl resonances in **36a, 36b,** and **38** with those in the NMR spectra of **33** and **35.**

The formation of **36a** from **24** is rationalized in Scheme VI. Protonation of the exocyclic double bond attached to ring B leads to ion A which undergoes cyclization with participation of the second $=CH_2$ group to ion B. The latter is stabilized by participation of the acetate group as in C. As in Scheme V, attack on C-8 is expected to occur preferentially from the α face of the molecule, thus leading to β orientation of the methyl group on C-8. Degradation of **38** to ketone **34** confirms this hypothesis.

The NMR spectrum of the less polar product $C_{20}H_{33}Cl$ **(37)** displayed three methyl singlets, a methyl doublet, and no resonances indicative of the presence of vinylic hydrogen. The IR spectrum showed the absence of functionality; the ^{13}C NMR spectrum established the absence of olefinic carbon and the presence of a tertiary C–Cl bond. On the basis of these observations and the following arguments the phyllocladane structure **37** (Scheme VII) rather than the kaurane formula **39** was assigned to this substance.

Loss of acetate ion from **24** leads to an allylic carbonium ion. Molecular models suggest that conformation A is preferred over conformation B due to steric interaction between C-10 methyl and the side chain of the latter. Cyclization of A to C and then to D leads to a tertiary ion with phyllocladane stereochemistry which reacts with Cl^- derived from $SnCl_4$ or abstracts Cl^- from the solvent[29] to form **37.** Cyclization from the unfavorable conformation B would have led to compound **39** with kaurane stereochemistry.

Thus carbonium ion D of Scheme V (equivalent to ion C of Scheme VII) can be generated from allylic carbonium ion **30,** but appears prone to further cyclization rather than deprotonation to a strobane derivative. The possibility exists that it could be trapped if the reaction were carried out in a highly nucleophilic medium. The behavior of allylic carbonium **7** remains to be investigated in more detail although there is evidence that it cyclizes to a five- rather than a seven-membered ring.

Experimental Section[30]

Reduction of Lactone 8. A solution of 20 g of **8** in 25 ml of THF was added dropwise with stirring to a slurry of 1 g of $LiAlH_4$ in 250 ml of THF (nitrogen atmosphere). Stirring was continued for 2 h, excess reducing agent was destroyed by addition of wet ethyl acetate, and the complex was destroyed by addition of water. The mixture was filtered and the residue was thoroughly washed with ethyl acetate. The combined filtrate and washings were evaporated to yield 18.7 g (92%) of **9a,** mp 135 °C after recrystallization from hexane–$CHCl_3$, which had IR absorption at 3250 cm^{-1} and NMR signals (90 MHz) at 0.66, 0.66, 0.73, 1.0 (C-4, C-8, and C-10 methyls), and 3.0 ppm m (two protons, H-12).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.40; H, 11.89; O, 12.71.

A solution of 18.7 g of **9a** in 10 ml of pyridine was stirred with 10 ml of acetic anhydride at room temperature for 8 h, poured onto crushed ice, and extracted with ether. The washed and dried ether extracts were evaporated, yield of gummy **9b** 21 g (88%). After purification by column chromatography, it had IR bands at 3450, 1740, and 1240 cm^{-1}, NMR signals (90 MHz) at 0.72, 0.72, 0.80, 1.10 (C-4, C-8, and C-10 methyls), 1.98 (acetate), and 4.05 ppm t (J = 7 Hz, H-12).

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.80; O, 16.19. Found: C, 73.19; H, 11.01; O, 15.51.

Dehydration of 9b. To a solution of 21 g of **9b** in 10 ml of anhydrous pyridine cooled to 0 °C was added 5 ml of $POCl_3$. The mixture was stirred for 8 h, poured onto crushed ice, and extracted with ether. The washed and dried ether layer was evaporated and the gummy residue, wt 18.6 g, was chromatographed over an alumina column impregnated with $AgNO_3$. The first component **11a,** wt 1.9 g, had IR bands at 1740 and 1240 cm^{-1}, NMR signals (60 MHz) at 0.83, 0.88, 0.93 (C-4 and C-10 methyls), 1.62 (C-8 methyl), 2.05 (acetate), and 4.05 ppm t (J = 8 Hz, H-12).

Anal. Calcd for $C_{18}H_{30}O_2$: mol wt, 278. Found: mol wt (MS), 278.

Reduction of **11a** with $LiAlH_4$ in the usual fashion (see below for **10a**) yielded **11b,** NMR signals at 0.80, 0.83, 0.90 (C-4 and c C-10 methyl), 1.5 g (C-8 methyl), and 3.56 ppm t (two protons, H-12), IR band at 3350 cm^{-1} (br).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.92; H, 12.04.

The second component **12a,** wt 7.4 g, had IR bands at 1740 and 1235 cm^{-1}, NMR signals (60 MHz) at 0.78, 0.90, 0.90 (C-4 and C-10 methyls), 1.72 br (C-8 methyl), 2.06 (acetate), 4.2 m (H-12), and 5.5 ppm br (H-7).

Anal. Calcd for $C_{18}H_{30}O_2$: mol wt, 278. Found: mol wt (MS), 278.

Reduction of **12a** with $LiAlH_4$ in the usual fashion (see below for **10a**) yielded **12b,** NMR signals at 0.79, 0.86, 0.87 (C-4 and C-10 methyls), 1.67 (C-8 methyl), 3.7 m (two protons, H-12), 5.43 ppm m (H-7), IR band at 3380 cm^{-1} (br).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.74; H, 12.06.

The last component (**10a**), wt 9.3 g, had IR bands at 1740, 1640, and 1240 cm^{-1}, NMR signals (90 MHz) at 0.57, 0.68, 0.73 (C-4 and C-10

methyls), 1.75 (acetate), 3.3 m (H-12), 4.65 and 4.85 ppm br (exocyclic methylene).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86; O, 11.49. Found: C, 77.04; H, 10.82; O, 11.91.

A solution of 5 g of **10a** in 10 ml of THF was added dropwise with stirring to a slurry of 0.25 g of $LiAlH_4$ in 50 ml of Thf and stirred for 4 h. The usual workup yielded 4.0 g of **10b** as a gum, which was purified by column chromatography and had IR bands at 3340 and 1640 cm^{-1}, NMR signals (60 MHz) at 0.7, 0.82, 0.89 (C-4 and C-10 methyls), 3.6 m (H-12), 4.55 br and 4.81 ppm br (exocyclic methylene group).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94; O, 6.77. Found: C, 81.10; H, 12.14; O, 6 76.

Oxidation of 10b. A. A solution of 3.2 g of **10b** in 5 ml of CH_2Cl_2 was added in one portion to a suspension of 2.4 g of CrO_3·2pyridine in 500 ml of CH_2Cl_2 (nitrogen atmosphere). The mixture was stirred for 15 min at room temperature, and filtered through a Florisil column. The residue was washed thoroughly with CH_2Cl_2 and the washings again filtered through Florisil. The combined filtrates were evaporated. The gummy residue was chromatographed over Florisil, yield of gummy **13**, wt 2.5 g (78%), which could be crystallized from hexane (mp 32–34 °C, lit. 35.6 °C),[27] IR bands at 1720 and 1640 cm^{-1}, NMR signals (90 MHz) at 0.71, 0.83, 0.91 (C-4 and C-10 methyls), 2.46 d (J = 1–2 Hz, H-11), 4.40 br and 4.83 br (exocyclic methylene), and 9.7 ppm t (J = 1–2 Hz, H-12).

B. Oxidation of 0.400 g of **10b** with a suspension of silver carbonate on Celite in refluxing benzene for 18 h followed by filtration through a Celite column and evaporation of the solvent yielded 0.315 g (80%) of **13.**

(*E*)-Labdε-8(17),13-dien-(12*R*)- and -(12*S*)-ols (6a and 6b). To a solution of 0.368 g of *cis*-2-bromo-2-butene in anhydrous ether kept at −78 °C was added 0.255 g of *tert*-butyllithium in ether. The mixture was stirred at −78 °C for 1 h; this was followed by dropwise addition of 0.177 g of aldehyde **13** in anhydrous ether. The reaction was monitored by TLC. When it was complete, the mixture was poured onto crushed ice, neutralized with NH_4Cl, and extracted with ether. The washed and dried extract was evaporated and the residue separated by preparative TLC into two components, **6a** (36 mg, 18%) and **6b** (70 mg, 35%). Alcohol **6a** had IR bands at 3600, 3450 (br), and 1640 cm^{-1}, and NMR signals (270 MHz) at 0.65, 0.78, 0.86 (C-4 and C-10 methyls), 1.58 d (J = 6 Hz, C-14 methyl), 1.68 br (C-13 methyl), 4.40 br and 4.77 br (H-17), 4.60 dbr (J = 10 Hz, H-12), 5.24 ppm qbr (J = 6 Hz, H-14).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.50; H, 11.68; O, 5.68.

Alcohol **6b** had IR bands at 3600, 3400 (br), and 1640 cm^{-1}, and NMR signals at 0.67, 0.77, 0.84 (C-4 and C-10 methyls), 1.50 d (J = 6 Hz, C-14 methyl), 1.66 br (C-13 methyl), 4.73 t (J = 6 Hz, H-12), 4.73 br and 4.87 br (H-17), and 5.37 ppm qbr (J = 6 Hz, H-14).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.52; H, 11.74; O, 5.17.

Oxidation of 6b. A. A solution of 35 mg of **6b** in 2 ml of CH_2Cl_2 was oxidized with 0.35 g of Collins reagent as described above for **10b.** The crude gummy product was purified by TLC, yield 20 mg of **15** (57%), which had an IR band at 1640 cm^{-1}, NMR signals (60 MHz) at 0.70, 0.80, 0.86 (C-4 and C-10 methyls), 1.45 (C-13 methyl), 2.00 (methyl ketone), 3.00 m (H-12), 4.73 br and 4.95 ppm br (H-17).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59; O, 10.51. Found: C, 79.00; H, 10.40; O, 10.60.

B. Attempts to oxidize 35 mg of **6a** or **6b** with active MnO_2 in $CHCl_3$ solution for 8 hr at room temperature resulted in complete recovery of the starting materials.

Epoxidation of Manool. To a solution of 20 g of manool and 0.5 g of vanadyl acetylacetonate in 150 ml of refluxing benzene was added dropwise 7.5 g of 80% *tert*-butyl hydroperoxide. The progress of the reaction was monitored by TLC. When reaction was complete, the solvent was evaporated. Chromatography of the residue over silica gel (solvent hexane–ether, 9:1) yielded 20 g (96%) of **19** as a gummy mixture of C-14 epimers, which exhibited NMR signals (60 MHz) at 0.70, 0.83, 0.90 (C-4 and C-10 methyls), 1.20 and 1.30 (together three protons, C-13 methyl), 2.80 m (H-14 and H-15), 4.53 br and 4.83 ppm br (H-17).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.33; H, 11.04; O, 10.63.

Labd-8(17)-ene-(13*R*,14*RS*)-diol (20a). A solution of 20 g of **19** in THF was added dropwise to 1 g of $LiAlH_4$ in 250 ml of THF with stirring (nitrogen atmosphere). After 1 h the mixture was worked up as usual, yielding 20 g (99%) of **20a** as a mixture of C-14 epimers, which had IR bands at 3400 and 1640 cm^{-1}, NMR signals (270 MHz) at 0.70, 0.81, 0.86 (C-4 and C-10 methyls), 1.13 (C-13 methyl), 1.08 d and 1.09 d (J = 7 Hz, together three protons, C-14 methyl), 3.63 q and 3.64 q (J = 7 Hz, together one proton, H-14), 4.58 br and 4.82 ppm br (H-17).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76; O, 10.37. Found: C, 77.98; H, 11.71; O, 10.31.

Acetylation of 15 g of **20a** in 10 ml of pyridine with 10 ml of acetic anhydride for 8 h at room temperature followed by the usual workup and chromatography over Florisil gave 13 g (80%) of **20b** as a mixture of C-14 epimers which had IR bands at 3490, 1740, 1640, and 1240 cm^{-1}, NMR signals (270 MHz) at 0.66, 0.80, 0.86 (C-4 and C-10 methyls), 1.13 (C-13 methyl), 1.15 d and 1.17 d (J = 7 Hz, C-14 methyl), 2.03 (acetate), 4.50 br and 4.80 br (H-17), and 4.8 ppm m (two superimposed quartets, together one proton, H-14).

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93; O, 13.69. Found: C, 75.80; H, 10.96; O, 13.24.

Acetate of Labd-8(17)-ene-(13*R*,14*S*)-diol (20dB). The mixture of acetates **20b** was dissolved in hexane and cooled to 0 °C. Compound **20bB** crystallized out and had mp 105 °C. The IR and NMR spectra were identical with those of **20b** except for the absence of the doublet at 1.15 ppm and the appearance of H-14 as a sharp quartet at 4.80 ppm.

Oxidations of 20a. A. To an ice-cold solution of 3.6 g of **20a** in 20 ml of acetone was added dropwise a solution of Jones reagent until the reaction was completed. The solvent was evaporated at reduced pressure and the residue was taken up in ether. Evaporation of the washed and dried extract gave a gum which was chromatographed over Florisil. Fraction 1, wt 1.8 g (65%), corresponded to ketone **22.**[20] Fraction 2, wt 0.54 g (15%), was **21** as a gum which had IR bands at 3450, 1700, and 1640 cm^{-1}, NMR signals (60 MHz) at 0.62, 0.76, 0.83 (C-4 and C-10 methyls), 1.31 (C-13 methyl), 2.16 (methyl ketone), 4.40 br and 4.80 ppm br (H-17).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.52; H, 11.33; O, 10.15.

B. Oxidation of 0.40 g of **20a** with 5 g of Collins reagent in CH_2Cl_2 (15 min) and chromatography gave 0.26 g (76%) of **22** and 0.08 g (20%) of **21.** Oxidation of 0.20 g of **20a** with 0.50 g of pyridinium chlorochromate in CH_2Cl_2 until reaction was complete (TLC) and preparative TLC of the crude product gave 100 mg (59%) of **22** and 30 mg (15%) of **21.** Oxidation of 1.4 g of **20a** with silver carbonate on Celite in refluxing benzene for 18 h followed by the usual workup (see oxidation of **10b**) and chromatography over Florisil gave 0.80 g (68%) of **22** and 0.40 g (28%) of **21.** Oxidation of 0.375 g of **20a** with 0.6 g of active MnO_2 in boiling $CHCl_3$ until the reaction was complete (TLC analysis), filtration, and evaporation of the filtrate gave 0.31 g of a gum which was **22** (95%) containing a trace of **21** (<5%, TLC analysis).

Dehydration of 20b. An ice-cold solution of 4.10 g of **20b** in 15 ml of pyridine was mixed with 5 ml of $POCl_3$ and allowed to stand, with stirring, at room temperature for 12 h until reaction was complete (TLC). The mixture was poured onto ice and extracted with ether. The washed and dried ether extract was evaporated. Chromatography over Florisil gave 2.93 g (80%) of a mixture containing **24** and **25** in the ratio 1:2 (NMR analysis). The two substances were separated by pressure liquid chromatography (Porasil column, eluting solvent 1:1 hexane–ether). Acetate **24**[31] had IR bands at 1740, 1640, and 1240 cm^{-1}; NMR signals (270 MHz) at 0.75, 0.81, 0.88 (C-4 and C-10 methyls), 1.30 d (J = 7 Hz, C-14 methyl), 2.03 (acetate), 4.50 br, 4.83 br (H-17), 4.87 br (H-17), 5.03 br (H-16b), and 5.30 ppm q (J = 7 Hz, H-14).

Acetate **25** had IR bands at 1740, 1640, 1240, and 740 cm^{-1}; NMR signals (270 MHz) at 0.70, 0.83, 0.90 (C-4 and C-10 methyls), 1.26 d (J = 7 Hz, C-14 methyl), 1.66 br (C-13 methyl), 2.00 (acetate), 4.43 br and 4.83 br (H-17), 5.41 t (J = 6 Hz, H-12), and 5.25 ppm q (J = 7 Hz, H-14).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91; O, 9.62. Found: C, 79.47; H, 10.88; O, 9.65.

(*Z*)-Labda-8(17),12-dien-(14*RS*)-ol (16). Reduction of 0.400 g of **25** with 0.03 g of $LiAlH_4$ in THF followed by the usual workup gave 0.188 g of **16** as a mixture of C-14 epimers which had IR bands at 3350, 1640, and 898 cm^{-1}; NMR signals at 0.66, 0.76, 0.83 (C-4 and C-10 methyls), 1.15 d (J = 7 Hz, C-14 methyl), 1.60 br (C-13 methyl), 3.96 q (J = 7 Hz, H-14), 4.25 br and 4.63 br (H-17), and 5.16 ppm t br (J = 6 Hz, H-12).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.49; H, 11.83; O, 5.68.

(*Z*)-Labda-8(17),12-dien-(14*S*)-ol (16b). A solution of 0.760 g of **20bB** in 1 ml of pyridine was dehydrated with 0.1 ml of pyridine as described above for **20b** and gave 0.600 g of a mixture of acetates. Reduction with 5 mg of $LiAlH_4$ in THF by the usual procedure yielded 0.480 g of a mixture of alcohols which was separated by high-pressure liquid chromatography using a Porasil column (solvent hexane–5% ether) to furnish 0.300 g of alcohol **16b.** The IR and NMR spectra were

similar to those of mixture **16**.

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.65; H, 11.80; O, 5.55.

Absolute Configuration of 16b. A solution of 400 mg of α-phenylbutyric anhydride (1.29×10^{-2} M) and 50 mg of **16b** (1.72×10^{-3} M) in 2 ml of pyridine was allowed to stand at room temperature for 48 h. Excess anhydride was destroyed by adding 1 ml of water and allowing to stand for 12 h at room temperature. The solution was extracted with ether. The extract was washed with water, three 10-ml portion of 5% sodium bicarbonate solution, and again several times with water. The combined aqueous extracts were washed with chloroform and acidified with an excess of 1 N sulfuric acid solution. The acidified solution was extracted with chloroform and the chloroform extract was dried and evaporated. This afforded 318 mg of α-phenylbutyric acid (pure on TLC), α_D in 5 ml of benzene (0.4-dm tube) 0.0179, $[\alpha]_D$ 1.22, theoretical $[\alpha]_D$ 96.5/[2 × 7.48 − 1] = 6.91. The optical yield therefore was 1.22/6.91 = 17.6%.

Oxidation of 16. Oxidation of 0.385 g of the mixture of epimers **16** with 3 g of Collins reagent in CH_2Cl_2 followed by the usual workup gave 0.375 g of a gummy mixture which was separated by pressure liquid chromatography on Porasil (eluent 1% ether in hexane). Fraction 1 (**17**, 0.123 g, 32%) was a solid, mp 91–93 °C, which had IR bands at 1700, 1640, 1450, 1370, and 900 cm^{-1}; NMR signals (270 MHz) at 0.70, 0.80, 0.88 (C-4 and C-10 methyls), 1.36 d (J = 6 Hz, C-14 methyl), 1.40 (C-13 methyl), 3.16 m (J = 6 Hz, H-14), 4.43 br and 4.73 ppm br (H-17).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59; O, 10.51. Found: C, 79.00, H, 10.40; O, 10.60.

The second fraction (**26**, 103 mg, 27%) was a gum which had IR bands at 1670, 1640, and 900 cm^{-1}; NMR signals (270 MHz) at 0.75, 0.83, 0.88 (C-4 and C-10 methyls), 1.80 br (C-13 methyl), 2.20 (methyl ketone), 4.43 br and 4.86 br (H-17), and 6.55 ppm tbr (J = 6Hz, H-12).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18; O, 5.55. Found: C, 82.65; H, 11.24; O, 6.11.

When chromous chloride was added to 43 mg of **17** in 2 ml of acetic acid, the color of the solution remained blue. The usual workup resulted in recovery of 40 mg of starting material.

Labda-8(17),13(16)-dien-14-ol (29). Reduction of 0.260 g of **24** with 0.03 g of $LiAlH_4$ in the manner described for **25** gave 0.17 g (75%) of **29** as a mixture of C-14 epimers which had IR bands at 3350, 1640, and 900 cm^{-1}; NMR signals (270 MHz) at 0.66, 0.80, 0.83 (C-4 and C-10 methyls), 1.31 d (J = 7 Hz, C-14 methyl), 4.05 q (J = 7 Hz, H-14), 4.33 br (H-17), 4.60 br (H-16), and 4.80 ppm br (H-17).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.49; H, 183; , 5.68.

Cyclization of 16. A mixture of 3.6 g of **16** and 1 ml of 90% formic acid was allowed to stand at room temperature for 1 h, diluted with water, and extracted with ether. The washed and dried extract was evaporated and the gummy residue was chromatographed over Florisil. Hexane eluted 0.43 g of a gum which was further separated by pressure liquid chromatography (eluent hexane) into two fractions. Fraction 1 (120 mg) was an inseparable mixture of hydrocarbons; fraction 2 (300 mg, 8%) was identified as **28**. The NMR spectrum (270 MHz) exhibited signals at 0.83, 0.86, 0.95 (C-4 and C-10 methyls), 1.5 d ($J \sim 1$ Hz, vinyl methyl), 1.50 d (J = 6 Hz, vinyl methyl) 2.78 m (two protons), and 5.2 ppm qbr (J = 6 Hz, vinyl proton). Owing to facile decomposition of this substance the elementary analysis was not satisfactory. The high-resolution mass spectrum indicated decomposition. The low-resolution mass spectrum gave the correct molecular ion.

Anal. Calcd for $C_{20}H_{32}$: mol wt, 274. Found: mol wt (MS), 274.

Elution of the Florisil column with hexane–ether (19:1) produced 1.25 g (38%) of the formate of **16** which had NMR signals at 0.72, 0.84, 0.89 (C-4 and C-10 methyls), 1.30 d (J = 7 Hz, C-14 methyl), 1.67 br (C-13 methyl), 4.40 and 4.80 br (H-17), 5.3 q br (J = 7 Hz, H-14), and 8.00 ppm (formyl proton).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 79.42; H, 10.56; O, 10.02.

Further elution of the Florisil column with hexane–ether (9:1) gave 0.20 g of starting material **16**.

Reaction of 0.21 g of **16** in CH_2Cl_2 with $SnCl_4$ in CH_2Cl_2 at −78 °C for 5 min followed by the usual workup gave 0.19 g of a hydrocarbon mixture (NMR analysis) which could not be separated chromatographically.

Cyclization of 29. To a solution of 0.14 g of **29** in 10 ml of CH_2Cl_2 kept at −78 °C was added dropwise with stirring (nitrogen atmosphere) 0.18 g of anhydrous $SnCl_4$ in 10 ml of CH_2Cl_2. Stirring was continued at room temperature for 30 min, at which time there was added 5 ml of pyridine. The mixture was poured into 10 ml of 1 N hydrochloric acid and extracted with ether. The washed and dried ether extract was evaporated and the residual gum was purified by preparative TLC. This yielded 0.10 g (60%) of ketone **32** (mp 86 °C, crystallized from hexane–chloroform) which had IR bands at 1725, 1460, and 1375 cm^{-1}, NMR signals (270 MHz) at 0.82, 0.83, 0.86, 0.96 (C-4, C-8 and C-10 methyls), and 2.06 ppm (methyl ketone).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.45; H, 11.81; O, 5.74.

A solution of 0.275 g of **32** and 0.200 g of *m*-chloroperbenzoic acid in 10 ml of $CHCl_3$ was allowed to stand for 24 h in the dark. The washed and dried $CHCl_3$ was evaporated at reduced pressure; the residual gum upon purification by preparative TLC yielded 0.267 g (92%) of **33a** which had IR bands at 1725, 1460, 1440, 1380, 1360, and 1240 cm^{-1}; NMR signals (270 MHz) at 0.77, 0.80, 0.83, 0.96 (C-4, C-8 and C-10 methyls), 1.96 (acetate), and 4.88 ppm m (H-13).

Anal. Calcd for $C_{20}H_{34}O_2$: mol wt, 306. Found: mol wt (MS), 306.

Reduction of 0.230 g of **33a** in 2 ml of THF with 50 mg of $LiAlH_4$ in 10 ml of THF followed by the usual workup and purification of the crude product by preparative TLC gave 0.19 g (96%) of gummy **33b** which had IR bands at 3290, 1460, 1380, and 1360 cm^{-1}; NMR signals (270 MHz) at 0.79, 0.80, 0.83, 0.93 (C-4, C-8 and C-10 methyls), and 3.66 ppm m (H-13).

Anal. Calcd for $C_{18}H_{32}O$: C, 81.75; H, 12.20; O, 6.05. Found: C, 81.52; H, 12.09; O, 6.39.

Oxidation of 0.21 g of **33b** in 10 ml of acetone with Jones reagent as described for **20a** and preparative TLC of the crude product afforded 0.175 g of gummy **34** which had an IR band at 1720 cm^{-1} and NMR signals (270 MHz) at 0.84, 0.86, 0.89, and 0.90 ppm (C-4, C-8, and C-10 methyls).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52; O, 6.10. Found: C, 82.62; H, 11.41; O, 5.97.

$LiAl(t\text{-}BuO)_3H$ reduction of 0.12 g of **34** followed by the usual workup and purification by preparative TLC yielded 0.10 g of **35** (mp 126–128 °C, crystallized from hexane–chloroform) which had NMR signals at 0.80, 0.82, 0.84 (C-4 and C-10 methyls), 1.12 (C-8 methyl), and 4.05 ppm m (H-13).

Anal. Calcd for $C_{18}H_{32}O$: C, 81.75; H, 12.20; O, 6.05. Found: C, 81.50; H, 12.10; O, 6.40.

Cyclization of 24. To a solution of 2.8 g of **24** in 125 ml of CH_2Cl_2 cooled to −78 °C was added dropwise, with stirring, 2.5 g of anhydrous $SnCl_4$ in 20 ml of CH_2Cl_2. Stirring was continued at −78 °C for 1 h, and 20 ml of pyridine was added. The mixture was worked up as described for the cyclization of **29**. Chromatography of the crude product over silica gel gave two fractions. Fraction 1 (a mixture of epimers at C-15), wt 1 g (36%), was **36a** which had IR bands at 3530 and 1715 cm^{-1}; NMR signals (270 MHz) at 0.81, 0.82, 0.83 (C-4 and C-10 methyls), 1.10 (C-8 methyl), 1.15 d and 1.16 d (together three protons, C-15 methyl), 2.05 and 2.06 (together three protons, acetate), 4.61 q and 4.62 ppm q (J = 7 Hz, together one proton, H-15).

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93; O, 13.69. Found: C, 75.60; H, 10.86; O, 13.54.

Fraction 2, wt 0.5 g (18%), was **37**. The IR spectrum had bands at 1460, 1440, 1390, 1370, and 970 cm^{-1}; the NMR spectrum exhibited signals (270 MHz) at 0.78, 0.85, 0.9 (C-4 and C-10 methyls), and 0.98 ppm d (J = 6 Hz, C-16 methyl).

Anal. Calcd for $C_{20}H_{33}Cl$: C, 77.50; H, 11.05; Cl, 11.43. Found: C, 77.45; H, 10.91; Cl, 11.57.

Reduction of 0.290 g of **36a** with 30 mg of $LiAlH_4$ in the usual fashion and preparative TLC of the crude product gave 0.173 g of diol **36b** which had IR absorption at 3500 cm^{-1} and NMR signals (60 MHz) at 0.83, 0.83, 0.83 (C-4 and C-10 methyls), 1.11 (C-8 methyl), 1.11 d (J = 7 Hz, C-15 methyl), and 3.40 ppm q (J = 7 Hz, H-15).

Anal. Calcd for $C_{20}H_{36}O_2$: mol wt, 308. Found: mol wt (MS), 308.

Oxidation of 0.10 g of **36b** with silver carbonate on Celite in refluxing benzene for 18 h, filtration, and purification of the crude product by preparative TLC furnished hydroxy ketone **38**, wt 0.09 g (90%): IR absorption at 3500 and 1705 cm^{-1}; NMR signals at 0.80, 0.83, 0.83 (C-4 and C-10 methyls), 1.13 (C-8 methyl), and 2.16 ppm (methyl ketone).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.19; H, 11.32; O, 10.49.

Oxidation of 0.173 g of 38 in acetone with Jones reagent at 0 °C for 15 min followed by the usual workup yielded 0.15 g of ketone **34** which was identical with material obtained by degradation of **32**.

Registry No.—**6a**, 61047-01-6; **6b**, 61091-81-4; **8**, 30450-17-0; **9a**, 41747-05-1; **9b**, 61047-02-7; **10a**, 61047-03-8; **10b**, 31207-72-4; **11a**, 61047-04-9; **11b**, 31222-15-8; **12a**, 61047-05-0; **12b**, 31207-73-5; **13**, 3243-36-5; **15**, 61046-83-1; **16a**, 61046-84-2; **16a** formate, 61046-85-3; **16b**, 61091-75-6; **16b** formate, 61091-76-7; **17**, 61046-86-4; **18**, 596-85-0;

19 14α isomer, 54780-63-1; **19** 14β isomer, 54809-24-4; **20aA,** 61046-87-5; **20aB,** 61116-61-8; **20bA,** 61046-88-6; **20bB,** 61091-77-8; **21,** 61091-78-9; **22,** 19884-98-1; **25,** 61046-89-7; **26,** 61046-90-0; **28,** 61046-91-1; **29** 14α epimer, 61091-79-0; **29** 14β epimer, 61091-80-3; **32,** 61046-92-2 **33a,** 61046-93-3; **33b,** 61046-94-4; **34,** 18102-90-4; **35,** 61046-95-5; **36a** 15α epimer, 61046-96-6; **36a** 15β epimer, 61046-97-7; **36b,** 61046-98-8; **37,** 61046-99-9; **38,** 61047-00-5; *cis*-2-bromo-2-butene, 3017-71-8.

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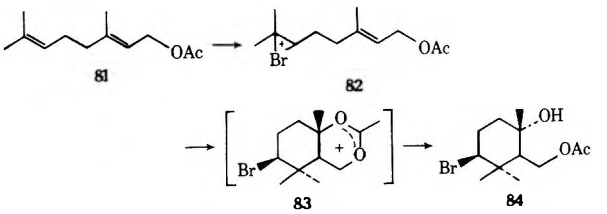

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Oxidative Rearrangements of Tertiary and Some Secondary Allylic Alcohols with Chromium(VI) Reagents. A New Method for 1,3-Functional Group Transposition and Forming Mixed Aldol Products[1]

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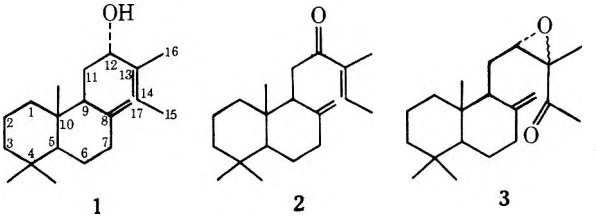
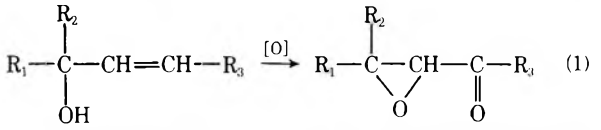
Oxidation of tertiary allylic and some secondary allylic alcohols with Collins reagent results in oxidative rearrangement to α-epoxy aldehydes or ketones. Oxidation of tertiary allylic alcohols and some secondary alcohols with pyridinium chlorochromate results in oxidative rearrangement to α,β-unsaturated aldehydes or ketones. These reactions are useful for effecting the 1,3-transposition of oxygen and for carrying out mixed aldol condensations. A detailed study of the reaction of labda-8(17),12-dien-14-ol with Cr(VI) reagents was carried out. Possible mechanisms for the oxidative rearrangements are discussed.

In connection with work on a biogenetic-type synthesis of the strobanes, we had occasion to attempt the oxidation of the allylic alcohol **1** to the α,β-unsaturated ketone **2**.[2] Oxidation with active manganese dioxide failed; oxidation with Collins reagent[3] furnished as sole product and in good yield the epoxy ketone **3**.

The formation of an epoxy ketone from an allylic alcohol with Collins reagent was unprecedented, although there are



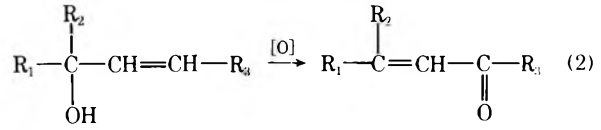
several reports of the formation of epoxy ketones from steroidal allylic alcohols with Jones and Sarett reagent.[4-6] These reactions, however, are not synthetically useful whereas the conversion of **1** to **3** is. The success of the reaction in the case of **1** seemed to be due to the difficulty encountered by the reagent in abstracting hydrogen from the carbon atom carrying the hydroxyl group, as suggested by the resistance of **1** toward oxidation by MnO_2.[7] If this were so, the oxidation of tertiary allylic alcohols with Collins reagent might provide a general and useful means of synthesizing rearranged α-epoxy aldehydes and ketones (eq 1). The verification of this hy-



(1)

pothesis is reported in this communication; the result of the observed oxidative rearrangement shown in eq 1 is a reversal of the Wharton reaction.[8,32]

We have also observed that oxidation of tertiary allylic alcohols with pyridinium chlorochromate is a general and useful method for carrying out the oxidative rearrangement depicted in eq 2. Since the allylic alcohols serving as substrates can be



(2)

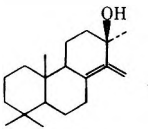
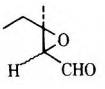
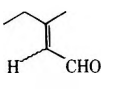
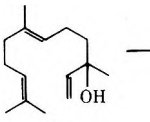
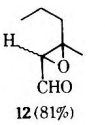
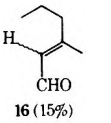
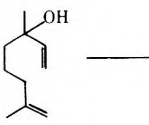
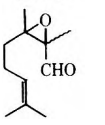
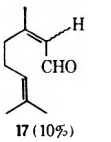
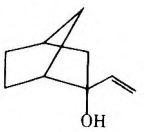
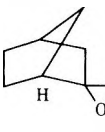
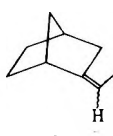
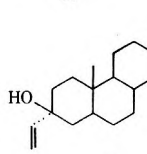
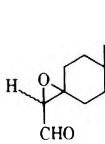
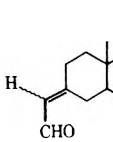
made by reaction of vinyllithiums with ketones, this two-step sequence provides a simple and efficient method for carrying out mixed aldol condensations.

Results

Oxidations with Collins Reagent. Oxidation of manool (**4**), a diterpene alcohol possessing the required functionality, with Collins reagent gave three fractions in 69, 10, and 11% yield, respectively, which were separated by high-pressure liquid chromatography. The NMR spectrum of the major fraction, $C_{20}H_{32}O_2$, showed that it was a 1:1 mixture of two epimers, since in addition to the presence of three methyl singlets at 0.60, 0.78, and 0.80 ppm each integrating for three protons (methyls on C-4 and C-10), it exhibited two methyl singlets at 1.33 and 1.36 ppm, together integrating for three protons, and two doublets at 3.08 and 3.10 ppm (J = 8 Hz), the sum of which integrated for one proton. The chemical shifts of these signals were appropriate for a methyl resonance attached to carbon bearing an oxygen atom and a proton attached to epoxidic carbon. In addition there were two doublets at 9.46 and 9.53 ppm (J = 8 Hz), together equivalent to 1 H, showing the presence of an aldehyde. Consequently, the major product was a 1:1 mixture of the epimeric aldehydes **5**. The other two compounds had very similar NMR spectra, both exhibiting the presence of a vinyl methyl group at 1.90 and 2.13 ppm, respectively, and an aldehydic proton at 9.8 (or 10.00) ppm coupled to a vinylic hydrogen at 5.83 ppm. The IR spectra displayed a band at 1690 cm^{-1} showing the presence of a conjugated carbonyl group. Hence the two minor products were **6** and **7**, the E isomer **6** being identified with the substance exhibiting the vinyl methyl resonance at lower field.[10]

The oxidative rearrangement depicted in eq 1 had thus been found applicable to manool. A series of other tertiary alcohols **8** (nerolidol), **9** (linalool), **10**, and **11** were also studied; in each case, a 1:1 mixture of epimeric epoxy aldehydes **11**–**14** represented the major, if not the exclusive, products. The results are presented in Table I. Structure assignments were based on NMR spectra, the epoxy aldehydes exhibiting the relevant resonances near 1.3 (methyl), 3 (proton under epoxide), and

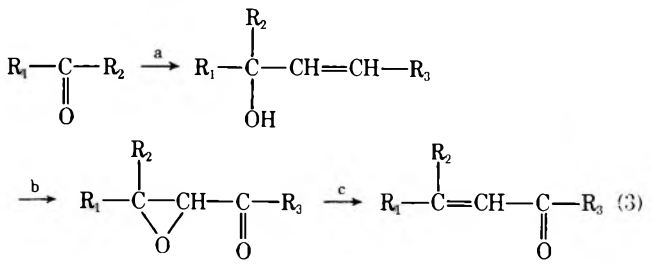
Table I. Oxidation of Allylic Alcohols with Collins Reagent[a]

Compd	Epoxy aldehydes[b]	Olefinic aldehydes[c]
 4	 5 (69%)	 6,7 (21%)
 8	 12 (81%)	 16 (15%)
 9	 13 (50%)	 17 (10%)
 10	 14 (50%)	 18 (trace)
 11	 15 (70%)	 19 (trace)

[a] All yields are isolated yields. [b] 1:1 mixture of epimers. [c] 1:1 mixture of geometrical isomers.

9 ppm (aldehyde). Compounds **10** and **11** were prepared by reaction of vinyllithium with norbornanone and 3-cholestanone, respectively. The stereochemistry assigned to **10** and **11** is based on the assumption that the vinyllithium reagent approaches the substrate from the least hindered side (exo in the case of **10**, α in the case of **11**). The stereochemistry at C-2 of **14** and at C-3 of **15** is based on the finding that configuration is retained at the site of the tertiary hydroxyl in the oxidation of manool (vide infra).

This interesting oxidative rearrangement appears to be an excellent method of converting a ketone to the bishomologous epoxy aldehyde since the tertiary allylic alcohols used as substrates can be prepared by reaction of a ketone with vinyllithium. The product α-epoxy aldehyde (or ketone in the case of **3**) may or may not be convertible to the α,β-unsaturated carbonyl compounds obtained as by-products in the case of **4**, **8**, and **9** by reagents such as chromous chloride (depending on the degree of steric hindrance); if so, the overall result is the product expected of a mixed aldol condensation and eq 1 can be expanded to eq 3. Thus, chromous chloride



(3)

reduction of the epoxy aldehyde mixture **12** from nerolidol afforded a 1:1 mixture of (E)- and (Z)-farnesals (**16**) in quantitative yield.

Oxidations with Pyridinium Chlorochromate. Forma-

Table II. Oxidation of Allylic Alcohols with Pyridinium Chlorochromate[a]

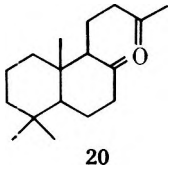
Compd	Product[b]	Yield, %
4	6, 7	98
8	16	98
9	17	80
10	18	79
11	19	72

[a] All yields are isolated yields. [b] 1:1 mixture of geometrical isomers.

tion of α-epoxy aldehydes and ketones by oxidation of tertiary allylic alcohols with Collins reagent prompted an investigation into the possible use of other Cr(VI) oxidizing agents. One of these is pyridinium chlorochromate, whose use for oxidation of alcohols to aldehydes and ketones has been demonstrated by Corey and Suggs.[9]

Oxidation of manool (4) with this reagent gave a quantitative yield of the *E* and *Z* aldehydes 6 and 7 in a 1:1 ratio, i.e., use of the reagent seems to obviate the need for carrying out steps b and c in eq 3 above. The generality of the reaction was shown by carrying out the oxidation on the same series of tertiary allylic alcohols, as before; the results are summarized in Table II. In each case the mixture of unsaturated aldehydes was obtained in very good yield. Apparently, the addition of a vinyllithium reagent to a ketone followed by oxidation with pyridinium chlorochromate is a very efficient method for synthesizing the product of a mixed aldol reaction. The development of techniques for carrying out directed aldol condensations with ketones has received considerable attention in recent years;[11-19] the simple two-step process presented here, while not stereoselective, will undoubtedly be useful in a number of situations.

Oxidation of Manool with Other Reagents. As a matter of interest, the reaction of manool as a typical tertiary allylic alcohol with two other Cr(VI) reagents was examined. Oxidation of manool with chromium trioxide–3,5-dimethylpyrazole[20] yielded **6, 7,** and **20,** whereas oxidation with Jones reagent and extensive chromatography gave **6, 7,** and **21**



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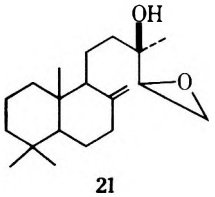


21

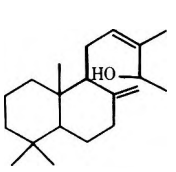
(mixture of epimers at carbon 14), as well as a mixture of highly polar substances, probably acids, which were not identified.

Oxidations of Labda-8(20),12-dien-14-ol (22). The formation of different products from tertiary allylic alcohols with different Cr(VI) reagents raised the question of mechanism. Now it had been observed, incidental to our work on strobane synthesis,[2] that oxidation of the epimeric mixture **22** with Collins reagent gave a mixture of keto epoxides **25** as well as the expected "normal" product **23.** Formation of the rearranged keto epoxides **25** suggested that **22** might be somewhat hindered, thus reducing the rate of the "normal" process (which involves abstraction of H-14 in the chromate ester of **22**) and permitting the observation of competing reactions. Since **22** was relatively accessible, a more detailed study of the oxidation of mixture **22** (~1:1 mixture of epimers) and the epimer **22A,** whose syntheses are described elsewhere,[2] was undertaken in the hope of shedding light on the mechanism of the oxidative rearrangements.

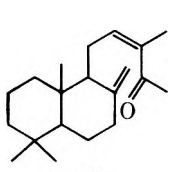
Table III. Oxidation of 22

Reagents	Yields, %[a] 23	24	25
Jones[b]	14.5	25	9.6
Modified Collins[c]	38	17.3	31[d]
Pyridinium chlorochromate[e]	30	11	11
CrO_3–3,5-dimethylpyrazole	22	18.8	26

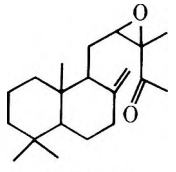
[a] Yields are isolated yields. [b] Overall yield low owing to formation of highly polar substances which were not identified. [c] R. Ratliff and R. Rodehorst, *J. Org. Chem.*, **35,** 4000 (1970). [d] Not detected in run using Collins reagent (ref 2). [e] Compounds **26** and **27** were also isolated from this run.



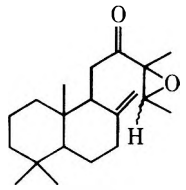
22, OH α and β
22A, OH, β



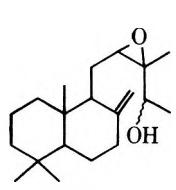
23



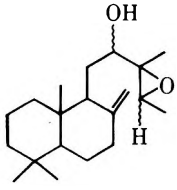
24, 24A



25, H-14 α and β
25A, H-14, β



26, OH α and β
26A, OH β



27, H-14 α and β
27A, H-14, β

Oxidation of **22** with the four Cr(VI) reagents employed previously gave the three products **23**[2] and **25,**[2] but also the new keto epoxide mixture **24** in the proportions detailed in Table III. Ketone **2** was not detected. During the earlier stages, TLC showed the presence of two polar constituents **26** and **27** which were isolated from the runs with pyridinium chlorochromate.

As might have been expected, **24, 26,** and **27,** like **25** reported previously,[2] were inseparable mixtures of at least one epimer pair as shown by NMR spectrometry at 270 MHz. The IR spectra showed that **24** was a ketone and that **26** and **27** were alcohols. The NMR spectrum of **24** exhibited methyl singlets at 1.43 and 2.00 ppm characteristic of methyl on carbon carrying oxygen and $CH_3C{=}O$, respectively; but H-12 appeared as a multiplet at 3.02 ppm. The NMR spectrum of **26** resembled that of **24**[2] with the exception that the methyl ketone singlet was replaced by a somewhat broadened methyl doublet (H-16) and a pair of slightly overlapping quartets (H-14), while the spectrum of **27** was similar to that of **25** except for a multiplet near 3.4 ppm representing H-12.[21]

The simultaneous formation of the normal keto epoxide **24** and the rearranged keto epoxide **25** led to the surmise that one

Table IV. Oxidation of 22A

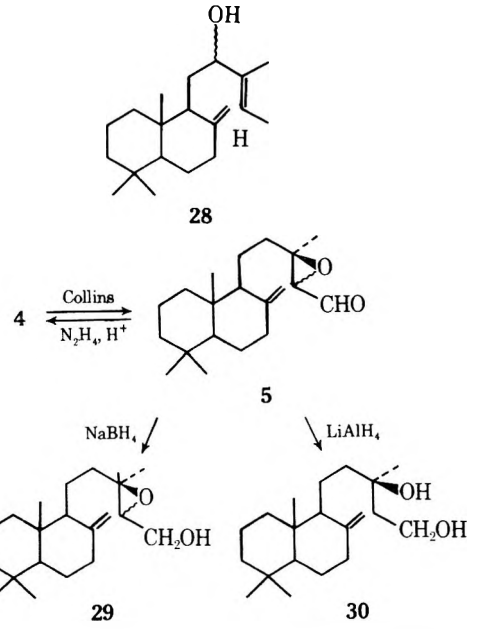
Reagent	Yields, %[a] 23	24A	25A
Jones[b]	15	24	7.2
Modified Collins	40	15.3	30
Pyridinium chlorochromate[c]	39	11	11
CrO_3–3,5-dimethylpyrazole	35	13.8	25

[a] Yields are isolated yields. [b] Yields low owing to formation of unidentified polar products. [c] Yields relatively low owing to formation of **26A** and **27A.**

of them might arise from one epimer of alcohol **22**, whereas the other might be produced by the second epimer. To check this hypothesis, alcohol **22A** was prepared;[2] however, oxidation of **22A** provided both keto epoxides **24A** and **25A**, this time as individual compounds, in approximately the same proportions as previously (Table IV). The stereochemistry assigned to C-14 of **25A** is based on the finding that the configuration at C-13 of manool was retained during the oxidation; the stereochemistry of **25A** at C-13 and that of **24A** at C-12 and C-13 is unknown.[22]

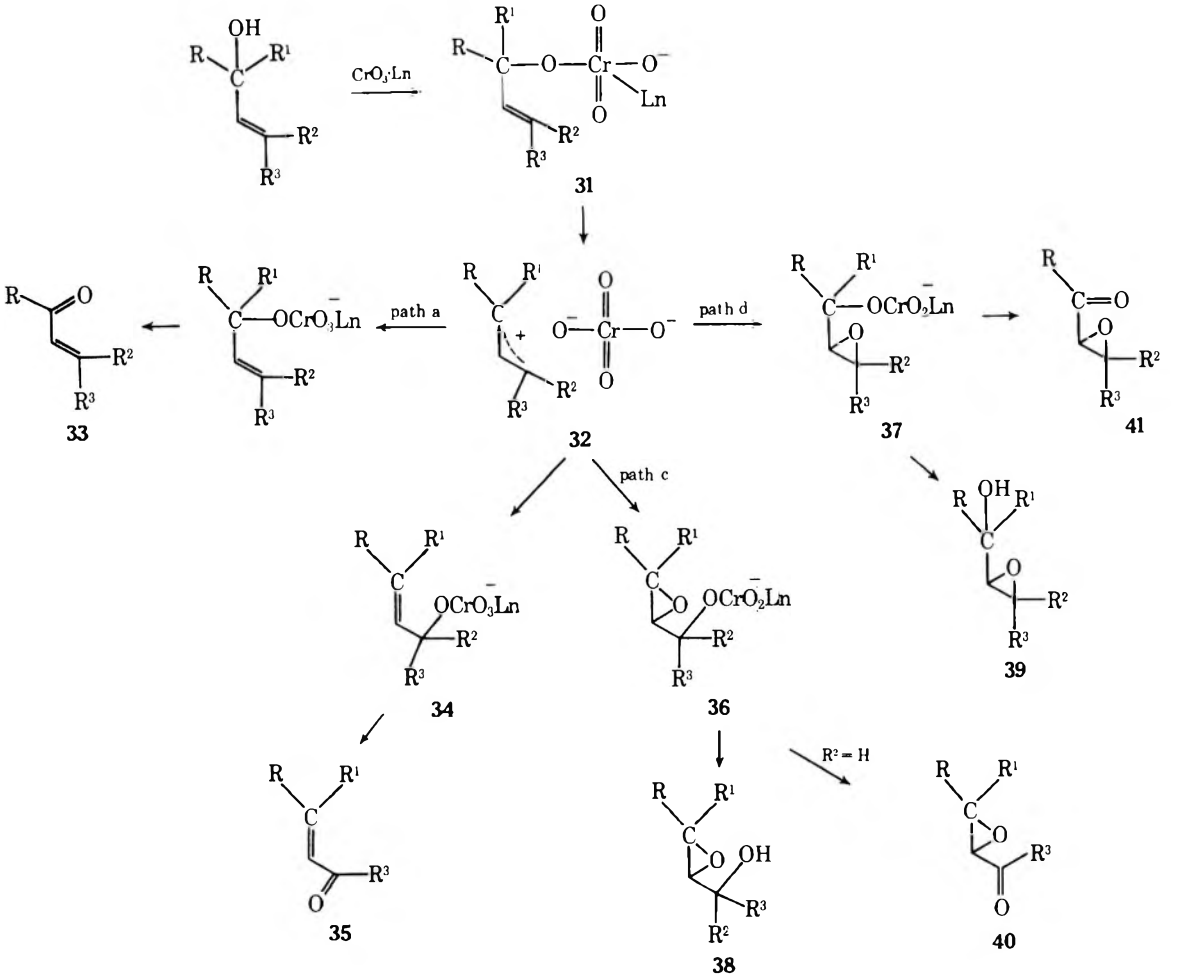
Possible Oxidation Mechanisms. Prior to discussing possible oxidation mechanisms, two additional results must be noted. (1) Alcohol **22** was recovered quantitatively on exposure to 8 N H_2SO_4 in acetone. Since rearrangement to alcohol **28** did not occur in the acid environment, **28** cannot be a precursor of **27** and **25** when **22** is oxidized with Jones reagent. (2) Manool (**4**) was the only product when **5**, which is a mixture of epimers as shown by the doubling of the H-16 resonance, was subjected to the Wharton reaction.[23] This shows that the C-13 stereochemistry of **5** is that of manool; hence the origin of diastereoisomerism must be C-14. Reduction of **5** with $NaBH_4$ gave the epoxy alcohol **29** whose NMR spectrum showed that it was a mixture of C-14 epimers, the H-16 resonance appearing as two singlets at 1.26 and 1.38 ppm. On other other hand, reduction of **5** with $LiAlH_4$ gave the diol **30** whose NMR spectrum indicated that it was a pure substance, the H-16 resonance appearing as a sharp singlet at 1.31 ppm which integrated for three protons. These observations taken together indicate that the configuration at C-13 is retained in the oxidation of manool (**4**) with Collins reagent.

Three possible mechanisms can be advanced for the oxidative rearrangements of allylic alcohols exemplified by eq 1 and 2.



Mechanism I (Scheme I). The first step in this mechanism is the formation of chromate ester **31**, the same as the first step in the oxidation of alcohols with chromium(VI),[24] which undergoes ionization to ion pair **32**. The ion pair can undergo recombination and oxidation (path a) to give the normal ketone **33**, or recombination with rearrangement (path b) to **34** which is oxidized to **35**. Since **32** has a chromate moiety, it can also transfer oxygen to the double bond to give the epoxy es-

Scheme I

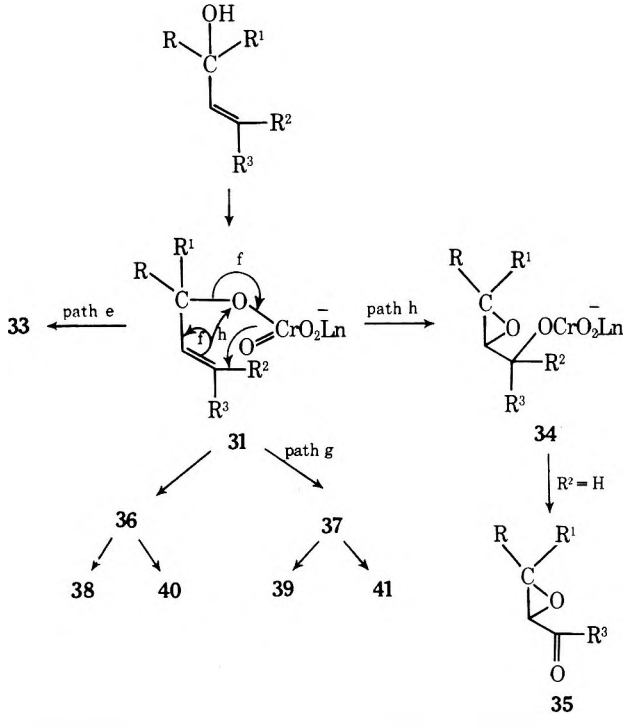


ters **36** (path c) or **37** (path d). The latter are subject to hydrolysis to give **38** or **39**, or can undergo oxidation to give epoxy aldehydes or ketones **40** or **41**.

Although this scheme accounts for all products, it does not explain the dramatic contrast between the results of oxidation with Collins reagent (Table I) and pyridinium chlorochromate (Table II) nor the following observations. Formation of ion pair **32** implies that configuration at the starting point is lost. This is not in accordance with the observation that **4** and **5** have the same configuration at C-14. The difficulty could be overcome if we assume that **32** is a tight ion pair and that the chromate moiety travels on the surface of the carbonium ion. Another objection to this mechanism is that in the oxidation of manool, rearranged epoxy aldehyde was obtained only when Collins reagent was used. If **32** is a reality, the chromate moiety should be formed regardless of reagent, thus leading at least partially to **40** and **41**. Finally, in the oxidation of **22**, there was no evidence for the formation of the rearranged α,β-unsaturated ketone, whereas oxidation of manool led to the rearranged conjugated compounds **6** and **7**.

Mechanism II (Scheme II). Chromate ester **31** undergoes normal oxidation to ketone **33** (path e) or rearrangement via a six-membered transition state (path f) to rearranged ester **34** which is oxidized to rearranged ketone **35**. Alternatively, oxygen transfer to the double bond of **31** (path g) could provide **37** which undergoes hydrolysis to **39** or oxidation to **41**. Finally **31** could undergo rearrangement (path h) to **36** which undergoes hydrolysis to **38** or oxidation to **40**.

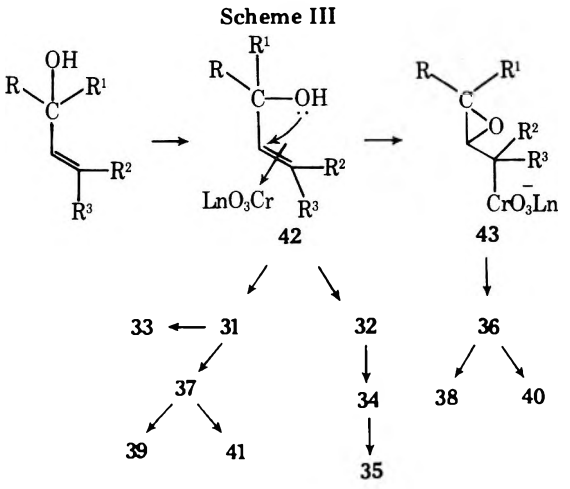
Scheme II



This mechanism explains the retention of configuration, since the C–O bond is not broken in the transition state. In other respects, however, it suffers from the same deficiencies as mechanism I, i.e., it does not explain the difference in the nature of the products depending on the oxidizing agent employed and that in the oxidations of manool, **5** was obtained only with Collins reagent and that **2** is not formed from **22**.

Mechanism III (Scheme III). The first step in this mechanism is the formation of π complex **42** which can rearrange to chromate ester **31** which as mentioned earlier can undergo oxidation to **33** or oxygen transfer to **37**. Alternatively, π complex **42** may undergo rearrangement to intermediate **43** with a C–Cr σ bond which can further rearrange to ester **36**, the precursor of **38** and **40**.[25]

Scheme III



Rearrangement of π complex **42** to chromate ester **31** is favored in those instances where the chromium complex possesses a ligand suitable for ester formation. Such ligands are present in pyridinium chlorochromate (Cl^-, eliminates HCl to form ester), Jones reagent, and CrO_3–3,5-dimethylpyrazole complex ($-OH^-$, eliminates water to form ester). No such ligand is present in Collins reagent, hence formation of ester **31** is not particularly favored. Ester **31** transfers oxygen to the double bond to give **37** which undergoes hydrolysis to **39**. This explains the formation of **21** from manool on oxidation with Jones reagent and the formation of **26** and **27** on oxidation of alcohol **22**. On the other hand, ester **37** can undergo oxidation to give **41** which explains the formation of **24** from **22**. Ester **31** can undergo ionization to the ion pair **32**. Such ion pair formation is facilitated by crowding in **31**, hence tertiary alcohol **4** can follow this route, whereas secondary alcohol **22** does not. This explains why ketone **2** is not formed from **22**. Ion pair formation is also highly favored in the case of bulky complexes such as pyridinium chlorochromate, Collins reagent, and 3,5-dimethylpyrazole complex, which explains why epoxy alcohol **21** was not obtained from manool except with Jones reagent. The postulated neighboring group participation in the rearrangement of **42** to **43** satisfies the requirement that the configuration of the C–O bond be maintained in the conversion of manool to **5**. Lastly, since ester formation is repressed in the case of Collins reagent, rearranged epoxide is formed to a larger extent than with the other three reagents.

Although mechanism III thus accounts for most of our observations, neither it nor mechanisms I and II explain the formation of ketone **20** from manool on oxidation with the pyrazole complex. We surmise that it arises from **5**, since oxidation of **5** with pyrazole complex yielded **20**, albeit in poor yield. Hence we conclude that mechanism III accommodates the facts more satisfactorily than the other proposals, although there is no conclusive evidence in its favor.

Experimental Section[26]

Oxidations of Manool. A. With Collins Reagent. A solution of 0.5 g of manool in 5 ml of CH_2Cl_2 was added in one portion to a suspension of 5 g of CrO_3·2Py in 100 ml of CH_2Cl_2. After 15 min the reaction mixture was filtered through a column of Florisil; the solid residue was washed several times with CH_2Cl_2. The combined filtrate and filtered washings were evaporated at reduced pressure. The residue was taken up in ether. The washed and dried ether extracts were evaporated; the residue was separated into three fractions by pressure liquid chromatography using a 12-ft Porasil column and hexane–1% ether as solvent. Fraction 1 (0.36 g, 69%) was a 1:1 mixture of the epimers **5**: IR band at 1705 cm^{-1}, NMR signals (270 MHz) at 0.60, 0.78, 0.80 (C-4 and C-10 methyls), 1.33 and 1.36 (together three protons, C-13 methyl), 3.08 d, 3.10 d (together 1 proton, H-14), 4.43 br and 4.80 br (H-17), and 9.46 d, 9.53 ppm d (J = 8 Hz, together one proton, H-15).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59; O, 10.51. Found: C, 78.89; H, 10.70; O, 10.41.

Fraction 2, a 1:1 mixture[30] of **6** and **7** (0.11 g, 21%), exhibited an IR band at 1690 cm^{-1} and had NMR signals (60 MHz) at 0.66, 0.80, 0.86 (C-4 and C-10 methyls), 1.90 and 2.13 ppm (together three protons, C-13 methyl).

B. Oxidation with Pyridinium Chlorochromate. A solution of 0.5 g of manool in 5 ml of CH_2Cl_2 was added in one portion to a suspension of 1 g of pyridinium chlorochromate in 20 ml of CH_2Cl_2. The reaction was followed by TLC. At the end of the reaction, the mixture was diluted with an equal amount of ether and filtered and the residual solid was washed thoroughly with ether. The combined filtrate and washings were evaporated; the residue (0.5 g, 98%) was a 1:1 mixture of **6** and **7**.

C. Oxidation with Jones Reagent. To an ice-cold solution of 0.4 g of manool in 10 ml of acetone was added Jones reagent dropwise until the reaction was complete (~20 min). The solvent was evaporated and the residue was taken up in ether. The washed and dried extract was evaporated and the residue was separated by preparative TLC into two fractions. IR and NMR spectra of the first fraction (80 mg, 20%) demonstrated that it was a 1:1 mixture of **6** and **7**. Fraction 2 (**21**,[2] 105 mg, 36%) had an IR band at 3500 cm^{-1} and NMR signals (270 MHz) at 0.70, 0.80, 0.90 (C-4 and C-10 methyls), 1.20, 1.30 (together three protons, C-13 methyl), 2.86 m (three protons, H-14, H-15), 4.53 hr and 4.83 ppm br (H-17).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.19; O, 10.44. Found: C, 78.33; H, 11.04; O, 10.53.

D. Oxidation with Chromium Trioxide–3,5-Dimethylpyrazole Complex. A solution of 0.5 g of manool in 5 ml of CH_2Cl_2 was added in one portion to a solution of the reagent prepared by addition of 1.5 g of 3,5-dimethylpyrazole to a suspension of 1.5 g of anhydrous CrO_3 in 20 ml of CH_2Cl_2. The reaction was followed by TLC. After the reaction was complete, the mixture was diluted with anhydrous ether and filtered. Evaporation of the filtrate gave a gum which was separated by preparative TLC into two fractions. Fraction 1 was the known ketone **20**, which had an IR band at 1705 cm^{-1} and NMR signals (60 MHz) at 0.70, 0.80, 0.87 (C-4 and C-10 methyls), 2.08 (C-14 methyl), 4.45 br and 4.70 ppm br (H-17). Fraction 2 was a 1:1 mixture of **6** and **7**.

Conversion of 5 to Manool. To a solution of 280 mg of **5** in 10 ml of methanol was added 120 mg of hydrazine hydrate and then 1 drop of acetic acid. The mixture was stirred at room temperature for 1 h, diluted with water, and extracted with ether. Evaporation of the washed and dried extract followed by preparative TLC gave 60 mg of manool.

Oxidations of Nerolidol. The crude product mixture obtained by oxidation of 0.5 g of nerolidol with Collins reagent was separated by pressure liquid chromatography (Porasil column, solvent hexane–1% Et_2O). The major fraction (0.39 g, 81%) was **12**: IR band at 1705 cm^{-1}, NMR signals (60 MHz) at 1.40, 1.43 (together three protons, C-3 methyl), 1.63 and 1.68 (three vinyl methyls), 3.16 d, 3.20 d (J = 6 Hz, together one proton, H-2), 5.15 br (two protons, H-6 and H-10), 9.40 d and 9.45 ppm d (J = 6 Hz, together one proton, H-1).

Anal. Calcd for $C_{15}H_{24}O_2$: mol wt, 236.1772. Found: mol wt (MS), 236.1793.

The minor fraction, 33 mg (15%), was a 1:1 mixture of farnesals (**16**) as evidenced by the NMR spectrum.

Application of procedure B to 0.5 g of nerolidol gave a 1:1 mixture of farnesals (98%).

Reduction of 12. To a solution of 0.15 g of **12** in 5 ml of acetic acid was added a solution of chromous chloride until the blue color persisted. The reaction was carried out in a CO_2 atmosphere. After dilution with water and neutralization with solid Na_2CO_3, the mixture was extracted with ether. Evaporation of the washed and dried ether extract furnished 0.125 g (90%) of the isomeric farnesals **16**.

Oxidations of Linalool. Oxidation of 0.5 g of linalool with 3 g of Collins reagent (procedure **A**) gave a mixture which was separated by pressure liquid chromatography. The first fraction (0.2 g) was a 1:1 mixture of isomeric 2,3-epoxy-3,6-dimethyloct-2-en-1-als (**13**)[27] which had an IR band at 1705 cm^{-1} and NMR signals (60 MHz) at 1.41, 1.44 (together three protons, C-3 methyl), 1.63 br and 1.68 br (three vinyl methyls), 3.18 d, 3.20 d (J = 6 Hz, together one proton, H-2), 5.15 br (vinyl proton), and 9.45 d, 9.50 ppm d (J = 6 Hz, together one proton, H-1).

The second fraction was a 1:1 mixture of geranial and neral (**17**) as evidenced by the NMR spectrum.

Oxidation of 0.5 g of linalool by procedure B gave 0.4 g (80%) of mixture **17**.

***exo*-2-Vinylbicyclo[2.2.1]heptan-2-ol (10).** A solution of 1 g of vinyllithium in THF was added dropwise with stirring to 2 g of norbornanone in THF. After 2 h, the mixture was poured onto crushed ice, neutralized with NH_4Cl, and extracted with ether. The washed and dried ether extract was evaporated and the residual gum was chromatographed over a Florisil column. Hexane–ether (9:1) eluted 2 g (95%) of gummy **10**, whose NMR spectrum (60 MHz) exhibited the typical ABC pattern of the vinyl group. This substance decomposed on standing and gave an unsatisfactory elemental analysis. For similar reasons, the high-resolution mass spectrum did not have the required accuracy in the second decimal place.

Anal. Calcd for $C_9H_{14}O$: mol wt, 138. Found: mol wt, 138.

Oxidations of 10. A. Oxidation of 0.64 g of **10** with 5 g of Collins reagent by procedure A followed by preparative TLC gave 0.343 g (50%) of mixture **14** which had an IR band at 1720 cm^{-1} and NMR signals (60 MHz) at 3.2 d, 3.36 d (J = 6 Hz, together 1 H), and 9.25 d, 9.40 d (J = 6 Hz, together 1 H).

Anal. Calcd for $C_9H_{12}O_2$: mol wt, 152.0836. Found: mol wt (MS), 152.0838.

B. Oxidation of 0.25 g of **10** by procedure B with 0.5 g of the reagent gave 0.2 g (79%) of the aldehyde mixture which had an IR band at 1690 cm^{-1} and NMR signals (60 MHz) at 5.70 d, 5.90 d (J = 6 Hz), together 1 H), and 9.70 d, 9.80 ppm d (J = 6 Hz, together 1 H). This mixture decomposed on standing and gave an unsatisfactory elemental analysis. The high-resolution mass spectrum also did not give the molecular ion within the required accuracy in the second decimal place.

Anal. Calcd for $C_9H_{12}O$: mol wt, 136. Found: mol wt (MS), 136.

3α-Vinylcholestan-3β-ol (11). Reaction of 1 g of vinyllithium with 2 g of choestan-3-one in the manner described above followed by chromatography over Florisil gave in the 19:1 hexane–ether fraction 1.0 g of recovered cholestanone and in the 9:1 hexane–ether fraction 0.9 g (84%) of **11**: after recrystallization from hexane it had mp 110 °C, and exhibited a hydroxyl band in the infrared at 3400 cm^{-1} and the typical ABC pattern of the vinyl group in the NMR spectrum.[26]

Anal. Calcd for $C_{29}H_{50}O$: mol wt, 414.3860. Found: mol wt (MS), 414.3876.

Oxidations of 11. A. Oxidation of 0.385 g of **11** by procedure A followed by high-pressure liquid chromatography on a Porasil column yielded 0.275 g of solid **15**, mp 107–109 °C after recrystallization from hexane, which had an IR band at 1705 cm^{-1} and significant NMR signals at 3.13 d (J = 5 Hz) and 9.55 ppm d (J = 5 Hz). On the basis of the NMR spectrum, the substance appeared to be homogeneous.[29]

Anal. Calcd for $C_{29}H_{48}O_2$: mol wt, 428.3653. Found: mol wt (MS), 428.3643.

B. Oxidation of 0.250 g of **11** with 0.5 g of pyridinium chlorochromate and chromatography of the crude product by preparative TLC yielded 72% of solid, mp 118–120 °C after recrystallization from hexane–chloroform, which had IR bands at 1672 and 1620 cm^{-1}, significant NMR signals at 5.83 d (J = 7 Hz) and 10.08 ppm d (J = 7 Hz).

Anal. Calcd for $C_{29}H_{48}O$: mol wt, 412.3703. Found: mol wt (MS), 412.3695.

Oxidation of the Labda-8(17),12-dien-14-ol Mixture (22). A. Oxidation of 0.2 g of mixture **22**[2] with Jones reagent by procedure C and chromatography gave 20 mg (10%) of **25**,[2] 53 mg (25%) of **24**, and 29 mg (15%) of **23**.[2] The previously unreported mixture of epimers **24** had IR bands similar to those previously[2] reported for **24A** (compound **15** of ref 2).

Oxidation of 0.2 g of **22** by procedure B and chromatography gave 61 mg (30%) of **23**, 21 mg (11%) of **24**, and 23 mg (11%) of **25**. Oxidation of 0.25 g of **22** by procedure A gave 95 mg (30%) of **23**, 45 mg (14%) of **24**, and 80 mg (31%) of **25**. Oxidation of 0.25 g of **22** by procedure D gave 65 mg (22%) of **23**, 49 mg (19%) of **24**, and 68 mg (26%) of **25**.

Oxidation of Labda-8(17),12-dien-14(*S*)-ol (22A). Oxidation of 200 mg of **22A**[2] by procedure C gave 15 mg (7%) of **25A**, mp 91–93 °C from hexane, in whose NMR spectrum H-14 appeared as a sharp quartet (J = 7 Hz) at 3.20 ppm, 50 mg (24%) of gummy **24A**, where the H-12 resonance was a sharp doublet of doublets (J = 8, 3 Hz), and 30 mg (15%) of **23**. Oxidation of 0.25 g of **22A** by procedure A gave **23** (102 mg, 40%), **24A** (40 mg, 15%), and **25A** (78 mg, 30%). Oxidation of 0.2 g of **22A** by procedure B gave **23** (78 mg, 39%), **24A** (23 mg, 11%), and **25A** (19 mg, 10%). Procedure D yielded **23** (85 mg, 35%), **24A** (36 mg, 14%), and **25A** (65 mg, 35%) from 0.25 g of **22A**.

Anal. for **25A**. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.00; H, 10.40.

Isolation of 26 and 27. Oxidation of mixture **22** with pyridinium chlorochromate and TLC of the crude product revealed, in addition to **23**, **24**, and **25**, two spots corresponding to substances **26** and **27**. Substance **26** was a gum which had IR signals at 3480 and 1640 cm^{-1};

NMR signals at 0.66, 0.80, 0.86 (C-4 and C-10 methyls), 1.26 (C-13 methyl), 1.16 d (J = 7 Hz, C-14 methyl), 3.00 (H-12), 3.4 q (J = 7 Hz, H-14), 4.43 br and 4.83 ppm br (H-17).

Anal. Calcd for $C_{20}H_{34}O_2$: mol wt, 306.2559. Found: mol wt (MS), 306.2558.

Substance **27** melted at 134 °C after recrystallization from $CHCl_3$–hexane and had IR bands at 3490 and 1640 cm^{-1}; NMR signals at 0.66, 0.80, 0.86 (C-4 and C-10 methyls), 1.23 (C-13 methyl), 1.28 d (J = 6 Hz, C-14 methyl), 3.00 q (J = 6 Hz, H-14), 3.2 m (H-12), 4.33 br and 4.00 ppm br (H-17).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.59, H, 10.99; O, 10.42.

Hydride Reductions of 5. A solution of 1.25 g of **5** in 10 ml of methanol was added to 200 mg of $NaBH_4$ in 25 ml of methanol at room temperature. The reaction mixture was stirred at room temperature, excess reducing agent was destroyed by adding dilute hydrochloric acid, solvent was evaporated, and the residue was taken up in ether and washed with water. Evaporation of the dried ether extract gave a gum which upon chromatography gave 1.00 g (80%) of epimeric mixture of epoxy alcohols[31] **29:** NMR signals at 0.70, 0.80, 0.86 (C-4 and C-10 methyl), 1.30 and 1.33 (together three protons, C-13 methyl), 2.96 t br (H-14), 3.76 m (two protons, H-15), 4.50 br (H-17), and 4.83 ppm br (H-17); IR signals at 3350 and 1640 cm^{-1}.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 77.89; H, 11.49.

A solution of 0.31 g of **5** in 2 ml of THF was added dropwise with stirring to a slurry of 0.09 g of $LiAlH_4$ in 10 ml of THF (nitrogen atmosphere). Stirring was continued for 1 h, excess reducing agent was destroyed by addition of wet ethyl acetate, and the complex was destroyed by addition of water. The mixture was filtered and the residue was thoroughly washed with ethyl acetate. The combined filtrate and washings were evaporated to yield a gum which upon chromatography over Florisil gave 0.30 g (>90%) of diol: NMR signals at 0.77, 0.88, 0.95 (C-4 and C-10 methyls), 1.31 (C-13 methyl), 3.94 m (H-15), 4.62 br (H-17), and 4.91 ppm br (H-17) and IR signals at 3400 and 1640 cm^{-1}.

Registry No.—**4,** 596-85-0; *cis*-**5,** 61063-26-1; *trans*-**5,** 61116-89-0; **6,** 17633-79-3; **7,** 38237-44-4; **8,** 142-50-7; **9,** 78-70-6; **10,** 61063-16-9; **11,** 61116-81-2; *cis*-**12,** 61063-27-2; *trans*-**12,** 61116-90-3; *cis*-**13,** 61063-17-0; *trans*-**13,** 61063-18-1; *cis*-**14,** 61063-19-2; *trans*-**14,** 61116-82-3; *cis*-**15,** 61063-20-5; *trans*-**15,** 61116-83-4; *E*-**18,** 61063-21-6; *Z*-**18,** 61063-22-7; *E*-**19,** 61116-84-5; *Z*-**19,** 61116-85-6; **20,** 10266-75-8; **21,** 61116-86-7; **22**-OHα, 61045-84-2; **22A,** 61091-75-6; **24A,** 61046-83-1; **25A,** 61046-86-4; **26,** 61063-23-8; **27,** 61063-24-9; **29** α isomer, 61116-87-8; **29** β isomer, 61116-88-9; **30,** 61063-25-0; norbornanone, 497-38-1; cholestan-3-one, 15600-08-5.

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Additions and Cycloadditions of 2-Phenylallylmagnesium Phenoxide to Carbon–Carbon Double Bonds

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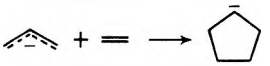
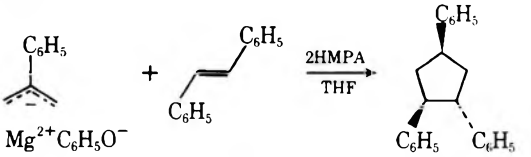
2-Phenylallylmagnesium phenoxide in tetrahydrofuran containing 2 molar equiv of hexamethylphosphoramide reacts readily with carbon–carbon double bonds which are activated by electron-withdrawing substituents. Stilbene, α-methylstyrene, β-methylstyrene, and phenanthrene give products from formal [3 + 2] cycloaddition of the allyl anion to the double bond. Acenaphthylene, α,α′-difluorostilbene, 1,1,1,4,4,4-hexafluoro-2,3-diphenyl-2-butene, and 2-[(*E*)-2-phenylethenyl]-4,4-dimethyloxazoline give adducts with formation of only one new carbon–carbon bond. 1,1-Diphenylethylene gives a cyclic adduct which is a secondary reaction product. Anthracene rapidly gives an acyclic adduct which is slowly transformed to a cyclic adduct. Attempts to determine the stereochemistry of cycloaddition of the 2-phenylallylmagnesium phenoxide to *cis*-stilbene and to *cis*-β-methylstyrene were frustrated by the rapid conversion of the olefins to their trans isomers. A stepwise carbanionic mechanism for both acyclic and cyclic additions is consistent with the results but not rigorously proven.

Cycloaddition of an allyl anion to a carbon–carbon multiple bond (eq 1) is the anionic analogue of the Diels–Alder reaction. Conservation of orbital symmetry predicts it to be a $[_\pi 4_s + _\pi 2_s]$ reaction in which the olefin configuration is retained in the product cyclopentyl anion.[2] Many heterocyclic analogues of the Diels–Alder reaction, 1,3-dipolar cycloadditions,[3] and also transition metal promoted [3 + 2] cycloadditions[4] are known. However, 2-phenylallyllithium, -sodium, -potassium, and -magnesium compounds,[5-8] 2-cyano-1,3-diphenylallyllithium,[9] the lithium derivative of 1,3-diphenylpropyne,[5,8] and a 2-thiomethylenecyclohexanone derivative[10] are the only formal allyl anions known to form five-membered carbocycles by intermolecular addition to carbon–carbon double bonds. Although these allyl anion cycloadditions have often been assumed to be concerted, in no case has the stereochemical course been firmly established. Kauffmann and co-workers have reported numerous cycloadditions of azaallyl anions to multiple bonds.[5] The adducts of 2-azaallyllithium with *trans*- and *cis*-stilbene appear to be those predicted by conservation of orbital symmetry.[11] Two structural features which promote anionic [3 + 2] cycloaddition are electron-withdrawing substituents on the carbon–carbon double bond and stabilization of charge in the cyclopentyl anion by a nitrogen atom (in the form of a pyrrolidine anion), or a carbonyl, cyano, or aryl substituent.



(1)

We recently reported that a variety of crown ethers, cryptands, and hexamethylphosphoramide (HMPA) catalyze cycloaddition of 2-phenylallylmagnesium phenoxide (1) to *trans*-stilbene to give *r*-1,*t*-2,*c*-4-triphenylcyclopentane (2)[8].



1 2

Eidenschink and Kauffmann[6] had previously obtained 2 from 2-phenylallyllithium and *trans*-stilbene but had not established its configuration. In tetrahydrofuran (THF) in the absence of complexing agents 1 does not react with *trans*-stilbene. In this paper we describe additions of 1 HMPA to a wide variety of electron-deficient carbon–carbon double bonds.

Results

2-Phenylallylmagnesium phenoxide (1) was prepared by Maercker's[12] method, cleavage of 2-phenylallyl phenyl ether (3) with magnesium metal in refluxing THF. The structure of 1 was confirmed by carbonation to produce 3-phenyl-3-butenoic acid (4), treatment with chlorotriphenyltin to produce 2-phenylallyltriphenyltin (5), and hydrolysis to produce α-methylstyrene and 2,5-diphenyl-1,5-hexadiene (6). When cleavage of 3 was attempted with lithium metal in THF only polymeric material was obtained.

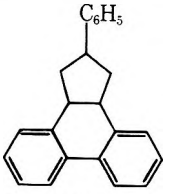
$$1 + CO_2 \rightarrow CH_2{=}C(C_6H_5)CH_2CO_2H \text{ (4)}$$

$$1 + (C_6H_5)_3SnCl \rightarrow CH_2{=}C(C_6H_5)CH_2Sn(C_6H_5)_3 \text{ (5)}$$

$$1 + NH_4Cl\ (aq) \rightarrow CH_2{=}C(C_6H_5)CH_3 + [CH_2{=}C(C_6H_5)CH_2]_2 \text{ (6)}$$

Reaction of 1 HMPA with Olefins. The remarkable catalytic effect of HMPA on reaction of 1 with *trans*-stilbene prompted us to study the reactions of 1 HMPA with a variety of other olefins. The progress of each reaction was followed by GLC. The reactants and products are shown in Table I. All of the adducts were isolated by either preparative GLC or preparative liquid chromatography and characterized primarily by analyses of their mass and NMR spectra. Details are in the Experimental Section.

Reaction of phenanthrene with 1 HMPA gave the 9,10-dehydro 1:1 adduct **10**. Since **10** must be formed by dehydrogenation of the corresponding 9,10-dihydrophenanthrene (11), and atmospheric oxygen is known to convert dihydrophenanthrenes to phenanthrenes,[13] we attempted but failed to isolate the initial adduct **11** by carrying out all experimental

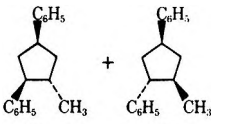
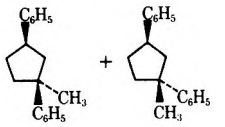
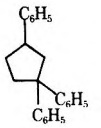
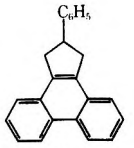
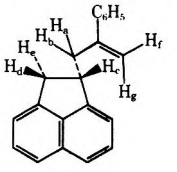
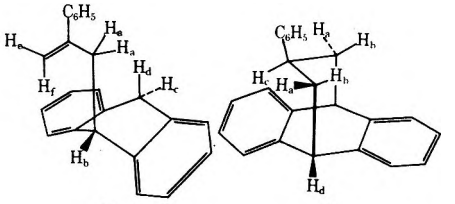
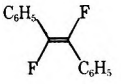
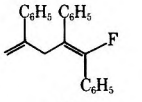
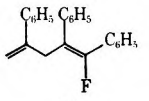
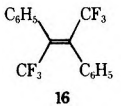
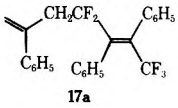
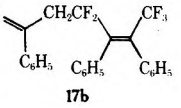


11

operations under nitrogen. Since unsubstituted 9,10-dihydrophenanthrene also was detected in the reaction mixture, **11** may have produced **10** by hydrogen transfer to phenanthrene.

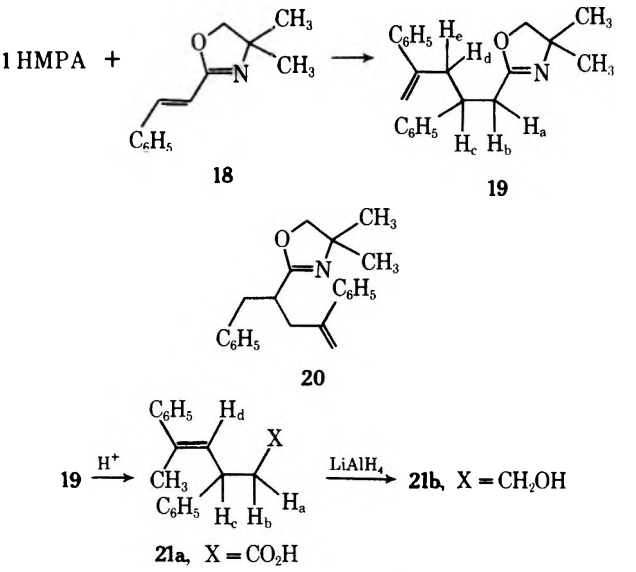
Reaction of anthracene with 1 HMPA produced acyclic adduct **13** almost immediately, but **13** disappeared and cyclic adduct **14** appeared over a period of 98 h. Bulky substituents in 9,10-dihydroanthracenes are known to prefer the less hindered axial position[14] as shown in Table I. The unusually high field resonance of H_f in **13** at δ 4.50 indicates that in the preferred conformation, H_f is deshielded by a benzene ring of the dihydroanthracene. Molecular models and the coupling

Table I. Additions of 1 HMPA to Olefins

Reactant	Product
cis- or *trans*-β-Methylstyrene	 7a + 7b
α-Methylstyrene	 8a + 8b
1,1-Diphenylethylene	 9
Phenanthrene	 10
Acenaphthylene	 12
Anthracene	 13 + 14
	  15a  15b
	 16  17a  17b

constants in the NMR spectrum of **14** support the conformation illustrated in Table I. The dihedral angle between H_b and H_d in a model of **14** is about 90°. Such a dihedral angle is known to minimize vicinal coupling constants. No coupling between H_b and H_d was observed. The UV spectra of **13** and **14** were nearly the same as the sums of the spectra of 9,10-dihydroanthracene and α-methylstyrene and of 9,10-dihydroanthracene and benzene, respectively.

Reaction of 1 HMPA with oxazoline **18** for 0.5 min gave the acyclic adduct (**19**) in 64% yield. Although the IR, mass, and NMR spectra all indicated a 1:1 adduct, even the 220-MHz NMR spectrum, which could be analyzed on a approximate first-order basis, did not distinguish between **19** and the isomer **20** which would result from addition of 1 HMPA to the other terminus of the carbon–carbon double bond of **18**. An attempt to distinguish **19** from **20** by NMR spectra in the presence of the paramagnetic reagent Eu(fod)$_3$ [tris-(6,6,7,7,8,8 8-heptafluoro-2,2-dimethyl-3,5-octanedioate) europium] failed because the Eu(fod)$_3$ broadened the resonances more than it shifted them. Hydrolysis of oxazoline **19**



to carboxylic acid **21a** followed by reduction with $LiAlH_4$ gave alcohol **21b** which was identified unambiguously. The broad singlet at δ 2.5 disappeared upon addition of D_2O or Eu(fod)$_3$. Addition of increments of Eu(fod)$_3$ caused the following relative shifts: $CH_2OH > H_a$, $H_b > H_c > H_d > CH_3$. The NMR spectrum of **21a** is quite similar to that of **21b**. Although the double bond of **19** shifted from the terminal to an internal position during hydrolysis to **21a**, no breaking and making of carbon–carbon single bonds should have occurred. Therefore **19** must have the same carbon skeleton as **21b**.

Reactions of 1 HMPA with a variety of other olefins were attempted without success. The strained double bond of norbornene did not react in 4 days at room temperature. *trans*-Cyclooctene produced only a trace of *cis*-cyclooctene and no adducts in 4 days in refluxing THF. Perfluoro-2-butene reacted at 0 °C and at −78 °C to give oligomeric mixtures which contained no single product with a yield of more than 5%. No attempt was made to isolate any of the perfluoro-2-butene products.

Reactions of 1 HMPA and of 2-Phenylallylithium with *cis*- and *trans*-Stilbene. Because the rapid isomerization of *cis*- to *trans*-stilbene by 1 HMPA might lie on the same reaction path as the cycloaddition of 1 HMPA to *trans*-stilbene, we sought to learn more about the mechanism of isomerization. Even at −5 °C 1 HMPA caused complete isomerization of *cis*-stilbene (within limits of GLC detection) in 1 min. In the same time <1% of cycloadduct **2** was formed. In the absence of HMPA 2-phenylallylmagnesium phenoxide (**1**) failed to react with *trans*-stilbene in 4 days at room temperature and isomerized *cis*- to *trans*-stilbene with a half-life of about 30 h at room temperature. Two equivalents of HMPA is required to catalyze the cycloaddition; when only 1 equiv of HMPA was added, the solution of **1** did not change color and **1** failed to react with *trans*-stilbene. Isomerization of *cis*-stilbene-α,α′-d_2 by 1 HMPA at −5 °C proceeded with no loss of deuterium.

We also reinvestigated the cycloaddition of 2-phenylallyllithium to *trans*-stilbene under the conditions originally reported by Eidenschink and Kauffmann.[6] They found that a mixture of α-methylstyrene, *trans*-stilbene, and lithium diisopropylamide (LDIA) in THF gave a 41% yield of **2** in 150 h at 45 °C, but they did not establish the configuration of **2**. We verified their results and determined the configuration of **2** from its 220-MHz NMR spectrum. As we followed the reaction under their conditions by GLC–mass spectrometry, not one but four compounds appeared with molecular ions at *m/e* 298. After 166 h yields of the four fractions by GLC were 27.9, 6.2, 5.7, and 1.3%. The major isomer was **2**. The mass

spectra of the minor fractions were very similar to one another and markedly different from that of **2** and their ^{1}H NMR spectra indicated that they were mixtures of compounds. This suggests that most or all of the minor fractions contain acyclic isomers of **2** since there are only two other possible 1,2,4-triphenylcyclopentanes. The materials responsible for the GLC peaks corresponding to yields of 6.2 and 5.7% were isolated by preparative GLC. The complex 220-MHz NMR spectrum of each fraction appeared to be due to a mixture of two or more acyclic triphenylpentenes because of several vinyl hydrogen multiplets of nonintegral areas. Further identification was not attempted.

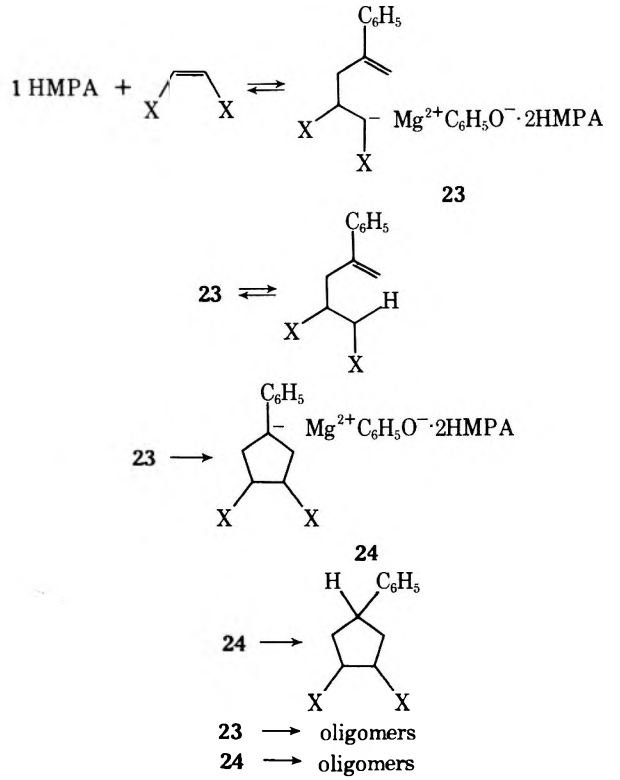
A careful examination of the reaction mixture from 1 HMPA and *trans*-stilbene by the same GLC–mass spectrometric method did not detect any of the minor isomers found in the LDIA-catalyzed reaction mixture. However, a compound was found with a molecular ion at *m/e* 416, which corresponds to a 2:1 adduct of α-methylstyrene and *trans*-stilbene. The 2:1 adduct decomposed during attempts to isolate it by preparative GLC.

When *cis*-stilbene was treated with LDIA and α-methylstyrene at 45 °C, it isomerized with a half-life of about 0.8 h. The isomerization was repeated with *cis*-stilbene-α,α'-d_2. After 4.5 h the hydrolyzed mixture contained 53% *cis*-stilbene which had lost 9% of one atom of deuterium and 47% *trans*-stilbene which had lost 50% of one atom of deuterium.

Discussion

HMPA-solvated 2-phenylallylmagnesium phenoxide in THF adds to a variety of carbon–carbon double bonds. The chief limitation is that the double bond must be substituted with at least one electron-withdrawing, carbanion-stabilizing substituent. Highly strained cycloalkenes such as norbornene and *trans*-cyclooctene do not react with 1 HMPA in refluxing THF. Several mechanisms might be invoked to explain the results, but we favor the general stepwise addition/cycloaddition mechanism in Scheme I for two reasons: (1) Scheme I can be used to explain both the cycloadducts formed from *trans*-stilbene, *trans*-β-methylstyrene, α-methylstyrene, and phenanthrene, and the acyclic products formed from acenaphthylene, anthracene, α,α'-difluorostilbene, and oxazoline **18**. (2) In every reaction higher oligomers than simple 1:1 adducts were formed. Even in the cases where the major product is a 1:1 cycloadduct, there must be pathways available for stepwise addition of the intermediate cyclopentyl anion **24** or acyclic anion **23** to carbon–carbon double bonds to account for production of sizable amounts of higher molecular weight materials. We did not attempt either to trap intermediates such as **23** or **24** with alkylating or acylating agents, or to generate **23** independently and determine whether it cyclized to **24**. Successful execution of such experiments would strengthen greatly our stepwise cycloaddition interpretation, but we chose instead to explore the generality of 1 HMPA cycloadditions.

Scheme I



The cycloadditions could proceed by a concerted $[{}_\pi 4_s + {}_\pi 2_s]$ mechanism, but the concerted cycloaddition transition states cannot be much lower in energy than the transition states which lead to higher oligomers. In principle concerted and stepwise cycloadditions can be distinguished stereochemically. The concerted reaction must proceed with retention of the configuration of the starting olefin. Rotation about single bonds in intermediate **23** of a stepwise cycloaddition should lead to isomeric adducts which differ in configuration at the X-substituted carbon atoms. Our attempts to determine the stereochemical courses of cycloaddition of 1 HMPA to *cis*-stilbene and *cis*-β-methylstyrene were frustrated by rapid isomerization of the olefins to their more stable trans isomers under the reaction conditions.

The failure of 1 HMPA to add to norbornene and *trans*-cyclooctene does not help distinguish between concerted and stepwise cycloaddition. In the stepwise mechanism of Scheme I a carbanion-stabilizing substituent X promotes formation of intermediate **23**. In a concerted cycloaddition conjugating substituents on the ${}_\pi 2$ addend stabilize the transition state by making the frontier molecular orbitals of the ${}_\pi 2$ addend closer in energy to the frontier molecular orbitals of the 2-phenylallyl anion.[15,16] Thus an electron-rich allyl anion should add more readily to an electron-deficient phenyl-substituted double bond than to an electron-rich cycloalkene double bond regardless of the mechanism.

Cycloaddition of 1 HMPA to anthracene clearly is a stepwise process. The rapidly formed acyclic adduct **13** is slowly converted to cycloadduct **14** over a period of days.

The cycloadducts **8a** and **8b** obtained from 1 HMPA and α-methylstyrene are apparently the same as the α-methylstyrene dimer obtained much earlier by Pines and co-workers[7] by catalysis with sodium or potassium metal and alkylbenzenes at >100 °C. Our **8a** and **8b** are probably also the same compound obtained (but incorrectly assigned) from treatment of α-methylstyrene with dibenzylmagnesium.[17]

Reaction of 1 HMPA with α,α'-difluorostilbene is formally a substitution of 2-phenylallyl anion for fluoride ion at vinyl carbon. It most likely proceeds by addition of 1 HMPA to the carbon–carbon bond to form intermediate **23**, followed by loss of fluoride ion. This addition–elimination mechanism explains formation of stereoisomers **15a** and **15b** from isomerically pure α,α'-difluorostilbene.

Reaction of 1 HMPA with **16** is formally a displacement of fluoride ion by 2-phenylallyl anion at saturated carbon. An alternative electron transfer mechanism for production of **17** is (1) electron transfer from 1 HMPA to **16**; (2) loss of fluoride ion from the radical anion of **16**; (3) coupling of the 2-phenylallyl and 2,3-diphenyl-1,1,4,4,4-pentafluorobutenyl free radicals.

The isomerizations of *cis*-stilbene catalyzed by 1 HMPA and by LDIA apparently proceed by different mechanisms. The 1 HMPA process takes place without loss of deuterium

from *cis*-stilbene-α,α'-d_2 and can be explained by either reversible addition of 1 HMPA to the double bond of the stilbene as in Scheme I or reversible electron transfer from 1 HMPA to stilbene. HMPA is known to promote electron transfer reactions of organomagnesium and -lithium compounds.[18] In an electron transfer mechanism both the stilbene radical anion and the stilbene dianion formed by disproportionation of two stilbene radical anions are known to isomerize.[19] We have not attempted to detect radical anion intermediates by ESR in either the stilbene isomerizations or the cycloadditions.

Isomerization of *cis*-stilbene-α,α'-d_2 by LDIA in THF at 45 °C proceeds with partial loss of deuterium from both the *trans*-stilbene and the remaining *cis*-stilbene. This result suggests that isomerization proceeds via a vinyl carbanion intermediate. To account for the isotopically exchanged stilbenes the vinyl carbanion must abstract a proton from either THF or diisopropylamine. (LDIA and THF react slowly at room temperature to form diisopropylamine, ethylene, and the lithium enolate of acetaldehyde.)[20]

In their initial treatment of α-methylstyrene and *trans*-stilbene with LDIA to form a triphenylcyclopentane, Eidenschink and Kauffmann[6] reported a single cycloadduct of undetermined configuration. We have established that the cycloaddition proceeds stereospecifically to form **2**.[8] Because **2** is undoubtedly more stable than its isomers which have phenyl groups at C-1 and C-2 cis to one another, its exclusive formation does not distinguish between concerted and stepwise cycloadditions. Our detection of simultaneous formation of **2** and acyclic isomers from the LDIA-catalyzed reaction of α-methylstyrene and *trans*-stilbene suggests that an intermediate analogous to **23** is formed in the reaction mixture. Very likely the cycloadduct **2** is formed by the same stepwise mechanism as the acyclic adducts.

1 HMPA is not the only organomagnesium compound which adds readily to carbon–carbon double bonds. Intramolecular examples are plentiful.[21] Lehmkuhl and co-workers[22] have obtained acyclic adducts from allylmagnesium halides and a variety of olefins including norbornene, styrene, and acyclic 1-alkenes. Their experiments were carried out in diethyl ether or in hydrocarbon solvents in which the mechanism is probably a coordinative addition of the magnesium alkyl to the double bond rather than the ionic mechanism we propose for reactions of 1 HMPA. HMPA also is known to promote the 1,4 addition of ethylmagnesium bromide to 2,4,6-cyclooctatrien-1-one and the alkylmagnesium bromide initiated polymerization of α-methylstyrene.[23]

Experimental Section[24]

Temperatures are uncorrected. Preparative GLC separations were performed with a Varian A-90P chromatograph using the following columns made with copper tubing and 60/80 Chromosorb W support: A, 0.25 in. × 6 ft 10% OV-17; B, 0.25 in. × 4 ft 10% OV-17; C, 0.25 in. × 1.0 ft 8.4% SE-30. Analytical GLC was performed with a Hewlett-Packard Model 700 chromatograph equipped with a thermal conductivity detector on column D, 0.125 in. × 6 ft 10% OV-17 on 60/80 Chromosorb W in copper tubing, or with a Varian Model 2700 chromatograph equipped with flame ionization detectors using 2 mm i.d. glass columns: E, 6 ft 3% SE-30 on 100/120 Gas Chrom Q; F, 6 ft 3% OV-17 on 100/120 Gas Chrom Q. Unless otherwise noted analytical GLC runs were programmed from 75 to 290 °C at 15 °C/min with a He flow rate of 40 ml/min. *n*-Dodecane was used as the internal standard. GLC–mass spectrometry was performed on a Varian-MAT CH-7 instrument interfaced with a Varian Model 2700 gas chromatograph using column E. Medium-resolution mass spectra and deuterium analyses were performed on a Varian-MAT CH-5 instrument. Exact mass determinations of molecular ions were performed on a Varian MAT 731 instrument. ^{1}H NMR spectra were obtained with Varian A-60A, HA-100, and HR-220 spectrometers. ^{19}F NMR spectra were obtained with Varian A-56/60 and HA-100 spectrometers. Infrared spectra were obtained with a Beckman IR-12 instrument. Combustion analyses were performed by J. Nemeth and associates, University of Illinois.

Materials. THF and diethyl ether were distilled from sodium naphthalenide or sodium–benzophenone under N_2 immediately before use. Diisopropylamine, α-methylstyrene, and HMPA were distilled from CaH_2 and stored under N_2. *Caution.* Preliminary animal tests indicate that *HMPA may be carcinogenic.*[25] *n*-Butyllithium in hexane and phenyllithium in benzene/ether were obtained from Matheson Coleman and Bell or Alfa and were standardized by the 1,2-dibromoethane double titration method.[26] Magnesium turnings were washed with diethyl ether and dried under vacuum. *cis*-Stilbene[27] was vacuum distilled and found to contain 97% *cis*- and 3% *trans*-stilbene by GLC on column D. *cis*-β-Methylstyrene[28] was isolated by GLC on column B because of severe foaming encountered during attempted distillation. *trans*-Stilbene, phenanthrene, acenaphthylene, and anthracene were recrystallized. Unless noted otherwise all other materials were used as obtained from commercial sources.

Bromination of α-Methylstyrene. A mixture of 365 g of *N*-bromosuccinimide, 250 ml of α-methylstyrene, 175 ml of CCl_4, and 1.0 g of benzoyl peroxide was heated with stirring to reflux. The mixture refluxed for 15 min without additional heating. The mixture was cooled to room temperature over 3 h, filtered to remove succinimide, and partially distilled under vacuum to remove CCl_4 and excess α-methylstyrene. Vacuum distillation of the remaining material gave 258 g (74%) of mixed bromides, bp 63–72 °C (1 mm) [lit.[29] bp 56–64 °C (1 mm)]. The areas of the signals at δ 4.7 and 5.4 in the 60-MHz NMR spectrum of the mixture indicated 63% 3-bromo-2-phenylpropene and 37% 1-bromo-2-phenylpropene. *Warning: 3-Bromo-2-phenylpropene is a severe lachrymator.*

2-Phenylallyl Phenyl Ether (3). The mixed bromo-2-phenylpropenes (258 g) were treated with dry phenol and K_2CO_3 in acetone by a standard procedure.[30] Distillation gave 98% recovery of the original 1-bromo-2-phenylpropene and 157 g (91%) of **3**: bp 94–100 °C (0.02 mm); NMR ($CDCl_3$) δ 4.8 (s, 2 H), 5.4 (s, 1 H), 5.6 (s, 1 H), 6.9 (m, 3 H), 7.2 (m, 7 H); IR (neat) 3080 (m), 1620 (s), 1510 (s), 1325 (m), 1250 (s), 1190 (m), 1095 (m), 1055 (s), 1040 (s), 920 (s), 795 (m), 755 (s), 710 (s), 695 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 210 (100), 209 (12), 195 (20), 118 (13), 117 (100), 116 (32), 115 (100), 105 (23), 94 (35), 91 (65), 77 (28).

Anal. Calcd for $C_{15}H_{14}O$: C, 85.71; H, 6.66. Found: C, 85.68; H, 6.70.

2-Phenylallylmagnesium phenoxide (1) was prepared from **3** and magnesium turnings in refluxing THF.[8,12] The preparation and all reactions of 1 were performed in an atmosphere of dry nitrogen.

3-Phenyl-3-butenoic Acid (4). Dry CO_2 was bubbled through a solution of 15 mmol of 1 in 50 ml of THF for 1.0 h. The solution was hydrolyzed with 50 ml of 2 N HCl and extracted four times with ether. The combined organic solutions were extracted three times with 50 ml of saturated aqueous Na_2CO_3. The combined aqueous solution was added slowly to 20 ml of concentrated HCl and extracted three times with ether. The ether extracts were dried and evaporated to 0.84 g (37%) of **4**, mp 40–44 °C. Recrystallization from hexane yielded 0.71 g of white crystals: mp 45–46 °C (lit.[31] mp 48–49 °C); NMR ($CDCl_3$) δ 11.4 (s, 1 H), 7.1 (m, 5 H), 5.5 (s, 1 H), 5.1 (s, 1 H), 3.2 (s, 2 H).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.21. Found: C, 74.14; H, 6.09.

2-Phenylallyltriphenyltin (5). A solution of 5.7 g of chlorotriphenyltin in 10 ml of THF was added to a solution of 15 mmol of 1 in 50 ml of THF. A white solid began to form in 15 min. The mixture was stirred overnight, hydrolyzed with 50 ml of 2 N HCl, and extracted three times with ether. The combined ether solution was dried and evaporated to a light yellow oil which was chromatographed on a 3 × 30 cm column of alumina with hexane as eluent. Evaporation of the fourth 200-ml fraction left 3.13 g (45%) of **5**: NMR ($CDCl_3$) δ 7.2 (m, 20 H), 5.0 (s, 2 H), 2.8 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 468 (3.0), 467 (1.5), 466 (2.2), 465 (1.2), 404 (1.2), 356 (3.1), 355 (18.0), 354 (3.0), 353 (16.6), 352 (20.7), 351 (100.0), 350 (40.0), 349 (75.2), 348 (31.4), 347 (43.8).

General Procedure for Reactions of 1 HMPA. An equimolar amount of the reactant and 0.33 molar equiv of *n*-dodecane were added to the solution of 1 in THF in a N_2 atmosphere at room temperature. Two molar equivalents of HMPA was added with stirring. At various times 1–5-ml aliquots were withdrawn by syringe through a serum cap and rapidly added to excess dilute aqueous NH_4Cl. A few milliliters of hexane were added, and the organic phase was washed twice with 1 HCl, twice with 10% NaOH, once with 50% saturated $NaCO_3$, and once with water. The solution was dried over $MgSO_4$ and analyzed by GLC. GLC–mass spectrometry experiments were performed with the same solutions. Unless noted otherwise the samples

for NMR, IR, and elemental analysis were isolated by preparative GLC from the same solutions after evaporation of most of the solvent. Yields were determined by GLC and were not corrected by GLC response factors.

***trans*-Stilbene and 1 HMPA.** A solution of 15 mmol of 1 HMPA and 15 mmol of *trans*-stilbene was stirred for 48 h at room temperature. Periodically 5-ml aliquots of the solution were analyzed by GLC on column E. Two products were detected with molecular ions at *m/e* 298 and 416, respectively, by GLC–mass spectrometry. The former was isolated by GLC on column A at 290 °C, but the latter decomposed during attempted isolation. The compound with *m/e* 298 was identified as *r*-1,*t*-2,*c*-4-triphenylcyclopentane (**2**) by its 220-MHz NMR spectrum:[8] IR (C_2Cl_4) 3100 (m), 3080 (m), 3040 (s), 2950 (m), 1600 (s), 1500 (s), 1450 (s), 1060 (m); mass spectrum *m/e* (rel intensity) 298 (55), 207 (11), 194 (54), 193 (100), 180 (11), 179 (27), 178 (23), 168 (20), 165 (43).

Exact mass (70 eV) calcd for $C_{23}H_{22}$, 298.1723; found, 298.1722.

***cis*-Stilbene and 1 HMPA.** A reaction at room temperature conducted by the procedure used for *trans*-stilbene gave a product mixture identical with that obtained from *trans*-stilbene. The reaction was repeated by the same procedure except that the solution of 1 and *cis*-stilbene was cooled to −5 °C before addition of HMPA. GLC analysis showed the stilbene in an aliquot taken at 0.5 min to be 95% trans, and in an aliquot taken at 1.0 min to be 100% trans. In the 1.0-min aliquot the compounds of mol wt 298 and 416 were barely detectable by GLC.

***cis*-Stilbene-α,α'-d_2 and 1 HMPA.** *cis*-Stilbene-α,α'-d_2[32] was 99% cis and 1% trans by GLC and contained 98% d_2 and 2% d_1 material by mass spectrometry at low enough eV to prevent fragmentation of the molecular ions. A solution of 7.5 mmol of 1 and 15.0 mmol of HMPA in 25 ml of THF was cooled to −5 °C, and 4.5 mmol of *cis*-stilbene-α,α'-d_2 was added with stirring. After 1.0 min the entire mixture was hydrolyzed with aqueous NH_4Cl. GLC showed only α-methylstyrene and *trans*-stilbene. Both compounds were isolated and identified by mass spectrometry and NMR. By mass spectrometry at low eV the *trans*-stilbene was 98% d_2 and 2% d_1.

β-Methylstyrene and 1 HMPA. Commercial β-methylstyrene (95% trans) was dried over 3A molecular sieves. A solution of 15 mmol of β-methylstyrene and 1 HMPA in 50 ml of THF was stirred for 2.5 h at room temperature. Periodically 5.0-ml aliquots were analyzed by GLC on column E. One major product peak appeared in a maximum yield of 13% after 50 min. This material was isolated by GLC on column A at 210 °C. From the 220-MHZ NMR and mass spectra it was identified as a mixture of isomeric 1-methyl-2,4-diphenylcyclopentanes **7a** and **7b**: NMR (CCl_4) δ 1.01 (d, J = 6 Hz), 1.02 (d, J = 6 Hz), 1.35–1.6 (m), 1.75–2.8 (m), 3.2–3.4 (m), 7.14 (br s); mass spectrum *m/e* (rel intensity) 236 (87), 194 (27), 193 (41), 179 (14), 178 (10), 158 (20), 145 (20), 143 (19).

Exact mass (70 eV) calcd for $C_{18}H_{20}$, 236.1566; found, 236.1565.

When *cis*-β-methylstyrene (>99% cis) was treated in the same manner and reaction aliquots were analyzed on column F, it isomerized completely to the trans isomer in <1 min. The mixture isolated by preparative GLC had mass and 220-MHz NMR spectra identical with those obtained from the reaction of *trans*-β-methylstyrene with 1 HMPA. In the absence of HMPA under otherwise identical conditions with 1 in THF at room temperature, *cis*-β-methylstyrene underwent no isomerization in 155 h.

α-Methylstyrene and 1 HMPA. A solution of 15 mmol of α-methylstyrene and 15 mmol of 1 HMPA in 50 ml of THF was stirred for 24 h at room temperature. Periodically 5.0-ml aliquots of the solution were analyzed by GLC on column E. One major and several minor peaks were observed. The yield of the major product maximized at 35% after 3.0 h. It was isolated by GLC on column A at 280 °C and identified by 220-MHz NMR and mass spectra as a mixture of isomeric 1-methyl-1,3-diphenylcyclopentanes **8a** and **8b**: NMR (CCl_4) δ 1.36 (s, 3 H), 1.42 (s, 3 H), 1.75–2.4 (m, 11 H), 2.59 (d of d, J = 12, 8 Hz, 1 H), 3.12 (m, 1 H), 3.36 (m, 1 H), 7.0–7.4 (m, 20 H); mass spectrum *m/e* (rel intensity) 236 (37), 221 (15), 157 (12), 143 (28), 131 (16), 119 (21), 118 (100), 117 (55), 114 (24).

Exact mass calcd for $C_{18}H_{20}$, 236.1566; found, 236.1565.

1,1-Diphenylethylene and 1 HMPA. A solution of 15 mmol of 1,1-diphenylethylene and 15 mmol of 1 HMPA in 50 ml of THF was stirred for 45 h at room temperature. Periodically 5.0-ml aliquots of the solution were analyzed. GLC–mass spectrometry with column E showed four significant products with molecular ions at *m/e* 298, 368, 416, and 478. Only the first product, 1,1,3-triphenylcyclopentane (**9**), could be isolated by GLC on column B at 290 °C in sufficient quantity for identification by 220-MHz NMR spectroscopy. The complete disappearance of 1,1-diphenylethylene in <1 min and slow appearance of **9** to a yield of 28% after 45 h indicate that **9** is not a primary product of the reaction: NMR (CCl_4) δ 1.95 (m, 1 H), 2.35 (m, 3 H), 2.71 (m, 1 H), 2.87 (m, 1 H), 3.17 (m, 1 H), 7.0–7.4 (m, 15 H); mass spectrum *m/e* (rel intensity) 298 (54), 296 (26), 220 (39), 219 (10), 207 (24), 194 (30), 193 (54), 192 (21), 191 (29).

Exact mass (70 eV) calcd for $C_{23}H_{22}$, 298.17226; found 298.17210.

Phenanthrene and 1 HMPA. A solution of 15 mmol of phenanthrene and 15 mmol of 1 HMPA in 50 ml of THF was stirred for 48 h at room temperature. Periodically 5.0-ml aliquots were quenched with aqueous NH_4Cl and extracted with hexane/dichloromethane. GLC–mass spectrometry with column E showed a product with a molecular ion at *m/e* 294 which was isolated by GLC on column B at 290 °C and identified as **10** by its 220-MHz NMR and mass spectra. Its yield maximized at 20% after 18 h. The only other product detected was 9,10-dihydrophenanthrene in a maximum yield of 17% after 80 min: NMR of **10** (CCl_4) δ 3.38 (d of d, J = 13, 6 Hz, 2 H), 3.77 (m, 3 H), 7.0–7.3 (m, 9 H), 7.51 (m, 4 H), 7.73 (m, 2 H), 8.60 (m, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 296 (5), 295 (32), 294 (100), 292 (15), 280 (10), 279 (44), 278 (14), 259 (12), 219 (13), 218 (13), 217 (14), 216 (41), 215 (28).

To determine the origin of the small *m/e* 296 peak in the mass spectrum, exact mass measurements were made on both the 294 and the 296 peaks: calcd for $C_{23}H_{18}$, 294.1409; found, 294.1407; calcd for $^{13}C_2{}^{12}C_{21}H_{18}$, 296.1477; found, 296.1478.

In an attempt to identify cycloadduct **11** before oxidation to **10**, the reaction was repeated, the entire isolation procedure was carried out in a N_2 atmosphere, and the solution of product in THF and hexane was stored at −20 °C until analysis. GLC–mass spectrometry showed a mass spectrum identical with that obtained when the hydrolyzed reaction mixture was handled in air.

Acenaphthylene and 1 HMPA. A solution of 15 mmol of acenaphthylene and 15 mmol of 1 HMPA in 50 ml of THF was stirred for 4.0 h at room temperature. Periodically 5.0-ml aliquots of the solution were quenched in aqueous NH_4Cl, extracted with hexane/dichloromethane, and analyzed by GLC on column E. GLC–mass spectrometry showed only one product, which had a molecular ion at *m/e* 270. Its yield maximized at 43% after 1.0 min. It was isolated by GLC on column C at 300 °C and was identified by 220-MHz NMR and mass spectra as **12**: NMR (CCl_4) δ 2.65 (d of d, H_a, J_{ab} = 14.5, J_{ac} = 10 Hz), 3.04 (d of d, H_e, J_{de} = 17, J_{ce} = 3 Hz), 3.11 (d of d, H_b, J_{bc} = 5 Hz), 3.40 (d of d, H_d, J_{cd} = 8 Hz), 3.73 (m, H_c), 5.14 (s, H_g), 5.26 (s, H_f), 7.1–7.6 (m, 11 H); mass spectrum *m/e* (rel intensity) 270 (5), 253 (3), 189 (2), 165 (16), 154 (30), 153 (100), 152 (100), 127 (4), 126 (5), 115 (22).

Exact mass calcd for $C_{21}H_{18}$, 270.1409; found, 270.1410.

Anthracene and 1 HMPA. A solution of 15 mmol of anthracene and 15 mmol of 1 HMPA in 50 ml of THF was stirred for 98 h at room temperature. Periodically 5.0-ml aliquots of the solution were quenched in aqueous NH_4Cl, extracted with hexane/dichloromethane, and analyzed by GLC on column E. An aliquot taken after 0.5 min showed a single peak in 51.5% yield. Subsequent aliquots showed two GLC peaks. The first decreased and the second increased in area with time until after 98 h their yields were 6 and 27%, respectively. By GLC–mass spectrometry both compounds had molecular ions at *m/e* 296. 9,10-Dihydroanthracene also was detected by GLC–mass spectrometry. Its yield maximized at 8% after 18 h and then decreased to 0.7% after 98 h.

The reaction was repeated twice. One mixture was hydrolyzed after 0.5 min and the other after 98 h. After the usual extractions and drying, anthracene was precipitated from the first mixture by addition of hexane. Removal of solvent and α-methylstyrene under vacuum left a light yellow oil which was chromatographed with hexane over a 1 × 20 cm column of silica gel. Evaporation of solvent left a colorless oil which was stored at −10 °C under vacuum because it turned yellow when exposed to air. GLC analysis of yellowed material showed several new peaks in addition to the compound originally isolated. The colorless oil was identified as acyclic adduct **13** by its 220-MHz NMR and mass spectra: NMR (CCl_4) δ 2.70 (br d, H_a, J_{ab} = 7 Hz), 3.82 (d, H_d, J_{cd} = 18.5 Hz), 3.88 (t, H_b), 3.96 (br d, H_c), 4.50 (br d, H_f, J_{ef} = 2 Hz), 5.10 (d, H_e), 6.8–7.5 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 296 (0.69), 294 (3.98), 181 (9), 180 (85), 179 (100), 178 (98), 177 (26), 176 (38), 152 (20), 151 (15).

Anal. Calcd for $C_{23}H_{20}$: C, 93.20; H, 6.80. Found: C, 93.19; H, 6.94.

The product from the reaction mixture hydrolyzed after 98 h was isolated by GLC on column B at 290 °C and identified as **14** by its 220-MHz NMR and mass spectra: NMR (CCl_4) δ 1.69 (t, H_b, J_{ab} = J_{bc} = 12 Hz), 2.06 (quintet, H_a, J_{ac} = J_{ad} = 6 Hz), 2.21 (m, H_c), 4.02 (d, H_d), 6.75–7.25 (m, 13 H); mass spectrum (70 eV) 296 (83), 219 (9), 218 (45), 217(17), 203(14), 193 (21), 192 (99), 191 (96), 190 (17), 189 (35).

Exact mass (70 eV) calcd for $C_{23}H_{20}$, 296.1566; found, 296.1565.

α,α'-Difluorostilbene[33] was prepared by reaction of tetrafluoroethylene and phenyllithium[34] in THF at −78 °C and recrystallized from 95% ethanol: mp 72–73 °C (lit.[33] mp 74 °C); ^{19}F NMR (CCl_4) δ 154.3 ppm from $CFCl_3$ (s, $J_{^{13}CCF}$ = 92, $J_{^{13}CF}$ = 281, J_{FF} = 121 Hz).

α,α'-Difluorostilbene and 1 HMPA. A solution of 15 mmol of difluorostilbene and 15 mmol of 1 HMPA in 50 ml of THF was stirred for 4.0 h at room temperature. Periodically 2.0-ml aliquots of the solution were analyzed by GLC on column E. Two products were detected in 12.7 and 1.4% yield after 1.0 min. Both had molecular ions at *m/e* 314 by GLC–mass spectrometry. They were isolated separately by GLC on column A at 290 °C and identified by their ^1H NMR, ^{19}F NMR, and mass spectra as isomers of 1,2,4-triphenyl-1-fluoro-1,4-pentadiene **15a** and **15b:** NMR (CCl_4) of major isomer δ 3.57 (m, 2 H), 5.15 (m, 1 H), 5.30 (m, 1 H), 7.0–7.6 (m, 15 H); ^{19}F NMR δ 99.6 (s); mass spectrum (70 eV) *m/e* (rel intensity) 314 (100), 295 (6), 294 (18), 238 (4), 237 (16), 236 (83), 235 (13), 224 (16), 223 (83), 222 (13).

Exact mass calcd for $C_{23}H_{19}F$, 314.14717; found 314.14643.

NMR (CCl_4) of minor isomer δ 3.72 (m, 2 H), 4.99 (m, 1 H), 5.18 (m, 1 H), 6.7–7.5 (m, 15 H); ^{19}F NMR δ 99.6 (s); mass spectrum (70 eV) *m/e* (rel intensity) 314 (100), 295 (4), 294 (15), 238 (2), 237 (15), 236 (61), 235 (11), 224 (12), 223 (39), 222 (12). The yields of the two isomers were 13 and 2% in samples taken from 1.0 min to 4 h reaction time.

***trans*-1,1,1,4,4,4-Hexafluoro-2,3-diphenyl-2-butene (16)**[35] was prepared by reaction of phenyllithium and perfluoro-2-butene at room temperature and recrystallized from ethanol, mp 181–182 °C (lit.[35] mp 179–181 °C).

16 and 1 HMPA. A solution of 3.0 mmol of 1 HMPA in 10 ml of THF was chilled to 0 °C and added to 3.0 mmol of **16.** The mixture was stirred at 0 °C and sampled as usual. GLC–mass spectrometry with column E showed a single sharp product peak with a molecular ion at *m/e* 414. Its yield maximized at 38% after 90 min. This material was isolated by GLC on column A at 260 °C and identified by its 60-MHz ^1H NMR, ^{19}F NMR, and mass spectra as a 70/30 mixture of isomers **17a** and **17b.** NMR (CCl_4) of major isomer δ 2.82 (t, J_{HF} = 17 Hz, 2 H), 4.94 (m, 1 H), 5.31 (m, 1 H), 6.7–7.3 (m); ^{19}F NMR δ 84.3 (t, *J* = 2 Hz, 3 H), 85.6 (t, *J* = 17 Hz, 2 H).

NMR of minor isomer δ 3.20 (t, J_{HF} = 17 Hz, 2 H), 5.25 (m, 1 H), 5.43 (m, 1 H), 6.7–7.3 (m). ^{19}F NMR same as major isomer; mass spectrum of mixture (70 eV) *m/e* (rel intensity) 414 (13), 413 (47), 394 (12), 290 (11), 278 (13), 277 (60), 180 (100). The composition of the mixture did not change in samples taken from 1.5 to 91 h.

Anal. of mixture. Calcd for $C_{25}H_{19}F_5$: C, 72.46; H, 4.62. Found: C, 72.36; H, 4.62.

2-[(*E*)-2-Phenylethenyl]-4,4-dimethyloxazoline (18). By a general procedure[36] 0.44 mol of 2-amino-2-methyl-1-propanol and 0.22 mol of cinnamoyl chloride gave a 67% yield of *N*-(2,3-dimethyl-3-hydroxypropyl)cinnamide (**22**), mp 133–134 °C.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.38. Found: C, 71.38; H, 7.91; N, 6.40.

Treatment of 0.15 mol of **22** with 0.31 mol of thionyl chloride by a general procedure[36] gave a colorless oil which was distilled to give a 32% yield of **18,** bp 187 °C (25 mm) [lit.[37] bp 112–120 °C (0.4–0.6 mm)].

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.57; H, 7.51; N, 6.90. Found: C, 77.72; H, 7.28; N, 7.22.

18 and 1 HMPA. A solution of 15.0 mmol of **18** and 15.0 mmol of 1 HMPA in 50 ml of THF was stirred for 22 h at room temperature. Periodically 5.0-ml aliquots were quenched in 50% aqueous $NaHCO_3$, washed with two portions each of dilute NaOH, dilute $NaHCO_3$, and water, and dried over $MgSO_4$. GLC on column E showed a single product which had a molecular ion at *m/e* 319 by GLC–mass spectrometry. It was isolated by liquid chromatography on a 3 × 60 cm silica gel column at a flow rate of 1000 ml/h of 78% dichloromethane, 20% acetonitrile, and 2% diethyl ether (by volume) in the fractions collected between 800 and 1700 ml of eluate. After evaporation of solvent, the remaining colorless oil was identified as **19** by its IR, ^1H NMR, and mass spectra, and by chemical conversion to **21b.** NMR (CCl_4) of **19** δ 1.00 (s, 3 H), 1.09 (s, 3 H), 2.48 (AB q of d, Δδ = 27 Hz, H_a at δ 2.42 and H_b at δ 2.54, J_{ab} = 15, J_{ac} = 8, J_{bc} = 7 Hz), 2.70 (d of d, H_d, J_{cd} = 8.5, J_{de} = 14 Hz), 3.01 (d of d, H_e, J_{ce} = 6 Hz), 3.14 (m, H_c), 3.59 (s, 2 H), 4.81 (m, 1 H), 5.13 (m, 1 H), 7.0–7.3 (m, 10 H); IR (neat) 3060 (m), 2990 (s), 1670 (s), 1450 (m), 1360 (m), 1270 (s), 1200 (s), 1040 (m), 1000 (s), 900 (m), 775 (s), 710 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 319 (5), 201 (32), 200 (19), 187 (15), 186 (100), 170 (12), 158 (11), 130 (29), 115 (29), 113 (14).

Exact mass calcd for $C_{22}H_{25}NO$, 319.1938; found, 319.1933.

3,5-Diphenyl-4-hexenoic Acid (21a). Oxazoline **19** (4.3 g) was hydrolyzed in 15 min in boiling 3 N HCl to 3.6 g of waxy solid, which was purified by liquid chromatography through a 3 × 60 cm column of silica gel with 10% methanol in CH_2Cl_2 (by volume). The recovered white solid was identified as **21a** by IR, NMR, and mass spectra and reduction to alcohol **21b:** NMR (CCl_4) δ 2.1 (d, *J* = 1 Hz, CH_3), 2.75 (d, *J* = 8 Hz, $H_a + H_b$), 4.2 (q, H_c), 5.85 (d, J_{cd} = 9 Hz, H_d), 7.3 (br s); IR (KBr) 3090 (m), 2950 (m), 1710 (s), 1500 (m), 1450 (m), 1420 (m), 1300 (m), 1260 (m), 950 (m), 760 (s), 700 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 266 (20), 251 (12), 208 (18), 207 (98), 206 (15), 192 (11), 191 (26), 178 (13), 130 (14), 129 (100), 127 (26).

Exact mass calcd for $C_{18}H_{18}O_2$, 266.13047; found, 266.13042.

3,5-Diphenyl-4-hexen-1-ol (21b). By a general procedure[38] 1.4 g of **21a** was reduced with $LiAlH_4$ in THF to a light yellow oil. Chromatography through a 3 × 60 cm silica gel column with 2% diethyl ether in CH_2Cl_2 gave 1.05 g of a colorless oil. GLC analysis on column E showed three sharp peaks with relative areas of 6.25, 8.75, and 85.0, respectively. GLC–mass spectrometry showed molecular ions at *m/e* 252 and nearly identical fragmentation patterns for all three compounds. The major component of the oil was identified by Eu(fod)$_3$-shifted NMR spectra of the mixture as **21b** (see Results): NMR (CCl_4) δ 2.1 (d, *J* = 2 Hz, CH_3), 1.9 (q, *J* = 7 Hz, $H_a + H_b$), 2.5 (br s, OH), 3.55 (t, *J* = 7 Hz, CH_2OH), 3.85 (m, $J_{ac} = J_{bc}$ = 7, J_{cd} = 9 Hz, H_c), 5.9 (br d, H_d), 7.2 (m); IR of mixture (C_2Cl_4) 3620 (m), 3080 (m), 3060 (m), 3040 (s), 2940 (s), 1600 (m), 1500 (s), 1450 (m), 1400 (m), 1380 (m), 1050 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 252 (16), 219 (13), 208 (23), 207 (100), 178 (10), 129 (13), 128 (78), 127 (16), 118 (27), 116 (27).

Exact mass calcd for $C_{18}H_{20}O$, 251.1515; found, 251.1515.

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.98. Found: C, 85.41; H, 7.98.

α-Methylstyrene, *trans*-Stilbene, and LDIA. To a solution of 15.0 mmol of LDIA in 50 ml of THF was added 15.0 mmol of α-methylstyrene and 15.0 mmol of *trans*-stilbene, and the solution was held at 45 ± 2 °C for 166 h. Samples of the reaction mixture were isolated and analyzed as described for experiments with 1 HMPA. GLC–mass spectral analyses showed four principal fractions of which the first three were isolated. The first was identified by its 220-MHz ^1H NMR spectrum as 2. Yields of all four components increased throughout the reaction to 27.9, 6.2, 5.7, and 1.3% after 166 h, in order of increasing GLC retention time.

***cis*-Stilbene and LDIA.** A solution of 15 mmol of LDIA and 15 mmol of *cis*-stilbene in 50 ml of THF was held at 45 ± 2 °C. The *cis*-stilbene was 43% isomerized after 0.66 h and 99% isomerized after 19 h by GLC on column D.

***cis*-Stilbene-α,α'-d_2 and LDIA.** A solution of 3.0 mmol of LDIA and 3.0 mmol of *cis*-stilbene-α,α'-d_2 in 10.0 ml of THF was held at 45 °C for 4.5 h and hydrolyzed in the usual manner. Analytical GLC on column D showed 53% *cis*- and 47% *trans*-stilbene. Each isomer was collected by preparative GLC on column A at 230 °C. Deuterium analysis by mass spectrometry showed 90% d_2, 9% d_1, and 1% d_0 for *cis*-stilbene and 50% d_2, 48% d_1, and 2% d_0 for *trans*-stilbene.

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Registry No.—**1,** 58688-36-1; 1 HMPA, 61062-62-2; **2,** 58688-37-2; **3,** 36963-72-1; **4,** 5155-87-3; **5,** 61025-10-3; **7a,** 61025-11-4; **7b,** 61091-26-7; **8a,** 61025-12-5; **8b,** 61025-13-6; **9,** 61025-14-7; **10,** 61025-15-8; **12,** 61025-16-9; **13,** 61025-17-0; **14,** 61025-18-1; **15a,** 61025-19-2; **15b,** 61025-20-5; **16,** 29030-86-2; **17a,** 61025-21-6; **17b,** 61025-22-7; **18,** 61025-23-8; **19,** 61025-24-9; **21a,** 61025-25-0; **21b,** 61025-26-1; α-methylstyrene, 98-83-9; *N*-bromosuccinimide, 128-08-5; 3-bromo-2-phenylpropene, 3360-54-1; 1-bromo-2-phenylpropene, 3360-53-0; chlorotriphenyltin, 639-58-7; *trans*-stilbene, 103-30-0; *cis*-stilbene, 645-49-8; *trans*-β-methylstyrene, 873-66-5; *cis*-β-methylstyrene, 766-90-5; 1,1-diphenylethylene, 612-00-0; phenanthrene, 85-01-8; acnaphthylene, 208-96-8; anthracene, 120-12-7; α,α'-difluorostilbene, 20488-54-4; 2-amino-2-methyl-1-propanol, 124-68-5; cinnamoyl chloride, 102-92-1; *N*-(2,3-dimethyl-3-hydroxypropyl)cinnamide, 30687-08-2; LDIA, 4111-54-0; tetrafluoroethylene, 116-14-3; phenyllithium, 591-51-5.

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Rate Enhancement of the Meerwein–Ponndorf–Verley–Oppenhauer Reaction in the Presence of Proton Acids[1]

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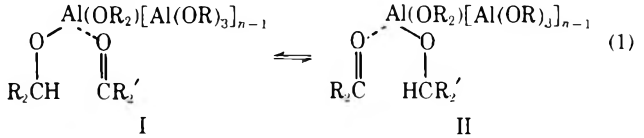
The effects of various protic acids upon the aluminum *tert*-butoxide catalyzed oxidation of cyclohexanol by benzaldehyde are studied. The rate of oxidation is found to be markedly enhanced by an acid to aluminum ratio of 0.5 for HCl, FSO_3H, $CH_3CH_2CO_2H$, and CF_3CO_2H, with CF_3CO_2H giving the greatest rate enhancement. Synthetic applications of this method, however, are limited by the observation that trifluoroacetic acid–aluminum alkoxide mixtures are potent aldol catalysts.

The Meerwein–Ponndorf–Verley–Oppenhauer (MPVO) reaction is the aluminum alkoxide catalyzed equilibration of alcohols with aldehydes or ketones[2], eq 1. A key step in the

$$R_2CHOH + R_2'CO \xrightleftharpoons{[Al(OR)_3]_n} R_2CO + R_2'CHOH$$



(1)

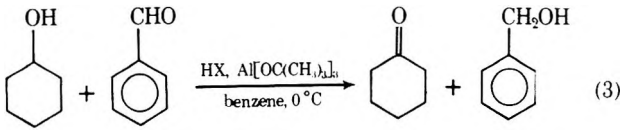
I II

reaction is thought to be hydride transfer within the polymeric aluminum complexes I and II.[3]

Replacement of alkoxy groups on aluminum with more electronegative ligands should increase the rate of MPVO reactions by facilitating coordination of aluminum to the carbonyl compound.[4] This replacement should be achieved most simply by addition of a suitable proton acid (HX) to a solution of the aluminum alkoxide (eq 2).

$$[Al(OR)_3]_n + HX \rightarrow HOR + [XAl(OR)_2]_n \quad (2)$$

For study, we chose the reaction between cyclohexanol and benzaldehyde catalyzed by aluminum *tert*-butoxide in benzene solution at 0 °C (eq 3). The rate of reaction was followed by removing aliquots at various times and analyzing by GLC for cyclohexanone. With a twofold excess of benzaldehyde, equilibrium is established when 88% of the starting cyclohexanol is converted to cyclohexanone. Results obtained in the presence of a variety of proton acids are shown in Table I.



(3)

The most effective catalyst is trifluoroacetic acid, present at an acid to aluminum ratio of 0.5. Data obtained with this acid are presented graphically in Figure 1.

With all acids studied, the reaction fails when a critical ratio of acid to aluminum is exceeded. In some cases this is perhaps due to the precipitation of aluminum compounds which occurs with the higher ratios of acid. However, with trifluoroacetic acid no precipitate is formed at an acid to aluminum ratio of 2.0, yet at this point the MPVO reaction fails. It is conceivable that only nonbridging alkoxy groups in complexes I and II are able to transfer hydride[5] and that at a critical acid to aluminum ratio all such groups are replaced with trifluoroacetate ligands.

^1H NMR examination of the catalyst system is hampered by precipitation of aluminum compounds in the absence of added alcohol or aldehyde. Thus, when 0.3 equiv of trifluoroacetic acid was added to aluminum *tert*-butoxide in benzene, a precipitate was formed and ^1H NMR analysis of the supernatent revealed only the normal spectrum of the aluminum *tert*-butoxide dimer[6] together with 0.3 equiv of *tert*-butyl alcohol.

Table I. MPVO Reaction of Cyclohexanol with Benzaldehyde in the Presence of Proton Acids (HX)[a]

Registry no.	HX	HX/Al[b]	T_{50}[c]	T_{80}[d]
	e		8	80
76-05-1	CF_3CO_2H	0.5	<1	1
	CF_3CO_2H	1.0	<1	5
	CF_3CO_2H	2.0	*f*	
7647-01-0	HCl	0.5	<1	9
	HCl	1.0	*f*	
79-09-4	$CH_3CH_2CO_2H$	0.5	5	40
	$CH_3CH_2CO_2H$	1.0	*f*	
7789-21-1	FSO_3H	0.5	2	30
	FSO_3H	1.0	*f*	

[a] Reactions run at 0 °C in benzene solutions, 1 M in cyclohexanol, 2 M in benzaldehyde, and 0.05 M in $Al[OC(CH_3)_3]_3$. [b] Molar ratio of proton acid to Al. [c] Time in minutes for 50% of the starting cyclohexanol to be oxidized to cyclohexanone. [d] Time in minutes for 80% of the starting cyclohexanol to be oxidized to cyclohexanone. [e] No proton acid was added. [f] No oxidation of starting cyclohexanol occurred after at least 12 h.

We have observed rate enhancements for the trifluoroacetic acid promoted MPVO reaction of a number of alcohols with aldehydes or ketones. However, synthetic applications of the method are limited by the fact that trifluoroacetic acid–aluminum alkoxide mixtures are potent aldol catalysts, especially for simple aliphatic aldehydes. As an example, the rate of condensation of heptanal in benzene solutions containing aluminum *tert*-butoxide in the presence and absence of trifluoroacetic acid was observed (eq 4).

$$CH_3(CH_2)_5CHO \xrightarrow[\text{benzene, 0 °C}]{Al(OR)_3} CH_3(CH_2)_5CHOHCH(CHO)(CH_2)_4CH_3 \quad (4)$$

With no added trifluoroacetic acid, 50% of the heptanal was condensed in 3 h. In the presence of trifluoroacetic acid (acid to aluminum ratio of 0.5), over 90% of the aldehyde was condensed in 5 min. Trifluoroacetic acid alone, in the absence of aluminum alkoxide, did not cause condensation.

Experimental Section

Trifluoroacetic acid was obtained from Matheson Coleman and Bell. Fluorosulfonic acid was obtained from Aldrich Chemical Co. Hydrogen chloride gas was purchased in a lecture bottle from Matheson Gas Corp. Propanoic acid was obtained from Fisher Scientific Co. Aluminum *tert*-butoxide was obtained from Alfa Inorganics and stored in a vacuum desiccator. Benzene was dried by distillation from calcium hydride and stored under a nitrogen atmosphere. Other reagents were obtained commercially and distilled before use. GLC analyses were performed on a Varian 920 gas chromatograph equipped with a 4 ft × 0.25 in. stainless steel column of 10% Carbowax 20M on Chromosorb W 80/100 mesh. ^1H NMR spectra were determined on a Varian T-60.

MVPO Reactions. The following procedure for the oxidation of cyclohexanol with benzaldehyde using aluminum *tert*-butoxide and trifluoroacetic acid (acid/aluminum ratio of 0.5) is representative. A 100-ml round-bottomed flask equipped with a septum inlet, magnetic stirring, and mercury bubbler is flushed with nitrogen and charged with 0.246 g (1 mmol) of aluminum *tert*-butoxide dissolved in 20 ml of benzene. The flask is immersed in an ice–water bath and stirring is initiated. Cyclohexanol (2.08 ml, 20 mmol) is injected, followed by 37 μl (0.5 mmol) of trifluoroacetic acid. Tridecane (2.44 ml, 10 mmol) is added as GLC standard. After 5 min of stirring, benzaldehyde (4.08 ml, 40 mmol) is injected to start the reaction. One-milliliter aliquots are removed periodically and quenched by addition to 4 ml of a saturated solution of tartaric acid in H_2O (to dissolve aluminum salts), extracted with 8 ml of pentane, dried with $MgSO_4$, and analyzed by GLC for cyclohexanone.

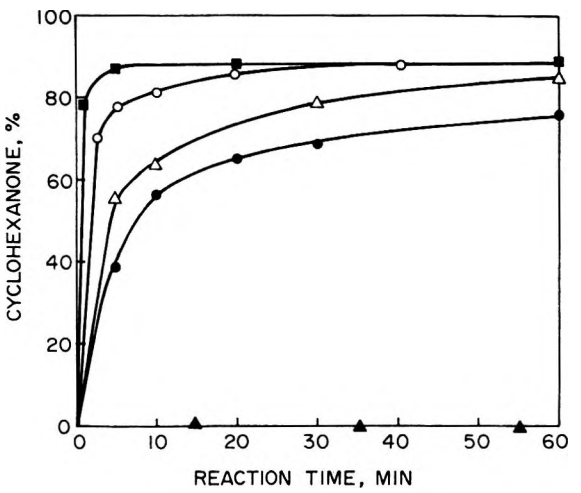


Figure 1. Formation of cyclohexanone in the trifluoroacetic acid promoted MPVO reaction of cyclohexanol with benzaldehyde: ●, no HX; △ HX/Al 0.1; ■, HX/Al 0.5; ○, HX/Al 1.0; ▲, HX/Al 2.0

Aldol Condensation of Heptanal. A solution of aluminum *tert*-butoxide (0.123 g, 0.5 mmol) in benzene (10 ml) containing 0.73 ml (2.5 mmol) of hexadecane as internal GLC standard is cooled in an ice–water bath. Heptanal (1.35 ml, 10 mmol) is injected and aliquots are removed periodically and analyzed for remaining heptanal. After 2 days of stirring the aldol product, 2-*n*-pentylnonanal was isolated by preparative GLC and identified by infrared spectroscopy. Experiments in the presence of trifluoroacetic acid were conducted in a similar fashion except that 18.5 μl (0.25 mmol) of CF_3CO_2H was added prior to addition of heptanal.

^1H NMR Examination of Catalyst System. ^1H NMR spectra were obtained on 0.1 M solutions of aluminum *tert*-butoxide in benzene containing internal tetramethylsilane standard. After addition of trifluoroacetic acid the precipitate was allowed to settle and spectra of the clear supernatant were obtained. The amount of *tert*-butyl alcohol formed on addition of acid was determined by integration of spectra for solutions containing known amounts of anisole as internal integration (methoxy signal) standard. The assignment of ^1H NMR signals was based on Shiner's report:[6] δ 1.5, singlet (bridging *tert*-butoxy); 1.4, singlet (nonbridging *tert*-butoxy); 1.1, singlet (*tert*-butyl alcohol).

Registry No.—$Al[OC(CH_3)_3]_3$, 3099-76-1; cyclohexanol, 108-93-0; benzaldehyde, 100-52-7.

References and Notes

(1) Grateful acknowledgment is made to the National Science Foundation for partial support of this work.

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Fluorochloro-, Fluorobromo-, and Monofluorocarbene Generation via Organolithium Reagents

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Low temperature (−116 °C) reactions of fluorotrichloromethane and fluorotribromomethane with *n*-butyllithium have been explored as routes to fluorochloro- and fluorobromocyclopropanes and gave moderate yields with tetrasubstituted olefins. Fluorodichloromethyllithium showed little stability even at −116 °C. Fluorodibromomethyllithium gave reasonably good yields of cyclopropanes with tetra-, tri-, and disubstituted olefins. The reactions were stereospecific with *cis*- and *trans*-2-butene. The *Z*/*E* ratios with 2-methyl-2-butene and cyclohexene implicate lithium carbenoid as the reactive species. Except for monosubstituted olefins, this synthetic approach permits a facile synthesis of fluorobromocyclopropanes. Direct attempts at fluorocarbene generation via lithium reagents met with little success. In situ reduction of fluorobromocyclopropanes—from olefin and fluorodibromomethyllithium—gave fluorocyclopropanes in an overall yield of ~20%.

Halogenated carbenes are classically generated via the base hydrolysis of haloforms. Acid–base reactions of the carbon acids generate a trihalomethyl carbanion which subsequently eliminates halide ion to generate the carbene.

$$CHXYZ \xrightarrow{base} {}^{-}CXYZ \rightarrow [:CXY] + Z^{-}$$

In some cases (i.e., bromodifluoromethane), this process is considered to be concerted.

The role of organolithium reagents in the generation of nonfluorinated halocarbenes has been thoroughly investigated.[1] However, few studies on organolithium generated fluorocarbenes have been reported. Fluorochlorocarbene generation from fluorodichloromethane and *n*-butyllithium appears comparable with generation by other bases.[2] The best preparation of fluorobromocarbene is base hydrolysis of fluorodibromomethane.

A logical improvement to the base hydrolysis of haloforms with organolithium reagents might be expected to be the utilization of lithium–halogen exchange reactions rather than the classic metalation (lithium–proton exchange) reactions. In other systems, lithium–halogen exchange has been shown to be up to several orders of magnitude faster than metalation.[3] In reactions to form vinyl organolithium reagents, increased velocity of lithium–halogen exchange eliminates the problem of side reactions found in metalation.[4] Lithium–halogen exchange has been used in a number of carbene-formation reactions, but no successful fluorochloro- or fluorobromocarbene generation using this method has been reported.

This paper describes the synthetic utility of lithium–halogen exchange reactions in the generation of fluorochloro-, fluorobromo-, and monofluorocarbenes (carbenoids) for cyclopropanation reactions. Fluorobromocyclopropanes and to a lesser extent fluorochlorocyclopropanes can be successfully generated.

Results and Discussion

Fluorotrichloromethane is a convenient and inexpensive fluorochlorocarbene precursor, although lithium–chlorine exchange is generally not greatly faster than the metalation reactions. Generally, lithium carbenoids are stabilized by low reaction temperatures and coordinating solvents. Table I shows the results when an equimolar amount of *n*-butyllithium in hexane is added to olefins and fluorotrichloromethane in THF at −116 °C. The yields are quite similar to those of the reaction of *n*-butyllithium with fluorodichloromethane reported by Schlosser.[2] Although the yield of 2,3-dimethyl-2-butene is moderate, the yields fall drastically for less substituted olefins. Apparently, the electrophilic carbenoid intermediate is effectively trapped only by olefins with high electron density.

The reaction with 2-methyl-2-butene is stereoselective, forming a greater amount of the more sterically hindered *Z* isomer. The *Z*/*E* ratio of 2.4 is similar to that reported in other methods of generation.[5] Reaction with *trans*-2-butene is completely stereospecific, indicating that cyclopropanation probably proceeds via a concerted addition.

Stabilization of the carbenoid intermediate is important in these reactions. When the reaction of 2,3-dimethyl-2-butene is carried out at −78 °C, the yield of cyclopropane drops from 49% to 35%. The temperature, however, is limited to −116 °C on the lower end by the freezing point of the reaction mixture. The solvent is also important in the stabilization of the intermediate. When the reaction of 2,3-dimethyl-2-butene is carried out in hexane rather than THF–hexane, the yield drops to 14%. Highly coordinating reagents also fail to improve the yields. For example, when 2,3-dimethyl-2-butene reacts in hexane with TMEDA coordinated *n*-butyllithium, only 7% cyclopropane is obtained. The reaction in an HMPA–THF–hexane solvent mixture gives only 24%.

When the reactions are carried out in excess olefin in the absence of solvent (the procedure used by Schlosser for reaction of chlorodifluoromethane) the yields are similar at −78 °C but reduced at −116 °C or at warmer temperatures. No significant improvement is observed to warrant the necessity of the excess olefin. It appears that lithium–chlorine exchange and metalation are quite similar in the generation of fluorodichloromethyllithium.

Attempts to pregenerate the carbenoid have failed. When fluorodichloromethyllithium is generated at −116 °C and then quenched with olefin or hydrogen chloride, none of the expected products were formed. These reactions indicate that the intermediate fluorodichloromethyllithium is not stable under the reaction conditions.

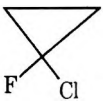
All of the results indicate that the yield of cyclopropane depends on the ability of the olefin to rapidly trap a transient carbenoid intermediate. The low stability of fluorodichloromethyllithium demonstrates the poorer carbanion stabilizing ability of fluorine when compared to chlorine. Trichloromethyllithium is stable to just above −90 °C;[1] however, fluorodichloromethyllithium is quite unstable even at −116 °C in this study.

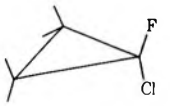
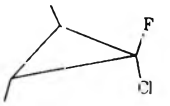
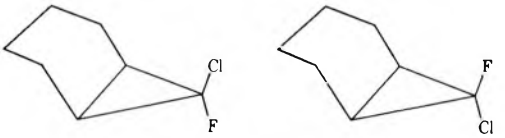
Fluorotribromomethane (**5**), a logical fluorobromocarbene precursor, is commercially available or can be readily prepared by fluorination of carbon tetrabromide.[6]

$$CBr_4 + SbF_3 + Br_2 \xrightarrow[\text{neat}]{125\text{–}150\ ^\circ C} \underset{\mathbf{5}}{CFBr_3}$$

Table I. Preparation of Fluorochlorocyclopropanes in THF–Hexane

$$CFCl_3 + n\text{-BuLi} + \text{olefin} \xrightarrow[\text{THF–hexane}]{-116\ ^\circ C}$$



Olefin	Products	Yield,[a] %	Z/E ratio[a]
2,3-Dimethyl-2-butene	 1	49	
2-Methyl-2-butene	 (Z)-2 (E)-2	32	2.4
trans-2-Butene	 3	8	
Cyclohexene	 (Z)-4 (E)-4	0	

[a] Determined by ^{19}F NMR using benzotrifluoride as internal standard.

Since lithium–bromine exchange is much faster than metalation and bromine is a better carbanion stabilizer than chlorine, we would expect a more stable and more easily formed carbenoid than found with fluorotrichloromethane.

The results of the reaction of olefins with equimolar amounts of *n*-butyllithium and **5** at −116 °C in THF–hexane are recorded in Table II. The yields are recorded for reactions using freshly prepared base with magnetic stirring, freshly prepared base with mechanical stirring, and commercial base with mechanical stirring.

All of the olefins except 1-hexene afforded good yields of cyclopropanes. The monosubstituted 1-hexene is expected to be the least reactive of the olefins surveyed and this method of fluorobromocarbene generation is apparently not applicable for such unreactive olefins.

The reactions are greatly dependent on effective mixing, particularly the less reactive olefins with a relatively high melting point. The drastic change in yields from cyclohexene (from 19% to 57%) emphasizes the importance of efficient mixing at these low temperatures. The problem is underscored by the reactions of 2-methyl-2-butene. With magnetic stirring the yield of **7** is 44% at −116 °C but 59% at −98 °C where the solution is not nearly as viscous. With mechanical stirring, the yield is 71% at −116 °C, indicating that the intermediate carbenoid is more stable at the lower temperature.

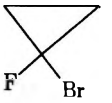
Reactions with *cis* and *trans*-2-butene indicate that cyclopropanation is stereospecific with no cis–trans or trans–cis scrambling, indicating that concerted addition is likely. All reactions of olefins possessing an axis of symmetry produce only one cyclopropane product and unsymmetrical olefins afford two products. The structural assignments of the geometrical isomers are easily made from the ^{19}F NMR.[7,8]

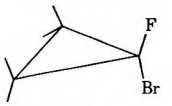
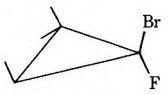
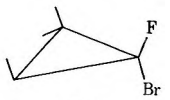
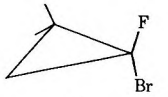
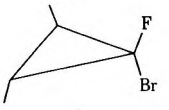
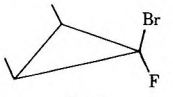
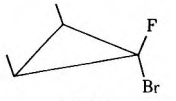
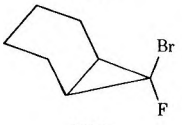
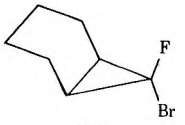
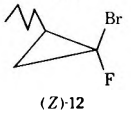
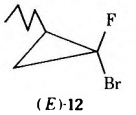
The *Z*/*E* ratios cited in Table II represent an average of at least four reactions. Note that the *Z*/*E* ratio of 1.8 for 2-methyl-2-butene is somewhat smaller than the *Z*/*E* ratio of 2.4 found for the addition of fluorochlorocarbene to the same olefin. This might be expected since, although bromine is more polarizable than chlorine (thus increasing the *Z*/*E* ratio), it is also more sterically hindered (thus decreasing the *Z*/*E* ratio). The difference in *Z*/*E* ratios found here underscores the importance of the balance of electronic and steric factors in determining the stereoselectivity of cyclopropanation reactions. The magnitude of the *Z*/*E* ratio indicates that the reactive species is a carbenoid rather than a free carbene.

Using 10 equiv of each olefin, the relative reactivities of the various olefins toward fluorobromocarbene generated from **5** and *n*-butyllithium were investigated. The internal consistency of the results was not good, and the values obtained from individual competition reactions could not be reproduced accurately. These difficulties probably are a direct result of the reaction solutions at this temperature being quite viscous and at times semisolid. Although mechanical stirring is used, effective stirring may not be achieved and complete solvation of both olefins is not unequivocal. Also, relative reactivities of olefins toward cyclopropanation are temperature dependent in other carbene systems.[5] Lithium–bromine exchange is an exothermic process, and complete temperature control in the reaction flask is difficult when a slush bath is used at such low temperatures. Despite these difficulties and the lack of preciseness of the relative reactivity data, several conclusions can be drawn from the relative reactivity study. The order of relative reactivity of olefins toward fluorobromocarbene is definitely 2,3-dimethyl-2-butene > 2-methyl-2-butene > isobutylene > *cis*-2-butene > *trans*-2-butene > cyclohexene. This order is common to most carbene systems.[5] Similarly to other lithium carbenoids, the fluorobromocarbene precursor investigated here appears to be quite selective in its reactions with olefins, a fact that is reinforced by the failure of cyclopropanation in the case of 1-hexane.

Preparation of fluorocyclopropanes via the generation of monofluorocarbene with *n*-butyllithium has failed. Precursors investigated include fluorodibromomethane, fluorodiiodomethane, difluoromethane, and difluorobromomethane; however, none of the yields were greater than 10%. Fluorocyclopropanes can, however, be formed by in situ reduction of fluorobromocyclopropanes with trimethyltin hydride. The reaction mixture from the preparation of fluorobromocyclopropanes is simply refluxed with lithium aluminum hydride

Table II. Preparation of Fluorobromocyclopropanes



Olefin	Products	Yields,[a] % Mechanical stirring	Commercial n-BuLi	Magnetic stirring	Z/E ratio
2,3-Dimethyl-2-butene	 6	73	61	53	
2-Methyl-2-butene	 (Z)-7  (E)-7	71	70	44	1.8 ± 0.2
Isobutylene	 8	60	55		
trans-2-Butene	 9			57	
cis-2-Butene	 (Z)-10  (E)-10		60	68	2.4 ± 0.4
Cyclohexene	 (Z)-11  (E)-11	57	47	19	2.9 ± 0.8
1-Hexene	 (Z)-12  (E)-12	Trace	Trace	Trace	

[a] Determined by integration of ^{19}F NMR using benzotrifluoride as an internal standard.

and trimethyltin hydride for 24–48 h using this method. 1-Fluoro-2,2,3,3-tetramethylcyclopropane is formed in 21% yield based on starting olefin. Isolation of products from some of the simple olefins (such as butene) can be difficult, since fluorocyclopropanes are generally low boiling and cannot be easily separated from the solvents (ether, hexane, and THF) used in this reaction. While this method is not as simple and does not give comparable yields to the photolysis of fluorodiiodomethane,[9] it does provide a convenient route from 2-substituted olefins which are unreactive via the photolysis method.

Experimental Section

All ^{19}F NMR spectra were recorded with a Varian HA-100 spectrometer operated at 94.075 MHz. Chemical shifts are reported in parts per million upfield from internal $CFCl_3$ and coupling constants are reported in hertz. ^1H NMR spectra were recorded with a Varian A-60 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-66 spectrometer. Analytical gas chromatography (GLC) was performed on a Hewlett-Packard 5750 chromatograph, and preparative GLC was performed with a Varian Autoprep A-700. The procedure of Jones and Gilman[10] was used for the preparation of *n*-butyllithium and the concentration determined by the method of Gilman and Cartledge.[11]

General Procedure for the Preparation of Fluorochloro- and Fluorobromocyclopropanes. A 50-ml round-bottom flask with septum port is oven dried and thoroughly flushed with argon. If a gaseous olefin is to be reacted, the flask is equipped with a cold-finger condenser which is filled with dry ice–2-propanol and connected to an argon reservoir. If a liquid olefin is to be reacted, the flask is equipped with a glass "T" connected to an argon reservoir. The reaction flask is equipped with a magnetic or mechanical stirrer and cooled in an ethanol slush bath (−116 °C). The flask is charged with 15 ml of dry THF (distilled from benzophenone ketyl) and 1.37 g (10 mmol) of fluorotrichloromethane (Du Pont) or 2.707 g (10 mmol) of fluorotribromomethane (**5**),[12] and 10 mmol of olefin. With vigorous stirring, 10 mmol of *n*-butyllithium in hexane is very slowly (over approximately 20 min) added to the reaction via syringe. The reaction mixture is stirred at −116 °C for approximately 0.25 h after the addition is complete. Then 1 ml of water is added to quench any remaining *n*-butyllithium, the reaction mixture is allowed to warm to room temperature, and 0.438 g (3 mmol) of benzotrifluoride is added for internal ^{19}F NMR standard.

The reaction mixtures are analyzed and yields determined by ^{19}F NMR. The product cyclopropanes are isolated by preparative [10 ft × 0.5 in., 20% silicone gum rubber (SE-30)] or analytical [10 ft × 0.25 in., 20% silicone gum rubber (SE-30)] GLC after the low boiling solvent is removed by fractional distillation through a 2 × 50 mm vacuum-jacketed glass helices column.

1-Fluoro-1-chloro-2,2,3,3-tetramethylcyclopropane (1). ^{19}F NMR ϕ^* 148.0 ppm agrees with previously reported values.[8,13] Mass spectrum *m/e* (rel intensity) 137 [(P + 2) − 15] (1), 135 (P − 15) (2), 115 (27), 114 (100), 99 (90), 97 (14), 85 (13), 79 (45), 77 (32), 73 (21), 61 (11), 59 (26), 55 (11), 53 (45), 51 (17), 42 (12), 41 (34), and 39 (36).

1-Fluoro-1-chloro-2,2,3-trimethylcyclopropane (2). The *Z* and

E isomers could not be separated via glc. ^{19}F NMR (*Z*)-**2** ϕ^* 138.2 ppm, $J_{F,H\text{-}cis}$ = 20.4 Hz. (*E*)-**2** ϕ^* 154.3 ppm agrees with previously reported values.[8,13] Mass spectrum *m/e* (rel intensity) 123 [(P + 2) − 15] (8), 121 (P − 15), 102 (100), 100 (10), 93 (13), 85 (29), 81 (12), 79 (10), 73 (36), 72 (62), 71 (60), 65 (15), 61 (18), 59 (25), 57 (5), 56 (16), 55 (17), 53 (23), and 51 (9).

1-Fluoro-1-chloro-*trans*-2,3-dimethylcyclopropane (3). ^{19}F NMR ϕ^* 145.7 ppm, $J_{F,H\text{-}cis}$ = 22 Hz, agrees with previously reported values.[8,13] Mass spectrum *m/e* (rel intensity) 112 (P) (8), 87 (15), 85 (80), 84 (18), 71 (61), 70 (30), 57 (100), 55 (42), and 55 (26).

7-Fluoro-7-chloronorcarane (4). ^{19}F NMR analysis of the reaction solution indicates that **4** was not produced.

1-Fluoro-1-bromo-2,2,3,3-tetramethylcyclopropane (6). Owing to thermal instability **6** could not be isolated but was identified by enhancement of a NMR with an authentic sample[13] and also reduction of 1-fluoro-2,2,3,3-tetramethylcyclopropane. ^{19}F NMR ϕ^* 141.2 ppm (reported 140.4 ppm[13]).

1-Fluoro-1-bromo-2,2,3-trimethylcyclopropane (7). The *Z* and *E* isomers could not be efficiently separated by GLC. ^{19}F NMR (*Z*)-**7** ϕ^* 132.1 ppm, $J_{F,H\text{-}cis}$ = 20 Hz (reported 129.6 ppm, *J* = 23.5 Hz[14]). (*E*)-**7** ϕ^* 149.5 ppm. Mass spectrum *m/e* (rel intensity) 167 [(P + 2) − 15] (3), 165 (P − 15) (3), 146 (7), 101 (66), 100 (67), 99 (6), 86 (10), 85 (100), 81 (11), 79 (19), 77 (15), 73 (30), 72 (87), 71 (83), 65 (22), 61 (14), 59 (45) 57 (39), 56 (19), 55 (17), 53 (25), and 51 (17).

1-Fluoro-1-bromo-2,2-dimethylcyclopropane (8). ^{19}F NMR ϕ^* 137.0 ppm, $J_{F,H\text{-}cis}$ = 19 Hz. Mass spectrum *m/e* (rel intensity) 168 (P + 2) (1), 166 (P) (1), 153 (38), 151 (40), 87 (100), 86 (20), 85 (14), 71 (16), 67 (11), 59 (38), 51 (16), 41 (46), and 39 (26). These data agree well with the previously published values.[15]

1-Fluoro-1-bromo-*trans*-2,3-dimethylcyclopropane (9). ^{19}F NMR ϕ^* 141.9 ppm, $J_{F,H\text{-}cis}$ = 21 Hz (reported 142.2 ppm, *J* = 21 Hz[16]). Mass spectrum *m/e* (rel intensity) 168 (P + 2) (2), 166 (P) (2), 153 (10), 151 (10), 88 (10), 87 (100), 86 (11), 85 (18), 72 (11), 71 (21), 67 (20), 65 (11), 59 (69), and 57 (28).

1-Fluoro-1-bromo-*cis*-2,3-dimethylcyclopropane (10). The *Z* and *E* isomers could not be effectively separated by GLC. ^{19}F NMR (*Z*)-**10** ϕ^* 121.0 ppm, $J_{F,H\text{-}cis}$ = 22 Hz (reported 121.2 ppm, *J* = 20 Hz[16]), (*E*)-**10** ϕ^* 162.0 ppm (reported 161.9 ppm[16]). Mass spectrum *m/e* (rel intensity) 168 (P + 2) (3), 166 (P) (3), 153 (10), 151 (10), 87 (100), 85 (12), 72 (68), 71 (73), 67 (25), 65 (10), 59 (59), 57 (30), 56 (13), and 51 (11).

7-Fluoro-7-bromonorcarane (11). The two isomers could not be separated by GLC. ^{19}F NMR (*Z*)-**11** ϕ^* 118.0 ppm, $J_{F,H\text{-}cis}$ = 20 Hz (reported 117.6 ppm, *J* = 21 Hz[14]), (*E*)-**11** ϕ^* 155.2 ppm (reported 152.6 ppm[14]). Mass spectrum *m/e* (rel intensity) 96 (P − Br) (8), 86 (7), 85 (39), 84 (9), 71 (30), 70 (15), 57 (38), 56 (21), 55 (13), 43 (100), 42 (15), 41 (38), and 39 (11).

1-Fluoro-1-bromo-2-*n*-butylcyclopropane (12). Owing to the small quantities produced, **12,** was not isolated, but only observed in solution. ^{19}F NMR (*Z*)-**12** ϕ^* 126.5 ppm, (*E*)-**12** ϕ^* 149.4 ppm.

Competition Reactions. Reactions to determine the relative reactivities of various olefins toward fluorobromocarbene are carried out according to the following procedure. A 100-ml three-neck flask, equipped with rubber septum, mechanical stirrer, and cold-finger condenser filled with dry ice–2-propanol and connected to an argon reservoir, is oven dried and thoroughly flushed with argon. The flask is charged with 15 ml of dry THF and 2.707 g (10 mmol) of **5** and cooled to −116 °C in an ethanol slush bath. Each of the two olefins (100 mmol) is added to the reaction via syringe or condensation through the cold-finger condenser. With vigorous stirring, 10 mmol of freshly prepared *n*-butyllithium in hexane is slowly added to the reaction via syringe. The reaction mixture is stirred at −116 °C for approximately 0.25 h and then allowed to warm to room temperature. The reaction solution is too dilute for accurate analysis by ^{19}F NMR. Therefore, low-boiling olefins and solvent are removed by vacuum distillation through a 2 × 150 mm vacuum jacketed glass helices column. The temperature during distillation is maintained below 40 °C to minimize any thermal degradation.

The concentrated reaction mixture is analyzed using ^{19}F NMR. The relative yields are calculated by integration of the ^{19}F NMR peaks by cut and weigh. The order of relative reactivity is 2,3-dimethyl-2-butene > 2-methyl-2-butene > isobutylene > *cis*-2-butene > *trans*-2-butene > cyclohexene. While this order is consistent, the reactivity values calculated are not internally consistent and are not reproducible.

Preparation of Fluorocyclopropanes by in Situ Reduction. 1-Fluoro-2,2,3,3-tetramethylcyclopropane (13). In a typical procedure, a 50-ml three-neck flask equipped with septum port, mechanical stirrer, and water-cooled condenser connected to an argon reservoir through a glass "T" is oven dried and thoroughly flushed with argon. The flask is charged with 10 ml of dry THF, 2.707 g (10 mmol) of **5,** and 0.842 g (10 mmol) of 2,3-dimethyl-2-butene, and cooled to −116 °C in an ethanol slush bath. With vigorous stirring, 11 mmol of *n*-butyllithium in hexane is slowly added to the reaction via syringe. After the addition is complete, the reaction mixture is allowed to slowly warm to room temperature.

The reaction mixture is cooled to 0 °C in an ice–water bath, and 11 mmol of lithium aluminum hydride ($LiAlH_4$) in diethyl ether is added to the reaction via syringe after the mechanical stirrer has been replaced by a magnetic stirrer. After the addition is complete, the reaction mixture is allowed to warm to room temperature and is stirred for several hours.

Then 11 mmol of additional $LiAlH_4$ in diethyl ether is added to the reaction mixture via syringe. While the reaction mixture is protected from the atmosphere by a blanket of argon, 2.19 g (11 mmol) of trimethyltin chloride (Alfa) is added to the reaction mixture and the reaction mixture is stirred at room temperature overnight.

The reaction mixture is cooled in an ice–water bath and slowly hydrolyzed with 10 ml of distilled water after which 0.292 g (2 mmol) of benzotrifluoride is added to the reaction solution for an internal ^{19}F NMR standard. The organic layer is separated from the aqueous layer.

Analysis of the reaction solution by ^{19}F NMR indicates that **13** is formed in 21% yield. The product is identified by comparison of GLC and ^{19}F NMR data with an authentic sample synthesized by photolysis of fluorodiiodomethane in the presence of 2,3-dimethyl-2-butene.[9] ^{19}F NMR ϕ^* 224.2 ppm, $J_{F,H\text{-}gem}$ = 62 Hz.

Registry No.—**1,** 1727-63-5; (*Z*)-**2,** 16496-04-1; (*E*)-**2,** 16496-05-2; **3,** 16496-08-5; **5,** 353-54-8; **6,** 34636-25-4; (*Z*)-**7,** 34217-06-6; (*E*)-**7,** 34217-07-7; **8,** 34636-24-3; **9,** 41391-59-7; (*Z*)-**10,** 41391-58-6; (*E*)-**10,** 41391-72-4; (*Z*)-**11,** 19144-90-2; (*E*)-**11,** 19144-91-3; (*Z*)-**12,** 58413-57-3; (*E*)-**12,** 58413-59-5; **13,** 17370-50-2; fluorotrichloromethane, 75-69-4; *n*-butyllithium, 109-72-8; 2,3-dimethyl-2-butene, 563-79-1; 2-methyl-2-butene, 513-35-9; *trans*-2-butene, 624-64-6; cyclohexene, 110-83-8; isobutylene, 115-11-7; *cis*-2-butene, 590-18-1; 1-hexene, 592-41-6.

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The Effect of Metal Ions on the Hydroxylation of Fluorobenzene and Toluene by Peroxydisulfate

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The hydroxylation of fluorobenzene and toluene and the attempted hydroxylation of anisole, nitrobenzene, and benzonitrile by $SO_4\cdot^-$ has been investigated. Fluorobenzene forms almost exclusively phenol and *p*-fluorophenol and toluene forms *o*- and *p*-cresol, bibenzyl, benzyl alcohol, and benzaldehyde. The proportions of these products depend on oxidizing metal salts and pH. The phenol isomer distribution is consistent with a nucleophilic attack by H_2O at the α and para positions of the radical cation. SCF–MO calculations (INDO) of the radical cations show the highest positive charge at the α and para positions. The results show that in the homolytic hydroxylation of fluorobenzene and toluene a reversible acid-catalyzed dehydration will lead to an isomerization of the initially formed hydroxycyclohexadienyl radicals. The absence of hydroxylation of nitrobenzene, benzonitrile, and anisole is probably due to the smaller positive charges at the ring carbons of the radical cations of these aromatics as compared to toluene and fluorobenzene radical cation.

In the homolytic hydroxylation of aromatic compounds usually only a small fraction of the OH radicals are converted to phenols. It has been recognized for some time that in the hydroxylation of benzene in the presence of oxidizing agents, like oxygen[2] or metal salts,[3] the yield of phenol increases considerably. In recent work on the hydroxylation of nitrobenzene,[4] toluene,[5] benzonitrile,[6] anisole,[6] and fluorobenzene[6] in the presence of metal salts we have observed a quantitative conversion of OH radicals to phenols. The isomer distribution of the phenols however, varied in some cases quite dramatically depending on the metal salt. It seems that the initially formed hydroxycyclohexadienyl radicals undergo isomerization during the course of the reaction. Several mechanisms for this isomerization have been discussed.[6] Walling and Camaioni[7] have recently presented evidence that the well-known dehydration of the hydroxymethyl–cyclohexadienyl radicals is reversible, and proceeds via the toluene radical cation. We have suggested[6] that this reversible dehydration may in some cases be responsible for the change in isomer distribution in the presence of different metal salts. To test this hypothesis we have now investigated the hydroxylation and attempted hydroxylation of a number of aromatic compounds with peroxydisulfate and metal salts.

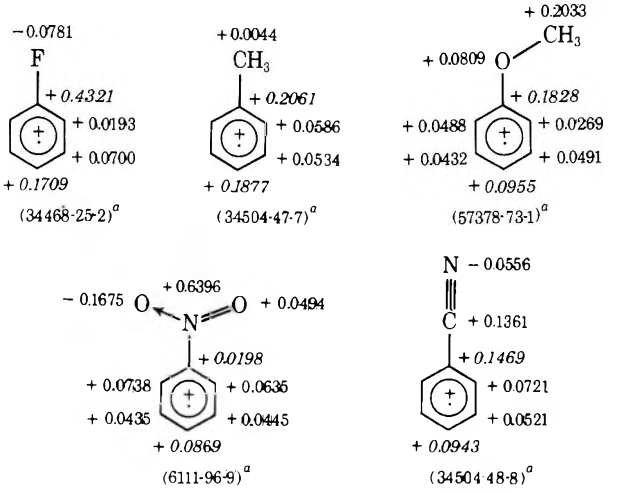
Results

Fluorobenzene. The results of the hydroxylation of fluorobenzene are summarized in Table I. Under identical conditions as those shown in expt 2, no hydroxylation was observed with anisole, nitrobenzene, and benzonitrile. The products are mainly phenol and *p*-fluorophenol, whose proportions depend on the oxidizing metal salts and the pH. With Cu^{2+} as oxidizing agent we observe with decreasing pH an increase in the ratio of phenol to *p*-fluorophenol (expt 7–9). This change in product distribution with decreasing pH was, however, not observed if $K_3Fe(CN)_6$ was the oxidizing agent (expt 2, 3, 4). At constant pH the ratio of phenol to *p*-fluorophenol increases in the series $Fe(CN)_6^{3-}$, Cu^{2+}, Fe^{3+} (expt 3, 8, 6).

Toluene. The results in Table II again show a considerable variation in product distribution, depending on oxidizing metal salts. With $K_3Fe(CN)_6$ we observe exclusively cresols, whereas with Cu^{2+} and Fe^{3+} large amounts of benzaldehyde, benzyl alcohol, and bibenzyl are also formed in addition to cresols. Analogous to the hydroxylation of fluorobenzene (Table I) the cresol isomer distribution depends on the oxidizing metal salt. With Fe^{3+} or Cu^{2+} we obtain much more *o*-cresol and less *p*-cresol than with $Fe(CN)_6^{3-}$. Interesting is the comparison between Cu^{2+} and Fe^{3+} at the same pH (expt 6 and 9). With Fe^{3+} we obtain large amounts of bibenzyl, whereas with Cu^{2+} we obtain only traces of bibenzyl, but instead more benzaldehyde and benzyl alcohol.

SCF–MO Calculations. The results are shown in Chart I. The calculations were carried out in the INDO approximation.[8] The following bond distances and bond angles were used: C_{ar}–C_{ar}, 1.40 Å; C_{ar}–H, 1.085 Å; C_{ar}–N, 1.46 Å; N=O, 1.10 Å; N→O, 1.18 Å; C_{ar}–CN, 1.419 Å; C≡N, 1.15 Å; C_{ar}–CH_3, 1.52 Å; C_{ar}–O, 1.36 Å; O–CH_3, 1.35 Å; C_{ar}–F, 1.30 Å; C_{ali}–H, 1.09 Å; tetrahedral angles 109.5°, all other angles 120°.

Chart I. Positive Charge Distributions of Some Aromatic Radical Cations (INDO Calculations)



[a] Registry no.

Discussion

The mechanism of reaction of $SO_4\cdot^-$ with aromatics has been discussed by a number of investigators. Norman et al.[9,10] have proposed addition of $SO_4\cdot^-$ to the aromatic ring, whereas a number of other investigators[11–13] have proposed the formation of a radical cation. Recently Schulte-Frohlinde and co-workers[14] have clearly shown that radical cations are formed in the reaction of $SO_4\cdot^-$ with methoxylated benzenes. The formation of radical cations is further supported by recent work of Neta et al.[15] These authors determined the rate constants of the reaction of $SO_4\cdot^-$ with a number of aromatics, and have shown that these rate constants follow a Hammett relationship with a ρ value greater than 2. A comparison of this ρ value with the one obtained from the reaction with OH (0.5) and e_{aq}^- (3.8) suggests that the reaction involves an electron transfer and does not take place via addition like OH.

The mechanism of the hydroxylation is shown in Scheme

Table I. Hydroxylation of Fluorobenzene with Peroxydisulfate in Presence of Metal Salts[a]

Expt no.	Conditions[b]			Fluorobenzene consumed mol/l.	Total phenols produced, mol/l. × 10^4	Fluorophenols and phenol, %			
						Ortho	Meta	Para	Phenol
1	$K_4Fe(CN)_6$		5 h	6.5×10^{-4}	4.65	4.7	Trace	60.2	35.1
2	$K_4Fe(CN)_6 + K_3Fe(CN)_6$	pH 6.3	2 h	N.D.[c]	2.90	4.5	Trace	62.4	33.1
3	$K_4Fe(CN)_6 + K_3Fe(CN)_6$	pH 2.8[d]	24 h	N.D.[c]	4.72	5.8	Trace	61.2	33.0
4	$K_4Fe(CN)_6 + K_3Fe(CN)_6$	pH 1.6[d]	1 h	N.D.[c]	2.60	6.0	Trace	65.0	29.0
5	$Fe(NH_4)_2(SO_4)_2$		5 h	N.D.[c]	6.29	4.0	Trace	11.8	84.3
6	$Fe(NH_4)_2(SO_4)_2 + Fe(NH_4)(SO_4)_2$	pH 2.8	15 min	2.5×10^{-3}	6.20	4.2	Trace	13.5	82.3
7	$Fe(NH_4)_2(SO_4)_2 + CuSO_4$	pH 4.2	15 min	2.5×10^{-3}	7.97	5.9	Trace	38.9	55.2
8	$Fe(NH_4)_2(SO_4)_2 + CuSO_4$	pH 2.8[d]	15 min	N.D.[c]	7.46	5.8	Trace	31.2	62.9
9	$Fe(NH_4)_2(SO_4)_2 + CuSO_4$	pH 1.8[d]	15 min	N.D.[c]	7.88	2.2	Trace	2.0	95.8

[a] In all experiments the concentration of fluorobenzene and peroxydisulfate was 5×10^{-3} M. [b] Concentration of all metal salts was 5×10^{-3} M. [c] N.D. = not determined. [d] In these experiments the pH was adjusted with H_2SO_4.

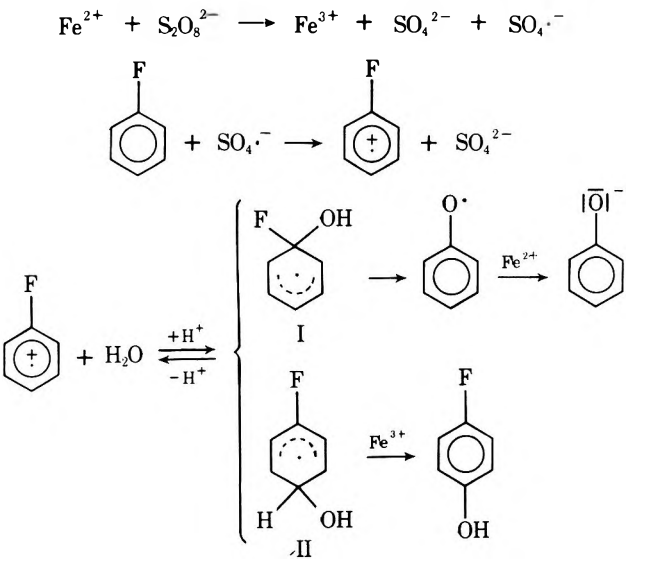
Table II. Hydroxylation of Toluene with Peroxydisulfate in Presence of Metal Salts[a]

Expt no.	Conditions[b]			Toluene consumed, mol/l. × 10^3	Products, mol/l. × 10^5						% Cresol		
					Ph-CHO	Ph-CH_2OH	Ph-$CH_2)_2$	*o*-Cresol	*m*-Cresol	*p*-Cresol	Ortho	Meta	Para
1	$K_4Fe(CN)_6 + K_3Fe(CN)_6$	pH 5.8	1 h	1.1				7.3	0.5	9.8	41.5	2.8	55.7
2	$K_4Fe(CN)_6 + K_3Fe(CN)_6$	pH 5.8	2.5 h	1.3				17.0	1.2	23.2	41.1	2.9	56.0
3	$K_4Fe(CN)_6 + K_3Fe(CN)_6$	pH 5.8	5 h	1.7				24.3	1.7	33.4	40.9	2.9	56.2
4	$K_4Fe(CN)_6 - K_3Fe(CN)_6$	pH 2.6[c]	24 h	2.3				29.2	3.1	40.7	40.0	4.2	55.8
5	$K_4Fe(CN)_6 - K_3Fe(CN)_6$	pH 1.7[c]	24 h	1.1				12.7	1.1	14.6	44.7	3.9	51.4
6	$Fe(NH_4)_2(SO_4)_2 - Fe(NH_4)(SO_4)_2$	pH 2.5	115 min	2.3	2.8	14.6	38.0	9.3	0.4	6.7	56.7	2.4	40.9
7	$Fe(NH_4)_2(SO_4)_2 - Fe(NH_4)(SO_4)_2$	pH 2.5	1 h	2.3	2.8	16.9	39.0	8.5	0.3	5.3	60.3	2.1	37.6
8	$Fe(NH_4)_2(SO_4)_2 - CuSO_4$	pH 4.1	15 min	2.4	13.0	62.5	Trace	51.0	2.7	27.0	63.2	3.4	33.4
9	$Fe(NH_4)_2(SO_4)_2 - CuSO_4$	pH 2.4[c]	15 min	2.8	17.6	76.5	Trace	29.4	1.6	14.3	64.9	3.5	31.6

[a] In all experiments the concentration of toluene and peroxydisulfate was 5×10^{-3} M. [b] All metal salts were at a concentration of 5×10^{-3} M. [c] In these experiments the pH was adjusted with H_2SO_4.

I for the reaction with fluorobenzene. The fluorobenzene radical cation undergoes nucleophilic attack by water to give 1-fluoro-1-hydroxycyclohexadienyl radical (I) and 1-fluoro-4-hydroxycyclohexadienyl radical (II). These radicals are converted by metal salts to phenol and *p*-fluorophenol, respectively. The results in Table I show that almost exclusively phenol and *p*-fluorophenol are formed. The small amount of *o*-fluorophenol and the trace amounts of *m*-fluorophenol show that only an insignificant amount of ortho or meta hydroxyl radical adduct is formed, since previous results have shown that all isomeric hydroxyfluorocyclohexadienyl radicals are quantitatively oxidized by $K_3Fe(CN)_6$ to the corresponding fluorophenols (43% ortho, 21% meta, 36% para). The preferred formation of I and II is to be expected on the basis of the charge distribution in the fluorobenzene radical cation. Results of SCF–MO calculations (INDO) of a number of radical cations are shown in Chart I. In the fluorobenzene radical cation the biggest positive charges are at the α and para positions, and nucleophilic attack by water is expected to take place at these positions. We have pointed out[6] that in absence of oxidizing agents, because of the reversibility of the dehy-

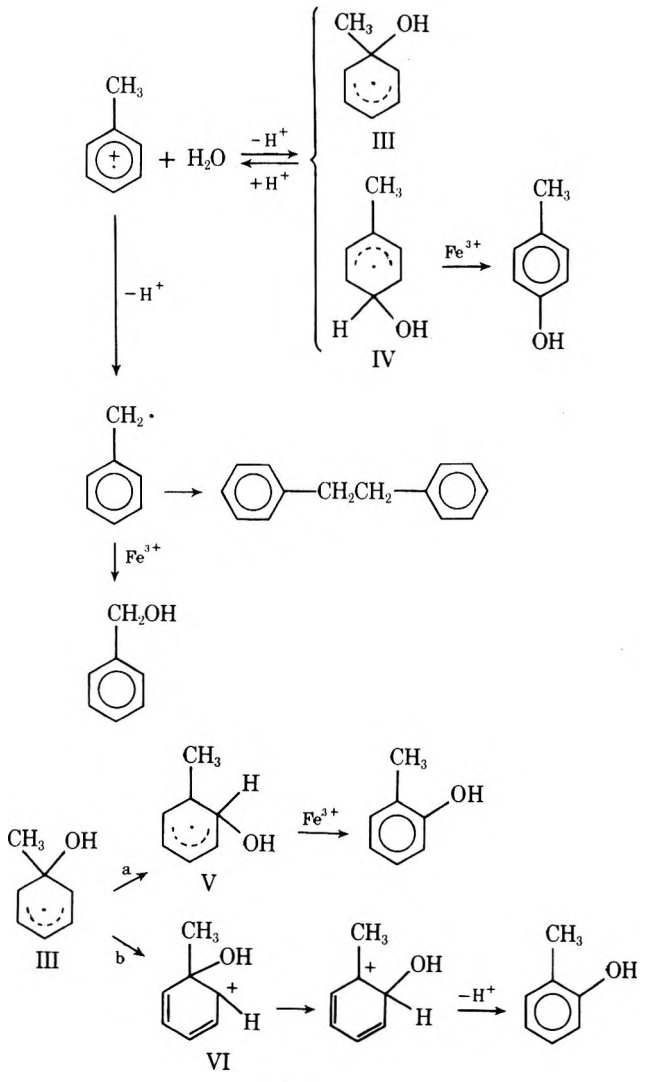
Scheme I



dration, all hydroxyfluorocyclohexadienyl radicals will eventually give phenol. In the radiation induced hydroxylation of fluorobenzene at low pH in absence of metal salts we indeed obtained an almost quantitative conversion of OH radicals to phenol. We have further shown[6] that the rate constants for oxidation of the cyclohexadienyl radicals decrease in the sequence $Fe(CN)_6 > Cu^{2+} > Fe^{3+}$. This sequence can also be deduced from our results in Table I. The ratio of phenol to *p*-fluorophenol increases in this series. The ratio also increases with decreasing pH (expt 17–19) consistent with our mechanism outlined in Scheme I, and in agreement with results on the radiation induced hydroxylations.[6] We can conclude that the hydroxyl radical adducts to fluorobenzene can isomerize to the α and para adducts via a reversible dehydration involving the fluorobenzene radical cation.

The reaction of $SO_4^{\cdot -}$ with toluene has been studied in absence of oxidizing metal salts,[16,17] and only products arising from side chain attack have been observed. Walling and Camaioni[7] recently reported that in the presence of oxidizing metal salts mostly cresols were formed. The hydroxylation of toluene with $SO_4^{\cdot -}$ in the presence of $K_3Fe(CN)_6$, Fe^{3+}, and Cu^{2+} gives almost exclusively o- and *p*-cresol (Table II). The charge distribution of the toluene radical cation again shows the highest positive charges at the α and para positons, and we expect to obtain radicals III and IV as shown in Scheme II.

Scheme II



The small amount of *m*-cresol shows that very little *m*-hydroxyl radical adduct is formed, since $K_3Fe(CN)_6$ oxidizes all isomeric hydroxymethylcyclohexadienyl radicals quantitatively to cresols[5] (50% ortho, 24% meta, 26% para).

The acid-catalyzed dehydration of hydroxymethylcyclohexadienyl radicals is well established. We therefore conclude that in the hydroxylation of toluene with hydroxyl radicals, the intermediate *m*-hydroxyl radical adduct can isomerize to the α and para adduct via a reversible dehydration, consistent with previous results.[5,6]

The α hydroxyl radical adduct (III) does not have the same reaction pathway available as the corresponding adduct to fluorobenzene (I). o-Cresol can be produced by rearrangement of III either before or after the oxidation step (pathways a or b). Eberhardt and Yoshida[18] have shown by SCF–MO calculations that the intermediate (V) is of lower energy than III, so rearrangement appears energetically possible. However, the present data do not allow us to distinguish between these two pathways. The absence of either of these two pathways for the intermediate 1-fluoro-1-hydroxycyclohexadienyl radical is consistent with the short lifetime of this intermediate as observed by pulse radiolysis.[19]

The ratio *o*-:*p*-cresol, as well as the ratio of cresols to benzyl radical derived products, depends on the oxidizing metal salt. Owing to the reversibility of the hydration, the slower the rate of oxidation of the cyclohexadienyl radicals the more bibenzyl and benzyl alcohol do we expect in agreement with experiment. We again obtain the sequence $Fe(CN)_6^{3-} > Cu^{2+} > Fe^{3+}$ for the rate of oxidation. The ratio *o*-:*p*-cresol is higher with Cu^{2+} and Fe^{3+} than with $Fe(CN)_6^{3-}$. A faster rate of dehydration from IV compared to III is consistent with this result. The highest percentage of *p*-cresol is obtained with the most effective oxidizing agent, the ferricyanide ion. Comparing the experiments with Cu^{2+} and Fe^{3+} we can see that the rate of oxidation of benzyl radical is much faster with Cu^{2+} than with Fe^{3+} (Table II, expt 6 and 9).

Attempted Hydroxylation of Anisole, Nitrobenzene, and Benzonitrile. No phenols were obtained in the reaction of $S_2O_8^{2-}$, $K_4Fe(CN)_6$, and $K_3Fe(CN)_6$ with anisole, nitrobenzene, and benzonitrile under the same conditions as expt 2, Table I. Since the hydroxymethoxy, hydroxynitro, and hydroxycyanocyclohexadienyl radicals are oxidized by $K_3Fe(CN)_6$ to substituted phenols,[4,6] we conclude that in the reaction of these aromatics with $SO_4^{\cdot -}$ none of the above intermediates are formed. According to our mechanism (Scheme I) the formation of hydroxycyclohexadienyl radicals involves two steps, either of which may not take place. Recent work of Neta et al.[15] has shown that $SO_4^{\cdot -}$ reacts with nitrobenzene and benzonitrile but at much slower rates ($k = 10^6$ M^{-1} s^{-1} and 1.2×10^8 M^{-1} s^{-1}, respectively) than with anisole ($k = 5 \times 10^8$ M^{-1} s^{-1}). We may therefore conclude that in these cases the radical cations do not become hydrated to the hydroxycyclohexadienyl radicals. Since in the hydroxylation of anisole by OH radicals the acid-catalyzed dehydration is well established,[20] this dehydration must be irreversible consistent with the $H_2{}^{18}O$ exchange experiments of Shevchuck and Vysotskaya,[21] and also in agreement with recent results of O'Neill et al.[14] A possible explanation for this behavior may be obtained from a consideration of the positive charge distribution of the radical cations of anisole, nitrobenzene, and benzonitrile (Chart I). The highest positive charges at the α and para positions are smaller than those in the fluorobenzene and toluene radical cations. Nucleophilic attack by water at the ring positions does not take place because of the lower nucleophilicity of these radical cations.

Experimental Section

Materials. All experiments were carried out using water which was doubly distilled from an all-glass still. Then it was further distilled over alkaline permanganate and acidic dichromate, and one final distillation was performed. The aromatic components were reagent grade quality, and were distilled prior to use. All metal salts were of

reagent grade quality. Aqueous solutions containing the metal salts were deoxygenated by bubbling argon through 1 l. of the solution for 1 h. The saturation was enhanced by frequent shaking. The aromatic compound was added and the solution was shaken to enhance the saturation. Then $Na_2S_2O_8$ was added at once and the solution was shaken and left to react for different times. All solutions were homogeneous and the reactions were carried out at room temperature. The solutions were extracted once with 200 ml of ether and four times with 100 ml of ether. The ether extracts were dried over Na_2SO_4, concentrated to 10 ml, and analyzed by vapor phase chromatography. The analytical procedure has been described in detail in previous publications.[4-6]

Registry No.—Toluene, 108-88-3; peroxydisulfate, 15092-81-6; fluorobenzene, 462-06-6; anisole, 100-66-3; nitrobenzene, 98-95-3; benzonitrile 100-47-0; $K_4Fe(CN)_6$, 13943-58-3; $K_3Fe(CN)_6$, 13746-66-2; $Fe(NH_4)_2(SO_4)_2$, 10045-89-3; $Fe(NH_4)(SO_4)_2$, 10138-04-2; $CuSO_4$, 10124-44-4.

References and Notes

(1) This paper was prepared in connection with work under Contract E-(40-1)-1833 with the U.S. Energy Research and Development Administration (ERDA). ERDA retains a nonexclusive, royalty-free license in and to any copyright covering this paper, with the right to authorize others to reproduce all or any part of the copyrighted paper.
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Studies on Selective Preparation of Aromatic Compounds. 12. Selective Reductive Dehalogenation of Some Halophenols with Zinc Powder in Basic and Acidic Media[1]

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The reductive dehalogenation of 2,4,6-trihalophenols (**1a–c**), *m*-alkylhalophenols (**7a–c** and **8c**), and *o*-alkylhalophenols (**15a–e**) were carried out with zinc powder in basic and acidic media under various conditions. 2-Bromo-6-chloro- (**3a**), 2,4-dichloro- (**3b**), 2-chloro- (**4a**), 2,6-dichloro-3-methyl- (**10b**), 2-bromo-6-chloro-3-*tert*-butyl- (**10c**), 6-bromo-3-*tert*-butyl- (**11c**), 2-chloro-3-*tert*-butyl- (**12c**), 6-bromo-2-*tert*-butyl- (**17a**), and 6-chloro-2-*tert*-butylphenol (**17b**) were selectively prepared by reduction with zinc powder in basic medium such as 10% sodium hydroxide solution. The reductive dehalogenation of halophenols with zinc powder in acidic media such as 10% HCl aqueous–EtOH and Zn–AcOH was also discussed in this paper.

It has been previously reported that *tert*-butyl,[2-5] chloro,[6,7] and bromo groups[6-8] could serve as positional protective groups for the preparation of some phenolic compounds. In the previous paper,[1] 2-bromo- and 2,4-dibromophenol were prepared in good yields by the selective reductive debromination of 2,4,6-tribromophenol with zinc powder in 10% sodium hydroxide and 10% hydrochloric acid–ethanol solution, respectively.

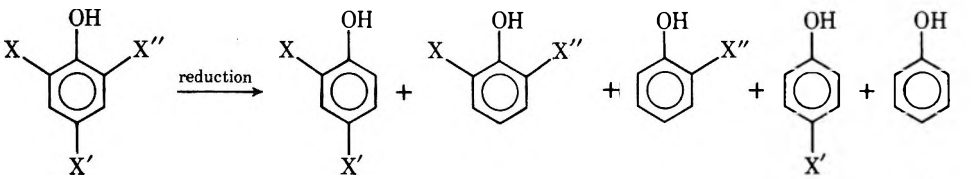
This paper presents additional applications of the selective reductive dehalogenation of halophenols with zinc powder in basic or acidic media.

Results and Discussion

The reductive dehalogenations of 2,4-dibromo-6-chloro- (**1a**), 4-bromo-2,6-dichloro- (**1b**), and 2,4,6-trichlorophenol (**1c**) were carried out under various conditions as summarized in Table I. Possible reductions products are **2, 3, 4, 5,** and **6.**

Unlike 2,4,6-tribromophenol,[9] the treatment of **1a** with zinc

Scheme I



	X	X′	X″
a	Br	Br	Cl
b	Cl	Cl	Br
c	Cl	Cl	Cl

	X	X′
a	Br	Br
b	Br	Cl
c	Cl	Br
d	Cl	Cl

	X	X″
a	Br	Cl
b	Cl	Cl

	X″
a	Br
b	Cl

	X′
a	Br
b	Cl

Table I. Reductive Dehalogenation of Halophenols with Zinc Powder in Basic and Acidic Media

Run	Substrate	Method[a]	Temp, °C	Time, h	Product (%)
1	**1a**	A	Reflux	2	**1a** (100)
2	**1a**	B	Reflux	2	**1a** (100)
3	**1a**	C	20	2	**3a** (85)
4	**1a**	C	100	0.5	**4b** (86)
5	**1b**	C	100	1	**3b** (76)
6	**1c**	C	100	2	**1c** (100)
7	**1c**	D	20	2	**6** (100)
8[b]	**7a**	C	100	2	**8a** (0.5), **9a** (0.5), **10a** (5), **11a** (41), **12a** (37), **14a** (16)
9[b]	**7a**	C	20	2	**7a** (9), **8a** (9), **9a** (10), **10a** (63), **11a** (4), **12a** (5)
10	**7b**	C	100	1	**10b** (84)
11	**7c**	C	100	5	**12c** (96)
12	**7c**	C	20	0.5	**10c** (84)
13	**7c**	A	Reflux	1	**10c** (91)
14	**8c**	C	20	1	**11c** (83)
15	**15a**	C	20	0.5	**17a** (87)
16	**15b**	C	20	0.5	**17b** (83)
17[b]	**15c**	C	100	0.5	**17a** (67), **18** (33)
18	**15d**	C	100	1	**17b** (82)
19	**15e**	C	100	2	**15e** (100)

[a] A, Zn–10% HCl aqueous–EtOH; B, Zn–AcOH; C, Zn–10% NaOH aqueous; D, Ni–Al–10% NaOH aqueous. [b] The distribution of products was shown.

powder in acidic media afforded no reduction product; **1a** was quantitatively recovered. In contrast 10% NaOH solution selectively gave only 2-bromo-6-chlorophenol (**3a**) at 20 °C, and 2-chlorophenol (**4b**) at 80 °C.

Similarly 2,6-dichlorophenol (**3b**) was obtained in good yield from the reduction of **1b** in zinc–10% NaOH solution. However, the same treatment of **1c** gave no reduction although treatment with Raney Ni–Al alloy in 10% NaOH solution even at 20 °C gave phenol (**6**) in quantitative yield.

Thus the *p*-bromo group of **1a** was more easily debrominated than o-bromo while a chloro group was not removed with zinc powder in 10% NaOH solution.

This synthetic route to **3a, 3b,** and **4b** is useful as **3a** and **3b** cannot be prepared by the directive halogenation of **6**, and the separation of pure **4b** from the mixture of chlorination of **6** is not easy. The indirect method for the preparation of **3a, 3b,** and **4b** was previously reported.[2]

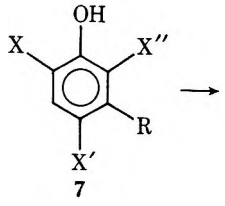
The compounds **4a** and **4b** were prepared by the $AlCl_3$–CH_3NO_2 catalyzed transalkylation of 4-*tert*-butyl-2-halophenol, and **3a** and **3b** were also obtained by $AlCl_3$–CH_3NO_2 catalyzed transalkylation of the corresponding 4-*tert*-butyl-2,6-dihalophenols.

However, the present method seem to be more handy than the previous work, since the starting compound in one-step preparation of **3a** and **4b** is same, that is, **1a.**

The reductive dehalogenations of the following *m*-alkylphenols, 2,4,6-tribromo-3-methyl- (**7a**), 4-bromo-2,6-dichloro-3-methyl- (**7b**), 4,6-dibromo-2-chloro-3-*tert*-butyl- (**7c**), and 4,6-dibromo-3-*tert*-butylphenol (**8c**), were carried out with zinc powder in basic and acidic media, and the results are summarized in Table I. Seven possible products are **8, 9, 10, 11, 12, 13,** and **14** (Scheme II).

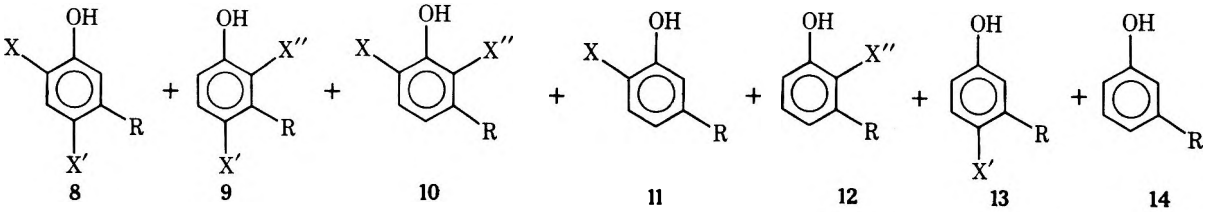
Although the reaction of **7a** at 80 and 20 °C reaction temperature afforded many products as shown in runs 8 and 9, the

Scheme II



7

	R	X	X′	X″
a	CH_3	Br	Br	Br
b	CH_3	Cl	Br	Cl
c	*t*-Bu	Br	Br	Cl



8 **9** **10** **11** **12** **13** **14**

	R	X	X′
a	CH_3	Br	Br
b	CH_3	Cl	Br
c	*t*-Bu	Br	Br

	R	X′	X″
a	CH_3	Br	Br
b	CH_3	Br	Cl
c	*t*-Bu	Br	Cl

	R	X	X″
a	CH_3	Br	Br
b	CH_3	Cl	Cl
c	*t*-Bu	Br	Cl

	R	X
a	CH_3	Br
b	CH_3	Cl
c	*t*-Bu	Br

	R	X″
a	CH_3	Br
b	CH_3	Cl
c	*t*-Bu	Cl

	R	X′
a	CH_3	Br
b	*t*-Bu	Br

	R
a	CH_3
b	*t*-Bu

main products at 80 °C are **11a** and **12a**; that at 20 °C is **10a**. Thus some selectivity in the reduction of **7a** was observed.

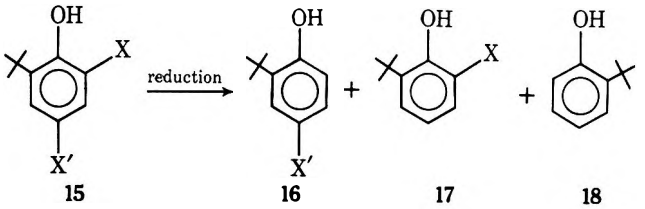
In contrast to the mixture from **7a**, **7b** afforded a high yield of 2,6-dichloro-*m*-cresol (**10b**) by the selective reduction of the *p*-bromo group. Highly selective reductive debromination was observed for **7c** and **8c** also as shown in runs 11, 12, and 14. That is, the desired product, 6-bromo-2-chloro-3-*tert*-butylphenol (**10c**), was obtained in good yield from the reduction of **7c** at 20 °C in basic media, and 2-chloro-3-*tert*-butylphenol (**12c**) was obtained in good yield at 80 °C reaction temperature. Also 6-bromo-3-*tert*-butylphenol (**11c**) was selectively formed in the reduction of **8c**.

Reductive debromination of **7c** in acidic medium resulted in loss of the *p*-bromo group to form **10c** rather than loss of o-bromo group to form **9c** which would be analogous to loss of o-bromo group by 2,4,6-tribromophenol in acidic media.[1,9]

The structures of **10b**, **10c**, **11c**, and **12c** were confirmed by their spectral data as well as elemental analyses. This selective reduction was applicable to **10b**, **10c**, **11c**, and **12c** as well as **3a**, **3b**, and **4b**, but not applicable to the reductive dehalogenation of **7a** owing to formation of a mixture.

Next examined was the possibility that the desired 2-*tert*-butylhalophenols could be prepared by the reductive dehalogenation of the corresponding 2-*tert*-butyldihalophenols (**15**). Reductions of 6-bromo-4-iodo- (**15a**), 6-chloro-4-iodo-

Scheme III



15 **16** **17** **18**

	X	X'
a	Br	I
b	Cl	I
c	Br	Br
d	Cl	Br
e	Cl	Cl

	X'
a	I
b	Br
c	Cl

	X
a	Br
b	Cl

(**15b**), 4,6-dibromo- (**15c**), 4-bromo-6-chloro- (**15d**), and 4,6-dichloro-2-*tert*-butylphenol (**15e**) were carried out with zinc powder in 10% NaOH solution as summarized in Table I.

The expected products, 6-bromo- (**17a**) and 6-chloro-2-*tert*-butylphenol (**17b**), were obtained in good yields from **15a** and **15b** at 20 °C. However, the reduction of **15c** at 20 °C afforded 4-bromo-2-*tert*-butylphenol (**16b**) and **17a** with large amount of the recovered **15c**, while at 100 °C **17a** and 2-*tert*-butylphenol (**18**) were obtained. Also **17b** was selectively prepared in good yield by the reduction of **15a** at 100 °C. In the case of **15e**, no reduction product was obtained and starting compound **15e** was recovered in quantitative yield.

The structures of **17a** and **17b** were confirmed by their spectral data as well as elemental analyses. The bromination of **17a** and **17b** with molecular bromine in MeOH afforded **15c** and **15d**, which were also prepared by the bromination of **18** and **17b**, respectively. These results support the structure assigned to **17a** and **17b**.

Results indicate that the iodo group is more easily removed than the bromo group and that the chloro group is never removed under these conditions. Thus bromine and iodine can serve as positional protective groups for the preparations of chlorophenols, as they can be removed with zinc powder in 10% NaOH solution. It is also interesting that zinc powder in basic medium removes the *p*-bromo group more easily than the *o*-bromo group to afford *o*-bromophenols.

An unidentified dark-violet compound[10] was precipitated in good yield when a solution of **15a**, **15b**, and **15c** in 10% NaOH was kept at room temperature for a few minutes. Therefore, it should be noted that **15a**, **15b**, **15c**, and **15d** must be added to the suspension of zinc powder in 10% NaOH solution.

Experimental Section

All melting and boiling points are uncorrected. IR spectra were measured as KBr pellets on a Nippon Bunko IR-A spectrophotometer and NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer with Me_4Si as an internal reference.

Analytical Procedure. The analyses were carried out by gas chromatography using a Yanagimoto gas chromatograph, Yanaco YR-101: column, 30% high vacuum silicon grease, 75 cm; increase rate of column temperature, 12 °C/min, carrier gas hydrogen, 30 ml/min.

From the areas of individual peaks, mol % figures were calculated for each product after the relative response data had been determined by the internal standard method. Nitrobenzene was used as an internal standard substance.

Reduction of 2,4-Dibromo-6-chlorophenol (1a). A. Using Zn–10% HCl–EtOH. To a mixture of 0.5 g (1.85 mmol) of **1a**,[11] 0.5 g of zinc powder, and 15 ml of ethanol was added 2.5 ml of 10% hydrochloric acid. After the reaction mixture was refluxed for 1 h, unchanged zinc powder was removed by filtration. The filtrate was evaporated in vacuo leaving 0.5 g (100%) of **1a**.

B. Using Zn–AcOH. To a solution of 0.5 g of **1a** in 15 ml of acetic acid was added 0.5 g of zinc powder. After the reaction mixture was refluxed for 1 h, the unchanged zinc powder was removed by filtration. The filtrate was poured into a large amount of water and extracted with benzene. The benzene extract was washed with water, dried over sodium sulfate, and evaporated in vacuo to afford 0.5 g (100%) of **1a**.

C. In Zn–10% NaOH at 20 °C. To a solution of 2.0 g (7.4 mmol) of **1a** in 20 ml of 10% sodium hydroxide was added 4 g of zinc powder at 20 °C. After the reaction mixture was stirred at 20 °C for 2 h, the unchanged zinc powder was filtered off. The filtrate was acidified with 10% hydrochloric acid and extracted with benzene. The benzene extracted was dried over sodium sulfate and evaporated in vacuo, leaving 1.2 g (85%) of **3a** which has been prepared as previously reported.[2]

D. In Zn–10% NaOH at 100 °C. To a solution of 2 g of **1a** in 20 ml of 10% sodium hydroxide was added 4 g of zinc powder. The reaction mixture was heated at 100 °C under stirring for 30 min, then treated and worked up as described above to afford 0.71 g (86%) of **4b**.

Reduction of 4-Bromo-2,6-dichlorophenol (1b). To a solution of 2.0 g (8.27 mmol) of **1b**[12] in 20 ml of 10% sodium hydroxide was added 4 g of zinc powder. The reaction mixture was stirred at 100 °C for 1 h, then treated and worked up as described above, affording 1.03 g (76%) of **3b** which was prepared as previously reported.[2,8,13]

Reduction of 2,4,6-Trichlorophenol (1c). A. In Zn–10% NaOH. After a mixture of 2 g (10.13 mmol) of **1c**, 4 g of zinc powder, and 20 ml of 10% sodium hydroxide was heated at 100 °C for 2 h, the reaction mixture was treated and worked up as described above, affording 2 g of **1c**.

B. In Raney Alloy–10% NaOH. To a solution of 0.1 g (0.51 mmol) of 1c in 3 ml of 10% sodium hydroxide was added 0.2 g of Raney Ni–Al alloy at 20 °C under stirring and the stirring was continued for 2 h. The reaction mixture was treated and worked up as described above, affording **6** in quantitative yield.

Reduction of 2,4,6-Tribromo-*m*-cresol (7a). To a solution of 2 g (5.8 mmol) of **7a**[14] in 20 ml of 10% sodium hydroxide was added 4 g of zinc powder. The reaction mixture was stirred at 20 and 100 °C for 2 h, respectively, and then both reaction mixture were treated and worked up, affording 1.37 and 0.75 g of oily products which were analyzed by gas chromatography. The results are shown in Table I. The structure of these products were determined by comparison with authentic samples. The authentic samples of **8a**,[15] **9a**,[2] **11a**,[16] and **12a**[17] were prepared according to the reported method.

Reduction of 4-Bromo-2,6-dichloro-*m*-cresol (7b). To a solution of 2 g (7.24 mmol) of **7b**[12] in 20 ml of 10% sodium hydroxide was added 4 g of zinc powder. The reaction mixture was stirred at 100 °C for 1 h, and then worked up as described above, affording 1.2 g (84%) of **10b** which was identified with an authentic sample,[8] mp 26–28 °C.

Reduction of 4,6-Dibromo-2-chloro-3-*tert*-butylphenol (7c).[18] **A. At 100 °C.** To a solution of 2 g (5.84 mmol) of **7c** in 20 ml of 10% sodium hydroxide was added 4 g of zinc powder. The reaction mixture

was stirred at 100 °C for 5 h, and then treated and worked up as described above, affording 0.75 g (70%) of **12c** as a colorless oil: bp 233 °C (760 mm); IR (NaCl plate) 3540 cm^{-1} (ν_{OH}); NMR (CCl_4) δ 1.45 [9 H, s, $(CH_3)_3$], 5.75 (1 H, broad s, OH), 6.7–7.00 (3 H, m, aromatic protons). Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.04; H, 7.09. Found: C, 64.66; H, 6.35.

B. At 20 °C. To a solution of 1 g (2.92 mmol) of **7c** in 15 ml of 10% sodium hydroxide was added 2 g of zinc powder. The reaction mixture was stirred at 20 °C for 30 min and then treated and worked up as described above, affording 0.65 g (84%) of **10c** as colorless prisms (*n*-hexane): IR (KBr) 3420 cm^{-1} (ν_{OH}); NMR (CCl_4) δ 1.45 [9 H, s, $CH_3)_3$], 5.95 (1 H, broad s, OH), 6.78 and 7.26 (each 1 H, s. J = 8.25 Hz, aromatic protons). Anal. Calcd for $C_{10}H_{12}OClBr$: C, 45.57; H, 4.59. Found: C, 45.32; H, 4.76.

C. In Acidic Medium. A mixture of 2 g of **7c**, 60 ml of ethanol, 10 ml of 10% hydrochloric acid, and 2 g of zinc powder was refluxed and then treated and worked up as described above, affording 1.4 g (91%) of **10c**.

Reduction of 4,6-Dibromo-3-*tert*-butylphenol (8c). To a suspension of 3 g (9.74 mmol) of **8c**[18] in 30 ml of 10% sodium hydroxide was added 6 g of zinc powder. After the reaction mixture was stirred at 20 °C for 2 h, it was treated and worked up as described, affording 1.85 g (83%) of **11c**.[18]

2-*tert*-Butyl-4-iodophenol (16a). To a solution of 45 g (300 mmol) of **15a** was added 50 g (308 mmol) of ICl in 40 ml of acetic acid at 25 °C under stirring, and the reaction mixture was stirred for 3 h, longer, then it was poured into a large amount of water and extracted with benzene. The benzene extract was washed with aqueous $Na_2S_2O_3$ solution, dried over Na_2SO_4, and evaporated in vacuo to leave 60 g of crude I which was purified by distillation under reduced pressure to afford 50 g (60.4%) of **16a**: bp 106–108 °C (3 mm); IR (KBr) 3560 cm^{-1} (ν_{OH}); ^1H NMR (CCl_4) δ 1.36 (s, 9, *t*-CH_3), 4.60 (s, 1, OH), 6.30 (d, J_{ac} = 8.25 Hz), 7.24 (dd, J_{ac} = 8.25, J_{ab} = 3.0 Hz), and 7.24 (s, J_{ab} = 3.0 Hz, each 1, aromatic protons). Anal. Calcd for $C_{10}H_{13}OI$: C, 43.50; H, 4.75. Found: C, 43.17; H, 4.64.

2-Chloro-4-iodo-6-*tert*-butylphenol (15b). To a solution of 5.53 g (20 mmol) of **16a** in 15 ml of CH_3NO_2 was gradually added 5 g (37 mmol) of SO_2Cl_2 at 20 °C. After the reaction mixture was kept at 20 °C for 10 min, it was poured into a large amount of water and extracted with benzene. The benzene extract was dried over Na_2SO_4 and evaporated in vacuo to leave pale yellow, resinous material which was treated with a small amount of MeOH–H_2O to afford 3.80 g (61.2%) of **15b**, mp 45.5–47.0 °C, colorless prisms recrystallized from a mixed solvent, MeOH–H_2O (1:1): IR (KBr) 3540, 3500 cm^{-1} (ν_{OH}); ^1H NMR ($CDCl_3$) δ 1.37 [s, 9, $(CH_3)_3$], 5.85 (s, 1, OH), 7.42 and 7.51 (d, J_{ab} = 2.25 Hz, each 1, aromatic protons). Anal. Calcd for $C_{10}H_{12}OClI$: C, 38.67; H, 3.90. Found: C, 38.98; H, 3.80.

2-Bromo-4-iodo-6-*tert*-butylphenol (15a). To a solution of 14 g (51 mmol) of **16a** in 50 ml of MeOH was added gradually 9 g (56 mmol) of Br_2 at 5–10 °C. After the reaction mixture was kept at 25 °C for 30 min, it was poured into a large amount of water to give 17 g (94.4%) of **15a**, mp 67–67.5 °C, as colorless needles recrystallized from MeOH–H_2O: IR (KBr) 3520, 3500 cm^{-1} (ν_{OH}); ^1H NMR (CCl_4) δ 1.38 [s, 9, $C(CH_3)_3$], 5.73 (s, 1, OH), 7.39 and 7.59 (d, J_{ab} = 2.25 Hz, each 1, aromatic protons). Anal. Calcd for $C_{10}H_{12}OBrI$: C, 33.83; H, 3.41. Found: C, 34.06; H, 3.36.

2-Chloro-6-*tert*-butylphenol (17b). To a suspension of 5 g of zinc powder in 30 ml of 10% NaOH was added 3.1 g (10 mmol) of **15b** at 28 °C in the period of 15 min under stirring, and the stirring was continued for 15 min longer. After the reaction mixture was warmed at 90 °C for 1 min, the unchanged Zn was filtered off. The filtrate was extracted with benzene. The benzene extract was dried over Na_2SO_4 and evaporated in vacuo, leaving 1.52 g (82.5%) of **17b**, bp 72–73 °C (3 mm), as a pale yellow liquid: IR (KBr) 3560 cm^{-1} (ν_{OH}); ^1H NMR (CCl_4) δ 1.38 (s, 9, *t*-CH_3), 5.76 (s, 1, OH), 6.55–7.20 (m, 3, aromatic protons). Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.04; H, 7.10. Found: C, 64.83; H, 7.06.

2-Bromo-6-*tert*-butylphenol (17a). To a suspension of 15 g of zinc powder in 100 ml of 10% NaOH was added 10 g (28 mmol) of **15a** and the reaction mixture was treated and worked up as described above, affording 5.58 g (86.5%) of **17a**, bp 80–81 °C (3 mm), as a pale yellow liquid: IR (KBr) 3530 cm^{-1} (ν_{OH}); ^1H NMR (CCl_3) δ 1.38 (s, 9, *t*-CH_3), 5.72 (s, 1, OH), and 6.64–7.26 (m, 3, aromatic protons). Anal. Calcd for $C_{10}H_{13}OBr$: C, 52.42; H, 5.72. Found: C, 51.90; H, 5.62.

2,4-Dibromo-6-*tert*-butylphenol (15c). A. Bromination of 18. To a solution of 25 g (166.4 mmol) of **18** in 50 ml of MeOH was added 55 g (343.8 mmol) of Br_2 at room temperature. The reaction mixture was stirred for 10 min and evaporated in vacuo, affording 51.2 g (99.9%) of **15c**, mp 57–58 °C, as colorless prisms (MeOH–H_2O).

B. Bromination of 17a. To a solution of 100 mg (0.44 mmol) of **17a** in 2 ml of MeOH was added 0.2 g (1.35 mmol) of Br_2, and the reaction mixture was treated and worked up as described above, affording 130 mg (96.7%) of **15c**, mp 57–58 °C.

Reduction of 4,6-Dibromo-2-*tert*-butylphenol (15c). To a suspension of 10 g of zinc powder in 50 ml of 10% sodium hydroxide was added 0.16 g (20 ml) of **15c**.[19] After the reaction mixture was stirred at 100 °C for 30 min, it was treated and worked up as described above, affording 3.0 g of oily material which was analyzed by gas chromatography, and the result is shown in Table I.

4-Bromo-6-chloro-2-*tert*-butylphenol (15d). To a solution of 11.5 g (50 mmol) of 2-*tert*-butylphenol[20] in 50 ml of nitromethane was added 10 g (75 mmol) of sulfuryl chloride at 25 °C. After the reaction mixture was stirred for 30 min, it was poured into a large amount of ice–water and extracted with benzene. The benzene extract was dried over sodium sulfate and evaporated in vacuo, leaving 10 g of crude material which was chromatographed over silica gel using benzene as an eluent, affording 8.5 g (64.5%) of **15d** as pale yellow product: mp 39.5–41.0 °C; IR (KBr) 3520 cm^{-1} (ν_{OH}); NMR (CCl_3) δ 1.39 [9 H, s, $(CH_3)_3$], 5.75 (1 H, s, OH), 7.22 and 7.32 (each 1 H, d, J = 2.25 Hz, aromatic protons). Anal. Calcd for $C_{10}H_{12}OBrCl$: C, 45.57; H, 4.59. Found: C, 45.48; H, 4.48.

Bromination of 17b. To a solution of 0.19 g (1 mmol) of **17b** was added gradually a solution of 0.2 g (1.25 mmol) of bromine in 2 ml of CCl_4 at 20 °C. The reaction mixture was stirred for 2 h and evaporated in vacuo to leave 0.25 g of oily product which was chromatographed over silica gel using benzene as an eluent, affording 0.19 g (70%) of **15d**.

Reduction of 4-Bromo-6-chloro-2-*tert*-butylphenol (15d). To a suspension of 2 g of zinc powder in 15 ml of 10% sodium hydroxide was added 1 g (3.8 mmol) of **15d**. After the reaction mixture was stirred at 100 °C for 1 h, it was treated and worked up as described above, affording 0.56 g (80%) of **17b**.

Registry No.—**1a**, 4526-56-1; **1b**, 3219-15-0; **1c**, 88-06-2; **7a**, 4619-74-3; **7b**, 56037-74-2; **7c**, 60935-47-9; **8c**, 1131-12-0; **10b**, 13481-70-4; **10c**, 60935-48-0; **12c**, 60935-49-1; **15a**, 60803-27-2; **15b**, 60803-28-3; **15c**, 15460-12-5; **15d**, 60935-50-4; **15e**, 13395-86-3; **16a**, 60803-25-0; **17a**, 23159-87-7; **17b**, 4237-37-0; **18**, 88-18-6; zinc, 7440-66-6.

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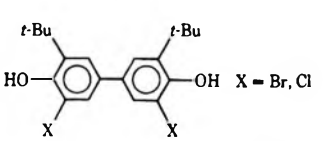

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Resonance Stabilization Energies in Polycyclic Aromatic Hydrocarbon Radicals

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It is shown that relative values of π-bonding resonance stabilization energies for benzyl-type polycyclic aromatic radicals, as calculated by SCF–MO methods, closely correspond to energies calculated by the simple resonance theory approach of Herndon. The formula derived for the latter type of π-bonding resonance stabilization energy is $E_{\pi RSE}$ (kcal mol^{-1}) = 22.68 ln [CSC(R·)] − 27.33 ln [CSC(RH)], where CSC(R·) and CSC(RH) are the corrected structure counts (number of stable Kekulé isomers) for the radical and parent molecule, respectively. Two methods are then suggested for modifying this formula to estimate empirical radical stabilization energies for use in predicting standard heats of formation of stabilized hydrocarbon radicals.

Herndon and co-workers[1] have shown that the number of stable Kekulé isomers (CSC, for corrected structure count) for polycyclic aromatic hydrocarbons (PCAH) can be related to resonance energies,[1,2] and reactivity parameters[3] derived from modern SCF–MO calculations. Herndon's resonance theory (HRT) has also been applied for the accurate calculation of bond orders,[4] ionization potentials,[4,5] and heats of formation[6] of PCAHs.

We have extended HRT to accurately reproduce SCF–MO π-bonding stabilization energy differences, $\Delta E_{\pi RSE}$, for benzyl-type polycyclic aromatic radicals.

With available experimental measurements as a basis, we suggest modification of the $E_{\pi RSE}$ formula to estimate thermodynamic radical stabilization energy, E_{RSE}. A paucity of relevant experimental values prohibits thorough testing of the absolute accuracy of this method, although estimates of this scheme do agree with existing data. Relative, if not absolute, estimates of E_{RSE} will find application in the guidance and interpretation of PCAH kinetics.

Method and Discussion

The π-bonding stabilization energy of a conjugated radical may be defined as the difference between the π-bonding energy of the radical, E_π(R·), and the π-bonding energy in the parent molecule, E_π(RH):

$$E_{\pi RSE} = E_\pi(\text{R}\cdot) - E_\pi(\text{RH}) \quad (1)$$

Herndon has shown that E_π(RH) calculated by highly parameterized SCF–MO procedures are reproduced with an average deviation of 1.0 kcal mol^{-1} for 27 PCAHs by the formula[2]

$$E_\pi\,(\text{RH})\ (\text{kcal mol}^{-1}) = 27.33 \ln [\text{CSC(RH)}] \quad (2)$$

If we assume that E_π(R·) is proportional to the logarithm of the number of resonance structures, and set this proportionality constant equal to 22.60 kcal mol^{-1}, then the resulting formula (3) (incorporating eq 1 and 2) reproduces published[7] relative $E_{\pi RSE}$ values with an average deviation of 0.60 kcal mol^{-1} (see Table I).[9]

$$E_{\pi RSE}\ (\text{kcal mol}^{-1}) = 22.68 \ln [\text{CSC(R}\cdot)] - 27.33 \ln [\text{CSC(RH)}] \quad (3)$$

Empirically, resonance stabilized radicals may be characterized by a total resonance stabilization energy, E_{RSE}. This energy, in effect, represents a lowering of the thermodynamic energy due to odd-electron delocalization over conjugated π bonds. By definition, E_{ESE} is the difference between the heat of the reaction RX → R· + X· and the reaction $R_pX \rightarrow R_p\cdot$ + X·, where R· is the resonance stabilized radical of interest and $R_p\cdot$ is its paraffinic analogue.

In general, σ-bonding energies (E_σ) also contribute to E_{RSE}, since an increased stability in π-bonding system distorts the molecular σ-bonding framework. Formally,

$$E_{RSE} = E_{\pi RSE} + E_\sigma \quad (4)$$

For instance, electron delocalization over the aromatic carbons in the benzyl radical reduces its heat of formation, while resulting steric interactions in the radical that are not present in its parent molecule can tend to work in the opposite direction. Therefore, generally $E_{\pi RSE}$ is not expected to be equal to E_{RSE}. Also, the quantitative accuracy of calculated $E_{\pi RSE}$ values is uncertain, although relative values are probably reliable.

At present, the only well-established E_{RSE} value for benzyl-type aromatic radicals is for the benzyl radical itself. This is accepted[8] as 13 ± 1.5 kcal mol^{-1}. Since CSC($C_6H_5CH_2\cdot$) = 5 and CSC($C_6H_5CH_3$) = 2, formula 3 yields E_{RSE} = 17.6 kcal mol^{-1}; formally, E_σ = −3.6 kcal mol^{-1}. Based on these values, we suggest two formulas for deriving E_{RSE} for larger benzyl-type resonance stabilized radicals.

The first method simply scales down formula 3 to yield 13 kcal mol^{-1} for the benzyl radical:

$$E_{RSE}\ (\text{kcal mol}^{-1}) = 16.75 \ln [\text{CSC(R}\cdot)] - 20.19 \ln [\text{CSC(RH)}] \quad (5)$$

This scheme may be viewed as a result of either of two assumptions: (1) E_σ is negligible ($E_{RSE} \cong E_{\pi RSE}$), and for absolute accuracy, $E_{\pi RSE}$ values must be multiplied by a factor 13.0/17.6 = 0.74, or (2) $E_{\pi RSE}$ is an accurate absolute value, and $E_\sigma = -0.26E_{\pi RSE}$ for all benzyl-type resonance stabilized radicals.

A second formula may be derived, based on the assumptions that E_σ = −3.6 kcal mol^{-1}, and $E_{\pi RSE}$ is accurate for these stabilized radicals:

$$E_{RSE}\ (\text{kcal mol}^{-1}) = E_{\pi RSE} - 3.6 \quad (6)$$

In Table II are given E_{RSE} values estimated by using these two formulas for a number of benzyl-type PCAHs. The average difference in estimated E_{RSE} values from these two formulas is 1.4 kcal mol^{-1}; this is of the same magnitude as experimental uncertainty in E_{RSE} determinations. However, for the more highly stabilized radicals, such as 9-anthryl and 5-naphthacenyl, predictions of these two formulas differ by more than 3 kcal mol^{-1}. For these species, accurate experimental determinations can potentially distinguish between these two models.

In Table III predictions using eq 5 are compared with measured E_{RSE} values for other conjugated hydrocarbon radicals. Intuitively, one expects E_σ, and perhaps $E_{\pi RSE}$, to vary with the class of radical; however, E_{RSE} calculated for alternant radicals are generally within the experimental

Table I. Calculated Differences in π-Bonding Stabilization Energies[a] (kcal mol^{-1}) for a Series ot Benzyl-Type Polycyclic Aromatic Radicals

Radical	CSC(R·)	CSC(RH)	ΔE_{RSE}(SCF)[b]	$\Delta E_{\pi RSE}$(SCF) − $\Delta E_{\pi RSE}$(method A)	$\Delta E_{\pi RSE}$(SCF) − $\Delta E_{\pi RSE}$(method B)
Benzyl	5	2	(0.0)	(0.0)	(0.0)
3-Phenanthryl	17	5	1.38	−1.33	−2.62
2-Triphenylenyl	31	9	1.57	−1.29	−2.60
1-Triphenylenyl	32	9	1.75	−0.75	−2.83
2-Naphthyl	9	3	1.75	0.50	−0.62
1-Phenanthryl	18	5	3.21	−0.80	−1.53
1-Naphthyl	10	3	4.04	0.60	0.30
9-Phenanthryl	18	5	4.10	−0.09	−0.64
6-Chrysyl	34	8	4.93	0.66	−1.97
2-Anthryl	14	4	4.96	−0.55	0.59
1-Anthryl	16	4	7.84	−0.40	1.73
1-Pyrenyl	27	6	8.12	0.11	0.48
9-Anthryl	20	4	11.97	0.53	2.96
Average deviation				0.60	1.45

[a] $E_{RSE} = A$ ln [number stable Kekulé structures for radical] − B ln [number stable Kekulé structures for molecule], $\Delta E_{\pi RSE} = E_{\pi RSE}$(radical) − $E_{\pi RSE}$(benzyl). Method A: $A = 22.38$; $B = 27.33$; B value from Herndon, ref 2. Method B: $A = B = 13.0$. [b] Reference 7.

Table II. Estimated E_{RSE} (kcal mol^{-1}) for Benzyl-Type Radicals

Radical	CSC(R·)	CSC(RH)	Eq 5	Eq 6	Δ
1-Naphthyl	10	3	16.4	17.6	1.2
2-Naphthyl	9	3	14.7	15.2	0.5
1-Phenanthryl	18	5	16.0	17.0	1.0
2-Phenanthryl	16	5	14.0	14.3	0.3
3-Phenanthryl	17	5	15.0	15.7	0.7
4-Phenanthryl	17	5	15.0	15.7	0.7
9-Phenanthryl	18	5	16.0	17.0	1.0
1-Anthryl	16	4	18.5	20.4	1.9
2-Anthryl	14	4	15.3	17.4	2.1
9-Anthryl	20	4	22.3	25.5	3.2
1-Pyrenyl	27	6	19.1	21.2	2.1
2-Pyrenyl	19	6	13.2	13.3	0.1
4-Pyrenyl	23	6	16.2	17.6	1.4
1-Chrysyl	31	8	15.5	16.5	1.0
2-Chrysyl	27	8	13.3	13.4	0.1
3-Chrysyl	29	8	14.5	15.0	0.5
4-Chrysyl	29	8	14.5	15.0	0.5
5-Chrysyl	29	8	14.5	15.0	0.5
6-Chrysyl	34	8	17.1	18.6	1.5
1-Naphthacenyl	23	5	20.1	22.6	2.5
2-Naphthacenyl	20	5	17.7	19.4	1.7
5-Naphthacenyl	32	5	25.6	30.1	4.5
1-Triphenylenyl	32	9	13.7	14.0	0.3
2-Triphenylenyl	31	9	13.2	13.3	0.1
1-Perylenyl	46	9	19.8	22.2	2.4
2-Perylenyl[a]	9	3	14.7	15.2	0.5
3-Perylenyl	49	9	20.9	23.7	2.8

[a] For this radical species, no stable resonance structures can be written for electron delocalization in a naphthyl moiety. As a result, this radical is formally identical with the 2-naphthyl species.

uncertainties. Predictions of eq 6 are not appreciably different.

For the nonalternant cyclopentadienyl and cycloheptatrienyl radicals, predicted E_{RSE} values are clearly too large if CSC(R·) is defined as the number of resonance isomers. For alternant radicals, structures contributing to the CSC have the radical "centered" on roughly half of the carbon atoms within the π-bonding framework. Since for nonalternant radicals, the radical site may be on any carbon within the π-bonding system, we are tempted to define the CSC for these stabilized radicals as one-half of the total number of Kekulé structures. By doing so, calculated E_{RSE} match experimental values well (Table III).

Conclusions

The computational scheme proposed by Herndon for resonance energy calculation has been shown to be capable of yielding relative π-bonding stabilization energies for benzyl-type radicals of SCF–MO quality. Comparison of these calculated energies with the measured thermodynamic stabilization energy for the benzyl radical has led us to suggest two simple formulas for estimating E_{RSE} for other benzyl-type radicals. These two formulas lead to fairly similar values for E_{RSE}. This method has also been applied for calculation of E_{RSE} values to other classes of alternant conjugated radicals, and has been shown to yield E_{RSE} generally within experi-

Table III. Comparison of Experimental and Estimated E_{RSE}

	CSC(R·)	CSC(RH)	E_{RSE} (eq 3)	E_{RSE} (exptl)	Exptl ref
Allyl	2	1	11.6	10.0 ± 1.5	*a*
Cyclohexen-3-yl	2	1	11.6	12.5 ± 1.0	*b*
Methylallyl	2	1	11.6	12.5 ± 1.5	*a*
1,3-Hexadien-5-yl	3	1	18.4	18 ± 3	*a,c*
1,3-Cyclohexadien-5-yl	3	1	18.4	24 ± 6	*d,e*
Cyclopentadienyl	5[h]	1	27.0	17.5 ± 2.5	*f*
Cyclopentadienyl	5/2[i]	1	15.4	17.5 ± 2.5	*f*
Cycloheptatrienyl	7[h]	1	32.6	21.5	*g*
Cycloheptatrienyl	7/2[i]	1	21.0[g]	21.5	*g*

[a] Reference 8. [b] S. Furuyama, D. M. Golden, and S. W. Benson, *Int. J. Chem. Kinet.*, **3**, 93 (1970). [c] K. W. Egger and M. Jola, *ibid.*, **2**, 265 (1970); H. M. Frey and A. Krantz, *J. Chem. Soc. A*, 1159 (1969). [d] D. G. L. James and R. D. Suart, *Trans. Faraday Soc.*, **64**, 2752 (1968). [e] S. W. Benson, "Thermochemical Kinetics", 2d ed, Wiley, New York, N.Y., 1976. [f] S. Furuyama, D. M. Golden, and S. W. Benson, *Int. J. Chem. Kinet.*, **3**, 237 (1971). [g] G. Vincow, H. J. Dauben, F. R. Hunter, and W. V. Volland, *J. Am. Chem. Soc.*, **91**, 2823 (1969). [h] CSC has not been previously defined for such nonalternant systems; it is assumed to be equal to the total number of distinct resonance structures. [i] E_{RSE} (eq 3) is derived using CSC(R·) defined as one-half of the number of resonance structures.

mental uncertainty. The current paucity and inaccuracy of existing data, however, make a convincing test of these methods impossible. For nonalternant conjugated radicals, the proposed estimation method yields E_{RSE} substantially higher than measured values. By halving the total structure count to yield a corrected structure count for these radicals, E_{RSE} predictions accurately match the measured values.

Acknowledgment. This work has been supported by the U.S. Energy Research and Development Administration, Office of Coal Research, under Contract E(49-18)-2202.

Registry No.—Benzyl, 2154-56-5; 3-phenanthryl, 61062-76-8; 2-triphenylenyl, 61062-77-9; 1-triphenylenyl, 61062-78-0; 2-naphthyl, 10237-50-0 1-phenanthryl, 61062-79-1; 1-naphthyl, 2510-51-2; 9-phenanthryl, 20199-82-0; 6-chrysyl, 61062-80-4; 2-anthryl, 61062-81-5; 1-anthryl, 27735-76-8; 1-pyrenyl, 27735-78-0; 9-anthryl, 27735-77-9; 2-phenanthryl, 61062-82-6; 4-phenanthryl, 61062-83-7; 2-pyrenyl, 61062-84-8 4-pyrenyl, 61062-85-9; 1-chrysyl, 61062-86-0; 2-chrysyl, 61062-87-1; 3-chrysyl, 61062-88-2; 4-chrysyl, 61062-89-3; 5-chrysyl, 61062-90-6; 1-naphthacenyl, 61062-91-7; 2-naphthacenyl, 61062-92-8; 5-naphthacenyl, 61062-93-9; 1-perylenyl, 61062-94-0; 2-perylenyl, 61092-32-8; 3-perylenyl, 61062-95-1; allyl, 1981-80-2; cyclohexen-3-yl, 15650-80-3; methylallyl, 15157-95-6; 1,3-hexadien-5-yl, 61062-96-2; 1,3-cyclohexadien-5-yl, 15819-51-9; cyclopentadienyl, 2143-53-5; cycloheptatrienyl, 3551-27-7.

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(9) Table I also shows the results of optimizing an equation of the form $E_{\pi RSE} = A \ln [CSC(R\cdot)]/[CSC(RH)]$. Equation 3 is better.

Production of Nitric Oxide in the Pyrolysis of Aromatic Nitro Compounds

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The pyrolysis of nitrobenzene in the temperature range 400–600 °C was studied in a continuous-flow apparatus consisting of pyrolyzer, gas chromatograph, and mass spectrometer. Several of the observed products (benzene, biphenyl, naphthalene) could arise from phenyl radical, but, in contrast to earlier suggestions, there is no evidence supporting a primary fission to phenyl radical and nitrogen dioxide. Pyrolysis of nitrosobenzene yields products similar to those from nitrobenzene, and a two-step mechanism, nitrobenzene → nitrosobenzene → phenyl, is proposed. Although the details of the mechanism are not conclusively proven, there is considerable evidence for a heterogeneous mechanism and none supporting a homogeneous mechanism.

Recent experience in this laboratory[1] and others[2] has shown that nitric oxide is a prominent product of the pyrolysis of aromatic nitro compounds, and that nitrogen dioxide is not produced in detectable quantities. This is not necessarily a surprising result inasmuch as the possible rearrangement to an aryl nitrite leads to compounds which should readily undergo homolytic fission to nitric oxide plus aryloxy radicals. Photochemical nitro–nitrite rearrangements are known,[3] and the analogous rearrangement of the positive ion occurs in the mass spectrum of nitrobenzene.[4] Even though there is little

evidence that such a process takes place by thermal stimulus at ordinary temperatures, it is quite possible that it occurs readily at high temperature.

The bond dissociation energy corresponding to the homolytic fission of phenyl nitrite into nitric oxide and phenoxy radicals is 23.7 kcal/mol.[5] By comparison, the homolytic fission of an aromatic nitro compound to an aryl radical and NO_2 should be less favorable; a lower limit to $D(PhNO_2)$ of 63 ± 3 kcal may be estimated from the heats of formation of phenyl radical,[6] NO_2, and nitrobenzene.[7] Thus, if the nitro–nitrite rearrangement is not a rapid one, the production of NO_2 should compete favorably with the production of NO in the pyrolysis of nitrobenzene, and by extension, of other aromatic nitro compounds as well. If on the other hand the thermal nitro–nitrite rearrangement is a facile one, little, if any, NO_2 would be expected in the pyrolysis of an aromatic nitro compound.

Several recent publications[2,8,9] concern the pyrolysis of nitrobenzene in a packed-tube reactor at 600 °C. The products of pyrolysis under these conditions were explained on the basis of primary fission of the C–N bond, yielding phenyl radical and nitrogen dioxide. However, as in our experience, no NO_2 was observed in the reactor effluent. The available evidence does not, therefore, favor primary C–N fission over other possibilities for the formation of phenyl radical.

Experimental Section

Nitrogen dioxide was purchased from Matheson, and subjected to several freeze–thaw cycles at −78 °C before use. Nitrobenzene and nitrosobenzene (reagent grade) were purchased from Eastman, and used as received. Samples to be pyrolyzed were injected into a Fisher-Victoreen pyrolyzer, and passed directly into a gas chromatograph and thence into the ion source of a Bendix MA-2 time-of-flight mass spectrometer.

In the Fisher-Victoreen instrument the pyrolysis chamber is a straight stainless steel tube of 0.6 cm i.d. and length 10 cm; the tube is rapidly (<1 s) raised from room temperature to a preselected pyrolysis temperature by resistive heating and held there for a preselected time. In our experiments that hold time always exceeded the reactor residence time (~20 s). Samples were either directly injected through a rubber septum, or else introduced via small stainless steel boats inserted into the reactor. All connectlng tubing was maintained at a temperature (100 °C) insufficient for pyrolysis, as shown by blank runs. The GC column was stainless steel, 6 ft × 0.125 in., 10% SE-30 on Chromosorb W, or in some experiments, a dummy column (10 ft × 0.125 in. stainless steel tubing, no packing). Helium carrier gas was used at a flow rate of 10 ml/min.

The quantity to be determined in most experiments was the amount of NO_2 produced in pyrolyses. Monitoring of the mass spectral intensity at *m/e* 46 is not an adequate test for the presence of *trace* quantities of NO_2; CO_2, which is produced in the pyrolyses and/or present as impurity or background, also has a peak (isotopic) at *m/e* 46. The natural abundance of ^{18}O is such that, in the mass spectrum of pure CO_2, the ratio I_{46}/I_{44} should be close to 4×10^{-3}.

The mass spectrometer was therefore arranged for simultaneous monitoring of the intensities at *m/e* 44 and 46, and any increase of the ratio $R = I_{46}/I_{44}$ from the value obtained from a sample of pure CO_2 was taken as evidence of the presence of NO_2. Several calibration runs with pure CO_2 were made before each nitrobenzene pyrolysis in order to establish the relative instrumental response factors for the two output channels; the relative sensitivities were such that for pure CO_2 $I_{46}/I_{44} = 3.7 \times 10^{-3}$.

Results

Loss of NO_2 in the Column and Pyrolyzer. Preliminary runs were made to determine whether NO_2, if produced in pyrolyses, would survive the journey to the mass spectrometer ion source. Several 10-μl samples of NO_2/N_2O_4 at atmospheric pressure were injected into the pyrolyzer, which in these experiments was held at room temperature. The results were uniform and unambiguous: NO_2 is completely consumed, and large quantities of NO appear during the ca. 1.5-min journey through the SE-30 column at 100 °C. Conversely, when the packed column was replaced with the dummy column and no other element of apparatus or procedure was changed, large amounts of NO_2 survived. Little, if any, NO was formed under these conditions: the peak heights at *m/e* 46 and 30 were in proportion appropriate to the mass spectrum of pure NO_2, but the reliability of this type of measurement is such that up to perhaps 10% of the original NO_2 could have been converted to NO. In any case, it is clear that NO_2 survives the dummy column but not the packed column.

The possibility that NO_2 is consumed in the pyrolyzer itself was also checked, by the introduction of several 10-μl samples of NO_2 into the pyrolyzer at 400 °C; the dummy column was used for these runs. The results of five determinations were $0.002 < R < 0.004$, showing clearly that NO_2 is entirely consumed. (That R is in fact less than that expected for CO_2 may be due to the presence of some N_2O, for which $R = 0.002$. However since these results were obtained from rather small peak heights, the results should not be taken to prove the presence of N_2O.) Similar determinations with the same sample and the pyrolyzer at room temperature gave $500 < R < 1700$, showing that NO_2 survives.

These observations could be explained if carbonaceous deposits from previous pyrolyses of organic samples remained in the pyrolyzer and thus provided an efficient surface for the heterogeneous reduction of NO_2, e.g., $C + NO_2 \rightarrow CO + NO$. Accordingly the surface was treated with pure oxygen flowing at ca. 60 ml/min through the pyrolyzer, held at 600 °C. This treatment was continued for 0.5 h, and produced a marked effect on NO_2 survival.

When several 10-μl samples of NO_2 were injected into the oxygenated pyrolyzer at 400 °C, values of R were obtained which were greater by 3–4 orders of magnitude than the values obtained with the unoxygenated pyrolyzer. The R values varied, probably owing to varying amounts of CO_2 in the NO_2 sample,[10] and/or variable surface effects. On the two different days this experiment was carried out, average values of 2.5 and 2.0 were obtained. Control experiments with the pyrolyzer at room temperature yielded values of 4.3 and 7.3 on two different days. Apparently some NO_2 is destroyed at higher temperatures, but for the most part it survives. Similar experiments with the pyrolyzer at 500 °C yielded lesser values of R (~1.0) showing increasing NO_2 destruction as the pyrolyzer temperature is raised. Subsequent NO_2 determinations were therefore done only at 400 °C, a temperature sufficiently great for pyrolysis but not so high as to cause complete destruction of NO_2.

Pyrolysis of Nitrobenzene. When 0.1-μl samples of neat nitrobenzene were injected into the pyrolyzer at 400 °C two distinct results were obtained, depending on the temperature of the dummy column. If the column was at 125 °C, all material was eluted in a single peak, which showed a 46/44 ratio of about 0.7. If the dummy column temperature was 50 °C, some separation took place and three peaks were eluted. These are (1), CO_2, NO, and benzene; (2), nitrosobenzene; and (3), unpyrolyzed nitrobenzene. Any NO_2 present would be eluted with the $CO_2/NO/C_6H_6$ fraction. The value of R obtained for this fraction in four separate determinations was in the range 0.002–0.004. That is, no NO_2 was observed.

It has been suggested[8] that NO_2 is produced in pyrolyses, but is converted to NO via a nitrous acid mechanism:

$$NO_2 + RH \rightarrow HNO_2 + R$$

$$2HNO_2 \rightarrow H_2O + NO_2 + NO$$

where the H-atom donor in the first step is primarily nitrobenzene itself. In the present work this possibility was checked by the 400 °C pyrolysis of a mixture of NO_2 (4×10^{-7} mol) and nitrobenzene (10^{-5} mol), under conditions such that the NO_2 and nitrobenzene fractions were well separated by the dummy column. The resulting intensity ratio 46/44 of 7.8 indicates

Table I. Products of Nitrobenzene Pyrolysis

Product	Pyrolysis temp, °C				
	400	450	500	550	600
NO_2 + NO[a]	0.7[b] (0.8)	0.8 (0.7)	2.9 (2.4)	7.5 (6.9)	14.8 (19.0)
Benzene	0.3 (0.03)	0.6 (0.2)	1.9 (1.6)	7.0 (5.5)	15.5 (14.8)
Nitrosobenzene	3.1 (1.3)	2.2 (0.3)	(0.2)	0.08 (0.03)	0.2 (<0.5)
Aniline	9.6 (0.03)	4.1 (0.5)	7.0 (3.1)	12.2 (7.5)	15.1 (17.9)
Nitrobenzene	86.3 (93.6)	92.3 (94.7)	74.6 (84.4)	44.3 (57.5)	14.5 (7.4)
Naphthalene			(0.4)	1.6 (1.1)	4.3 (4.0)
Biphenyl + phenyl ether[a]	(1.7)	(1.0)	3.5 (2.9)	6.3 (5.1)	10.8 (9.7)
Dibenzofuran	(2.5)	(0.8)	3.8 (2.6)	6.5 (6.0)	10.5 (9.8)

[a] Not separated under these chromatographic conditions. [b] Percentage of the total integrated area of the chromatogram. Numbers in parentheses are the results of a repeated determination.

that much of the NO_2 survived in spite of the 25-fold excess of nitrobenzene. Thus the above mechanism cannot explain the absence of NO_2 in pure nitrobenzene pyrolyses.

Products of Nitrobenzene Pyrolysis. Several pyrolyses of 0.1 μl of nitrobenzene were carried out with the SE-30 column rather than the dummy, in order to identify and measure the products. The column was temperature programmed for 2 min at 70 °C, then 25 °C/min to 240 °C, with a helium flow rate of 20 ml/min. Under these conditions the residence time in the reactor was about 10 s. Quantitative analysis was obtained by digital integration of the GC peak areas, using the mass spectrometer total ion current monitor as the detector. These results are collected in Table I. Not shown in Table I is some high molecular weight material formed in amounts too small for mass spectral identification.

Discussion

Several points should be made in regard to the results in Table I. In the first place, the extent of agreement between the results of repeated determinations indicates that attention should be focussed on general trends rather than on numerical results. Lack of precise agreement is expected if there is a variable heterogeneous contribution to the pyrolysis mechanism, and we have already demonstrated a variable heterogeneous effect on NO_2 consumption (reactor oxygenation experiments, vide supra).

The lack of reproducibility of product distribution is more striking and significant when the results of previous investigations are considered. For example, in nitrobenzene pyrolysis at 700 °C, Patterson et al.[9] found the ratio of dibenzofuran to aniline among the products to be 83:1; the same ratio observed by Fields and Myerson[2] at 600 °C was 11:1 and in this work at 600 °C, 0.8:1. In both the other laboratories the pyrolysis chamber was quartz or Vycor, whereas in our experiments it was stainless steel. Secondly, the relatively large amount of aniline formed at all temperatures in the present work also indicates a significant heterogeneous contribution, since this product could hardly be formed via a homogeneous mechanism.

It is interesting that the results from three laboratories are in much better agreement when the dibenzofuran–biphenyl ratios are considered, since both these compounds could be formed homogeneously. Patterson et al. found 0.85:1, Fields and Myerson found 0.75:1, and we found 0.97:1.

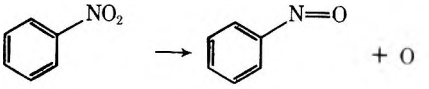
Thirdly, the behavior of nitrosobenzene is unique: it alone is produced to a decreasing extent as the reaction temperature is increased. When this fact is considered together with our finding that NO_2 is not produced in significant quantities, it lends support to the hypothesis that the mechanism of nitrobenzene pyrolysis involves a nitrosobenzene intermediate rather than the direct cleavage to NO_2 and phenyl radical.

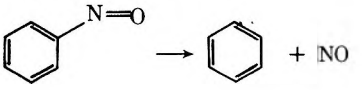
In order to confirm the hypothesis of the intermediacy of nitrosobenzene, several experiments were performed in which nitrosobenzene itself was pyrolyzed. These experiments differed from the nitrobenzene pyrolyses in that the sample, solid at room temperature, was dissolved in benzene (~170 mg of nitrosobenzene/ml benzene); 0.3 μl of the solution was then injected into the pyrolyzer. Thus there was present in the nitrosobenzene pyrolyses a larger amount of benzene than in the case of nitrobenzene pyrolysis. A second difference was that much lower temperatures sufficed for nitrosobenzene pyrolysis, as might be expected from the behavior of the nitrosobenzene produced in nitrobenzene pyrolyses.

The results of these experiments were striking in their similarity to nitrobenzene pyrolysis, and lend strong support to the hypothesis of nitrosobenzene intermediacy. In the pyrolysis of nitrosobenzene (in benzene solution) at 275 °C the products were CO_2 + NO (3.4), benzene (62.9), nitrosobenzene (8.4), aniline + phenol (3.1), nitrobenzene (1.9), naphthalene (trace), biphenyl (6.7), dibenzofuran (1.7), and hydroxyphenylbenzene (3.9). The numbers in parentheses give the percentage of the total integrated area of the chromatogram. Also, the identification of hydroxyphenylbenzene is probable rather than certain, since it is not confirmed by comparison with literature or authentic sample spectra. As in the case of nitrobenzene pyrolysis, some high molecular weight material was formed, in amounts insufficient for mass spectral identification.

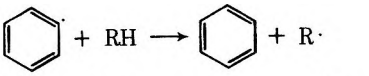
Conclusion

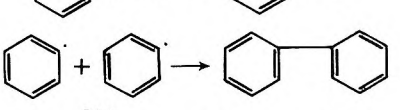
We propose that the initial phase of nitrobenzene pyrolysis is the formation of phenyl radical via the intermediate formation of nitrosobenzene:

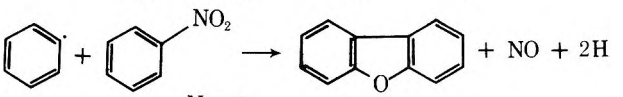


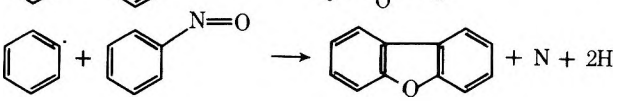


The major products benzene, biphenyl, and dibenzofuran are the expected products of phenyl radical reactions:

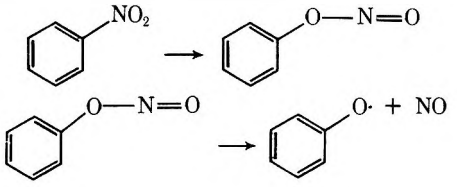




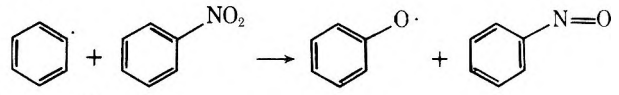




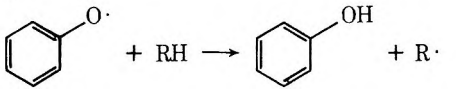
The major difference between this mechanism and that proposed by Fields and Meyerson[8] is that we do not postulate as a primary step the direct fission of nitrobenzene to NO_2 and phenyl radical, a step which, in our view, is not supported by the evidence. Also, in our experiments phenol was not observed as a product of nitrobenzene pyrolysis under any circumstances, whereas Fields and Meyerson reported phenol as the most prominent product at 600 °C. This again supports the conclusion that heterogeneous processes are of great importance in pyrolyses of aromatic nitro compounds. Formation of phenolic products most probably involves the prior production of phenoxy radical, either by



or by



followed by



without specifying whether these are homo- or hetereogeneous processes.

As we have stressed, surface reactions play a dominant role in pyrolyses. It might therefore be asked, what is the evidence for a *homogeneous* mechanism. The answer, considering both present and previous results, is that even though many of the reactions discussed above could proceed as uni- or bimolecular gas phase reactions, there is *no* evidence that nitrobenzene pyrolysis takes place to any extent by a homogeneous mechanism.

Registry No.—Nitric oxide, 10102-44-0; nitrobenzene, 98-95-3.

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(10) The NO_2 was stored in a flask equipped with a rubber septum, which after a time was degraded by the NO_2, with the resulting production of CO_2. As described above, our test for NO_2 was not affected by the presence of CO_2, even in relatively large amounts.

Dry Ozonation of Amines. Conversion of Primary Amines to Nitro Compounds

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An efficient synthetic method for the conversion of primary amines into their nitro derivatives is described. The amines, adsorbed on dry silica gel, are ozonized to give mainly the corresponding nitro compounds. The dependence of the product yields on several experimental factors was investigated.

Saturated primary amines undergo oxidation reactions by ozone in solution.[1,3] These reactions, thoroughly investigated by Bailey and his co-workers[1,2] result in the corresponding nitroalkanes accompanied by several other compounds depending on the reaction conditions. The by-products are derived mainly from the partially oxidized amines, which react with the solvent, with the solvent oxidation products, or with each other. In addition, competitive reactions of ozone with C atoms were intermittently observed. Therefore nitroalkanes are formed in modest yields and their isolation necessitates separation from the accompanying by-products limiting the preparative value of ozonation in solution.

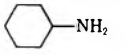
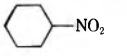
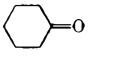
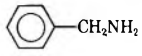
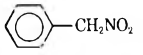
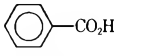
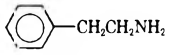
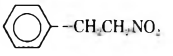
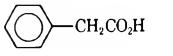
In order to overcome these drawbacks, we have applied our recently described method of ozonation on silica gel.[4] We have used this dry ozonation method to convert primary amines (alkyl, alkyl aryl, and aryl) into the corresponding nitroalkanes.

The oxidation procedure is carried out as follows. The amine is absorbed on the silica gel ca. 100 times its weight, either by mixing the dry materials in a closed flask or by impregnation using volatile solvent. The adsorbed silica gel is then cooled to −78 °C and ozone is passed through it (3 equiv of ozone is needed). After warming to room temperature, the product may be eluted from the silica gel with an appropriate solvent or by direct vacuum distillation.

Ozonation of Alkyl and Alkyl Aryl Amines. Table I lists the primary amines which were ozonized by our method. Elution of the silica gel with either ether or chloroform gave in all cases, as a major product, the corresponding nitroalkanes, whose yields were between 44 and 70%. The only by-product isolated (except for *tert*-butylamine, whose sole product is the *tert*-nitrobutane) was the respective α-carbonyl derivative (Table I) formed in yields between 2 and 6%. No other products were eluted from the silica gel neither with the solvents mentioned above nor with ethyl acetate.

To obtain optimal conditions for the formation of nitroalkanes we have determined the dependence of the yields of the two reaction products as a function of four experimental factors: concentration of the amine in the silica gel, concentration of water absorbed on the silica gel, reaction temperature, and reaction time. In the first three experiments *sec-*

Table I. Product Yields from Dry Ozonation of Aliphatic Primary Amines

Registry no.	Starting material	Nitro derivative	Yield	Carbonyl derivative	Yield
13952-84-6	$CH_3CH_2CH(CH_3)NH_2$	$CH_3CH_2CH(CH_3)NO_2$	70%	$CH_3CH_2COCH_3$	2%
75-64-9	$(CH_3)_3NH_2$	$(CH_3)_3CNO_2$	70%		
109-73-9	$CH_3(CH_2)_3NH_2$	$CH_3(CH_2)_3NO_2$	65%	$CH_3(CH_2)_2CO_2H$	5%
108-91-8			69%		4%
100-46-9			66%		6%
64-04-0			44%		*a*

[a] Not determined.

Table II. Product Distribution as a Function of *sec*-Butylamine Concentration in Silica Gel.[a]

Amine concn, w/w	2-Nitropropane, %	Ethyl methyl ketone, %
0.13	70.2	1.9
0.21	67.8	1.9
0.37	64.3	3.3
0.60	61.3	5.6
1.00	55.0	6.0
1.7	45.0	6.4
2.7	38.7	7.5
5.2	35.4	7.3
10.5	30.0	9.1

[a] Dry silica gel was used and ozonation performed at −78 °C.

Table III. Product Distribution as a Function of Temperature[a]

Temp, °C	2-Nitropropane, %	Ethyl methyl ketone, %
20	26.9	10.1
0	33.6	7.3
−23	44.8	4.6
−45	51.5	4.5
−63	54.0	4.2
−78	55.5	3.7

[a] Samples of *sec*-butylamine (1%) on dry silica gel were used.

Table IV. Product Distribution as a Function of Water Content in Silica Gel[a]

Water, %	2-Nitropropane, %	Ethyl methyl ketone, %
0	70.0	1.9
0.8	63.3	2.1
2.8	30.6	1.8
4.9	17.6	2.1

[a] Ozonation of *sec*-butylamine (0.12%) was performed at −78 °C.

Table V. Product Distribution as a Function of Reaction Time[a]

Reaction time, min	Nitrocyclohexane, %	Cyclohexanone, %
0.25	22.7	1.0
0.5	40.1	1.6
1	53.0	3.0
2	58.8	4.4
5	60.2	4.2
20	64.5	4.4
30	66.4	4.3

[a] Samples of 10 g of dry silica gel containing cyclohexylamine (0.26%) were ozonized at −78 °C, the ozone flow rate being 0.5 mmol/min.

butylamine was used and the two reaction products were 2-nitrobutane and ethyl methyl ketone. In the last experiment cyclohexylamine was used as a substrate, the products being nitrocyclohexane and cyclohexanone.

Table II describes yields as a function of the *sec*-butylamine starting concentration. On increasing concentration the yield of nitrobutane decreases, at first sharply and, after reaching ca. 2%, slowly.

At higher concentration of the amine, new unidentified dark-colored polar products are formed which were eluted from the silica gel with ethyl acetate. These may be derived from intermolecular reactions between the ozonation intermediates and the starting amines, since at concentration above 2%, all the silica grains are already covered with monolayer,[5] by the absorbed material. The yields of nitrobutane decrease with temperature increase (Table III) and with the increase of water content of the silica gel (Table IV).

It appears from Table V that the oxidation rate at −78 °C is fast and the formation of nitrobutane is completed after only 2 min. During this time ca. 3 equiv of ozone (in relation to the starting amine) has passed through the silica, which amounts to the quantity necessary for a complete conversion of the butylamine to 2-nitrobutane. Thus the reaction between ozone and the primary amine is instantaneous, the reaction rate probably being equal to the diffusion rate of ozone into the silica grains.

The ozonation mechanism of amines is probably similar to that proposed by Bailey et al.[1,2] for ozonation in solution. The pathway leading to the formation of nitro derivatives involves an electrophilic attack of ozone on the amine nitrogen, leading to an adduct, which is in an equilibrium with the anion radical. Decomposition of the adduct leads to the amine oxide, the precursor of the nitro derivative.

The fact that the yield of the carbonyl compounds is less dependent on the reaction conditions than the yield of the nitro derivatives points to different pathways for their formation. We assume that a direct attack of ozone on the activated α-carbon hydrogen bond occurs concurrently with that on the amine nitrogen leading to the α-hydroxy amines, whose decomposition generates the carbonyl function (Scheme I). This second pathway was also suggested originally by Bailey[1b,6,7,8] as an alternative mechanism for the formation of carbonyl derivatives on ozonation in solution. Similar insertion of oxygen into C–H bonds was previously observed in other saturated compounds.[4,9,10]

Scheme I

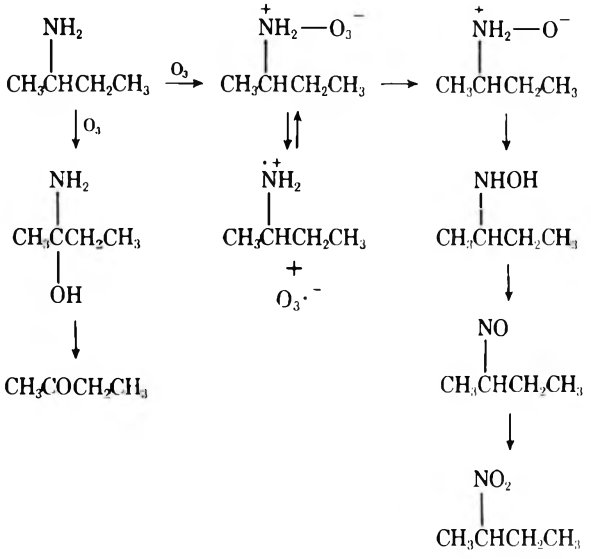
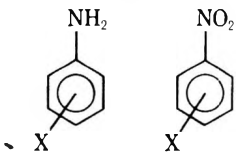


Table VI



Registry no.	X	Yield, %
618-87-1	3,5-di-NO_2	2.8
99-09-2	*m*-NO_2	3.2
100-01-6	*p*-NO_2	5.5
106-49-0	*p*-CH_3	9.6
62-53-3	H	12.5
104-94-9	*p*-OCH_3	13.2
106-47-8	*p*-Cl	20.5
106-40-1	*p*-Br	19.8

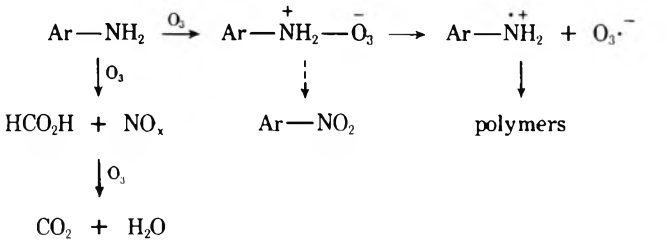
Ozonation of Anilines. Series of anilines were ozonized under similar conditions as for the aliphatic amines (Table VI). Since most of these aromatic amines were solids, the adsorption was done by dissolving the amines in methylene chloride, followed by evaporation on the rotatory evaporator. The products were eluted from the silica gel with methylene chloride. Although the yields of the nitro derivatives were generally low, they were obtained as pure crystalline materials.

Though the yields of the various nitrobenzenes formed from anilines upon peracid oxidations (Emmons reaction)[11,12] are considerably higher than upon ozonation, there is a distinct relationship between yields of the respective nitrobenzenes formed by the two methods. This similarity derives from the fact that both oxidations proceed by electrophilic attack of oxygen atom on the aniline nitrogen atom.

The low yields of the nitrobenzenes may be explained by the reduced nucleophilicity of the NH_2 group and by the competitive oxidation of the benzene ring. Thus substitution with the electron-withdrawing NO_2 group further reduces the NH_2 nucleophilicity while substitution with electron-donating OCH_3 or CH_3 functions increases the nucleophilicity of the benzene ring, both contributing to the low yield of the nitrobenzenes. On the other hand, the substitution by halogens deactivates the amine function less than the aromatic ring resulting in moderate yields of the halogenonitrobenzenes.

The yield of nitrobenzenes depends on the water content of the silica gel and on the reaction temperature (as in the case of alkyl and alkyl aryl amines) but it is independent of the concentration of the starting materials. At higher concentration, although the yield of nitrobenzene remained constant, an increasing amount of nitrogen oxides, carbon dioxide, formic acid, and black polymeric materials (aniline black) were formed. These products are a result of a direct oxidation of the aromatic ring leading to nitrogen oxide and formic acid, which gives upon further oxidation carbon dioxide. It is to be pointed out that the nitrobenzenes themselves under these conditions are generally stable to ozone.

Scheme II



The mechanism for aniline ozonation is depicted in Scheme II. It appears that the ozone–aniline adduct is less stable than the corresponding adduct of alkylamines,[10] decomposing rapidly in two independent pathways. In one, molecular oxygen is evolved resulting in formation of nitrobenzene, and in the other the radical formed from the adduct irreversibly leads to polymeric materials.

The particular advantages of the dry ozonation of amines are the simplicity of the experimental procedure, the ease of product isolation, the purity of the isolated products, and short reaction times. Further application of this method to other functionalized amines, like amino acids and polypeptides, is under investigation.

Experimental Section

General Procedure for Dry Ozonation of Alkyl and Aryl Alkyl Amines. The alkyl and aryl alkyl amines (which are all liquids) were absorbed on the silica gel by thorough mixing with dry silica gel (Merck, Kieselgel 60, 70–230 mesh, dried for 24 h at 450 °C). The silica gel (ca. 30 g) containing the adsorbed material (0.1–0.2% w/w) was cooled to −78 °C and a stream of 3% ozone (in oxygen) (generated from a Welsbach ozonizer) passed through it.

The silica gel was allowed to warm to room temperature, and the material was eluted with an organic solvent. All the products were identified with authentic samples by means of NMR, GC, and IR spectra. The quantitative estimations were done by integration of the GC peaks in relation to reference substances using a 3 m × 0.125 in. column of 20% Carbowax 20M on Chromosorb W as follows.

***sec*-Butylamine.** Elution was done with anisole which was directly injected into the GC, at 109 °C together with 1-nitropropane serving as internal standard. Two products, 2-nitrobutane (70%) and ethyl methyl ketone (2%), were identified. ***tert*-Butylamine.** The products were eluted with diethyl ether and the solution containing 1-nitropropane as internal standard was injected into GC (107 °C). 2-Methyl-2-nitropropane (70% yield) was the only detected product. ***n*-Butylamine.** Elution with diethyl ether. The reference material was diethyl malonate (160 °C); the main product was 1-nitrobutane (65%) accompanied by 5% butyric acid. **Cyclohexylamine.** Elution as above. Diethyl malonate was used as internal standard (163 °C). The main product was nitrocyclohexane (69%) accompanied by cyclohexanone (4%). **β-Phenylethylamine.** Elution of the product was done by chloroform. The product, 2-phenyl-1-nitroethane (44% yield), was pure and no other products were eluted from the silica gel. **Benzylamine.** Elution of the product was done with chloroform. The main product was α-nitrotoluene (66%) accompanied by 6% of benzoic acid.

General Procedure for Dry Ozonation of Anilines. The anilines were impregnated on dry silica gel by dissolving them in methylene chloride, adding the silica gel, and evaporation of the solvent, using a rotatory evaporator, their concentration in the silica gel being 0.15–0.20%. Ozonation was done as described above. Elution of the products was done with methylene chloride, which was evaporated to dryness, resulting in crystalline nitrobenzenes in high degree of purity, as shown by their NMR and UV spectra. Quantitative esti-

mations were done by measuring the optical density of their methanolic solutions; yields are given in Table VI.

Product Distribution as a Function of the Aniline Concentration. The experiment was performed with aniline and *p*-nitroaniline, the concentration range being between 0.1 and 13% w/w. The yields of nitrobenzene and *p*-dinitrobenzene were 12.5 ± 0.5 and 5.5 ± 0.5%, respectively, in all concentrations. At concentrations above 0.5, increasing amounts of dark viscous polymers and formic acid were eluted with a mixture of methanol–ethyl acetate (1:1). Water extract of the silica gel gave positive test for nitrate ions (precipitation in the presence of nitron solution[13]).

Ozonation of Formic Acid. Silica gel, adsorbed with pure formic acid (1%), was saturated with ozone at −78 °C. The outlet gas was allowed to bubble through a aqueous barium hydroxide solution. A white precipitate of barium carbonate indicated the formation of carbon dioxide. After 0.5 h 47% of formic acid was regenerated by ether extraction of the silica gel.

Registry No.—Anisole, 100-66-3; 1-nitropropane, 108-03-2.

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Study on the Adduct of Ketenimine and Aziridine

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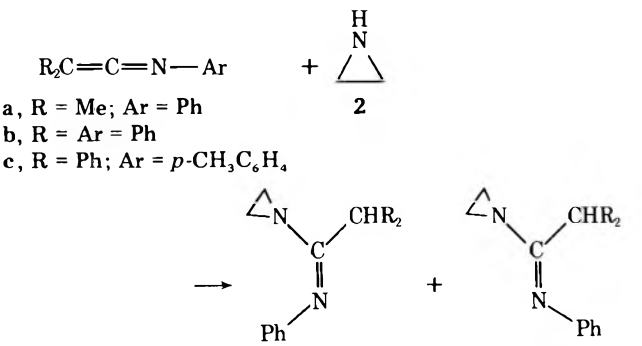
The reaction of *N*-arylketenimines **1a–c** with aziridine gave the imidoylaziridines **3a–c** in excellent yields. However, *N*-cyclohexylketenimine **1d** gave the rearranged product, the imidazoline **5d.** Syn–anti isomerism of the imidoylaziridines was found by NMR spectroscopy. Acidic treatment of **3a,b** in ethanol resulted in ring expansion to the imidazolines **5a,b** or addition of the solvent to the aziridine ring according to acids. Diphenylketene cycloadded to the C=N bond of the imidoylaziridine **3a,** while no reaction with phenyl isocyanate and phenyl isothiocyanate was observed.

For preparative purposes the addition of aziridine to heterocumulenes followed by ring expansion seems to provide a convenient method.[1] This reaction seems not to have been studied. In the present paper we report the addition of ketenimines with aziridine and some chemical properties of the adducts, imidoylaziridines.[2] We also discuss syn–anti isomerism of the imidoylaziridines by NMR spectroscopy.

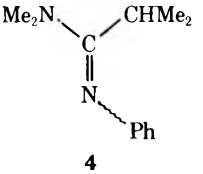
Preparation and Syn–Anti Isomerism. The reactions of *N*-arylketenimines **1a–c** with aziridine (**2**) gave imidoylaziridines **3a–c** quantitatively at room temperature. On the other hand, preparation of **3a** from *N*-phenylisobutyrimidoyl chloride and aziridine was not successful because of ring expansion of the expected aziridine during workup. Therefore the reaction of ketenimines is superior to the other method with respect to avoiding contaminants and handling with unstable aziridines. The isolated products consisted of syn and anti isomers.



	syn	anti[a]
3a	52%	48%
3b	68	32
3c	73	27

[a] Determined by NMR at 23 °C in $CDCl_3$.

The NMR spectrum of **3a** (at 23 °C) had two singlets at δ 1.82 and 2.15, which were assigned to the protons of the aziridine ring. The methyl protons exhibited two doublets at δ 1.15 and 1.27. At 100 °C, the signals of aziridinyl and methyl protons converted into one singlet at δ 1.94 and one doublet at δ 1.18 (in Me_2SO-d_6), respectively. These signals returned to the original pattern by lowering the temperature. Though aziridinyl protons are often observed as multiplets, rapid inversion of the aziridine ring caused the four ring protons to become equivalent in this case. The signal of aziridinyl protons of the syn isomer appeared in lower field than that of the anti isomer because of the shielding effect of the phenyl group lying close to the aziridine ring. In comparison with the adduct **4**

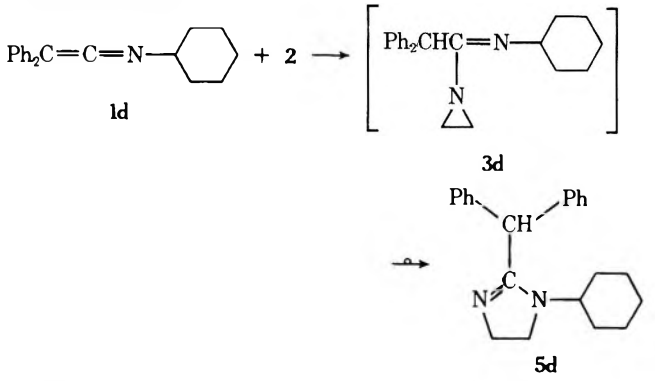


4

from dimethylamine and the ketenimine **1a,** whose NMR spectrum showed only one set of isopropyl and *N*-methyl signals at 23 °C,[3] syn–anti isomerization of **3a** was slower than that of **4.** The rate of the isomerization seemed to depend on the electron-donating ability of the amino group to the C=N bond.

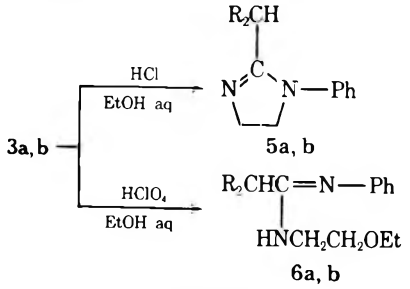
Similar phenomena were observed in the NMR spectra of the adducts **3b** and **3c**, and the ratios of syn and anti isomers were 68:32 and 73:27, respectively. The syn–anti ratio was dependent on the extent of steric repulsion between Ar and R of **3**.

In the case of the ketenimine **1d**, the addition of aziridine did not occur at room temperature, whereas the addition was accomplished by heating at 80 °C for 150 h in benzene. The difference in reactivity between *N*-arylketenimine and *N*-cyclohexylketenimine was considered to be due to the electron deficiency of the central carbon atom of the cumulative system.[4] The product obtained was the imidazoline **5d**, which showed the C=N absorption at 1630 cm^{-1} in the IR spectrum and two multiplets, assigned to the ring methylene protons, at δ 3.1–3.4 and 3.6–3.8 in the NMR spectrum. Low-field shift of the methylene protons indicated the ring cleavage of the aziridine ring and rearrangement to the imidazoline **5d** as described below.



Alcoholysis and Rearrangement of the Adducts. A three-membered ring attached to a double bond often rearranges to a five-membered ring compound upon heating or by treating with catalysts.[1,5]

The acidic treatments of the adducts **3** in aqueous ethanol yielded the different products according to the nature of the acids. With hydrochloric acid, the aziridines **3a** and **3b** rearranged to the imidazolines **5a** and **5b** quantitatively. In the IR spectra, the C=N absorptions appeared between 1610 and 1605 cm^{-1}. The NMR spectra of **5a** and **5b** showed multiplets at δ 3.7–3.8 and 3.7–4.0, respectively. This type of rearrangement was previously reported by Heine.[2]



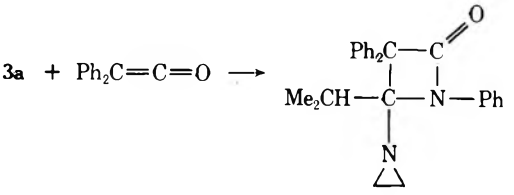
a, R = Me
b, R = Ph

Though hydrochloric acid caused the ring expansion of the aziridine ring, perchloric acid led to addition of the alcohol to the aziridine ring of **3** without the formation of **5**. The products **6a** and **6b** showed the C=N absorptions at 1620 and 1615 cm^{-1}, respectively. The NMR spectra of the products fully supported the structures.

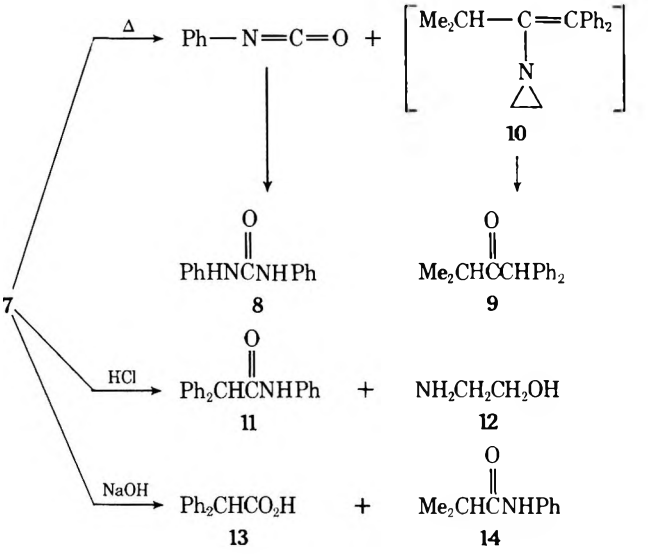
The thermal rearrangement of **3d** to **5d** was observed in the course of the reaction. On the other hand, the treatment of **3a** in refluxing toluene did not cause the rearrangement. This may be due to difference in nucleophilicity of the nitrogens of the imino functions.

Cycloadduct with Diphenylketene. The cycloaddition of heterocumulenes to azomethines[6] or 1-substituted aziridines[7] has been investigated. With azomethines, 1,2-cycloaddition occurred across the C=N bond, and 1,3-cycloaddition reaction involving ring cleavage was observed for 1-substituted aziridines. The compound **3** has both a C=N and an aziridinyl group; therefore, it is interesting to know which function of **3** will initiate the reaction with heterocumulenes.

Phenyl isocyanate and phenyl isothiocyanate did not react with the aziridine **3a** even in refluxing benzene. However, diphenylketene reacted with **3a** at room temperature to give the 1:1 adduct, the azetidine **7**, formed by the addition of the ketene across the C=N bond of **3a**. No cycloadduct was obtained in the reaction of the aziridine **3b** and the ketene. This was presumably because of the steric effect of the phenyl groups.



The structure of **7** was supported by pyrolysis and hydrolyses. Pyrolysis of **7** gave phenyl isocyanate, which was identified as *N,N'*-diphenylurea (**8**, 72%), and diphenylmethyl isopropyl ketone (**9**, 80%). The compound **9** was formed by hydrolysis of the enamine **10** during column chromatography.



Acidic hydrolysis of the compound **7** afforded diphenylacetanilide (**11**, 98%) and 2-aminoethanol (**12**). Alkaline hydrolysis of the azetidine **7** gave diphenylacetic acid (**13**, 68%) and isobutyranilide (**14**, 85%).

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. IR, NMR, and mass spectra were obtained on a JASCO IR-E spectrometer, JEOL LNM-3H-60 and JNM-PS-100 spectrometers, and a Hitachi RMU-6E spectrometer, respectively.

As contact with aziridine should be avoided, all the procedures were carried out in a draft chamber.

Materials. Ketenimines **1a**,[8] **1b**, and **1c**[9] were prepared by the reported methods. Commercially available aziridine was distilled over sodium hydroxide prior to use.

Reaction of Dimethylketene-*N*-phenylimine (1a) and Aziridine (2). To a solution of the ketenimine **1a** (2.7 g, 19 mmol) in ether (25 ml), 1.5 g (35 mmol) of **2** was added dropwise with cooling. The

reaction occurred exothermically and soon the characteristic infrared absorption of the ketenimine disappeared. After 15 min, the solvent and excess aziridine were evaporated in vacuo. Distillation of the residue gave 3.4 g (97%) of *N*-phenylisobutyrimidoylaziridine (**3a**): bp 82–85 °C (2 mm); IR (neat) 1625 cm^{-1} (C=N); NMR ($CDCl_3$, 23 °C) δ 1.15 (d, 3.1, J = 7.5 Hz, syn Me), 1.27 (d, 2.9, J = 7.5 Hz, anti Me), 1.82 (s, 1.9, anti aziridinyl protons), 2.15 (s, 2.1, syn aziridinyl protons), 2.4–2.8 (m, 1, J = 7.5 Hz, $CHMe_2$), 6.5–7.4 (m, 5, aromatic protons), the ratio of syn and anti isomers was 52:48 [(Me_2SO-d_6, 100 °C) 1.18 (d, 6, J = 7.5 Hz, 2 Me), 1.94 (s, 4, aziridinyl protons), 2.72 (septet, 1, J = 7.5 Hz, $CHMe_2$), 6.4–7.4 (m, 5, aromatic protons)]; mass spectrum m/e 188 (M^+, calcd 188).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found; C, 76.66; H, 8.34; N, 14.94.

Reaction of Diphenylketene-*N*-phenylimine (1b) and Aziridine (2). The ketenimine **1b** (2.7 g, 10 mmol) was treated with **2** (0.64 g, 15 mmol) in ether (25 ml) at 25 °C and the characteristic IR absorption of **1b** disappeared immediately. Pale yellow crystalline 1-(*N*-phenyldiphenylacetimidoyl)aziridine (**3b**, 3.1 g, 99%) was obtained upon evaporation of the solvent. Recrystallization of **3b** from ethanol gave colorless needles: mp 103–105 °C; IR (Nujol) 1630 cm^{-1} (C=N); NMR ($CDCl_3$, 23 °C) δ 1.80 (s, 2.7, syn aziridinyl protons), 1.82 (s, 1.3, anti aziridinyl protons), 5.14 (s, 0.7, syn $CHPh_2$), 5.19 (s, 0.3, anti $CHPh_2$), 6.5–7.5 (m, 15, aromatic protons), the ratio of syn and anti isomers was 68:32 [(Me_2SO-d_6, 100 °C) 1.81 (s, 4, aziridinyl protons), 5.12 (s, 1, $CHPh_2$), 6.7–7.5 (m, 15 aromatic protons)]; mass spectrum m/e 312 (M^+, calcd 312).

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.66; H, 6.60; N, 8.96.

Reaction of Diphenylketene-*N*-*p*-tolylimine (1c) and Aziridine (2). After the same treatment as described above, the reaction of 5.7 g (20 mmol) of **1c** and 1.3 g (30 mmol) of **2** gave 5.4 g (83%) of 1-(*N*-*p*-tolyldiphenylacetimidoyl)aziridine (**3c**), which was recrystallized from ethanol to give colorless needles: mp 138–139 °C; IR (Nujol) 1620 cm^{-1} (C=N); NMR ($CDCl_3$, 23 °C) δ 1.80 (s, 2.9, syn aziridinyl protons), 1.81 (s, 1.1, anti aziridinyl protons), 2.25 (s, 3, Me), 5.15 (s, 0.7, syn $CHPh_2$), 5.23 (s, 0.3, anti $CHPh_2$), 6.4–7.4 (m, 14, aromatic protons), the ratio of syn and anti isomers was 73:27; mass spectrum m/e 326 (M^+, calcd 326).

Anal. Calcd for $C_{23}H_{22}N_2$: C, 84.62; H, 6.79; N, 8.58. Found: C, 84.52; H, 6.77; N, 8.30.

Reaction of Diphenylketene-*N*-cyclohexylimine (1d) and Aziridine (2). A mixture of the ketenimine **1d** (2.8 g, 10 mmol) and **2** (0.85 g, 20 mmol) in benzene (20 ml) was stirred for 8 h at room temperature. As no change was observed in the IR spectrum, the mixture was heated to reflux for 150 h until the characteristic absorption of **1d** disappeared. After removal of the solvent and excess aziridine, 3.0 g (94%) of 2-diphenylmethyl-3-cyclohexylimidazoline (**5d**) was isolated by adding petroleum ether, and was recrystallized from hexane to give colorless needles: mp 75–76 °C; IR (Nujol) 1630 cm^{-1} (C=N); NMR ($CDCl_3$) δ 0.8–1.8 [m, 10, $(CH_2)_5$], 3.1–3.4 (m, 3, CH and CH_2), 3.6–3.8 (m, 2, CH_2), 4.87 (s, 1, $CHPh_2$), 7.1–7.3 (m, 10, aromatic protons); mass spectrum m/e 318 (M^+, calcd 318).

Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.98; H, 8.29; N, 8.77.

Preparation of the Amidine 4. An excess amount of gaseous dimethylamine was bubbled into an ethereal solution of dimethylketene-*N*-phenylimine (2.1 g) at room temperature. After the characteristic IR absorption of the ketenimine had disappeared, the solvent was removed and the residue was distilled to give 2.6 g (95%) of N^1,N^1-dimethyl-N^2-phenylisobutyramidine (**4**): bp 75–78 °C (1 mm); IR (neat) 1615 (shoulder), 1595, and 1585 cm^{-1}; NMR ($CDCl_3$, 23 °C) δ 1.10 (d, 6, J = 7.5 Hz, $CHMe_2$), 2.92 (s, 6, NMe_2), 3.10 (septet, 1, J = 7.5 Hz, $CHMe_2$), 6.5–7.2 (m, 5, aromatic protons); mass spectrum m/e 190 (M^+, calcd 190).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.89; H, 9.51; N, 14.78.

Rearrangement of the Aziridine 3a with Hydrochloric Acid. A mixture of 6 N hydrochloric acid (4 ml), ethanol (20 ml), and 1.8 g of **3a** was kept refluxing for 5 h. The mixture was neutralized with aqueous NaOH solution and extracted with ether. The organic layer was dried (Na_2SO_4), concentrated, and distilled to give 1.36 g (76%) of 2-isopropyl-3-phenylimidazoline (**5a**): bp 77 °C (1 mm); IR (neat) 1610 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.10 (d, 6, J = 7.0 Hz, 2 Me), 2.61 (septet, 1, J = 7.0 Hz, $CHMe_2$), 3.7–3.8 [m, 4, $(CH_2)_2$], 7.0–7.4 (m, 5, aromatic protons); mass spectrum m/e 188 (M^+, calcd 188).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.47; H, 8.70; N, 14.85.

Rearrangement of the Aziridine 3b with Hydrochloric Acid. The aziridine **3b** (0.6 g) was treated under the same conditions as above to give 0.26 g (43%) of 2-diphenylmethyl-3-phenylimidazoline (**5b**). Recrystallization from ethanol gave colorless granules: mp 111–113 °C; IR (Nujol) 1605 cm^{-1} (C=N); NMR ($CDCl_3$) δ 3.7–4.0 [m, 4, $(CH_2)_2$], 5.95 (s, 1, $CHPh_2$), 6.8–7.3 (m, 15, aromatic protons); mass spectrum m/e 312 (M^+, calcd 312).

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.52; H, 6.57; N, 9.03.

Alcoholysis of the Aziridine 3a with Perchloric Acid. A mixture of 1.0 g of the aziridine **3a**, 1.5 ml of 40% perchloric acid, and 20 ml of ethanol was heated to reflux for 5 h. The mixture was neutralized (NaOH aqueous), extracted (ether), and concentrated to give 0.95 g (79%) of N^1-2-ethoxyethyl-N^2-phenylisobutyramidine (**6a**), which was purified by pot distillation (75 °C, 1 mm): IR (neat) 3400–3300 (NH), 1620 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.05 (d, 6, J = 7.0 Hz, $CHMe_2$), 1.21 (t, 3, J = 7.5 Hz, CH_2Me), 2.74 (septet, 1, J = 7.0 Hz, $CHMe_2$), 3.3–3.7 [m, 6, $(CH_2)_2$ and CH_2], 4.5–4.8 (broad, 1, NH), 6.6–7.3 (m, 5, aromatic protons); mass spectrum m/e 234 (M^+, calcd 234), 161 ($M^+ - CH_2CH_2OEt$).

Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.75; H, 9.46; N, 11.96. Found: C, 72.03; H, 9.45; N, 12.51.

Alcoholysis of the Aziridine 3b with Perchloric Acid. From 0.60 g of the aziridine **3b**, 0.49 g (82%) of crude N^1-2-ethoxyethyl-N^2-phenyldiphenylacetamidine (**6b**) was obtained by the same treatment as above. The compound **6b** was recrystallized from hexane to afford colorless needles: mp 129–130 °C; IR (Nujol) 3320 (NH) and 1615 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.08 (t, 3, J = 7.0 Hz, Me), 3.39 (q, 2, J = 7.0 Hz, CH_2), 3.4–3.6 [m, 4, $(CH_2)_2$], 4.5–4.8 (broad, 1, NH), 6.5–7.3 (m, 15, aromatic protons); mass spectrum m/e 358 (M^+, calcd 358), 285 ($M^+ - CH_2CH_2OEt$).

Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.82. Found: C, 80.22; H, 7.53; N, 7.78.

Reaction of the Aziridine 3a and Diphenylketene. To a solution of 5.0 g (27 mmol) of the aziridine **3a** in benzene, 5.2 g (27 mmol) of diphenylketene was added dropwise. The mixture was stirred at room temperature for 15 min until the characteristic IR absorption of the ketene disappeared. The mixture was concentrated in vacuo to give 6.5 g (64%) of 1,3,3-triphenyl-4-isopropyl-4-(1-aziridinyl)azetidin-2-one (**7**), which was recrystallized from benzene–hexane: colorless granules; mp 147–148 °C; IR (Nujol) 1740 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.82 (d, 3, J = 6.5 Hz, Me), 1.16 (d, 3, J = 6.5 Hz, Me), 1.2–1.4 and 1.6–1.8 (m, 2, aziridinyl protons, respectively), 2.5–2.9 (m, 1, J = 6.5 Hz, $CHMe_2$), 7.2–7.6 and 7.8–8.0 (m, 15, aromatic protons); mass spectrum m/e 382 (M^+, calcd 382), 263 ($M^+ - PhNCO$), 188 ($M^+ - Ph_2CCO$).

Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.92; H, 6.80; N, 7.30.

Pyrolysis of the Azetidine 7. The azetidine **7** (2.0 g, 5 mmol) was heated for 2 h in refluxing toluene (25 ml). The resulting phenyl isocyanate was distilled off under reduced pressure and led to N,N'-diphenylurea (**8**) by addition of aniline. The urea **8** was recrystallized from ethanol to give colorless needles (72%). The IR spectrum of **8** was in fair agreement with that of an authentic sample and no depression of melting point was observed for the mixture of **8** and the authentic sample. The residue was chromatographed (Al_2O_3, benzene–hexane) to isolate 1.0 g (80%) of diphenylmethyl isopropyl ketone (**9**), which was recrystallized (ethanol) to give colorless needles: mp 78–79 °C; IR (Nujol) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.07 (d, 6, J = 7.5 Hz, 2 Me), 2.77 (septet, 1, J = 7.5 Hz, $CHMe_2$), 5.25 (s, 1, $CHPh_2$), 7.1–7.3 (m, 10, aromatic protons); mass spectrum m/e 238 (M^+, calcd 238).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.47; H, 7.58.

Acidic Hydrolysis of the Azetidine 7. An alcoholic solution of 2.0 g (5 mmol) of the azetidine **7** and 4 ml of 6 N hydrochloric acid was kept refluxing for 5 h. The mixture was poured into water and extracted with ether. From the organic layer, 1.5 g (98%) of diphenylacetanilide (**11**) was obtained. Recrystallization of **11** from ethanol afforded colorless needles, mp 191–192 °C. The IR spectrum of **11** agreed with that of an authentic sample prepared from diphenylacetyl chlolide and aniline, and the melting point of **11** was not depressed by mixing with the authentic sample. The aqueous layer was made alkaline (sodium hydroxide) and extracted (ether). The extract contained 2-aminoethanol (**12**), which was identified by GLC.

Alkaline Hydrolysis of the Azetidine 7. An alcoholic solution of the azetidine **7** (2.0 g) and 2 N sodium hydroxide (12 ml) was refluxed for 6 h. The mixture was extracted (ether) after addition of water. From the ethereal layer, 0.72 g (85%) of isobutyranilide (**14**) was isolated, and was recrystallized from ethanol to give colorless needles, mp 110–111 °C. The IR spectrum of **14** agreed with that of an authentic sample prepared from corresponding acid chloride and aniline, and the melting point of **14** was not depressed by mixing with the

authentic sample. The aqueous layer was acidified (hydrochloric acid) and extracted (ether). Evaporation of ether gave 0.41 g (68%) of diphenylacetic acid (13). Recrystallization of 13 from benzene gave colorless granules, mp 147–148 °C. The melting point and IR spectrum of 13 were in good agreement with those of an authentic sample.

Registry No.—**1a**, 14016-34-3; **1b**, 14181-84-1; **1c**, 5110-45-2; **1d**, 24932-57-8; **2**, 151-56-4; *syn*-**3a**, 61047-06-1; *anti*-**3a**, 61047-07-2; *syn*-**3b**, 61047-08-3; *anti*-**3b**, 61047-09-4; *syn*-**3c**, 61047-10-7; *anti*-**3c**, 61047-11-8; **4**, 29172-31-4; **5a**, 61047-12-9; **5b**, 61047-13-0; **5d**, 61047-14-1; **6a**, 61047-15-2; **6b**, 61047-16-3; **7**, 61047-17-4; **9**, 7495-04-7; **11**, 4695-14-1; **14**, 4406-41-1; dimethylamine, 124-40-3; diphenylketene, 525-06-4.

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Acid-Catalyzed Addition of Secondary Amines to Cyclopropyl Ketones. Mass Spectra of Some Cyclic Aminobutyrophenones

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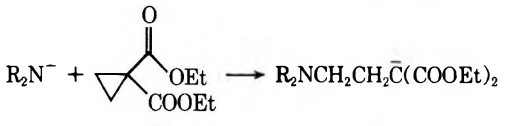
Four cyclic secondary amines [morpholine (**a**), piperidine (**b**), pyrrolidine (**c**), and 2-(1-piperazinyl)ethanol (**d**)] were induced to react with five cyclopropyl ketones of the structure RCO-c-C_3H_5 (**16–20**, R = *p*-anisyl, phenyl, *p*-chlorophenyl, methyl, and cyclopropyl, respectively) in presence of acid to yield ring-opened γ-amino ketones (**21–27**). The products were characterized by their spectroscopic properties (IR, UV, NMR, and MS), derivatives, and other analytical data. The reactivity of the ketones increases in the order cyclopropyl < *p*-anisyl < phenyl < *p*-chlorophenyl. Since this cannot be reconciled with a cyclopropylcarbinyl–homoallylic cation mechanism, the intermediacy of a carbinolamine (**31**) is invoked.

Our studies concerning addition of organomagnesium halides to cyclopropyl ketones,[1] which were accompanied by ring opening, directed our interest to examining the behavior of these ketones toward other nucleophiles such as secondary amines.

Stewart and co-workers[2] have shown that secondary amines add to 1,1-disubstituted cyclopropanes **1** bearing two electron-withdrawing groups in a 1,4 fashion, leading to ring-opened γ-amino esters **2**. The highly conjugated ("bisected")



1

$\xrightarrow{R_2NH}$ $R_2NCH_2CH_2CH_2(COOEt)_2$

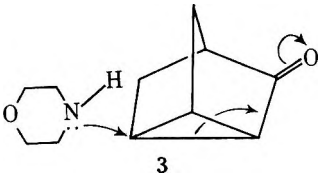
2

nortricyclanone **3** was shown[3] to add morpholine in a 1,4 manner to give exclusively *exo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**4**), indicating ring rupture by backside nucleophilic attack.

Acid-induced addition of secondary amines to cyclopropanes substituted by carbonyl groups was demonstrated by Cook et al.,[4] who obtained diamino- and aminoimonium salt products (**5** and **6**) from nortricyclanone and pyrrolidine or hexamethylenimine in presence of acids.

The sequence of incorporation of the amines is not known; the role of the catalyst is, apparently, in a dehydration stage.

Direct attack on the carbonyl carbon without ring opening was demonstrated by Cook et al.,[4] on treating nortricyclanone



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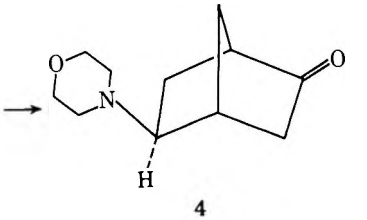

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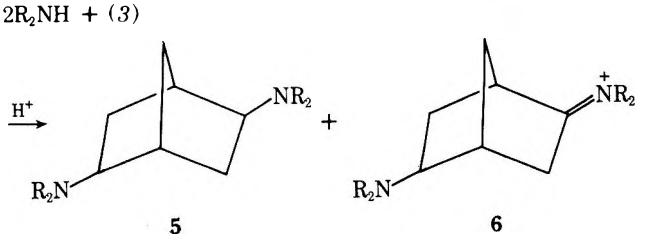
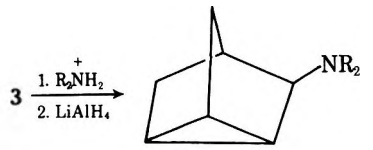


5 6

with amine salts rather than with free nucleophilic amines, followed by $LiAlH_4$ reduction (**3** → **7**). They have also obtained[5] ring-retained products from cyclopropanecarboxaldehyde and methyl cyclopropyl ketone in presence of basic and acidic catalysts, respectively.

A rather esoteric reaction of ammonia with 1,1-dicarbethoxy-2,2,3,3-tetracyanocyclopropane (**8**) was reported by Regan.[6] Although the ring becomes highly deficient of elec-



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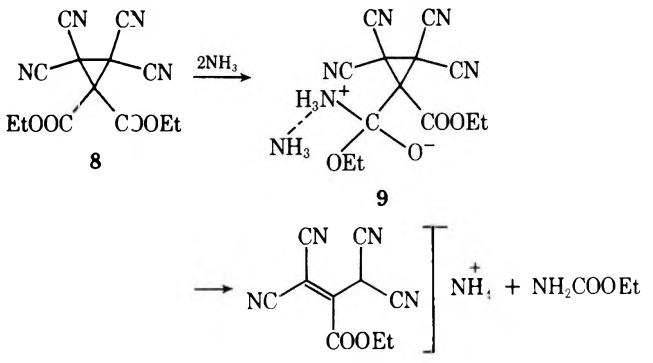
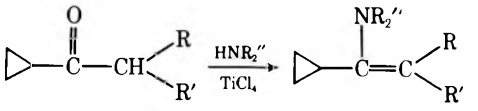
trons due to *six* electron-withdrawing groups, the nucleophilic attack occurs initially at the carbonyl group. The emerging carbinolamine (**9**) collapses with ring opening by intramolecular Michael type addition to yield ammonium 2-carbethoxy-1,1,3,3-tetracyano-2-propenide (**10**):



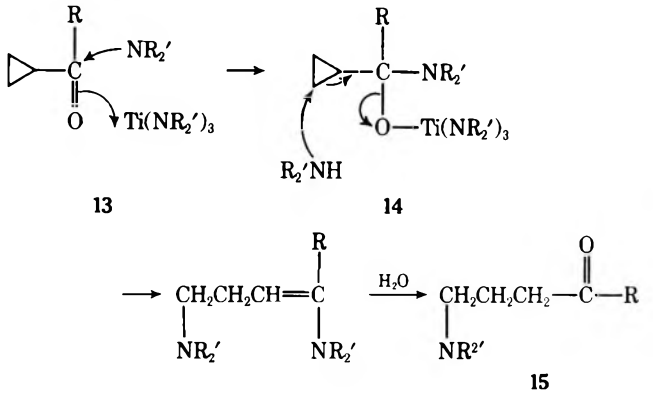
8 9 10

Recently, Pocar and his collaborators[7] have demonstrated two modes of reaction between secondary amines and cyclopropyl ketones under the influence of $TiCl_4$. Ketones possessing α hydrogen other than cyclopropyl methinic (**11**) gave enamines with ring retention (**12**):



11 12

Ketones lacking enolizable protons (**13**) yielded γ-amino ketones by the route portrayed below:



13 14 15

Our study concerns structural factors influencing yields of open-chain products resulting from addition of cyclic secondary amines (**a–d**) to alkyl and aryl cyclopropyl ketones (**16–20**) in presence of proton acid. The reaction conditions and products were virtually uniform: a mixture of the ketone, slight excess of the amine, and 10 mol % *p*-TsOH was boiled for 20–30 h neat or with toluene or xylene as diluent, yielding γ-amino ketone (**21–27**) as the sole product.

The products were isolated by vacuum distillation or crystallization and freshly purified by GLC for the analytical and spectral measurements, since they darken on aging (Table I).

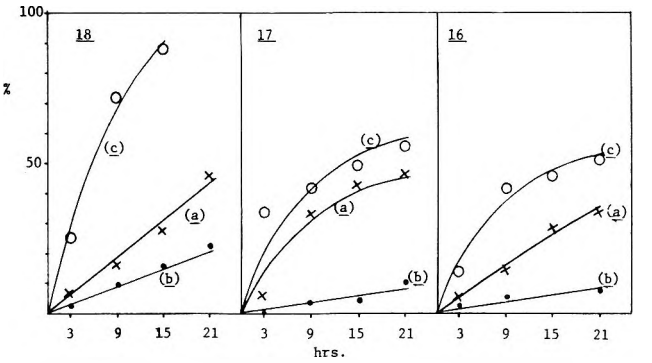
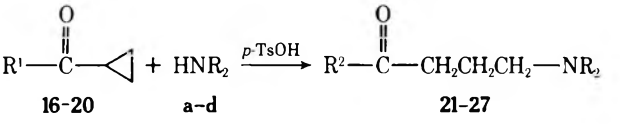


Figure 1. Consumption of aryl cyclopropyl ketones by addition of secondary amines. Ketone:amine:*p*-TsOH 1:1.3:0.1; external temperature 120–125 °C.

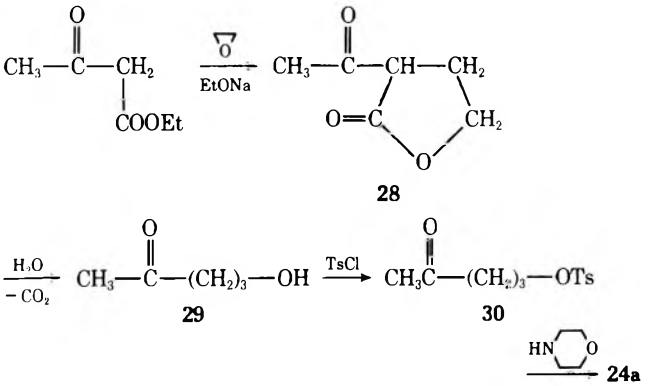


16-20 a–d 21-27

16, **21**, $R^1 = R^2$ = *p*-anisyl
17, **22**, $R^1 = R^2$ = phenyl
18, **23**, $R^1 = R^2$ = *p*-chlorophenyl
19, **24**, $R^1 = R^2$ = methyl
20, **25**, $R^1 = R^2$ = cyclopropyl
26, R^2 = 3-morpholinopropyl
27, R^2 = *p*-hydroxyphenyl

a, HNR_2 = morpholine
b, HNR_2 = piperidine
c, HNR_2 = pyrrolidine
d, HNR_2 = 2-(1-piperazinyl)ethanol

Elemental analysis of the free amino ketones and their respective picrate salts (Table III) and molecular weight determination by mass spectrometry of the latter[8] show that the products are 1:1 adducts (except **26a**, where dicyclopropyl ketone added two molecules of morpholine, one to each of the rings). The $R^1C{=}O$ portions of the starting ketones are retained in the products (**26a** and **27a** excluded) as evidenced by the carbonyl stretching vibration absorption (1676–1701 cm^{-1} for the aromatic ketones and 1710–1735 cm^{-1} for the aliphatic ones) and UV absorption bands (λ_{max} 241–242, 251–252, and 272–275 nm for phenyl, *p*-chlorophenyl, and *p*-anisyl ketones, respectively) detailed in Table II. Cyclopropyl signals are absent in the NMR spectra (Table II; **25a** is an obvious exception) and are replaced by three new methylene signals—a triplet for the methylene α to carbonyl, a quintuplet for the β-CH_2 group,[13] and a signal for the methylene bonded to nitrogen appearing with those of the amine and revealed by integration. The structures were further substantiated by some derivatizations (hydrochlorides of **22d** and **26a**, methiodides of **24a** and **26a**, deuteration of **21a**, carbinols from **24a** by $LiAlH_4$ reduction and from **21a**, **21c**, and **22a** by Grignard addition; see Table III) and by independent alternative synthesis of **24a** as follows:



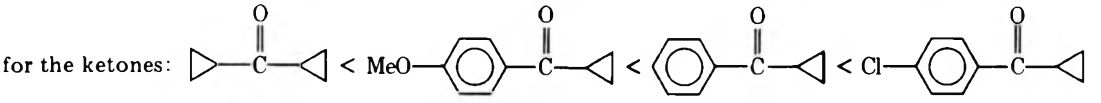
28 29 30 24a

Table I. Analytical Data of γ-Amino Ketones[j]

γ-Amino ketone	Method[a]	Yield[b]	Bp, °C (mmHg) or mp, °C	n^{25}D	Mol wt[c]
21a	C	55	55–56[h]		263
21b	A	40	125 (0.6)	1.5562	261
21c	A	43	164–169 (0.9)	1.5483	247
21d	B	27	87–88		306
22a	A	65	139–141 (0.3)[h]	1.5346	233
22b	A	26	132–136 (0.7)[e]	1.5361[e]	231
22c	A	58	154–160 (3.6)	1.5369	217
22d	D	64	83–84		276
23a	A, B	26	160–165 (0.6)[h]	1.5305	267
23b	A	50	152–155 (0.8)[f]	1.5317	265
23c	B	42	64–65[g]		251
23d	B	51	73–74		310
24a	A	55	72–73 (0.4)[d]	1.4615[d]	171
25a	E	11	120–122 (2.0)	1.4795	197
26a	E	28	178–180 (0.8)	1.4875	284
27a	C	2.5	172–173		249[i]

[a] See Experimental Section. [b] Percent of isolated material. [c] By MS of the corresponding picrate.[8] [d] Lit.[9] 81 °C (0.5 mm); n^{24}D 1.4630. [e] Lit.[10] 144–146 °C (3 mm); n^{20}D 1.5348. [f] Lit.[11] 148–150 °C (0.25 mm). [g] Lit.[11] 58–60 °C. [h] Reported in the literature[12] as HCl salt. [i] By MS of the free base. [j] Satisfactory analytical data (±0.4% for C, H, N) for all new compounds were submitted for review.

The yields listed in Table I relate to the amounts of isolated products, not to those actually formed. Estimation of the relative reaction rates could be determined from experiments run in parallel under identical conditions of concentration, temperature, and duration, following the consumption of the starting ketone by GLC analysis.[14] The results of such study at 120–125 °C are represented graphically in Figure 1; dicyclopropyl ketone (**20**) is not represented because it was totally inactive toward all the amines under these conditions, which are ca. 25 °C lower than the preparative reflux temperature. Two sequences of the relative reactivities can be deduced from the data:



for the amines: piperidine < morpholine < pyrrolidine

The order in the ketone series cannot be reconciled with a cyclopropylcarbinyl–homoallylic cation mechanism. Initial formation of a cation $R^+C(OH)$-c-C_3H_5 by protonation of the ketone should be enhanced by electron-donating R groups and hampered by electron-withdrawing ones,[15] contrary to the order observed. The order observed reflects an increase in the electrophilicity of the carbonyl carbon atom on going along the series from cyclopropyl to *p*-chlorophenyl, suggesting initial attack of the amine at this site rather than at the ring, to form a carbinolamine (**31** in Scheme I).

In the amine series the lower tendency of piperidine ($K = 1.6 \times 10^{-3}$) to react with ketones as compared with that of the

Table II. Spectral and NMR Data of γ-Amino Ketones

Registry no.	Compd	$\nu_{C=O}$, cm^{-1}	λ_{max}, nm (log ε) (in EtOH)	τ (*J*, Hz),[d] O=CCH$_2$(t)	CH$_2$N (m)	CH$_2$CH$_2$CH$_2$ (q)
5170-66-1	**21a**[e]	1686[b]	274 (4.19)	7.05 (7.0)	7.46–7.70	8.08 (7.0)
61025-28-3	**21b**	1695[a]	275 (4.22)	7.07 (7.0)	7.33–7.75	8.09 (7.0)
61025-29-4	**21c**	1701[a]	273 (4.12)	7.03 (6.7)	7.30–7.70	8.07 (6.7)
37133-86-1	**21d**	1676, 3415[b,c]	272–273 (4.23)	7.05 (6.5)	7.28–7.75	8.10 (6.5)
3935-01-1	**22a**	1701[a]	242–243 (4.06), 280 (3.01)	6.99 (7.0)	7.38–7.74	8.06 (7.0)
4476-25-9	**22b**	1695[a]	242–243 (4.14), 279 (3.03)	7.04 (7.0)	7.40–7.80	8.10 (7.0)
59921-83-4	**22c**	1695[a]	242 (4.06), 279 (3.04)	6.97 (7.0)	7.30–7.65	8.06 (7.0)
61025-30-7	**22d**	1687, 3415[b,c]	241 (4.14), 278 (3.17)	6.99 (6.5)	7.32–7.70	8.06 (6.5)
5487-31-0	**23a**	1689[a]	252 (4.22)	6.98 (7.0)	7.40–7.75	8.09 (7.0)
2888-40-6	**23b**	1686[a]	252 (4.20)	7.05 (7.0)	7.45–7.80	8.08 (7.0)
2895-68-3	**23c**	1672[b]	252 (4.18)	7.00 (7.0)	7.30–7.70	8.06 (7.0)
61025-31-8	**23d**	1685, 3415[b,c]	251 (4.22)	7.04 (7.0)	7.34–7.72	8.07 (7.0)
59127-81-0	**24a**	1735[a]		7.35–7.80		8.25 (7.0)
61025-32-9	**25a**	1710[a]		7.25–7.82		7.92–8.42
61025-33-0	**26a**	1730[a]		7.30–7.75		8.20 (7.0)
61025-34-1	**27a**[f]	1681, 3400[b,c]	280–281 (4.26)	7.13 (7.0)	7.63–7.93	8.27 (7.0)

[a] Neat. [b] In KBR. [c] ν_{OH}, broad. [d] 60 MHz in $CDCl_3$, Me_4Si; d = doublet; t = triplet; q = quintuplet; s = singlet; m = multiplet. Other signals appear as follows. Aromatic protons: *p*-$MeOC_6H_4$, $A_2'B_2'$ centered at τ 2.55–2.60 with $\Delta\nu_{AB} \sim 60$ Hz; C_6H_5, m at τ 1.90–2.17 and 2.36–2.77; *p*-ClC_6H_4, $A_2'B_2'$ centered at τ 2.30–2.35 with $\Delta\nu_{AB} \sim 30$ Hz. Cyclic CH_2 not adjacent to N: morpholine, A_2' of $A_2'X_2'$ at τ 6.10–6.52; piperidine, broad single band at τ 8.26–8.82; pyrrolidine, m at τ 8.10–8.41; CH_3O, s at τ 6.13–6.20; CH_2OH, t at τ 6.36–6.39 (*J* 5.0 Hz); CH_3CO, s at τ 7.84; cyclopropyl CH_2, m at 8.92–9.31; cyclopropyl CH, m at 7.92–8.42. [e] 100-MHz NMR. [f] NMR in Me_2SO-d_6.

Scheme I

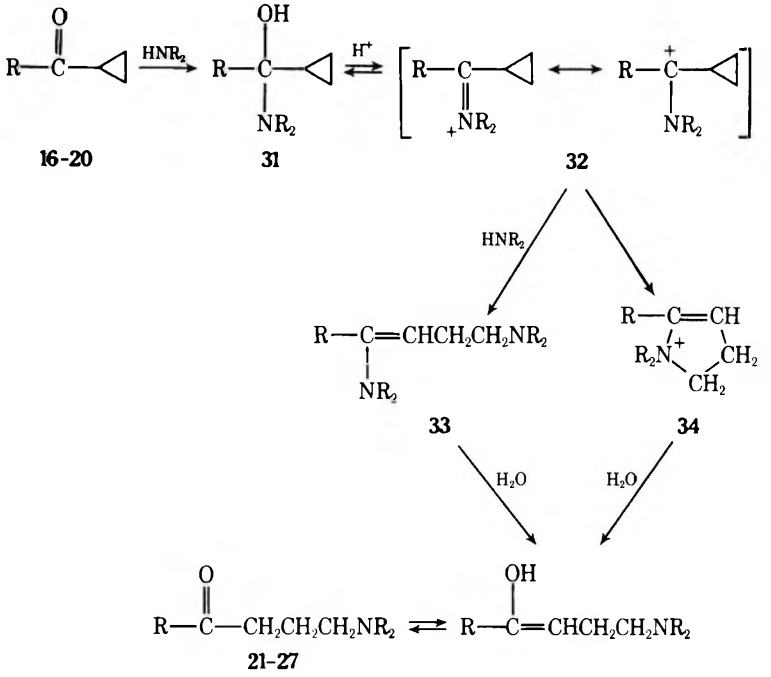


Table III. Derivatives of γ-Amino Ketones[k]

Registry no.	Derivative[a]	Mp, °C	NMR, τ[b]
61025-35-2	**21a** picrate	169–171	
61025-36-3	**21a**-d_2[c]		7.46–7.70 (m, 6 H), 808 (6, J = 7.0 Hz, 2 H)[d]
61062-59-7	**21b** picrate	128–129	
61025-37-4	**21c** picrate	139	
61025-38-5	**21d** dipicrate	238	
61025-39-6	**22a** picrate	140	1.24 (s, 2 H), 5.85–6.00 (A_2' of $A_2'X_2'$, 4 H), 6.18–6.50 (m, 2 H), 6.60–6.96 (m, 6 H), 7.80 (q, J = 7.0 Hz, 2 H)[d]
61025-40-9	**22b** picrate	127	
61025-41-0	**22c** picrate	104–105	
61025-42-1	**22d** dipicrate	215–216	
61025-43-2	**22d** 2HCl[e]	231	
61025-44-3	**23a** picrate	188–190	
61025-45-4	**23b** picrate	153–154	
61025-46-5	**23c** picrate	158	
61025-47-6	**23d** dipicrate	236 dec	
61025-48-7	**24a** picrate	132–133	
61025-49-8	**24a** HCl[f]	155–156	5.95–6.20 (A_2' of $A_2'X_2'$, 4 H), 6.60–7.10 (m, 6 H), 7.32 (t, J = 6.8 Hz, 2 H), 7.89–8.41 (m, 2 H)[g]
61062-60-0	**24A** MeI[h]	110–111	
61025-50-1	**24a** OH[i]		4.95 (s, 1 H), 6.08–6.48 (m, 5 H), 7.30–7.80 (m, 6 H), 8.13–8.65 (m, 4 H), 8.86 (d, J = 6.8 Hz, 3 H)
61025-51-2	**24a** OH MeI[h]	141	
61025-52-3	**25a** picrate	57–59	
61025-53-4	**26a** dipicrate	199	
61025-54-5	**26a** 2HCl	231	5.80–6.20 (m, 8 H), 6.36–7.03 (m, 12 H), 7.32 (t, J = 6.8 Hz, 4 H), 7.67–8.33 (m, 4 H)[g]
61025-55-6	**26a** 2MeI[h]	256–257	
61025-56-7	**37**	98	2.83 ($A_2'B_2'$, $\Delta\nu_{AB} \sim 35$ Hz, 4 H), 2.33–2.87 (m, 5 H), 6.23 (s, 3 H), 7.39–7.81 (m, 8 H), 8.16–8.60 (m, 2 H)
61025-57-8	**38**	123–124	2.53–3.50 (m, 8 H), 6.29 (s, 3 H), 7.45–7.88 (m, 8 H), 8.20–8.63 (m, 2 H)
972-05-4	**39**	117–118[j]	2.20–2.80 (m, 10 H), 7.45 (t, J = 6.0 Hz, 2 H), 7.50–7.76 (m, 6 H), 8.34 (q, J = 6.0 Hz, 2 H)
61025-58-9	**40**	145	2.48–3.38 (m, 8 H), 6.29 (s, 3 H), 7.33–7.87 (m, 8 H), 8.08–8.62 (m, 6 H)

[a] Experimental Section for methods of preparation and crystallization. [b] For experimental conditions, notation, and signals missing in the tabulated spectra, refer to Table II and footnote *d* therein. [c] 4′-Methoxy-4-morpholino-2,2-dideuteriobutyrophenone. [d] 100 MHz. [e] Prepared by method D. [f] Hygroscopic. [g] In D_2O/TSP. [h] Methiodide. [i] Methyl-3-morpholinopropylcarbinol by $LiAlH_4$ reduction of **24a** in dry THF; 70% yield, bp 82–83 °C (0.3) mm, $n^{28}D$ 1.4685. [j] Lit.[23] 128–130 and lit.[24] 123 °C. [k] Satisfactory analytical data (±0.4% for C, H, N, and halogen) for all compounds, except as noted, were submitted for review. Exceptions [found (calcd)]—**22d** 2HCl: C, 55.50 (55.01); H, 6.90 (7.45); N, 7.58 (8.02); Cl, 19.81 (20.30). **23c** picrate: C, 50.42 (49.95); H, 4.82 (4.40). **25a** picrate: C, 47.38 (47.88). **26a** dipicrate: C, 43.16 (43.68); H, 4.09 (4.58). **26a** 2HCl: C, 50.91 (50.42); H, 8.76 (8.40); N, 7.38 (7.84); Cl, 20.30 (19.89).

equally basic pyrrolidine ($K = 1.3 \times 10^{-3}$) finds analogy in enamine chemistry.[16] It can be attributed to the acid-induced dehydration stage of the carbinolamine (**31** → **32**). This conversion entails rehybridization of the nitrogen atom orbitals from tetrahedral to trigonal, which is faster in the five-membered than in the six-membered cyclic amine.

The collapse of the imonium–carbonium mesomeric ion (**32**) can occur by two different pathways, both having analogies in the literature. Ion **32** can undergo homoallylic rearrangement concomitant with attack of a second amine molecule to yield γ-aminoenamine (**33**). Similar products were reported recently from reactions with $TiCl_4$ catalyst.[7] The hydrolysis of **33** to the final product is now straightforward. An alternative route worthy of consideration involves the cyclopropyl ketimine–pyrroline rearrangement. This rearrangement has been shown to proceed with enhanced rate in acid medium, where the ketiminium form, such as **32**, is the active species.[17] This route has been advantageously exploited recently in synthesis of alkaloids.[18] In the cases reported here, the rearrangement should give rise to pyrrolinium ions (**34**) which easily hydrolyze to the products.

The formation of the bis adduct **26a** is the result of addition of morpholine to the mono adduct **25a**. The product **27a** was obtained in low yield from the reaction of **16** with morpholine by hydrolysis of the methyl ether function during the long boiling period, either at the starting ketone **16** or at the product **21a**.

Some of the amino ketones produced in this study were previously shown to possess biological activity as psychotropic[12b,19] or antihypertensive[20] agents. The synthetic method described here provides an easy and convenient access to this class of compounds.

Mass Spectra. Fragmentation paths of amino ketones under electron impact are classified according to the alleged triggering site—amine-directed decompositions and carbonyl-directed ones. Interpretation of the fragmentation patterns must take into account not only the distribution of "localized" charge between the sites but also the relative rates of the various decompositions. Wagner[20] applied the standard unimolecular decay law for kinetic analysis of the charge distribution in γ-dimethylaminobutyropheone (DMAB) as compared to separate amine and ketone model compounds, and demonstrated clearly the predominance of charge residence at the nitrogen. Extending Wagner's treatment to the compounds produced in the present work brings forth the question of mutual influence of the two ionizable centers as a function of either changes in the amine or in the ketone portions of the molecule. We shall confine our discussion here to the different amines when attached to unsubstituted butyrophenone.

The three most prominent cracking processes are depicted in Scheme II, their intensities under 70 eV are assembled in Table IV, and their relative kinetic parameters are assembled in Table V.

Scheme II

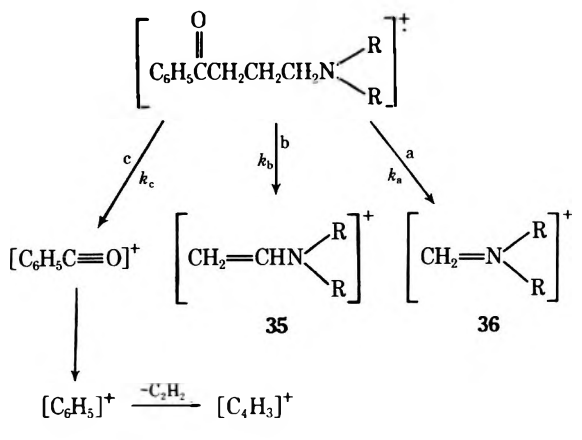


Table IV. Major Intensities in Mass Spectra of Some γ-Aminobutyrophenones

m/e	DiMe amine DMAB[e]	Pyrrolidine 22c	Piperidine 22b	Morpholine 22a
51[c]	265	220	55	145
58	4350[a]			
71	3130[b]			
77[c]	630	530	270	525
84		4240[a]		
97		2800[b]		
98			1750[a]	
100				2285[a]
105[c]	340	440	285	580
111			1450[b]	
113				1830[b]
120	15	20	20	110
191	100[d]			
217		100[d]		
231			100[d]	
233				100[d]
total intensity $(\sum_{40})$	12 000	17 530	8370	12 000

[a] α to nitrogen cleavage (route a in Scheme II), base peak. [b] McLafferty rearrangement with charge residing on the amine portion (route b in Scheme II). [c] Benzoyl ion and ions of its further decomposition. [d] Molecular ion. [e] Data from ref 21.

Table V. Relative Kinetic Constants for Major Fragmentation Processes of γ-Amino Ketones

	DMBA	22c	22b	22a
k_a	1.9	1.4	1.0	1.0
k_b	1.7	1.1	1.0	1.0
k_c[a]	1.5	1.1	1.0	1.5
$[M^+]/\sum_{40}$	1.5	1.0	2	1.5

[a] Figured from the sum of the intensities of peaks at m/e 105, 77, and 51.

A twofold increase in the abundance of the molecular ion is noticed upon going from pyrrolidino to morpholino and dimethylamino to piperidino ketone. This implies that the tendency of the molecular ion to fragment is affected by a variety of factors, suggesting a considerable degree of charge delocalization in the ionized amino ketones. The higher rate of α to nitrogen cleavage (k_a) in DMAB and **22c** may be attributed to the higher stability of the product, the iminium ion **36**, in parallel to solution chemistry. The significant differences in the values of k_c may indicate proximity of the amine and the carbonyl, while those of k_b draw distinction between the open-chain and the cyclic amines.

Experimental Section

Materials. Commercial cyclopropyl ketones and p-TsOH–H_2O were used without further purification. Commercial amines were freshly distilled from KOH.

Instrumentation. All melting points are uncorrected and recorded as observed on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Zeiss spectrophotometer PMQ II. Proton magnetic resonance spectra were determined in deuteriochloroform with Me_4Si internal standard on either Varian A-60 or JEOL GNM-C-60H (60 MHz) and Varian HA-100 (100 MHz) spectrometers. Mass spectra were recorded on a Varian MAT CH-5 spectrometer. Gas–liquid chromatography was performed on a Varian Aerograph Model A-90-P3 gas chromatograph (thermal

conductivity detector) with the following columns: column A, 2 ft × 0.25 in., 10% of 4:1 Apiezon L–KOH on 60/80 Chromosorb W at 240 °C and 40 ml/min He flow rate, for identification and comparison; column B, 5 ft × 0.25 in., 10% cyanosilicone XF-1150 on 30/60 Chromosorb W, with He flow of 30 ml/min and suitable temperature in the range 220–270 °C, for preparative purification.

General Methods for Addition of Secondary Cyclic Amines to Cyclopropyl Ketones. Method A. A mixture of cyclopropyl ketone (0.1 mol), amine (0.13–0.15 mol), and *p*-TsOH (0.01 mol) is refluxed for ca. 20 h, cooled, and poured into 100–150 ml of ether. The precipitated amine tosylate is filtered off, and the filtrate dried over anhydrous $MgSO_4$ and distilled. The products darken on storing in the refrigerator. Pure samples for analytical and spectroscopic measurements were obtained freshly by GLC.

Method B. A mixture of cyclopropyl ketone (50 mmol), amine (50–75 mmol), *p*-TsOH (5 mmol), and 10–15 ml of toluene is refluxed for 20–30 h, then poured into 100–150 ml of 5% HCl. The mixture is extracted with 200 ml of ether. The ethereal solution is dried over anhydrous $MgSO_4$ and evaporated to dryness under vacuum. The crude product is purified by crystallization from benzene.

Method C. Reaction of *p*-Anisyl Cyclopropyl Ketone (16) with Morpholine (a). Method A is applied with the following changes: The final ethereal solution is concentrated to ca. 10–15 ml and allowed to stand for 24 h. **27a** separates and is filtered. The remaining solvent is removed in vacuo from the filtrate, the residue dissolved in a few milliliters of acetone, and **21a** precipitated by cooling in dry ice–acetone mixture.

Method D. Reaction of Phenyl Cyclopropyl Ketone (17) with 1-(2-Hydroxyethyl)piperazine (d). Method B is applied with the following change: on pouring the reaction mixture into 5% HCl the di-HCl salt of the addition product (**22d**) separates and is filtered and twice recrystallized from alcohol. The free base is obtained by dissolving the salt in 40% NaOH, extracting with chloroform, evaporating to dryness, and crystallizing from benzene.

Method E. Dicyclopropyl ketone (**20**, 5.5 g, 50 mmol), 5.5 g (63 mmol) of dry morpholine, and 0.86 g (5 mmol) of *p*-TsOH in 50 ml of xylene (dried over Na) were refluxed for 15 h. After cooling some precipitated morpholine tosylate was filtered, the filtrate boiled with charcoal and refiltered, the solvent removed under vacuum (hot water bath, 1 mm), and the residue fractionated.

Alternative Synthesis of 24a. 1. α-Acetyl-γ-butyrolactone (**28**) was prepared by condensing ethyl acetoacetate with ethylene oxide (NaOEt catalyst).[22]

2. Methyl ε-hydroxypropyl ketone (**29**) was prepared by hydrolysis and decarboxylation of α-acetyl-γ-butyrolactone with 5% H_3PO_4.[23]

3. Methyl ε-tosyloxypropyl ketone (**30**) was prepared by the method of Tipson.[24] Separate solutions in dry pyridine of **29** (10 g in 30 ml) and *p*-TsCl (21 g in 70 ml) were cooled in an ice–salt bath, then mixed and kept in the cooling bath for 2 h. Water (110 ml) was added in portions keeping the temprature below 5 °C. The mixture was extracted with three 100-ml portions of chloroform and the extract washed successively with ice-cold dilute H_2SO_4, water, and sodium bicarbonate solution. After drying (anhydrous Na_2SO_4) the solvent was removed under vacuum (without heating) and the oily residue [ν (SC) 1730 (C=O), 1380 and 1190 cm^{-1} (tosyl ester)] was used without further purification.

4. 24a was prepared according to Reynolds and Kenyon.[25] The crude tosyl ester **30** was added dropwise into a slight excess of stirred dry morpholine. Stirring was continued for 30 min and the excess amine removed under vacuum, causing the mixture to solidify. The mixture was dissolved in hot dry benzene, and on cooling, *p*-TsOH separated and was filtered off. The product was obtained from the filtrate by distillation.

Preparation of Derivatives. Picrates were prepared and recrystallized from alcohol.

Hydrochlorides were prepared by passing HCl through an ethereal solution of the substrate and crystallizing the precipitate from MeOH–Et_2O mixture.

Methiodides were prepared by warming with excess MeI and crystallizing as follows: **24a** MeI, by dropwise addition of *n*-BuOH to the cooled and stirred solution in MeOH; **26a** MeI, by Soxhlet extraction with MeOH; **24a** OH MeI, by trituration in Et_2O.

Deuteration was performed by dissolving in >98% D_2O and the minimal required amount of trifluoroacetic acid, allowing 48 h at room temperature, adding solid NaOH to alkalinity, extracting with ether, and isolating by GLC. Two such cycles complete the exchange

Grignard Addition. A solution of 20 mmol of ketone in 50 ml of dry ether is added dropwise to a solution of 40 mmol of Grignard reagent in ether. The mixture is refluxed for 30 min and hydrolyzed slowly with 10 ml of saturated NH_4Cl solution. The organic layer is decanted and the residue extracted by warming with additional ether. The combined etheral solution is dried ($MgSO_4$), concentrated, and allowed to stand. The separated crystalline carbinol is filtered and washed with a little cold ether. The following compounds were prepared by this method: *p*-anisylphenyl-3-morpholinopropylcarbinol (**37**), from **21a** and C_6H_5MgBr; *p*-anisyl-*p*-chlorophenyl-3-morpholinopropylcarbinol (**38**), from **21a** and *p*-ClC_6H_4MgBr; diphenyl-3-morpholinopropylcarbinol (**39**), from **22a** and C_6H_5MgBr; *p*-anisyl-*p*-chlorophenyl-3-(1-pyrrolidinyl)propylcarbinol (**40**), from **21c** and *p*-ClC_6H_4MgBr.

Registry No.—**16**, 7152-03-6; **17**, 3481-02-5; **18**, 6640-25-1; **19**, 765-43-5; **20**, 1121-37-5; **a**, 110-91-8; **b**, 110-89-4; **c**, 123-75-1; **d**, 103-76-4; C_6H_5Br, 108-86-1; *p*-ClC_6H_4Br, 106-39-8.

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(13) The proximity of the γ-methylene signal causes severe slanting of the pattern. In 60-MHz spectra it appears as a deceiving symmetrical quartet, but 100-MHz spectra and deuteration at the α position resolve the pattern unequivocally.
(14) Only three signals appear in the chromatogram throughout the process—amine, ketone, and amino ketone. The second is the most convenient to integrate, and this eliminates the need to account for differences in the specific detector responses to the various products. The ketone alone, heated similarly, is not consumed. Changes in the chromatographic conditions were corrected by repeated comparison of the reacted mixture with an unreacted sample. The results were reproducible within ±3%.
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Catalytic Dipolar Micelles. 3. Substrate and Surfactant Structural Effects in the Hydrolyses of Substituted Phenyl Esters in Presence and in Absence of Dipolar Cationic Micelles: Mechanistic Considerations

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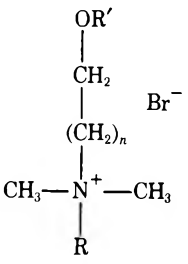
Herein are described the synthesis and kinetic parameters derived from a series of ten dipolar quaternary ammonium bromides of formula $(n\text{-}C_{10}H_{21}NR_2R')^+ Br^-$ in which R equals methyl (I, II, IV–IX) or ethyl (III) and R′ equals β,γ-dihydroxypropyl (V), α-carboxy-γ-hydroxypropyl (VI), ethyl (VII), carboxymethyl (VIII), β-methoxyethyl (Ib), and α-substituted γ-butyrolactone (IX), and the influence of the foregoing micellar systems on the rates of the base-catalyzed hydrolyses of the following substituted phenyl esters (μ = 0.8 M, KBr): 4-nitrophenyl acetate (PNPA), 4-nitrophenyl hexanoate (PNPH), 4-nitrophenyl decanoate (PNPD), 2,4-dinitrophenyl acetate (OPDNPA), 2,4-dinitrophenyl decanoate (OPDNPD), 2,4-dinitrophenyl esters of *n*-decyldimethyl(4′-carboxybutyl)ammonium bromide (OPDNPDE), phenyl decanoate (PD), 3-nitrophenyl decanoate (MNPD), 4-bromophenyl decanoate (PBPN), and 2,5-dinitrophenyl decanoate (OMDNPD), at 30 °C. Also included here is a comparative study of the reaction kinetics of the foregoing esters with nonmicellar catalysts of formula $[(CH_3)_3NR]^+ Br^-$ where R equals β-hydroxyethyl (Ia) and γ-hydroxypropyl (IIa) and $[(C_2H_5)_2CH_3NCH_2CH_2OH]^+ Br^-$ (IIIa). Two parameters for micelle formation from the surfactants I–V are presented: (1) the critical micelle concentrations (cmc), mainly from surface tension measurements; (2) the equilibrium constant of ester association into the micelle. The rates for alkaline hydrolyses were deduced from spectrophotometric measurements of the substituted phenol liberated in the course of the reaction, in the range of 295 and 450 nm. The second-order rate constants ($s^{-1} M^{-1}$) at 1–20 $\times 10^{-2}$ M and at pH 9.5–10.7 were computed from straight-line correlations with OH^- concentrations. All reactions in micellar systems exhibit considerable rate augmentation relative to the rate in water systems and the dependence of the rate constants with the micelle concentration. The respective β values of 0.36 and 0.31 obtained from the Brønsted plot for the hydrolysis of para- and meta-substituted phenyl esters in presence of micelles I and Ib indicate that the transition states in the catalytic reactions are highly sensitive to charge developments. Isotope effects (K_{H_2O}/K_{D_2O}) of 0.81, 0.59, and 0.76 were found for I, II, and VII, respectively. Evidence is adduced in favor of a nucleophilic mechanism involving an anionic transition state, which extrudes good leaving groups to give the products. The mechanistic pathway is discussed. The micellar models described here exhibit similarity to catalysis by relevant esterases with respect to the kinetic characteristics and mechanism.

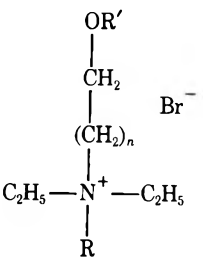
The importance of the serine hydroxyl group[1] and the carboxy residue[2] in enzymatic catalysis led to studies of systems containing these functional groups as models for enzyme–substrate intracomplex reaction.[3] Factors which might contribute to the catalytic efficiency of enzymes, such as proximity,[4] electrostatic catalysis,[5] and multifunctional catalysis,[6] were studied in the model compounds.

The similarities between the orientation of the side chain of proteins and the micellar structure[7-11] focused interest on use of micellar systems as models for enzymatic catalysis. Surfactant micelles containing groups such as imidazole,[12] amine,[13] thiol,[14] and hydroxamic[15] were found to catalyze the hydrolysis of esters.

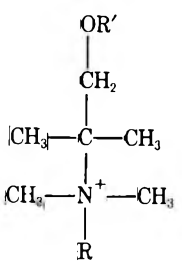
Accounts of enhanced micellar catalysis upon introduction of hydroxy groups to surfactant molecules have been recently reported.[16,17] To account for the role of the hydroxy group in the acceleration of the alkaline hydrolyses of esters, a kinetic study of the reaction in the presence of hydroxyammonium salt micelle-forming agents of structures I–VI was undertaken. We employed Ia, Ib, IIa, VII, and VIII as reference compounds. The structural variations in these cationic micelles



I, Ia, Ib, II, IIa



III, IIIa



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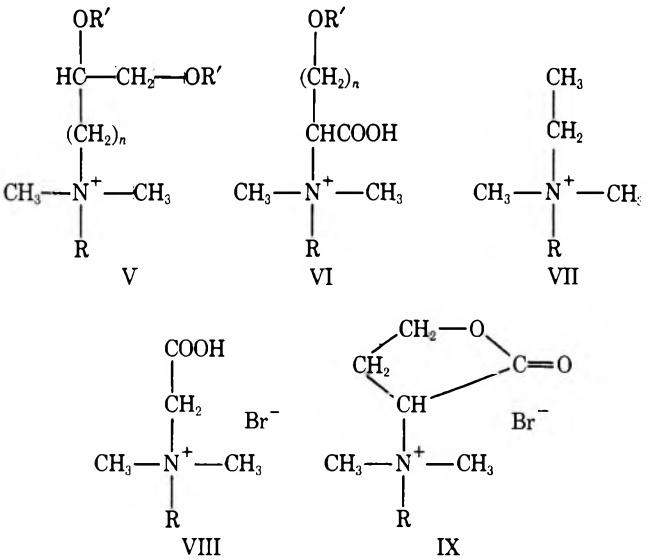


V VI VII VIII IX

I, n = 1; R = $C_{10}H_{21}$; R′ = H Ia, n = 1; R = CH_3; R′= H Ib, n = 1; R = $C_{10}H_{21}$; R′ = CH_3
II, n = 2; R = $C_{10}H_{21}$; R = H IIa, n = 2; R = CH_3; R′ = H
III, n = 1; R = $C_{10}H_{21}$; R′ = H
IIIa, n = 1; R = CH_3; R′ = H IV, R = $C_{10}H_{21}$; R′ = H
V, n = 1; R = $C_{10}H_{21}$; R′ = H VI, n = 2; R = $C_{10}H_{21}$; R′= H
VII, R = $C_{10}H_{21}$ VIII, R = $C_{10}H_{21}$ IX, R = $C_{10}H_{21}$

aimed at providing deeper insight into the ability of micellar systems to serve as models for enzymatic action.

Experimental Section

Surface Active Agents. All compounds were prepared according to the following general literature procedures[19] A or B

A $(CH_3)_2N(CH_2)_nCH_3 + Br(CH_2)_mX \xrightarrow{solv} CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mX\ Br^-$

B $CH_3(CH_2)_nBr + (CH_3)_2N(CH_2)_mX \xrightarrow{solv} CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_mX\ Br^-$

where X is the head group on the cationic micelle, and the solvents used were ether, benzene, and methanol. In some cases methods A and B were carried out under neat conditions and are assigned as methods A′, B′. The preparation of *N,N*-dimethyl-*N*-decylamine [$n^{21}D$ 1.4307, bp 68 °C (1.4 Torr)] used in method A was according to Clarke et al.[20] All other reagents used were obtained from commercial sources. Examples of all four procedures follow.

***n*-Decyldimethyl(2-hydroxyethyl)ammonium bromide (I)** was synthesized either from 2-bromoethanol with dimethyldecylamine, or from 2-(dimethylamino)ethanol with freshly distilled decyl bromide, following usual methods.[21a] The reacting materials (0.1 mol each) were refluxed for 24 h in dry benzene, and the oily crude product recrystallized from acetone–ethyl acetate solution.

***n*-Decyldimethyl(2-methoxyethyl)ammonium Bromide (Ib).** Compound I was transformed to Ib by the method of Stoochnof and Benoitan[21b] with some modification. To a solution of I (0.05 mol) in 1,4-dioxane, NaH (0.06 mol) was added portionwise, and stirred for 24 h under a nitrogen environment. The solution was cooled to −10 °C and methyl bromide (100 ml) added. The reaction mixture was stirred for an additional 24 h, and then excess methyl bromide removed by evaporation at room temperature. Methanol was added to the residue, and the solution acidified (HBr). After solvent removal, the product (Ib) was extracted with dry acetone, ethyl acetate added, and the white precipitate collected after cooling.

Formation of VI from IX. The lactone (7.48 g, 0.02 mol) was dissolved in 100 ml of KOH (0.03 M) and left at room temperature for 5 days. Titration of a sample with HCl to phenolphthalein showed full hydrolysis of the lactone. It was then neutralized and used for the kinetic runs after adjusting the ionic strength.

Substituted Phenyl Esters. The mono- and dinitrophenyl esters were synthesized according to known methods as follows: *p*-nitrophenyl acetate (PNPA) (mp 79 °C) and 2,4-dinitrophenyl acetate (OPDNPA) (mp 71.5 °C) from the appropriate phenols and acetic anhydride, by the general method of Bender and Nakamura;[23] *p*-nitrophenyl hexanoate (PNPH) [bp 118 °C (0.5 Torr)], *p*-nitrophenyl decanoate (PNPD) (mp 35 °C), and 2,4-dinitrophenyl decanoate (OPDNPD) (mp 30 °C) from the respective acid chlorides and the appropriate phenols;[24] 2,5-dinitrophenyl decanoate (OMDNPD) (mp 36 °C), *m*-nitrophenyl decanoate (MNPD) (mp 36 °C), *p*-bromophenyl decanoate (PBPD) [bp 154 °C (0.1 Torr)], and phenyl decanoate (PD) [bp 125–132 °C (1–2 Torr)] using DCC as dehydrating agent.[25]

All the esters were checked by spectroscopic methods as well as by elemental analysis.

The micellar ester $CH_3(CH_2)_9N^+(CH_3)_2(CH_2)_3COOPh(NO_2)_2$-($Br^-$) (OPDNPDE$^+$) was prepared according to Bodansky and du Vigneaud.[25] Dicyclohexylcarbodiimide (0.05 mol) was dissolved in hot acetone together with equimolar quantities of 2,4-dinitrophenol and *n*-decycldimethyl(4-carboxybutyl)ammonium bromide. The crude OPDNPDE$^+$ was recrystallized from acetone–ether, bp 125–132 °C (1–2 Torr). Anal. Calcd for $C_{22}H_{37}N_3O_6Br$: C, 50.87; H, 7.13; Br, 15.41. Found: C, 50.45; H, 7.56; Br, 15.43.

Determination of Critical Micelle Concentration (cmc). Determination of cmc values of the micelle forming agents I–V was made by two methods: A, measurements of surface tension; B, measurements of refractive index. An attempt to measure the cmc of the above compounds by the determination of the specific volume was not suceessful.

Method A. Ten solutions of detergent were prepared in the range of 1×10^{-3} to 2×10^{-1} M and ionic strength of 0.8 μ. The solution was thermostated at 30 °C and the surface tension measured by a Fisher Surface Tentiomat apparatus, Model 21.

Method B. The refractive index of the solution prepared above was measured by a Zeiss refractive index apparatus. The temperature of 30 °C was attained by circulation of thermostated water through the lens block. A plot of surface tension or refractive index against the concentration of the micelle-forming compound showed a break in the curve at the cmc.

Kinetic Measurements. Rates of liberation of the phenol, *p*-nitrophenol, *m*-nitrophenol, *p*-bromophenol, 2,4-dinitrophenol, and 2,5-dinitrophenol were measured spectrophotometrically at 295, 350, 400, 310, 325, and 450 nm, respectively. A Unicam SP800 recording spectrophotometer with scale expansion and constant wavelength unit was used. The temperature of 30 °C in the cell block was attained by circulation of water from an external thermostated bath. The reaction was initiated by addition of 20 μl of ester (7.5×10^{-3} M) dissolved in acetonitrile to a thermally equilibrated solution in a stoppered 10-mm silica cell containing 3 ml of $K_2CO_3/KHCO_3$ buffer (0.035 M) and the appropriate micelle in KBr (0.8 M).[18d] The concentration of esters in solution was 5×10^{-5}. The absorbance of the solution during the kinetic run was monitored by a coupled recorder connected to the instrument. The pH of the solutions was measured before and after each run on a Radiometer pH-meter-26 with combined glass electrode type GK 2322C at 30 °C. The first-order rate constants were calculated either by means of a linear least-squares method with a CDC computer or by a regression least-squares program 18b with an Olivetti Program 101. Rates were measured at a series of micelle-forming agent concentrations $1–20 \times 10^{-2}$ M and at a series of pH values between 9.5 and 10.7 and exhibit linear dependence with hydroxide ion concentration. The second-order rates were obtained from the slope of the plot of k_{obsd} vs. OH^- concentration.

Results

The first-order rate constants for all the esters discussed are linearly dependent on the hydroxide ion concentration.

In Table II we have summarized the rate constants of the short-chain esters of various micellar systems (I–V) in a micelle concentration range of 0–0.2 M, at three cmc values. A

Table I. Analytical Data of Compounds I–IX

Registry no.	Compd	Method	Formula	Anal., % C Calcd	C Found	H Calcd	H Found	N Calcd	N Found	Br Calcd	Br Found	Crystd from[a]	Mp, °C
39995-55-6	I	A, B, B′	$C_{14}H_{32}NOBr$	54.19	54.20	10.32	10.30	4.51	4.50	25.78	25.68	F, C	152
1927-06-6	Ia	A′	$C_5H_{14}NOBr$	32.61	32.55	7.61	7.80	7.61	7.47	43.49	43.56	D	305 dec
61063-28-3	Ib	See text	$C_{15}H_{34}NOBr$	55.55	55.43	10.49	10.40	4.37	4.39	24.69	25.01	F	112
61063-29-4	II	B, B′	$C_{15}H_{34}NOBr$	55.55	55.61	10.49	10.46	4.37	4.47	24.69	24.75	F	70
61063-30-7	IIa	A′	$C_6H_{16}NOBr$	36.36	36.28	8.08	8.21	7.07	6.92	40.40	40.52	E	174–175
60535-37-7	III	B′	$C_{16}H_{36}NOBr$	56.80	56.70	10.50	10.50	4.14	4.20	23.67	23.80	F	77
61063-31-8	IV	B′	$C_{16}H_{36}NOBr$	56.80	56.63	10.65	10.42	4.14	4.25	23.67	23.42	F	160
61063-32-9	V	B	$C_{15}H_{34}NO_2Br$	52.94	53.16	10.0	9.84	4.12	4.32	23.53	23.38		Wax
39995-56-7	VII	A	$C_{14}H_{32}NBr$	57.14	56.80	10.88	11.23	4.76	4.84	26.13	26.31	D	151
39995-54-5	VIII	A[22]	$C_{14}H_{30}NO_2Br$	51.85	51.82	9.26	8.97	4.32	4.19	24.71	24.69	D	153
61063-33-0	IX	A	$C_{16}H_{32}NO_2Br$	54.86	54.66	9.14	9.19	4.00	4.04	22.86	23.15	F	79–80

[a] C, acetone; D, methanol–ether; E, methanol; F, acetone–ethyl acetate.

Table II. Second-Order Rate Constants k' (s^{-1} M^{-1}) of PNPA, PNPH, and OPDNPA Basic Hydrolyses in Various Concentrations of Micelles I–V at 30 °C, μ = 0.8 M (KBr), Buffer 0.035 M $K_2CO_3/KHCO_3$

Ester	Micelle concn, M	Type of micelles I	II	III	IV	V
	0.00	12.0	12.0	12.0	12.0	12.0
	0.01	26.3	15.2	30.3	26.4	28.4
	0.02	72.0	19.0	87.5	45.5	46.5
	0.06	234.0	34.2	219.0	78.0	93.0
PNPA	0.08	244.0	31.0	260.0	94.0	114.0
	0.10	248.0	39.1	304.0	104.0	139.0
	0.15	270.0	42.5	350	119.0	
	0.20	280.0	44.0	399.0	135.0	
	0.00	7.9	7.9	7.9	7.9	7.9
	0.01	18.1	8.3	17.9	14.2	15.9
	0.02	61.8	10.3	106.0	27.5	41.0
	0.06	96.0	13.1	121.0	34.0	45.8
PNPH	0.08	100.0	13.5	126.0	36.0	48.0
	0.10	103.0	13.5	127.0	35.2	52.5
	0.15	108.0	13.7	136.0	40.0	
	0.20	110.0	14.2	144.0	44.0	
	00.0	64.9	64.9	64.9	64.9	64.9
	0.01	220.0	82.5	327.3	148.4	120.0
OPDNPA	0.02	610.0	111.1	840.0	296.5	264.0
	0.06	1632	210.7	2215	821.0	504.0
	0.08	1942	226	2520	930	600.0
	0.10	2150	230	2820	1020	641.0
	0.15		241	3250	1100	
	0.20		260	3450	1253	

nonlinear least-squares program was used to fit the data given in Table III with eq 1

$$k_{obsd} = \frac{k_{OH} + k_{mH}K_s(mH - cmc)}{1 + K_s(mH - cmc)} \times [OH^-] \qquad (1)$$

$$k' = k_{obsd}/[OH^-]$$

k_{mH} and k_{OH} are the second-order rates of the ester hydrolysis in the presence and the absence of the micelle, respectively. K_s is the equilibrium constant of ester association into the micelle divided by the aggregation number and mH is the monomer concentration of the micelle-forming agent, in an undissociated form. Two parameters, k_{mH} and K_s, and cmc were used on fitting data, while the cmc was constrained to the experimental region measured.

The cmc values given in Table III were determined by surface tension measurements, as well as by refractive index determinations. The above measurements indicate that all the cmc values are lower than 0.02 M.[18c]

For comparative purposes, we included in this study some kinetic measurements related to other types of dipolar micelles such as Ib, VI, VII, and VIII. The second-order rate constants k' (s^{-1} M^{-1}) measured for the long-chain ester PNPD in the presence of 0.1 M concentration of Ib, VI, VII, and VIII are 2.88, 4.3, 1.43, and 0.56, respectively (30 °C, μ = 0.8 M).

To acquire a quantitative estimate of the kinetic effect of the catalytic group in micelles I–V, kinetic measurements in analogous nonmicellar systems Ia and IIa were performed. The rate of hydrolysis of PNPA, PNPH, and OPDNPA with choline bromide (Ia) and homocholine bromide (IIa) is linearly dependent on hydroxide ion and catalyst concentration in accordance with eq 2, which is kinetically equivalent with eq 3

$$k_{obsd} = k_{AH}[ROH][OH] \qquad (2)$$

$$k_{obsd} = k_A[RO^-] \qquad (3)$$

where $k_{AH} = k_A K_a/K_w$.

Table III. Calculated Parameters K_s and Second-Order Rate Constants k_{mH} (s^{-1} M^{-1}) for Three cmc Values in the Hydrolysis of Substituted Nitrophenyl Esters Catalyzed by Micelles I–V at 30 °C, μ = 0.8 (KBr), Buffer 0.035 M K_2CO_3/ $KHCO_3$

Esters	Kinetic cmc × 10^3	I, 1–2 × 10^{-2} [a] k_{mH}	K_s	II, 0.5–1 × 10^{-2} [a] k_{mH}	K_s	III, 0.5–1 × 10^{-2} [a] k_{mH}	K_s	IV, 0.5–1 × 10^{-2} [a] k_{mH}	K_s	V, 2–2 × 10^{-2} [a] k_{mH}	K_s
PNPA	5			54.3	18.8	595	10	194	10.2	234	10.3
	10	398.2	18.9	52.2	23.3	565	11.8	178	13.3	196	17.1
	15	354	28.6			537	14.2				
PNPH	5					11		42.2	71.5	59.9	71.3
	10	113	102.8	15.6	40.4	148	94	38.9	153	54.2	161
	15							37.9	282	51.4	384
OPDNPA	5	5202	7.5			4772	14.3	1625	16.7	1112	13.3
	10	3889	13.2	355.5	16.9	3809	27.3	1430	24.8	939	21.1
	15			312	27.1					800	35.5
PNPD		78		8.3		86		39		50	
OPDNPD		505		63		700		405		276	
$OPDNPDE^+$		6000		1500		12000		3200			

[a] Experimental cmc, M.

Table IV. Third-Order Rate Constants k_{AH} (s^{-1} M^{-2}) of PNPA, PNPH, and OPDNPD Hydrolysis Catalyzed by the Nonmicellar Agents Ia, IIa, and IIIa (0.05–0.5 M), 30 °C, μ = 0.3 (KBr), Buffer 0.0035 M $K_2CO_3/KHCO_3$[a]

Ester	Ia	IIa	IIIa
PNPA	185	40.8	249
	(0.127)	(0.102)	(0.15)
PNPH	73	27.6	144
	(0.05)	(0.069)	(0.086)
OPDNPD	1450	400	1660
	(1)	(1)	(1)

[a] The numbers in parentheses are the relative rates compared to OPDNPA.

The third-order rate constants k_{AH} were derived from the plots of the second-order rate constants $k' = k_{obsd}/OH$ against concentrations of [Ia], [IIa], and [IIIa], and are assembled in Table IV.

Catalysts Ia, IIa, and IIIa exhibit similar catalytic effects on esters examined, but IIIa is shown to be a better catalyst than Ia and IIa.

The micellar catalysis is manifested from the higher rate in ester hydrolysis in presence of the catalytic (I) as compared with that of the noncatalytic (Ib) micelle, amounting to a ratio of $k'(I)/k'(Ib)$ = 27.1 for PNPD. This catalysis could in principle be due to either of the two oxygen forms, the dissociated (RO^-) or the undissociated (ROH) forms of the head groups.

The rate constants due to these two forms of the head groups should obey eq 2 and 3, and can be related by the equation $k_m = k_{mH}K_w/K_a$ where k_m is a first-order rate constant.

To distinguish between these two hydrolytic pathways we examined the reaction with added nucleophile such as azide ion and *N*-decylimidazole which are not subject to general catalysis for activated esters or amides.[26,27a] The second-order rate constants for the nucleophilic catalysis of the azide ion on PNPD and $OPDNPDE^+$ in various dipolar micelles I, Ib, III, and VII are given in Table V.

The nature of the transition state in catalytic reactions has been discussed in the literature.[27] On the basis of Brønsted and Hammett criteria, the nucleophilic catalysis has been shown to be more sensitive to charge developing in the transition state (i.e., to β and ρ parameters) than in general catalysis. The changes in ρ values between the intermolecular and the intramolecular reactions were also attributed to different transition states.

Catalytic micelles I–V differ in their physical properties (hydrogen bonding, solvation, etc.) in comparison with the noncatalytic micelles Ib and VII. In the case the transition-state structure is affected by physical factors, changes in the Brønsted and Hammett plots should follow. To examine this

Table V. Second-Order Rate Constants (s^{-1} M^{-1}) of Nucleophilic Attack by Azide Ion on Substituted Phenyl Esters, 30 °C, μ = 0.8 (KBr)

	Micelles				
Ester	Ib, $k \times 10^3$	VII, $k \times 10^3$	I, $k \times 10^3$	III, $k \times 10^3$	II, $k \times 10^3$
PNPD	21[a]	19.6[a]	24[a]	32[b] 28[c]	17.4[d]
$OPDNPDE^+$		2625[e]	1850[f]		1940[e]

[a] pH 9.15 [b] pH 9.25. [c] pH 9.93. [d] pH 9.52. [e] pH 7.48. [f] pH 7.00. Buffer 0.035 M $K_2CO_3/KHCO_3$.

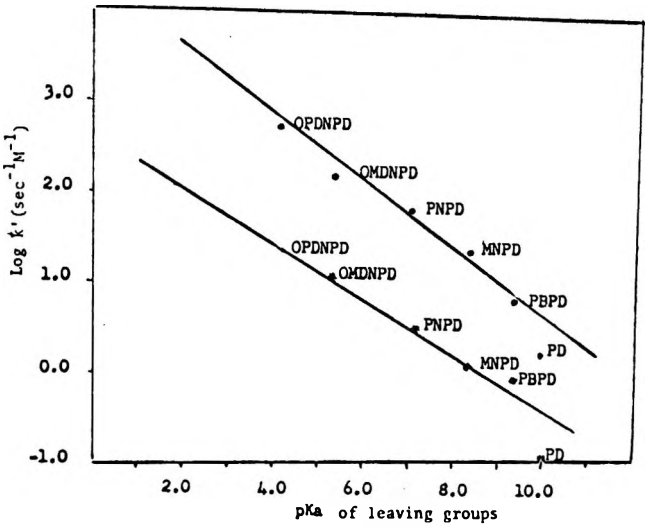


Figure 1. Brønsted plot for the hydrolysis of substituted phenyl decanoate esters in the presence of micelles I (● — ●) and Ib (★ — ★) at 30 °C, μ = 0.8 (KBr), micelle concentration 0.1 M. For pK_a values, see ref 29.

possibility the variations in rates of hydrolysis of substituted phenyl decanoates in I and Ib were investigated. The data obtained are presented in Figure 1. The β values derived from the plots in micelle I and Ib are 0.36 and 0.31, respectively. The corresponding ρ values are 1.0 and 1.1. This suggests that the nucleophilic attack of negatively charged species in the two systems are similar.

The deuterium isotope effect in the hydrolysis of PNPD (Figure 2) was studied in order to gain deeper insight on the microscopic reaction pathway. The experimental isotope effects for the second-order rate constant $k'(H_2O)/k'(D_2O)$ of micelles I, II, and VII were 0.81, 0.59, and 0.76, respectively.

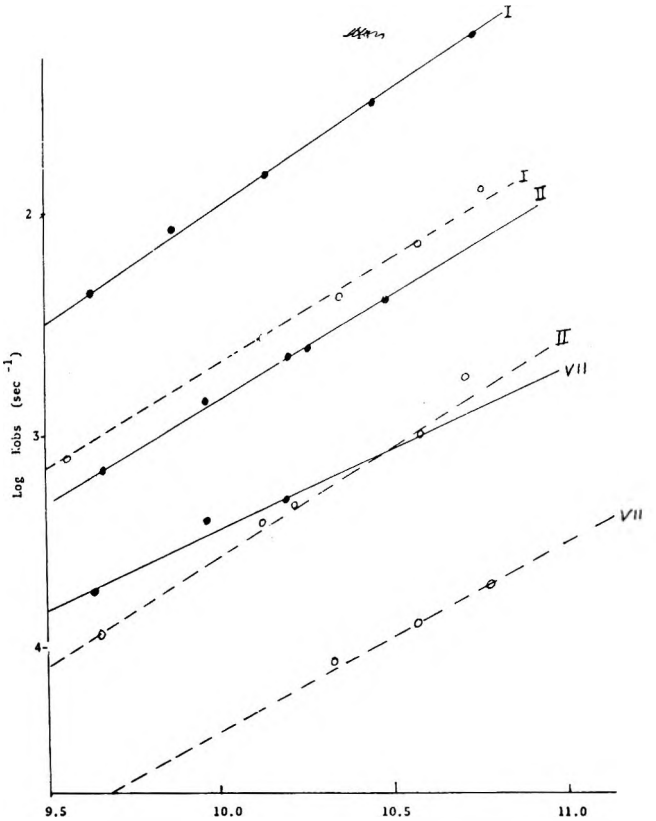


Figure 2. Log k_{obsd} vs. pH (● — ●) and pD (○ - - - ○) for the hydrolysis of PNPD in the presence of micelles I, II, and VII at 30 °C, μ = 0.8 M (KBr), buffer 0.035 M $K_2CO_3/KHCO_3$.

Table VI. Second-Order Rate Constants for Acid Hydrolysis of PNPA, PNPD, and PNPH in the Presence of Micelles I, VII at 60 °C, μ = 0.8 (KCl)

Esters	$10^5 K$ (s^{-1} M^{-1}) None	I	VII
PNPA	50.6	53.3	54.0
PNPH	41.6	13.0	12.5
PNPD		3.5	4.1

Based on the value of 0.76 found for the ratio $k(OH^-)/k(OD^-)$ (as observed for micelle VII), and assuming a ratio of 2–3 for isotope effect in the case of a general acid or general base catalysis[40] the isotope effect of a general-acid specific-base pathway can be estimated[41] and falls within the range of 1.3–2. Therefore the experimental values found for micelles I and II point to a nucleophilic attack.

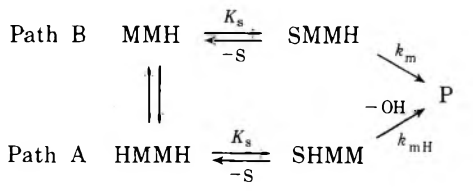
For comparison, the effect of the dipolar micelle on acid catalysis was also studied. In the acidic medium the contribution of the hydroxy group as a catalyst is diminished, suggesting that other effects such as solvation and electrostatic effects might be more pronounced. In Table VI are given the second-order rate constants of PNPA, PNPH, and PNPD hydrolysis at 60 °C. The rates were measured in the range of pH 0.5–1 and μ = 0.8 (KCl). cmc measurements as well as additional kinetic investigations in acidic media[18d] confirm the existence of a micellar system also in these acidic conditions.

Discussion

The acceleration of alkaline hydrolyses by micelles containing neighboring phenoxide on alkoxide groups can be attributed to the intramolecular assistance either of the undissociated alkoxy group or of the dissociated moiety. In the first case the acceleration can be described mechanistically by general acid–specific base catalysis, or electrophilic assistance due to hydrogen bonding in the ground state[30,31] and microscopic solvation of the transition state by hydroxy group.[32] When the oxy anion is involved (second case) the microscopic pathway could result either from nucleophilic catalysis in the formation of the less reactive esters[28a] or from general base catalysis involving water molecule.[33]

A general outline for the micellar catalysis of ester hydrolyses is shown in Scheme I.

Scheme I



In Scheme I two types of micelles are operating; MMH represents a mixed micelle aggregate containing dissociated and undissociated forms of monomers while HMMH represents an un-ionized micelle, composed only of the undissociated monomers.

When $H^+ \gg K_a$ the two pathways A and B results a first-order dependence in hydroxide ion concentration. The same rate equation can also be attributed to a different type of model in which a mixed micelle composed of undissociated and dissociated monomers is formed.

Kinetically pathways A and B are represented by the same rate equations. The data presented here strongly suggest that the hydrolyses of the substituted phenyl esters in the micellar phase do not follow pathway A.

(1) The nucleophilic attack of azide ion was measured with two esters: PNPD and $OPDNPE^+$. Since the esteric head groups are presumably located at different regions on the micellar surface, rate enhancement due to electrophilic assistance by the hydroxy head group on the micelle should not be similar. Yet the experimental results given in Table V show that the enhancement of both esters in presence of micelle I are very similar.

(2) Addition of decylimidazole (0.005–0.05 M) to 0.1 M micelle I and Ib at pH 9.54 linearly increased the hydrolytic rates of PNPD.[44] The second-order rate constants obtained are 1.0×10^{-1} and 1.1×10^{-1} s^{-1} M^{-1}, respectively. This fact argues against electrophilic assistance to the nucleophilic attack of PNPD by decylimidazole, as indicated by pathway A.

The kinetic effect of compound VIII resembles that of an anionic micelle. The rate of hydrolysis in basic solution of PNPD in 0.1 M VIII is 2.55 times slower than in 0.1 M VII, and 5.1 times slower than in 0.1 M Ib. For PNPH, the rate in 0.1 M VIII was eightfold slower than in water. If route A is operating, micelle VI is expected to exhibit inhibitory effect on the hydrolysis of PNPD, which was not the case. The fact that the rate of hydrolysis of PNPD in VI is two times slower than in II can be attributed to other factors.

This conclusion was deduced from an additional study concerning micellar catalysis by polyfunctional cationic systems, as well as by mixed micelles containing the corresponding monofunctional monomers in 1:1 molar ratio.

On the basis of estimations for the expected isotope effect in general catalysis, it is concluded that a mechanism via electrophilic assistance in the transition state of the hydroxy head group in micelles I and II is not operative. The "microscopic solvent effect" can also be ruled out since in hydrolytic reactions attributed to a "microscopic solvent effect" by vicinal hydroxy group the deuterium isotope effect ranged between the values 0.2 and 0.4.

The Brønsted β coefficients in the presence of I and Ib indicates that the reaction proceeds via an anionic transition state and that the values obtained are in accord with what was expected in a reaction between strong nucleophiles and good leaving groups. (For hydroxide ion attack on a series of substituted phenyl esters the β value is 0.3.[26a]) Since the β value for acyl transfer reaction is 1.7, the small β values obtained indicate that the transition state occurs early in the reaction pathway. In intramolecular general base transesterification systems such as 2-hydroxymethylbenzamide[35] and ethyl 2-hydroxymethylbenzoate,[33] the β coefficients obtained were 0.2 and 0.87, respectively. The difference between these values was attributed to the need for development of full negative charge in the less activated acyl group during the nucleophilic attack. If the β values observed in the micellar reaction reflect charge development in general catalysis, a specific base assistance to nucleophilic attack of the undissociated hydroxy head group would have been expected to yield β coefficients of 1.0 since the acyl group is more activated.

General base catalysis originating from an oxy ion (i.e., alcoholate ion-activated water) can also be ruled out. In the intramolecular hydrolysis of substituted phenylsalicylates Bruice[33f] has shown that the general base participation of the phenoxide ion results in a Brønsted slope of $\beta = 0$. For the case in which hydroxy micelles catalyzed the rate of hydrolysis, the attacking group is more basic than the leaving group compared to substituted phenyl salycilate esters, so that the expected β value should be near 1, which is not the case.

The same conclusion is reached by comparing the ρ paramater obtained in micellar systems with ρ values in bimolecular and monomolecular systems. For specific base and alkoxide ion catalyzed hydrolysis of substituted phenyl acetate the ρ values are 0.8–1.1[27e,36] and for phenyl 4-hydroxybutyr-

ate, $\rho = 1.1$.[23a] The experimental ρ values obtained in this study (i.e., $\rho = 1.0$ and $\rho = 1.1$) for catalysis in micelle Ib and I, respectively, are in accord with a nucleophilic pathway brought about by the dissociated hydroxy head group.

The conclusions we came to about the nucleophilicity of the catalysis by micelles I and II are in accord with the findings of Bunton and Diaz,[42] who attained similar results in their studies on phosphate esters' hydrolysis catalyzed by hexadecyl(2-hydroxyethyl)dimethylammonium bromide [$Br^-C_{16}H_{33}(CH_3)_2N^+CH_2CH_2OH$].

Martineck et al.[43] have found that cationic micelles of the general structure $Br^-C_{18}H_{37}(Et)_2N^+CH_2CH_2OH$ behave as nucleophilic agents, exhibiting similarity to the catalysis by serine proteinases.

Since the alkoxide ion is assumed to be the reactive species in the micellar system I–VI according to Scheme I, it should be expected that as a result of the very low concentration of these species most of the substrate will be in an unproductive surrounding. The experimental results show that the hydrolysis of substrate (i.e. [SHMM], [MMHS]) is stoichiometric. The explanation may be based either on the dynamic structure of the micelle[18] or on hydrogen exchange within the micellar phase or between the micellar phase and the bulk solution.

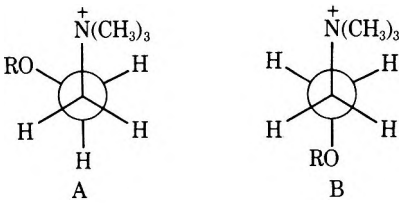
Comparison of the Models I–V. From inspection of Tables II and III several phenomena are apparent: (1) Compared of the hydrolysis of the esters in the bulk solution, all the hydroxy micelles I–V enhanced the second-order reaction rate (k_{mH}), initially by a factor of 2 in the case of micelle II and with PNPH, up to a factor of 59 in the case of micelle I with OPDNPA. (The comparison was done at cmc 1×10^{-1} M). (2) The enhancement is more pronounced with dinitrophenyl esters than with *p*-nitrophenyl esters and with micelles and III. (3) The rates are retarded as the chain length of the ester is increased; the K (association) values (K [association] = K_sN, $N \simeq 50$) are small and range between 650–1250 in the short chain esters and 2000–8000 in the hexanoate series.

Although the association constants are small, it should be mentioned that they are still greater than in compounds bearing methyl groups only on the quaternary nitrogen.[45] Lengthening the chain of the core by six carbon atoms has been shown to increase the solubility of PNPA by a factor of 3.[39] The comparison of the associated constants of hydroxylic micelles with those obtained for VII and VIII[44] shows interesting solubilization properties of micelles: (1) an apolar head group (ethyl) increases the association constant; (2) carboxylate ion separated by one carbon atom from the positively charged nitrogen center also increases the association constant (K_s for PNPH in VII and VIII is 1000 and 920, respectively); (3) the hydroxy group separated by two carbon atoms decreases the association constant. The interference of the hydroxy head group in the hydrophobic interaction is indicated by comparing K_s values with those found for PNPH and PNPA in tetradecyltrimethylammonium chloride detergent.[45] The very high ratio [K_s(PNPH)/K_s(PNPA) = 16 000:33] in TDTAC compared to the same esters in micelle I [K_s(PNPH)/K_s(PNPA) = 100:19] is in accordance with the above conclusion. The change in free energy of transfer PNPH from micelle VII to micelle I can be calculated according to eq 4.

$$\Delta(\Delta G) = -RT \ln \text{eif} K_s^{VII}/K_s^{I} \quad (4)$$

From the ratio $K_s^{VII}/K_s^{I} = 10$ (assuming the same aggregation number for the two micelles), the free energy of transfer can be shown to be 1380 cal/mol. Since the change in ΔG of transfer of a methylene group from water to a micellar solution is reportedly 6401 cal/mol,[12c,46] the difference in solubility of PNPH in VII as compared to I approximates the difference of hydrophobic interaction by the two methylene groups. Thus, the two methylene groups in micelle I are in a polar environment (i.e., in the outer part of the surface) and are nonpenetrating into the interior of the micelles. The difference in the free energy of solubilization found for micelle I as compared to VII cannot be explained on the basis of hydrogen bonding since kinetically the data do not conform with assistance (through hydrogen bonding) either in the ground state or in the transition state (see results of azide, Table V). The lack of hydrogen bonding by the hydroxy head groups to the ester examined here is in accordance with the free area of 102 A^2/molecule found for the hydroxy group in 2-dodecylaminoethanol hydrobromide. The additional interaction in the outer region of micelle I could instead result from different charge distribution compared to micelle VII. Molecular orbitals calculations[47] point to a very high charge delocalization. In a conformation of {50,50} only 11% of the positive charge is located on the nitrogen, while 82% of the charge is localized on the methylene groups bonded to the nitrogen. (This delocalization is one of the reasons for the roughness of the micellar surface.) The β carbon also exhibits a strong positive charge on the carbon which is ~4 times greater than that on the nitrogen. The appearance of a large positive charge on the outer hydrocarbon chain of the micelle containing a polar head group is likely to increase solvation and solute binding interactions. In esters of short carbon chain, these electrostatic interactions compensate part of the hydrophobic interaction between the solute and the hydrocarbon core of micelle I. Therefore, comparison between dipolar micelles I, Ib and micelle VII allows the anticipation that (1) the partition coefficient of the esters in the two systems are different, and (2) in a noncatalytic dipolar micelle (Ib) the transition state involved in the nucleophilic attack is relatively more stabilized than in micelle VII. With long-chain esters these effects are minimized. The twofold decrease in the second-order rate constant of the basic hydrolysis of PNPD in micelle VII as compared to that in Ib can be explained on the basis of the above argument. It is anticipated that with dipolar micelles in acidic media both solvation and destabilization of the transition state will be affected more by excess positive charge distribution than in micelle VII. Indeed, inspection of Table VI reveals that the rate constants in micelle I are very close to those in VII.

Substrate orientation in the outer part of the micellar phase is very important, especially when the nucleophile is part of the micelle monomer and hindrance to nucleophilic attack might arise. NMR analysis revealed[48] that choline, acetylcholine, and 2-methoxycholine populate almost exclusively the gauche conformation A, while ethyltrimethylammonium bromide adopts 88% of the anti form B.



The preference of conformation A is explained in terms of an interaction between the onium group and the partial negative charge on the β oxygen.[49]

Although in the micellar phase most of the positive charge is neutralized by the negatively charged ions from the bulk solution, the gauche conformation can still be dominant as a consequence of the anionic nucleophile on the β oxygen.

In micelles I–V this entails restriction in orientation of the substrate during the nucleophilic attack.

Kinetic data are in consonance with the above assumption. In contrast to the hydroxy dipolar system, the electrophilic catalysis in cationic surfactant becomes more pronounced as the chain length of the substrate increases.[45] The observed decrease in rate with the increase of the hydrocarbon chain of esters of the hydroxy dipolar micelles indicates that the hydrophobic interaction between the substrate and the interior core of the micelle expels the carbonyl group from the vicinity of the nucleophile. The relative rates k_{mH}/k_{OH} for the short chain dinitrophenyl esters (Table III) are of higher value than those of the *p*-nitrophenyl esters, indicating that the former tend to dwell in the waterlike region of the micelle, in the vicinity of the hydroxy head group. The increase in the relative rate is more pronounced in the presence of I and III than of II, IV, and V, but it is rather small in the presence of II existing presumably in a more flexible conformation. In OPDNPDE$^+$ the hydrocarbon chain of the ester is assumed to be incorporated into the micellar core where the positively charged ammonium group lies on the Stern layer and the carbonyl group points outward of the micellar surface (i.e., in the vicinity of the attacking nucleophile). Interestingly, the rates of hydrolysis of OPDNPDE$^+$ are accelerated in the presence of micelles I, II, and III (Table III) by a factor of 12–18 relative to OPDNPD, whereas in the presence of IV the factor is 5.7 only. Since in a noncatalytic micelle (Ib) the rates of hydrolysis of OPDNPDE$^+$ and OPDNPD are 1500 and 20 s^{-1} M^{-1}, respectively, evidently the effect of the ionized hydroxy head group on the nucleophilic catalysis is smaller for OPDNPDE$^+$ than for OPDNPD.

The relative rates of OPDNPD $k'(I)/k'(Ib)$ for micelles I, II, III, and IV are 505/20 = 25.2, 63/20 = 3.15, 700/20 = 35, and 405/20 = 20.2, respectively, while for the ester OPDNPDE$^+$ the relative rates for the above micelles are 4, 1, 8, and 2, respectively.

Data indicate that the catalysis by hydroxylic micelles becomes more efficient as the electrophilic center of the carbonyl ester resides in the region between the cationic and the hydroxy head group. When the residence of the carbonyl ester occurs above the micellar hydroxy head group as in the case of OPDNPDE$^+$, the catalysis, although it still exists, has rather low efficiency. The lower rate of hydrolysis of OPDNPDE$^+$ relative to OPDNPD in micelle IV can also be rationalized in terms of the micellar conformation depicted by rotamer A. In this conformation the steric interference of the dimethyl groups in the α position with the ester moiety in OPDNPDE$^+$ is greater than in OPDNPD, which is placed at the internal region of the micelle surface.

The rate constant (k') in the presence of IV is in general smaller than in I. The decrease in catalysis can be attributed to the differences in pK_a between the monomers of the two systems. From analogy between the hydroxy compounds and the carboxylic acids one can attribute an increase of 0.17 pK_a units to the dimethyl groups (the pK_a values of propionic acid and trimethylacetic acid are 4.87 and 5.04, respectively) and the relative first-order rate constants $[k_m(IV)/k_m(I)]$ should therefore be equal to 1.5-fold of the second-order rate ratio. Such an estimation shows that in the case of the long-chain ester OPDNPD and PNPD, where the ester group occupies a more restricted area than in the short-chain counterparts, the catalytic efficiency of IV is 120 and 75% of I, respectively.

The greater acceleration effect in III than in I cannot be attributed to differences in micellar volume since the same effect is noted in the case of the short-chain catalyst IIIa. We believe that replacement of the dimethyl by a diethyl group should entail a change in the microscopic environment of the oxy nucleophile which could be manifested either by a lower pK_a value of the hydroxy group or by exerting influence on the binding in the transition state.

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Registry No.—IIIa, 5455-95-8; PNPA, 830-03-5; OPDNPA, 4232-27-3; PNPH, 956-75-2; PNPD, 1956-09-8; OPDNPD, 61063-34-1; OMDNPD, 61063-35-2; PBPD, 61063-36-3; PD, 14353-75-4; OPDNPDE$^+$, 61063-37-4; hexanoyl chloride, 142-61-0; decanoyl chloride, 112-13-0; *p*-nitrophenol, 100-02-7; 2,4-dinitrophenol, 51-28-5; MNPD, 61063-38-5.

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(18) (a) No buffer effect was observed in the concentration range between 0.01 and 0.08 M, in ionic strength of 0.8 M (KBr). (b) The authors wish to thank Professor T. C. Bruice for supplying his programs for the Olivetti calculator. (c) The validity of the cmc values assembled in Table IV could be inferred from ESR measurements with spin labeling.[16b] In a forthcoming paper, Part 5, we shall present kinetic evidences establishing the reliability of the above cmc values. (d) Progress of investigations in various ionic strengths and various pH ranges will be described in following publications.
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Reaction of Atomic Fluorine with Benzotrifluoride

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A radio-frequency excited plasma has been used to generate atomic fluorine. Using a molecular beam type of reactor, monofluorination of benzotrifluoride has been achieved with yields up to 28.3%. The atomic fluorine to benzotrifluoride ratio has been found to determine which isomer(s) will be produced and to control the total overall yield of monofluorinated products.

Direct introduction of fluorine into an aromatic ring without corresponding loss of aromaticity has been an unsolved problem for years. Early attempts at direct fluorination led to explosions, the only products being tars.[1-3] Having obtained only a polymer, Bockemuller[4] concluded that under the conditions for direct liquid-phase fluorination aromatic compounds form addition products or polymers instead of the desired substitution products. In 1969, Grakauskas[5] reported the direct liquid-phase fluorination of benzene, toluene, bromobenzene, and several other aromatic compounds. Based on the distribution of ortho, meta, and para isomers of the monosubstituted fluorobenzenes, an ionic electrophilic substitution mechanism was proposed for these reactions.

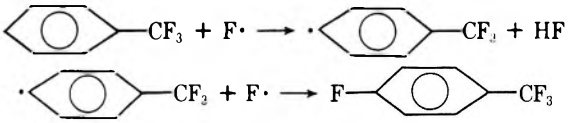
Recently, substitution of fluorine into an aromatic ring by direct reaction with atomic fluorine generated in an electrodeless radio-frequency glow discharge has been reported.[6,7] The isomer distribution of the products indicated that the introduction of fluorine into an aromatic ring via radical mechanism can occur with much more selectivity than previously thought.

Discussion

In an effort to determine the relative chemical activity of atomic fluorine with respect to molecular fluorine, reactions E and F were undertaken. The two reactions were carried out under as near identical conditions as possible except for the fact that in reaction E atomic fluorine was used and in reaction F molecular fluorine was used. Since the atomic fluorine was generated by passing molecular fluorine through a radio-frequency discharge, it was a relatively simple matter to perform experiments with and without the radio-frequency activation. In Table I it can be seen that in reaction E (where atomic fluorine was used) the yield was 28.3% monofluorinated product, while in reaction F (where molecular fluorine was used) the yield was less than 1% monofluorinated product. The use of atomic fluorine increased the percent of monofluorinated product(s) and greatly reduced polymer formation.

Figure 1 related the fluorine to substrate ratio to the recognizable fluorinated products. As the ratio was increased in the experiment, the percent recognizable product also increased.

If the original attack of the benzotrifluoride occurs as shown below, the benzotrifluoride radical produced can react in three



ways: (1) with atomic fluorine to produce monofluorobenzotrifluoride; (2) with another benzotrifluoride radical to produce bis(trifluoromethyl)biphenyl; (3) with a benzotrifluoride molecule to initiate polymerization.

Increasing the availability of the fluorine atoms with respect to benzotrifluoride radicals increases the amount of monofluorinated products and decreases the amount of polymer formed. Figure 1 shows this relationship.

In earlier atomic fluorine work Vasek and Sams[7] reported finding greater selectivity than would have been pictured from literature discussions of free-radical reactions. The findings of this study show a definite relationship between the fluorine to substrate ratio and isomer distribution. The ortho and meta

Table I. Reaction Conditions and Yields

Reaction	Fluorine / benzotrifluoride	Fluorine mmol	Benzotrifluoride, mmol	Reaction time, h	Monofluorobenzotrifluoride / reactant benzotrifluoride (100)	Isomer of monobenzotrifluoride / benzotrifluoride (100) Ortho	Meta	Para
A	0.918	25.82	28.11	3	1.63	0.694	0.242	0.694
B	1.56	25.82	16.58	3	1.98	0.302	1.01	0.669
C	3.91	25.82	6.57	3	3.62	0.301	1.36	1.96
D	10.7	59.02	5.54	4	17.2	0	0	17.2
E	15.8	59.02	3.74	4	28.3	0	0	28.3
F	15.7	29.51	1.58	2	0.836	0.356	0.477	0.00211

[a] All reactions were with atomic fluorine, except F, which was with molecular fluorine.

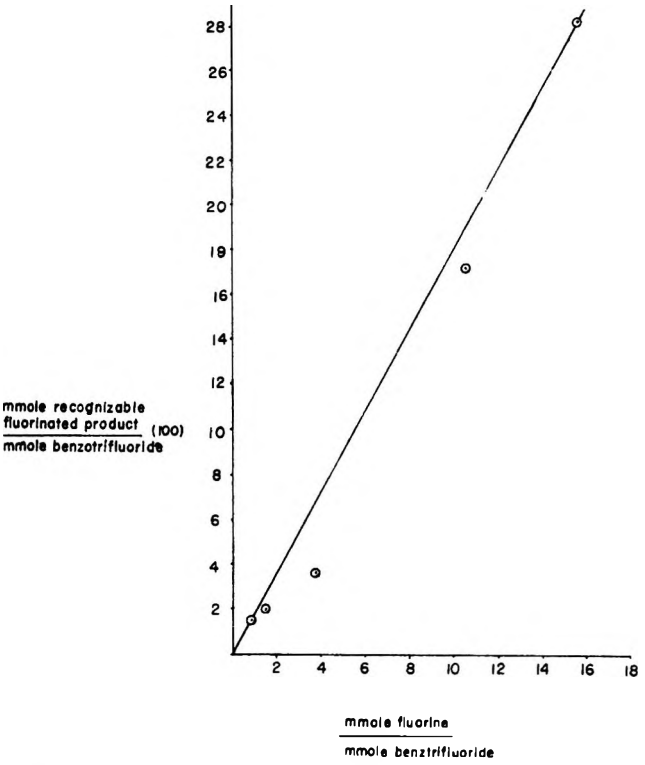


Figure 1.

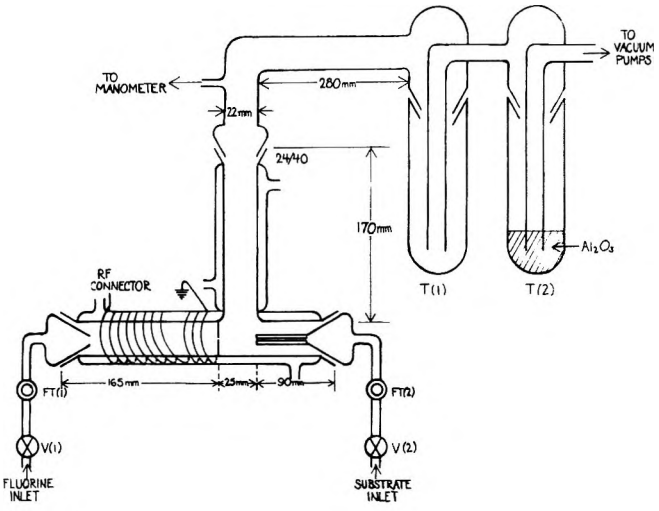


Figure 2.

isomers are only produced when the fluorine to substrate ratio is less than 10.7, while above this point only the para isomer is produced. The question has arisen as to why only the para isomer was found above the fluorine to substrate ratio of 10.7. One possibility was that the ortho and meta isomers were not stable under the conditions of the reaction and may have been converted to the para isomer. In order to answer this question, several reactions were carried out under identical conditions as before except that the ortho isomer and the meta isomer were consecutively used as substrates. Following the reaction the products were analyzed as before. No para isomer was found in either product. These data show that under the conditions of the reactions the ortho and meta isomers are stable and rule out the possibility of isomer interconversion. From Table I it is evident that the para isomer production is proportional to the increasing ratio. Unlike the ortho and meta isomers, the para isomer continued to increase in a somewhat linear fashion up to the limits of experimental capability.

Since this study reports remarkable isomer specificity, a discussion is called for. When the fluorine to benzotrifluoride ratio is above 10.7, the para isomer is the exclusive product. One explanation, as stated earlier, is that under these conditions the ortho and meta isomers are first formed and then converted to the para isomer. This hypothesis, however, has been discounted because the ortho and meta isomers have been found to be stable under the conditions of the reaction.

A second explanation seems indicated from previous work. While studying the reaction between fluorobenzene and atomic fluorine, Vasek and Sams[7] found that the ortho and para fluoro isomers predominated. One would expect to find that the trifluoromethyl group would also be very electronegative and direct into the ortho and para positions. The trifluoromethyl group is much larger in size than the fluoro group and it can be shown to sterically hinder the ortho position. Considering the above, it follows that the reaction products would be almost entirely para.

Experimental Section

Materials. Benzotrifluoride was obtained from PCR, Inc. o-Fluorobenzotrifluoride, *m*-fluorobenzotrifluoride, and *p*-fluorobenzotrifluoride were purchased from Pierce Chemical Co. After the infrared spectra checked with the literature,[8] the compounds were used as received.

A new reactor using the molecular beam design was constructed of Pyrex glass according to Figure 2. The reactor was activated inductively with a radio-frequency generator (Johnson Viking Model II) with deliverable power from minimum up to 180 W. The experimental setup contained a Johnson Viking impedence matching box. All experiments were carried out at a radio frequency of 29.1 MHz.

The fluorine gas and benzotrifluoride vapor used throughout were measured by means of Hasting Mass Flowmeters Model LF-20 which were equipped with Monel metal fittings. The flow rates of both gases were regulated with Hoke fine metering valves V(1) and V(2).

The reaction products were analyzed by gas chromatography using a Benton-34 column in a fashion similar to that previously described by Seiler, Durrance, and Sams.[9] The quantity of each isomer was determined by comparison of peak areas to that of calibration curves

derived from authentic compounds. Product isomers were identified by comparison of their infrared spectra to that of the authentic compounds.

The light emitting from the fluorine plasma glow discharge has been analyzed during a reaction using a Welch No. 3690A spectrometer with a 600-mm grating and the following wavelengths were observed: 6242, 6353, 6412, 6908, and 6862 Å. These values are consistent with those reported for atomic fluorine by Stringanov and Sventitskii.[10] This laboratory found the shorter wavelength lines to be the most intense while Stringanov and Sventitskii reported the longer wavelength lines to be the most intense. This should be expected since our lines were measured on light coming from a high-energy plasma discharge and their lines were measured on light coming from a low-energy arc discharge. Realizing that it would have been very helpful to know the exact percentage of atomic fluorine passing from our plasma generator, a careful survey of the literature has been undertaken. Rosner and Allendorf[11] endeavored to determine atomic fluorine concentrations in several different ways. They included in their methods chemiluminescent titration reactions and calorimetric probes. In the chemiluminescent titration reactions using NOCl the simultaneous presence of molecular fluorine seriously complicates the determination, since molecular fluorine is able to react with NO to form NOF as well as atomic fluorine. Although Rosner and Allendorf studied calorimetrically the reactions of atomic fluorine with many different metals, their data regarding atomic fluorine concentration resulted only in qualitative estimates. In an effort to gain quantitative data regarding the output of the atomic fluorine generator used, our group undertook a study involving the reaction between silver mirrors and atomic fluorine which resulted again only in qualitative information. The best information regarding atomic fluorine concentration has come from the relative intensity of the atomic fluorine emission lines known to originate from atomic fluorine.[10]

In Table I reactions A–E were carried out in a manner as indicated below. The fluorine and benzotrifluoride flow rates were established in a manner necessary to give increasing fluorine to benzotrifluoride ratios.

In a typical reaction undiluted elemental fluorine was passed through metering valve V(1) and flow transducer FT(1) into the previously evacuated reactor which was cooled by condensers maintained at 0 °C. The fluorine was then allowed to pass into the discharge region where the red glow characteristic of atomic fluorine[12] was initiated by the radio-frequency field. A beam of fluorine atoms then passed into the reaction chamber by way of a 0.75-mm hole in a glass septum, as shown in Figure 2. The temperature of the beam of fluorine atoms was measured after passing through the 0.75-mm hole and was found to be 14 °C. Following the stabilization of the fluorine flow, benzotrifluoride vapor was introduced by placing the substrate in a small flask, maintained at 25 °C, and allowing the autogenous vapor pressure (≃23 Torr) to cause a flow through metering valve V(2), flow transducer FT(2), and then into the reaction chamber through the 0.75-mm i.d. capillary tube. The flow carried the products from the reaction chamber and they were condensed in trap T(1) which was cooled by liquid nitrogen.

At completion of the reaction the contents of trap T(1) were removed and analyzed according to Seiler.[9]

Registry No.—Atomic fluorine, 14762-94-8; benzotrifluoride, 98-08-8.

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The Apparent Oxidation of Triphenylmethane by Triflic Acid[1]

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The apparent oxidation of triphenylmethane to triphenylcarbonium ion by triflic acid is shown to be the result of dealkylation of one of the benzene rings followed by hydride transfer from unreacted triphenylmethane to the diphenylcarbonium ion, a disproportionation rather than an oxidation. Some other apparent oxidations in strong acid solvents may be similar. Triflic acid is a convenient solvent in which to study the chemistry of stabilized carbonium ions.

The apparent abstraction of hydride ion from hydrocarbons by Lewis and/or Brønsted acids is a well-known process.[2-5] Three mechanisms have been demonstrated.[4] The purpose of this paper is to demonstrate a fourth mechanism and to show that trifluoromethanesulfonic acid (triflic acid) is a convenient solvent for such reactions.

Results

Treatment of triphenylmethane with about ten times its own weight of triflic acid gave about a 50% yield of the triphenylcarbonium ion, a 76% yield of benzene, and a 22% yield of diphenylmethane, as judged by the visible (Figure 1) and NMR spectrum of the reaction mixture and the products obtained after quenching with aqueous base. A 0.1% yield of antracene was also formed. No gas is produced or consumed in this reaction.

On the other hand, a dilute solution of triphenylmethane in triflic acid (7×10^{-3} M) gave an essentially quantitative yield of diphenylcarbonium ion, as judged by its visible spectrum (Figure 2). At intermediate concentrations intermediate results were obtained, as shown in Table I.

Diphenylmethane was not completely soluble in ten times its own weight of triflic acid. After stirring for 1 h at room temperature and quenching, the steam distillate was mostly starting material but also contained 0.8% yield of anthracene, which dominated its visible and UV spectrum because of its spectral intensity (Figure 3).

For comparison purposes the visible and UV spectroscopic behavior of a number of aromatic hydrocarbons and ions was examined in triflic acid. Benzene gave essentially the same spectrum as in cyclohexane. Toluene gave an additional broad band centering around 320 nm. The apparent extinction

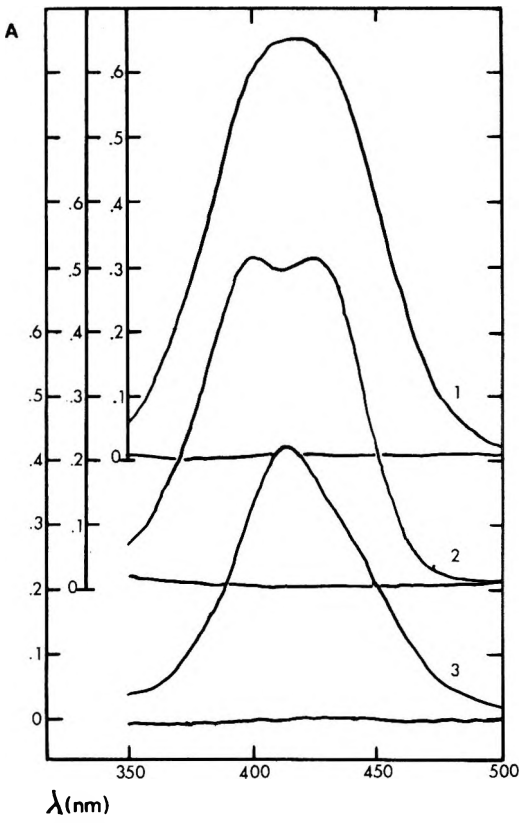


Figure 1. (1) Spectrum of a solution originally made up to contain 7.9×10^{-2} M triphenylmethane in triflic acid and then diluted to a nominal concentration of 3.2×10^{-4} M. (2) Spectrum of 1.3×10^{-4} M triphenylcarbonium ion in triflic acid, generated from triphenylcarbinol. (3) Spectrum of a solution nominally containing 3.9×10^{-4} M diphenylmethane in triflic acid. The spectrum is thought to be mainly that of its conjugate acid. All the spectra were obtained in cells of 1.0 nm path and all show the experimental baselines. Spectrum 1 is thought to be a combination of 2 and 3.

Table I. Product Dependence on the Initial Concentration of Triphenylmethane, $[(C_6H_5)_3CH]_i$

$[(C_6H_5)_3CH]_i$	$[C_6H_5)_3C^+]$	$[(C_6H_5)_2CH^+]$ all $\times 10^2$, M	$\{2[(C_6H_5)_3C^+] + [(C_6H_5)_2CH^+]\}$
1.58	0.44	0.67	1.55
2.84	1.04	0.93	3.01
3.30	1.25	0.96	3.46
3.99	1.88	0.36	4.12
4.48	2.14	0.29	4.57

coefficient, ϵ_{max}, is low (around 200) but this may be due to incomplete reaction. A similar band, formed in $AlCl_3$–HCl, has been attributed to ring-protonated toluene.[6,7] The spectrum generated by diphenylmethane in triflic acid is shown in Figure 1. It is similar in ϵ_{max} to protonated aromatics, but its long wavelength λ_{max} is larger than might have been expected.[7] Benzyl alcohol could not be dissolved in triflic acid without depositing an insoluble material; the visible and UV spectrum of the supernatant was not reproducible, and seemed to be generated by several species formed in varying proportions. One of these, with λ_{max} around 250 nm, appears to be the benzyl cation.[8] Small quantities of diphenylcarbinol could be dissolved in triflic acid, either at room temperature or at −15 °C, and gave spectra (Figure 2) previously identified with the diphenylcarbonium ion.[9] This spectrum is unchanged after several hours of standing at room temperature. Triphenylcarbinol gave the spectrum previously identified with the triphenylcarbonium ion.[9]

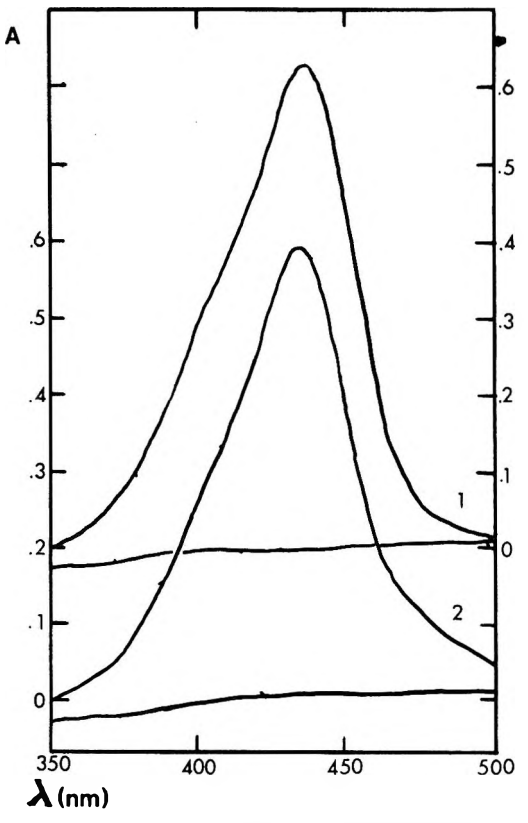
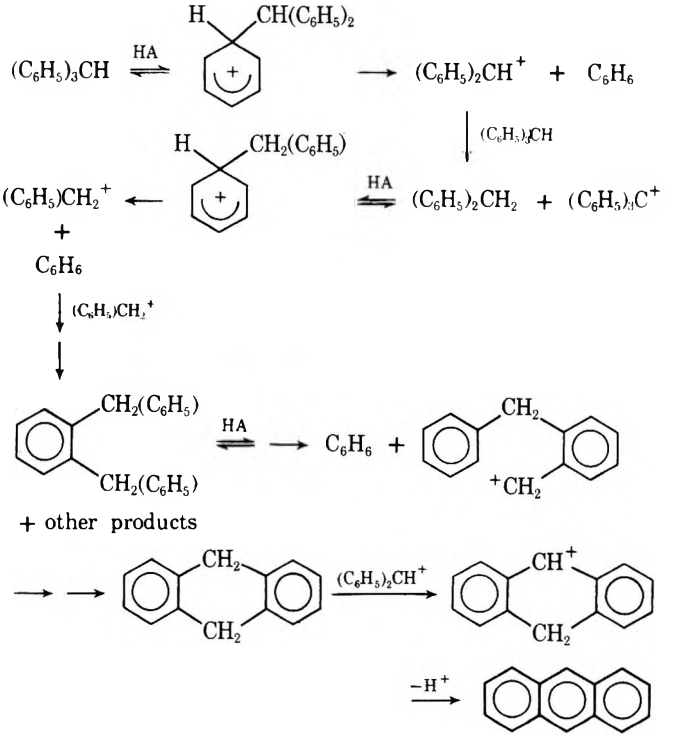


Figure 2. (1) Spectrum of a solution originally made up to contain 7.0×10^{-3} M triphenylmethane in triflic acid, diluted to a nominal concentration of 1.4×10^{-4} M, and thought to contain that concentration of diphenylcarbonium ion. (2) Spectrum of 1.36×10^{-4} M diphenylcarbonium ion in triflic acid, derived from a similar concentration of diphenylcarbinol. Both spectra were obtained in cells of 1 mm path.

Discussion

All the foregoing observations can be rationalized as shown by Scheme I. When high initial concentrations of triphenylmethane are used, the first-formed diphenylcarbonium ion

Scheme I



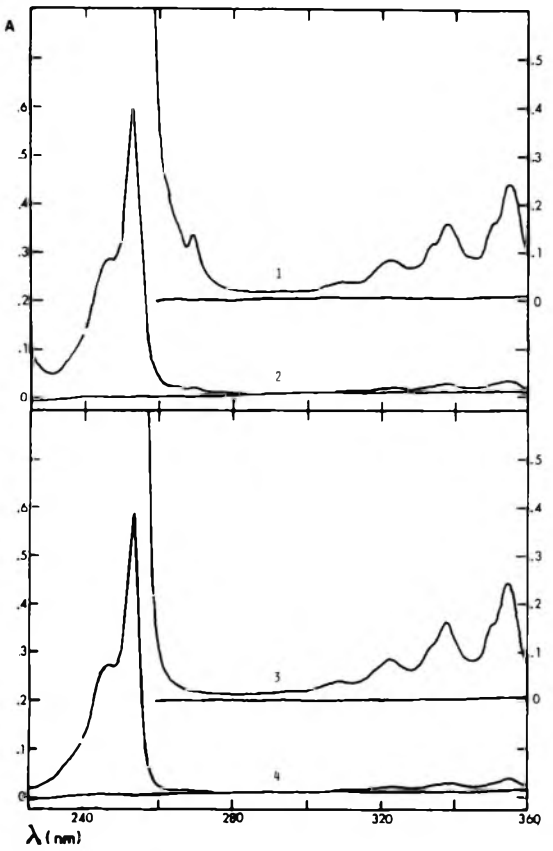


Figure 3. (1) The UV spectrum of the cyclohexane extract of the steam distillate obtained after diphenylmethane was treated with ten times its own weight of triflic acid and then quenched. (2) The same material, diluted ten times with cyclohexane. (3) Anthracene, 2.9×10^{-4} M, in cyclohexane. (4) Anthracene, 2.9×10^{-5} M, in cyclohexane. All spectra were obtained in 0.1-cm cells.

abstracts a hydride ion from the starting material to give triphenylcarbonium ion, diphenylmethane, and the further products shown. There are, undoubtedly, other minor products formed from the phenylcarbonium ion, but its unique volatility and the intensity of its spectrum make anthracene observable. At very low initial triphenylmethane concentrations the diphenylcarbonium ion is persistent, since, as shown by the experiments with diphenylcarbinol, it is stable in triflic acid, and the concentration of unreacted triphenylmethane is too low for the hydride transfer to be significant. Scheme I is really a disproportionation rather than a simple oxidation. Oxidation and reduction products are produced in equivalent amounts, and nothing other than the substrate itself is reduced.

Dealkylation and hydride transfer, the basic reactions of Scheme I, are well known and widespread reactions.[2,3,10,11] The cleavage of triphenylmethane in superacid medium, to give benzene and the diphenylcarbonium ion, has been previously reported.[12] The combination should, therefore, be added as a fourth general mechanism for apparent oxidations in strong acid medium, in addition to the three listed by Larsen et al.[4] For example, the "oxidation" of xanthene, 4,4′-dimethoxydiphenylmethane, and 4,4′,4″-trimethoxytriphenylmethane by sulfuric and phosphoric acids may be an example of its working[13] (although others have obtained different results under similar conditions[5]). Dealkylation, at least, definitely seems to occur on treatment of 4,4′,4″-trimethoxytriphenylmethane with very strong acids.[14]

Experimental Section

Materials. Triflic acid was twice distilled, the last time within one day of use, since it darkened on standing, bp 164 °C, reported[15] 162 °C. Triphenylmethane (Eastman Kodak Co.) was recrystallized from methanol, mp 93–94.5 °C, reported[16] 92.5 °C. Triphenylcarbinol (Matheson Coleman and Bell) was recrystallized from methanol, mp 159–161.5 °C, reported[17] 159 °C. All other materials were of the best quality commercially available and were used without further purification. Their suitability for the present work was verified spectroscopically.

Spectrophotometric Measurements. Visible and UV spectra were obtained with a Beckman DK-2 spectrophotometer using quartz cells of 1 cm or 1 mm path length, as required by the absorptivity of the solutions.

In determining the product compositions shown in Table I the method of Baughman and Kreevoy[18] was used. The two wavelengths chosen were 404 (λ_1) and 432 nm (λ_2). It was assumed that triphenylcarbonium ion and the conjugate acid of diphenylmethane would always occur in the same proportions in these experiments, so that they could be treated as a single substance. By making concentrated solutions of triphenylmethane in triflic acid and then diluting them as required, this "substance" was found to have ϵ_1 1.76×10^4 and ϵ_2 1.79×10^4. Extinction coefficients for diphenylcarbonium ion were obtained from very dilute solutions of triphenylmethane in triflic acid, ϵ_1 being 2.14×10^4 and ϵ_2 4.32×10^4. These measurements were all made with a Beckman DU spectrophotometer, modernized with a Gilford Update, at 25.0 ± 0.2 °C.

Each mole of triphenylmethane that reacts as shown in Scheme I can produce 1 mol of diphenylcarbonium ion, but 2 mol of triphenylmethane is required to produce 1 mol of triphenylcarbonium ion. Therefore, the methodology outlined above can be tested by comparing the sum, $2[(C_6H_5)_3C^+] + [(C_6H_5)_2CH^+]$, with the initial triphenylmethane concentration. This is done by comparing columns 1 and 4 of Table I. It is entirely satisfactory.

Infrared spectra were made in the usual way with a Perkin-Elmer 537 infrared spectrophotometer.

NMR spectra were made with a Varian T-60 NMR spectrophotometer. For isolated products, carbon tetrachloride or deuteriochloroforam were used as solvent with tetramethylsilane as reference. For solutions in triflic acid, tetramethylammonium chloride was used as a reference. Its signal was assumed to come 3.10 ppm below tetramethylsilane.[19] The NMR spectrum of triphenylcarbonium ion in triflic acid consists of peaks at 7.7, 7.8, 8.0, 8.1, and 8.25 ppm, essentially as previously reported.[20] Other required NMR spectra were compared with those of knowns, and were unexceptional.

Gasometric Measurements. The absence of gas evolution or uptake was determined using 0.1 g of triphenylmethane and 25 ml of triflic acid in a Warburg constant volume respirometer.[21]

Product Isolation. Triphenylmethane (3.3 g, 13.5 mmol) was dissolved in 25 ml of triflic acid and the solution allowed to stand at room temperature for 1 h. It was then quenched by pouring it slowly into 30 ml of chilled 20% aqueous sodium hydroxide. The aqueous solution was steam distilled and the steam distillate was extracted with cyclohexane. From its UV spectrum 10.2 mmol of benzene and 1.9×10^{-2} mmol of anthracene were identified in the cyclohexane solution. The residue from the steam distillation was a waxy, orange solid. It was shown by IR and NMR spectroscopy to contain 6.8 mmol of triphenylcarbinol and 3.0 mmol of diphenylmethane. From this material a poor yield of pure triphenylcarbinol, mp 151–158 °C, was obtained by twice recrystallizing from carbon tetrachloride.

Product isolation from the reaction of diphenylmethane was carried out similarly.

Registry No.—Triphenylmethane, 519-73-3; triflic acid, 1493-13-6; triphenylcarbinol, 76-84-6; triphenylcarbonium ion, 13948-08-8; diphenylcarbonium ion, 709-82-0; diphenylmethane, 101-81-5; diphenylcarbinol, 91-01-0.

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Semipinacol Rearrangements Involving Trifluoromethylphenyl Groups[1]

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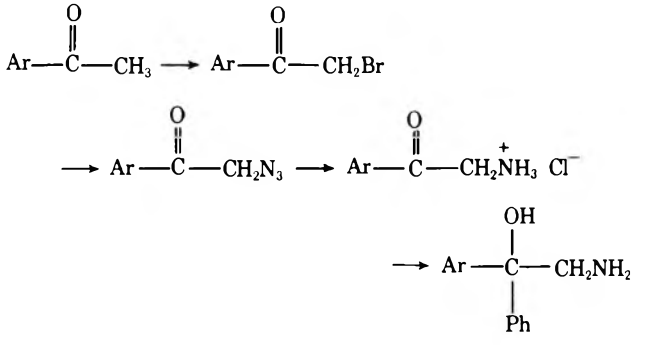
Semipinacolic deamination of 2-amino-1-(3-trifluoromethylphenyl)-1-phenylethanol (**1**) with sodium nitrite in aqueous acetic acid yields 3′-trifluoromethyldeoxybenzoin (**3**) and 3-trifluoromethyldeoxybenzoin (**4**). The migratory aptitude of the *m*-trifluoromethylphenyl group (phenyl = 1.0) is 0.47 at 0 °C and 0.39 at 25 °C. Similarly, deamination of 2-amino-1-(4-trifluoromethylphenyl)-1-phenylethanol (**2**) yields 4′-trifluoromethyldeoxybenzoin (**5**) and 4-trifluoromethyldeoxybenzoin (**6**). The migratory aptitude of the *p*-trifluoromethylphenyl group is 0.30 at 0 °C.

Little information is available regarding the behavior of trifluoromethylphenyl groups in pinacol-type reactions.[2] Our interest in deaminative rearrangements has led us to investigate semipinacol rearrangements of 2-amino-1-(3-trifluoromethylphenyl)-1-phenylethanol (**1**) and 2-amino-1-(4-trifluoromethylphenyl)-1-phenylethanol (**2**).

Results

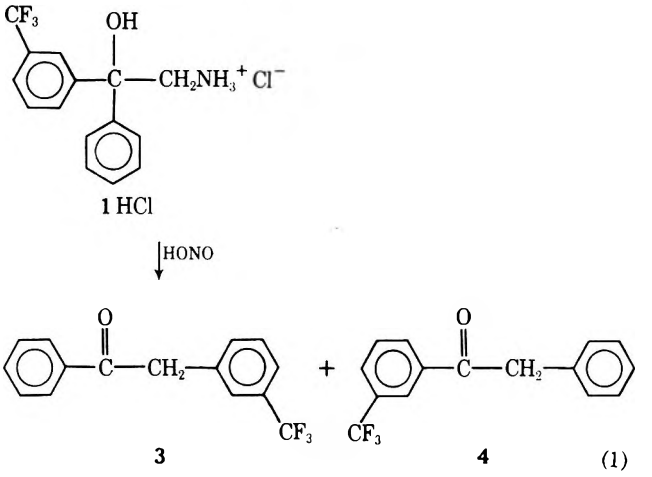
The amino alcohols were synthesized according to the general outline of Scheme I (see Experimental Section).

Scheme I



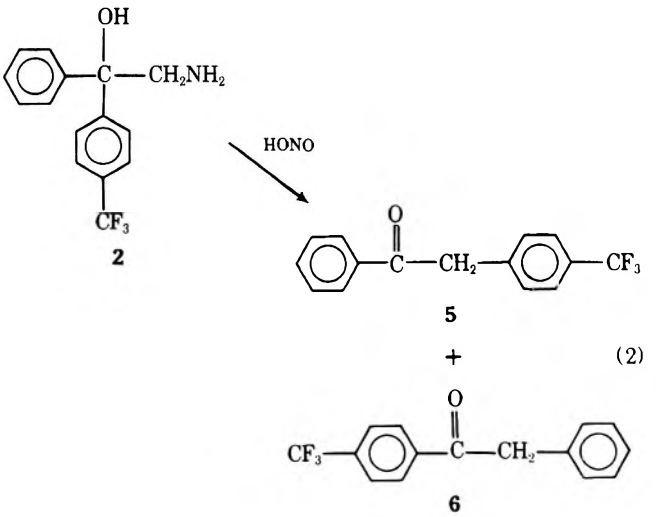
Ar = *m*- or *p*-$CF_3C_6H_4$; Ph = C_6H_5

Deamination of the meta-substituted amino alcohol hydrochloride, 1 HCl, was carried out with sodium nitrite in aqueous acetic acid at 0 °C[3] and at 25 °C (eq 1). The ketones **3** and **4** (combined yield 77% of theoretical at 0 °C) were separated from nonketonic products by column chromatography on alumina, and the ratios of **3** to **4** were determined by ^1H NMR and also by ^{19}F NMR spectroscopy using comparisons with authentic samples of **3** and **4** independently prepared (see Experimental Section). Results are summarized in Table I. The ketones were shown to be stable to the deamination conditions.



(1)

Deamination of the para-substituted amino alcohol **2** was carried out with sodium nitrite at 0 °C in aqueous acetic acid (eq 2). The ketonic fraction (67% of theoretical) was isolated



(2)

Table I. Ketone Composition from Amino Alcohol Deaminations

Amino alcohol	Temp, °C	Ketone	Percentage (migratory group)	Migration ratio aryl/phenyl
1	0	3	32 (m-$CF_3C_6H_4$)	3/4 = 0.47
		4	68 (C_6H_5)	
1	25	3	28 (m-$CF_3C_6H_4$)	3/4 = 0.39
		4	72 (C_6H_5)	
2	0	5	23 (p-$CF_3C_6H_4$)	5/6 = 0.30
		6	77 (C_6H_5)	

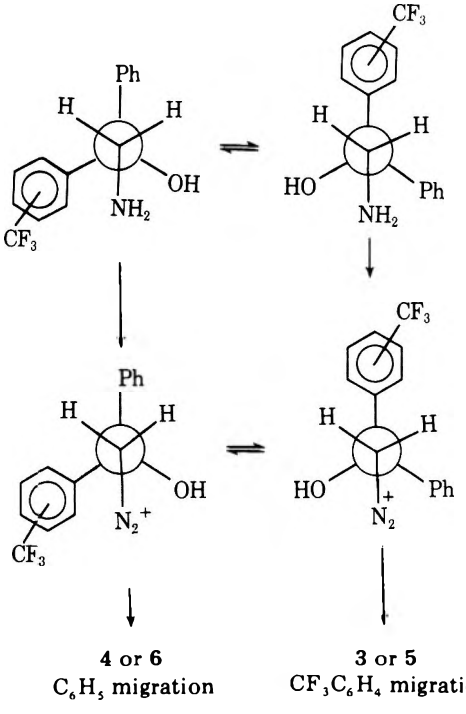
and analyzed as above using comparisons with authentic samples of 5 and 6 independently prepared (see Experimental Section). Results are summarized in Table I. The ketones were shown to be stable to the deamination conditions.

Discussion

The migration ratios (phenyl = 1.0) observed for the trifluoromethylphenyl groups (see Table I) are less than 1. In general, for cases in which the migration terminus is primary, the relative migratory aptitudes of aryl groups during deamination of amino alcohols follow the order expected from consideration of relative rates of electrophilic aromatic substitution.[4] Some representative examples[4] are p-methoxyphenyl, 1.5; p-tolyl, 1.3; p-chlorophenyl, 0.9.

Scheme II presents our analysis of the observed results of

Scheme II



the deamination reactions. A gauche relationship between hydroxy and amino groups has been shown to be preferred.[5] We represent the reactive intermediates as diazonium ions in which aryl migration takes place in an anti relationship with the leaving group; the rationale for such a scheme has been presented previously.[6] Migration is presumably competitive with central C–C bond rotation.[7]

The fact that the m-trifluoromethylphenyl group has a higher migratory aptitude than its para analogue under the same conditions is reasonable, since Hammett substituent constants indicate more electron withdrawal by CF_3 in the meta position.[8] However, any detailed analysis of the significance of the migration ratios would be highly speculative since we have no data concerning rates of loss of N_2 and aryl migration relative to C–C bond rotation or about the conformational equilibria involved.

We are currently attempting to learn more about the conformational preferences of systems such as the amino alcohols involved here.

Experimental Section

All melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Beckman IR-8 and Perkin-Elmer 700 spectrophotometers. Nuclear magnetic resonance (NMR) spectra were taken on a Hitachi Perkin-Elmer R-20 60-MHz spectrometer. Combustion analyses were carried out by Schwarzkopf Microanalytical Laboratories, Woodside. N.Y.

***m*-Trifluoromethylbenzyl Alcohol (7).** m-Trifluoromethylbenzoic acid (Sigma Chemicals) (5 g, 26 mmol) was reduced with $LiAlH_4$ in the usual way. Distillation provided 3.8 g (83%) of a clear liquid, bp 82–83 °C (3.3 Torr): IR (neat) 3350 cm^{-1} (OH, broad); NMR (CCl_4) δ 7.4 (4 H, m, ArH), 4.5 (2 H, s, $-CH_2-$), 4.3 (1 H, s, OH).

***m*-Trifluoromethylbenzyl Chloride (8).** Compound 7 (7.5 g, 42.5 mmol) and thionyl chloride (16.8 g, 142 mmol) were heated at reflux for 10 h. Distillation gave 7.5 g (90%) of a clear liquid, bp 71–74 °C (10 Torr).

3′-Trifluoromethyldeoxybenzoin (3). 3-Trifluoromethylbenzylmagnesium chloride was prepared from dry compound 8 (7.5 g, 38.5 mmol) and magnesium turnings (0.9 g, 34 mmol) in absolute ether (70 ml). To the stirred solution was added dropwise freshly distilled benzaldehyde (3.7 g, 34.9 mmol) in absolute ether (10 ml). The solution was stirred at reflux for 15 min. The cooled solution was poured into an ice-cold solution of 3 N sulfuric acid (150 ml). When the hydrolysis was complete, the ether layer was separated, and the aqueous phase was extracted with several small portions of ether. The combined ether extracts were concentrated to half volume in a rotary evaporator. To the cold, stirred ether solution was added, dropwise, a solution of sodium dichromate (7.4 g, 28.3 mmol) and concentrated sulfuric acid (6.3 ml) in water (25 ml). The mixture was stirred at 5 °C until it turned blue-green (3 h). The ether layer was separated and the aqueous phase was extracted with two small portions of ether. The combined ether extracts were washed with water, saturated sodium carbonate, and water. After drying (Na_2SO_4), the ether was removed in a rotary evaporator, and the residue was distilled to give a clear liquid that solidified to white crystals in the receiver. Yield of 3, 5.4 g (60%), bp 146–148 °C (2 Torr); mp (petroleum ether) 35–37 °C; IR ($CHCl_3$) 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.6 (9 H, m, ArH), 4.35 (2 H, s, CH_2CO); 2,4-dinitrophenylhydrazone (2,4-DNP) mp 185–187 °C (from methanol). Anal. Calcd for $C_{15}H_{11}F_3O$: C, 68.18; H, 4.20. Found: C, 68.15; H, 4.22.

***m*-Trifluoromethylbenzoyl Chloride (9).** Thionyl chloride (13.3 g, 110 mmol) was added to m-trifluoromethylbenzoic acid (Sigma Chemicals) (10 g, 52 mmol). After the initial reaction subsided, the mixture was heated at reflux for 26 h. The excess thionyl chloride was distilled at atmospheric pressure. The acid chloride 9 was distilled to yield 9.8 g (90%) of a clear liquid, bp 84.3–85 °C (10 Torr).

3-Trifluoromethyldeoxybenzoin (4). Benzylmagnesium bromide was prepared from dry benzyl bromide (15.4 g, 90 mmol) and magnesium turnings (2.4 g, 90 mmol) in absolute ether (100 ml). The solution was heated at reflux (30 min) with stirring, and then cooled to 0 °C. To the cold, stirred solution dry cadmium chloride (8.6 g, 47 mmol) was added in small portions. After the addition was complete, the mixture was heated at reflux (50 min) with vigorous stirring. The ether was distilled from the stirred solution until a very viscous, dark residue remained. At this point 100 ml of dry, thiophene-free benzene

was added. The mixture was stirred and an additional 30 ml was distilled. The mixture was cooled in an ice bath, and *m*-trifluoromethylbenzoyl chloride (**9**, 10.4 g, 49.9 mmol) in benzene (20 ml, dried over sodium) was added dropwise to the stirred mixture. Stirring was continued for 24 h at room temperature. The mixture was poured into a solution of concentrated sulfuric acid (15 ml) and ice (130 g). After hydrolysis was complete, the organic layer was separated, and the aqueous phase was extracted with three small portions of ether. The combined organic layers were washed with water, saturated sodium carbonate, and water. After drying ($MgSO_4$) the solvent was removed in a rotary evaporator. The residue was distilled to yield 1.4 g (11%) of **4** as a yellow oil: bp 150–153 °C (2 Torr); IR (neat) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.6 (9 H, m, ArH), 4.3 (2 H, s, ArCH_2); 2,4-DNP (from methanol) mp 164–166 °C (lit.[9] 166 °C).

2-Amino-3′-trifluoromethylacetophenone Hydrochloride (10). Anhydrous $AlCl_3$ (50 mg) was added to a stirred, ice-cold solution of 3-trifluoromethylacetophenone (Chemical Procurement) (10 g, 53.2 mmol) in 20 ml of dry ether. Then bromine (8.4 g, 52.6 mmol) was added dropwise to the stirred solution. After the bromine color disappeared (25–35 min) the ether and dissolved hydrogen bromide were removed at once under reduced pressure. The residue, a yellow oil (a lachrymator), was washed with water (10 ml).

To the yellow oil from above (2-bromo-3′-trifluoromethylacetophenone) dissolved in 20 ml of absolute ethanol was added at once a slurry of sodium azide (14 g, 215 mmol) in 4 ml of water. The mixture was stirred at room temperature for 3 h. At the end of that time, the mixture was diluted with water to twice its volume, and extracted with several portions of ether. The combined ether extracts were dried and the ether was removed in a rotary evaporator. A yellow oil, 2-azido-3′-trifluoromethylacetophenone, remained: IR (neat) 2100 (N_3), 1685 cm^{-1} (C=O).

To the azido ketone from above, dissolved in 40 ml of absolute ethanol, were added 4 ml of concentrated hydrochloric acid and 2 g of 5% palladium on charcoal. The mixture was hydrogenated at atmospheric pressure for 36 h. The mixture was filtered and the catalyst was washed with several small portions of absolute ethanol. The solution was concentrated in a rotary evaporator until a precipitate began to form. At this point the solution was removed from the rotary evaporator, and absolute ether (400 ml) was added. After 3 days of refrigeration the solid was collected, washed with absolute ether, and dried to yield 7.6 g (60%) of the white, crystalline salt (**10**): mp (methanol–ether) 225–227 °C dec; IR (KBr) 3000 (NH_3^+ broad), 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.8 (3 H, s, broad, NH_3^+), 8.1 (4 H, m, ArH), 4.75 (2 H, s, $CH_2NH_3^+$).

2-Amino-1-(3-trifluoromethylphenyl)-1-phenylethanol Hydrochloride (1 HCl). Phenylmagnesium bromide was prepared by reaction of dry bromobenzene (7.8 g, 50 mmol) with magnesium turnings (1.4 g, 50 mmol) in absolute ether (50 ml). The finely powdered keto amine salt **10** (2 g, 8.13 mmol) was added in small portions with stirring over a period of 15 min to the cold (5 °C) Grignard reagent. The mixture was stirred for an additional 50 min at room temperature. The reaction mixture was then poured into a solution of ammonium chloride (2 g) in water (100 ml plus 3 drops of concentrated ammonium hydroxide). After hydrolysis was complete, the layers were separated and the aqueous layer was extracted with two small portions of ether. The combined ether layers were washed with two small portions of water. After drying (Na_2SO_4), the solution was diluted with absolute ether (100 ml) and then saturated with gaseous hydrogen chloride. The solution was further diluted with absolute ether (150 ml) and refrigerated for 3 days. A white solid was formed during the refrigeration period. The product was filtered, washed with absolute ether (50 ml), and allowed to dry. Yield of **1** HCl, 1.9 g (73%); mp (ethanol) 195–198 °C dec; IR (KBr) 3360 (OH), 2980 cm^{-1} (NH_3^+, broad); NMR (Me_2SO-d_6) δ 8.15 (3 H, s, broad, NH_3^+), 7.6 (9 H, m, ArH), 6.85 (1 H, s, OH), 3.8 (2 H, s, $CH_2NH_3^+$).

Anal. Calcd for $C_{15}H_{15}ClF_3NO$: C, 56.70; H, 4.76; N, 4.41. Found: C, 56.71; H, 4.75; N, 4.55.

The free amine (**1**) was obtained by dissolving the hydrochloride (1.1 g) in water (5 ml) and adding 1 M sodium hydroxide dropwise until pH 8 was obtained. The solution was extracted with several small portions of ether. After drying (Na_2SO_4), the ether was removed in a rotary evaporator. The residue, a clear oil, 0.7 g (72%), decomposed very slowly on standing: IR (neat) 3400 (OH), 3100 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 7.5 (9 H, m, ArH), 4.2 (2 H, s, CH_2NH_2), 3.35 (1 H, s, broad, OH), 2.6 (2 H, s, broad, NH_2).

2-Amino-4′-trifluoromethylacetophenone Hydrochloride (11). The procedure followed was that for compound **10**. The yield obtained was 44%; mp (methanol) 245–247 °C dec; IR (KBr) 3000 (NH_3^+, very broad), 1680 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.7 (3 H, s, broad, NH_3^+), 8.2 (4 H, m, ArH), 4.7 (2 H, s, $CH_2NH_3^+$).

2-Amino-1-(4-trifluoromethylphenyl)-1-phenylethanol (2). This compound was prepared in the same way as compound **1** HCl except that gaseous hydrogen chloride was not passed through the ether solution, which rather was evaporated in a rotary evaporator. The residue was dissolved in hot pentane. Upon cooling a light yellow solid (**2**) was isolated by filtration in 57% yield: mp (pentane) 99–101 °C; IR (KBr) 3100 (OH, broad), 2800 cm^{-1} (NH_2); NMR (Me_2SO-d_6) δ 7.4 (9 H, m, ArH), 3.3 (2 H, s, CH_2NH_2), 2.7 (3 H, very broad, OH and NH_2).

Anal. Calcd for $C_{15}H_{14}F_3NO$: C, 64.05; H, 5.02; N, 4.98. Found: C, 64.14; H, 4.98; N, 4.71.

***p*-Trifluoromethylbenzaldehyde (12).** Compound **12** was synthesized by the procedure of Trahanovsky[10] et al., using 50% acetic acid–water as the solvent. The yield thus obtained was 81% of a clear liquid: bp 40–43 °C (2 Torr); IR (neat) 1700 cm^{-1} (C=O).

4-Trifluoromethyldeoxybenzoin (6). This compound was synthesized using compound **12** (4.8 g, 27.6 mmol) in a procedure similar to that with the deoxybenzoin **3**: yield 4%; mp (petroleum ether) 127–129 °C; IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.5 (9 H, m, ArH), 4.29 (2 H, s, ArCH_2); 2,4-DNP (from ethanol) mp 186–187 °C.

Anal. Calcd for $C_{15}H_{11}F_3O$: C, 68.18; H, 4.20. Found: C, 67.88; H, 4.54.

4′-Trifluoromethyldeoxybenzoin (5). This compound was prepared by the same procedure as compound **4**. 4′-Trifluoromethylphenylacetic acid (Chemical Procurement) was converted to the acid chloride and used as in the above procedure. The yield of **5** was 10% as a white solid: 2,4-DNP (from ethanol) mp 205–207 °C; IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.5 (9 H, m, ArH), 4.31 (2 H, s, CH_2C=O).

Anal. Calcd for $C_{15}H_{11}F_3O$: C, 68.18; H, 4.20. Found: C, 68.05; H, 4.38.

Deaminations. The aminoethanol hydrochloride **1** HCl (217 mg, 0.683 mmol) was dissolved in 50% aqueous acetic acid (ca. 10 ml) at 0 °C. A solution of sodium nitrite (238 mg, 3.45 mmol) in water (10 ml) was added dropwise over about 30 min, and the resulting mixture was stirred at 0 °C for 14 h. The reaction was quenched by adding a 10% aqueous sulfamic acid solution dropwise until the solution no longer gave a positive test with starch–iodide paper. The solution was extracted with ether. After drying (Na_2SO_4), the ether was removed at reduced pressure to leave 198 mg of crude product which was subjected to column chromatography on neutral alumina. Elution with pentane removed a nonpolar substance which was not fully characterized; it did not contain nitrogen or fluorine and had no aromatic protons in its ^1H NMR spectrum. Elution with chloroform provided a mixture of ketones **3** and **4** (138 mg, 77%) which was subjected to the analysis described below. An apparently polymeric material remained on the column. Duplicate runs gave similar results; similar runs were conducted at 25 °C. Results are recorded in Table I. A mixture of ketones **3** and **4** was subjected to the deamination conditions and shown to be unchanged.

The aminoethanol **2** (45 mg, 0.160 mmol) in 50% aqueous acetic acid (10 ml) was treated as above with sodium nitrite (4 equiv) in water (ca. 3 ml) for 24 h at 0 °C. Similar workup gave 43 mg of crude material which upon chromatography as described provided 28 mg (67%) of a mixture of ketones **5** and **6**, along with contaminants similar to those mentioned above. The ketone mixture was analyzed as described below. Duplicate runs gave similar results. Results are recorded in Table I. Ketones **5** and **6** were shown to be stable to the deamination conditions.

Analysis of Ketone Mixtures. The ketone product mixtures were analyzed by two separate methods which agreed within ±1%. Standard mixtures of the ketone were prepared and the ^1H NMR signals for the methylene protons (δ 4.35 for **3** and 4.30 for **4**; 4.31 for **5** and 4.29 for **6**) were scanned at an expanded sweep width (60 Hz) and integrated. Since baseline was not reached between signals, corrections were applied to make integrated values agree with known composition. The product mixtures were then analyzed in the same manner, with appropriate corrections as determined from the standard samples.

Similarly, ^{19}F NMR spectra of the standard mixtures were recorded, and the well-separated peaks were integrated. Product mixtures were then analyzed and compared with the standard samples.

NMR analysis of the deamination product mixtures before and after column chromatography demonstrated that no fractionation of ketones occurred during such treatment.

Acknowledgment. We wish to thank Mr. Kent Campbell for his assistance in computer simulation of NMR spectra of

the product mixtures. Dr. Edward Rosenberg supplied helpful comments regarding preparation of the manuscript.

Registry No.—**1**, 61062-52-0; **1**, HCl, 61062-53-1; **2**, 61062-54-2; **3**, 30934-66-8; **3** 2,4-DNPH, 30934-67-9; **4**, 1533-04-6; **5**, 30934-68-0; **5** 2,4-DNPH, 30934-69-1; **6**, 61062-55-3; **6** 2,4-DNPH, 61062-58-6; **7**, 349-75-7; **8**, 705-29-3; **9**, 2251-65-2; **10**, 61062-56-4; **11**, 339-58-2; **12**, 455-19-6; *m*-trifluoromethylbenzoic acid, 454-92-2; 3-trifluoromethylacetophenone, 349-76-8; 2-bromo-3′-trifluoromethylacetophenone, 2003-10-3; 2-azido-3′-trifluoromethylacetophenone, 61062-57-5; 4′-trifluoromethylphenylacetic acid, 32857-62-8; 2-amino-4′-trifluoromethylacetophenone HCl, 339-58-2; benzaldehyde, 100-52-7; benzyl bromide, 100-39-0.

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A Comparison of the Addition of Bromine and 4-Chlorobenzenesulfenyl Chloride to β-Substituted Styrenes and Ethylenes[1]

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A comparison has been made of the rates and products of addition of bromine and 4-chlorobenzenesulfenyl chloride to a series of β-substituted styrenes ($C_6H_5CH{=}CHR$) and ethylenes ($CH_2{=}CHR$), where R = $CH(OCOCH_3)_2$, CH_2Cl, CH_2OCOCH_3, CH_2OCH_3, CH_2OH, H, CH_3, C_2H_5. On the basis of structure–reactivity correlations and product compositions, it is concluded that the rate- and product-determining transition states in the mechanism of bromination of styrene derivatives have different structures. The rate-determining transition state is bridged while the product-determining transition state resembles an open α-bromocarbonium ion.

The structure of the rate-determining transition state in the mechanism of electrophilic additions to alkenes is principally a function of the electrophile, the alkene structure, and the solvent.[2] For some electrophiles the effect of alkene structure on the mechanism seems to be negligible. For example, the mechanism of hydration involves an open carbonium-ion-like rate-determining transition state[3] while a bridged one is involved in the mechanism of the reaction of arenesulfenyl chlorides.[4]

The effect of alkene structure on the mechanism of bromination of alkenes is not clear. It is generally agreed that a bridged rate-determining transition state is involved in the addition to simple alkenes.[5,6] However, the involvement of such a structure in the addition to styrene derivatives has been the subject of debate.

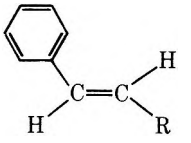
Yates and McDonald have used a thermochemical–kinetic method to probe the structure of the rate-determining transition state.[7] They found that the initial enthalpy difference between pairs of cis–trans isomeric alkenes was increased at the bromination transition state. The results were interpreted as evidence for a bridged rate-determining transition state.

Dubois[6] has compared the bromination of β-substituted styrenes ($C_6H_5C_\alpha H{=}C_\beta HR$) with the corresponding alkenes ($C_\alpha H_2{=}C_\beta HR$) and found that the reactivity of the former series is related to that of the later by a linear equation with slope 0.75. From the value of the slope together with the log k vs. σ^* correlations it was concluded that for the styrene series the rate-determining transition state corresponds to an open carbonium ion with the charge on C_α.

To resolve this problem, we have made a structure–reactivity comparison between bromination and an electrophilic addition whose mechanism is well established. We have chosen the addition of 4-chlorobenzenesulfenyl chloride as our model of a reaction whose mechanism involves a bridged rate-determining transition state independent of olefin structure.[8] Such a comparison should make it possible to arrive at a decision on the structure for the rate-determining transition state of the bromination of styrene derivatives.

Results

We have measured the rates of addition of 4-chlorobenzenesulfenyl chloride to a series of β-substituted trans styrenes, **1a–h**, and to the corresponding alkenes **2a–h** in acetic



1

$CH_2{=}CHR$

2

a, R = $CH(OCOCH_3)_2$	**e**, R = CH_2OH
b, R = CH_2Cl	**f**, R = H
c, R = CH_2OCOCH_3	**g**, R = CH_3
d, R = CH_2OCH_3	**h**, R = C_2H_5

acid at 25.0 °C. The addition was found to obey a second-order rate law, first order in alkene and first order in sulfenyl chloride to at least 80% completion of the reaction. The rate data are presented in Table I.

The product compositions were determined by NMR spectroscopy. The basis of this method is that protons α or β to chlorine are considerably deshielded relative to those α or β to sulfur.[9,10] The NMR parameters of the adducts obtained in this study are reported in Table II with the exception of data reported previously.[11,12] In every case it was possible to find at least one nonoverlapping signal from which the isomer distribution could be calculated.

The kinetically controlled product composition was determined by immediate NMR analysis of the reaction mixture.

Table I. Second-Order Rate Constants for the Addition of 4-Chlorobenzenesulfenyl Chloride to β-Substituted Ethylenes and Trans Styrenes in Acetic Acid at 25 °C

R	No. of runs	*trans*-$C_6H_5CH{=}CHR$, k_2, l./mol s	No. of runs	$CH_2{=}CHR$, k_2, l./mol s
C_2H_5	8	37.9 ± 0.1	6	18.0 ± 0.1
CH_3	4	30.0 ± 0.1	4	13.7 ± 0.1
H	6	15.9 ± 0.7	4	7.68 ± 0.03
CH_2OH	4	9.90 ± 0.04	7	4.19 ± 0.02
CH_2OCH_3	4	3.51 ± 0.01	3	1.55 ± 0.01
CH_2OCOCH_3	3	0.895 ± 0.006	2	0.340 ± 0.001
CH_2Cl	4	0.602 ± 0.003	4	0.368 ± 0.002
$CH(OCOCH_3)_2$	3	0.0709 ± 0.0004	4	0.0541 ± 0.0013

Table II. NMR Parameters of 4-Chlorobenzenesulfenyl Chloride Adducts

$C_6H_5{-}\underset{\alpha}{CH}(Cl){-}\underset{\beta}{CH}(SC_6H_4Cl){-}R$

Registry no.	R	Chemical shifts, δ, ppm; coupling constants, Hz: δH_α	$J_{\alpha\beta}$	δH_β	$J_{\beta\gamma}$	δH_γ
61062-65-5	$CH_{\gamma_2}OH$	5.03 d	9.5	3.56 dt	4.5	4.01 d
61062-66-6	$CH_{\gamma_2}OCH_3$	5.23 d	7.5	3.36–4.07 m	*	3.36–4.07 m
61062-67-7	$CH_{\gamma_2}OCOCH_3$	5.11 d	8.5	3.70 dt	5.0	4.53 d
61062-68-8	$CH_{\gamma_2}Cl$	5.20 d	8.0	3.47–4.17 m	*	3.47–4.17 m
61062-69-9	$CH_\gamma(OCOCH_3)_2$	4.95 d	10.0	3.77 dd	4.4	6.60 d

$C_\alpha H_2(Cl){-}C_\beta H(SAr){-}R$

Registry no.	R	Chemical shifts, δ, ppm: H_α	H_β	H_γ
61062-70-2	$CH_{\gamma_2}OH$	3.80 d	3.20–3.80 m	3.70 d
61062-71-3	$CH_{\gamma_2}OCH_3$	3.73 d	3.20–3.60 m	3.65 d
61062-72-4	$CH_{\gamma_2}OCOCH_3$	3.70 d	3.30–3.57 m	4.20 d
61062-73-5	$CH_{\gamma_2}Cl$	3.90 d	3.20–4.00 m	3.90 d
61062-74-6	$CH_\gamma(OCOCH_3)_2$	3.70 d	3.43–4.00 m	7.10 d

Table III. Kinetically Controlled Product Composition of the Addition of 4-Chlorobenzenesulfenyl Chloride to β-Substituted Ethylends and Trans Styrenes in Acetic Acid at 25° C

R (X = H)	$\overset{X}{\underset{H}{}}C{=}C\overset{H}{\underset{R}{}}$ % M	% aM	% solvent incorporated product
CH_2CH_3	45	55	0
CH_3	43	57	0
H			0
CH_2OH		95	5
CH_2OCH_3		100	0
CH_2OCOCH_3		100	0
CH_2Cl		90	10
$CH(OCOCH_3)_2$		100	0

R ($X = C_6H_5$)	% erythro M	% solvent incorporated product
CH_2CH_3	≥99	≤1
CH_3	100	0
H	98	2
CH_2OH	82	18
CH_2OCH_3	100	0
CH_2OCOCH_3	100	0
CH_2Cl	≥99	≤1
$CH(OCOCH_3)_2$	100	0

This in situ determination of the adduct isomer ratio is necessary because of the known tendency of many β-chloro sulfides to isomerize.[11-13] The kinetically controlled product compositions are given in Table III.

For all the trans styrene derivatives, the α-chloro β-sulfides are formed as products while for the ethylene series the product composition changes from nonregiospecific to anti-Markownikoff regiospecific as the electronegativity of the substituents increase. Small amounts of solvent incorporated products were also observed.

The NMR data are consistent with products formed by stereospecific anti addition. Unsymmetrical alkenes form two different products whose identity, as established by NMR, is consistent with a pair of Markownikoff and anti-Markownikoff isomers. Furthermore, their isomerization serves to establish their relative configuration. The sole examples of nonstereospecific addition occur in the case of the addition of 2,4-dinitrobenzenesulfenyl chloride to *cis*- and *trans*-1-phenylpropenes containing methoxy, isopropoxy, and phenoxy substituents on the ring.[8] These alkenes are all capable of forming highly stabilized benzylic cations. Our results as well as previous evidence clearly establish that the addition of alkane- and arenesulfenyl chlorides to acyclic alkenes occurs stereospecifically anti.[13]

Discussion

The rates of addition of 4-chlorobenzenesulfenyl chloride to the alkenes studied correlate well with the Taft substituent constants σ_R^*.[14] The following linear relationships were obtained for both series.

For $C_\alpha H_2{=}C_\beta HR$

$$\log k_2 = -1.47\sigma_R^* + 1.18$$

(R = 0.958; standard deviation on the slope = 0.18).

For $C_6H_5C_\alpha H{=}C_\beta HR$

$$\log k_2 = -1.58\,\sigma_R^* + 1.55$$

(R = 0.967; standard deviation on the slope = 0.17).

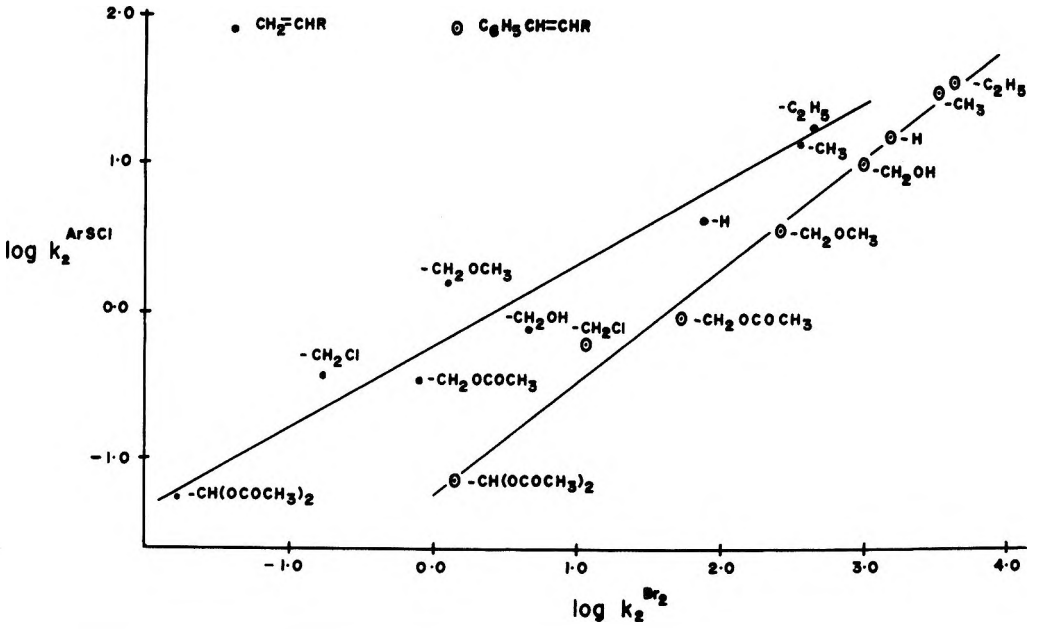


Figure 1. Substituent effects on the rates of addition of bromine and 4-chlorobenzenesulfenyl chloride to ethylene and styrene derivatives.

Since most of the positive charge in the transition state of this reaction is localized on the sulfur atom, the reactivities could be also related to a first approximation to the Taft polar substituents $\sigma_{CH_2R}^*$. Such a correlation again generates two straight lines, described by the following equations.
For $C_\alpha H_2{=}C_\beta HR$

$$\log k_2 = -2.97\ \sigma_{CH_2R}^* + 0.91$$

(R = 0.976; standard deviation on the slope = 0.26).
For $C_6H_5C_\alpha H{=}C_\beta HR$

$$\log k_2 = -3.16\ \sigma_{CH_2R}^* + 1.26$$

(R = 0.978; standard deviation on the slope = 0.27).

For both correlations the corresponding ρ^* values are the same for both unsaturated systems within the standard deviation. This is to be expected due to the similar structure of the rate-determining transition states for both systems.

It is instructive to compare these results with those of Dubois.[6] Dubois found that the reactivity of the ethylene derivatives for bromination correlates well with σ_R^* values ($\log k_{Br_2} = -3.10\sigma_R^* +$ constant), while for the aromatic series the best correlation was obtained when the reactivities were plotted against $\sigma_{CH_2R}^*$ constants ($\log k_{Br_2} = -4.80\sigma_{CH_2R}^* + 3.23$). This was explained as a consequence of the different substituent–positive charge distance in the transition state for both series of compounds. The additional argument presented by Dubois is that the reaction constant sequence ($|\rho^*|_{styrenes} > |\rho^*|_{alkenes}$) remains in agreement with the expected carbonium-ion-like and bridged bromonium-ion-like transition state structures for these two systems.

This last argument does not seem convincing, since the ρ^* values compared were evaluated from different sets of substituent constants (σ_R^* and $\sigma_{CH_2R}^*$). The attenuation factor introduced in the calculation of the $\sigma_{CH_2R}^*$ constants results in an increase in the slope of the log k_2 vs. σ^* plot. This is clearly demonstrated by our results where the slopes of the log k_2 vs. $\sigma_{CH_2R}^*$ for both series are twice as large as the corresponding slopes of the log k_2 vs. σ_R^* plots.

The validity of the use of $|\rho|$ as a quantitative measure of charge on a particular carbon in the rate-determining transition state of a reaction is questionable. The values of $|\rho|$ obtained for the addition of chlorine, bromine, and arenesulfenyl chloride in acetic acid at 25 °C to a series of phenyl-substituted styrenes, −3.22,[15] −4.87,[16] and −2.41,[17] respectively, illustrate the point. On the basis of accumulated data, the relative ability to form a bridged ion should be S > Br > Cl. Therefore if $|\rho|$ were really a good measure of bridging and consequently of the amount of charge on the benzylic carbon, the values should decrease in the order $\rho_{Cl_2} > \rho_{Br_2} > \rho_{ArSCl}$. Since this is not the case, we must question the validity of such an argument.

To avoid the problems of substituent constants, we have plotted log k_{ArSCl} vs. log k_{Br_2} for both series as illustrated in Figure 1. For $C_\alpha H_2{=}C_\beta HR$ the following equation is obtained

$$\log k_2^{Br_2} = 1.7 \log k_2^{ArSCl} + 1.62$$

(R = 0.936, std dev of the slope = 0.3).
For $C_6H_5C_\alpha H{=}C_\beta HR$

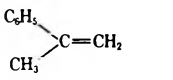
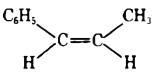
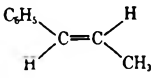
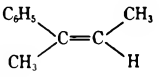
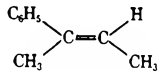
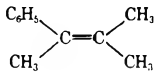
$$\log k_2^{BR_2} = 1.30 \log k_2^{ArSCl} + 2.07$$

(R = 0.994, std dev of the slope = 0.05).

From these correlations, it is clear that a change in alkene structure has a greater effect on the rate of bromination than on the rate of addition of arenesulfenyl chlorides. This is in accord with previous work.[11] From the slopes it is clear that the effect of substituents on the rate of bromination more closely resembles that of addition of 4-chlorobenenesulfenyl chloride to the β-substituted styrenes than it does to the substituted ethylenes. Because of such a similarity in structure reactivity, the conclusion that a similar bridged rate-determining transition state is involved in both the additions of bromine and arenesulfenyl chlorides to these styrene derivatives seems inescapable.

A similar conclusion is evident from a comparison of the effect of methyl substituents on the side chain of styrene on the rates of addition of bromine and 4-chlorobenzenesulfenyl chloride. These data are summarized in Table IV.[12,18] The compounds are separated into two series: those which contain and those which lack a β-methyl cis to phenyl. The effect on the rate of the position of the methyl group is similar for both electrophiles. Thus an α-methyl group has the largest effect while a cis β-methyl group has a general rate-depressing effect. These results are consistent with a bridged rate-determining transition state in which the bridging is less symmetrical for bromine than for sulfur. This similarity between the two electrophiles does not extend to the product-determining transition state. The products of bromination are formed by

Table IV. Rates of Addition of Bromine and 4-Chlorobenzenesulfenyl Chloride to a Series of Side Chain Methyl Substituted Styrenes at 25 °C[12,18]

Compd	Registry no.	Bromine[18] (HOAc)[a] k_2, M^{-1} s^{-1}	k_{rel}	ArSCl[12] (TCE)[a] k_2, M^{-1} s^{-1}	k_{rel}	Compd	Registry no.	Bromine[18] (HOAc)[a] k_2, M^{-1} s^{-1}	k_{rel}	ArSCl[12] (TCE)[a] k_2, M^{-1} s^{-1}	k_{rel}
$C_6H_5CH=CH_2$		11.2	1	62.0	1	$C_6H_5CH=CH_2$		11.2	1	62.0	1.0
	98-83-9	680	61	265	4.3		766-90-5	8.89	0.8	43.0	0.7
		12.3	1.1	118.3	1.9	$C_6H_5CH=C(CH_3)_2$	768-49-0	14.7	1.3	26.0	0.42
							767-99-7	61.7	5.5	42.0	0.7
	768-00-3	300	26.8	442	7.1		769-57-3	56.0	5	9.05	0.15

[a] TCE = tetrachloroethane, HOAc = acetic acid.

Table V. Analytical Data for Sulfenyl Chloride Adducts

Registry No.		% C Calcd	% C Found	% H Calcd	% H Found	% S Calcd	% S Found
61062-75-7	$CH_2=CHCH_2CH_3$	51.07	51.09	5.14	5.26	13.63	13.74
32326-69-5	$CH_2=CHCH_3$	48.88	48.97	4.56	4.77	14.50	14.49
14366-73-5	$CH_2=CH_2$	46.39	46.48	3.89	3.93	15.48	15.49
	$CH_2=CHCH_2OCH_3$	47.82	47.78	4.82	4.74	12.76	13.25
	$CH_2=CHCH_2OCOCH_3$	47.32	47.51	4.33	4.35	11.48	11.69
	$CH_2=CHCH(OCOCH_3)_2$	47.25	46.72	4.27	3.64	9.70	9.54
	$C_6H_5CH=CHCH_2OCH_3$	58.72	58.55	4.93	5.22	9.79	9.86
	$C_6H_5CH=CHCH_2OCOCH_3$	57.47	57.96	4.54	4.53	9.02	8.75
	$C_6H_5CH=CH(OCOCH_3)_2$	55.24	54.83	4.39	4.54	7.76	8.26

nonstereospecific addition while those of addition of 4-chlorobenzenesulfenyl chloride are formed stereospecifically anti.

Further evidence for the bromination transition state structure can be obtained by considering the effect of phenyl substituents upon the rate of electrophilic additions to alkenes. Substituting a phenyl ring for a hydrogen on ethylene has little effect upon the rate of addition of 4-chlorobenzenesulfenyl chloride ($k_{CH_2=CH_2}$ = 65 ± 3 M^{-1} s^{-1};[11] $k_{C_6H_5CH=CH_2}$ = 62.0 ± 0.2 M^{-1} s^{-1}).[12] This observation indicates that stabilization by the phenyl ring is nearly the same in both the ground and the transition states. However, a similar substitution causes a tremendous increase in the rate of hydration. The rate of hydration of styrene is about 10^5 times faster than that of ethylene.[18-20] For a reaction involving an open carbonium-ion-like rate-determining transition state, stabilization by a phenyl ring is much more important in the transition state than in the ground state. The substitution of a phenyl ring for the α hydrogen of any of the ethylene derivatives in this study increases the rate of bromination by a factor of 10–100. This effect of changing structure on the rates of bromination more closely resembles that for the addition of arenesulfenyl chloride than hydration consistent with a bridged rate-determining transition state.

On the basis of structure–reactivity correlations and product compositions, it seems clear that the rate- and product-determining transition states in the mechanism of bromination of styrenes have different structures. The data presented here point to a bridged rate-determining transition state while product studies suggest an open ion-like product-determining transition state. A similar situation has been observed for the addition of 2,4-dinitrobenzenesulfenyl chloride to a series of phenyl substituted *cis*- and *trans*-1-phenylpropenes.[8] Such a result suggests that more than one intermediate may exist on the reaction coordinate between these two transition states. Thus the first formed bridged intermediate may rearrange to an open ion prior to the product-determining step. Unfortunately, the present data do not permit a more detailed description of the reaction mechanism.

Experimental Section

All melting and boiling points are uncorrected. Microanalyses were carried out by A. B. Gygli, Microanalysis Laboratory, Toronto, Ontario, Canada.

Materials. Acetic acid was purified by refluxing for several hours with chromium trioxide and acetic anhydride and then distilled through a column.[21]

4-Chlorobenzensulfenyl chloride was prepared as previously described.[13]

***trans*-3,3-Diacetoxy-1-phenylpropene-1** was synthesized from cinnamic aldehyde and acetic anhydride by the method of Hill, mp 86 °C (lit. mp 86 °C[22]).

3,3-Diacetoxypropene-1 was prepared by the method of Wohl,[23] bp 78.5 °C (15 mm) [lit.[23] bp 77 °C (12 mm)].

***trans*-3-Methoxy-1-phenylpropene-1** was obtained from cinnamyl alcohol by treatment with sodium amide followed by methyl iodide according to the preceedure of Beaufour,[24] bp 64 °C (5 mm) [lit.[24] bp 117 °C (16 mm)].

3-Methoxypropene-1 was prepared by methylation of allyl alcohol in the presence of silver oxide.[25] The product contained significant amounts of methyl iodide which could not be removed by fractional distillation. The reaction product was refluxed with methanolic KOH,

filtered, and distilled fractionally through a spinning-band column yielding the pure product, bp 43 °C (lit.[25] bp 43 °C).

***trans*-3-Acetoxy-1-phenylpropene-1** was prepared from cinnamyl alcohol and acetic anhydride,[26] bp 95 °C (5 mm) [lit.[26] bp 135–150 °C (18 mm), 141–142 °C (14 mm)].

3-Acetoxypropene-1 was obtained from allyl alcohol and acetyl chloride in the presence of pyridine,[27] bp 102 °C (lit.[27] bp 103.5 °C).

***trans*-3-Chloro-1-phenylpropene-1** was prepaned from cinnamyl alcohol and hydrogen chloride in CCl_4,[28] bp 104–105 °C (12 mm) [lit.[28] bp 119 °C (17 mm)].

The remaining unsaturated substrates were commercially available and their purity was checked by GLC and NMR.

Kinetics. All kinetic runs were carried out as previously described,[13] following the decrease in 4-chlorobenzenesulfenyl chloride concentration at 385 nm.

Products. 4-Chlorobenzenesulfenyl chloride (20 ml of 0.2 M solution) in acetic acid was added dropwise at 25 °C to 20 ml of 0.2 M solution of an alkene in acetic acid with stirring. The reaction mixture was transferred to a separatory funnel containing 75 ml each of water and benzene. The aqueous layer was removed and the benzene solution was washed with water (100 ml), saturated aqueous $NaHCO_3$ (100 ml), and twice with 100-ml portions of water. After drying ($MgSO_4$), solvent was removed on a rotary evaporator at room temperature. The product composition was then determined in $CDCl_3$.

Elemental Analyses. Attempts to separate the reaction mixtures containing solvent incorporated products by standard methods led to decomposition. Consequently elemental analyses were obtained for only those additions in which no solvent incorporated products were formed. The data are given in Table V.

Registry No.—**1a,** 37973-54-9; **1b,** 21087-29-6; **1c,** 21040-45-9; **1d,** 22688-03-5; **1e,** 4407-36-7; **1f,** 100-42-5; **1g,** 873-66-5; **1h,** 1005-64-7; **2a,** 869-29-4; **2b,** 107-05-1; **2c,** 591-87-7; **2d,** 627-40-7; **2e,** 107-18-6; **2f,** 74-85-1; **2g,** 115-07-1; **2h,** 106-98-9; bromine, 7726-95-6; 4-chlorobenzenesulfenyl chloride, 933-01-7.

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Triphase Catalysis. Applications to Organic Synthesis[1]

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The triphase catalysis principle, as previously developed for *organic phase–aqueous phase* reactions catalyzed by suitable polystyrene-based catalysts (*solid phase*), has been applied to cyanide ion displacement on activated (benzylic) as well as unactivated organic halides and provides a convenient and effective method of preparation of the corresponding nitriles. Other useful transformations to which the triphase catalysis technique has been successfully applied are the synthesis of ethers, dichlorocyclopropanes, organic chlorides, bromides, and iodides as well as the dehalogenation of *vic*-dibromides and oxidation of alcohols.

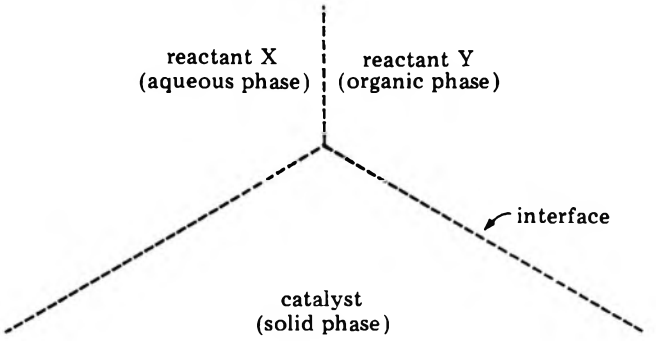
A significant and recurring problem in organic synthesis stems from the use, or desired use, of a water-soluble reagent in chemically altering a water-insoluble organic substrate. If the reaction is conducted as a heterogeneous process (e.g., organic phase–aqueous phase reaction) observed reaction rates are normally very slow owing to the low concentration of at least one of the reactants in each phase. Techniques currently available to circumvent this problem rely on the use of rapid stirring, cosolvent, and phase-transfer methods. If chemical reaction takes place at a liquid–liquid phase boundary, rapid stirring may have an accelerating effect by increasing interfacial contact.[2] Alternatively, the addition of a cosolvent can bring about a homogeneous state and thereby completely eliminate phase separation. Although this latter approach is often useful, product mixtures are necessarily made more complex and the resulting workup made more difficult. In addition, with aqueous phase–organic phase reactions, use of a cosolvent not only renders the organic substrate accessible to the reagent, but also increases the substrate's contact with water and can promote competing hydrolytic pathways. Recently, a third technique has been developed which appears to have considerable potential; this method has been referred to as phase-transfer catalysis.[3] In brief, an organic-soluble, partially water-soluble catalyst (most commonly a tetraalkylammonium or tetraalkylphosphonium salt) accelerates an aqueous phase–organic phase reaction, presumably, by extracting a given ionic reagent out of water and into the bulk organic phase where reaction can ensue.[4] Based on enhanced reaction rates, high yields of products, and the convenience found with this method, it seems likely that many industrial applications will be forthcoming. One practical limitation to the phase-transfer method, however, is that many of the catalysts used promote the formation of stable emulsions.

It occurred to us that the development of a technique centering around the use of a solid phase catalyst to accelerate

aqueous–organic phase reactions (triphase catalysis) would have considerable advantages over those methods described above (Scheme I). Not only would catalyst recovery and

Scheme I

triphase catalysis



product isolation be greatly simplified, but also, owing to the three-phase nature of the system, continuous flow methods could be employed making the technique particularly attractive for industrial applications.

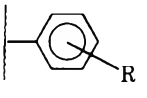
We have previously demonstrated the feasibility of triphase catalysis for the displacement of cyanide ion (aqueous phase) on 1-bromooctane (organic phase) catalyzed by suitable polystyrene ion exchange resins (solid phase).[5,6] The work described in this paper was carried out in order to expand the scope of this technique by applying it to a variety of useful synthetic transformations.

Results and Discussion

Synthesis of Nitriles. Nucleophilic displacement by cyanide ion on organic halides represents the most commonly used method for the preparation of nitriles. Despite the usefulness of this approach, however, the required use of water and/or other polar and potentially nucleophilic solvents needed to dissolve both the cyanide salt and the organic substrate introduces distinct limitations. In particular, competing hydrolysis and ether formation can lead to low yields of nitrile.[7] Phase-transfer catalysis procedures have been successfully utilized in cyanide displacement reactions involving simple alkyl halides.[4,9] Durst has recently reported that phase-transfer catalyzed cyanide displacement on activated halides, e.g., benzyl chloride (or bromide), gave significantly higher yields of nitrile when conducted as liquid–solid rather than liquid–liquid systems.[10]

We have found that triphase catalysis, as previously developed for the displacement of cyanide ion on 1-bromooctane (eq 1),[5] provides a simple and effective means for converting

$$\underset{\text{(organic phase)}}{n\text{-}C_8H_{17}Br} + \underset{\text{(aqueous phase)}}{NaCN} \xrightarrow[\text{(solid phase)}]{\text{1a}} \underset{\text{(organic phase)}}{n\text{-}C_8H_{17}CN} + \underset{\text{(aqueous phase)}}{NaBr} \quad (1)$$



cross-linked polystyrene resin (2% divinylbenzene)

1a, R = $CH_2N(CH_3)_2(n\text{-}C_4H_9)Cl$; 12% ring substitution
b, R = $CH_2N(CH_3)_3Cl$; 12% ring substitution
c, R = $CH_2N(CH_3)_3Cl$; 76% ring substitution
d, R = $CH_2N(CH_3)_3Cl$; 70% ring substitution

activated (benzylic) as well as unactivated organic halides to their corresponding nitriles (Table I).

In addition to the synthetic significance of these results, the observation that competing hydrolytic pathways are not important suggests that the microenvironment of the reactive sites along the polymer backbone is predominantly nonaqueous.[11]

Halogen Exchange. Although many procedures are available for exchanging halogen in organic halides, few have proven useful for converting alkyl bromides to alkyl chlorides.[12,13] We have found that the triphase catalysis technique furnishes a very convenient method for carrying out such transformations. Examples illustrating the utility of triphase catalyzed halogen exchange are provided in Table I. The fact that no significant yield of hydrolysis products could be detected with benzyl bromide and benzyl chloride as the substrates, and also the observation that catalyst activity of the resin falls off with increasing percent ring substitution (compare resins **1a–d**),[14] suggest here, too, that the microenvironment of the reactive sites in the polymer matrix is largely nonaqueous.

Synthesis of Ethers. Conventional methods for the preparation of alkyl and aryl ethers are many in number.[15] Despite this fact, considerable effort is still being expended in developing new and more convenient procedures.[16–19] In order to determine the applicability of triphase catalysis to the synthesis of ethers, we have examined the displacement by phenoxide ion and *n*-butoxide ion, generated by treatment with aqueous sodium hydroxide, on 1-bromobutane dissolved in toluene catalyzed by **1a**. In each case, useful triphase catalytic systems were achieved. As in the cases of cyanide displacement and halogen exchange, resin activity is reduced significantly upon increasing the concentration of quaternary ammonium groups along the polymer backbone.

Synthesis of Dichlorocyclopropanes. Dichlorocarbene addition to alkenes provides an attractive route to dichlorocyclopropanes.[20–22] We have found that dichlorocarbene can be conveniently generated by the addition of **1a** to mixtures of 50% aqueous sodium hydroxide and chloroform at 25 °C. When an appropriate alkene is added to the mixture, high yields of the corresponding dichlorocyclopropane are formed. Tabushi has reported the use of dichlorocarbenes in the conversion of certain alcohols to alkyl chlorides.[23] We have also found that dichlorocarbene generated under triphase conditions is also capable of carrying out similar transformations (Table I).

Dehalogenation of *vic*-Dibromides. Dehalogenation of *vic*-dibromides to alkenes can be carried out through the use of a variety of reagents.[24–26] More recent procedures have relied on the use of sodium thiosulfate[27] and combinations of sodium iodide and sodium thiosulfate.[28] Dehalogenation of certain *vic*-dibromides can also be carried out under triphase conditions employing catalytic amounts of sodium iodide, **1a**, and an excess of sodium thiosulfate at 110 °C as described in the Experimental Section. Stereochemical studies conducted with *meso*- and *dl*-stilbene dibromide[29] indicated a completely stereospecific trans debromination with the former leading to exclusively *trans*-stilbene and a predominantly trans debromination for the *dl* isomer yielding *cis*-stilbene as the major alkene component. Control experiments outlined in the Experimental Section indicate a moderate instability of *cis*-stilbene with regard to isomerization under debromination conditions, suggesting even a higher degree of stereospecificity in the dehalogenation of *dl*-stilbene dibromide.

Oxidation of Alcohols. Attempted reaction of a toluene solution of cyclododecanol with 10% aqueous sodium hypochlorite in the presence of **1d** yielded no observable cyclododecanone even after heating for 70 h at 50 °C.[30] When resin **1a** was suspended at the interface of similar heterogeneous mixtures, however, a triphase catalytic oxidation system was established.

Table I. Synthetic Applications of Triphase Catalysis

Transformation	Reactant	Registry no.	Product	Registry no.	Catalyst	Temp, °C	Time, h	Yield,[a] %
Cyanide displacement	Benzyl chloride	100-44-7	Benzyl cyanide	140-29-4	1a	110	15	95
	Benzyl bromide	100-39-0						85
	4-Chlorobenzyl chloride	104-83-6	4-Chlorobenzyl cyanide	140-53-4				88
	4-Bromobenzyl bromide	589-15-1	4-Bromobenzyl cyanide	16532-79-9				99
	4-Methylbenzyl chloride	104-82-5	4-Methylbenzyl cyanide	2947-61-7				92
	1-Bromooctane	111-83-1	1-Cyanooctane	2243-27-8				98
					1b			95
					1c			0
					1d			0
	1-Chlorooctane	111-85-3			1a			50
Halogen exchange	1-Bromooctane		1-Chlorooctane				70	97
	1-Chlorooctane		1-Bromooctane				280	54
	Benzyl chloride		Benzyl bromide				24	72
	Benzyl bromide		Benzyl chloride					97
	1,4-Dibromobutane	110-52-1	1,4-Dichlorobutane	110-56-5			60	97
	1-Bromobutane	109-65-9	1-Chlorobutane					87
	1-Bromobutane		1-Iodobutane					90
	1-Chlorobutane	109-69-3	1-Bromobutane					32
	1-Chlorobutane		1-Iodobutane					72
	1-Iodobutane	542-69-8	1-Chlorobutane					59
	1-Iodobutane		1-Bromobutane				70	50
	1-Bromodecane	112-29-8	1-Chlorodecane	1002-69-3			100	94
							240	93[b]
					1b		24	40
					1c			0
					1d			0
Dichlorocarbene addition	α-Methylstyrene	300-57-2	1,1-Dichloro-2-methyl-2-phenylcyclopropane	3591-42-2	1a	25	72	99
	trans-β-Methylstyrene	873-66-5	1,1-Dichloro-*trans*-2-methyl-3-phenylcyclopropane	60434-40-4			48	100
	Styrene	100-42-5	1,1-Dichloro-2-phenylcyclopropane	2415-80-7			48	99
	Cyclohexene	110-83-8	7,7-Dichlorobicyclo[4.1.0]heptane	823-69-8			96	98
					1d			15
Dichlorocarbene chlorination	Benzyl alcohol	100-51-6	Benzyl chloride		1a		48	67
	1-Adamantyl alcohol	768-95-6	1-Adamantyl chloride	935-56-8			120	25
Alkoxide and phenoxide displacement[c]	1-Butanol	71-36-3	*n*-Butyl ether	142-96-1			24	19
	Phenol	108-95-2	*n*-Butyl phenyl ether	1126-79-0		90	10	97
Dehalogenation of *vic*-dibromides	1,2-Dibromooctane	6269-92-7	1-Octene	111-66-0	1a	110	48	15
								1[d]
								0.2[e]
					1a		60	20
	dl-Stilbene dibromide	13027-48-0	*trans*-Stilbene	103-30-0			40	35
			cis-Stilbene					49
			trans-Stilbene		1d		40	2
			cis-Stilbene					1
	meso-Stilbene dibromide[f]	13440-24-9	*trans*-Stilbene		1a		12	100
			cis-Stilbene					0
	cis-Stilbene[g]	645-49-8	*trans*-Stilbene				40	11
			cis-Stilbene					89
Oxidation of alcohols	Benzyl alcohol		Benzaldehyde	100-52-7		50	50	51
	1-Octanol	111-87-5	Octanal	124-13-0			70	5
	Cyclododecanol	1724-39-6	Cyclododecanone	830-13-7				34
					1d			0

[a] Yields are determined by GLC based upon the reactant. [b] Isolated yield. [c] Alkoxide and phenoxide displacement reactions employ *n*-bromobutane as the alkylating agent. [d] Reaction carried out in the absence of sodium iodide. [e] Reaction carried out in the absence of **1a**. [f] Solvent used as organic phase was 1,1,2,2-tetrachloroethane. [g] Attempted isomerization of *cis*-stilbene (100% initial isomer purity) under debromination conditions.

Experimental Section

General Methods. Unless stated otherwise, all reagents were obtained commercially and were used without further purification. Chloromethylated polystyrene beads (2% divinylbenzene, 200–400 mesh) were obtained from Bio-Rad Laboratories and were used without further purification. *N,N*-Dimethyl-*n*-butylamine was available from K & K Laboratories and used as obtained. All alkyl and benzyl halides and their corresponding nitriles as well as styrene, α-methylstyrene, *trans*-β-methylstyrene, cyclohexene, benzyl alcohol, 1-adamantyl alcohol, *n*-butyl ether, *n*-butyl phenyl ether, *trans*-stilbene, 1-octene, and phenol were purchased from Aldrich Chemical Co. and used as obtained. We are grateful to our colleague Michael McKinney for gifts of 1,1-dichloro-2-methyl-2-phenylcyclopropane and 1,1-dichloro-*trans*-2-methyl-3-phenylcyclopropane. 1,1-Dichloro-2-phenylcyclopropane[22] and 7,7-dichlorobicyclo[4.1.0]heptane[31] were prepared using established procedures. 1,2-Dibromooctane,[32] *cis*-stilbene,[33] *meso*-stilbene dibromide,[34] and *dl*-stilbene dibromide[34] were also prepared using methods previously described in the literature. Benzene, toluene, and tetrahydrofuran were each purified by distillation from sodium and benzophenone under a nitrogen atmosphere. All ^{1}H NMR spectra were recorded using a Varian A-60 spectrometer. Product mixtures were analyzed by GLC on a Hewlett-Packard Model 5710A flame ionization instrument using either a 1.7 ft × 0.125 in. UCW-98 on Chromosorb W column or a 4 ft × 0.125 in Carbowax on Chromosorb P column. The GLC instrument was also equipped with a Hewlett-Packard Model 3380A integrator. Appropriate response factors relative to an internal standard were determined for each different substance analyzed. The temperature of the oil bath was controlled with the aid of a "Therm-O-Watch" Electronic Controller Model L6-1000 (I^2R Co., Cheltenham, Pa.) attached to a thermometer. Culture tubes (Corning no. 9826, 13 × 100 mm) equipped with Teflon-lined screw caps were used as reaction vessels. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Resin Catalysts 1a–d. Resins catalysts **1a**, **1b**, and **1c** were prepared employing procedures previously described.[6] Resin **1d** was commercially available from Bio-Rad Laboratories.

Displacement of Cyanide Ion on Organic Halides. Procedures similar to that described for the conversion of 4-bromobenzyl bromide to 4-bromobenzyl cyanide were followed for all of the nitrile forming reactions described in Table I. To a Corning no. 9826 culture tube containing 0.09 g of **1a** was added a solution of 0.8 g (16.3 mmol) of sodium cyanide dissolved in 2.5 ml of distilled water followed by 0.063 g (0.250 mmol) of 4-bromobenzyl bromide plus 2 ml of toluene. An internal standard (*n*-dodecane) was added to the reaction mixture and the tube was shaken vigorously for 2 min, placed in an oil bath maintained at 110 °C for 15 h, withdrawn, and cooled to room temperature. Analysis of the organic phase by GLC using a UCW-98 on Chromosorb W column indicated a 99% yield of 4-bromobenzyl cyanide.

Halogen Exchange. Procedures similar to that described for the conversion of 1-bromodecane to 1-chlorodecane were followed for all of the small-scale halogen exchange reactions described in Table I. To a Corning no. 9826 culture tube containing 0.08 g of **1a** was added a solution of 0.67 g (11.6 mmol) of sodium chloride dissolved in 2 ml of distilled water followed by 0.069 g (0.31 mmol) of bromodecane plus 2 ml of toluene. An internal standard (*n*-dodecane) was added to the reaction mixture and the tube was sealed with a Teflon-lined screw cap, shaken vigorously for 2 min, placed in an oil bath maintained at 110 °C for 100 h, withdrawn, and cooled to room temperature. Analysis of the organic phase by GLC (Carbowax column) indicated a 94% yield of 1-chlorodecane.

For conversion to organic bromides and iodides, aqueous solutions of sodium bromide and sodium iodide, respectively, were used.

Preparative Scale Conversion of 1-Bromodecane to 1-Chlorodecane. A mixture of 2.3 g (10.4 mmol) of 1-bromodecane dissolved in 20 ml of benzene, 27.0 g (465.5 mmol) of sodium chloride dissolved in 80 ml of water and 0.5 g of **1a** was sealed in a 125-ml Pyrex tube and was placed in an oil bath, maintained at 110 °C for 240 h, withdrawn, cooled to room temperature, and filtered. The resin was washed with 100 ml of benzene and the combined organic phase dried (Na_2SO_4) and concentrated by rotary evaporation leaving a liquid (1.8 g) which was found to be 1-chlorodecane having a ^{1}H NMR spectrum and GLC retention time indistinguishable from those of an authentic sample. Further GLC analysis revealed that the product contained 5% 1-bromodecane.

Dichlorocarbene Addition to Alkenes. Procedures similar to that described for the conversion of α-methylstyrene to 1,1-dichloro-2-methyl-2-phenylcyclopropane were followed for all of the dichlorocyclopropane syntheses described in Table I. α-Methylstyrene (0.118 g, 1.0 mmol) dissolved in 2 ml of chloroform (spectrophotometric grade) was added to 2 ml of 50% aqueous sodium hydroxide solution, plus **1a** (0.1 g) contained in a no. 9826 culture tube. After addition of an internal standard (*n*-dodecane) the mixture was shaken vigorously for 5 min and allowed to remain at 25 °C for 72 h. Analysis of the organic phase by GLC (UCW-98 column) indicated a 99% yield of 1,1-dichloro-2-methyl-2-phenylcyclopropane. Procedures used for conversion of alcohols to alkyl chlorides were similar to that described above except that α-methylstyrene was replaced by the appropriate alcohol.

Phenoxide Displacement on 1-Bromobutane. To a Corning no. 9826 culture tube containing 0.1 g of **1a** was added 2 ml of 2.5 M sodium hydroxide followed by 0.094 g (1.0 mmol) of phenol in 2 ml of toluene, 0.206 g (1.5 mmol) of 1-bromobutane, and an internal standard (*n*-decane). The mixture was shaken vigorously for 5 min and placed in an oil bath maintained at 90 °C for 10 h, withdrawn, and cooled to room temperature. Analysis of the organic phase by GLC (UCW-98 column) indicated a yield of *n*-butyl phenyl ether of 97% based on starting phenol.

***n*-Butoxide Displacement on 1-Bromobutane.** 1-Butanol (0.074 g, 1.0 mmol) dissolved in 2 ml of toluene was added to 2 ml of 50% aqueous sodium hydroxide solution plus **1a** (0.1 g) contained a no. 9826 culture tube. After addition of an internal standard (*n*-dodecane) the mixture was shaken vigorously for 5 min and allowed to remain at 25 °C for 24 h. Analysis of the organic phase by GLC (Carbowax column) indicated a yield of *n*-butyl ether of 20%.

Dehalogenation of *vic*-Dibromoalkanes. Procedures similar to that described for the conversion of *dl*-stilbene dibromide to a mixture of *cis*- and *trans*-stilbene were followed for all debromination experiments. A heterogeneous mixture of *dl*-stilbene dibromide (0.088 g, 0.259 mmol) dissolved in 2 ml of toluene, sodium iodide (0.005 g, 0.033 mmol), and sodium thiosulfate ($Na_2S_2O_3$·$5H_2O$; 1.0 g, 4.0 mmol) dissolved in 2 ml of water and 0.15 g of **1a** along with an internal standard (*n*-dodecane) was sealed in a culture tube shaken vigorously for 5 min and placed in an oil bath, maintained at 110 °C. After a reaction time of 40 h, the tube was withdrawn and cooled to room temperature. Analysis of the organic phase by GLC (UCW-98) indicated a 35% yield of *trans*-stilbene plus a 49% yield of *cis*-stilbene.

Oxidation of Cyclododecanol. Cyclododecanol (0.055 g, 0.3 mmol) dissolved in 2 ml of toluene was added to 5 ml of 10% aqueous sodium hypochlorite (commercial swimming pool bleach) plus **1a** (0.05 g) contained in culture tube. After addition of an internal standard (*n*-octadecane), the mixture was shaken vigorously for 5 min and heated to 50 °C for 70 h. Analysis of the organic phase by GLC (Carbowax column) indicated a 34% yield of cyclododecanone.

Procedures similar to that described above were used for all oxidation reactions described in Table I.

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One-Electron Redox Reactions of Water-Soluble Vitamins. 4. Thiamin (Vitamin B_1), Biotin, and Pantothenic Acid

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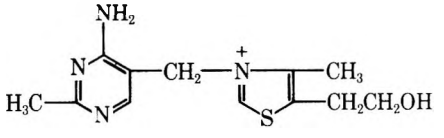
The technique of pulse radiolysis and kinetic absorption spectrophotometry was used to study the one-electron reduction of thiamin, thiazole, 4-aminopyrimidine, biotin, and pantothenic acid in aqueous solution. The acetone ketyl radical and e_{aq}^- were used as the one-electron reducing agents. The reaction rate constants of e_{aq}^- and $(CH_3)_2\dot{C}OH$ with these compounds were determined at different pH values, taking into account the dissociation constants of the substrates. The transient optical absorption spectra of the intermediates produced, their extinction coefficients, decay kinetics, and ionization constants were determined. For thiazole (Tz), the radical formed in neutral solution (·TzH) has a λ_{max} 317 nm, ϵ_{317} 3.8×10^3 M^{-1} cm^{-1}, decays with $2k \sim 2 \times 10^8$ M^{-1} s^{-1}, and has a pK_a (radical) = 3.1. This is close to that of the parent compound, pK = 2.5. For 4-aminopyrimidine (4-Am-Pm), the radicals formed have maxima at λ <260 nm, and the pK_a of the dihydro radical cation 4-Am-PmH$_2$·$^+$ is 6.4. Thiamin in neutral solution forms intermediates with maxima at 317 and 350 nm, and $\epsilon \sim 6.5 \times 10^3$ M^{-1} cm^{-1}. One-electron reduction of the thiazolium ring of thiamin is suggested, based on the formation of dihydrothiamin as a final product. Other assignments for these radicals are suggested and discussed. The reaction of OH radicals with biotin and pantothenic acid leads, primarily, to H atom abstraction at various sites in the molecule. The formation and ionization of the –C(OH)CONH– radical from pantothenic acid, $pK_a = 6.0 \pm 0.3$, is proposed.

Thiamin (vitamin B_1, I), in the form of its pyrophosphate (at OH group), is the coenzyme for a number of biochemical reactions involved in carbohydrate metabolism, e.g., cleavage



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of carbon–carbon bonds adjacent to carbonyl compounds (as in pyruvic acid).[2,3] Many common foods contain appreciable quantities of thiamin. Thiamin contains a pyrimidine and a thiazole nucleus. The activity of this vitamin is probably linked primarily to the thiazolium ring.[4] Reduction (hydrogenation) of the thiazolium ring results in a complete loss of activity. The mechanism of thiamin action has been suggested[4] to involve the ionization of the thiazolium ring, through the loss of a proton from the C_2 carbon, resulting in the formation of a zwitterion. Biotin (vitamin H) serves as an acceptor molecule for bicarbonate ion in enzymes which catalyze several biosynthetic reactions.[5] The function of the sulfur atom in biotin is still not well characterized. Protonation of biotin, $pK_2 = -1.1$ ($pK_a \sim 4.8$ for the –COOH), has been suggested[6] to occur on the ureido group, presumably on the carbonyl oxygen atom. More recent results indicate that there is no sulfur–carbonyl transannular interaction in biotin (see ref 6, 7). Pantothenic acid[2] is a component of coenzyme A, functions in acetylation reactions in amino acid, carbohydrate, and fat metabolism, and is involved in various biosynthesis with other vitamins.

The fast-reaction technique of pulse radiolysis and kinetic absorption spectrophotometry was used to study the one-electron reduction of these vitamins and related compounds in water. The hydrated electron and the acetone ketyl radical were used as one-electron reducing agents. The reactions with OH radicals were also examined. The results obtained are reported below.

Experimental Section

The pulse radiolysis setup[8,9] and the experimental conditions used have been described.[10] The one-electron reduction of the compounds was brought about by reaction with e_{aq}^- and/or $(CH_3)_2\dot{C}OH$ radicals. The necessary conditions for these experiments have already been described.[10,11]

The extinction coefficients given below are based on $G(e_{aq}^-) = G(OH) = 2.8$. Dosimetry[8] was carried out using KCNS. The transient spectra presented were corrected for depletion of the ground-state absorption of the molecules.

The chemicals used were the highest purity commercially available and were obtained from Calbiochem, Cyclochemicals, and Sigma Chemicals. The reagents used were purchased from Mallinckrodt, Baker and Adamson, Aldrich, and Eastman Chemicals. Solutions were buffered using perchloric acid, potassium hydroxide, phosphate, and tetraborate.

Results and Discussion

Reactivity toward e_{aq}^-, $(CH_3)_2\dot{C}OH$, and OH Radicals. The reaction rate constants of e_{aq}^- with thiazole, 4-aminopyrimidine, and thiamin were determined at pH 6–8, taking

Table I. Reaction Rate Constants of Substrates with e_{aq}^-, $(CH_3)_2\dot{C}OH$, and OH Radicals in Water

Substrate	pK_a	e_{aq}^- [a] pH	e_{aq}^- [a] k, M^{-1} s^{-1}	$(CH_3)_2\dot{C}OH$ [b] pH	$(CH_3)_2\dot{C}OH$ [b] k, M^{-1} s^{-1}	OH [c] pH	OH [c] k, M^{-1} s^{-1}
Thiazole	2.5	8.0	2.1×10^9	0.8	6.2×10^8		
				13.3 [d]	e		
4-Aminopyrimidine	5.9	8.2	1.1×10^{10}	0.8–13.0	e		
Thiamin	4.8	6.1	3.4×10^{10}	0.5	2.2×10^8	4.7	3.2×10^9
				6.6	1.9×10^8	4.7	3.0×10^9 [c]
Biotin	−1.1, 4.8	9.0	$\leq 5 \times 10^7$			3.6	3.8×10^9
Pantothenic acid	4.4	6.6	1.2×10^8			6.6	4.5×10^9

[a] Rate determined in presence of ~0.5 M *t*-BuOH by monitoring decay kinetics of e_{aq}^- at 700 nm. [b] Rate determined by monitoring formation kinetics of transient species. [c] Rate determined by competition kinetics with KCNS, taking $k(OH + CNS^-) = 1.1 \times 10^{10}$ M^{-1} s^{-1}. [d] $(CH_3)_2\dot{C}O^-$ radical present at this pH. [e] No electron transfer at this pH.

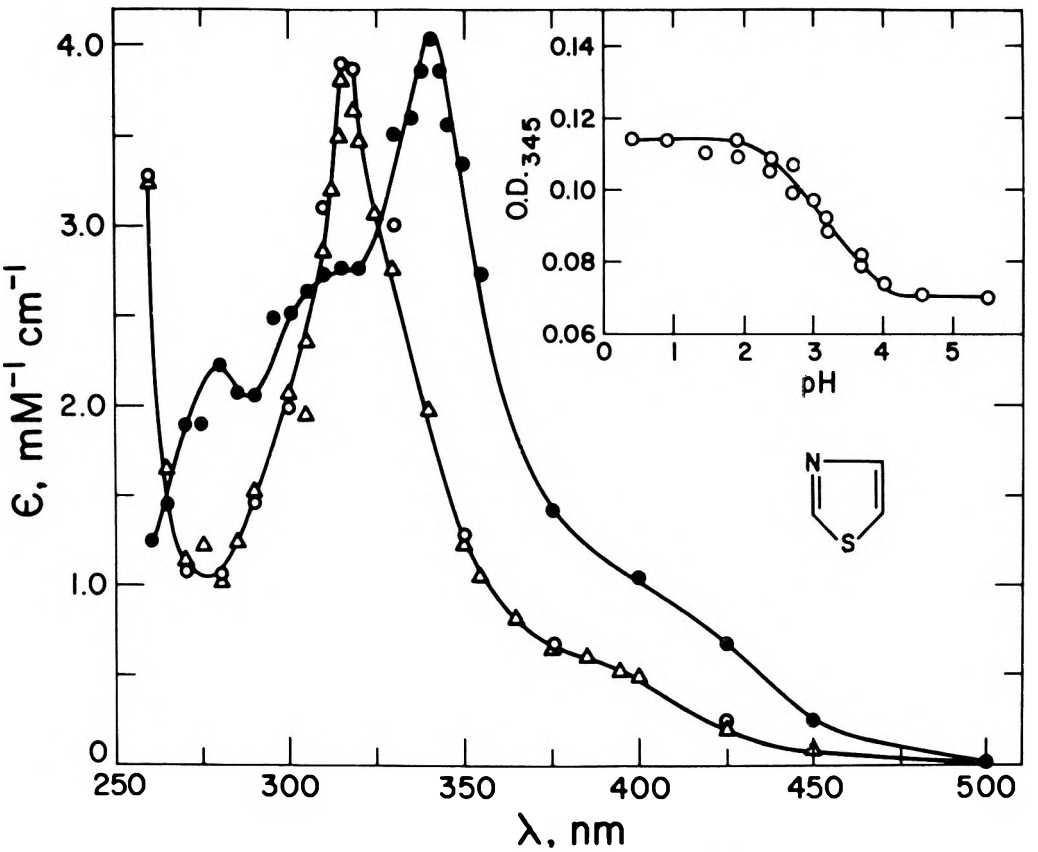


Figure 1. Adsorption spectra of intermediates produced from the one-electron reduction of thiazole (2×10^{-3} M) by (a) e_{aq}^- (in presence of 1.0 M *t*-BuOH, 1 atm argon) at pH 5.3, △, and pH 13.0, ○, and (b) $(CH_3)_2\dot{C}OH$ radicals (1.0 M *i*-PrOH, 1 atm argon) at pH 0.8, ●. Insert: change in absorbance at 345 nm with pH from solutions containing 2×10^{-2} M thiazole, 2.0 M *i*-PrOH, 1 atm argon (data at pH 4.0–5.5 are under same conditions as a above). Total dose ~4–8 krad/pulse.

into account the dissociation constants of these molecules; see Table I. A $k = 2.1 \times 10^9$ M^{-1} s^{-1} was found for thiazole. This value is considerably higher than that for thiophene (6.5×10^7 M^{-1} s^{-1})[12] and pyrrole (6.0×10^5 M^{-1} s^{-1})[12], but agrees well with the value 2.5×10^9 M^{-1} s^{-1} given in the literature[12] for thiazole. The $k = 1.1 \times 10^{10}$ M^{-1} s^{-1} for 4-aminopyrimidine is somewhat less than that recently[13] found for pyrimidine, $k = 2.0 \times 10^{10}$ M^{-1} s^{-1}. The lower value for 4-aminopyrimidine may be connected with the presence of the electron-donating amino group. With thiamin, the value of 3.4×10^{10} M^{-1} s^{-1} can be rationalized on the basis of the expected high reactivity of the thiazolium cation.

The one-electron reduction of these compounds by $(CH_3)_2\dot{C}OH$ radicals was observed to occur with the thiazolium species, but not with 4-aminopyrimidine or thiazole; see Table I. This is in general agreement with observations[10,11,13] that the protonated forms of nitrogen heteroaromatic compounds (which have higher redox potentials than the neutral forms) are readily reduced by this donor radical. In the case of 4-aminopyrimidine, even the protonated form is not reduced by $(CH_3)_2\dot{C}OH$ radicals. This is to be compared with pyrimidine itself, whose protonated form has a much higher redox potential and is reduced by $(CH_3)_2\dot{C}OH$ radicals.[13] The difference between pyrimidine and 4-aminopyrimidine might be attributed to the strong electron-donating property of the amino group.

Table I shows the reaction rate constants of e_{aq}^- with biotin and pantothenic acid. With both vitamins the reactivity is relatively low, $k \leq 10^8$ M^{-1} s^{-1}, and it was not possible to adjust the experimental conditions in order to examine the transient species formed from the reduction of these compounds by e_{aq}^-. The reduction potentials of these vitamins are also very low (i.e., negative) to enable their reduction by electron donor radicals such as $(CH_3)_2\dot{C}OH$.

Table II. Absorption Maxima, Extinction Coefficients, Decay Kinetics, and Ionization Constants of Intermediates Produced from the Reaction with e_{aq}^- of Thiazole, 4-Aminopyrimidine, and Thiamin in Water

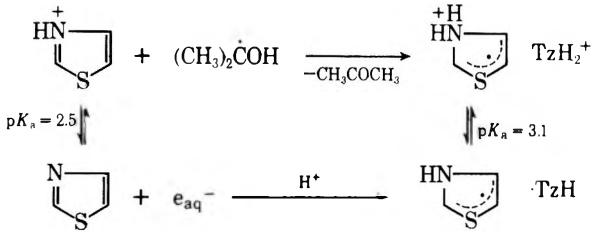
Substrate	pH	λ_{max}, nm	ϵ, M^{-1} cm^{-1}	$2k$, M^{-1} s^{-1}	pK_a (radical)
Thiazole	5.3, 13.0[a]	317	3.8×10^3	2.2×10^8	3.1
	0.8[b]	340	4.1×10^3	1.5×10^8	
		280	2.2×10^3		
4-Amino-pyrimidine	3.5[a]	<300	3.1×10^3	*d*	6.4
	13.3[a]	<260	3.7×10^3	1.7×10^9[c]	
Thiamine	4.4, 6.6[b]	317	6.5×10^3		
		350	6.6×10^3	*f*	~1.6[e]
	0.5[b]	345	6.7×10^3	*f*	
		362	6.3×10^3	*f*	

[a] Determined in presence of 1.0 M *t*-BuOH; decay kinetics may, in part, be due to reaction with β-alcohol radicals. [b] Determined in presence of 1.0 M isopropyl alcohol. [c] A very long-lived intermediate is produced from this second-order decay. [d] Mixed kinetics. [e] Estimated ±0.3; see text. [f] Decay at all λ's to an intermediate with only slightly lower ε than the initial transient; the intermediate decays by second-order kinetics with $2k = 7.6 \times 10^5$ M^{-1} s^{-1} at pH 4.4, and decays over a period of $t > 20$ s at pH 0.5.

The reaction rate constants of the vitamins with OH radicals were determined at appropriate pH values (see Table I), and were found to be $\sim 4 \times 10^9$ M^{-1} s^{-1}.

Thiazole. Relatively strong transient absorption spectra are observed from the one-electron reduction of thiazole (Tz, pK_a = 2.5) in water by e_{aq}^- and thiazolium ion by $(CH_3)_2\dot{C}OH$ radicals. These were determined at pH 0.8 (using acetone ketyl radicals) and at pH 5.3 and 13.0 (using e_{aq}^-) and are shown in Figure 1 and Table II.

At pH 0.8, the absorption maximum at 340 nm is red shifted compared to λ_{max} 317 nm at pH 5.3. The acid form of carbon-centered free radicals is usually[14] blue shifted compared to the basic form of the radical. A recent study[13] of nitrogen-centered heteroaromatic free radicals has shown that the absorption spectra of the radical cations are red shifted compared to those of neutral radicals. No change in transient spectrum was observed between pH 5.3 and 13.0. However, the change in acidic solutions was titrated (see insert in Figure 1), and a pK_a ~3.1 was observed. This value is close to the pK_a = 2.5 of thiazole itself. The following reaction scheme is suggested:

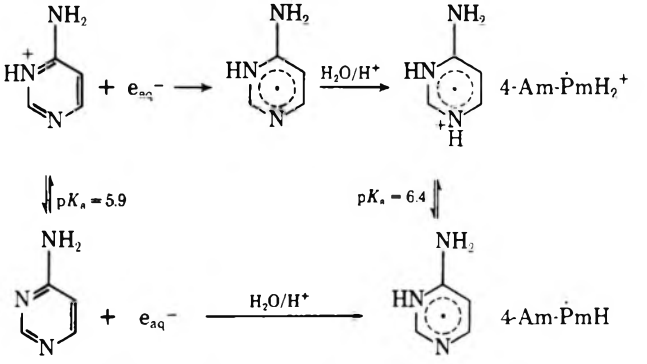


The protonation of ·TzH and ·Tz$^-$ was too fast to be observed under our experimental conditions. The reaction rate constants for the protonation step of some other N-heteroaromatic radicals are slower and have been observed.[10,11,13] The radical forms present at pH 2.0 and 5.0 could also be the neutral ·TzH and the ·Tz anion radicals. However, since the radical anions of many nitrogen heteroaromatic compounds are rapidly protonated in aqueous media (even in neutral and alkaline solutions),[13] one can expect the same to be the case for thiazole, unless the sulfur atom helps to stabilize the radical anion against protonation. The shifts in the absorption maxima are also in agreement with the above assignment.

These radicals decay by second-order kinetics (Table II). The apparent slightly higher decay rate at pH 5.3–13.0 may be due, in part, to the reaction between thiazole radicals and the β-alcohol radical produced from *t*-BuOH.

4-Aminopyrimidine. 4-Aminopyrimidine (4-Am-Pm) has a pK_a = 5.9 due to protonation at the N_1 position. This is to be compared to a pK_a = 1.3 for pyrimidine itself. One-electron reduction at pH 3.5 by e_{aq}^- gives rise to a relatively weak transient absorption immediately after the 30-ns pulse; see Figure 2. This absorption increases with time, and the full spectrum ~5 μs later is also shown. At pH 13.3, the spectrum observed is the same as the initial spectrum formed at pH 3.5; see Figure 2. By monitoring the change in absorbance at 345 nm with pH,a pK_a (radical) = 6.4 was observed (insert, Figure 2).

The following reactions are suggested:



The scheme presented above is similar to that recently suggested[13] for pyrimidine (Pm) and other diazabenzenes. The pK_a of the ·PmH$_2^+$ radical to form ·PmH was found[13] to be 7.6 ± 0.1. The spectral characteristics of the 4-aminopyrimidine and the pyrimidine radicals, and their changes with pH, are very similar. This supports the assignment given above.

At pH 13.3, the radicals decay by second-order kinetics. One may conclude that unimolecular deamination is not the mode of decay of these radicals. In acidic media, however, the decay kinetics are complex. There are indications that the β-alcohol radical from *t*-BuOH present in solution interacts with the 4-Am-ṖmH$_2^+$ cation to give secondary transient species. Similar reactions were observed with other diazine radicals.[13]

Thiamin. Thiamin (Tm) has a pK_a = 4.8, which has been assigned to protonation on the pyrimidine ring. It is unstable[15] at pH ≥ 7.0 and no experiments were therefore performed in alkaline solutions. One-electron reduction of thiamin at pH 0.5 by $(CH_3)_2\dot{C}OH$ radicals gave a transient spectrum with maxima at 345 and 362 nm. At pH 6.6, reduction of thiamin gives a spectrum which is blue shifted compared to that produced at pH 0.5; see Figure 3. The relatively small change in absorbance at 365 nm was monitored as a function of pH, and a pK_a ~ 1.6 ± 0.3 could be derived. The transient spectrum remained unchanged in the pH range 3–6, i.e., over the pK_a = 4.8 of thiamin.

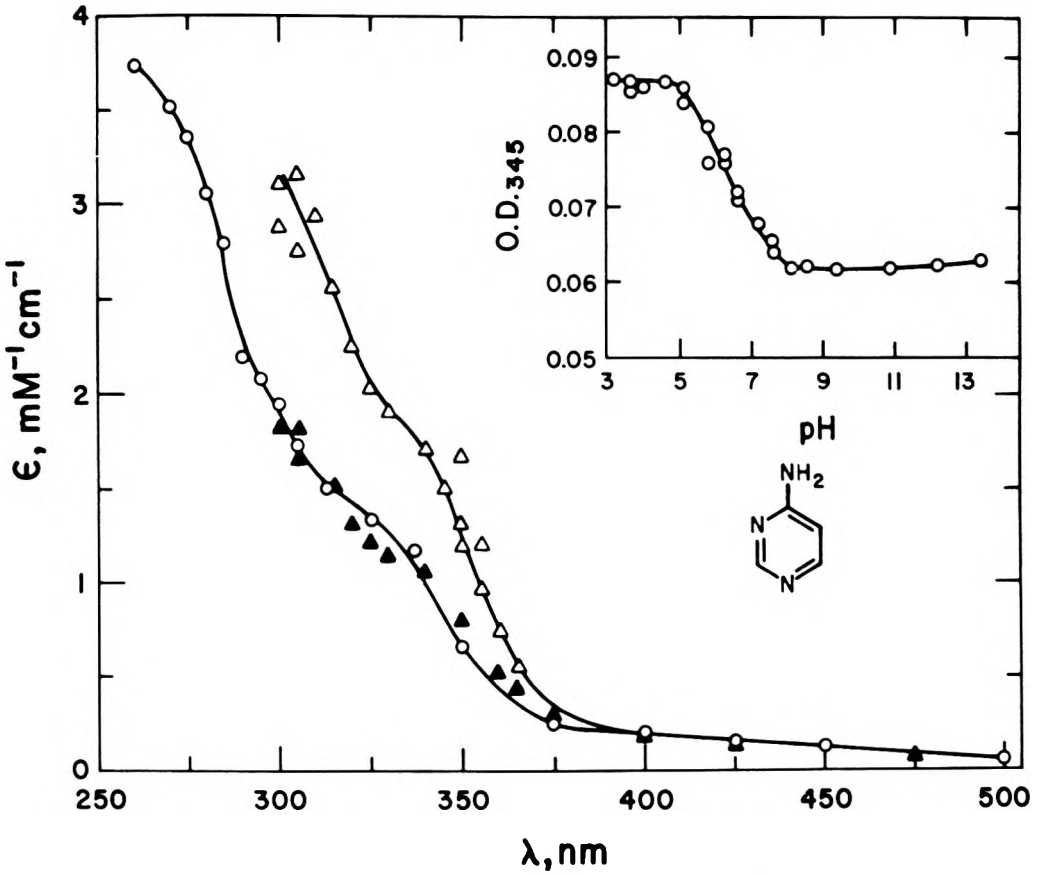


Figure 2. Absorption spectra of intermediates produced from the one-electron reduction by e_{aq}^- of 4-aminopyrimidine (in presence of 1–2 M *t*-BuOH, 1 atm argon) at pH 3.5 (10^{-2} M, transient species T_1, ▲, and T_2, △, measured at ≤0.5 and ~5.0 μs after the pulse, respectively) and pH 13.3 (10^{-3} M, ⊙) at ≤0.5 μs. Total dose ~10 krad/pulse. Insert: change in absorbance at 345 nm with pH (solutions contained 10^{-2} M 4-aminopyrimidine, 2.0 M *t*-BuOH, 1 atm argon).

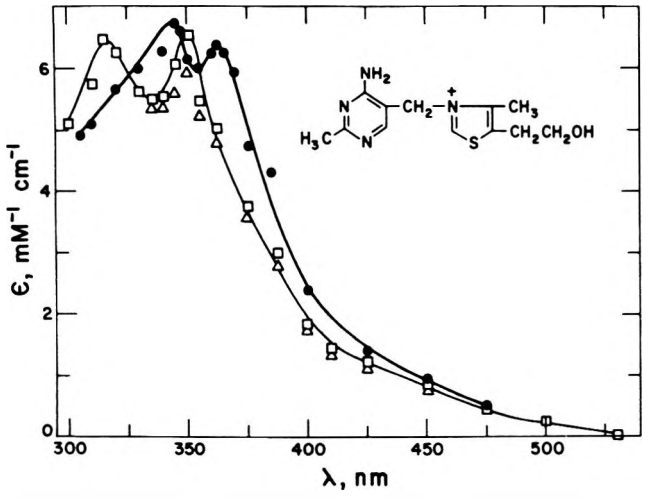
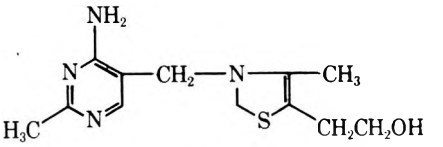


Figure 3. Absorption spectra of intermediates produced from the one-electron reduction by $(CH_3)_2\dot{C}OH$ and e_{aq}^- of thiamin (5×10^{-3} M thiamin, 1.0 M *i*-PrOH, 1 atm N_2O) at pH 6.6 (transient species T_1, □, and T_2, △, read at "zero" time and ~200 μs after the pulse, respectively) and pH 0.5, ●. Total dose ~3 krad/pulse.

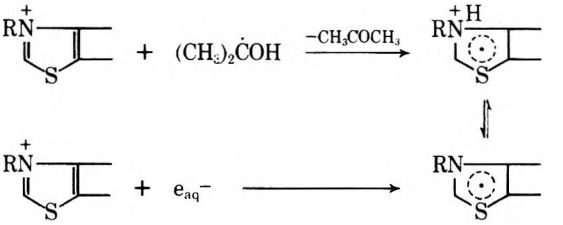
From the reactivity of thiamin toward one-electron reducing agents, and from the nature of the absorption spectrum of the transient species formed, as compared to thiazole, it would appear that the thiazolium ring is the primary site for one-electron reduction. The thiazolium ring has been found[16] to be the site of attack in the chemical, as well as electrochemical, reduction of thiamin to form dihydrothiamin (II). In steady state radiolysis experiments (solution contained 10^{-4} M thiamin, 1.0 M isopropyl alcohol, 1 atm N_2O, pH ~5.0)



II

the UV spectrum of the solution was identical with the absorption spectrum of dihydrothiamin.

Based on the above considerations, the following reaction scheme is suggested:



As suggested above for thiazole, one could also consider a different assignment for these radicals. The strong delocalization of the lone pair of electrons on the sulfur atom leaves the S atom in the thiamin with a net positive charge,[3] thus facilitating the interaction of one-electron reducing agents with the molecule.

The decay kinetics of the electron adduct to thiamin are somewhat unusual. At all pH's, the initial absorbance decreases by ~10% in ~200 μs after the 30-ns pulse at all wavelengths. The transient spectrum at ~200 μs after the pulse is essentially identical with the initial spectrum observed at ~0.1 μs after the pulse. It decays by second-order kinetics with $2k = 7.6 \times 10^5$ M^{-1} s^{-1} at pH 6.6 and 8.8×10^4 M^{-1} s^{-1} at pH 4.4

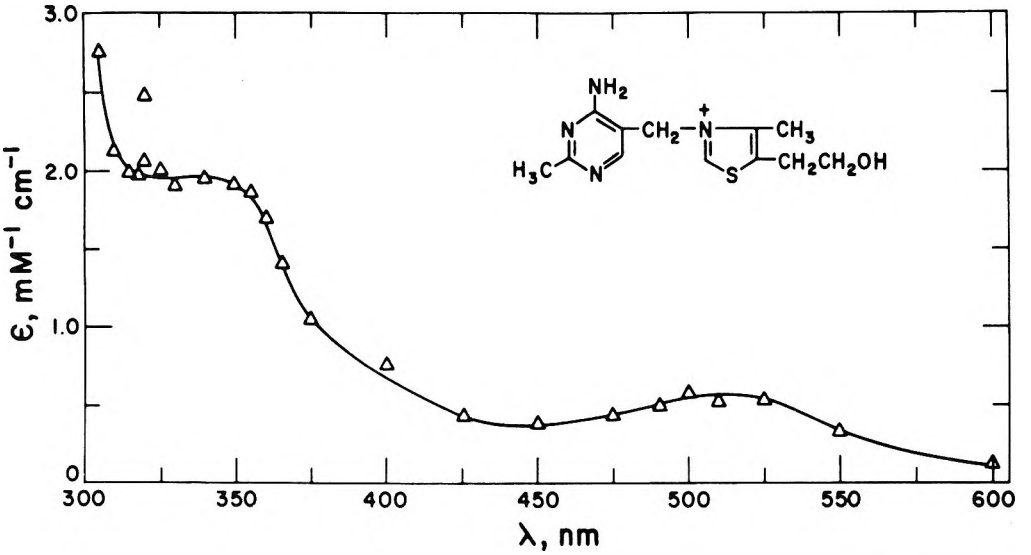


Figure 4. Absorption spectrum of intermediates produced from the reaction of OH radicals with thiamin (10^{-3} M, 1 atm N_2O, pH 4.4, ~7 krad/pulse).

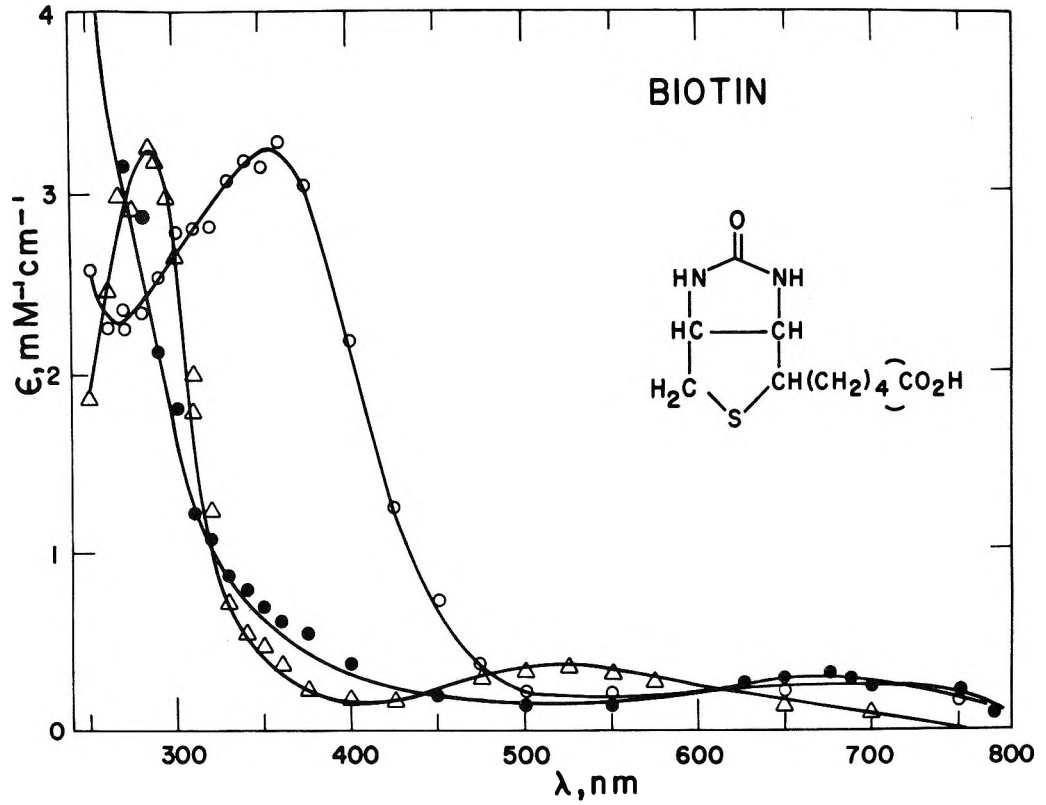


Figure 5. Transient species produced from the reaction of OH radicals with biotin (10^{-3} M, in presence of 1 atm N_2O) at pH 10.4 (T_1, ○), pH 3.7 (T_2, △), and pH 13.3 (T_3, ●). Total dose ~10 krad/pulse (see text).

(see Table II). At pH 0.5 it has a lifetime >20 s. The small initial decay may be due to reaction with the β-hydroxy radical formed (~15%) from isopropyl alcohol on reaction with OH radicals. Similar reactions were observed[13] between nitrogen heterocyclic radicals and the β-hydroxy radical of *t*-BuOH. The pH dependence of the bimolecular decay may be attributed to the overall charge of +1 on the transient species (due to protonation of the pyrimidine ring, pK_a = 4.8). At still lower pH's, viz., below the pK_a (radical) = 1.6, the species bears two positive charges, which could explain its relatively slow decay.

An experiment was carried out to observe the transient species produced from the reaction of OH radicals with thiamin. The spectrum observed is shown in Figure 4. Absorption maxima at 515, ~340, and <305 nm can be seen. The OH radicals are expected to add primarily to the pyrimidine ring[18] and to the thiazolium ring (possibly at the C_2 position). In addition, H-atom abstraction by OH from the side chains may occur. The radical produced decays by second-order kinetics with $2k = 1.6 \times 10^8$ M^{-1} s^{-1} at pH 4.7.

Biotin. The reaction of OH radicals with biotin produces a transient optical absorption spectrum T_1 at pH 10.4 with absorption maxima at ~350 and ~680 nm and ϵ_{350} 3.2×10^3 and ϵ_{680} 250 M^{-1} cm^{-1}; see Figure 5. This intermediate decays relatively fast in a pH-dependent manner. In acidic solutions it decays by reaction with H^+ with a $k = 7.4 \times 10^4$ M^{-1} s^{-1}.

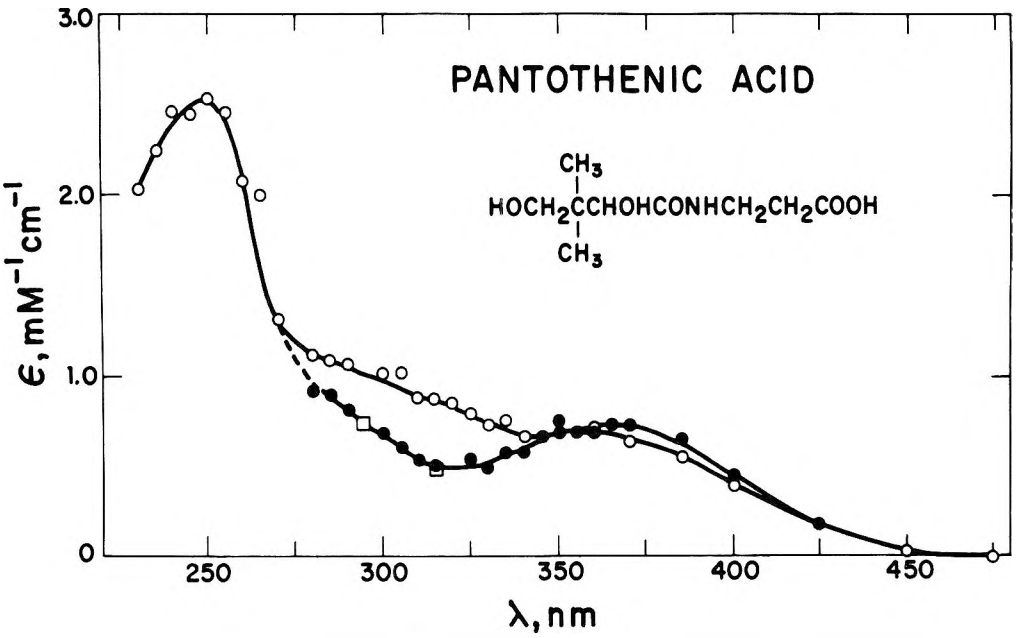
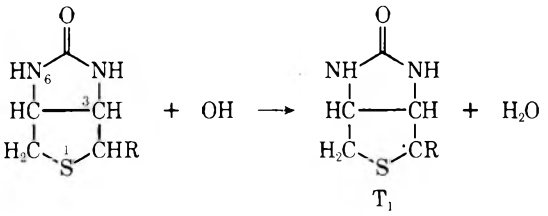


Figure 6. Transient species produced from the reaction of OH radicals with pantothenic acid (2×10^{-3} M, 1 atm N_2O) at pH 6.7. Dark symbols, ●, observed immediately after the pulse and open symbols, ○, ~2 μs later. At pH 4.7, □, only one transient spectrum is observed in the wavelength range 270–340 nm. Total dose ~20 krad/pulse.

The initial T_1 transient produces in acid solutions a spectrum (T_2) with $\lambda_{max} \sim 285$ and 520 nm and ϵ_{285} 3.2×10^3 and ϵ_{520} 380 M^{-1} cm^{-1} (Figure 5). The change of T_1 to T_2 can also be brought about by $H_2PO_4^-$ ions with $k = 4.4 \times 10^8$ M^{-1} s^{-1}. Protonation by water occurs with $k \sim 6.0 \times 10^3$ M^{-1} s^{-1}.

Transient T_1 decays in alkaline solution by reaction with OH^- with $k = 2.7 \times 10^7$ M^{-1} s^{-1} to give an intermediate (T_3) with maxima at ~680 and <250 nm, with ϵ_{680} 300 and ϵ_{250} 4.6×10^3 M^{-1} cm^{-1}; see Figure 5. Both T_2 and T_3 species decay by second-order kinetics. For T_2, $2k = 6.4 \times 10^8$ M^{-1} s^{-1} at pH 3.6, monitored at 290 nm. For T_3, $2k = 4.2 \pm 2 \times 10^8$ M^{-1} s^{-1} at pH 13.3, monitored at 300, 360, and 675 nm.

The attack on biotin by OH radicals can occur at various sites: H atom abstraction at C_2, C_3, C_7, and C_8 positions, as well as abstraction from the side chain. It is suggested that one of the more important sites is at the C_2 position:

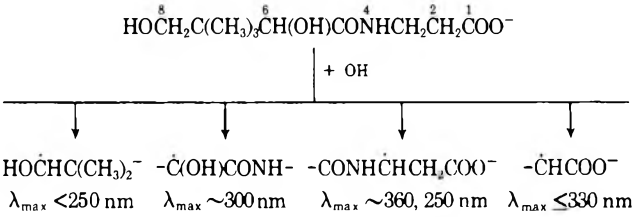


T_1

The protonation reaction of T_1 with H^+ or $H_2PO_4^-$ is suggested to occur at the sulfur atom, with the formation of $>^+SH$. The reaction T_1 with OH^- ions is less clear, and may involve ring opening of biotin. Alternatively, some H-atom abstraction at the C_3 position may also be occurring, resulting in ionization of the $-N_4H-$group in alkaline solution.

Pantothenic Acid. The reaction of OH radicals with pantothenic acid can result in the formation of a number of free radicals, as a result of attack at various sites in the molecule. Figure 6 shows the transient absorption spectrum observed. In the wavelength region ~270–340 nm, the initial absorption at pH 6.7 increased with time, as shown, whereas at pH 4.7 there was no such change—the spectrum was identical with the initial spectrum at pH 6.7. This change in absorbance at 315 nm was monitored as a function of pH. A titration curve was found with a pK_a ~6.0 ± 0.3.

Four major sites for H-atom abstraction from pantothenic acid can be considered:



(a) At the C_2 position. Such a radical is expected[19] to absorb weakly at λ below ~330 nm with a relatively low extinction coefficient. (b) At the C_3 position. Such a radical, $-CONHCHCH_2COO^-$, is expected[20] to have two absorption maxima at ~360 and ~250 nm. These bands can be observed in Figure 6. (c) At the C_6 position. Such a radical, $-C(OH)-CONH-$, is expected[21] to absorb at λ ~300 nm. Such an α-diketone ketyl radical should have[14] a relatively low pK_a (radical) value. The observed $pK_a = 6.0 \pm 0.3$ from pantothenic acid can be assigned to this radical:

$$-C(OH)CONH- \underset{pK_a = 6.0 \pm 0.3}{\rightleftharpoons} -C(O^-)CONH- + H^+$$

(d) At the C_8 position. With the formation of an α-alkylhydroxy radical $HOCHCH(CH_3)_2$. Such a radical would have[14] a $pK_a \geq 11.0$. Because of the instability of pantothenic acid at pH ≥ 7.0, this region has not been investigated.

The presence of the $-C(O^-)CONH-$ radical anion in neutral solution of pantothenic acid would indicate that it is a good reducing agent[22] for one-electron transfer reactions. Such a radical is expected to have a low (i.e., negative) oxidation potential.[22]

Registry No.—Thiazole, 288-47-1; 4-aminopyrimidine, 591-54-8; thiamin, 59-43-8; biotin, 58-85-5; pantothenic acid, 79-83-4; $(CH_3)_2COH$, 5131-95-3; OH, 3352-57-6.

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Stable Heptamethine Pyrylium Dyes That Absorb in the Infrared

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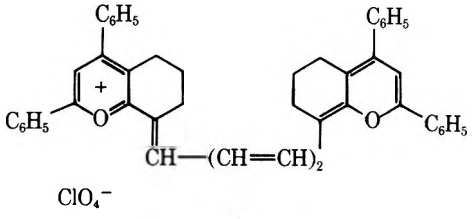
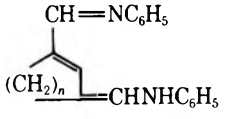
The stability of heptamethine pyrylium dyes has been greatly increased by incorporating all but two of the methine groups in rings. The effect of ring size and a chlorine atom in the center of the methine chain on the absorption maxima of the dyes is described. By the suitable choice of these factors, a dye which absorbs at about 1.2 μ was obtained. Heptamethine pyrylium dyes were prepared from an indene-1,3-dialdehyde derivative as well as the corresponding 3-chloro derivative. These dyes were not as stable nor did they absorb at as long wavelengths as other similar dyes containing five- and six-membered rings at the center of the methine chain. It has been shown that heptamethine pyrylium dyes containing only the three central methine groups in a ring are as stable as the dyes that contain all but two of the methine groups in rings, and that a thiopyrylium homologue is the most stable heptamethine dye that we have prepared.

For many years, chemists have been interested in preparing dyes that show electronic absorptions further into the infrared region of the spectrum than existing dyes, and cyanine dyes have proved to be exceptionally useful in this respect. The work with cyanine dyes has been reviewed.[1] A particularly useful route to infrared-absorbing dyes has taken advantage of the fact that the pyrylium nucleus, compared to other heterocyclic nuclei, gives large bathochromic shifts when incorporated in polymethine dyes.[2] For example, the relatively simple dye **1** (in methylene chloride) shows absorption at 1040 nm with ϵ 125 000.



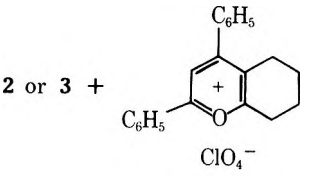
1

The present paper describes more recent work on preparing polymethine pyrylium dyes that absorb in the infrared. The successful preparation of **1** depended on partially rigidizing the polymethine chain by incorporating two of the methine groups in rings. Attempts to prepare the pyryloheptamethine dye without these rings were unsuccessful. Evidently, we have reached the limits of stability with **1**, since the next higher vinylog could not be prepared. This result was not surprising because the stability of **1**, although much better than that of other polymethine dyes absorbing in this region of the spectrum, is still not good. It was apparent that the most obvious way to increase the stability of **1** or prepare higher vinylogs would be to incorporate more methine groups in rings. Unfortunately, the reported methods[1] for doing this failed with

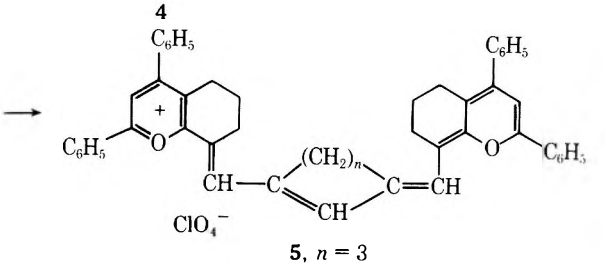


2, $n = 3$
3, $n = 2$

pyrylium dyes. It was, therefore, with interest that we noted the recent preparation[3] of **2** and **3**, which have been used by Russian workers to prepare some pyrylium, thiopyrylium, and selenopyrylium dyes.[4] We have used these bisaldehyde derivatives to prepare heptamethine dyes **5** and **6** which contain all but two of the methine groups in rings.



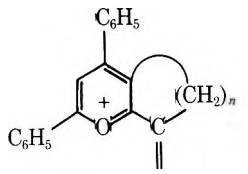
4



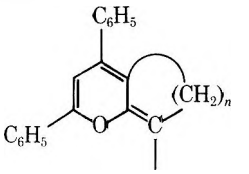
5, $n = 3$
6, $n = 2$

The λ_{max} of **5** and **6**, 1090 nm (ϵ 140 000) and 1138 (70 000), respectively, illustrate two characteristics that are common to dyes of this type, namely, that the dyes containing five-

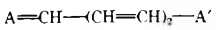
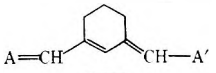
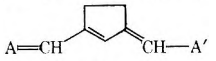
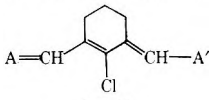
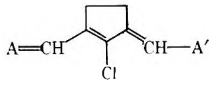
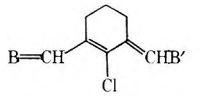
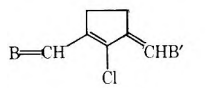
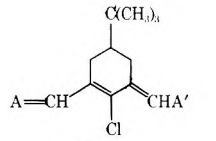
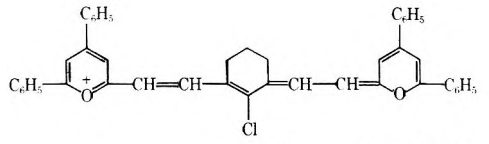
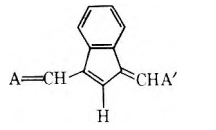
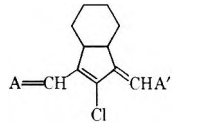
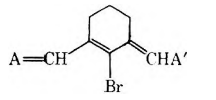
Table I. Polymethine Dyes



A, $n = 3$
B, $n = 2$

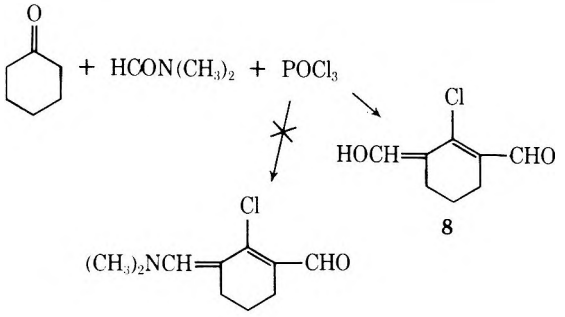


A′, $n = 3$
B′, $n = 2$

Dye structure	Compd	λ_{max}, nm ($\epsilon \times 10^{-3}$)	Rel stability
	1	1040 (125.0)	1
	5	1090 (140.0)	76
	6	1138 (70.0)	37
	10	1120 (113.0)	128
	11	1145 (143.0)	178
	12	1152 (120.0)	190
	13	1180 (95.0)	49
	14	1120 (111.0)	170
	15	1072 (107.0)	78
	18	1042 (185.0)	7.6
	19	1040 (175.0)	8.7
	24	1125 (112.0)	201

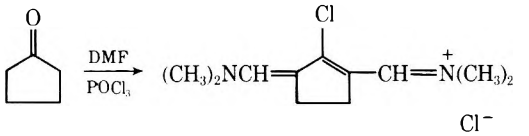
membered rings absorb at longer wavelengths than those with six-membered rings but sometimes with a decrease in the extinction coefficient, and the presence of the central ring results in a bathochromic shift compared to the dye with hydrogen atoms at the 3 and 5 positions of the methine chain (compare λ_{max} of **1** with **5** and **6**). The effect of chain substituents on the absorption of polymethine dyes is very interesting. Reichardt has investigated extensively the effect of substituents at the central carbon atom of various pentamethine cyanine dyes and found that electron-withdrawing groups give large shifts to shorter wavelengths.[5] This can be understood on the basis of the electron gas model for the π-electron system of cyanine dyes.[6] The sign of the absorption shift should depend on the number of double bonds (even or odd) between the end groups of the dye. Therefore, we can expect a shift toward longer wavelengths if an electron-withdrawing substituent is introduced at the central carbon atom of a heptamethine dye. Substitution of the hydrogen atom at the central carbon atom of **1**, **4**, or **5** by a more electronegative atom should result in a bathochromic shift of the dye.

To test this prediction, it was necessary to prepare a suitably substituted bisaldehyde as a precursor to the dye. For this purpose, the work of Zemlicka and Arnold[7] was repeated. It was reported[7] that cyclohexanone reacted with the Vilsmeier–Haack reagent to give **7**, but we consistently obtained



7

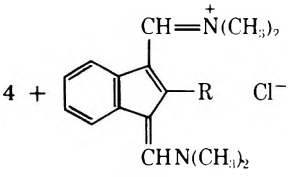
8 as the product. The formation of **9** from cyclopentanone was substantiated. Since **8** and **9** are readily prepared in high yield, they served as ideal starting materials for the synthesis of polymethine dyes bearing a chlorine atom as an electron-withdrawing group on the central carbon of the methine chain.



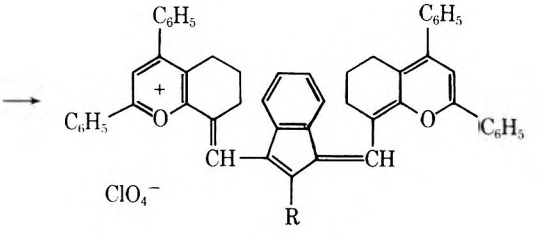
9

The dyes prepared from **8** and **9** and their long-wavelength absorptions (in methylene chloride) are shown in Table I. It is seen that substantial bathochromic shifts were obtained by replacing the methine hydrogen with the weakly electronegative atom, chlorine, and also by incorporating five-membered rings throughout the dye.

Arnold has described[9] the preparation of two additional cyclic bisaldehyde derivatives **16** and **17** that we have used to prepare the rigidized dyes **18** and **19**.



16, R = H
17, R = Cl

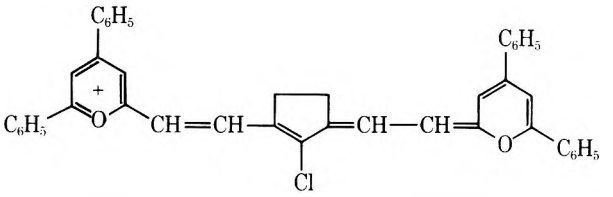


18, R = H
19, R = Cl

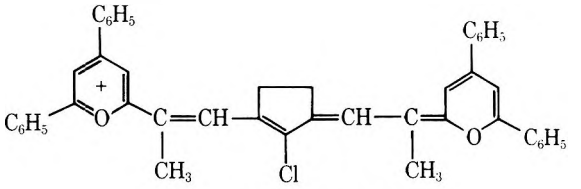
The dyes **18** and **19** differed from the corresponding dyes **5** and **6** in that the λ_{max} of **18** and **19** are at shorter wavelengths and the chlorine atom did not cause a shift to longer wavelengths. The exact values for the dyes under discussion are given in Table I. Although it may be coincidental, dyes **18** and **19** absorb at the same wavelength as the straight chain pentamethine dye **1**.

In order to determine the stabilizing effect of the chain rings, the stability of the dyes was determined by irradiating a sample (optical density 1 in 1,2-dichloroethane) with the light source of a Cary Model 14 spectrophotometer equipped with a filter to eliminate light below 650 nm. The stabilities of the dyes are compared on a relative basis in Table I using **1** as the basis of comparison.

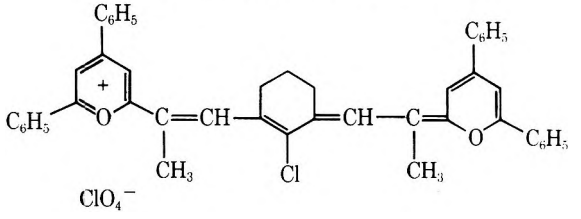
We had made the assumption in our attempts to synthesize stable heptamethine pyrylium dyes that an increase in the number of methine groups that are contained in rings should result in more stable dyes. It was, therefore, with great interest that we noted that **15** (relative stability 78) was as stable as the corresponding dye **5**. We decided to prepare other examples similar to **15**, and the following compounds were synthesized.



20, λ_{max} 1095 nm (ϵ 167 000) in CH_2Cl_2
relative stability 35



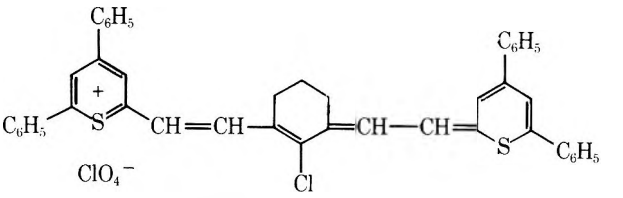
21, λ_{max} 1110 nm (ϵ 52 800)



22

The λ_{max} of these compounds again illustrate the bathochromic shift caused by a five-membered ring and also that alkyl groups at the 1 and 7 positions of the chain result in a small bathochromic shift. Evidently compound **21** is in a crowded configuration since the ϵ value is only about 1/3 the value of similar dyes. We have not measured the relative stability of **21** but predict that it will be relatively unstable. Compound **22** was rather interesting. The first time the absorption spectrum was measured, there was no absorption in the near infrared. After we received the elemental analysis and were convinced that the compound had been obtained, the absorption spectrum was rechecked. It was found that if a 5×10^{-5} M solution of the dye in CH_2Cl_2 was placed in the spectrophotometer, which was set at 1100 nm, the optical density dropped from approximately 1 to zero in less than 1 min. We can offer no plausible explanation for the greater instability of **22** compared to **21**.

Since thiapyrylium salts absorb at longer wavelengths than the corresponding pyrylium salts, an example of a heptamethine thiapyrylium dye was prepared to determine the magnitude of the effect. The dye **23** showed a substantial (88 nm) bathochromic shift in comparison with the corresponding pyrylium dye **15**. The most unusual effect, however, was the large increase in stability relative to pyrylium dyes.



23, λ_{max} 1160 nm (ϵ 105 000)
relative stability >2000

We believe that the best way to obtain large bathochromic shifts in the heptamethine dyes would be through replacement of the chlorine atom at the center of the chain with a more electronegative atom or group, but the only example we have been able to prepare is the bromo derivative **24** (see Table I), which showed absorption and stability very similar to those of the corresponding chloro derivative **10**.

Experimental Section

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-2,4-trimethylene-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium Perchlorate (5). All runs were carried out on a 5-mmol scale except where indicated. A mixture of 1.9 g (0.005 mol) of 2,4-diphenyl-5,6,7,8-tetrahydro-1-benzopyrylium perchlorate[8] (**4**), 0.81 g (0.0025 mol) of **2**, 0.4 g (0.005 mol) of sodium acetate, 20 ml of acetic acid, and 15 ml of acetic anhydride was refluxed for 15 min, and after chilling, the solid was collected, washed with water and then alcohol, and recrystallized from nitromethane, yield 1.4 g, mp 291–292 °C dec. The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 510 (30.0), 620 (6.0), 690 (4.0), ~880 (35.0), 965 (92.0), and 1090 nm (143.0).

Anal. Calcd for $C_{50}H_{43}ClO_6$: C, 77.5; H, 5.6. Found: C, 77.3; H, 5.5.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-2,4-dimethylene-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium perchlorate (6) was prepared from **4** and **3**, 3-mmol scale, yield 0.5 g (not recrystallized), mp 225–227 °C. The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 360 (17.8), 510 (9.1), ~560 (6.5), 640 (4.5), 1005 (38.5), and 1138 nm (70.0).

Anal. Calcd for $C_{49}H_{41}ClO_6$: C, 77.3; H, 5.4. Found: C, 77.0; H, 5.7.

2-Chloro-1-formyl-3-hydroxymethylenecyclohexene (8). A solution of 40 ml of dimethylformamide in 40 ml of methylene chloride was chilled in an ice bath and 37 ml of phosphorus oxychloride in 35 ml of methylene chloride was added dropwise with stirring, followed by 10 g of cyclohexanone. The solution was refluxed for 3 h, cooled, poured onto 200 g of ice, and allowed to stand overnight. The yellow solid was collected and dried, yield 16 g, mp 125–127 °C. A sample was crystallized from a small volume of acetone cooled with dry ice, to give material melting at 130–131 °C.

Anal. Calcd for $C_8H_9ClO_2$: C, 55.7; H, 5.3; Cl, 20.5. Found: C, 55.4; H, 5.4; Cl, 20.4.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-3-chloro-2,4-trimethylene-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium Perchlorate (10). The general procedure was used with **4** and **8** giving 1.9 g of **10**, mp 234–235 °C (from nitromethane). The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 360 (27.0), 500 (21.0), 530 (22.8), 620 (5.7), 695 (3.8), 1000 (67.5), and 1120 nm (113.0).

Anal. Calcd for $C_{50}H_{42}Cl_2O_6$: C, 74.2; H, 5.2. Found: C, 74.2; H, 5.3.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-3-chloro-2,4-dimethylene-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium Perchlorate (11). Compound **11** was prepared by the general procedure from **4** and **9**, yield 1.7 g, mp 240–242 °C (from nitromethane). The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 365 (22.0), 530 (17.0), 632 (10.5), 1012 (73.5), and 1145 nm (143.0).

Anal. Calcd for $C_{49}H_{40}Cl_2O_6$: C, 74.0; H, 5.1. Found: C, 74.2; H, 5.0.

7-[5-(2,4-Diphenyl-5,6-dihydrocyclopenta[*b*]pyran-7-yl)-

3-chloro-2,4-trimethylene-2,4-pentadienylidene]-2,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrylium Perchlorate (12). The general procedure was used with 2,4-diphenylcyclopenta[*b*]-pyrylium perchlorate and **8** and the yield of dye was 2 g, mp 245–247 °C. The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 375 (17.5), ~510 (12.0), 530 (14.8), 630 (6.7), 722 (2.0), 1010 (58.0), and 1152 nm (120.0).

Anal. Calcd for $C_{48}H_{38}Cl_2O_6$: C, 73.7; H, 4.9. Found: C, 73.5; H, 5.0.

7-[5-(2,4-Diphenyl-5,6-dihydrocyclopenta[*b*]pyran-7-yl)-3-chloro-2,4-dimethylene-2,4-pentadienylidene]-2,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyrylium Perchlorate (13). The yield of dye, prepared from 2,4-diphenylcyclopenta[*b*]pyrylium perchlorate and **9** in the usual manner, was 1.9 g, mp 248–250 °C. The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 368 (32.0), 550 (12.0), 670 (11.0), 1030 (46.0), and 1180 nm (112.0).

Anal. Calcd for $C_{47}H_{36}Cl_2O_6$: C, 73.5; H, 4.7. Found: C, 73.6; H, 4.8.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-3-chloro-2,4-[2-*tert*-butyltrimethylene-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium Perchlorate (14). Compound **14** was prepared from **4** and 5-*tert*-butyl-2-chloro-1-formyl-3-hydroxymethylenecyclohexene (prepared as described for **8**, mp 122–123 °C) by the general procedure, yield 1.2 g, mp 247–248 °C (from nitromethane). The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 360 (27.0), 500 (21.0), 530 (23.8), 620 (7.6), 690 (4.3), 1000 (65.0), and 1120 nm (110.0).

Anal. Calcd for $C_{54}H_{50}Cl_2O_6$: C, 75.0; H, 5.7; Cl, 8.2. Found: C, 75.0; H, 6.0; Cl, 8.1.

2-[7-(4,6-Diphenyl-2*H*-pyran-2-ylidene)-4-chloro-3,5-trimethylene-1,3,5-heptatrienyl]-4,6-diphenylpyrylium Perchlorate (15). Compound **15** was prepared from **8** and 2-methyl-4,6-diphenylpyrylium perchlorate, yield 2.1 g, mp 220–221 °C. The λ_{max} ($\epsilon \times 10^{-3}$) in CH_2Cl_2 are 370 (22.5), 505 (13.3), 610 (6.7), 670 (3.6), 950 (63.0), 1072 nm (107.0).

Anal. Calcd for $C_{44}H_{34}Cl_2O_6$: C, 72.4; H, 4.7. Found: C, 72.0; H, 4.8.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-2,4-(1,2-phenylene)-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium perchlorate (18) was prepared from **4** and **16**, yield 1.8 g, mp 245–247 °C (from acetic anhydride). The λ_{max} ($\epsilon \times 10^{-3}$) in methylene chloride are 1042 (185.0), 930 (51.0), 615 (5.2), 565 (4.3), 518 (6.3), 395 (11.5), 335 (24.8), 285 (29.0), and 250 nm (25.4).

Anal. Calcd for $C_{53}H_{41}ClO_6$: 78.7; H, 5.1; Cl, 4.4. Found: C, 78.5; H, 5.2; Cl, 4.3.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-3-chloro-2,4-(1,2-phenylene)-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium perchlorate (19) was prepared from **4** and **17**, yield 2 g, mp 226–277 °C (from a mixture of acetic anhydride and acetic acid). The λ_{max} ($\epsilon \times 10^{-3}$) in methylene chloride are 1040 (175.0), 930 (70.0), 515 (9.0), 465 (8.0), 418 (11.0), 300 (14.0), 335 (34.5), and 290 nm (42.0).

Anal. Calcd for $C_{53}H_{40}Cl_2O_6$: C, 75.4; H, 4.8; Cl, 8.4. Found: C, 75.1; H, 5.0; Cl, 8.0.

2-[7-(4,6-Diphenyl-2*H*-pyran-2-ylidene)-4-chloro-3,5-dimethylene-1,3,5-heptatriene]-4,6-diphenylpyrylium perchlorate (20) was prepared from 2-methyl-4,6-diphenylpyrylium perchlorate and **3**, yield 0.8 g, mp 214–215 °C dec (from acetic acid plus acetic anhydride). The λ_{max} ($\epsilon \times 10^{-3}$) in methylene chloride are 1095 (167.0), 970 (107), 610 (21.3), 530 (25.6), 365 (42.8), 315 (37.3), and 285 nm (37.0).

Anal. Calcd for $C_{43}H_{32}Cl_2O_6$: C, 72.7; H, 4.5; Cl, 9.9. Found: C, 72.4; H, 4.6; Cl, 9.6.

2-[8-(4,6-Diphenyl-2*H*-pyran-2-ylidene)-5-chloro-4,6-dimethylene-2,4,6-nonatrien-2-yl]-4,6-diphenylpyrylium perchlorate (21) was prepared from 2-ethyl-4,6-diphenylpyrylium perchlorate and **3**, yield 0.9 g, mp 220–222 °C dec (from a mixture of acetic anhydride and acetic acid). The λ_{max} ($\epsilon \times 10^{-3}$) in methylene chloride are 1110 (52.8), 1055 (54.0), 635 (6.6), 560 (9.2), 520 (11.0), and 360 nm (32.0).

Anal. Calcd for $C_{45}H_{36}Cl_2O_6$: C, 72.7; H, 4.9; Cl, 9.6. Found: C, 72.5; H, 4.8; Cl, 9.5.

2-[8-(4,6-Diphenyl-2*H*-pyran-2-ylidene)-5-chloro-4,6-trimethylene-2,4,6-nonatrien-2-yl]-4,6-diphenylpyrylium perchlorate (22) was prepared from 2-ethyl-4,6-diphenylpyrylium perchlorate and **2**, yield 2.0 g, mp 227–229 °C dec (from a mixture of acetic anhydride and acetic acid).

Anal. Calcd for $C_{46}H_{38}Cl_2O_6$: C, 72.9; H, 7.3; Cl, 9.4. Found: C, 73.0; H, 7.1; Cl, 9.3.

2-[7-(4,6-Diphenyl-2*H*-thiapyran-2-ylidene)-4-chloro-3,5-trimethylene-1,3,5-heptatrienyl]-4,6-diphenylthiopyrylium perchlorate (23) was prepared from 2-methyl-4,6-diphenylthiopyrylium perchlorate and **2**, yield 2.1 g, mp 236–238 °C (from acetic anhydride). The λ_{max} ($\epsilon \times 10^{-3}$) in methylene chloride are 1160 (105.0), 1038 (74.5), 630 (7.0), 530 (13.2), and 380 nm (23.6).

Anal. Calcd for $C_{44}H_{34}Cl_2O_4S_2$: C, 69.4; H, 4.5. Found: C, 69.3; H, 4.3.

8-[5-(6,7-Dihydro-2,4-diphenyl-5*H*-1-benzopyran-8-yl)-3-bromo-2,4-trimethylene-2,4-pentadienylidene]-5,6,7,8-tetrahydro-2,4-diphenyl-1-benzopyrylium Perchlorate (24). To 100 ml of DMF which was stirred in an ice bath was added 17 g of $POBr_3$. A white precipitate separated. The mixture was stirred for 30 min at room temperature, 2 g of cyclohexanone was added, and then the mixture was heated for 1 h on a steam bath. There was still undissolved material present so the mixture was heated by a heating mantle until the solid dissolved, and the solution was cooled and then poured into water. After standing overnight, the pale yellow solid was collected, washed with water, and dried, yield 2 g, mp 135–136 °C. The IR of the solid was very similar to that of **2**. Compound **24** was prepared from this material and **4**, yield 1.5 g, mp 223–224 °C (from nitromethane).

Anal. Calcd for $C_{50}H_{42}BrClO_6$: C, 70.3; H, 5.0; Br, 9.4. Found: C, 69.9; H, 4.9; Br, 9.2.

Registry No.—**1**, 22371-56-8; **2**, 61009-98-1; **3**, 61009-97-0; **4**, 15997-44-1; **5**, 61010-01-3; **6**, 61010-03-5; **8**, 61010-04-6; **9**, 61010-05-7; **10**, 61010-07-9; **11**, 61010-09-1; **12**, 61010-11-5; **13**, 61010-13-7; **14**, 61010-15-9; **15**, 61047-19-6; **16**, 61010-16-0; **17**, 61010-17-1; **18**, 61010-19-3; **19**, 61010-21-7; **20**, 61010-23-9; **21**, 61010-25-1; **22**, 61010-27-3; **23**, 61010-29-5; **24**, 61010-31-9; dimethylformamide, 68-12-2; phosphorus oxychloride, 10025-87-3; cyclohexanone, 108-94-1; 2,4-diphenylcyclopenta[*b*]pyrylium perchlorate, 21016-30-8; 5-*tert*-butyl-2-chloro-1-formyl-3-hydroxymethylenecyclohexane, 61009-99-2; 2-methyl-4,6-diphenylpyrylium perchlorate, 7654-52-6; 2-ethyl-4,6-diphenylpyrylium perchlorate, 18228-01-8; 2-methyl-4,6-diphenylthiopyrylium perchlorate, 41494-44-4.

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Reactions of Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. 6.[1] Revision of the Structure of the Reaction Product of Cyclohexane-1,3-dione and Dimethyl β-Ketoglutarate and Conversion to 4-Substituted 5,6,7,8-Tetrahydro-5-oxo-2-quinolones

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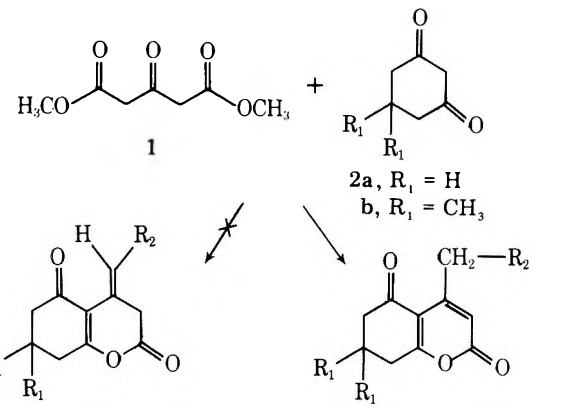
In our first report concerning the reactions of 1,2- and 1,3-dicarbonyl compounds with dimethyl β-ketoglutarate (1), we proposed structure **3a** for the product obtained from reaction of cyclohexane-1,3-dione (**2a**) with 1 at pH 6.8. This structure has now been revised to methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (**4a**) based on UV and ^{13}C NMR data. In addition, the tetrahydro-5-oxocoumarin derivatives **4a** and **4b** were converted to the corresponding 5,6,7,8-tetrahydro-5-oxo-2-quinolones **10a**, **11a**, **10b**, and **11b**, respectively, by reaction with *N*-benzylamine or ammonia. The ^{13}C NMR spectra of these 2-quinolones are presented and discussed.

During studies on the reaction of dicarbonyl compounds[1,2a-c] with dimethyl β-ketoglutarate (1) we reported, in preliminary form,[3] that stirring cyclohexane-1,3-dione (**2a**) with 1 at pH 6.8 provided the lactone **3a.** We would now like to revise the structure of this reaction product to the α-pyrone derivative, methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (**4a**),[4] based on analogies between the UV and ^{13}C NMR spectra of **4a** with the spectra of 4-methyl-5,6,7,8-tetrahydro-5-oxocoumarin (**4c**).[5,6]

Scheme I

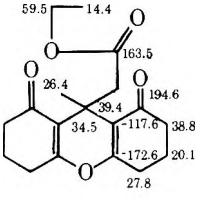


In the UV spectrum of the compound in question (**3a** or **4a**, λ_{max} 260 nm, log ε 4.06; 295 nm, sh, log ε 3.74) the shoulder at 295 nm was nearly obscured by the intense absorption at 260 nm and this led to the initial assignment (**3a**).[3] However, on closer examination of this spectrum, a shoulder (295 nm) was observed and in fact the spectrum was very similar to that of the known 5-oxocoumarin (**4c**, λ_{max} 261 nm, log ε 3.99; 299 nm, sh, log ε 3.63) and to that of the 7,7-dimethyl analogue (**4d**)[6] as illustrated in Table I. In addition, the band at 295 nm in the spectrum of **4a** has ε almost identical with that of α-pyrones[7] such as **5,** but much different from the oxo-enol ether system **6**[8] or the keto lactone **7.**[7]

It was felt, at this point, that the structure of the reaction product of 1 and **2a** was **4a**[4] and not the previously reported **3a.**[3] While IR and ^1H NMR favored structure **4a,** they were not very useful in distinguishing unambiguously between the two possibilities. However, the ^{13}C NMR spectra of **4c** and the reaction product (**4a**) were almost identical, when the difference between the group ($CH_2CO_2CH_3$ vs. CH_3) attached to C-4 of the heterocyclic ring was taken into consideration (see Table II). Furthermore, the absorption (169.3 ppm) due to the ester carbonyl in the ^{13}C NMR spectrum of the reaction product clearly eliminated the possibility of the α,β-unsaturated ester function, which would be present in **3a.** Saturated methyl ester carbonyls appear at 169–170 ppm in ^{13}C NMR spectra while their α,β-unsaturated counterparts are found at 163–164 ppm.[9] All of the compounds (α-pyrones and α-pyridones), whose spectra are illustrated in Table II, have signals in their ^{13}C NMR spectrum in the range of 169–170 ppm, and are certainly due to saturated methyl ester functions. This evidence, taken together with UV data, rules out structure **3a** as the product from reaction of **1** with **2a** and confirms the assignment of this derivative as **4a.** By analogy, stirring dimedone (**2b**) with 1 (at pH 6.8) furnished the 7,7-dimethyl analogue **4b.** The model compound, 4-methyl-5,6,7,8-5-oxocoumarin (**4c**), was prepared in several ways: by acid-catalyzed hydrolysis and decarboxylation of **4a;** by *heating* the reaction mixture of **2a** and 1 to 70 °C at pH 6.8; and also by reacting ethyl acetoacetate (8) and **2a** in pyridine.[5]

In addition, stirring the 1,3-dione (**2a**) with 8 at room temperature (pH 6.8) resulted in production of a small amount of **4c** along with larger amounts of ethyl 1,2,3,4,5,6,7,8-octahydro-9-methyl-1,8-dioxoxanthen-9-yl acetate (**9a**). The structure of the xanthene derivative was determined by comparing the spectral properties of **9a** to those of 9,9-dimethylxanthene (**9b**).[10] The structure of **9a** was further corroborated by comparison of its ^{13}C NMR spectrum (see Chart I) to the spectra of model compounds (see ref 11, 12). A set of

Chart I. ^{13}C NMR Chemical Shifts[a,b] for Xanthene (9a)



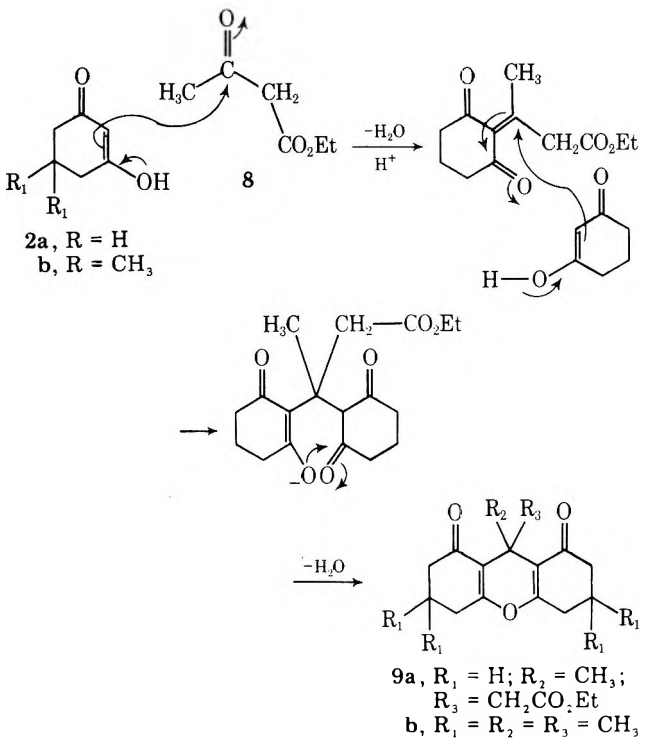
9a[c]

[a] Solvent $CDCl_3$. [b] $(CH_3)_4Si$ as internal standard. [c] Some of the methylene carbon assignments of 9a are tentative, their signals being too close to permit distinction between similar carbon atoms.

steps depicting a rational pathway to **9a** is outlined in Scheme II.[13]

Synthesis of 5-hydroxy-5,6,7,8-tetrahydrocarbostyrils and 5-hydroxy-5,6,7,8-tetrahydro-2-quinolines[14a] have not re-

Scheme II



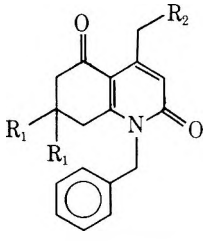
2a, R = H
b, R = CH_3

8

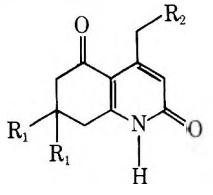
9a, R_1 = H; R_2 = CH_3; R_3 = CH_2CO_2Et
b, R_1 = R_2 = R_3 = CH_3

ceived much attention in the past; however, reports of the activity of bis-5-hydroxycarbostyrils against allergic asthma have stimulated new interest in this area.[14b] Since conversion of α-pyrones to α-pyridones is well known,[15] it was felt that reaction of the 5-oxocoumarin derivatives (**4a–d**) with amines might provide a facile route to 5,6,7,8-tetrahydro-5-oxo-2-quinolones, which could be converted (via the acetic acid function) to a variety of C-4 (alkyl) substituted-2-quinolones and quinolines.

In general, heating **4a** or **4b** in benzene with benzylamine gave poor yields of the corresponding tetrahydro-5-oxo-2-quinolones **10a** and **10b,** respectively. In the case of **4b,** a small amount of the amide (**10c**) was also obtained. However, when **4a** and benzylamine were stirred at room temperature in methanol for several days, there appeared to be one major



10a, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CH_3; R_2 = CO_2CH_3
c, R_1 = CH_3; R_2 = CONHBz
d, R_1 = R_2 = H



11a, R_1 = H; R_2 = COOH
b, R_1 = CH_3; R_2 = COOH HCl
c, R_1 = H; R_2 = $COONH_4$
12a, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CH_3; R_2 = CO_2CH_3

Table I. Ultraviolet[a] Spectra of 4a and Related Model Compounds

Compd	λ, nm	ε	Log ε
4a	260	11 430	4.06
	295	5 540	3.74
4b	263	9 375	3.97
	299	5 280	3.71
4c	261	9 780	3.99
	299	4 279	3.63
4d	262[b]	12 100	4.08
	296	5 960	3.76
5	300[c]	5 000	3.69
6	263[d]	28,024	4.45
7	271[e]		

[a] Solvent CH_3OH. [b] Reference 10. [c] Reference 7. [d] Authentic sample provided by Professor Clayton Heathcock. See *J. Org. Chem.*, **41**, 636 (1976). [e] Reference 7.

compound (**10a**), isolated in 80% yield, with only traces of **4a** remaining.

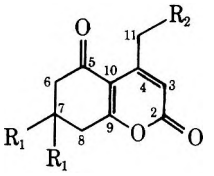
Slightly different behavior was observed on reaction of **4a** with anhydrous ammonia. Initially, ammonia was bubbled into a methanolic solution of **4a,** but yields of 5-oxo-2-quinolone **11a** were quite low. However, when the same transformation was carried out in a solution of 1:1 methanol/ether, a 92% yield of the quinolone carboxylic acid derivative (**11a**) precipitated as a white solid. The salt, 5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-ylacetic acid hydrochloride (**11b**), was prepared by treating **4b** with ammonia in much the same manner as the preparation of 5,6,7,8-tetrahydro-5-oxo-2-quinolon-4-ylacetic acid (**11a**). Treatment of a solution of **4a** in methanol with ammonium hydroxide again caused reaction at both oxygen-substituted carbonyls to generate, in this case, the ammonium salt (**11c**). This appears to be the first route to tetrahydro-5-oxo-2-quinolones with the 4 position of the heterocyclic ring available for further functionalization. Both **11a** and **11b** were esterified to generate the methyl esters **12a** and **12b,** respectively, in excellent yield.

The ^{13}C NMR spectra of the 5,6,7,8-tetrahydro-5-oxocoumarins and the 5,6,7,8-tetrahydro-5-oxo-2-quinolones, mentioned above, have been obtained. A summary of the chemical shifts is presented in Table II.

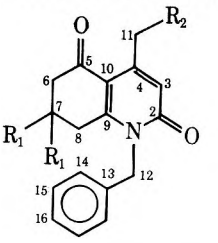
From examination of the data in Table II, it can be seen that the carbonyl carbon at position 5 is the signal which appears at lowest field (δ 195 ppm) and which undergoes the smallest change on transformation of the 5-oxocoumarin chromophore to the 5-oxo-2-quinolone moiety. The methyl ester carbonyl was more strongly deshielded than either the coumarin (δ 159 ppm) or the 2-quinolone (δ 162 ppm) carbonyl. These trends are in complete agreement with the chemical shifts of a number of α-pyridones, α-pyrones, and coumarins which have been reported recently in the literature.[11,12,16] Further support for the assignments made in Table II was obtained by examination of the partially proton coupled spectra of **4b** and **10b;** the multiplicities observed in the carbon spectra were exactly those predicted for methyl, methylene, and methine carbon atoms contained in heterocycles such as **4b** and **10b.**

The magnitude of the chemical shift at carbon 9 upon going from 5-oxocoumarin to 5-oxo-2-quinolone derivatives (i.e., **4a** → **10a,** Δ 17 ppm), as illustrated in Chart II, indicated that this position was a more sensitive probe for predicting the presence

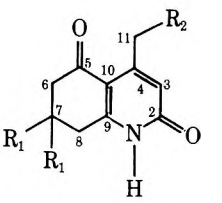
Table II. ^{13}C NMR Chemical Shifts[d]



4a, R_1 = H; R_2 = $COOCH_3$
b, R_1 = CH_3; R_2 = $COOCH_3$
c, R_1 = R_2 = H



10a, R_1 = H; R_2 = $COOCH_3$
b, R_1 = CH_3; R_2 = $COOCH_3$
d, R_1 = R_2 = H

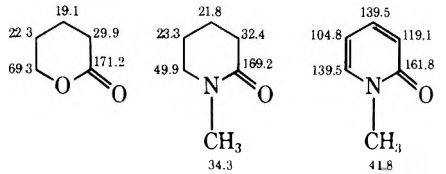


12a, R_1 = H;
R_2 = $COOCH_3$

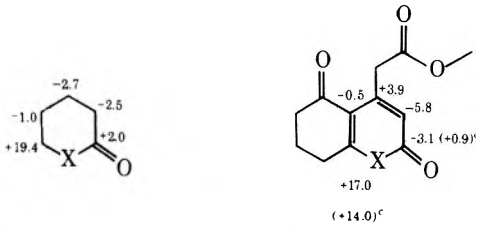
	4a	4b[b]	4c	10a	10b[b]	10d	12a[c]
2	159.1	159.4	159.5	162.2	162.3	162.0	164.7
3	115.4	115.1 d	113.0	121.2	120.8 d	118.9	120.7
4	150.4	150.2	156.2	146.5	146.2	151.9	149.5
5	195.4	195.4	195.4	195.5	195.5	195.5	195.2
6	38.0	51.9 t	38.6	37.7	51.2 t	38.2	38.7
7	19.6	31.8	19.7	20.8	31.9	20.8	20.8
R_1 = CH_3		28.0 q			27.9 q		
8	29.0	42.6 t	29.1	28.2	41.6 t	28.2	28.2
9	175.2	173.7	174.7	158.2	156.7	157.7	157.4
10	114.0	113.1	114.8	114.5	113.6	115.3	114.0
11	40.3	40.2 t	22.7	41.5	41.3 t	23.4	41.3
C=O, ester	169.2	169.7		170.8	170.6		170.6
OCH_3	52.1	52.1 q		51.9	51.8 q		52.0
12				47.2	46.9 t	46.8	
13				135.4	135.5	135.7	
14				126.3	126.0	126.1	
15				129.1	128.9	128.8	
16				127.8	127.6	127.6	

[a] $CDCl_3$ solvent, $(CH_3)_4Si$ internal standard. [b] Partially proton coupled multiplicities. [c] This spectrum courtesy of Professor Hutchinson, University of Wisconsin, School of Pharmacy. [d] Registry no.: 4a, 61062-39-3; 4b, 610 62-4-6; 4c, 3265-68-7; 10a, 61062-41-7; 10b, 61062-42-8; 10d, 61076-92-4; 12a, 61062-43-9.

Chart II. ^{13}C NMR Chemical Shifts



13[a] 14[a] 15[b]



$\Delta(\delta)$ X = O ⟶ X = NCH_3 $\Delta(\delta)$ X = O ⟶ X = NBz
13 14 4a 10a

[a] See ref 12. [b] See ref 16. [c] The shifts for carbon atoms 2 and 9 in 10a are very close and could be interchanged. The numbers in parentheses reflect this possibility: (+) upfield shift, (−) downfield.

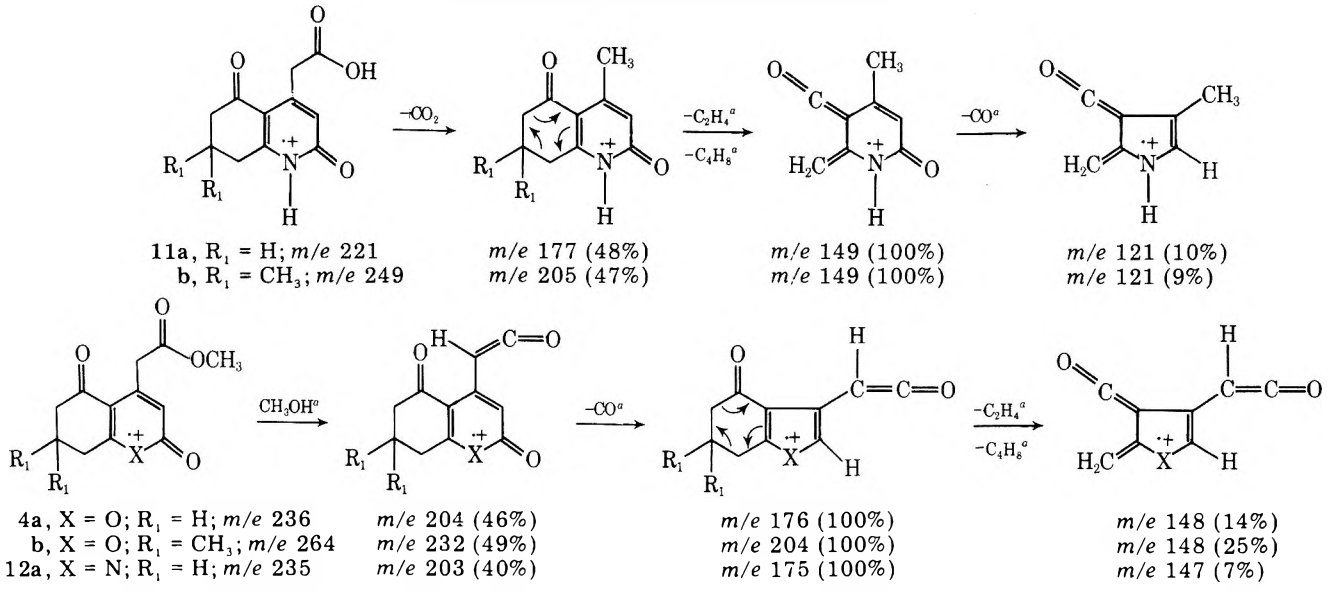
of nitrogen than either the change in carbonyl chemical shift at carbon 2 (3.1 ppm) or the change in the methine chemical shift at carbon 3 (5.8 ppm).

In a recent study, Hirsch[12] examined the ^{13}C NMR chemical shifts for the carbon atom α to the heteroatom in 1-hetero-2-cyclohexanones by comparison of the spectra of **13** and **15** with that of cyclohexanone.[12] He reported that the effect of a nitrogen heteroatom on the electron density of the carbon atoms in a six-membered heterocycle is best described as a through-bond inductive effect,[12,17,18] although the effect could also be explained from dipole-induced σ-polarization in combination with changes in nitrogen hybridization.[12] The magnitude of the substituent effect on the α carbon was O ≫ NCH_3 > NBz > NH. In the series of compounds described in Table II the substituent effect was O ≫ NBz > NH, which is in accord with the results for the saturated system.[12] This must indicate that a similar effect is influencing the electron density at the α-carbon atom (carbon 9) in the coumarin and 2-quinolone derivatives. The shifts outlined in Chart II demonstrate, at least qualitatively, that the changes in chemical shift α and β to the heteroatom in the saturated (**13** → **15**) and unsaturated (**4a** → **10a**) systems agree reasonably well.

The mass spectra of the tetrahydro-5-oxocoumarin and tetrahydro-5-oxo-2-quinolones showed a unique substituent effect on the mode of fragmentation of these heterocycles. The initial decomposition of the parent ion proceeded from the side chain attached to carbon 4. When the free acid was present (see Scheme III), as in **11a** or **11b**, the molecular ion lost the elements of carbon dioxide to provide a 4-methyl-α-pyridone (*m/e* 177, from **11a**) which then underwent a retro-Diels–Alder reaction to yield the base peak at *m/e* 149.[19] Extrusion of carbon monoxide, typical of α-pyridones,[20] then furnished the ion found at *m/e* 121 mass units.

When the side chain was substituted as a methyl ester, as in **4a, 4b,** or **12a,** the parent ion decomposed to furnish what can best be described as a ketene intermediate by loss of methanol in either a concerted or two-step elimination process. The new fragment (from the loss of methanol) then preferentially lost the carbonyl group at C-2 to give an ion represented by the furan (*m/e* 176) in the case of **4a,** or the pyrrole (*m/e* 175) in the case of the 2-quinolone (**12a**). The tetrahydrofuran and pyrrole species then underwent a retro-Diels–Alder reaction to provide the five-membered

Scheme III. Mass Spectral Fragmentation Scheme for the Tetrahydro-5-oxocoumarin and Tetrahydro-5-oxo-2-quinolone Derivatives



[a] Metastables were observed.

heterocyclic ions at *m/e* 148 (from **4a** or **4b**) or at *m/e* 147 (from **12a**).

The interesting feature of the mass spectra of these tetrahydro-5-oxo compounds was the observed order of fragmentation. Thus, the 4-methyl-5-oxo-2-quinolones (formed from the free acids) lost the 2-keto group after the retro-Diels–Alder reaction in ring A, while the ketene derivatives (formed from the methyl esters) first extruded the carbonyl group and then underwent the retro-Diels–Alder reaction.

The reaction of cyclohexane-1,3-dione with dimethyl β-ketoglutarate (**1**), followed by treatment of the product with amines, furnishes a general route to 5,6,7,8-tetrahydro-5-oxo-2-quinolones, with the possibility of further functionalization via the acetic ester group at carbon atom 4. No other sequence found in the literature offers this possibility. The symmetry of dimethyl β-ketoglutarate permits this procedure to be carried out with few side products, in contrast to similar reactions performed with ethyl acetoacetate. The sequence described here appears to be a useful procedure to obtain 4-alkyl carbostyrils and work is in progress to convert the tetrahydro-5-oxo compounds to 4-alkyl-5-hydroxycarbostyrils.

Experimental Section

Microanalyses were performed on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and CFT-20 spectrometers with $(CH_3)_4Si$ internal standard. All mass spectra were taken on either a Hitachi Perkin-Elmer RMU-6 or AEI MS 902 instrument. Infrared spectra were obtained on a Beckman IR-8 in either chloroform or KBr. Analytical TLC was performed on EM precoated sheets, silica gel F-254, 0.25 mm thickness while column chromatography was carried out with Baker Analyzed silica gel 60–200 mesh.

Dimedone, cyclohexane-1,3-dione, dimethyl β-ketoglutarate, and *N*-benzylamine were purchased from Aldrich Chemical Co. The citrate–phosphate buffer (pH 6.8) was prepared by dissolving $Na_2HPO_4 \cdot 7H_2O$ (2.60 g) and citric acid (0.82 g) in water (200 ml).

Methyl 5,6,7,8-Tetrahydro-5-oxocoumarin-4-yl Acetate (4a). Cyclohexane-1,3-dione (**2a**, 22.4 g, 0.20 mol) was dissolved in citrate–phosphate buffer (400 ml, pH 6.8) and stirred for 10 min. To this solution dimethyl β-ketoglutarate (**1**, 104.4 g, 0.60 mol) was added and after 20 min the cloudy solution became clear. The reaction mixture was stirred at room temperature for 60 days. After 20 days the mixture was seeded with **4a** and crystals precipitated from the solution. The white solid was filtered off and the filtrate allowed to stir for the remaining 40 days. Crystals were again filtered from the reaction at the end of the 60-day period. The combined precipitates were recrystallized from methanol to furnish **4a** (26.0 g) in 55% yield. An additional 7 g of **4a** could be obtained by extraction of the filtrate with chloroform, concentration to small volume, and column chromatography of the residue on silica gel: overall yield 33.0 g, 70% yield; mp 123–125 °C; UV λ_{max} (CH_3OH) 260 nm (log ε 4.06), 295 (3.74); IR ($CHCl_3$) 1739 (s), 1682 (s), and 1628 cm^{-1} (w); NMR ($CDCl_3$) δ 2.16 (m, 2 H, *J* = 6 Hz), 2.53 (t, 2 H, *J* = 6 Hz), 2.90 (t, 2 H, *J* = 6 Hz), 3.72 (s, 3 H, OCH_3), 3.80 (s, 2 H), and 6.03 (s, 1 H); mass spectrum (80 eV) *m/e* 236 (M^+, 12), 208 (6), 205 (22), 204 (46), 177 (22), 176 (100), 152 (10), 149 (18), 148 (14), 120 (6).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.28; H, 5.28.

Methyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxocoumarin-4-yl Acetate (4b). Dimedone (**2b**, 10.0 g, 0.071 mol), tetrahydrofuran (150 ml), methanol (20 ml), and **1** (26.5 g, 0.154 mol) were dissolved in citrate–phosphate buffer (200 ml, pH 6.8). The solution was stirred for 44 days at room temperature and then extracted with chloroform (4 × 200 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. After the chloroform solution was cooled for several days, a white, crystalline solid (**4b**, 5.41 g) precipitated and was filtered from the solution. The filtrate was concentrated under reduced pressure and the residue chromatographed on silica gel (Skelly B, benzene, ethyl acetate, gradient elution) to provide an additional 5.16 g of **4b**: combined yield of **4b** 10.57 g (56%); mp 115–116 °C (recrystallized from benzene); UV λ_{max} (CH_3OH) 263 nm (log ε 3.97), 299 (3.72); IR ($CHCl_3$) 1739 (s), 1680 (s), and 1630 cm^{-1} (w); NMR ($CDCl_3$) δ 1.12 (s, 6 H), 2.36 (s, 2 H), 2.75 (s, 2 H), 3.65 (s, 3 H), 3.80 (s, 2 H), and 5.98 (s, 1 H); mass spectrum (80 eV) *m/e* 265 (3), 264 (M^+, 15), 236 (7), 233 (13), 149 (5), 148 (25), 93 (8).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.35; H, 6.16.

4-Methyl-5,6,7,8-tetrahydro-5-oxocoumarin (4c). Cyclohexane-1,3-dione (**2a**, 20.0 g, 0.18 mol) and **1** (93.4 g, 0.53 mol) were dissolved in citrate–phosphate buffer (400 ml, pH 6.8) and the mixture was stirred at room temperature for 64 h. The reaction mixture was then heated for 21 h, after which time it was cooled and extracted with chloroform (3 × 300 ml) followed by reextraction of the aqueous layer with benzene (3 × 300 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The oily residue was chromatographed on silica gel (Skelly B, benzene, ethyl acetate, gradient elution) to provide **4a** (10.6 g, 25%) and **4c** (6.4 g, 20%). The oil (**4c**) was dissolved in water from which white crystals precipitated: mp 98–99.5 °C (lit.[5] 98 °C); UV λ_{max} (CH_3OH) 261 nm (log ε 3.99), 299 (3.63); IR ($CHCl_3$) 1739 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (m, 2 H, *J* = 6 Hz), 2.45 (s, superimposed on a triplet, 5 H), 2.85 (t, 2 H, *J* = 6 Hz), and 5.96 (s, 1 H); mass spectrum (80 eV) *m/e* 178 (M^+, 43), 150 (72), 122 (100).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.67. Found: C, 67.42; H, 5.97.

Conversion of 4a to 4c by Acid Hydrolysis. Methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (**4a**, 5.0 g, 0.021 mol) was dissolved in a solution of hydrochloric acid (12 N, 40 ml) and glacial acetic acid (50 ml) and the solution was refluxed for 24 h. The acidic solution was made basic (pH 8) with sodium hydroxide (3 N) and then extracted with chloroform (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to yield **4c** (1.5 g, mp 98 °C, 41% yield), identical in all respects with **4c** isolated in the previous experiment.

Preparation of Ethyl 1,2,3,4,5,6,7,8-Octahydro-9-methyl-1,8-dioxoxanthen-9-yl Acetate (9a) and (4c) from Ethyl Acetoacetate (8) and Cyclohexane-1,3-dione at pH 6.8. Cyclohexane-1,3-dione (60 g, 0.54 mol) was dissolved in citrate–phosphate buffer (1200 ml, pH 6.8). To the resulting cloudy solution, 8 (200 g, 1.54 mol) was added over a 2-min period. The turbid solution became clear and the mixture was allowed to stir at room temperare for 45 days. TLC indicated the presence of **4c** after 1 day. A small portion (200 ml) of the reaction mixture was taken out after 3 days and extracted with chloroform to furnish, after chromatography, a small amount of **4c**, mp 98 °C. The remainder of the mixture was allowed to stir until the 45-day period had ended. Crystals of **9a**, which formed in the reaction after 30 days, were filtered from the solution and were recrystallized from methanol: mp 160 °C; UV λ_{max} (CH_3OH) 304 nm (log ε 3.67), 229 (4.17); IR (KBr) 1730 (s), 1668 (s), 1610 (m), and 1125 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 1.63 (s, 3 H), 1.98 (m, 4 H, J = 6 Hz), 2.37 (q, 8 H, J = 6 Hz), 3.33 (s, 2 H), and 3.97 (q, 2 H, J = 7 Hz); mass spectrum (80 eV) m/e 318 (M^+, 1). The yield was 50% and no attempt has been made to maximize it.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.95; H, 7.18.

Methyl 1-Benzyl-5,6,7,8-tetrahydro-5-oxo-2-quinolon-4-yl Acetate (10a). In a round-bottom flask (100 ml) equipped with a magnetic stirrer, Dean-Stark trap, and condenser were placed **4a** (3.0 g, 0.013 mol), benzylamine (13.6 g, 0.13 mol), and dry benzene (30 ml). The reaction mixture was refluxed for 17 h, cooled, and then extracted with hydrochloric acid (3 × 50 ml of 10%), aqueous potassium carbonate (3 × 50 ml), and water (2 × 50 ml), respectively. The organic phase was dried (K_2CO_3) and filtered over Norit (1 g) and the solvent was removed under reduced pressure to provide a brown oil. The oil was chromatographed over silica gel (benzene, methanol, gradient elution) to yield **10a** (1.70 g, 45% yield): mp 106.5–110.0 °C (from Skelly B–ethyl acetate, 1:1); UV λ_{max} (CH_3OH) 282 nm (log ε 4.09), 3.08 (sh), 322 (sh); IR ($CHCl_3$) 1739 (m) and 1664 cm^{-1} (s); NMR ($CDCl_3$) δ 2.05 (m, 2 H, J = 6 Hz), 2.43 (t, 2 H, J = 6 Hz), 2.87 (t, 2 H, J = 6 Hz), 3.70 (s, 3 H), 3.83 (s, 2 H), 5.36 (s, 2 H), 6.37 (s, 1 H), and 7.23 (m, 5 H); mass spectrum (80 eV) m/e (rel intensity) 326 (44), 325 (M^+, 100), 324 (15), 294 (37), 293 (31), 266 (16), 265 (35), 235 (7), 234 (36), 219 (14).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.84; H, 5.69; N, 4.24.

The yields in refluxing benzene were generally quite low; however, merely stirring a 1:1 mixture of **4a** and benzylamine at room temperature in methanol for 6 days, followed by column chromatography on silica gel, provided 65–80% yield of **10a**. Some starting material was also recovered.

Methyl 1-Benzyl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-yl Acetate (10b). This reaction was carried out in refluxing benzene (15 ml) with **4b** (3.83 g, 0.014 mol) and benzylamine (3.10 g, 0.029 mol) under analogous conditions to that described in the previous experiment. A red oil was obtained which was chromatographed on silica gel (benzene, methanol gradient elution) to furnish **10b** (2.22 g, 45%) and **10c** (0.407 g, 8.5%).

The quinolone derivative (**10b**) was obtained as a white, crystalline solid: mp 141–143 °C (from Skelly B–ethyl acetate, 1:1); UV λ_{max} (CH_3OH) 282 nm (log ε 4.29), 308 (sh), and 323 (sh); IR ($CHCl_3$) 1739 (m) and 1662 cm^{-1} (s); NMR ($CDCl_3$) δ 0.93 (s, 6 H), 2.32 (s, 2 H), 2.72 (s, 2 H), 3.68 (s, 3 H), 3.88 (s, 2 H), 5.40 (s, 2 H), 6.38 (s, 1 H), and 7.25 (m, 5 H); mass spectrum (80 eV) m/e 353 (M^+, 100); CI mass spectrum (NH_3) m/e (rel intensity) 371 (M + 18, 1.9), 356 (7), 355 (30), 354 (M + 1, 100), 353 (2.5), 297 (26), and 296 [(M + 1) − 58, 45].

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.57; N, 3.66.

The structure of **10c** was deduced by comparison of the ^1H NMR with that of **10b** and the mass spectrum of **10c**: m/e (rel intensity) 429 (12), 428 (M^+, 35), 413 (4), 410 (4), 395 (7), 323 (8), 322 (25), 321 (53), 307 (4), 306 (12), 295 (14), 294 (8), 293 (15), 280 (8), 204 (8), 107 (3), 106 (20), 92 (12), 91 (100).

1-Benzyl-4-methyl-5,6,7,8-tetrahydro-5-oxo-2-quinolone (10d). *N*-Benzylamine (0.61 g, 0.0057 mol) and **4c** (1.01 g, 0.0057 mol) were dissolved in benzene (30 ml) and the resulting solution was refluxed for 24 h. The water was removed by means of a Dean-Stark trap. The reaction mixture was cooled and an additional amount of benzylamine (0.63 g) was added. The reaction mixture was refluxed for another 6 h and cooled and the benzene removed under reduced pressure. A red oil remained, which was subjected to column chromatography on silica gel (benzene, methanol, gradient elution) to remove decomposition products. The yellow glassy oil was rechromatographed on silica gel (CH_2Cl_2) to remove **4c** and then distilled, bp 119 °C (0.1 Torr), to provide **10d** (1.13 g, 74% yield) which later crystallized from methanol: mp 81–83 °C; UV λ_{max} (CH_3OH) 281 nm (log ε 4.2); IR ($CHCl_3$) 1680 (s) and 1660 cm^{-1} (s); NMR ($CDCl_3$) δ 1.90 (m, 2 H, J = 6 Hz), 2.43 and 2.50 (overlapping triplet and singlet, 5 H), 2.82 (t, 2 H, J = 6 Hz), 5.36 (s, 2 H), 6.33 (s, 1 H), and 7.23 (m, 5 H); Mass spectrum m/e 267 (M^+).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.35; H, 6.30; N, 5.04.

5,6,7,8-Tetrahydro-5-oxo-2-quinolon-4-ylacetic Acid (11a). Diethyl ether (100 ml), methanol (50 ml), and the 5-oxocoumarin derivative **4a** (11.31 g, 0.048 mol) were placed in a round-bottom flask (250 ml) equipped with magnetic stirrer, condenser, and gas inlet tube. Ammonia gas was bubbled into the solution for 15 min until a chalky white precipitate formed, at which time TLC indicated that starting material was no longer present. The white solid was filtered from the solution, washed with aqueous HCl (10%), and recrystallized from aqueous hydrochloric acid (10%) to provide white needles of **11a** (9.55 g, 90% yield): mp 272 °C dec; UV λ_{max} (CH_3OH) 280 nm (log ε 4.18) and 317 (sh); IR (KBr) 2985 (s), 1718 (s), 1639 (s), 1586 cm^{-1} (sh, m); mass spectrum (80 eV) m/e (rel intensity) 221 (M^+, 3), 205 (8), 203 (3), 177 (48), 176 (5), 175 (8), 150 (10), 149 (100), 121 (10), 94 (9), 93 (16), 44 (35).

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found C, 59.70; H, 5.07; N, 6.50.

5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-ylacetic Acid Hydrochloride (11b). The 7,7-dimethyl-5-oxocoumarin derivative **4b** (1.85 g, 0.007 mol) was dissolved in a solution of anhydrous ether (50 ml) and methanol (25 ml) in a setup analogous to the previous experiment. Ammonia (anhydrous) gas was bubbled in for 45 min at which time TLC indicated that **4b** had been completely consumed. A white precipitate was filtered from the reaction, dissolved in water, and reprecipitated by addition of aqueous, *concentrated* hydrochloric acid. The crystals of **11b** (1.38 g, 74% yield) resembled clear plates: mp 237 °C (changes from white to brown crystals which are stable to >289 °C); UV λ_{max} (CH_3OH) 282.5 nm (log ε 4.14) and 317 (sh); IR (KBr) 3479 (s), 3409 (sh, s), 2894 (s), 1716 (s), 1637 (s), 1496 (sh, s), 1466 (w); mass spectrum (80 eV) m/e (rel intensity) 249 (M^+, 3) 231 (3), 205 (49), 204 (6), 203 (10), 177 (6), 150 (11), 149 (100), 121 (9), 93 (12), and 44 (23).

Anal. Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64. Found: C, 54.50; H, 5.42.

Yields up to 80% were also obtained from this reaction.

This 2-quinolone was converted to its methyl ester (see below).

Methyl 5,6,7,8-Tetrahydro-5-oxo-2-quinolon-4-yl Acetate (12a). The acid **11a** (5.23 g, 0.024 mol) was dissolved in methanolic HCl and the solution refluxed for 20 h. The methanol was removed under reduced pressure and the residue was taken up in methylene chloride. The organic layer was washed with aqueous potassium carbonate (3 × 50 ml) and water (50 ml) and then dried ($MgSO_4$). The methyl ester (**12a**) crystallized from the solution as a white powder (2.92 g, 52% yield), mp 223–224 °C. An additional 2.2 g of **12a** could be obtained by column chromatography over silica gel: overall yield 92%; UV λ_{max} (CH_3OH) 281 nm (log ε 4.28), 303 (sh), and 317 (sh); IR (KBr) 3400 (broad), 1733 (s), 1632 (s), 984 (m), and 712 cm^{-1} (m); NMR ($CDCl_3$) δ 2.13 (m, 2.5 H, J = 6 Hz), 2.52 (t, 2 H, J = 6 Hz), 2.95 (t, 2 H, J = 6 Hz), 3.71 (s, 3 H), 3.85 (s, 2 H), 6.20 (s, 1 H), and 13.16 (0.5 H) (addition of D_2O reduced the integration of the signal at δ 2.13 to two protons and eliminated the signal at δ 13.16); mass spectrum (80 eV) m/e (rel intensity) 235 (M^+, 21), 204 (20), 203 (40), 176 (30), 175 (100), 149 (7), 148 (7), 147 (7), 120 (8), 119 (10).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.50; H, 5.31; N, 5.91.

Methyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2-quinolon-4-yl Acetate (12b). This reaction was run under the conditions described above with **11b** (0.650 g, 0.0026 mol) and methanolic HCl (40 ml). The same workup procedure provided **12b** as a white powder (0.416 g, 61% yield). The yield could be increased to 80% by chromatography of the mother liquors on silica gel. **12b:** mp 199–201 °C; UV λ_{max} (CH_3OH) 281 nm (log ε 4.22), 302 (sh), and 316 (sh); IR (KBr); 1730 (s), 1660 (very strong), 1606 (w), 1421 (s), and 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (s, 6 H, also a broad band integrating for 1 H appeared in this region), 2.37 (s, 2 H), 2.83 (s, 2 H), 3.67 (s, 3 H), 3.84 (s, 2 H), and 6.22 (s, 1 H);

mass spectrum *m/e* (rel intensity) 263 (M^+, 20), 232 (27), 231 (73), 217 (27), 216 (94), 204 (27), 203 (100), 189 (13), 188 (73), 175 (20), 147 (10).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.05; H, 6.45; N, 5.21.

Registry No.—**1**, 1830-54-2; **2a**, 504-02-9; **2b**, 126-81-8; **8**, 141-97-9; **9a**, 61062-44-0; **10c**, 61104-46-9; **11a**, 61062-45-1; **11b**, 61062-46-2; **12b**, 61062-47-3.

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Alkylations of 1-(4-Chlorophenyl)-3-ethoxy-1*H*-isoindole

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Abstraction of the benzylic proton from 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1a**) with sodium hydride gave the corresponding carbanion which was alkylated with a variety of alkyl halides to give the imino esters **1d–i**, **5** while oxidation yielded **1b**. Hydrolysis led to the lactams **2d–i**, **6** and 2-(4-chlorobenzoyl)benzoic acid ethyl ester, respectively. The tetrazolo compounds **4e–l** were prepared via the intermediates **3e–i**. Heating of **6** resulted in the formation of **7a** which could be reduced to the amine **7b**. From the imino ester **5** the triazole **9** was prepared.

Recently we have described the preparation of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1a**) and its conversion to 1-amino-4-(4-chlorophenyl)phthalazine[1] via reaction with hydrazine. As a continuation of our efforts to explore the synthetic usefulness of **1a** we have prepared[2] a variety of 3-alkylated derivatives and converted them to the novel tricyclic systems.

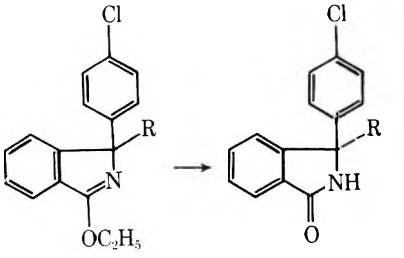
The proton of the benzylic position of **1a** was abstracted by sodium hydride in an aprotic solvent (DMF) to generate the corresponding carbanion of **1a**. Treatment of the carbanion with oxygen led to the crystalline hydroxy imino ester **1b** in 43% yield. For structure proof, **1b** was hydrolyzed to the known 2-(4-chlorophenyl)benzoic acid ethyl ester.[3] Spectral data indicated that **1b** exists in the cyclic form; no absorption for the open benzophenone tautomer was observed in the IR spectrum of **1b** (Nujol) in the region between 1650 and 1700 cm^{-1}. Furthermore, the UV spectrum of **1b** closely resembles that of the known methoxy homologue **1c**.[4]

The carbanion of **1a** on treatment with alkyl halides, e.g., methyl iodide, propargyl bromide, allyl bromide, isopropyl iodide, and benzyl chloride, gave the alkylated analogues **1e–i** (Tables II–IV). Reaction with methylene chloride led in good yield to **1d**, which was found to be inert in the presence of excess of carbanion.

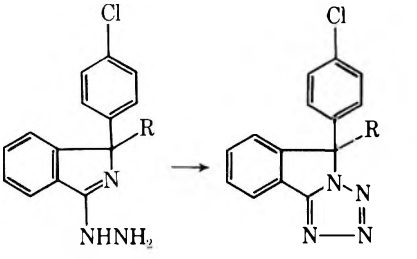
The substituted 1-alkyl-1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindoles **1d–i** on treatment with hydrochloric acid in ethanol were hydrolyzed to the corresponding 1-alkyl-1-(4-chlorophenyl)phthalimidines **2d–i**.[5a,b]

While the reaction of 1-(4-chlorophenyl)-3-ethoxy-1*H*-

Scheme I



1a–i **2d–i**



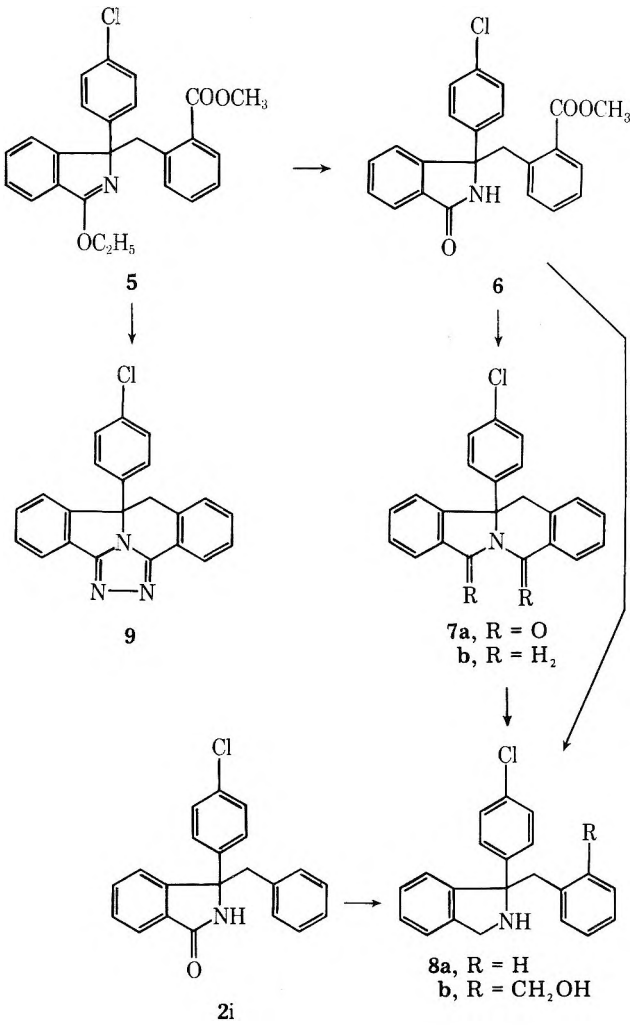
3e–i **4e–i**

a, R = H
b, R = OH
c, R = OCH_3
d, R = CH_2Cl
e, R = CH_3
f, R = $CH_2C{\equiv}CH$
g, R = $CH_2CH{=}CH_2$
h, R = *i*-C_3H_7
i, R = $CH_2C_6H_5$

isoindole (**1a**) with hydrazine led to 1-amino-4-(4-chlorophenyl)phthalazine,[1] the alkylated imino esters **1e–i** gave with hydrazine the 3-hydrazinoisoindoles **3e–i**. To ascertain that these reactions proceeded without rearrangement the hydrazinoisoindoles **3e–i** were cyclized[6] to the corresponding tetrazolo[5,1-*a*]isoindoles **4e–i**. Analytical and spectral data agreed with the proposed structures.

Treatment of the carbanion of **1a** with α-bromo-*o*-toluic acid methyl ester[12] gave the imino ester **5** as a liquid which was characterized by NMR and IR spectral data. After hydrolysis of **5** under acidic conditions the crystalline phthalimidine **6** was obtained in 46% overall yield. Pyrolysis of this ester lactam at 240 °C led to the tetracyclic imide **7a**, which was readily reduced to the tertiary amine **7b** in the presence of diborane. However, attempts to reduce the imide **7a** in the presence of lithium aluminum hydride gave the amino alcohol **8b**. The

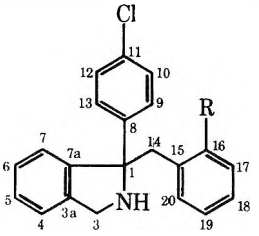
Scheme II



structure was assigned based on a comparative study of the ^{13}C NMR spectrum of **8b** with that of **8a**, a compound obtained from the reduction of **2i**. The chemical shifts of **8a** were assigned based on data available from the literature.[8a–c] The chemical shifts for the fully substituted aromatic carbons and all aliphatic carbons of **8a** are listed (see Table I) in juxtaposition to the corresponding values observed for the amino alcohol **8b**. The deviations are ≤0.4 ppm for the carbons 1–13, for which no changes are anticipated. The carbons 14–21 show the expected shifts due to the introduction of the hydroxymethyl group on C-16. The chemical shifts for the remaining aromatic carbons have been tentatively assigned as well.

For additional support of the assigned structure **8b**, we have reduced **6** in the presence of lithium aluminum hydride first at room temperature and then at elevated temperature. The reduction product was found to be identical with **8b** in every respect.

Table I. ^{13}C NMR Spectra of Compounds 8a and 8b



8a, R = H
b, R = CH_2OH (21)

8a			8b		
Absorption obsd, ppm	Rel intensity	Assignment	Absorption obsd, ppm	Rel intensity	Assignment
147.6	24	C-8	147.5	26	C-8
145.8	31	C-7a	146.1	35	C-7a
142.3	20	C-3a	142.1	35	C-3a
			141.6	38	C-16
137.6	50	C-15	135.7	52	C-15
131.3	21	C-11	131.4	20	C-11
130.7	219	C-16, 20	130.7	98	C-20
			129.0	100	C-17
128.7	170	C-10, 12	128.7	217	C-10, 12
128.0	166	C-9, 13	128.2	210	C-9, 13
127.9	189	C-17, 19			
127.2	112	C-6	127.4	126	C-6
			127.0	134	C-19
126.8	99	C-18	126.5	158	C-5, 18
126.4	89	C-5			
123.3	77	C-7	123.7	134	C-7
122.6	104	C-4	122.5	104	C-4
72.3	23	C-1	72.3	41	C-1
			61.7	150	C-21
50.5	110	C-3	50.6	125	C-3
46.9	103	C-14	43.0	135	C-14

The dual functionality of **5** prompted us to investigate the feasibility of a synthesis of the pentacyclic triazole **9**. We were successful in isolating the desired compound from **5** in the presence of hydrazine, albeit in low yield (10%). The product was obtained as a colorless solid and was fully characterized by spectral and analytical data.

Discussion

The NMR spectra of the compounds described in this paper exhibited the expected patterns[9,10] for the protons of the newly introduced side chains. Since spectral data for 2-benzyl-3-phenylphthalimide had been published,[9a] a direct comparison seemed of interest. For the *N*-benzyl case a difference in chemical shift of 1.75 ppm was observed for the two diastereotopic protons. In the case of our 3-benzyl-3-(4-chlorophenyl)phthalimidine (**2i**) a difference of only 7.5 Hz (0.125 ppm) was recorded and this despite the fact that the benzylic protons are located closer to the center of chirality than in the case of the *N*-benzyl compound. In accordance with the model[9a] both benzylic protons of **2i** are deshielded by the phenyl group in position 3 of the phthalimidine. It may therefore be concluded that in the lowest energy conformation the 1,2-diphenylethane portion of **2i** lies in a plane in an antiperiplanar arrangement with the chlorophenyl ring in and the phenyl ring perpendicular to the plane.

Compound **6** may be cited to illustrate this point further. The additional carbomethoxy group would preclude the presence of a "plane of symmetry" as defined above. That this is indeed the case may be concluded from the observation of

a quartet in the NMR spectrum of **6** centered at δ 4.04 ppm with a separation of the two doublets by 27.6 Hz (0.46 ppm).

A similar deshielding effect was observed for the chloromethyl compound **2d**. In this case a quartet centered at δ 4.19 ppm was observed, the two doublets being separated[11] by ($\Delta\nu$) 25.75 Hz (0.43 ppm).

Diastereotopic methyl groups[10] were observed in the NMR spectra of **2h**, **3h**, and **4h**. The largest degree of separation for the methyl groups in this series of compounds was recorded for the tetrazolo compound **4h**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. NMR spectra were measured on either a Varian A-60 and/or T-60 spectrometer and are recorded in δ (ppm) values from Me_4Si as internal standard. ^{13}C NMR spectra were measured on a Varian XL-100 spectrometer and are recorded in parts per million values from Me_4Si as internal standard. UV absorption spectra were measured in ethanol on a Cary spectrometer, Model 14. IR spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 chromatograph. Mass spectra were taken on a LKB 9000 mass spectrometer.

3-Ethoxy-1-hydroxyl-1-(4-chlorophenyl)-1*H*-isoindole (1b). To the solution of 1.5 g (0.005 mol) of imino ester **1a** in 40 ml of absolute DMF there was added a catalytic amount (25 mg) of NaH to give a dark brown solution. The mixture was stirred at room temperature and treated with a stream of dry air during 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water and extracted with methylene chloride. The solvent was evaporated to give 0.85 g of crude **1b** which was recrystallized from ethanol: yield 0.7 g (43%); mp 189–191 °C; *m/e* 287 (M^+); NMR ($CDCl_3$ + Me_2SO) δ 1.47 (t, 3, J = 7 Hz, CH_3) 4.6 (q, 2, J = 7 Hz, OCH_2), 6.7 (s, 1, exchangeable with D_2O, OH), 7.2–7.7 (m, 8, 2 C_6H_4); IR (Nujol) 3100 (OH), 1623 (C=N), 1580 cm^{-1}; UV 217 nm (ε 12 500), 325 (3500).

Anal. Calcd for $C_{16}H_{14}ClNO_2$ (287.8): C, 66.8; H, 4.9; N, 4.9; Cl, 12.3. Found: C, 66.8; H, 5.1; N, 4.8; Cl, 12.3.

Hydrolysis of 1b to 2-(4-Chlorobenzoyl)benzoic Acid Ethyl Ester. A mixture of 1.0 g (0.003 mol) of the imino ester **1b** and 1.0 ml of 1 N HCl solution in 30 ml of ethanol was heated to reflux for 3 h. The solid that precipitated from the cold solution was filtered off and recrystallized from ethanol to give 0.7 g (70%) of the benzoylbenzoic acid ethyl ester: mp 85–86 °C (lit.[4] mp 88 °C); *m/e* 288 (M^+); NMR ($CDCl_3$ + Me_2SO) δ 1.13 (t, 3, J = 7 Hz, CH_3), 4.16 (q, 2, J = 7 Hz, CH_2), 7.3–7.9 (m, 7, aromatic), 8.0–8.4 (m, 1, C_6H_1); IR (CH_2Cl_2) 1712 (COOEt), 1672 cm^{-1} (C=O).

1-Chloromethyl-1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (1d). To the stirred suspension of 3.4 g (0.08 mol) of sodium hydride in 50 ml of absolute DMF a solution of 21.0 g (0.08 mol) of **1a** in 250 ml of DMF was added dropwise. The dark solution was kept at room temperature under an atmosphere of nitrogen for 2 h. Then 10.2 g (0.12 mol) of methylene chloride was added to the mixture and stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the residue dissolved in methylene chloride and worked up in the usual way. The crude product (26 g) was chromatographed on silica gel to give 18.8 g (73%) of the product **1d** as a liquid: NMR ($CDCl_3$) δ 1.47 (t, 3, J = 7 Hz, CH_3), 4.06 (q, 2, J = 11 Hz, $\Delta\nu$ = 10.2 Hz, CH_2Cl), 4.56 (q, 2, J = 7 Hz, OCH_2), 7.1–7.8 (m, 8, 2 C_6H_4); IR (CH_2Cl_2) 1622 cm^{-1} (C=N).

3-Chloromethyl-3-(4-chlorophenyl)phthalimidine (2d). A mixture of 4.0 g (0.01 mol) of the imino ester **1d**, 75 ml of ethanol, and 4 ml of 2 N HCl was heated on the water bath during 3 h. From the cold solution 3.0 g (80%) of **2d** precipitated, mp 160–163 °C. A sample was recrystallized from methylene chloride/hexane: mp 165–167 °C; *m/e* 291 (M^+), 242 ($M^+ - CH_2Cl$); NMR ($CDCl_3$) δ 4.19 (q, 2, J = 11 Hz, $\Delta\nu$ = 24.7 Hz, CH_2Cl), 7.1–7.7 (m, 7, C_6H_4 + C_6H_3), 7.7–8.0 (m, 1, C_6H_1), 8.25 (broad, 1, NH); IR (CH_2Cl_2) 3420 (NH), 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{11}Cl_2NO$ (292.2): C, 61.7; H, 3.8; N, 4.8; Cl, 24.3. Found: C, 61.8; H, 3.8; N, 4.8; Cl, 24.6.

1-(4-Chlorophenyl)-3-ethoxy-1-[2-(methoxycarbonyl)benzyl]-1*H*-isoindole (5). To the stirred suspension of 2.64 g (0.11 mol) of sodium hydride in absolute DMF there was added dropwise a solution of 21.6 g (0.08 mol) of **1a** in 250 ml of absolute DMF. After 2 h at room temperature and under an atmosphere of nitrogen 26.0 g (0.11 mol) of methyl α-bromo-*o*-toluate[7] was added and the mixture was stirred overnight. The solvent was evaporated under reduced pressure. The residual liquid was dissolved in methylene chloride and washed with water. After evaporation of the solvent the residue was filtered through silica gel with benzene as eluent: yield 31 g (92%); NMR ($CDCl_3$) δ 1.38 (t, 3, J = 7 Hz, CH_2CH_3), 3.76 (s, 3, OCH_3), 4.15 (s, 2, $C_6H_4CH_2$), 4.49 (q, 2, J = 7 Hz, OCH_2), 6.9–7.8 (m, 8, aromatic); IR (CH_2Cl_2) 1720 (C=O), 1624 (C=N), 1600 cm^{-1}.

3-(4-Chlorophenyl)-3-[2-methoxycarbonyl)benzyl]phthalimidine (6). A mixture of 28.0 g (0.067 mol) of the liquid **5**, 150 ml of ethanol, and 40 ml of 1 N HCl solution was stirred at room temperature for 12 h. The resultant solid was filtered off to give 12.5 g (46% for two steps) of crude **6**, mp 165–170 °C. After recrystallization from ethanol 10.0 g of **6** was obtained: mp 182–184 °C; *m/e* 391 (M^+); NMR ($CDCl_3$) δ 3.84 (s, 3, OCH_3), 4.04 (q, 2, J = 13 Hz, $\Delta\nu$ = 27.6 Hz, CH_2), 6.3–6.6 (m, 1, aromatic H), 6.7–7.7 (m, 11, 1 exchangeable with D_2O, 10 aromatic H + NH), 7.7–8.0 (m, 1, 1 aromatic H); IR (CH_2Cl_2) 3400 (NH), 1690–1720 (C=O), 1595 cm^{-1}.

Anal. Calcd for $C_{23}H_{18}ClNO_3$ (391.9): C, 70.5; H, 4.6; Cl, 9.0. Found: C, 70.8; H, 4.6; Cl, 9.2.

12a-(4-Chlorophenyl)-12,12a-dihydro-5*H*-7*H*-isoindolo-[2,1-*b*]isoquinoline-5,7-dione (7a). Heating of 8.0 g (0.02 mol) of **6** to 240 °C resulted in the formation of 7.2 g (92%) of **7a** after recrystallization from methylene chloride/hexane: mp 307–308 °C; *m/e* 359 (M^+); NMR (CF_3COOH) δ 4.0 (q, 2, J = 16.5 Hz, $\Delta\nu$ = 39.7 Hz, CH_2), 7.0–8.0 (m, 10, aromatic H), 8.0–8.5 (m, 2, aromatic H); IR (Nujol) 1745 (C=O), 1672 (C=O), 1604 cm^{-1}; UV 263 nm (ε 18 900).

Anal. Calcd for $C_{22}H_{14}ClNO_2$ (359.8): C, 73.4; H, 3.9; N, 3.9; Cl, 9.9. Found: C, 73.8; H, 3.8; N, 4.1; Cl, 10.3.

12a-(4-Chlorophenyl)-12,12a-dihydro-5*H*,7*H*-isoindolo-[2,1-*b*]isoquinoline (7b). A suspension of 10.0 g (0.028 mol) of **7a** in 800 ml of dry THF was treated with 100 ml (0.1 mol) of 1 M diborane solution and kept at room temperature for 2 h under an atmosphere of nitrogen. The solvent was evaporated under reduced pressure and the residue was dissolved with methylene chloride and washed with water. After evaporation of the solvent 10.5 g of crude **7b** was obtained which was crystallized twice from ethanol to give 6.1 g (66%) of pure **7b**: mp 99–101 °C; *m/e* 331 (M^+); NMR ($CDCl_3$) δ 3.27 (q, 2, J = 16 Hz, $\Delta\nu$ = 9.3 Hz, CH_2), 3.94 (s, 2, CH_2), 4.23 (q, 2, J = 12 Hz, $\Delta\nu$ = 21.9 Hz, CH_2), 6.8–7.5 (m, 12, aromatic H); IR (CH_2Cl_2) 1585 cm^{-1}.

Anal. Calcd for $C_{22}H_{18}ClN$ (331.9): C, 79.6; H, 5.5; N, 4.2; Cl, 10.7. Found: C, 79.5; H, 5.4; N, 3.9; Cl, 10.7.

1-Benzyl-1-(4-chlorophenyl)isoindoline (8a). The mixture of 1.5 g (0.004 mol) of **2i** and 1.0 g (0.03 mol) of $LiAlH_4$ in 50 ml of THF was heated to reflux overnight under an atmosphere of nitrogen. After the usual workup the product was treated with maleic acid to give 0.4 g of **8a**: mp after recrystallization from methanol/ether 176–177 °C; ^{13}C NMR, see Table I; NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2N), 4.39 (q, 2, J = 15 Hz, $\Delta\nu$ = 16 Hz, $C_6H_5CH_2$), 6.05 (s, 2, maleic acid), 6.7–8.7 (m, 13, aromatic), 11.6–13.0 (broad, 3, NH); IR (Nujol) 2400–3400 (NH, acid), 1620 cm^{-1} (aromatic).

Anal. Calcd for $C_{21}H_{18}NCl{\cdot}C_4H_4O_4$ (438.9): C, 68.9; H, 5.1; N, 3.2; Cl, 8.1. Found: C, 69.1; H, 5.2, N, 3.6; Cl, 8.3.

The base was prepared from the salt in the usual way.

1-(4-Chlorophenyl)-1-[2-(hydroxymethyl)benzyl]isoindoline (8b). The mixture of 2.0 g (0.0055 mol) of **7a** and 2.0 g (0.053 mol) of $LiAlH_4$ in 110 ml of THF was kept at room temperature for 2 h and then heated to reflux overnight under an atmosphere of nitrogen. Following the usual workup there was isolated 1.7 g of crude material from which 0.3 g (16%) of **8b** was obtained: mp 163–165 °C; recrystallized from methanol/water mp 164–166 °C; *m/e* 349 (M^+); ^{13}C NMR, see Table I; NMR ($CDCl_3$) δ 2.5–3.3 (m, 2, CH_2), 3.7–4.1 (m, 2, CH_2), 4.65 (q, J = 11 Hz, $\Delta\delta$ = 9.5 Hz, CH_2OH), 5.9–6.2 (m, 1, aromatic), 6.6–7.6 (m, 11, aromatic), 4.2–5.6 (broad, 2, exchangeable with D_2O, NH, OH); IR (CH_2Cl_2) 3100 (NH, OH), 1590 cm^{-1} (weak).

Anal. Calcd for $C_{22}H_{20}NOCl$ (349.9): C, 75.5; H, 5.8; N, 4.0; Cl, 10.1. Found: C, 75.2; H, 5.4; N, 3.9; Cl, 10.1.

The same compound was obtained starting with **6** under conditions equivalent to those employed above.

6b-(4-Chlorophenyl)dibenzo[*af*]-*s*-triazolo[3,4,5-*cd*]indolizine (9). A mixture of 2.0 g (0.005 mol) of the imino ester **5** and 10.0 g (0.31 mol) of hydrazine was heated to reflux for 3 h. The excess of hydrazine was evaporated under reduced pressure and the residue was dissolved in methylene chloride to give 0.2 g (11%) of **9** as a white solid: mp 275–277 °C; *m/e* 355 (M^+); NMR ($CDCl_3$) δ 3.6 (q, 2, J = 15 Hz, $\Delta\nu$ = 34.9 Hz, CH_2), 7.0–7.7 (m, 10, aromatic H), 7.8–8.2 (m, 2, aromatic H); IR (CH_2Cl_2) 1612 cm^{-1} (weak); UV 219 nm (ε 36 900), 255 (9400), 285 (11 800).

Anal. Calcd for $C_{22}H_{14}ClN_3$ (355.8): C, 74.3; H, 4.0; N, 11.8; Cl, 10.0. Found: C, 74.1; H, 4.4; N, 12.1; Cl, 10.0.

Acknowledgment. We would like to thank Dr. S. Barcza for helpful discussions and also his staff for providing the spectral and analytical data. We are indebted to Dr. Renate Coombs and her staff for recording the mass spectra.

Registry No.—**1a,** 26859-66-5; **1b,** 61139-60-4; **1c,** 41581-41-3; **1d,** 61139-61-5; **1e,** 28006-50-0; **1f,** 36033-98-4; **1g,** 36033-95-1; **1h,** 36037-78-2; **1i,** 36033-91-7; **2d,** 61139-62-6; **2e,** 61139-55-7; **2f,** 61139-56-8; **2g,** 61139-57-9; **2h,** 61139-58-0; **2i,** 61139-59-1; **3e,** 36033-89-3; **3f,** 36033-99-5; **3g,** 36033-96-2; **3h,** 36037-79-3; **3i,** 36033-92-8; **4e,** 28006-52-2; **4f,** 36033-97-3; **4g,** 36033-94-0; **4h,** 36037-71-1; **4i,** 36033-90-6; **5,** 61139-63-7; **6,** 61139-64-8; **7a,** 61139-65-9; **7b,** 61139-66-0; **8a,** 61139-53-5; **8b,** 61139-54-6; **9,** 61139-67-1; 2-(4-chlorobenzoyl)benzoic acid ethyl ester, 51476-10-9; methyl α-bromo-*o*-toluate, 2417-73-4.

Supplementary Material Available. Additional experimental and spectral and analytical information (Tables II–IV) (4 pages). Ordering information is given on any current masthead page.

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(12) We have prepared this known compound[7] more conveniently from *o*-toluic acid methyl ester by direct bromination.

Furazans and Furazan Oxides. 7.[1] Interconversions of Anthranils, Benzofurazan Oxides, and Indazoles

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7-Nitroanthranil (1, R = R′ = H) and 4-formylbenzofurazan oxide (2, R = R′ = H) equilibrate on heating. The latter condenses with primary amines and the resulting imines rearrange to 7-nitroindazoles (8). The corresponding 6-methoxy and 6-chloro derivatives of 1 behave similarly. Neither 5- nor 6-nitroanthranil forms an indazole on heating with aniline or other primary amines.

An example of a general heterocyclic rearrangement which was first described some years ago[2] is the interconversion of 7-nitroanthranils with 4-acylbenzofurazan oxides (1 ⇌ 2). In the earliest case to be investigated[2,3] (1, R = Me; R′ = H) the reaction was found to proceed in the direction 2 → 1, to provide 1 exclusively. Later,[4] an example was discovered (1 ⇌ 2, R = H; R′ = Cl) in which at normal temperatures the furazan oxide isomer 2 was thermodynamically the more stable compound, and it was suggested that steric inhibition of resonance of the nitro group with the ring system of 1 led to its destabilization, with consequent preference for structure 2. We now find that, in the simplest example of this system (1 ⇌ 2, R = R′ = H) the equilibrium balance is finely poised, with only a moderate preference (K = [1]/[2] = ca. 2) for 1.

7-Nitroanthranil (1, R = R′ = H) was prepared as follows. 3-Nitrosalicylaldehyde (3) was warmed with tosyl chloride in dry pyridine. Initially, a small amount of the tosylate 4 separated: this redissolved, and the pyridinium salt[5a] 5 crystallized out. The salt 5 was dissolved in aqueous sodium azide solution, giving the azide 6, which was decomposed in hot toluene.

Condensation of the acyl group of 2 with a primary amine, followed by rearrangement, leads to the formation of 2-substituted indazoles (7 → 8).[2,3] Consistent with this, we find that reflux of the nitroanthranil (1, R = R′ = H) with aniline produces 7-nitro-2-phenylindazole (8, R′ = H; R″ = Ph), through condensation of the intermediate 4-formylbenzofurazan oxide (2, R = R′ = H) with the aniline. An attempt to extend this reaction to the preparation of 2-methyl-7-nitroindazole (8, R′ = H; R″ = Me), by heating 1 (R = R′ = H) with methylamine in ethanol, led to the formation of ethyl 3-nitroanthranilate (9), and the corresponding methylamide (10). It appears that the alkylamine is sufficiently strong a base to

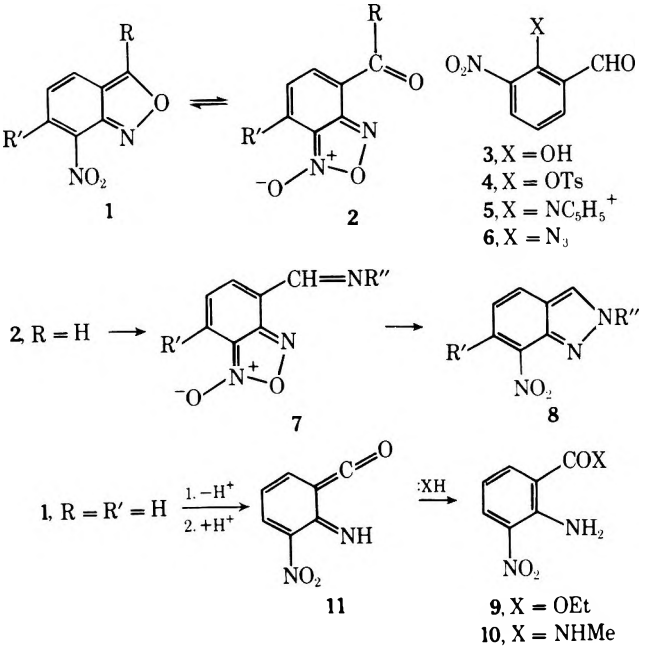


Table I. Indazoles 8 from Benzofurazan Oxides 2 and Amines

Compd	Indazoles 8 R′	Indazoles 8 R″	Mp, °C	Recrystn solvent	Yield, %	Mol formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
8a	H	Ph	168–169	C_6H_{14}/EtOAc	74	$C_{13}H_9N_3O_2$	65.3	3.8	17.6	65.2	3.8	17.4
8b	H	Me	145–146	EtOH/H_2O	36	(lit.[22] mp 146–147 °C)						
8c	H	Et	73–74	EtOH/H_2O	45	$C_9H_9N_3O_2$	56.5	4.7	22.0	56.0	4.9	21.3
8d	H	*t*-Bu	Oil		66	$C_{11}H_{13}N_3O_2$	60.3	6.0		59.9	6.1	
8e	H	CH_2Ph	122–123	EtOH/H_2O	37	$C_{14}H_{11}N_3O_2$	66.4	4.4	16.6	65.6	4.5	16.6
8f	Cl	Ph	145–146	EtOAc	71	$C_{13}H_8ClN_3O_2$	57.1	2.9	15.4	57.2	2.9	15.3
8g	Cl	Me	160–161	C_6H_{14}/EtOAc	28	$C_8H_6ClN_3O_2$	45.5	2.8	19.9	45.4	2.8	19.8
8h	OMe	Ph	183.5	C_6H_{14}/EtOAc	62	$C_{14}H_{11}N_3O_3$	62.4	4.1	15.6	62.3	4.0	15.6
8i	OMe	Me	153	EtOH	56	$C_9H_9N_3O_3$	52.2	4.4	20.3	52.3	4.3	20.4

Table II. NMR Spectra of the Nitroindazoles 8 in $CDCl_3$

Compd[a]	Chemical shifts, δ[b] H(3)	H(4)	H(5)	H(6)	$J_{4,5}$[c]	$J_{5,6}$[c]	Other spectral constants[b,c]
8a	8.63	8.09	7.20	8.34	8.2	7.5	Ph: 8.0 (m, 2 H), 7.5 (m, 3 H)
8b	8.22	8.05	7.15	8.32	8.3	7.3	Me: 4.35 (s)
8c	8.25	8.08	7.20	8.36	8.0	7.5	$J_{4,6}$ = 1 Hz. Et: 2.70 (t, 3 H), 4.64 (q, 2 H)
8d	8.30	8.05	7.14	8.27	8.0	7.3	$J_{4,6}$ = 1 Hz. *t*-Bu: 1.80 (s)
8e	8.01	7.98	7.17	8.34	8.2	7.5	CH_2: 5.72 (s), Ph: 7.36 (s)
8f	8.52	7.82	7.12	(Cl)	9.0		Ph: 7.8 (m, 2 H), 7.4 (m, 3 H)
8g	7.90	7.75	6.95	(Cl)	8.5		Me: 4.05 (s)
8h	9.24	8.19	7.29	(OMe)	9.0		OMe: 4.04 (s), Ph: 8.1 (m, 2 H), 7.3 (m, 3 H)
8i	7.96	7.77	6.97	(OMe)	9.0		OMe: 4.20 (s), NMe: 4.00 (s)

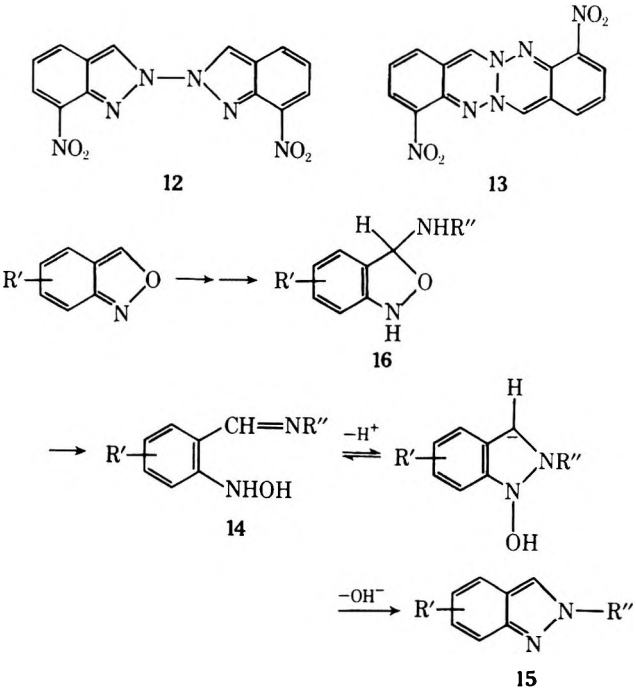
[a] See Table I. [b] δ in parts per million from Me_4Si. [c] *J* in hertz.

cause deprotonation from C(3) of the anthranil **1**; the ketene intermediate (**11**) reacts rapidly with any available nucleophile. Aniline, being less basic under the reaction conditions, does not decompose the anthranil, which therefore has time to rearrange and the formyl group to condense as indicated.

The above argument suggested that a successful reaction with methylamine might ensue if the intermediate 4-formylbenzofurazan oxide were used instead of the anthranil. This compound (**2**, R = R′ = H) was separated by PLC from the mixture produced by thermal equilibration of **1**, after enrichment of the content of the thermodynamically less stable **2**, taking advantage of the fact that the nitroanthranil is considerably less soluble in cold toluene than is the formylbenzofurazan oxide (see Experimental Section). The furazan oxide did indeed condense with a variety of amines (see Table I), to form the corresponding 2-substituted 7-nitroindazoles, but the reaction was not a clean one: with the alkylamines (R″ = Me, Et, $PhCH_2$) a purplish color was usually formed immediately on mixing the reactants, probably because of Meisenheimer complex formation, and the indazoles were contaminated with tarry by-products, which were, however, easily separated by thick layer chromatography. With hydrazine the diindazolyl **12** was formed, the mass spectrum of which showed cleavage of the molecule, with H transfer, to the 7-nitroindazole molecular ion. This provides evidence against the alternative formulation **13**, while the IR spectra contraindicated the unrearranged azine structure.

The substituted nitroanthranils (**1**, R = H; R′ = Cl and OMe) form equilibria with the corresponding furazan oxides **2**, which favor **2** to a greater extent than in the case where R = R′ = H. After a preliminary thermal equilibration of the nitroanthranils, indazoles were formed in satisfactory yields from both aliphatic and aromatic amines in these cases (see Table I).

A reasonable alternative mechanism for the indazole (**8**) formation involves attack of the aniline directly at the anthranil 3 position, followed by ring opening, and recyclization of the phenylhydroxylamine derivative **14**. There is literature precedent to support such a pathway. Thus, anthranil and hydroxylamine have long been known to react to form 2-hydroxylaminobenzaldoxime,[6] and, more recently, Taylor and Bartulin[7] have shown that carbanions condense with anthranil by nucleophilic attack at C(3), followed by ring opening and recyclization, to form a variety of quinoline derivatives. Such a mechanism does not require the presence of the 7-nitro group, and indeed Joshi and Gambhir[8a,b] have reported a number of reactions in which 6-nitroanthranils condense with aromatic amines, to give the corresponding indazoles. We believe, however, that in the present examples the rear-



rangement to the 4-formylbenzofurazan oxide *is* a necessary step in the reaction, and furthermore we have been unable to reproduce the results[8a] with 6-nitroanthranil. Indeed, it is clear that, with respect to the reaction with aniline, the report of Joshi and Gambhir must be erroneous: they quote for the product (6-nitro-2-phenylindazole, **15**; R′ = 6-NO_2; R″ = Ph) a melting point of 325 °C. This compound had already been reported[9] in 1940 as melting at 149 °C. We repeated the preparation of Chardonnens and Heinrich,[9] and were able to confirm the identity of their product by NMR and mass spectrometry. We could not isolate from the reaction of 6-nitroanthranil with aniline a product corresponding to that described by Joshi and Gambhir,[8a,c] and so can make no constructive suggestions concerning its structure. We were also unable to prepare the 6,6′-dinitro-2,2′-diindazolyl which they report as arising from 6-nitroanthranil with hydrazine acetate. 5-Nitroanthranil and aniline also gave no indazole: after prolonged heating, with considerable decomposition, only starting nitroanthranil was isolated.

Our results also have a bearing on the mechanism of base-induced decomposition of 3-unsubstituted anthranils, which we represented above as proceeding by initial proton abstraction from C(3) (**1** → **11**).[10] Taylor and Bartulin,[7] on the basis of their work on the reaction of carbon nucleophiles with anthranil, have suggested that addition of the base (as a nucleophile) is the first step, *in general,* and that deprotonation from C(3) of the adduct (cf. **16**) follows, leading to cleavage of the O–N bond and formation of anthranilic acid derivatives (cf. **9, 10**). This view has recently received support in an authoritative review,[11] which, however, cited in its favor the 6-nitroanthranil results[8a,b] which we now have shown to be, at least in part, incorrect. If nucleophilic addition preceded ring cleavage in the reaction of 7-nitroanthranil (**1**, R = R′ = H) with ethanolic methylamine, the major product (if an indazole is not formed) would be expected to be the amide **10,** not the ester **9**. We consider therefore that the mechanism of Taylor and Bartulin,[7] while essentially correct so far as it concerns their own results, should not be extended to cover the other cases of anthranil conversions into anthranilic acid derivatives.

Experimental Section

Spectrometric instrumentation was as described in earlier parts of this series.[1,12] Silica gel (SiO_2) for preparative layer chromatography (PLC) was Merck Kieselgel 60 PF_{254}. Light petroleum refers to the fraction bp 60–80 °C. Melting points are uncorrected.

1-(2-Formyl-6-nitrophenyl)pyridinium Chloride (5). 3-Nitrosalicylaldehyde[13] (5 g) and tosyl chloride (5.8 g) were separately dissolved in dry pyridine[14] (20 and 40 ml, respectively). The solutions were mixed and a mildly exothermic reaction led to the formation of plates of the tosylate **4**. The mixture was heated to 90 °C for 2 h, when the plates dissolved and yellow prisms of the pyridinium salt **5** separated. These were filtered off, after standing at 0 °C for 12 h, and washed with a little ether: yield 5.4 g (68%), mp 204–205 °C; IR (Nujol) 1690, 1530, 1340 cm^{-1}. Anal. Calcd for $C_{12}H_9ClN_2O_3$: C, 54.5; H, 3.4; N, 10.6; Cl, 13.4. Found: C, 54.3; H, 3.7; N, 10.4; Cl, 12.6.

2-Azido-3-nitrobenzaldehyde (6). Aqueous sodium azide (3 g in 10 ml) was added to the pyridinium chloride **5** (5.3 g) in water (20 ml). After 5 h at 20 °C the precipitated azide **6** was removed by filtration and washed with a little water. A further crop was formed on longer standing of the mother liquors and washings. The azide formed yellow needles, mp 60–61 °C (3.2 g, 82%), from aqueous ethanol: IR (KBr) 2140, 1690, 1525, 1340 cm^{-1}.

Anal. Calcd for $C_7H_4N_4O_3$: C, 43.8; H, 2.1; N, 29.2. Found: C, 44.3; H, 2.1; N, 28.2.

7-Nitroanthranil (1, R = R′ = H) and 4-Formylbenzofurazan Oxide (2, R = R′ = H). The azide **6** (3 g) was heated to reflux in toluene (50 ml) for 5 h. After cooling, some (ca. 0.5 g) impure 7-nitroanthranil separated. The toluene was removed, after filtration, and the residue was taken up in acetone and separated by PLC (SiO_2: two passes toluene/EtOH, 15:1). Two major bands developed, the faster running, after extraction with cold ethanol, affording the furazan oxide (**2**, R = R′ = H) (1.1 g, 42%), and the slower the anthranil (0.7 g, 28%), mp 144–145 °C (lit.[15] mp 144–145 °C). In addition, two fast-moving bands were resolved; one proved to be the unchanged azide **6** (ca. 10 mg), and the other was an isomeric azide (ca. 5 mg), which presumably arose from an impurity in the starting material (**3**).

For the conversion of the anthranil into the furazan oxide, the following procedure was adopted. The anthranil (**1**, R = R′ = H) (ca. 1 g) was heated in refluxing toluene (ca. 10 ml) for 3–4 h, in a recrystallization tube with a side arm containing a glass frit. On cooling, finally in ice, the 7-nitroanthranil, being much less soluble in toluene, largely crystallized out. The solution was expelled through the frit, further toluene was added to the tube, and the process of heating and cooling was repeated until no nitroanthranil crystals separated on cooling. The collected solutions were evaporated to dryness in vacuo, and the residue was separated by PLC as described above.

4-Formylbenzofurazan oxide formed yellow plates, mp 102 °C dec, from acetone: IR (KBr) 1680 (C=O), 1610, 1580, 1550 cm^{-1} (furoxan).

Anal. Calcd for $C_7H_4N_2O_3$: C, 51.2; H, 2.5; N, 17.1. Found: C, 51.7; H, 2.2; N, 16.8.

Thermal equilibration of **1** with **2** (R = R′ = H) at 100 °C in $CDCl_3$ (sealed tube) was established after several hours. The anthranil **1** predominated (ca. 62%); all the furazan oxide bands were exchange broadened (1-oxide = 3-oxide; cf. ref 4), and so appeared much weaker in the NMR spectrum than those of the anthranil.

6-Chloro-7-nitroanthranil and 7-chloro-4-formylbenzofurazan oxide (**1** and **2**, R = H; R′ = Cl) were prepared as described earlier,[4] but with the following procedural modifications. 4-Chloro-2-nitrotoluene (62 g) was converted into the corresponding benzal diacetate using CrO_3 (100 g) dissolved in acetic anhydride (cf. ref 16), rather than with the solid trioxide.[15] After quenching (ice/water) the crude diacetate (ca. 50 g) was washed with water until the washings were colorless. It was then stirred with 2% aqueous sodium carbonate (300 ml) and filtered. The dried solid was extracted with refluxing light petroleum (bp 60–80 °C) (300 ml), to remove unchanged chloronitrotoluene, and then recrystallized from toluene–light petroleum (1:3), giving the diacetate as prisms (38 g, 37%): mp 121–122 °C (lit.[15] mp 110–111 °C); IR (Nujol) 1760 (C=O), 1530, 1350 cm^{-1} (NO_2).

Anal. Calcd for $C_{11}H_{10}ClNO_6$: C, 45.9; H, 3.5; N, 4.9. Found: C, 46.0; H, 3.6; N, 4.9.

The diacetate was hydrolyzed (HCl/H_2O/EtOH) to the aldehyde,[15] which was reduced to 6-chloroanthranil using stannous chloride.[17] 4-Chloro-2-nitrobenzaldehyde (3.3 g, finely powdered) was added to a stirred solution of stannous chloride dihydrate (12 g) in hydrochloric acid (10 N, 45 ml) at such a rate that the exothermic reaction kept the temperature in the range 27–30 °C. After addition, stirring was continued for 2 h, maintaining the same temperature with a water bath. Water (500 ml) was added, and the mixture was extracted with methylene chloride (3 × 50 ml). The organic extracts were washed with water and 2% aqueous sodium bicarbonate, and were then dried (Na_2SO_4). Removal of solvent left a buff solid which crystallized from light petroleum as white plates (1.9 g, 72%), mp 66–67 °C (lit.[15] mp 61.5–62 °C). The anthranil slowly discolors in the presence of light and air.

The chloroanthranil could also be prepared more conveniently in a one-pot process from the benzal diacetate. The diacetate (10 g) was refluxed for 45 min, with stirring, in hydrochloric acid (10 N, 100 ml), water (20 ml), and ethanol (20 ml). The mixture was then cooled to 25 °C, and, with vigorous stirring, stannous chloride (24 g) in hydrochloric acid (10 N, 50 ml) and water (40 ml) was added slowly, to keep the temperatre at 27–30 °C. Further stirring and workup followed the procedure described above, giving 6-chloroanthranil (3.4 g, 61%). Sometimes a little of the aldehyde impurity was detected (TLC: SiO_2, toluene–ethanol, 15:1) in the product prepared in this way.

Nitration of the anthranil, and rearrangement of the product to the chloroformylbenzofurazan oxide (**2**, R = H; R′ = Cl) was as earlier described.[4] The nitroanthranil was very base sensitive, and a single rapid washing of its methylene chloride extract with ice-cold 1% aqueous sodium bicarbonate was needed to remove nitric acid traces without decomposing the product.

4-Formyl-7-methoxybenzofurazan Oxide (2, R = H; R′ = OMe). 2-Nitroanisaldehyde was prepared by the method of Woodward et al.,[18] and also from *p*-toluidine, by nitration in concentrated sulfuric acid, diazotization, and conversion into 4-hydroxy-2-nitrotoluene, then methylation (Me_2SO_4/NaOH), bromination (NBS), and conversion of the 4-methoxy-2-nitrobenzyl bromide into the aldehyde by Krōhnke's method.[19] The aldehyde was reduced ($SnCl_2$/HCl)[17] to form 6-methoxyanthranil, an oil (40–60% yields), which (0.5 g) was nitrated as described above for the 6-chloro compound. The product (0.45 g, 70%) formed yellow plates, mp 127–129 °C, from ethanol or

light petroleum. The IR spectrum indicated that the solid phase was, at least predominantly, in the formylfuroxan form **2**: ν_{max} (Nujol) 1685 s (C=O), 1618 vs, 1580 vs, 1530 vs, 1500 s, 1460 s, 1435 cm^{-1} s. NMR ($CDCl_3$, −20 °C): two $ABMX_3$ systems, relative intensities 2:1, with δ_A 7.93, δ_B 6.53, δ_M 10.11, δ_X 4.08 ppm, J_{AB} = 8.0 Hz, and $\delta_{A'}$ 8.00, $\delta_{B'}$ 6.70, $\delta_{M'}$ 10.46, $\delta_{X'}$ 4.12, $J_{A'B'}$ = 8.0 Hz. These sets of signals coalesced over the range 35–50 °C, to give a single $ABMX_3$ pattern (at 60 °C), with $\delta_{A''}$ 7.87, $\delta_{B''}$ 6.54, $\delta_{M''}$ 10.32, $\delta_{X''}$ 4.12 ppm, $J_{A''B''}$ = 8.0 Hz. These data are compatible with the existence in solution of a remarkably rapid (above 50 °C) equilibrium between the nitroanthranil (**1**, R = H; R′ = OMe) and *one* of the (1-oxide ⇌ 3-oxide) tautomers of the formylbenzofurazan oxide **2**, the other tautomer being present in undetectably small proportion, but we consider that the more probable explanation is that the NMR spectrum below 35 °C shows the *two* formylbenzofurazan oxide tautomers in a rather slow equilibrium,[20] with the nitroanthranil being an undetected intermediate in their formation, thermodynamically less stable than either furoxan form. The fact that the coupling constants J_{AB} and $J_{A'B'}$ are the same is more in harmony with the latter explanation.

Anal. Calcd for $C_8H_6N_2O_4$: C, 49.5; H, 3.1; N, 14.4. Found: C, 49.3; H, 3.1; N, 14.2.

7-Nitro-2-phenylindazole (8, R′ = H; R″ = Ph). Method A. 7-Nitroanthranil (**1**, R = R′ = H) (0.05 g) was heated under reflux for 20 h in dry tetrahydrofuran (6 ml) with aniline (0.08 g). The solvent was removed by distillation and the residue was recrystallized from hexane/ethyl acetate to give the indazole (0.045 g, 62%), mp 168–169 °C. For analytical and NMR spectral details see Tables I and II. MS M^+ *m/e* 239 (base peak).

Method B. 4-Formylbenzofurazan oxide (**2**, R = R′ = H) (0.06 g) and aniline (0.034 g) were stirred at 25 °C for 4 h in ethanol (25 ml) containing three drops of acetic acid. The yellow precipitate of the indazole (0.065 g, 74%) which formed was filtered off and recrystallized from ethanol.

Reaction of 7-Nitroanthranil with Methylamine. 7-Nitroanthranil (0.5 g) was heated to reflux for 30 min with 30% ethanolic methylamine (10 ml). Removal of solvent under reduced pressure, followed by PLC (SiO_2, hexane/ethyl acetate, 7:3) of the residue gave ethyl 3-nitroanthranilate (**9**, 0.2 g, 32%): mp 108 °C (lit.[21] mp 109 °C); IR (Nujol) 3450, 3350 (NH_2), 1690 (C=O), 1525, 1380 cm^{-1} (NO_2). A minor component was identified as the corresponding *N*-methylamide (**10**): mp 157 °C: IR (Nujol) 3480, 3400, 3370 (NH, NH_2), 1655 (C=O), 1580, 1340 cm^{-1} (NO_2). Anal. Calcd for $C_8H_9N_3O_3$: C, 49.2; H, 4.6; N, 21.5. Found: C, 49.4; H, 4.6; N, 21.4.

Various modifications of the conditions of the above reaction were tried, using buffered methylamine, and using ethanol and acetic acid mixtures as solvent, but in no case was any indazole isolated.

2-Methyl-7-nitroindazole (8, R′ = H; R″ = Me). 4-Formylbenzofurazan oxide (0.08 g) in ethanol (30 ml) and acetic acid (3 drops) was treated with methylamine in ethanol (30%, 0.06 ml). The color immediately changed from light yellow to purplish brown. After stirring for 4 h at 20 °C the now dark brown solution was diluted with water (60 ml) and extracted with dichloromethane (3 × 10 ml). The extracts were dried (Na_2SO_4), passed through a short silica gel column, and then concentrated to small volume and applied to SiO_2 PLC plates. Elution with toluene/ethanol (15:1) gave as the major mobile band the 2-methyl-7-nitroindazole, which was extracted with ethanol. For physical, analytical, and mass spectral data, see Tables I and II.

2-Ethyl-, 2-*tert*-butyl-, and 2-benzyl-7-nitroindazole (8, R′ = H; R″ = Et, *t*-Bu, CH_2Ph), and 2-methyl-6-chloro- and -6-methoxy-7-nitroindazole (8, R′ = Cl and OMe; R″ = Me) were prepared by methods similar to that described for the 2-methyl-7-nitroindazole, from the corresponding amine and the benzofurazan oxide **2**. The 2-phenyl compounds (8, R′ = Cl and OMe; R″ = Ph) were prepared from the benzofurazan oxides with aniline in refluxing tetrahydrofuran, the products being isolated by removal of solvent and recrystallization. Physical, analytical, and NMR spectral data are listed in Tables I and II. In addition, all the nitroindazoles showed the expected bands in their IR spectra due to the nitro groups, and a medium intensity peak at 1635–1630 cm^{-1}, from the indazole ring. Mass spectra were obtained for compounds **8a–f** (see Table I); in all but the *tert*-butyl case (**8d**), in which M^+ (219) was 53% of the base peak at *m/e* 163, the parent ion was the base peak.

7,7′-Dinitro-2,2′-diindazolyl (12). 4-Formylbenzofurazan oxide (0.05 g) in ethanol (20 ml) was stirred for 9 h at 20 °C with hydrazinium chloride (0.016 g) and sodium acetate (0.05 g). A yellow solid which separated was washed with water and recrystallized from aqueous ethanol, to afford the dinitrodiindazolyl **12** as a microcrystalline mass (0.015 g, 30%): mp 323 °C dec; MS *m/e* 324 (M^+, 100), 62 (52), 192 (47), 90 (30), 88 (23), 163 (21), 204 (20); IR (KBr) 1635 m, 1515 s (NO_2), 1445 m, 1380 m, 1360 m, 1335 s, 1310 cm^{-1} s (NO_2).

Reaction of 6-Nitroanthranil with Aniline. Repetition of the directions of Joshi and Gambhir,[8a] and also modifying the conditions by using both shorter and longer periods of reflux, led to a complex mixture of products, with, in some cases, recovery of a little starting nitroanthranil. Trituration with hot acetic acid left much material undissolved. The acetic acid soluble fraction again proved to be a mixture of components, from which no crystalline fraction was isolated. No 6-nitro-2-phenylindazole was found (TLC) to be present in the solution. We were likewise unsuccessful in our attempts to isolate a characterizable product from the reaction with hydrazine acetate.[8a]

6-Nitro-2-phenylindazole (15, R′ = 6-NO_2; R″ = Ph). 2-Amino-4-nitrotoluene was converted by the method of Chardonnens and Heinrich[9] into the indazole: mp 150 °C (lit.[9] mp 149 °C); NMR δ 8.82 (d, $J_{3,7}$ = 1 Hz, H-3), 8.57 (br s, H-7), 8.3–7.9 (m, H-5 and *o*-phenyl), 7.7–7.4 (m, H-4 and *m*-, *p*-phenyl); MS *m/e* 239 (M^+, 100), 192 (58), 193 (47), 77 (45), 166 (43), 181 (37), 209 (30).

Reaction of 5-Nitroanthranil with Aniline. 5-Nitroanthranil[15] was heated under reflux with aniline, both alone and in tetrahydrofuran. After a few hours the solutions became dark in color. Removal of solvent left a tarry residue which yielded only recovered nitroanthranil on extraction with light petroleum.

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Registry No.—**1** (R = R′ = H), 4104-37-4; **1** (R = H; R′ = Cl), 22950-43-2; **1** (R = H; R′ = OMe), 61062-97-3; **2** (R = R′ = H), 61062-98-4; **2** (R = R′ = H) 3-oxide derivative, 61062-99-5; **2** (R = H; R′ = Cl), 30080-04-7; **2** (R = H; R′ = Cl) 3-oxide derivative. 61063-00-1; **2** (R = H; R′ = OMe), 61063-01-2; **2** (R = H; R′ = OMe) 3-oxide derivative, 61063-02-3; **3**, 5274-70-4; **4**, 61063-03-4; **5**, 61063-04-5; **6**, 61063-05-6; **8a**, 61063-06-7; **8b**, 13436-58-3; **8c**, 41926-13-0; **8d**, 61063-07-8; **8e**, 61063-08-9; **8f**, 61076-93-5; **8g**, 4199-39-7; **8h**, 61063-09-0; **8i**, 61063-10-3; **9**, 61063-11-4; **10**, 61063-12-5; **12**, 61063-13-6; **15** (R′ = 6-NO_2; R″ = Ph), 61063-14-7; aniline, 62-53-3; methylamine, 74-89-5; ethylamine, 75-04-7; *tert*-butylamine, 75-64-9; benzylamine, 100-46-9; tosyl chloride, 98-59-9; pyridine, 110-86-1; 4-chloro-2-nitrotoluene, 89-59-8; 4-chloro-2-nitrobenzaldiacetate, 1530-56-9; 4-chloro-2-nitrobenzaldehyde, 5551-11-1; 6-chloroanthranil, 14313-60-1; *p*-toluidine, 106-49-0; 4-hydroxy-2-nitrotoluene, 2042-14-0; 4-methoxy-2-nitrobenzyl bromide, 57559-52-1; 4-methoxy-2-nitrobenzaldehyde, 22996-21-0; 6-methoxyanthranil, 61063-15-8; hydrazinium chloride, 14011-37-1.

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Photochemical Solvent Addition to 2(5*H*)-Furanone. Hydrocarbon Solvents

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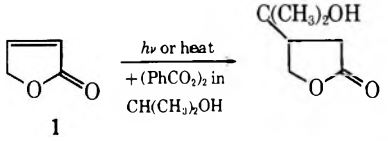
The α,β-unsaturated lactone 2(5*H*)-furanone was shown to add hydrocarbon solvent across its carbon–carbon double bond in three different ways characterized by different β/α addition product ratios. Direct irradiation with ultraviolet light or benzene sensitization afforded a $\beta/\alpha = 1$ while "chemical sensitization" using acetophenone or benzophenone gave a $\beta/\alpha \gg 1$. A benzoyl peroxide initiated reaction gave $\beta/\alpha = 2$.

Photochemical solvent additions to cyclic α,β-unsaturated carbonyl compounds have been reported by many workers.[1-8] In general, alcoholic and ether solvents have been found to add to the β position almost exclusively. In the case of 2-cyclopentenone evidence has been presented both in favor of[1] and against[2] a radical chain process. Ketone sensitizers have been discussed as energy[1-4] and hydrogen transfer[5a,9] agents.

The α,β-unsaturated lactone, 2(5*H*)-furanone (**1**), has been shown to add isopropyl alcohol in a similar (β) fashion under both photochemical and free radical chain (benzoyl peroxide initiated) conditions[5b] (see eq 1). Only in the cases of 2-cyclopentenone[1,2] and **1**[5b] has evidence been gathered concerning the mechanism of the solvent addition. We wish to report our results with this lactone in which we have evidence of at least three different patterns of solvent addition.

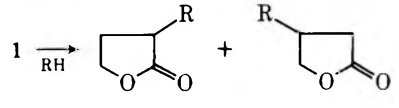


(1)

1

Results

The lactone **1** was allowed to react with cyclohexane or toluene solvent under the following conditions: (a) direct irradiation of dilute (7 mM) deoxygenated solutions at room temperature; (b) irradiation of dilute deoxygenated solutions containing benzoyl peroxide at room temperature; (c) irradiation of dilute deoxygenated solutions containing various sensitizers at room temperature; and (d) heating of dilute deoxygenated solutions containing benzoyl peroxide at the boiling point of the solution. The products derived from **1** in cyclohexane were 3- and 4-cyclohexyldihydro-2(3*H*)-furanone (**2** and **3**, respectively) in 90 ± 10% combined yield. In toluene the products were 3- and 4-benzyldihydro-2(3*H*)-furanone (**4** and **5**) (see eq 2). The structures of these photoproducts were confirmed by comparison with samples independently prepared by previously reported methods.[10] In each case the isomeric photoproducts were separated by gas chromatography (VPC) and the relative amounts of the isomers determined. The results are summarized in Table I. The product ratio in each case provides a "fingerprint" of the mechanism(s) involved in that reaction.



(2)

R = cyclohexyl **2** **3**
R = benzyl **4** **5**

A careful examination of the ultraviolet absorption spectra of **1**, acetophenone plus **1**, and acetophenone alone in cyclohexane showed no new bands and the presence of **1** did not modify or quench phosphorescence emission from acetophenone. No phosphorescence emission from **1** could be detected. The disappearance of **1** was not quenched by 0.10 M 1,3-cyclohexadiene in a direct irradiation but **2** and **3** were not among the products formed in this reaction.

A series of Pyrex-filtered irradiations of **1** in cyclohexane containing various concentrations of acetophenone and an experiment using a moderate concentration of benzophenone were done. The results are shown in Table II.

Discussion

The ratios of the solvent adducts (β/α) for the various addition reactions fall into three categories. We believe that these categories indicate at least three different pathways for the formation of these photoproducts.

The exclusive formation of the β adduct **3** in the acetophenone and the predominant formation of **3** in the benzophenone sensitized reactions is similar to the sensitized addition of solvent to 2-cyclopentenone reported by several workers.[1,2,6] A mechanism similar to that proposed by Wagner[5a] would involve hydrogen abstraction by the n,π^* triplet

Scheme I

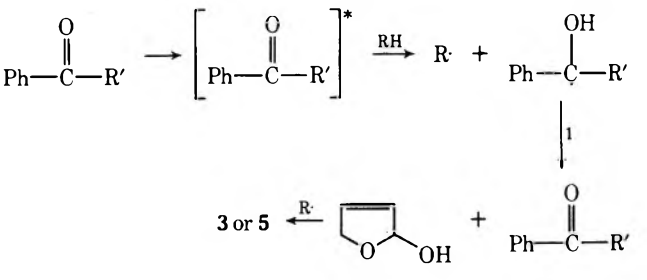


Table I. Results of the Reaction of 1[a] with Hydrocarbon Solvents

Conditions	Solvent	Sensitizer or initiator (concn)[b]	Filter[c]	Product ratio[d]
Photochemical	Cyclohexane	None	Vycor	1.2
Photochemical	Toluene	None	Corex	0.92
Photochemical	Cyclohexane	Benzene (0.30)	Vycor	0.85
Photochemical	Cyclohexane	Acetone (0.45)	Pyrex	2.0
Photochemical	Cyclohexane	Benzoyl peroxide (0.0030)	Corex	2.2
Thermal	Cyclohexane	Benzoyl peroxide (0.0030)		2.1
Thermal	Toluene	Benzoyl peroxide (0.0030)		2.0
Photochemical	Cyclohexane	Acetophenone (0.20)	Pyrex	>21

[a] 7.0 mM. [b] Molar. [c] See ref 15. [d] 3/2 or 5/4, ±10%.

Table II. Photochemical Reactions of 1 in Cyclohexane with Various Aryl Ketone Concentrations[a]

Sensitizer concn, mM	3/2[b]	Conversion, %
0[c]	1.2	40
0.36	4.0	18
0.60	4.5	22
4.0[d]	7.3	18
7.0	8.1	30
200	>21	42

[a] Standard conditions: 1 7.0 mM, Pyrex filter, 4-h irradiation. [b] ±10%. [c] Vycor filter. [d] Benzophenone as sensitizer; all others were with acetophenone.

state of the sensitizer, transfer of that hydrogen atom to either the carbonyl oxygen or (improbably) the α carbon of 1, and then collapse of this radical with a radical derived from the solvent (Scheme I). This process may represent one pathway for formation of solvent adduct. The radical apparently produced by hydrogen transfer to 1 must react slowly (if at all) with solvent. No dihydro-2(3*H*)-furanone (the product expected from such a reaction with solvent[4,7,9,11]) was detected in any of these reactions.

Several pieces of information are useful in excluding alternative explanations for the role of acetophenone in this reaction. The a priori possibility exists, for example, that acetophenone is simply transferring energy to 1. The triplet excited state of 1[12] involved in photocycloaddition reactions lies 75–80 kcal/mol above the ground state. Thus, direct energy transfer from acetophenone (E_t = 73.6 kcal/mol[13]) to 1 leading to reactions of excited 1 would be endothermic and very inefficient. Lack of simple energy transfer from acetophenone to 1 is confirmed by the fact that 1 does not quench the phosphorescence of acetophenone. The successful sensitization experiment using benzophenone (E_t = 68.5 kcal/mol[13]) certainly indicates a process other than energy transfer.

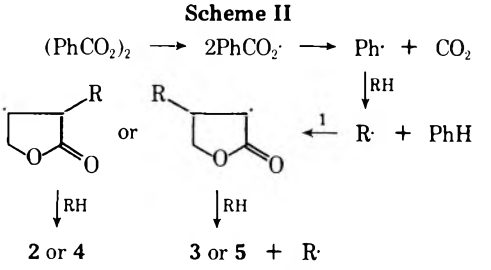
Another possibility to be considered is that the role of the acetophenone (or benzophenone) is simply to abstract a hydrogen atom[14] from cyclohexane to produce the cyclohexyl radical. The attack of the solvent-derived radicals on 1 cannot, however, account for the almost exclusive formation of the β adduct in the acetophenone or benzophenone sensitized reactions because generation of such radicals via a benzoyl peroxide initiated reaction gives a different product ratio (Table I).

The product ratio dependence on acetophenone concentration was at first interpreted as evidence for an intermediate trappable by ground-state acetophenone. However, close inspection of the ultraviolet absorption curves of acetophenone and 1 and the cutoff spectrum of the Pyrex filter used[15] showed that at low (<10 mM) acetophenone concentrations some direct light absorption by the lactone must occur. This may account for the concentration dependence. The predominance of β solvent addition (as compared with the direct irradiation results) at very low acetophenone concentrations may be due to acetophenone quenching of excited lactone. In any event, the trapping of intermediates by ground state acetophenone was shown to be either reversible or a minor process by the high yields in the acetophenone sensitized reactions (90% at 40% conversion).

The formation of equal amounts of both α and β solvent adducts in the direct irradiation of 1 in hydrocarbon solvents requires a different reaction pathway for solvent addition from that proposed in Scheme I. Certainly the lack of preference for the mode of addition (α or β) of hydrocarbon solvents to excited 1 is inconsistent with an n,π^* excited state which should clearly favor hydrogen abstraction by oxygen[14] and, hence, β addition. Supporting this analysis is the β/α ratio of 7 for the photoaddition of cyclohexane to 2-cyclopentenone,[4] a compound which reacts from a predominantly n,π^* excited state. A pathway for photochemical solvent addition which is decidedly different from that shown in Scheme I must exist. Although definitive information about this second pathway is not available, a reasonable suggestion is that excited 1 (presumable a π,π^* state) adds solvent to its carbon–carbon double bond in a manner not greatly dependent upon substituents attached to the carbons, perhaps in a concerted fashion.[16] Benzene and acetone are both sufficiently high in excited state energy to sensitize the photochemical reactions of 1 by simple energy transfer.

A third pathway for solvent addition to 1 is dictated by differing product ratios and by different reaction conditions. The benzoyl peroxide initiated addition of cyclohexane to 1 cannot, to any major extent, be following the pathway outlined in Scheme I since the β/α ratio observed (2.1) is very different from the ratio observed (>20) in reactions following that pathway. Obviously, the peroxide decomposition cannot be following a pathway which involves an excited state of 1 (the second pathway outlined above). The logical process for the peroxide initiated reaction is the well-known free-radical addition to a double bond,[17] the third mechanism for solvent addition to 1 (Scheme II).

Scheme II



The quenching results are ambiguous. Control experiments show that 1 is stable in the presence of 1,3-cyclohexadiene in

the dark. The fact that the disappearance of **1** is not quenched may indicate that the cyclohexane addition in the direct irradiation proceeds via an excited singlet state. However, the absence of **2** or **3** from the product mixture (many products were formed) may only indicate that the singlet or triplet excited state of **1** reacts with quencher in a process unrelated to the reaction occurring in the absence of the quencher.

Experimental Section

General. Proton magnetic resonance spectra were recorded on a Varian Associates T-60 instrument in deuteriochloroform with tetramethylsilane as an internal standard. Infrared spectra were determined on either a Beckman IR8 or an IR20 as thin films between salt plates. Gas chromatographic analyses were done using an Aerograph A90-P instrument with a 5 ft × 0.25 in. copper column containing 10% OV-1 on 80–100 mesh Gas-Chrom Q. Ultraviolet spectra were determined on a Cary 15 spectrometer and phosphorescence spectra on an Aminco-Bowman spectrophosphorimeter in a 2-methyltetrahydrofuran glass at liquid nitrogen temperature. The spectra of acetophenone were very similar to those reported.[13] Cyclohexane was purified by stirring it over 30% fuming sulfuric acid, washing it with dilute sodium carbonate solution, and distilling it onto sodium wire. Toluene was distilled onto sodium wire after the initial fraction was discarded.

Preparation of Photoproducts. The 3-cyclohexyldihydro-2(3*H*)-furanone (**2**) was prepared by the method of Reppe.[10a] This material (a clear oil) had these spectra: IR 2920, 2850, 1760 (C=O), 1445, 1158, 1020 cm^{-1}; NMR δ 1.0–2.66 (m, 14 H), 4.0–4.4 (m, 2 H, $-OCH_2-$). The 4-cyclohexyldihydro-2(3*H*)-furanone (**3**) was prepared by the method of Elderfield.[10b] The spectra follow: IR 2920, 2840, 1765 (C=O), 1438, 1158, and 1000 cm^{-1}; NMR δ 0.67–2.91 [m, 14 H, with a sharp singlet superimposed at 2.33, $-CH_2C(=O)-$], 3.72–4.53 (symmetrical m, 2 H, $-CH_2O-$). The 3-benzyldihydro-2(3*H*)-furanone (**4**) was prepared by the method of Reppe.[10a] It had these spectra: IR 2910, 1750 (C=O), 1680, 1470, 1360, 1190, 1120 cm^{-1}; NMR δ 1.33–3.33 (m, 5 H), 4.07–4.33 (m, 2 H, $-CH_2O-$), 7.17 (s, 5 H, aromatic). The 4-benzyldihydro-2(3*H*)-furanone (**5**) was prepared by the method of Zimmer.[10c] The spectra follow: IR 2920, 1770 (C=O), 1590, 1470, 1160, 1010 cm^{-1}; NMR δ 1.80–3.20 [m, 5 H, with a slightly broadened singlet superimposed at 2.7, $-CH_2C(=O)-$], 3.85–4.55 (symmetrical m, 2 H, $-CH_2O-$), 7.33 (br s, 5 H, aromatic).

Photochemical and Thermal Reactions. Irradiations were conducted with a 100-W Hanovia mercury vapor lamp in a quartz immersion well equipped with the appropriate filter and inserted into an irradiation flask that held a working volume of 350 ml. Solutions were deoxygenated by stirring them while bubbling nitrogen through them for 1 h before and then during the irradiation. Irradiations routinely were done for 4 h. Thermal reactions were conducted by heating and stirring 120 ml of deoxygenated solutions at reflux for 1 h. Product analyses were done in the following manner: solvent was removed from each reaction solution at aspirator pressure and room temperature to ensure that the starting lactone would remain in the mixture. NMR spectra of these mixtures at this stage indicated the presence of only **1**, the appropriate products (**2** and **3** or **4** and **5**), and, if added, sensitizer and sensitizer photoproducts. In the case of the cyclohexadiene reaction the only assignable NMR absorptions were due to **1**. In each case residual **1** and acetophenone or benzophenone, if present, were then removed at high vacuum and the resulting oil separated by VPC. Collected samples were compared to authentic materials. Relative amounts were determined from VPC peak areas. In the case of the attempted quenching, no identifiable materials could be collected from the more than 16 product peaks. The retention times of **2** and **3** were 13.0 and 16.0 min, respectively, at 200 °C with a flow rate of 60 ml/min. At 250 °C with a flow rate of 50 ml/min **4** and **5** eluted with retention times of 6.6 and 8.4 min, respectively.

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Registry No.—**1**, 497-23-4; **2**, 40541-50-2; **3**, 54996-29-1; **4**, 61129-28-0; **5**, 22530-98-9; cyclohexane, 110-82-7; toluene, 108-88-3.

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Photochemistry of 2(5*H*)-Furanone. Hydrogen Abstraction by the β-Carbon Atom

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It is now well established that α,β-unsaturated ketones, including cyclopentenone,[1,2] cyclohexenone,[1] and their related derivatives,[1-3] undergo photochemical solvent addition to yield α and β solvent adducts. These photochemical reactions have been postulated in several cases[2,3] to involve hydrogen abstraction both by the carbonyl group to yield β-solvent adducts, and by the β-carbon atom to yield α adducts (see Chart I).[4,5] Furthermore, Agosta and colleagues, in demonstrating the generality of these photochemical processes in α,β-unsaturated ketones, provided compelling evidence that the isomerization of several cyclopentenone[2,5b] and acyl cyclopentene[6] derivatives is both initiated by intramolecular hydrogen abstraction by the β-carbon atom and involves an intermediate diradical species. Collectively, these observations suggest that similar solvent addition and isomerization processes might also occur with other α,β-unsaturated carbonyl functionalities. This indeed appears to be the case. For example, irradiation of several α,β-unsaturated esters, so constrained as to prevent photochemical cis–trans isomerization, led in methanol to formation of α-solvent adducts as well as to photoreduction of the olefinic bonds.[7] The parent α,β-unsaturated lactone, 2(5*H*)-furanone (**1**)[8] and 3-benzylidene-2(3*H*)-furanone (**6**),[9] on the other hand, led exclusively to β-solvent adducts when irradiated in isopropyl alcohol, while 1,3-dimethyluracil gave both α and β adducts in tetrahydrofuran.[10] More recently, the intramolecular cyclization of several α,β-unsaturated amides, leading to β-lactams, was postulated to proceed via hydrogen abstraction by the β carbon.[11] In general, however, these studies did not provide detailed information on the reaction pathway. With this consideration in mind, we record here our experience with the photochemistry of 2(5*H*)-furanone in hydrocarbon solvent.[12] The results indicate that both α and β solvent adducts are formed. In addition, evidence is presented which demonstrates conclusively that the α adduct arises via hydrogen abstraction by the β-carbon atom.

Chart I

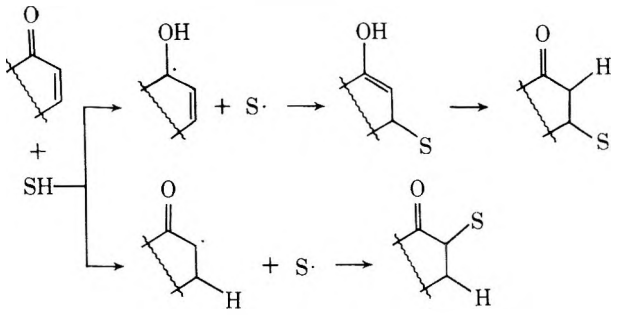
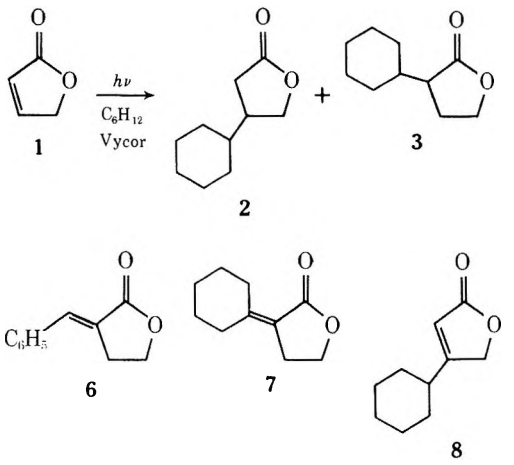


Chart II

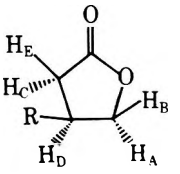


Results and Discussion

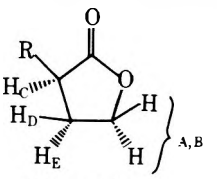
Irradiation of **1**[13] in cyclohexane (12 mM) through Corex (λ ≥2600 Å) or Vycor (λ ≥2100 Å) led to the formation of 4- and 3-cyclohexyldihydro-2(3*H*)-furanone (**2** and **3**) in 13–15 and 16–20% yield, respectively. Interestingly, even under these dilute conditions the previously described [2 + 2] cyclodimerization[14] of **1** also took place. Structures **2** and **3** were initially identified from their spectroscopic properties. In addition to a carbonyl frequency at 1780 cm^{-1}, typical of a five membered ring lactone, **2** and **3** yielded the 220-MHz NMR data shown in Table I. For comparison we have included the spectra of 4- and 3-methyldihydro-2(3*H*)-furanone (**4** and **5**). The five hydrogens associated with the lactone ring can in each case be assigned; a tentative structural assignment is therefore possible. Significant in this regard are the two methylene hydrogens on carbon bearing oxygen; in lactones **3** and **5** these hydrogens appear as a broad multiplet centered at δ 4.16, while in **2** and **4** the hydrogen cis to the vicinal alkyl substituent (e.g., H_b) experiences an expected[15] upfield shift (Δ ~0.40–0.60 ppm) relative to the trans hydrogen (H_a). Completion of the assignments derives from lanthanide shift reagent experiments as well as from further exploitation of the alkyl shielding. In particular the hydrogens α to the carbonyl group undergo a greater downfield shift relative to the β hydrogens when **2**–**5** are progressively doped with the shift reagent, Eu(fod)$_3$. Confirmation of structures **2** and **3** was obtained by spectral comparisons (IR, 220-MHz NMR, and VPC retention data) with authentic samples[16] prepared by hydrogenation of the known lactones **8**[17] and **7**.[18]

We next turned our attention toward defining the pathway for solvent addition. To this end **1** was irradiated through Corex in cyclohexane-d_{12} (99.5% D). In order to minimize the amount of cyclohexane-d_{12} required, experimental conditions involving repeated addition of **1** to the photolysis mixture and its subsequent destruction were devised.[19] In that event, **1** gave **2**-*d* and **3**-*d* in approximately the same ratio as observed previously; however, the overall yield was significantly reduced. Preparative VPC employing a Brownlee–Silverstein[20] thermal gradient collector provided a pure sample (ca. 400–600 μg) of each isomer for NMR analysis. As shown in Table I, **2**-*d* possessed deuterium only on the cyclohexane ring, while **3**-*d* contained in addition a total of one deuterium on the β carbon of the lactone ring. A combination of the previous NMR assignments and the results of NMR shift experiments with **3**-*d*, which allowed individual integration of the β hydrogens, indicated that this deuterium was equally apportioned cis and trans to the cyclohexyl ring thereby yielding lactones **3**-*d*-*cis* and **3**-*d*-*trans*. This labeling pattern provides, for the first time in a system other than an α,β-

Table I. NMR Spectra of 3- and 4-Alkyldihydro-2(3*H*)-furanones



2, R = C_6H_{11}
4, R = CH_3

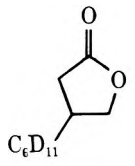


3, R = C_6H_{11}
5, R = CH_3

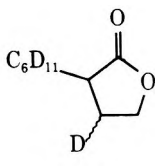
Registry no.		H_A	H_B	H_C	H_D	H_E	R
54996-29-1	2	4.29 dd, $J_{AB} = J_{AD}$ = 8 Hz, 1 H	3.84 dd, $J_{BA} = J_{BD}$ = 8 Hz, 1 H	2.41 dd, J_{CE} = 16 Hz J_{CD} = 8 Hz, 1 H	2.24 (m, 1 H)	2.06 dd, J_{EC} = 16 Hz J_{ED} = 9 Hz, 1 H	0.91–1.84 (br m, 11 H)
61129-25-7	2-*d*	4.29 dd, $J_{AB} = J_{AD}$ = 8 Hz, 1 H	3.84 dd, $J_{BA} = J_{BD}$ = 8 Hz, 1 H	2.41 dd, J_{CE} = 16 Hz J_{CD} = 8 Hz, 1 H	2.24 (m, 1 H)	2.06 dd, J_{EC} = 16 Hz J_{ED} = 9 Hz, 1 H	
40541-50-2	3	4.16 (m, 2 H)		2.30 (m, 1 H)	2.14 (m, 1 H)	2.03 (m, 1 H)	0.91–1.94 (br m, 11H)
61129-26-8 (cis)	3-*d*	4.16 (m, 2.00 H)[a]		2.30 (br d, 0.91 H)[a]	2.14 (m, 0.55 H)[a]	2.03 (m, 0.55 H)[a]	
61129-27-9 (trans)							
1679-49-8	4	4.34 dd, $J_{AB} = J_{AD}$ = 8 Hz, 1 H	3.78 dd, J_{BA} = 8 Hz J_{BD} = 6 Hz, 1 H	2.57 (m, 2 H)		2.01 dd, J_{ED} = 7 Hz J_{EC} = 15 Hz, 1 H	1.17 (d, J = 6 Hz, 3 H)
1679-47-6	5	4.19 (m, 2 H)		2.42 (m, 1 H)	1.87 (m, 1 H)	2.42 (m, 1 H)	1.25 (d, J = 7 Hz, 3 H)

[a] Integrations accurate to ± 5.0%.

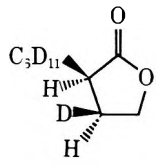
Chart III



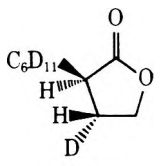
2-*d*



3-*d*



3-*d-cis*



3-*d-trans*

unsaturated ketone, direct evidence for hydrogen abstraction by the β-carbon atom.

The formation of the 1:1 mixture of 3-*d-cis* and 3-*d-trans* suggests, formally at least, that the abstraction process leading to α-solvent addition involves an intermediate radical pair, sufficiently long lived that its collapse occur in a totally nonstereoselective manner. This result would appear to rule out the theoretically interesting possibility that α-solvent addition proceed stereospecifically via a concerted $[_\sigma 2 + _\pi 2]$ cycloaddition of a cyclohexyl CH to the olefinic component of 1.[21] This, however, may not be the case. That is, under our rather lengthy irradiation conditions, required to secure 3-*d*, there is ample opportunity for the initially formed 3-*d-cis* to undergo photochemical equilibration via an α-cleavage process. In this regard, Simonaitis and Pitts demonstrated several years ago that α-methyl-γ-butyrolactone yields *cis*- and *trans*-crotyl formate via an efficient (i.e., Φ = 0.39) α-cleavage process.[22]

Finally, our observation of β adduct 2-*d*, labeled with deuterium only on the cyclohexyl ring, is completely consistent with the reaction pathway outlined in Chart I for β-solvent addition (i.e., hydrogen abstraction initiated by the carbonyl oxygen). However, it requires that the abstracted deuterium be completely lost to the environment during the course of the reaction. A similar, but incomplete, loss (ca. 90%) of deuterium in the photochemical cyclization of several α-methylene ketones was taken recently as strong support for the intermediacy of an enol.[23] All attempts on our part, however, to locate and/or retain a fraction of the initially abstracted deuterium on the α carbon of 2-*d* met with failure. In addition, irradiation of 1 in cyclohexane saturated with D_2O did not lead to incorporation of deuterium in 2. A detailed mechanism for formation of the β-solvent adduct therefore remains an open question.

Experimental Section

Materials and Equipment. VPC separations and yields were accomplished on either a Varian Aerograph Model 920 or a Perkin-Elmer Model 3920 gas chromatograph, the latter equipped with a thermal gradient collector. The following columns were employed: A,25% QF-1, 10 ft × 0.375 in.; B, 25% SE-30, 10 ft × 0.375 in.; C, 6% QF-1 10 ft × 0.25 in. The column oven was operated at 140–205 °C and the helium carrier gas flow rate was 100 ml/min. Compounds purified by VPC were obtained as colorless liquids. IR and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. Internal standard for the ^1H NMR spectroscopy was Me_4Si. Solutions were dried over $MgSO_4$. Spectroquality cyclohexane employed in the photochemical experiments was dried over 4A molecular sieves prior to use. Cyclohexane-d_{12} (99.5% D) was obtained from Stohler Isotope Chemicals. The photochemical experiments were carried out with a Hanovia Model L mercury lamp (no. 679A-36) in a quartz immersion well using Corex (no. 9700) or Vycor (no. 7910) as filter.

3-Cyclohexylidenedihydro-2(3*H*)-furanone (7).[17] Lactone 7 prepared by condensation of butyrolactone with cyclohexanone had the following spectral properties: IR 2935 (s), 1750 (s, br), 1655 (s), 1198 cm^{-1} (s); NMR (60 MHz) δ 1.4–3.18 (m, 12 H), 4.20 (t, J = 8 Hz, 2 H).

4-Cyclohexyl-2(5*H*)-furanone (8). Lactone 8, prepared by the method of Linville and Elderfield,[18] had the following spectral properties: IR 2930 (s), 1755 (s, br), 1640 (m), 1035 cm^{-1} (s); NMR (60 MHz) δ 0.97–2.50 (m, 11 H), 4.62 (d, J = 1.8 Hz, 2 H), 5.63 (dd, $J_1 = J_2$ 1.8 Hz, 1 H).

3-Cyclohexyldihydro-2(3*H*)-furanone (3). A suspension containing 447 mg (2.70 mmol) of lactone 7, 100 mg of palladium on carbon (10%), and 12 ml of MeOH was stirred under a H_2 atmosphere

for 5 h at room temperature. The resulting suspension was filtered, poured into H_2O, and extracted with ether. The organic phase was washed with H_2O and brine and dried. Removal of the solvent in vacuo afforded 383 mg (85%) of lactone **3**. After VPC purification on column A, **3** had the following spectral data: IR 2940 (s), 2870 (s), 1780 (s), 1455 (m), 1375 (m), 1160 (m), 1090 (m), 1030 cm^{-1} (m); NMR (60 MHz) δ 0.80–2.58 (m, 14 H), 3.95–4.40 (m, 2 H); for 220-MHz NMR data see Table I.

4-Cyclohexyldihydro-2(3*H*)-furanone (2). A suspension containing 15 mg (0.90 mmol) of lactone **8**, 6 mg of palladium on carbon (10%), and 6 ml of MeOH was stirred under a H_2 atmosphere for 4 h at room temperature. The suspension was then filtered, poured into H_2O, and extracted with ether. The organic phase was washed with H_2O and brine and dried. Partial removal of solvent in vacuo afforded an oily residue from which lactone **2** was isolated by preparative VPC employing column B. Lactone **2** had the following spectral data: IR 2940 (s), 2860 (s), 1780 (s), 1455 (m), 1175 (s), 1050 (m), 1020 cm^{-1} (s); for 220-MHz NMR data see Table I.

Photolysis of 2(5*H*)-Furanone (1) in Cyclohexane. A solution of 220 mg (2.62 mmol) of lactone 1[13] in 250 ml of cyclohexane was flushed with N_2 for 20 min and then irradiated through Corex for 7 h under nitrogen. The photolysate was then concentrated in vacuo to afford 261 mg of an oily liquid which contained **2** and **3** in 13 and 16% yield, respectively. After VPC separation on column A, **2** and **3** were identical in all respects (e.g., VPC retention time, IR, 220-MHz NMR) with the authentic samples prepared above.

Photolysis of 2(5*H*)-Furanone (1) in Cyclohexane-d_{12}. A solution containing 15 mg of lactone **1** and 5g of cyclohexane-d_{12} was placed in a quartz test tube (1 × 20 cm) fitted with a nitrogen inlet. The solution was flushed with nitrogen for 30 min and then irradiated through Corex for 20 h under nitrogen. After 20 h, the progress of the reaction was monitored by VPC on column C; approximately 80% of **1** was comsumed. To the photolysis mixture was added an additional 15 mg of **1**, and the mixture was irradiated for 20 h and then monitored. This process was continued until 480 mg of **1** had been destroyed. At this point the excess solvent was removed by distillation and the residue purified by VPC to yield (400–600 μg) **2-*d*** and **3-*d***. The deuterium incorporation as determined by Fourier transform 220-MHz NMR is given in Table I. Model studies with α-deuterio-α-methyl-γ-butyrolactone indicate that deuterium was not lost during purification. Examination of the recovered solvent by NMR revealed negligible hydrogen incorporation.

Acknowledgments. It is a pleasure to acknowledge the support of this investigation by Research Corporation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. The 220-MHz NMR spectra were obtained at the Middle Atlantic Regional NMR Facility (NIH RR542) at the University of Pennsylvania.

Registry No.—**1**, 497-23-4; **7**, 21681-63-0; **8**, 30088-97-2; butyrolactone, 96-48-0; cyclohexanone, 108-94-1; cyclohexane-d_{12}, 1735-17-7.

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Steroids and Related Natural Products. 94. Synthesis of Toad Venom Cardenolides[1]

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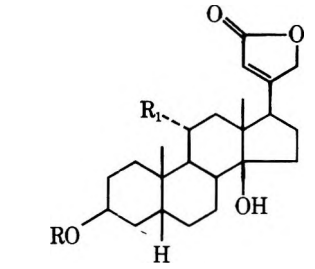
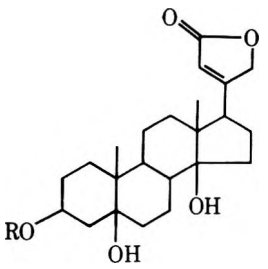
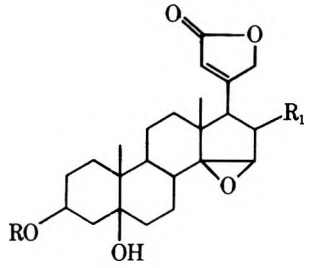
Some species of the milkweed butterfly family (Danaidae) have been found by Reichstein and colleagues to contain cardenolides.[3] The occurrence of such cardiac active plant constituents in these particular butterflies has been nicely correlated with their feeding habits which involve certain cardenolide containing plants (e.g., from the Asclepiadaceae family) and their need for an exogenous source of defensive substances. In 1970, Meyer and colleagues[4] reported the presence of seven cardenolides in the Chinese toad venom preparation Ch'an Su. The constituents included digitoxigenin (**1a**), sarmentogenin (**1b**), periplogenin (**2a**), and two previously unknown 14,15β-epoxycardenolides (**3a** and **3b**). Whether such cardenolides represent a normal biosynthetic pathway in venom production characteristic of certain amphibians of the Bufonidae family or instead are initially obtained by ingestion of Asclepiadaceae-type plant eating insects poses an interesting biochemical question. However, the discovery[4a] of two cardenolides bearing suberic acid ester groups (e.g., **1c**) in Ch'an Su and the more recent isolation[5] of sarmentogenin (**1b**), 3-suberoylarginine, and 3-pimeloylarginine esters from the skin of *Bufo vulgaris formosus*



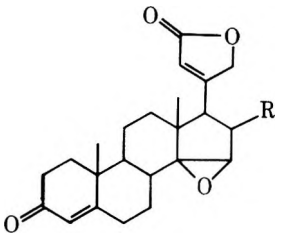
1a, R = R = H
b, R = H, R_1 = OH
c, R = $CO(CH_2)_6CO_2H$; R_1 = H



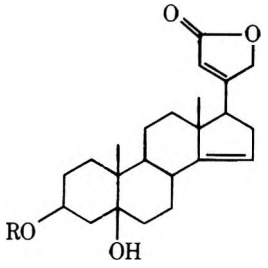
2a, R = H
b, R = $COCH_3$



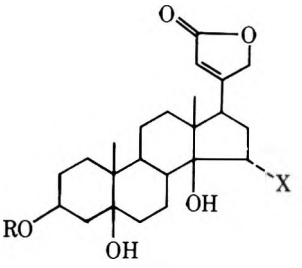
3a, R = R_1 = H
b, R = H; R_1 = $OCOCH_3$
c, R = $COCH_3$; R_1 = H



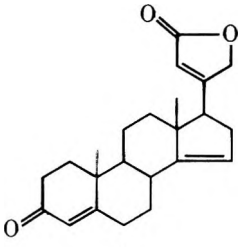
4a, R = H
b, R = $OCOCH_3$



5a, R = H
b, R = $COCH_3$



6a, R = H; X = I
b, R = H; X = Br
c, R = $COCH_3$; X = I
d, R = $COCH_3$; X = Br



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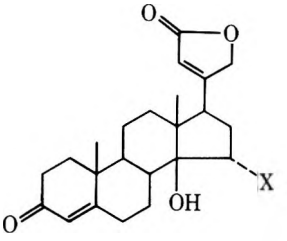

8a, X = I
b, X = Br

Boulenger suggests that cardenolide formation may reflect a normal biosynthetic avenue in toads of the genus *Bufo*.

After isolation of epoxycardenolides **3a** and **3b**, the Meyer group nicely assigned structures based on spectral evidence and analogous study of the compounds (**4a** and **4b**) resulting from a dehydration–oxidation sequence. In order to extend our cytotoxicity and antineoplastic evaluations of amphibian venom constituents we have completed a formal total synthesis of the toad venom cardenolide **3a** using periplogenin (**2a**) as relay. Our earlier synthesis of periplogenin (**2a**) from digitoxigenin (**1a**) was repeated to obtain sufficient starting material.[6] The subsequent route employed for obtaining epoxycardenolide **3a** was based on a series of reactions we developed previously for syntheses of bufotalin,[7a] marinobufotoxin,[7b] and bufalin.[7c] Thus, periplogenin (**2a**) was selectively dehydrated[7b] to 14-olefin **5a** which was converted[7c] to halohydrins **6a** and **6b**. Periplogenin acetate (**2b**) was analogously transformed via olefin **5b** to halohydrins **6c** and **6d**. Treatment of the halohydrins **6a** and **6b** or **6c** and **6d** with pyridine or basic aluminum oxide readily provided, respectively, the Ch'an Su constituent **3a** and acetate derivative **3c**. Epoxycardenolide **3a** was found to be identical with an authentic specimen obtained by the Meyer group[4] from Ch'an Su.

The stereochemical course of halohydrin addition to olefin **5** was conclusively established by selective reduction (Raney nickel)[7a] of the halohydrins represented by structure **6** to yield exclusively periplogenin (**2a**) and the corresponding acetate derivative **2b**. The very dependable stereochemical course of halohydrin reaction in this series was further demonstrated by conversion of 14-dehydrocanarigenone (**7**)[6] to the 3-oxo-4-ene **4a** by way of halohydrin **8**. Ketone **4a** was found identical with a specimen obtained by selective oxidation of epoxycardenolide **3a** followed by dehydration catalyzed by Amberlite CG-120 (H^+).

Experimental Section

The general experimental techniques in this study have been summarized in parts 93[1] and 91[6] of this series. The same procedures have been utilized for column and thin layer chromatography (on silica gel) and establishing the mutual identity of comparison specimens (e.g., infrared spectra in KBr).

14-Dehydroperiplogenin (5a). A mixture prepared from periplogenin (**2a**, 0.25 g), methanol (45 ml), and 35% hydrochloric acid (0.05 ml) was heated at reflux for 1.5 h, poured into ice–water, and extracted with chloroform. The solvent extract was washed with water and evaporated to dryness. The crude product was column chromatographed and the fraction eluted by *n*-hexane–acetone (5:1) was recrystallized from acetone–*n*-hexane to give 14-dehydroperiplogenin (**5a**, 0.13 g) as needles: mp 200–202 °C; λ_{max} (MeOH) nm (log ϵ) 217 (4.20); ν_{max} (KBr) 3500 (OH), 1798, 1777, 1726 (butenolide ring), 1630, 1623 (C=C), 1445, 1030, 898, 695 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 0.98 (3 H, s, 19-CH_3), 4.17 (1 H, broad s, 3α H), 4.76 (2 H, t, J = 2 Hz, 21-CH_2), 5.23 (broad s, 15-H), 5.89 (1 H, t, J = 2 Hz, 22-H); mass spectrum *m/e* 372 (M^+), 354 ($M^+ - H_2O$), 336 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.36; H, 8.70.

A 20-mg specimen of 14-dehydroperiplogenin was acetylated at room temperature with acetic anhydride (0.4 ml)–pyridine (0.28 ml) to give **14-dehydroperiplogenin acetate (5b,** 17 mg) as needles melting at 195–198°C (from acetone–*n*-hexane); λ_{max} (MeOH) nm (log ϵ) 217 (4.19); ν_{max} (KBr) 3480 (OH), 1784, 1752, 1730 (butenolide ring and ester CO), 1700, 1644, 1631 (C=C), 1450, 1255, 1245, 1240 (ester C–O), 1030, 890, 692 cm^{-1}; ^1h NMR (10% solution in $CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 1.01 (3 H, s, 19-CH_3), 2.09 (3 H, s, 3-$OCOCH_3$), 4.75 (2 H, t, J = 2 Hz, 21-CH_2), 5.05 (1 H, broad s, 3α H), 5.23 (1 H, broad s, 15α H), 5.88 (1 H, t, J = 2 Hz, 22-H); mass spectrum *m/e* 414 (M^+), 396 ($M^+ - H_2O$), 354 (M^+ – AcOH), 336 (M^+ – AcOH – H_2O).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.39; H, 8.25.

Synthesis of 3β,5β-Dihydroxy-14,15β-epoxycard-20(22)-enolide (3a). Method A. A solution of *N*-iodosuccinimide (30 mg) in acetone (3 ml)–water (3 ml) was added to 14-dehydroperiplogenin (**5a**, 30 mg) in acetone (4.5 ml). The mixture was stirred for 22 h at room temperature and a solution prepared from sodium sulfite (30 mg) and water (0.6 ml) was added. The solution was concentrated (to about one-third volume), poured into ice–water with stirring, and extracted with chloroform. The combined extract was washed with water, solvent was evaporated, and the crude iodohydrin (**6a**, 26 mg) was stirred in pyridine (2 ml) for 4 h at room temperature. Following removal of solvent the product was column chromatographed and the fraction eluted with *n*-hexane–acetone (5:1) was recrystallized from ethyl acetate–*n*-hexane to give **3β,5β-dihydroxy-14,15β-epoxycard-20(22)-enolide (3a,** 21 mg) as prisms melting at 217–220 °C.

When a 15-mg sample of the crude iodohydrin (**6a**, 15 mg), obtained as described above, was chromatographed on basic alumina with benzene–chloroform (19:1–9:1), the 14β,15β-epoxide (**3a**, 8.2 mg) was, after recrystallization, isolated as prisms melting at 217–219 °C.

Method B. Substitution of *N*-bromosuccinimide (15 mg) for *N*-iodosuccinimide in the method A reaction sequence with olefin **5a** (15 mg) led to 14 mg of the crude bromohydrin (**6b**). Conversion of the bromohydrin to 14β,15β-epoxide **3a** with pyridine provided an 8.4-mg (mp 216–219 °C) yield.

Method C. When *N*-bromoacetamide (15 mg) was substituted for *N*-iodosuccinimide or *N*-bromosuccinimide as described in method A or method B, olefin **5a** (15 mg) led to 16 mg of the crude bromohydrin (**6b**). Similar conversion of bromohydrin **6b** to 14β,15β-epoxide **3a** by use of pyridine as described in method A provided 8.7 mg of 14β,15β-epoxide **3a** (mp 217–220 °C): λ_{max} (MeOH) nm (log ε) 214 (4.19); ν_{max} (KBr) 3500 (OH), 3110, 3050 (CH), 1787, 1746 (butenolide ring), 1625 (C=C), 1445, 1170, 1135, 1030, 899, 697 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 1.00 (3 H, s, 19-CH_3) 3.47 (1 H, broad s, 15α-H), 4.16 (1 H, broad s, 3α-H), 4.76 (2 H, t, J = 2 Hz, 21-CH_2), 5.89 (1 H, t, J = 2 Hz, 22-H); mass spectrum m/e 388 (M^+), 370 ($M^+ - H_2O$), 352 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.23; H, 8.22.

The samples of 3β,5-dihydroxy-14,15β-epoxy-5β,14β-card-20(22)-enolide (**3a**) prepared by methods A–C were found to be identical with an authentic sample of the natural product (mp 200–221 °C, provided by Professor K. Meyer).

Synthesis of 3β-Acetoxy-5β-hydroxy-14,15β-epoxycard-20(22)-enolide (3c). Method A. Reaction of 14-dehydroperiplogenin acetate (**5b**, 25 mg) with hypoiodous acid prepared from *N*-iodosuccinimide (25 mg) was performed as described above for the preparation of iodohydrin **6a**. After treatment with pyridine and chromatographic purification (elution with 7:1 *n*-hexane–acetone and recrystallization from ethyl acetate–*n*-hexane) the crude iodohydrin acetate (**6c**, 23 mg) gave rise to 3β-acetoxy-5β-hydroxy-14,15β-epoxycard-20(22)-enolide (**3c**, 18 mg) as prisms melting at 217–220 °C.

Method B. The preceding reaction was repeated using 15 mg of olefin acetate **5b** and 15 mg of *N*-bromoacetamide. Alumina (basic) chromatographic treatment of the crude bromohydrin (**6d**, 14 mg) with benzene–chloroform (1:1) as eluent provided 7.8 mg of 14β,15β-epoxy acetate **3c** melting at 216–220 °C.

Method C. Alcohol **3a** (10 mg) was acetylated with acetic anhydride (0.014 ml)–pyridine (0.02 ml) and the product was isolated by column chromatography as described in method A. By this means 7 mg of 14β,15β-epoxy acetate **3c** was obtained which melted at 218–220 °C and was identical with the sample prepared by method A or method B; λ_{max} (MeOH) nm (log ε) 213 (4.18); ν_{max} (KBr) 3480 (OH), 3100, 3048 (CH), 1785, 1750, 1728 (butenolide ring and ester CO), 1700, 1642, 1626 (C=C), 1445, 1250, 1240 (ester C–O), 1170, 1135, 1030, 897, 695 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 1.02 (3 H, s, 19-CH_3), 2.08 (3 H, s, 3-$OCOCH_3$), 3.47 (1 H, broad s, 15α-H), 4.77 (2 H, a narrow quartet, J = 2.5 and 1.5 Hz, 21-CH_2), 5.24 (1 H, broad s, 3α-H), 5.88 (1 H, t, J = 2.5 Hz, 22-H); mass spectrum m/e 430 (M^+), 412 ($M^+ - H_2O$), 394 ($M^+ - 2H_2O$), 370 ($M^+ -$ AcOH).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.77; H, 7.89.

Periplogenin (2a). The crude iodohydrin (**6a**, 21 mg) prepared from 14-dehydroperiplogenin (**5a**, 22 mg) and *N*-iodosuccinimide (22 mg) was treated[7c] with freshly prepared Raney nickel (approximately 0.8 g) for 4 h at 18–20 °C in a nitrogen atmosphere. The solution was filtered and the filtrate was concentrated to provide an 18-mg residue, which was subjected to column chromatography. The fraction eluted by 1:3 *n*-hexane–acetone was recrystallized from methanol to afford 11 mg of periplogenin (**2a**) melting at 226–232 °C.

By an analogous reduction reaction the crude bromohydrin (**6b**, 10 mg) prepared from 14-dehydroperiplogenin (**5a**, 12 mg) and *N*-bromoacetamide (12 mg) was treated (under nitrogen) with freshly prepared Raney nickel (ca. 0.5 g). By the same isolation procedure, 5 mg of periplogenin (**2a**, mp 226–231 °C) was obtained. The specimens of periplogenin (**2a**) obtained by both procedures were found identical with natural periplogenin.

Periplogenin Acetate (2b). A sample of the crude iodohydrin acetate (**6c**, 18 mg) prepared from 14-dehydroperiplogenin acetate (**5b**, 20 mg) and *N*-iodosuccinimide (20 mg) was converted to periplogenin acetate (**2b**, 10 mg, mp 230–238 °C) using Raney nickel (about 0.5 g, 4 h at 18 °C) as summarized above for obtaining periplogenin (**2a**).

With the same nickel (approximately 0.3 g) procedure, 8 mg of the crude bromohydrin acetate (**6d**, obtained using *N*-bromosuccinimide) provided 3.8 mg of periplogenin acetate (**2b**) melting at 230–237 °C.

Both samples of periplogenin acetate (**2b**) were found identical with an authentic sample.

3-Oxo-14,15β-epoxycarda-4,20(22)-dienolide (4a). Method A. A solution of *N*-iodosuccinimide (30 mg) in acetone (3 ml)–water (3 ml) was added to 30 mg of 14-dehydrocanarigenone [3-oxocarda-4,14,20(22)-trienolide **7**] in acetone (4.5 ml). The remaining reaction sequence and isolation procedure was completed (except for 18 h with sodium sulfite and 3 h with pyridine) as described above for obtaining epoxycardenolide **3a**. Recrystallization from ethyl acetate–*n*-hexane afforded 20 mg of 3-oxo-14,15β-epoxy-14β-carda-4,20(22)-dienolide (**4a**) as prisms melting at 236–240 °C. The product was identical with the sample prepared below from 3β,5β-dihydroxy-14,15β-epoxy-card-20(22)-enolide (**3a**).

Method B. The preceding reaction was repeated using 15 mg of olefin **7** and 15 mg of *N*-bromoacetamide. Analogous treatment of the crude bromohydrin (**8b**, 14 mg) with pyridine provided epoxide **4a** (6.6 mg) melting at 236–239 °C which was identical with the sample prepared below from diol **3a**.

When the crude bromohydrin (**8b**, 10 mg) obtained by similar treatment of olefin **7** (12 mg) with *N*-bromosuccinimide (12 mg), was chromatographed in benzene–chloroform (14:1) on basic alumina 4.7 mg of epoxide **4a**, mp 237–240C, was isolated.

Method C (From 3β,5β-Dihydroxy-14,15β-epoxycard-20(22)-enolide, 3a). Epoxy alcohol **3a** (18 mg) in pyridine (0.48 ml) was oxidized (room temperature, 16 h) with chromium trioxide (17 mg)–pyridine (0.18 ml) complex. Excess reagent was removed with methanol and the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. The crude epoxy ketone (16 mg) was employed in the following dehydration reaction without further purification.

A mixture prepared from the epoxy ketone (15 mg), 0.15 g of Amberlite CG-120 (H^+ form), and methanol (1.5 ml) was stirred at room temperature for 8 h. The solution was filtered and concentrated to dryness and the crude product was purified by column chromatography. The fraction eluted with 9:1 *n*-hexane–acetone was recrystallized from ethyl acetate–*n*-hexane to yield 9.2 mg of epoxide **4a** melting at 237–241 °C (lit[7b] mp 237–248 °C); λ_{max} (MeOH) nm (log ε) 227–230 (4.33); ν_{max} (KBr) 3100, 3048, (CH), 1780, 1735, 1715 (butenolide ring and saturated ketone), 1700, 1623 (C=C), 1445, 1170, 1120, 1022, 890, 858, 780, 750 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 1.01 (3 H, s, 18-CH_3), 1.26 (3 H, s, 19-CH_3), 3.45 (1 H, broad s, 15α H), 4.78 (2 H, t, J = 2 Hz, 21-CH_2), 5.73 (1 H, broad s, 4-H), 5.88 (1 H, t, J = 2 Hz, 22-H); mass spectrum m/e 368 (M^+), 350 ($M^+ - H_2O$).

Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.95; H, 7.66. Found: C, 74.99; H, 7.63.

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Registry No.—**2a**, 514-39-6; **2b**, 13077-88-8; **3a**, 31655-31-9; **3c**, 31655-36-4; **4a**, 24366-48-1; **5a**, 60967-71-7; **5b**, 60967-72-8; **6a**, 60967-73-9; **6b**, 60967-74-0; **6c**, 60967-75-1; **6d**, 60967-76-2; **7**, 19637-08-2; **8**, 24366-46-9; *N*-iodosuccinimide, 516-12-1; *N*-bromosuccinimide, 128-08-5; *N*-bromoacetamide, 79-15-2.

References and Notes

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Novel Synthesis of 5,6,7,8-Tetrahydroindolizines[1]

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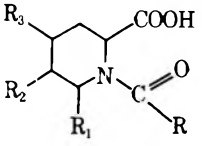
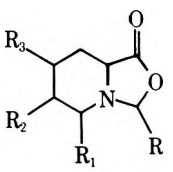
Several synthesis of 5,6,7,8-tetrahydroindolizines (THI) and octahydroindolizines (OHI) were developed in the past, with limitations in yields or substituents.[2]

We wish to report a new route to THI that allows the introduction of the desired substituents in all positions but 2. Since OHI can be obtained by reduction of THI this is also a new method of synthesis of OHI, some of which are biologically active natural compounds.[3-6]

The key step is the cycloaddition of ethyl propiolate to the easily available *N*-acyl-2-piperidinecarboxylic acid through a 1,3-dipolar intermediate[7,8] of type **2**. The cycloaddition of





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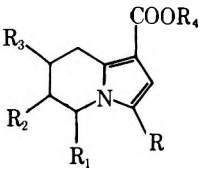
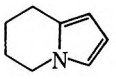
1, R = R_1 = R_2 = R_3 = H
3, R = R_1 = H; R_2–R_3 = C_6H_4
4, R = R_2 = R_3 = H; R_1 = COOH
5, R = CH_3; R_1 = R_2 = R_3 = H



6, R = R_1 = R_2 = R_3 = H; R_4 = C_2H_5
7, R = R_1 = H; R_2–R_3 = C_6H_4; R_4 = C_2H_5
8, R = CH_3; R_1 = R_2 = R_3 = H; R_4 = C_2H_5
9, R = R_2 = R_3 = H; R_1 = $COOC_2H_5$; R_4 = C_2H_5
10, R = CH_3; R_2 = R_3 = H; R_1 = $COOC_2H_5$; R_4 = C_2H_5
11, R = R_1 = R_2 = R_3 = R_4 = H



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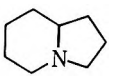

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propiolic esters to oxazolones has been described by Huisgen[7] as giving mixtures of 3- and 4-substituted pyrroles. Therefore, the cycloaddition of ethyl propiolate to substituted *N*-acyl-2-piperidinecarboxylic acids was expected to give 1- and 2-substituted THI, but as we found in pyrrolizidine synthesis[8] the reaction is regiospecific since only one isomer was isolated.

The NMR spectra of compounds **6** and **9** showed the presence of an AB quartet with $\Delta\nu$ values of 8 and 10 Hz, respectively, and therefore both are 1-substituted THI. We have found a smaller $\Delta\nu$ value for 1-carboethoxy-6,7-dihydropyrrolizidine (5 Hz),[8] and compound **7** has the same chemical shift for both protons as similar compounds reported in the literature.[9]

Decarboethoxylation of **6** was accomplished in 80% yield by hydrolysis and decarboxylation (**11** and **12**). A diester is isolated (**9, 10**) when the substituent on the 2-piperidinecarboxylic acid is a second carboxylic group because transesterification occurs owing to the sevenfold molar excess of ethyl propiolate.

By using this sequence of reactions δ-coniceine (**13**) (octahydroindolizine) was prepared in 67% overall yield after five steps, starting from commercially available 2-piperidinecarboxylic acid.

Experimental Section

Melting points were measured on a Kofler micro hot stage apparatus; infrared spectra were recorded using a Perkin-Elmer 735 B spectrometer. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R 12 spectrometer. Microanalyses were performed by Mrs. Martha Casanello of this university. Thin layer chromatography (TLC) and preparative thick layer chromatography were performed on silica gel GF-254.

***N*-Formyl-2-piperidinecarboxylic Acid (1).** Acetic anhydride (35 g) was added dropwise to a stirred and cooled (0–5 °C) solution of 2-piperidinecarboxylic acid (6.45 g, 0.05 mol) in 50 ml of formic acid (98%). Stirring was continued for 1 h at room temperature. Water (40 ml) was added and the solution evaporated to dryness to give 7.89 g (98%) of crystalline **1**. Recrystallization from ethanol gave analytically pure **1**: mp 85–87 °C; NMR ($CDCl_3$) δ 8.85 (s, 1, –COOH), 8.15 (s, 1, –COH), 5.30–3.30 (m, 3, protons on C_2 and C_6), 2.50–1.50 (m, 6, protons on C_3, C_4, and C_5); IR (Kbr) 1720, 1710 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 6.36; N, 8.91. Found: C, 53.40; H, 6.20; N, 9.03.

2-Formyl-3-carboxy-1,2,3,4-tetrahydroisoquinoline (3) was prepared in 98% yield by the same procedure, starting from 3-carboxy-1,2,3,4-tetrahydroisoquinoline prepared by us according to the procedure of Julian et al.[10] (recrystallized from ethanol): mp 114–116 °C; NMR ($CDCl_3$) δ 9.60 (s, 1, –COOH), 8.60 (s, 1, –CHO), 7.30 (s, 4, aromatic protons), 5.25 (t, 1, J = 6 Hz, proton on C_3), 4.90 (s, 2, protons on C_2), 3.45 (d, 2, J = 6 Hz, protons on C_4); IR (KBr) 1715, 1720 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3 \cdot H_2O$: C, 59.1; H, 5.90; N, 5.95. Found: C, 59.10; H, 6.10; N, 6.05.

***N*-Formyl-2,6-piperidindicarboxylic acid (4)** was prepared in 96% yield by the same procedure, starting from 2,6-piperidinedicarboxylic acid prepared by us according to Andersson and Soine[11] (recrystallized from ethanol), mp 190–192 °C. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.47; N, 6.96. Found: C, 47.65; H, 5.60; N, 6.83.

***N*-Acetyl-2-piperidinecarboxylic Acid (5).** The solution of 0.645 g (5 mmol) of 2-piperidinecarboxylic acid in 10 ml of acetic anhydride was stirred for 1 h. Water (10 ml) was added and the solution evaporated to dryness to give an oil. Chromatography on silica gel (15 g) and elution with dichloromethane–methanol (9:1) afforded **5** as a colorless oil (509 mg, 64%): NMR ($CDCl_3$) δ 8.60 (s, 1, COOH), 5.70–4.20 (m, 3, protons on C_2 and C_6), 3.70 (m, 2, protons on C_3), 2.30 (s, 3, CH_3–), 2.05–1.30 (m, 4, protons on C_4 and C_5). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.19. Found: C, 56.23; H, 7.68; N, 8.08.

Ethyl 5,6,7,8-Tetrahydroindolizine-1-carboxylate (6). A solution of 1.1 g (7 mmol) of **1** and 4.3 ml (50 mmol) of ethyl propiolate in 9 ml of acetic anhydride was heated for 2 h at 120 °C under a nitrogen atmosphere. The excess reagents were stripped to give an oil. Purification by column chromatography on 30 g of silica gel (elution with benzene–ethyl acetate, 1:1) gave 1.12 g (82%) of **6**: NMR ($CDCl_3$) δ 6.42 (AB quartet, 2, $\Delta\nu$ = 8, J = 3 Hz, olefinic protons), 4.25 (q, 2, J = 7 Hz, $-OCH_2-$), 3.88 (broad t, 2, protons on C_5), 3.05 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7), 1.35 (t, 3, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 67.00; H, 7.60; N, 7.10. Found: C, 67.20; H, 7.50; N, 6.80.

Ethyl benz[*f*]-5,10-dihydroindolizine-1-carboxylate (7) was prepared from **2** as **5** from **1**, but the reaction was carried out at 90 °C. The residue was purified by TLC (CH_2Cl_2) giving a 70% yield of **7**: NMR (D_2O) δ 7.30 (m, 4, aromatic protons), 6.68 (s, 2, olefinic protons), 5.08 (s, 2, protons on C_5), 4.35 (m, 6, $-OCH_2-$ and protons on C_{10}), 1.40 (t, 3, $-CH_3$). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 75.20; H, 6.09; N, 5.69. Found: C, 75.35; H, 6.14; N, 5.50.

Ethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1-carboxylate (8). A solution of 171 mg (1 mmol) of **5** and 0.5 ml (5 mmol) of ethyl propiolate in 1.5 ml of acetic anhydride was heated for 3 h at 120 °C under a nitrogen atmosphere. Solvents were evaporated to dryness giving an oily residue that was chromatographed on 5 g of silica gel (elution with dichloromethane) to give 130 mg (67%) of **8**: NMR ($CDCl_3$) δ 6.70 (s, 1, olefinic proton on C_2), 4.35 (q, 2, J = 7 Hz, $-OCH_2-$), 3.80 (m, 2, protons on C_5), 3.15 (m, 2, protons on C_8), 2.15 (s, 3, $-CCH_3$), 1.85 (m, 4, protons on C_6 and C_7), 1.4 (t, 3, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.59; H, 8.26; N, 6.76. Found: C, 69.70; H, 8.40; N, 6.80.

Diethyl 5,6,7,8-Tetrahydroindolizine-1,5-dicarboxylate (9). The procedure for the preparation of **9** was the same as the one described above, except that the residue was purified by TLC (CH_2Cl_2) affording 45% of the diester **9**: oil; NMR ($CDCl_3$) δ 6.50 (AB quartet,

2, $\Delta\nu$ = 10, J = 3 Hz, olefinic protons), 4.80 (t, 1, J = 4 Hz, proton on C_5), 4.40 (2 q superposed, 4, J = 7 Hz, $-OCH_2-$), 3.15 (m, 2, protons on C_8), 2.05–1.60 (m, 4, protons on C_6 and C_7), 1.35 (2 t superposed, 6, $-CH_3$). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 68.57; H, 7.75; N, 5.71. Found: C, 68.42; H, 7.80; N, 5.60.

Diethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1,5-dicarboxylate (10). It was prepared in 70% yield from 2,6-piperidinedicarboxylic acid as described for **9**. An analytical sample was obtained by TLC (CH_2Cl_2): NMR ($CDCl_3$) δ 6.30 (s, 1, proton on C_2), 4.80 (m, 1, proton on C_5), 4.25 (q, 4, J = 7 Hz, $-OCH_2-$), 3.40–1.60 [m, 9, $-CH_3$ and $-(CH_2)_3-$], 1.35 (t, 6, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.52; H, 7.52; N, 5.01. Found: C, 64.60; H, 7.75; N, 5.10.

5,6,7,8-Tetrahydroindolizine-1-carboxylic Acid (11). A solution of 386 mg (2 mmol) of **6** and 700 mg of KOH in 9 ml of methanol–water (2:1) was refluxed for 3 h, cooled, diluted with water (20 ml), and acidified to pH 1. The precipitate was filtered and dried giving 300 mg (90%) of **11** as colorless crystals. After recrystallization from ethanol it showed mp 151–153 °C dec; NMR ($CDCl_3$) δ 11.00 (broad s, 1, exchangeable with D_2O= –COOH), 6.68 (AB quartet, 2, $\Delta\nu$ = 10, J = 3 Hz, olefinic protons), 4.08 (broad t, 2, protons on C_5), 3.23 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7). Anal. Calcd for $C_9H_{11}NO_2$: C, 66.45; H, 6.66; N, 8.48. Found: C, 66.20; H, 6.69; N, 8.45.

5,6,7,8-Tetrahydroindolizine (12). A thin-walled glass tube containing 820 mg (5 mmol) of **11** was introduced in a bath at 240 °C until gas evolution ceased (5 min), leaving a brown oil. Chromatography on 60 g of silica gel using benzene as eluent afforded 520 mg (88%) of **12** as a colorless oil, which was homogeneous on TLC (benzene–ethyl acetate, 1:1): NMR ($CDCl_3$) δ 6.50 (d, 1, proton on C_1), 6.10 (t, 1, proton on C_2), 5.80 (d, 1, proton on C_3), 3.95 (broad t, 2, protons on C_5), 2.80 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7). This compound was not stable enough to be analyzed.

Octahydroindolizine (δ-Coniceine, 13). A solution of 242 mg (2 mmol) of **12** in 20 ml of ethanol was hydrogenated for 24 hr at 3 atm using 200 mg of 10% palladium on carbon. The catalyst was filtered off and the filtrate evaporated, giving 240 mg (98%) of pure **13**. The picrate, recrystallized from methanol, had mp 225–228 °C (lit.[4] 224–228 °C). Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.20; H, 5.60; N, 15.7. Found: C, 47.30; H, 5.50; N, 15.8.

Registry No.—**1**, 54966-20-0; **2**, 61009-74-3; **3**, 61047-23-2; **4**, 61009-75-4; **5**, 61009-76-5; **6**, 61009-77-6; **7**, 61009-78-7; **8**, 61009-79-8; **9**, 61009-80-1; **10**, 61009-81-2; **11**, 61009-82-3; **12**, 13618-88-7; **13**, 13618-93-4; **13** picrate, 5210-66-2; 2-piperidinecarboxylic acid, 535-75-1; ethyl propiolate, 623-47-2; 3-carboxy-1,2,3,4-tetrahydroisoquinoline, 35186-99-3; 2,6-piperidinedicarboxylic acid, 499-82-1.

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A Convenient Synthesis of (±)-Glaziovine and (±)-*N*-Methyloreoline

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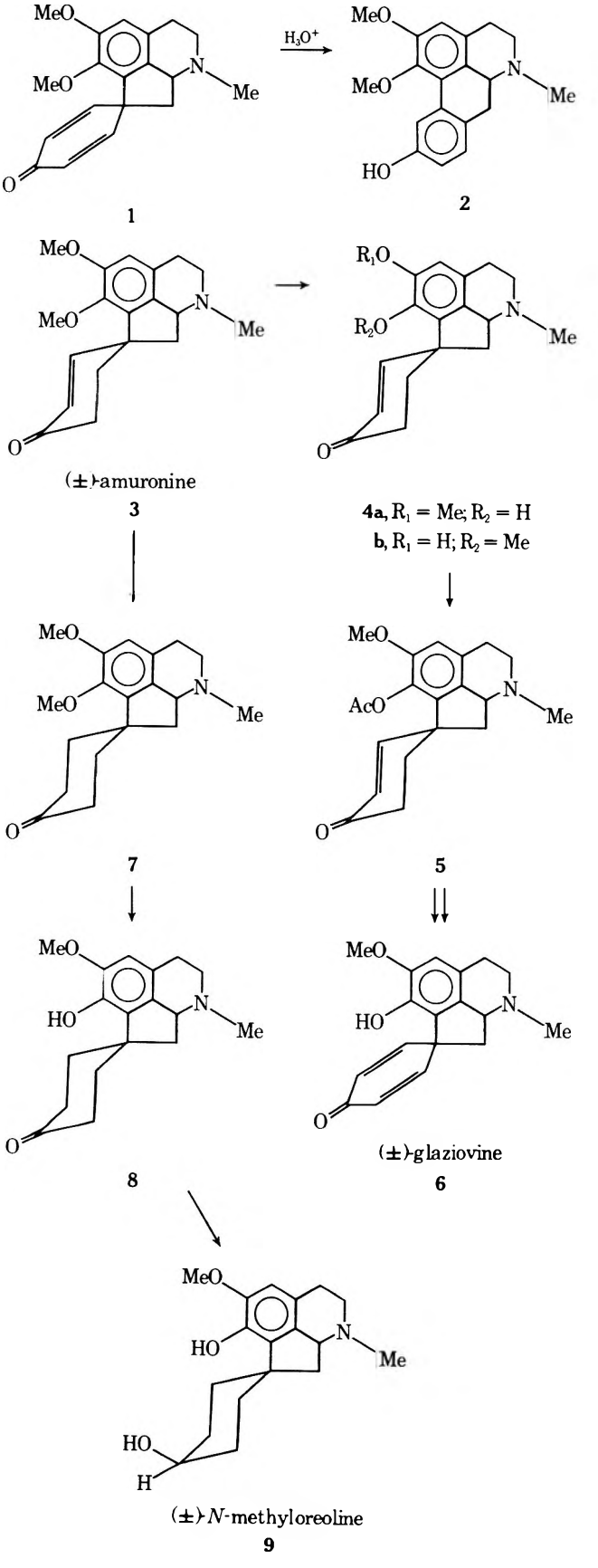
Preferential O-demethylation of isoquinolines with mineral acids under controlled conditions has provided access to a variety of phenolic isoquinoline alkaloids.[1] However, this process cannot be applied directly to proaporphine alkaloids containing a dienol or dienone system since these rearrange in the presence of strong acids to aporphines; e.g., pronuciferine (**1**) undergoes the dienone–phenol rearrangement in aqueous sulfuric acid to give 1,2-dimethoxy-10-hydroxyaporphine (**2**).[2] We have found that selective O-demethylation of amuronine (**3**) and tetrahydropronuciferine (**7**) proceeds smoothly in refluxing hydrochloric acid to furnish the corre-



sponding 1-hydroxy-2-methoxy proaporphines in good yield, providing a convenient synthesis of (±)-glaziovine (**6**)[3] and (±)-*N*-methyloreoline (**9**).[4] The preferential O-demethylation at C-1 is presumably due to a crowding of the C-1 methyl out of plane of the aromatic ring. Thus, when synthetic[5] (±)-amuronine (**3**) was refluxed with 20% aqueous hydrochloric acid it afforded (±)-11,12-dihydroglaziovine (**4a**) in 60% yield. The IR, NMR, and mass spectra were identical with those reported in the literature.[6] Evidence that the methoxyl group in **4a** was at C-2 rather than C-1 was forthcoming from a comparison of the methoxyl signal in the NMR spectrum of the corresponding 1-methoxy-2-hydroxy isomer linearisine (**4b**).[2,7] The structure of **4a** was unequivocally established by conversion of this compound to glaziovine. Acetylation of **4a** with acetic anhydride in the presence of *N,N*-dimethyl-4-pyridineamine[8] gave (±)-1-*O*-acetyl-11,12-dihydroglaziovine (**5**), which was converted to (±)-glaziovine by bromination and dehydrobromination essentially as described by Casagrande et al.[6]

(±)-8,9,11,12-Tetrahydropronuciferine (**7**), prepared from amuronine by catalytic hydrogenation,[5] was refluxed with 20% hydrochloric acid to give (±)-8,9,11,12-tetrahydroglaziovine (**8**), mp 97 °C (ether) (Casagrande et al.[6] report mp 160–162 °C), in 55% yield. The structure of **8**, based on analytical and spectral data, was confirmed by comparison with a sample prepared by catalytic hydrogenation of **4a**. Reduction of **8** with lithium triethylborohydride followed by chromatography gave predominantly the axial alcohol, (±)-*N*-methyloreoline (**9**), identical with a sample prepared by hydrogenation of glaziovine over platinum oxide.[6]

Experimental Section[9]

(±)-11,12-Dihydroglaziovine (4a). A solution of 1.4 g (4.47 mmol) of (±)-amuronine in 50 ml of 20% HCl was refluxed for a 24-h period under a N_2 atmosphere. The resulting dark solution was cooled and concentrated under vacuum to yield a dark residue which was dissolved in 25 ml of distilled water. The acidic solution was neutralized carefully with solid $NaHCO_3$ and extracted with chloroform (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to yield 0.9 g of a foam which crystallized from ether to yield (±)-11,12-dihydroglaziovine, mp 199–201 °C after further crystallization from ether (lit.[6] mp 199–200 °C), yield 60% (0.81 g): NMR δ_{CDCl_3} (Me_4Si) 2.4 (s, 3, *N*-methyl), 3.85 (s, 3, methoxyl), 6.09 (d, J = 10 Hz, 1, C-9 olefinic proton), 6.6 (s, 1, aromatic), 6.8 (d, J = 10 Hz, 1, C-8 olefinic proton); IR (KBr) 1681 cm^{-1} (C=O); UV λ_{max} (EtOH) 227 nm (log ϵ 4.66), 278 (3.45); MS *m/e* 299 (M^+, 100), 298 (87), 257 (19), 256 (99).

(±)-1-*O*-Acetyl-11,12-dihydroglaziovine (5). To a solution of 0.168 g (0.56 mmol) of **4a** in 10 ml of CH_2Cl_2 stirred at room temperature under N_2 was added 0.75 ml of triethylamine, 0.07 g of *N,N*-dimethyl-4-pyridineamine, and 0.05 ml of acetic anhydride. The reaction mixture was stirred for 30 min, diluted with 20 ml of CH_2Cl_2, and washed with water (3 × 5 ml) and saturated $NaHCO_3$ solution (1 × 5 ml). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to yield 0.234 g of a foam which was crystallized from ether to yield (±)-1-*O*-acetyl-11,12-dihydroglaziovine, 0.18 g (95% yield): mp 176–178 °C (lit.[6] mp 178 °C); NMR δ_{CDCl_3} (Me_4Si) 2.15 (s, 3, *O*-acetyl), 2.4 (s, 3, *N*-methyl), 3.75 (s, 3, methoxyl), 6.0 (d, J = 10 Hz, 1, C-8 olefinic proton), 6.65 (s, 1, aromatic), 6.7 (d, J = 10 Hz, 1, C-8 olefinic proton); IR (KBr) 1754, 1672 cm^{-1} (C=O); UV λ_{max} (EtOH) 223 nm (log ϵ 4.36), 283 (3.4); MS *m/e* 341 (M^+, 66), 340 (56), 298 (100), 256 (47).

(±)-8,9,11,12-Tetrahydropronuciferine (7):[5] mp 124–126 °C; NMR δ_{CDCl_3} (Me_4Si) 2.45 (s, 3, *N*-methyl), 3.85 (s, 6, methoxyls), 6.65 (s, 1, aromatic); IR (KBr) 1718 cm^{-1} (C=O); UV λ_{max} (EtOH) 285 nm (log ϵ 3.38); MS *m/e* 315 (M^+, 28), 314 (100), 272 (55).

(±)-8,9,11,12-Tetrahydroglaziovine (8) was prepared as described for **4a**, in 55% yield: mp 97 °C (ether); NMR δ_{CDCl_3} (Me_4Si) 2.45 (s, 3, *N*-methyl), 3.9 (s, 3, methoxyl), 6.55 (s, 1, aromatic), 6.45–6.9 (bd, s, 1 phenolic OH); IR (KBr) 1718 cm^{-1} (C=O); UV λ_{max} (EtOH) 285 nm (log ϵ 3.42); MS *m/e* 301 (M^+, 34), 300 (100), 259 (13), 258 (75).

(±)-*N*-Methyloreoline (9). To a stirred solution of 0.098 g (0.325 mmol) of **8** in 10 ml of THF cooled to −70° under a nitrogen atmosphere was added dropwise 0.33 ml (0.33 mmol) of a 1 M solution of lithium triethylborohydride in THF. After addition, the reaction mixture was stirred for 0.5 h, warmed to room temperature, and acidified with acetic acid–water (6:1). The resulting solution was neutralized with saturated $NaHCO_3$ and extracted with chloroform (3 × 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to yield 0.083 g of a foam which was chromatographed on silica gel (eluted with chloroform) and crystallized from ether to give (±)-*N*-methyloreoline: mp 189–192 °C (lit.[6] mp 187–189 °C); NMR δ_{CDCl_3} (Me_4Si) 2.39 (s, 3, *N*-methyl), 3.98 (s, 3, methoxyl), 6.49 (s, 1, aromatic); UV λ_{max} (EtOH) 286 nm (log ϵ 3.37); MS *m/e* 303 (M^+, 40), 302 (100), 261 (16), 260 (85).

Registry No.—**3**, 19647-85-9; **4a**, 54274-43-0; **5**, 54169-67-4; **6**, 17127-48-9; **7**, 19647-93-9; **8**, 50300-14-6; **9**, 58166-04-4.

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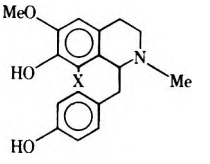

10, X = H
11, X = Br

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An Improvement in the Doebner–Miller Synthesis of Quinaldines

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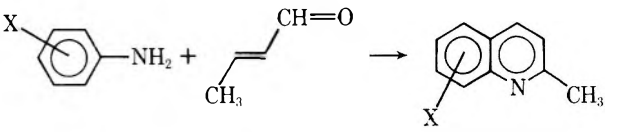
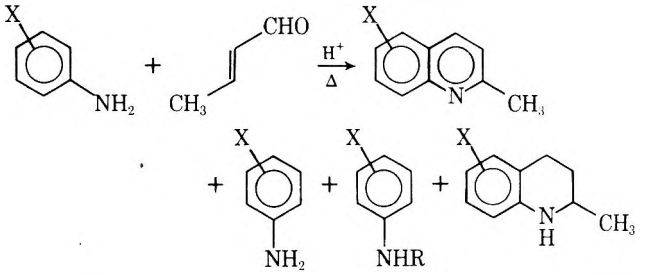
Since its discovery in 1881,[1] the Doebner–Miller reaction has found a great deal of synthetic utility for the preparation of substituted quinaldines (2-methylquinolines). Unlike the closely related Skraup synthesis of quinolines, the Doebner–Miller reaction is experimentally much simpler, and not nearly as hazardous to run.[2] However, the method does suffer from some major disadvantages. The yields reported are usually low owing to the many by-products formed in the reaction. Depending upon the particular conditions employed, a typical product mixture obtained from the reaction of an aniline with crotonaldehyde (or crotonaldehyde precursor) in strongly acidic solution consists of the desired quinaldine contami-

Table I



Aniline X	Registry No.	Quinaldine complex[n] (Q)	Registry no.	% yield	Mp, °C	Quinaldine mp, °C	Registry no.
4-F	371-40-4	6-F-Q·HCl·½$ZnCl_2$	61075-86-3	54	238–241	54–56[a]	1128-61-6
4-Cl	106-47-8	6-Cl-Q·HCl·½$ZnCl_2$	61075-87-4	53	238–241	94–95[b]	92-46-6
H	62-53-3	Q·HCl·½$ZnCl_2$·½H_2O	61075-88-5	55	240–243[c]	*d*	91-63-4
4-CH_3	106-49-0	6-CH_3-Q·HCl·½$ZnCl_2$	61075-89-6	52	210–212	55–58[e]	877-43-0
4-OCH_3	104-94-9	6-OCH_3-Q·HCl·½$ZnCl_2$·½H_2O	61075-90-9	51	198–200	65–67[f]	1078-28-0
2-Cl	95-51-2	8-Cl-Q·HCl·½$ZnCl_2$	61075-91-0	43	257–260 dec	66–68[g]	3033-82-7
2-CH_3	95-53-4	8-CH_3-Q·HCl·½$ZnCl_2$	61075-92-1	55	258–261 dec[h]	*i*	1463-17-8
2-Br	615-36-1	8-Br-Q·HCl·½$ZnCl_2$	61075-93-2	50	263–266 dec	67–68[j]	61047-43-6
2-OCH_3	90-04-0	8-OCH_3-Q·HCl·½$ZnCl_2$	61075-94-3	48	219–220 dec	124–125[k]	3033-80-5
3-Cl	108-42-9	7-Cl-Q·HCl·½$ZnCl_2$	61075-95-4	42	234–236	75–77[l]	4965-33-7
3-Br	591-19-5	7-Br-Q·HCl·½$ZnCl_2$	61075-96-5	47	250–253 dec	77–79[m]	4965-34-8

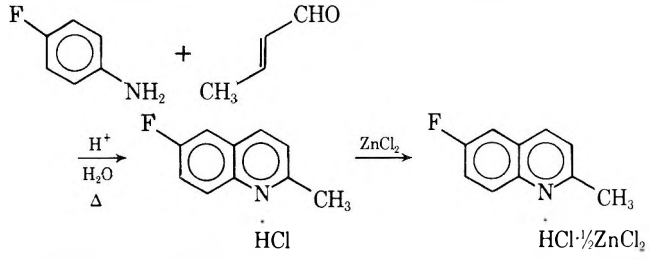
[a] Lit.[4] mp 57–59 °C. [b] Lit.[5] mp 93 °C. [c] Lit.[3] mp 240 °C. [d] Oil, IR identical with that of authentic material. [e] Lit.[6] mp 59.5 °C. [f] Lit.[6] mp 67 °C. [g] Lit.[5] mp 68 °C. [h] Lit.[3] mp 273 °C. [i] Oil, lit.[3] mp 27 °C. [j] Lit.[7] mp 69–69.5 °C. [k] Lit.[8] mp 125 °C. [l] Lit.[9] mp 76–78 °C. [m] Lit.[10] mp 77 °C. [n] Satisfactory analytical values were reported for all complexes.



nated with varying amounts of unreacted aniline, various *N*-alkylanilines, and 1,2,3,4-tetrahydroquinaldine. Isolation and purification of quinaldines from such reaction mixtures is often quite tedious, and the many manipulations involved also tend to lower the recovery of the desired product.

Since large amounts of 6-fluoroquinaldine were needed as an intermediate, we investigated the Doebner–Miller reaction as a potential method of preparation of this compound, and during the course of this work discovered an improved method of isolation of the product. Quite simply, it was found that when the reaction of *p*-fluoroaniline with crotonaldehyde under standard Doebener–Miller conditions was completed, addition of an equimolar amount of zinc chloride to the reaction mixture caused precipitation of a brown, curdy solid. Examination of the filtrate revealed that virtually all of the basic products had been removed.

When this crude, complex mixture was washed with 2-propanol, all of the impurities were dissolved and the bright yellow or gold crystalline solid which remained proved to be a pure 2:1 complex of 6-fluoroquinaldine hydrochloride and zinc chloride. The yield was consistently 50–55%.



A search of the literature revealed that only a few such complexes have been reported previously.[3,4] However, this method of purification seems to have received little attention over the years, perhaps because of a lack of experimental details and no reported yields in the earlier work.

The method was found suitable for the preparation of a number of other quinaldines. Starting with para- or ortho-substituted anilines, 6- and 8-substituted quinaldines, respectively, were obtained and isolated as their complexes. Of particular interest were results starting from meta-substituted anilines in which both 5- and 7-substituted quinaldines are formed with the 7 isomers as the major products. With only a slight variation in the workup procedure, the zinc chloride complexes of the 7 isomers could be isolated completely free of any of the 5 isomers. These results are summarized in Table I. Also included are the melting points of the free quinaldines which were recovered essentially completely from the complexes by treating an aqueous slurry with excess ammonium hydroxide.

Experimental Section

Melting points are uncorrected. Vapor phase chromatographic (VPC) analyses were performed on a Varian Aerograph 2100 instrument using a 6-ft 2% SE-30 on Chromosorb W column. Microanalyses were performed by Paul Olson and the microanalytical group of these laboratories.

Quinaldine Hydrochloride–$ZnCl_2$ Complex. General Procedure. To a solution of 0.20 mol of the aniline in 100 ml of 6 N HCl heated under reflux was added dropwise with stirring 17.3 g (0.21 mol) of 85% aqueous crotonaldehyde slowly over a 0.5–1-h period. After addition was complete, the dark solution was heated for an additional 0.5–1 h or until a VPC of a basified aliquot showed that no more aniline remained. The reaction mixture was cooled to room temperature and washed with ether to remove a small amount of tar. To the clear solution was added 27.2 g (0.20 mol) of anhydrous $ZnCl_2$ with vigorous stirring. A precipitate appeared as an oil or a solid usually in a few minutes. The mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C in an ice bath. After stirring for an additional 15 min at this temperature, the brown or yellow granular solid was filtered, washed with cold 3 N HCl, and sucked reasonably dry with air. The solid was transferred to a beaker, stirred with 150–200 ml of 2-propanol, and then filtered, washed with 2-propanol until the washings were almost colorless, and washed with ether and air dried to provide the quinaldine hydrochloride–zinc chloride coimplex as a bright yellow or gold crystalline solid.

7-Chloroquinaldine Hydrochloride–$ZnCl_2$ Complex. The Doebner–Miller reaction with *m*-chloroaniline was run exactly as above. Addition of $ZnCl_2$ caused precipitation of a dark oil and the whole mixture was heated to reflux to give a clear brown solution. Upon cooling to room temperature with stirring, a tacky brown solid was obtained. Purification in the usual manner with 2-propanol gave the 7-chloroquinaldine hydrochloride–$ZnCl_2$ complex as a pale yellow solid. The free base was pure by VPC.

7-Bromoquinaldine Hydrochloride–$ZnCl_2$ Complex. The complex obtained starting from *m*-bromoaniline in the usual manner proved to be a thick gum which was insoluble in boiling 6 M HCl. Addition of more acid and water had no effect, and the mixture was cooled to room temperature. Treatment of the brown gum even with

boiling 2-propanol failed to dissolve the impurities. The product was successfully purified by triturating with boiling anhydrous ethanol, cooling to room temperature, filtering, and washing with ethanol, then ether, then air drying to give the pure complex as a pale yellow solid.

Isolation of Quinaldines. Each complex from above was placed in a separatory funnel and shaken with ~150 ml of cold water. To this slurry was added ~50 ml of concentrated ammonium hydroxide and the slurry was shaken again. The resulting oil or solid was extracted into ether (two or three times), dried ($MgSO_4$), filtered, and evaporated to dryness. Except in the cases of quinaldine and 8-methylquinaldine (yellow-brown oils), the products were obtained as yellow or white crystalline solids which were >98% pure by VPC. The yields were approximately quantitative. To obtain the melting points listed in Table I, the quinaldines were transferred to a filter funnel with cold hexane and air dried.

Acknowledgment. The author wishes to express his sincere appreciation to Mr. David L. Anderson for his competent technical assistance.

Registry No.—Crotonaldehyde, 4170-30-3; $ZnCl_2$, 7646-85-7.

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Carbohydrate Thio Ortho Esters. 3.[1] Transformation to Thioglycosides with Deactivated Raney Nickel

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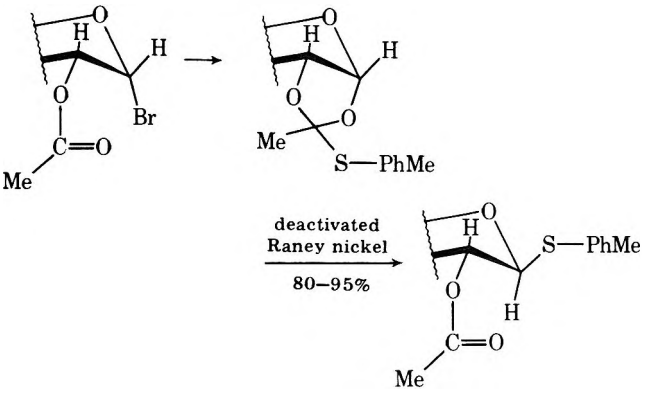
Phenyl 1-thioglycosides have been used inter alia for affinity chromatography (linked by a *p*-amino group substituent and a spacer to an insoluble matrix such as Sepharose) of glycosidases,[2] for stereoselective Hg^{2+}-mediated solvolysis to *O*-glycosides[3] and for synthesis of glycosyl benzoates and halides.

The phenyl 1-thioglycoside grouping has been synthesized by a number of different routes, for instance, nucleophilic substitution of the bromine in acetobromo sugars by sodium or potassium thiolates,[4] reduction of dithioacetals,[5] and thermal decomposition of arylazothioglycosides.[6] I now wish to report an improved, rapid, and efficient high-yield synthesis of peracetylated *p*-methylphenyl 1,2-*trans*-1-thioglycopyranosides using the route shown in Scheme I.

As mentioned in a previous report,[1] treatment of *p*-methylphenyl thio ortho esters in ethanol or 2-propanol with active Raney nickel gave the corresponding ethyl and isopropyl ortho esters in high yield instead of the expected 1,2-ethylidene acetals. An attempt to make cyclohexyl ortho esters by this method in toluene with azeotropically dried Raney nickel, gave a mixture of products, many of which still contained sulfur. Obviously the Raney nickel was deactivated by the toluene distillation so that desulfurization could not occur. Analysis of the reaction mixture revealed that the main

Scheme I



product formed was the *p*-methylphenyl 1,2-*trans*-1-thioglycoside. After testing different reaction conditions, a preparatively useful method was found for the synthesis of these compounds. Thioglycosides with the D-gluco, D-galacto, D-xylo, D-lacto, and D-glucurono configurations have been prepared in 80–95% yield.

The procedure is simple and consists of stirring the appropriate thio ortho ester[7] (mixture of exo and endo diastereomers) with deactivated Raney nickel (see Experimental Section) and a trace of *p*-methylthiophenol in toluene for ca. 10 min followed by filtration and evaporation. The residue (a colorless oil) was pure (TLC, NMR) 1-thioglycoside that crystallized on addition of a few drops of ethanol (except for the lacto derivative). The starting thio ortho esters were prepared from the appropriate acetobromo sugars and *p*-methylthiophenol.[7] The only detectable by-products in the preparation of the thio ortho esters are the corresponding thioglycoside and di-*p*-methylphenyl disulfide but these can easily be removed by chromatography if desired (cf. below).

A trial preparation of the thioglucoside, without purification of the thio ortho ester by chromatography, was made using a two-step sequence from acetobromoglucose. Treatment of the crude product with deactivated Raney nickel and a trace amount of *p*-methylthiophenol gave the *p*-methylphenyl 1-thio-β-D-glucopyranoside in ca. 80% overall yield. The only contaminant that could be detected was di-*p*-methylphenyl disulfide.

To give some idea of the mechanism of the present Raney nickel reaction, a test was made omitting the *p*-methylthiophenol. The reaction time had to be increased ca. tenfold to allow all the thio ortho ester to react and several by-products were found. It thus seems as if the reaction does *not* proceed via a fully developed acetoxonium ion that is stabilized only by the solvent but rather via a close ion pair with the *p*-methylthiophenoxy anion reversibly adsorbed to the nickel surface. Free *p*-methylthiophenol (which is regenerated in the reaction) can then make a nucleophilic attack at the anomeric center giving the thioglycoside. Evidence for ion-pair formation in thio ortho esters was also found when using active Raney nickel in ethanol[1] (see above).

Experimental Section

Melting points are uncorrected. IR spectra were run as KBr pellets. ^1H NMR spectra were run in $CDCl_3$ (Me_4Si) on a JEOL PMX-60 spectrometer and mass spectra on a Varian MAT 311 spectrometer. Deactivated Raney nickel was prepared as follows. Raney nickel in water (Merck hydrogenation catalyst) was washed with five portions of absolute ethanol and five portions of toluene (centrifugation). The catalyst was heated (toluene reflux) for 1 h and then dried by azeotropic distillation of the toluene. The resulting catalyst could be stored (in toluene) at room temperature without any noticeable decrease in reactivity.

General Procedure for Preparation of the Thioglycosides. The appropriate peracetylated thio ortho ester[7] (200 mg, mixture of exo and endo diastereomers) and *p*-methylthiophenol (<1 mg) were

dissolved in dry toluene (5 ml). Deactivated Raney nickel (ca. 2 g) was added using a few milliliters of toluene (gas evolution was noticed) and the mixture was stirred (magnet) at room temperature. When the reaction was complete (ca. 10 min, TLC: SiO_2/ethyl acetate–light petroleum; 1:2 for monosaccharides and 3:2 for the disaccharide) the mixture was filtered by suction through a pad of Celite. The residue was washed several times with ether and the filtrate was evaporated. This gave pure (TLC, NMR) thioglycoside as a colorless oil that crystallized (except for the lacto derivative) on addition of a few drops of ethanol.

***p*-Methylphenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside.** Yield 83%. Recrystallization from ethanol gave an analytical sample. For melting point, optical rotation, IR, ^1H NMR, ^{13}C NMR, and MS data, see ref 7.

***p*-Methylphenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-galactopyranoside.** Yield 94%. Recrystallization from ethanol gave an analytical sample: mp 117–118 °C; $[\alpha]^{24}_{578}$ +5.0° (c 1.0; $CHCl_3$) (lit.[8] mp 113–115 °C; $[\alpha]^{23}_D$ +4.4°); IR 1740, 804 cm^{-1}; NMR δ 7.37, 7.09 (rough AB q, 2 H each, J_{AB} = 8.4 Hz, aromatic H), 3.70–5.50 (m, 7 H, OCH), 2.34 (s, 3 H, CH_3Ph), 2.10 (s, 6 H, CH_3COO), 2.03, 1.96 ppm (s, 3 H each, CH_3COO); mass spectrum *m/e* (rel intensity) 454 (M^+, 0.1, $C_{21}H_{26}O_9S$), 331 (60), 271 (1), 229 (3), 187 (2), 169 (100, base peak), 127 (30), 109 (73).

Anal. Calcd for $C_{14}H_{19}O_9$: mol wt, 331.1029. Found: mol wt, 331.0998 (M − C_7H_7S).

***p*-Methylphenyl 2,3,4-Tri-*O*-acetyl-1-thio-β-D-xylopyranoside.** Yield 95%. Recrystallization from ethanol gave an analytical sample: mp 108–109 °C; $[\alpha]^{24}_{578}$ −68.4° (c 2.0; $CHCl_3$); IR 1747, 803 cm^{-1}; NMR δ 7.37, 7.13, (rough AB q, 2 H each, J_{AB} = 8.4 Hz, aromatic H), 3.10–5.35 (m, 6 H, OCH), 2.35 (s, 3 H, CH_3Ph), 2.09 (s, 3 H, CH_3COO), 2.03 ppm (s, 6 H, CH_3COO); mass spectrum *m/e* (rel intensity) 382 (M^+, 0.4, $C_{18}H_{22}O_7S$), 259 (50), 199 (37), 157 (79), 139 (84), 97 (100, base peak).

Anal. Calcd for $C_{18}H_{22}O_7S$: mol wt, 382.1085. Found: mol wt, 382.1059. Calcd: C, 56.5; H, 5.8; S, 8.4. Found: C, 56.4; H, 5.8; S, 8.3.

***p*-Methylphenyl 2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside.** Yield 80%. Column chromatography (SiO_2, 15 g, ethyl acetate–light petroleum, 3:2) gave an analytical sample: syrup; $[\alpha]^{24}_{578}$ −17.6° (c 1.7; $CHCl_3$); IR 1754, 809 cm^{-1}; NMR δ 7.34, 7.08 (rough AB q, 2 H each, J_{AB} = 8.2 Hz, aromatic H), 3.53–5.35 (m, 14 H, OCH), 2.33 (s, 3 H, CH_3Ph), 2.12, 2.07, 2.01, 1.94 ppm (s, 21 H, CH_3COO); mass spectrum *m/e* (rel intensity) 742 (M^+, 0.05, $C_{33}H_{42}O_{17}S$), 619 (50), 559 (37), 457 (14), 397 (2), 395 (6), 331 (70), 169 (100, base peak).

Anal. Calcd for $C_{26}H_{35}O_{17}$: mol wt, 619.1873. Found: mol wt, 619.1868 (M − C_7H_7S). Calcd for $C_{33}H_{42}O_{17}S$: S. 4.3. Found: S, 4.3.

***p*-Methylphenyl 2,3,4-Tri-*O*-acetyl-1-thio-β-D-glucopyranuronic Acid (Methyl Ester).** Yield 89%. Recrystallization from ethanol gave an analytical sample: mp 127–128 °C; $[\alpha]^{24}_{578}$ −25.0° (c 0.9; $CHCl_3$); IR 1763, 1744, 804 cm^{-1}; NMR δ 7.40, 7.14 (rough AB q, 2 H each, J_{AB} = 8.4 Hz, aromatic H), 3.87–5.50 (m, 5 H, OCH), 3.76 (s, 3 H, OCH_3), 2.35 (s, 3 H, CH_3Ph), 2.08 (s, 3 H, CH_3COO), 1.98 ppm (s, 6 H, CH_3COO); mass spectrum *m/e* (rel intensity) 440 (M^+, 0.4, $C_{20}H_{24}O_9S$), 317 (19), 257 (20), 215 (9), 197 (15), 155 (100, base peak), 127 (64).

Anal. Calcd for $C_{13}H_{17}O_9$: mol wt, 317.0872. Found: mol wt, 317.0877 (M − C_7H_7S). Calcd for $C_{20}H_{24}O_9S$: C, 54.5; H, 5.5. Found: C, 54.4; H, 5.6.

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Registry No.—*p*-Methylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside, 28244-94-2; *p*-methylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside, 28244-99-7; *p*-methylphenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside, 61025-08-9; *p*-methylphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside, 29019-41-8; *p*-methylphenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranuronic acid methyl ester, 61025-09-0; *p*-methylphenyl peracetyl-α-D-glucopyranosethio ortho ester isomer A, 60426-93-9; *p*-methylphenyl peracetyl-α-D-glucopyranosethio ortho ester isomer B, 60410-57-3; *p*-methylphenyl peracetyl-α-D-galactopyranosethio ortho ester isomer A, 60410-58-4; *p*-methylphenyl peracetyl-α-D-galactopyranosethio ortho ester isomer B, 60439-00-1; *p*-methylphenyl peracetyl-α-D-xylopyranosethio ortho ester isomer A, 60410-59-5; *p*-methylphenyl peracetyl-α-D-xylopyranosethio ortho ester isomer B, 60410-60-8; *p*-methylphenyl peracetyl-4-*O*-(β-D-galactopyranosyl)-α-D-glucopyranosethio ortho ester isomer A, 61091-25-6; *p*-methylphenyl peracetyl-4-*O*-(β-D-galactopyranosyl)-α-D-glucopyranosethio ortho ester isomer B, 60410-61-9; *p*-methylphenyl peracetyl-α-D-glucopyranuronic acid methyl ester thio ortho ester isomer A, 60410-62-0; *p*-methylphenyl peracetyl-α-D-glucopyranuronic acid methyl ester thio ortho ester isomer B, 60410-63-1; *p*-methylthiophenol, 106-45-6.

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Metal Catalysis in Organic Reactions. 3. Nickel-Promoted Reaction of Triisobutylaluminum with Terminal Acetylenes as a Synthetic Route to (*E*)-2,4-Dialkyl-1,3-butadienes and/or Trialkylbenzenes

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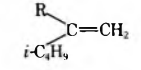
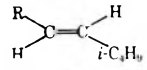
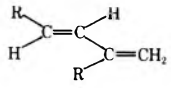
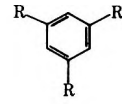
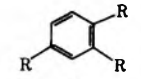
Recently we reported that the reaction of triisobutylaluminum with terminal acetylenes affords products which correspond to metalation, reduction, and carbalumination of the substrate.[1] In connection with studies on nickel-catalyzed organic reactions,[2] we have now investigated the influence of soluble nickel(II) complexes, such as bis(*N*-methylsalicylaldimine)nickel [$Ni(mesal)_2$],[3] on the selectivity of the above reaction.[1]

The stoichiometric reaction of triisobutylaluminum with terminal alkynes, at 25 °C and in the absence of solvent, is accelerated by the presence of catalytic amounts of $Ni(mesal)_2$ and a "head-to-tail" dimer [(*E*)-2,4-dialkyl-1,3-butadiene] and trialkylbenzenes are formed as main products (Table I). Thus, 1-hexyne is completely converted by this procedure into a mixture containing (*E*)-5-methylene-6-undecene (**5**),[4] 1,3,5-tri-*n*-butylbenzene (**6**), and 1,2,4-tri-*n*-butylbenzene (**7**), together with those products whose formation occurs even in the absence of the nickel complex[1] and minor amounts of linear trimers and C_{16} dienes[5] (Table I). The yields both of the dimer and the cyclotrimers are dependent on the molar ratio $(i\text{-}C_4H_9)_3Al$ to $Ni(mesal)_2$, at least in the stoichiometric reaction of 1-alkynes with triisobutylaluminum. In fact, decreasing the molar ratio $(i\text{-}C_4H_9)_3Al$ to $Ni(mesal)_2$ up to 60 substantially depresses the formation of the metalation (**1**) and reduction (**2**) products whereas it increases the yields of **5**, **6**, and **7** (entries 1–4). The use of higher nickel concentrations is not advisable because of the increasing formation of the by-products.

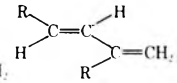
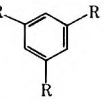
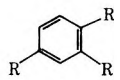
The extremely high selectivity in the dimerization of 1-hexyne had prompted us to explore the validity of the nickel-catalyzed reaction between 1-alkynes and triisobutylaluminum as a synthetic route to preparing 2,4-dialkyl-1,3-butadienes, whose preparation cannot be easily achieved using conventional methods.[6] For this purpose, some 3-alkyl-,

Table I. Reactions of RC≡CH with $(i\text{-}C_4H_9)_3Al$ in the Presence of $Ni(mesal)_2$[a]

Entry	R	$[(i\text{-}C_4H_9)_3Al]^b$ / $[Ni(mesal)_2]$	Products, yields %[c, d] RC≡CH[e] 1	RCH=CH$_2$ 2	 3	 4	 5	 6	 7
1	$n\text{-}C_4H_9$	240	27 (693-02-7)[f]	35 (592-41-6)	5 (52763-10-7)	6 (25127-82-4)	10 (61063-95-4)	5 (841-07-6)	3 (14800-16-9)
2	$n\text{-}C_4H_9$	120	28	26	4	4	15	9	5
3	$n\text{-}C_4H_9$	60	12	13	3	1	29	18	10
4	$C_2H_5CH(CH_3)$	60	2 (922-59-8)	7 (760-20-3)	Traces	2 (52763-12-9)	66 (61063-96-5)	14 (6565-55-5)	3 (61064-05-9)
5	$i\text{-}C_3H_7CH(CH_3)$	60	1 (61064-08-2)	5 (7385-78-6)		1 (61116-94-7)	76 (61063-97-6)	9 (61064-01-5)	3 (61139-52-4)
6	$t\text{-}C_4H_9CH(CH_3)$	60	26 (52763-16-3)	26 (564-03-4)			59 (61063-98-7)	9 (61064-02-6)	
7	$C_2H_5CH(CH_3)CH_2$	60	5 (52713-81-2)	7 (3769-23-1)	2 (61063-92-1)	Traces	27 (61063-99-8)	44 (61064-03-7)	3 (61064-06-0)
8	$C_2H_5CH(CH_3)(CH_2)_2$	60	11 (61064-09-3)	26 (13151-04-7)	3 (61063-93-2)	2 (61063-94-3)	27 (61064-00-4)	14 (61064-04-8)	8 (61064-07-1)

[a] The reactions were carried out in the absence of solvents, at 25 °C for 40 h. [b] [RC≡CH]/[$(i\text{-}C_4H_9)_3Al$] = 1. [c] By GLC (SE-301) of the reaction mixtures upon hydrolysis, other products being dienes containing the isobutyl group and traces of linear trimers. [d] For the data of the uncatalyzed reaction, see ref 1. [e] Present as alkynylalane before hydrolysis. [f] Registry no.

Table II. Oligomerization of RC≡CH by the $(i\text{-}C_4H_9)_3Al/Ni(mesal)_2$ System

Entry	R	[RC≡CH] / $[(i\text{-}C_4H_9)_3Al]$	[RC≡CH] / $[Ni(mesal)_2]$	Temp, °C	Recovered RC≡CH, %[a]	Products, yields %[b] RCH=CH$_2$ 2	 5	 6	 7	Linear trimers	Tetramers
9[c]	$n\text{-}C_4H_9$	0.5	60	25	3	24	37	13	7	6	
10[c]	$n\text{-}C_4H_9$	2.0	60	25	15	21	29	20	12	6	Traces
11[c]	$n\text{-}C_4H_9$	3.0	60	25	36	17	28	20	12	9	Traces
12[d]	$n\text{-}C_4H_9$	4.0	60	25	30	5	19	32	20	14	2
13[d]	$n\text{-}C_4H_9$	10.0	60	25	57		11	36	21	14	14
14[e]	$n\text{-}C_4H_9$	6.0	100	80	11	1	8	26	16	20	18
15[e]	$n\text{-}C_4H_9$	15.0	100	80	24		5	32	20	16	21
16[e]	$C_2H_5CH(CH_3)$	6.0	100	80	10	2	13	41	9	9	16
17[e]	$C_2H_5CH(CH_3)$	15.0	100	80	26	4	4	48	8	12	23

[a] Partially as alkynylalane. [b] By GLC (SE-301) of the hydrolyzed reaction mixtures. [c] Hydrolysis after 40 h. [d] Hydrolysis after 80 h. [e] In benzene as solvent, alkyne molar concentration 4 M, hydrolysis after 6 h.

4-alkyl-, and 5-alkyl-1-alkynes were used as substrates. The inspection of Table I show that the yields in the diene (**5**) are very improved, while the formation of trialkylbenzenes is substantially hindered, when the alkyne has the substituent alkyl group in the α position with respect to the triple bond. Thus, the reaction of 3-methyl-1-pentyne with $(i\text{-}C_4H_9)_3Al$ under the reported experimental conditions (Table I, entry 4), followed by successive hydrolysis, give a 45% isolated yield of (*E*)-3,7-dimethyl-4-methylene-5-nonene (**5**), having a satisfactory chemical purity (>90%). Unfortunately, the yields in the dimer drop when the substituent alkyl group of the alkyne is in the β or γ position with respect to the triple bond.

It is noteworthy that the increasing size of the alkyl group attached to the 3 position of the 1-alkyne results in a progressive decreasing of the yields of the aromatic products (Table I, entries 3–6). This result seems to indicate that the competitive aromatizing reaction has greater steric requirements than the dimerization reaction. The improved yields in the trialkylbenzenes when 4-methyl-1-hexyne and 5-methyl-1-heptyne are used are consistent with this consideration. Reasonably steric factors may be responsible for the prevailing formation of the symmetrical over the unsymmetrical trialkylbenzene too.[7]

In exploring more widely the influence of some variables on the reaction, we have found that the molar ratio 1-alkyne to $(i\text{-}C_4H_9)_3Al$ is important to determine the direction of the reaction toward dimerization or cyclotrimerization of the terminal acetylenes (Table II). In fact, while increasing the molar ratio 1-hexyne to $(i\text{-}C_4H_9)_3Al$ from 1.0 to 3.0 has little effect on the product yields, probably because of the intervention of the other two isobutyl groups of the organoaluminum compound,[8] the excess of $(i\text{-}C_4H_9)_3Al$ with respect to the acetylenic substrate results in an increase of the diene (**5**) yields with respect to those of the aromatic products (entry 9).[9] At molar ratio 1-alkyne to $(i\text{-}C_4H_9)_3Al$ higher than 3.0, the yields of the aromatic products are strongly improved, even if the rate of the reaction decreases appreciably and tetramerization may occur as a side reaction (Table II). The reaction rate is increased and comparable results are obtained when the reaction is carried out in refluxing benzene; thus, 3-methyl-1-pentyne may be converted into 1,3,5-tri-*sec*-butylbenzene (48% GLC yield) (Table II, entry 17).

The preparative possibilities of these nickel-catalyzed reactions should be borne in mind. In fact 2,4-dialkyl-1,3-butadienes of trans configuration, not otherwise available, can be prepared in satisfactory or excellent yields in relation to the structure of the 1-alkyne. Moreover, the highly selective cyclotrimerization of the monoalkylacetylenes we observed suggests the use of these reactions as an alternative method for the synthesis of benzene derivatives having bulk alkyl substituents in the 1,3,5 positions of the aromatic ring.[7,10]

Experimental Section[11]

Triisobutylaluminum and 1-hexyne were commercial products (Fluka A. G. Co., Buchs) which were carefully distilled before use. The other 1-alkynes (**1**) employed were prepared through the corresponding α olefins by published methods.[12] Bis(*N*-methylsalicylaldimine)nickel was prepared and purified as reported elsewhere.[3] All the reaction products were recovered by preparative GLC and were identified by analysis of NMR, IR, and mass spectra.

General Procedure. In a typical run (Table I, entry 4) a weighed amount of $(i\text{-}C_4H_9)_3Al$ (5.94 g, 30 mmol) was transferred from a sealed capillary glass vial to a two-necked flask (100 ml), equipped with a magnetic stirrer, a Versilic silicone cap, and a glass stopcock, containing the nickel complex (0.163 g, 0.5 mmol) cooled at 0 °C. 3-Methyl-1-pentyne (**1**, 2.46 g, 30 mmol) was injected by hypodermic syringe through the cap and then the flask was placed in a thermostated bath at 25 ± 0.3 °C. After 40 h and removal of the volatile products (isobutane, isobutene, and unreacted **1**), the residual reaction mixture was cautiously hydrolyzed with dilute sulfuric acid, extracted with ether, and analyzed by GLC (silicone SE 301, 50–190 °C). Removal of the solvent and careful distillation gave (*E*)-3,7-dimethyl-4-methylene-5-nonene (**5**, 1.12 g, 45% yield) in addition to a high-boiling fraction. By preparative GLC (butanediol succinate LAC 6R-860, 100–170 °C) pure **5**, bp 81 °C(17 mmHg), $n^{25}D$ 1.4575, IR (neat) 3090, 880 (C=CH_2), 1610, and 965 cm^{-1} (trans -CH=CH-), and pure 1,3,5-tri-*sec*-butylbenzene (**6**,[13] 0.09 g) were recovered.

Registry No.—$(i\text{-}C_4H_9)_3Al$, 100-99-2; $Ni(mesal)_2$, 14322-02-2.

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(4) The diene (**5**) is covalently bonded to the aluminum atom and can be recovered from the reaction mixture only after hydrolysis.
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(9) We might speculate that the hypothetical dienylnickel species formed cannot react rapidly with the 1-alkyne to give the benzene derivatives, because of the fast alkyl exchanges with the excess organoaluminum compound.
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(11) Distillation and handling of all the reactants were performed under dry, purified nitrogen. All reaction were carried out at least in duplicate under a nitrogen atmosphere. GLC analyses were performed on a Perkin-Elmer F 30 instrument with flame ionization detectors and nitrogen as carrier gas, while preparative GLC was carried out on a Perkin-Elmer F 21 chromatograph. Spectral measurements were determined with the following instruments: IR, Perkin-Elmer Model 225; NMR, Jeol JMN PS-100; mass spectra, Varian MAT CH 7.
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Correlation of the Gas Phase Basicities of Primary Amines with the New Gas Phase Alkyl Inductive Substituent Constants

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Precise measurements of the intrinsic base strengths of an extended series of amines have recently become available from ion cyclotron resonance spectroscopic equilibrium constants.[1] Brauman and Blair[2] interpreted their striking observation that alkyl groups increase both acidity and basicity in the gas phase as due primarily to the polarization of R by a nearby ionic center. That is, polarizable alkyl groups stabilize both positive and negative charge centers which are in close proximity. This polarizability effect, in the simple electrostatic model, falls off very rapidly (r^{-4}) with distance between the centers of polarizability and of charge.[2,3] Distant alkyl groups,

Table I. Relative Proton Affinities, ΔPA, of RNH_2, and the Corresponding σ_I (R) and $\Delta\sigma_I$ (R) Values

Registry no.	R	ΔPA,[a] kcal/mol	$-\sigma_I$[c]	$-10^2\,\Delta\sigma_I$	ΔE_I,[e] kcal/mol
74-89-5	Me	0.0[b]	0.046	0.0	0.0
75-04-7	Et	2.7	0.057	1.1	4.4
107-10-8	*n*-Pr	3.9	0.061	1.5	6.0
109-73-9	*n*-Bu	4.4	0.063	1.7	7.9[f]
75-31-0	*i*-Pr	5.0	0.065	1.9	7.9
78-81-9	*i*-Bu	4.9	0.065	1.9	8.3
13952-84-6	*sec*-Bu	6.1	0.069	2.3	8.3
5813-64-9	neo-Pt	5.8	0.069	2.3	9.5
75-64-9	*t*-Bu	7.0	0.074	2.8	9.4
110-58-7	*t*-Am	8.3	0.078[d]	3.2	10.6

[a] ±0.2 kcal, cf. ref 11. [b] $PA(MeNH_2) = 210 \pm 2$ kcal (ref 17); $\Delta PA = PA(RNH_2) - PA(MeNH_2)$; still more recent PA values (ref 5) yield ΔPA's consistently higher by around 0.4 kcal/mol than those given in the table, but a plot of these values vs. σ_I is not quite as good as the plot in Figure 1. [c] Reference 10. [d] L. S. Levitt and B. W. Levitt, *Tetrahedron*, **29**, 941 (1973); also ref 10. [e] Reference 5. [f] Reference 14 gives this as 7.6; $\Delta E_I = E_I(MeNH_2) - E_I(RNH_2)$; $E_I(MeNH_2) = 222.8$ kcal/mol (ref 5).

however, have been found[4] to destabilize rather than stabilize negative charge, i.e., gas-phase *acidities* are decreased in phenols, acetylenes, and carboxylic acids.[4] These destabilizing effects can be interpreted as a result of dipoles between R groups and sp^2 or sp hybridized C atoms.[4]

Aue, Webb, and Bowers[5] have recently shown that the orders of magnitude of the observed effects of alkyl groups on the gas-phase base strengths of amines are consistent with the simple electrostatic model. However, assumptions regarding polarizabilities of alkyl groups and uncertain distance factors (extended conformations were taken) were both necessary.[5]

An alternative approach to treating these data involves the use of substituent constants. Polar substituent constants, σ^*, for alkyl groups were originally obtained by the Ingold–Taft relationship,[6] from the rates of the acid- and base-catalyzed hydrolysis of esters. Although the polar and the directly related inductive (σ_I) substituent constants for alkyl groups have been strongly questioned,[7] applications to numerous series of ionization potential data, for both organic[8] and organometallic compounds,[9] have been quite successful. Very recently a review of the σ_I values for alkyl groups has been made,[10] and results from several different approaches, both empirical and theoretical, were found to give a consistent and precise set of inductive substituent parameters. Since both alkyl amines and their conjugate acids are formally saturated, and both involve very similar (approximately) sp^3 tetrahedral geometries at the nitrogen atom, the gas-phase base strengths appear ideally suited for testing the applicability of the σ_I values. The new σ_I values themselves are claimed[10] to be *intrinsic* measures of alkyl induction and polarizability, having been obtained both from statistical analysis of gas-phase ionization potential data and polarizability "models", neither of which involve any solvation effects.

Figure 1 shows a plot of the gas-phase basicities (relative proton affinities) for an extended series[11] of primary alkyl amines vs. the corresponding σ_I (R) values (data from Table I). That is, the standard free energy (or enthalpy) changes for the following gas-phase proton transfer reactions are plotted in Figure 1:

$$RCH_2NH_2 + CH_3NH_3^+ \rightleftharpoons RCH_2NH_3^+ + CH_3NH_2$$

The remarkable linear relationship shown in Figure 1 clearly demonstrates the applicability of the σ_I parameter to equilibria of this kind. The equation for the regression is

$$\Delta PA = -258\Delta\sigma_I \text{ kcal/mol} \qquad (1a)$$

which has s.d. = 0.1 kcal and $r = 0.999$. Equation 1a can also be written (with the limitations noted in reference 17).

$$PA(RNH_2) = 198 - 258\sigma_I\,(R)\ (\text{kcal}) \qquad (1b)$$

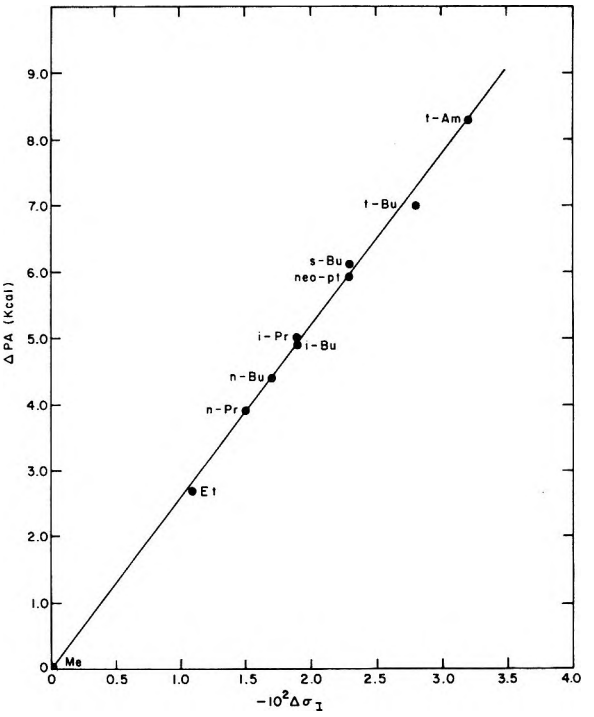

Figure 1. Correlation of the proton affinities of primary aliphatic amines, RNH_2, by the substituent parameter, σ_I (R). Abscissa: $-10^2\Delta\sigma_I = -[\sigma_{I(R)} - \sigma_{I(CH_3)}]10^2$. Ordinate: $\Delta PA = PA_{(RNH_2)} - PA_{(CH_3NH_2)}$.

Two alternative interpretations may be made of the excellent correlation found in Figure 1. First, the observed alkyl substituent effect on gas-phase base strengths and the σ_I parameters are both determined to quantitative approximation by polarizability effects, involving no internal inductive effects.[2,3] Second, the σ_I parameters are a measure of internal inductive effects of alkyl groups, but the observed alkyl substituent effects are a combination of polarizability and internal inductive effects, both having very nearly the same structural dependencies, i.e., on chain lengthening and branching. We cannot at the present time distinguish with certainty between these two interpretations. However, a recent comparison[12] of the quantitative effects of alkyl groups on the gas-phase acidity of alcohols with the corresponding gas-phase basicities of the amines does suggest that the second interpretation[12] is the correct one.

Since the ionization potentials, E_I, of the three classes of amines are also a linear function[13] of $\Sigma\sigma_I$, it necessarily follows that the ΔPA values for the primary amines are likewise a

linear function of their E_I's. The equation for the E_I–σ_I correlation was found to be[13]

$$E_I = 9.62 + 13.8\sum\sigma_I\,(R)\ (eV) \qquad (2)$$

Using, however, IP data very recently obtained[5] by the PES method (which yields vertical rather than the adiabatic E_I's by the PI method[14]), one obtains an excellent correlation with the new gas-phase σ_I values (with $r = 0.991$) for the complete series of primary amines discussed here. The new E_I–σ_I correlation equation is given by

$$E_I(RNH_2) = E_I(NH_3) + a_I\sigma_I = 10.19 + 11.49\sigma_I\,(R)\ (eV) \qquad (2a)$$

Eliminating σ_I (R) from eq 1b and 2a leads to

$$PA(RNH_2) = 18.44 - 0.966E_I\ (eV) \qquad (3)$$

from which good estimates of proton affinities can be made directly from the experimental ionization potentials, or vice versa. (The correct chronology of the relationships given above is, of course, ref 13, 1b, and 5 and eq 1a and 1b of the present paper.)

Good linear plots of PA vs. E_I for primary amines have previously been published.[1b,5] In accord with eq 3, as has already been demonstrated for the alcohols[15] and ethers,[16] the greater the basicity at the atom with a lone pair of electrons, the lower is the ionization potential at that atom.

In view of the fact that Figure 1 represents a nearly perfect correlation, it is tempting to actually *define* the σ_I (R) values in terms of the gas-phase proton affinities of primary amines. If this is done from the relation

$$-\sigma_I\,(R) = \Delta PA/258 + 0.046 \qquad (4)$$

the results for the alkyl groups in the order they appear in Table I are 0.046, 0.056, 0.061, 0.063, 0.066, 0.065, 0.070, 0.069, 0.074, and 0.079, almost precisely the same as the σ_I values obtained by detailed statistical analysis of ionization potential data.[10]

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A General Procedure for the Base-Promoted Hydrolysis of Hindered Esters at Ambient Temperatures

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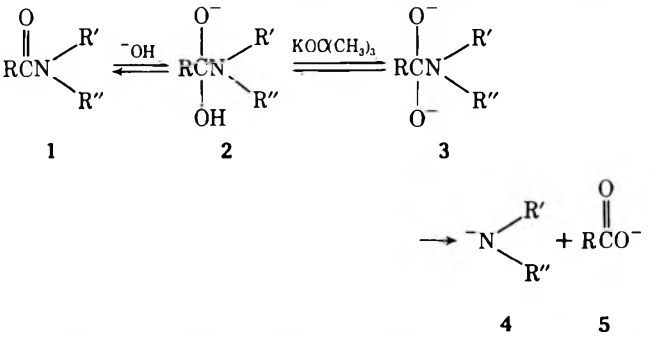
Recently, we reported that essentially "anhydrous hydroxide" was an excellent reagent for the hydrolysis of tertiary amides at ambient temperatures.[1] This reagent was generated via the reaction of 2 equiv of potassium *tert*-butoxide with 1 equiv of water.[2] Mechanistically, it appeared that the relatively unsolvated hydroxide added to the tertiary amide, **1**, to produce **2**. Removal of a hydroxylic proton from **2** would then produce the dianion, **3**. Fragmentation of **3** then produced the most stable pair of anions, which in this case was **4** and **5**. Utilizing this concept, a series of tertiary amides was



1 **2** **3** **4** **5**

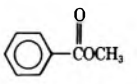
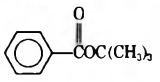
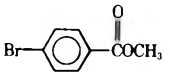
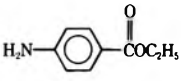
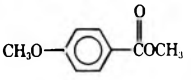
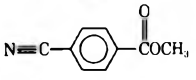
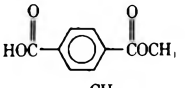
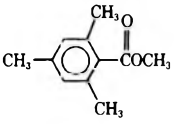
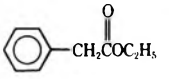
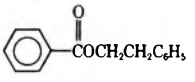
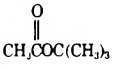
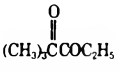
hydrolyzed in yields ranging from 65 to 100% in relatively short reaction times at room temperature. The facility of this process suggested to us that similar reaction conditions might permit the base-catalyzed hydrolysis of hindered esters at room temperature. This report provides the details of our study of the base-promoted hydrolysis of esters at ambient temperatures.

In any study of the saponification of hindered esters, the classes of esters which must be considered include esters of pivalic acid, mesitoic acid, and *tert*-butyl alcohol. Table I lists the yields obtained in the room temperature hydrolysis of these and other esters. In a typical procedure, approximately 1 equiv of ester, 2 equiv of water, and 8 equiv of potassium *tert*-butoxide were stirred as a slurry for 2–48 h at room temperature. As shown in Table I, close to quantitative yields could be obtained from most of the simple esters in relatively short times at room temperature. For highly hindered esters, longer reaction times were required, but hydrolysis could still be accomplished at room temperature.

While the heterogeneous nature of the reaction mixture made accurate kinetic data virtually unattainable, qualitative studies could be made. As shown in Table I, time vs. yield determinations were made for the hindered esters *tert*-butyl benzoate and methyl mesitoate. It would appear from this data that given sufficient time (5–6 days) even a very hindered ester such as methyl mesitoate could be saponified in close to quantitative yield at room temperature.

The mechanistic aspects of this ester hydrolysis are of interest. The mechanism of hydrolysis of hindered esters has been studied in detail[3–7] both in acid and in base. Although the vast majority of esters are saponified via a $B_{AC}2$ mechanism,[4,5,7] evidence has been presented that in special cases a $B_{AL}2$ mechanism can predominate.[5,6] In the normal hydrolysis of methyl mesitoate, acyl–oxygen cleavage has been shown to occur in aqueous media.[4,5] However, methoxide has been shown to react with methyl mesitoate to yield the mesitoate anion via alkyl–oxygen cleavage. Since little is known about

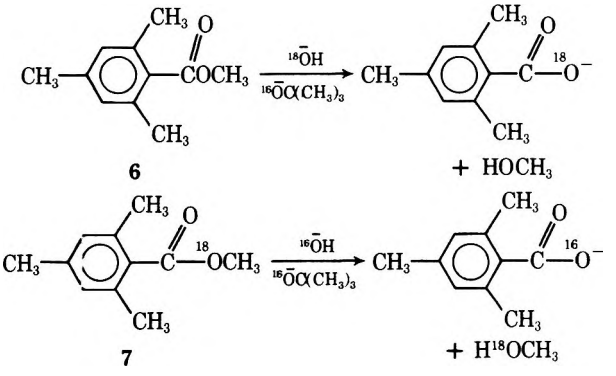
Table I. Hydrolysis of Esters with Potassium *tert*-Butoxide–Water at Ambient Temperatures

Registry no.	Ester	Hydrolysis time, h	% yield of acid isolated
93-58-3		0.5, 2	44, 100
774-65-2		0.5, 1, 2, 5	41, 70, 92, 100
586-76-5		1	100
94-09-7		16	100
121-98-2		24	80
1129-35-7		48	90[a]
1679-64-7		43	83
2282-84-0		24, 48, 72	50, 63, 72
101-97-3		16	80
94-47-3		24	97[b]
540-88-5		3	97[c]
3938-95-2		3	94[c]

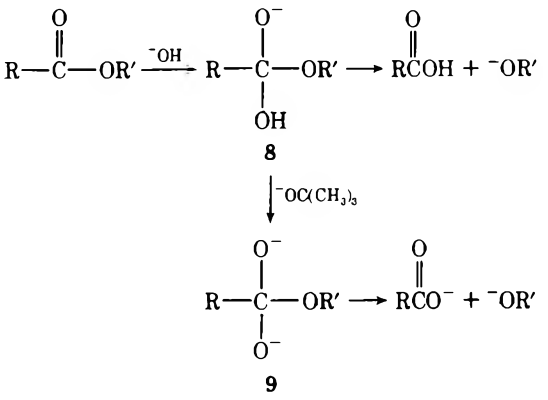
[a] Isolated as the half amide–half acid. [b] In addition, the alcoholic portion was isolated in 92% yield. [c] Aliphatic acids were analyzed according to our previously described method.[1]

the characteristics of the relatively anhydrous hydroxide prepared by our methods, we felt that it would be instructive to use the technique of Bender and co-workers to determine whether methyl mesitoate was hydrolyzing under our reactions conditions through acyl–oxygen or alkyl–oxygen cleavage.

In order to establish that our reaction conditions led to acyl–oxygen ($B_{AC}2$) cleavage, two labeling experiments were run. Methyl mesitoate (**6**) was hydrolyzed with hydroxide generated from 22.7% enriched oxygen-18 water. The methanol generated in this hydrolysis was analyzed by chemical ionization mass spectrometry[8] and was found to contain no excess oxygen-18. Aqueous workup gave mesitoic acid which was found to have 16% excess oxygen-18. The relatively large amount of oxygen-18 remaining in the acid, after neutralization with aqueous acid, agreed with the relatively slow rate of oxygen exchange previously observed for mesitoic acid.[4] In a second labeling experiment, methyl mesitoate prepared from 22% oxygen-18 methanol was hydrolyzed under our reaction conditions. We found that 7 hydrolyzed to yield mesitoic acid with no excess oxygen-18 and methanol containing 22% oxygen-18. Thus, it was firmly established that, under our hydrolysis conditions, acyl–oxygen cleavage predominated. In an additional mechanistic endeavor, the benzoate of 2-phenylethanol was hydrolyzed. The isolation of 2-phenylethanol established the absence of any type of elimination process when β hydrogens were present on the alcohol moiety.



In summary, we have illustrated that even very hindered esters can be hydrolyzed by essentially anhydrous hydroxide at room temperature. While acyl–oxygen cleavage has been established, we do not know whether cleavage occurs from the monoanion 8 or whether a dianion of general structure **9**[9] is



involved. Our present experiments do not allow us to distinguish between these two possibilities. However, the observation that methyl benzoate hydrolyzes only ca. 50 times faster than methyl mesitoate under our conditions indicates that our reaction may be more mechanistically complicated than normal hydrolyses in aqueous base.[10]

Experimental Section

General Procedure for the Hydrolysis of Benzoate Esters. To a stirred suspension of 2.66 g (0.026 mol) of potassium *tert*-butoxide in 50 ml of dry ether, cooled to 0 °C, was added 0.12 ml (0.0067 mol) of water via syringe. This slurry was stirred for 5 min. To this was added the benzoate ester (0.003 mol). The ice bath was removed and the reaction mixture was stirred at room temperature until the reaction was complete. The hydrolysis was monitored by TLC for the disappearance of the ester and was considered to be complete when the ester was no longer observed. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The acidified solution was extracted three times with 50-ml portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated to give the acid which was characterized by melting point and infrared spectra. The following acids were recovered by this method: benzoic acid, mp 121–122 °C; *p*-bromobenzoic acid, mp 252–253 °C; *p*-aminobenzoic acid, mp 184–186 °C; *p*-methoxybenzoic acid, mp 184.5–185 °C; 1,4-benzenedicarboxylic acid, sublimes ca. 300 °C; 1,4-benzenedicarboxylic acid monoamide, mp 345–348 °C; mesitoic acid, mp 153–154 °C.

General Procedure for the Hydrolysis of Aliphatic Esters. To a stirred suspension of 2.66 g (0.026 mol) of potassium *tert*-butoxide in 50 ml of dry ether, cooled to 0 °C, was added 0.12 ml (0.0067 mol)

of water via syringe. This slurry was stirred for 5 min. To this reaction mixture was added the aliphatic ester (0.003 mol). The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and stirred over acid-washed ion exchange resin (Amberlite IR-120) until a flame test for potassium ion was negative. The resin was removed by filtration and the filtrate was titrated with a standardized sodium hydroxide solution using phenolphthalein as indicator. The percent hydrolysis as determined by titration of the acid was as follows: acetic acid (97%), pivalic acid (94%). Routine titration of the acetic acid gave 92%. However, standardization of the procedure with sodium acetate showed that 5% of the acetic acid was taken up by the resin. The 97% yield reflects an adjustment for the method of analysis.

Synthesis of $CH_3{}^{18}OH$. Trimethyl phosphate (4.0 g, 0.0285 mol) and labeled water (3.67 g, 0.204 mol) containing 22.7 mol % oxygen-18 were sealed in a thick-walled glass tube.[11] This was heated in an oil bath at 105 °C for 26 h. After cooling to room temperature, the reactants were distilled at reduced pressure to yield 2.64 g of a water and methanol mixture. This mixture was distilled at atmospheric pressure to give 0.63 g of a mixture of methanol and water. The water was used as a chaser solvent in order to obtain the maximum yield of methanol. The distillation was stopped when the temperature of the distillate reached 90 °C.

Synthesis of Oxygen-18 Labeled Methyl Mesitoate. Freshly distilled mesitoyl chloride (9.44 g, 0.051 mol) was added dropwise to 0.63 g of the oxygen-18 labeled water–methanol mixture in 50 ml of dry ether which was cooled to 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 24 h. Water was added to hydrolyze the excess acid chloride. The mesitoic acid was extracted from the ether layer with two 25-ml portions of saturated sodium bicarbonate solution and one 25-ml portion of a 10% sodium hydroxide solution. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated to yield 2.47 g of labeled methyl mesitoate (49% based on trimethyl phosphate): IR (neat) 1730, 1270, 1090 cm^{-1}; mass spectrum *m/e* 180, 178, 148, 147, 146.

Acknowledgment. We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant which supported this investigation and to Mr. P. C. Price for the chemical ionization mass spectral measurements.

Registry No.—Benzoic acid, 65-85-0; 4-bromobenzoic acid, 586-76-5; 4-aminobenzoic acid, 150-13-0; *p*-anisic acid, 100-09-4; 4-(aminocarbonyl)benzoic acid, 6051-43-0; 1,4-benzenedicarboxylic acid, 100-21-0; mesoic acid, 480-63-7; benzeneacetic acid, 103-82-2; acetic acid, 64-19-7; pivalic acid, 75-98-9; $CH_3{}^{18}OH$, 5770-05-8; mesitoyl chloride, 938-18-1; ^{18}O labeled methyl mesitoate, 61076-10-6.

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(1) P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).
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(7) W. Roberts and M. C. Whiting, *J. Chem. Soc.*, 1290 (1965).
(8) Chemical ionization mass spectrometry was carried out on a Du Pont 21-490 B mass spectrometer modified as described by I. C. Wang, H. S. Swofford, Jr., P. C. Price, D. P. Martinsen, and S. E. Buttrill, Jr., *Anal. Chem.*, **48**, 491 (1976).
(9) A referee has suggested that O^{2-} might be formed and add directly to the ester to form **9**. We think that this is unlikely, although we cannot unequivocally rule out this possibility.
(10) In many respects, our results parallel those of Roberts and Whiting,[7] who explored the use of hydroxide in dimethyl sulfoxide as a solvent. In relation to our earlier work,[2] it is possible that the conditions used by both Roberts and Whiting and us involve the same intermediates.
(11) J. L. Borowitz, A. Raviv, P. Rona, D. Sadeh, D. Samuel, and F. S. Klein, *J. Labelled Compd.*, **1**, 259 (1965).

Conformational Control. An Important Factor in the Stereoselective Reduction of Ketones by Bulky Hydride Reagents

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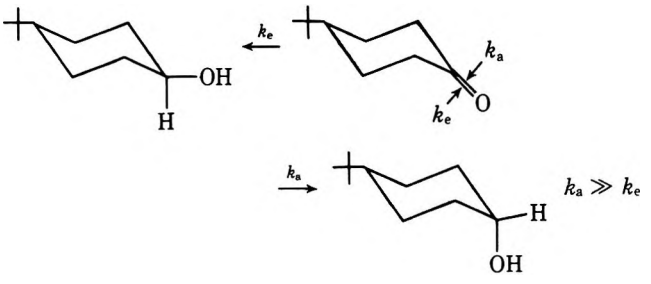
Received August 16, 1976

The recent interest accorded the development of highly hindered hydride reagents capable of stereoselective reduction of ketones to afford one diastereomer preferentially[1-5] prompts this discussion of an important factor which is frequently neglected but which subtly affects the product profile of such reductions.[6] This effect involves the conformational equilibria present in mobile ketones which is often at least partly responsible for decreasing the apparent stereoselectivity of hydride attacks.

The conformational effect is adequately illustrated by the reduction results from a series of alkyl substituted cyclohexanones by various di- and trialkyl borohydrides recently introduced[1-4] and recommended for their stereoselectivity of attack. Thus, the reagents approach predominantly from the equatorial side to afford largely the axial alcohol. As a case in point, 4-*tert*-butylcyclohexanone yields almost entirely *cis*-4-*tert*-butylcyclohexanol with various bulky hydrides as shown in Table II and illustrated in Scheme I. From the table,

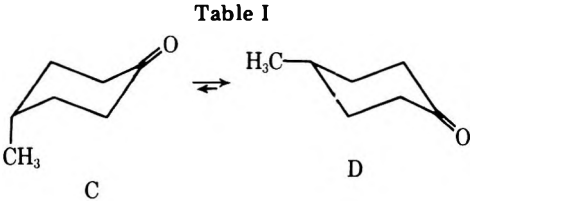
Scheme I



k_a must be substantially greater than k_e. In addition, the selectivity increases as the temperature is lowered as expected since a given difference in E_a between axial and equatorial attack is translated into a greater rate ratio as temperature decreases. The bulky trialkylborohydrides then, especially LTMBH and LTSBH, appear to offer an extremely high degree of discrimination toward equatorial attack which, for the *conformationally homogeneous* 4-*tert*-butylcyclohexanone, produces almost entirely one diastereomer (cis).

The expected situation is different for conformationally heterogeneous cyclohexanones. As presented in Scheme II, irrespective of the relative rate of ring inversion compared to

Table I



C D

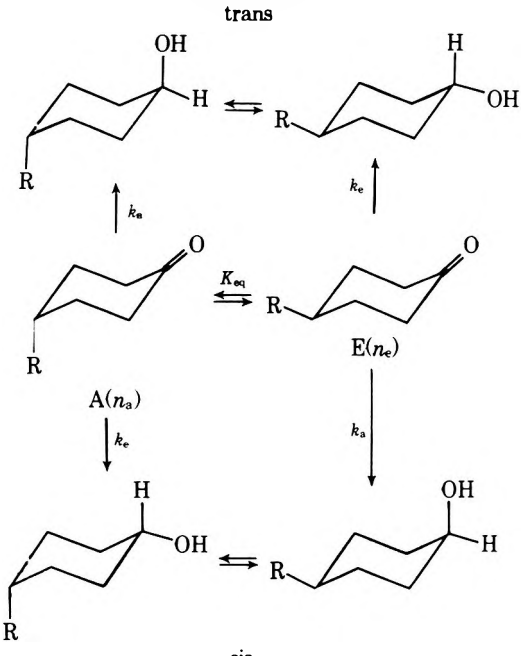
Temp, T°C	$K_{eq}{}^{10}$	% more stable equatorial isomer
100	9.87	90.8
25	17.57	94.7
0	22.86	95.8
−40	39.11	97.5
−78	79.91	98.8

Table II. Reduction of Substituted Cyclohexanones with Hydride Reagents

Cyclohexanone	Registry no.	Temp, °C	% equatorial alkyl computed[a]	% isomer from equatorial attack[b] (% expected axial-OH isomer)[c]			
				Li-*sec*-Bu_3BH[d]	$LDMBH_2$[e]	LTMBH[f]	LTSBH[f]
4-*tert*-Butyl-	98-53-3	0	>99	93	94		
		−78	>99	96.5		99.4	99.4
3-Methyl-	591-24-2	0	95.8	85 (89.4)	99 (90.3)		
		−78	98.8	94.5 (95.5)		99 (98.3)	99.6 (98.3)
4-Methyl-	589-92-4	0	95.8	80.5[g] (89.4)	94 (90.3)		
		−40	97.5		96 (91.8)		
		−78	98.9	90 (95.5)		98 (98.3)	99 (98.3)
		−78	98.9				99 (98.3)
2-Methyl-	583-60-8	0	95.8	99.3 (89.4)	99 (90.3)	>99.5 (98.3)	99.7 (98.3)

[a] The computations were performed assuming $-\Delta G°_{25}$ for methyl is ca. 1.70 kcal/mol; for ethyl, 1.75 kcal/mol (ref 7). [b] In each case the diastereomer produced is the less stable isomer; cis for the 2- and 4-alkylcyclohexanols and *trans*-3-methylcyclohexanol. [c] Computed as % expected axial-OH isomer = % equatorial isomer in ketone × fraction of equatorial attack + % axial isomer in ketone × % axial attack, where the fractions of axial and equatorial attack with a given reagent at a particular temperature are derived from the fractions of axial and equatorial product, respectively, obtained with 4-*tert*-butylcyclohexanone. [d] Reference 1. [e] Reference 3. [f] Reference 4. [g] The potassium derivative afforded 88% cis; ref 2.

Scheme II



reduction rates, these reactions should be less stereoselective than homogeneous cases and dependent upon the relative equilibrium between A and E (Scheme II). Thus, it can be readily demonstrated that if % A and % E are the percentages of axial and equatorial hydroxyl products, respectively, produced by reduction of the conformationally homogeneous 4-*tert*-butyl case (Scheme I, where % A/% E = k_a/k_e) then the % cis product in the conformationally heterogeneous case (Scheme II) is n_A % E + n_E % A and % trans = n_E % E + n_A % A.[7] It should be noted that this latter percentage must be larger than for 4-*tert*-butylcyclohexanone since n_A, the mole fraction of conformer A, is nonnegligible and % E (which relates the amount of axial attack) is small.

However, as indicated in Table II, in certain instances the stereoselectivities for a number of conformationally heterogeneous cyclohexanones are nearly as great as for 4-*tert*-butylcyclohexanone! This result is surprising in view of the above discussion and, in fact, has been attributed to some special, unknown effect.[4] What may not be appreciated at first glance is that the observed stereoselectivity is attributable to the temperature dependence of the conformational equilibria present in these systems. As a case in point, 4-methylcyclohexanone exists as a temperature dependent equilibrium mixture of the axial and equatorial methyl forms C and D, respectively (Table I). Assuming a conformational energy (ΔG value) of about 1.70 kcal/mol for a methyl group,[9] this translates to equilibrium mixtures composed of ca. 91% of the equatorial conformer at 100 °C to ca. 99% equatorial at −78 °C. In other words, *a methyl group is almost as good a conformation biasing group at −78 °C as is a tert-butyl substituent!* Thus, the increases in the axial-hydroxyl isomers with decreasing temperatures is anticipated; in particular, the extraordinary percentages of axial alcohols obtained with LTMBH and LTSBH at −78 °C are no longer unexpected and are irrespective of any temperature dependence of the reagent selectivity.[11]

The 2-alkyl case is an exception since k_a and k_e are not likely to be the same as for the 4-*tert*-butyl analogue. In this situation, the proximity of the adjacent 2-alkyl group does influence the approach of bulky reagents and directs attack so as to afford almost entirely one diastereomer (cis) at all temperatures.[12]

Two points are noteworthy. The stereoselectivities displayed by the new, sterically congested alkylborohydride reagents reside in the high preference shown for equatorial approach and not to any directive action of remote 3- and 4-positioned alkyl groups. In addition, a subtle and newly appreciated principle arises from the discussion in that while the intrinsic stereoselectivity of a particular reaction in a cyclohexane system may be impaired by the conformational heterogeneity of the substrate, such impairment may be alleviated by conducting the reaction at low temperatures in order to minimize the heterogeneity and subsequently obtain the greatest amount of the product resulting from attack on the most favored conformation. In fact, this principle applies to all conformationally heterogeneous systems in which one conformation predominates for enthalpic reasons (as is usually the case); such predominance will always be enhanced at low temperatures. The converse of the above is also true; the amount of a product resulting from attack of a less favored conformation will be maximized by conducting the reaction at the highest convenient temperature since the conformational heterogeneity will increase with increasing temperature.

Acknowledgments. I am extremely indebted to Professor Ernest C. Eliel for critical discussion, suggestions, and the loan of his superior communicative abilities. I also wish to thank Professor H. C. Brown for communicating some of the results

presented here prior to publication, and acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—*cis*-4-*tert*-Butylcyclohexanol, 937-05-3; *trans*-3-methylcyclohexanol, 7443-55-2; *cis*-4-methylcyclohexanol, 7731-28-4; *cis*-2-methylcyclohexanol, 7443-70-1; Li-*sec*-Bu_3BH, 38721-52-7; $LDMBH_2$, 51899-21-9; LTMBH, 60284-40-4; LTSBH, 61075-97-6.

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(2) Potassium tri-*sec*-butylborohydride (K-*sec*-Bu_3BH, K-Selectride): C. A. Brown, *J. Am. Chem. Soc.*, **95**, 4100 (1973).
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(5) For an example of an application of hindered borohydrides to prostaglandin synthesis see E. J. Corey, K. B. Becker, and R. K. Varma, *J. Am. Chem. Soc.*, **94**, 8616 (1972).
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(7) Expansion of the equation given by Eliel[8] to the situation where each conformer yields two products gives

$$\frac{d\,\%_{cis}/dt}{d\,\%_{trans}/dt} = \frac{k_a[E] + k_e[A]}{k_a[A] + k_e[E]} = \frac{k_aK + k_e}{k_a + k_eK}$$

$$= \frac{k_a(n_E/n_A) + k_e}{k_a + k_e(n_E/n_A)} = \frac{n_Ek_a + n_Ak_e}{n_Ak_a + n_Ek_e} = \frac{n_E(k_a/k_e) + n_A}{n_E + n_A(k_a/k_e)}$$

$$= \frac{n_E(\%\ A/\%\ E) + n_A}{n_E + n_A(\%\ A/\%\ E)} = \frac{n_E\ \%\ A + n_A\ \%\ E}{n_E\ \%\ E + n_A\ \%\ A}$$

Integration over the entire course of reaction gives fraction (or %) cis product/fraction (or %) trans product = $(n_E\%\ A + n_A\%\ E)/(n_E\%\ E + n_A\%\ A)$ as indicated in the discussion. If the Curtin–Hammett principle does not apply (i.e., fast reactions, slow conformer interconversion) each conformer is converted independently to the two products as in Scheme I. Since the initial mole fractions of A and E are n_A and n_E, the result in the above discussion follows directly.
(8) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 238.
(9) J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
(10) Calculated from $-\Delta G = RT \ln K_{eq}$.
(11) Along these lines, the data in Table II further suggest that Hoozs' reagent, $LDMBH_2$,[3] should also show superior selectivity at low (i.e., −78 °C) temperatures.
(12) The situation is complicated for the 3-alkylcyclohexanones at temperatures high enough so that the axial conformer makes a significant contribution. In this situation, the axial alkyl group may interfere with axial approach of the bulky reagents. In addition, equatorial attack may be slowed by the developing syn-axial OX/alkyl interaction. These possible complications disappear at low temperatures where only the equatorial alkyl conformer is significantly populated.

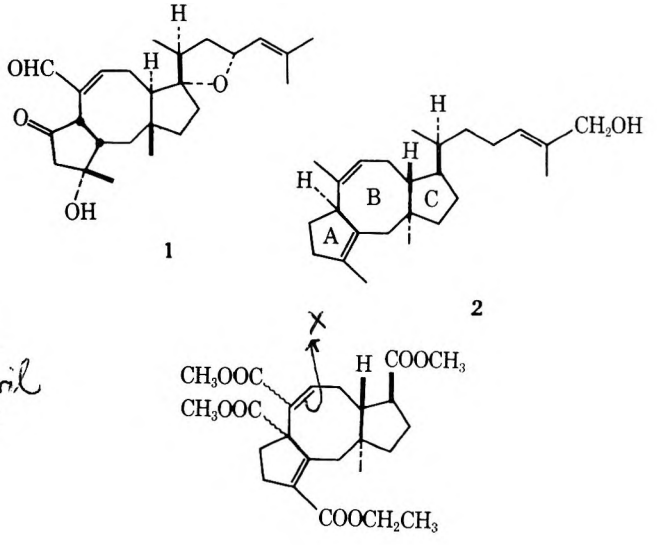
Communications

A Synthesis of the Ophiobolin Nucleus[1]

Summary: A ring contraction–ring expansion–annelation reaction sequence was followed for the synthesis of functionalized carbon skeleton of the ophiobolins.

Sir: The ophiobolins are the most abundant members of the relatively new class of C-25 terpenoids known as sesterterpenes.[2] Representatives of this class of natural products are ophiobolin A (**1**),[3] a metabolite of the plant pathogenic fungus *Cochliobolus miyabeanus*, and ceroplastol II (**2**),[4] a component of the desiccant wax produced by females of insect family *Ceroplastes albolineatus*.[5] The ring system of the ophiobolins is also found in a large family of diterpene aglycones known as fusicoccins.[6] The novel structure and biological activity[7] of the ophiobolins make them attractive targets for total synthesis. We would like to report the preparation of tetraester **3**, the first synthesis of the tricyclo[9.3.0.$0^{3,7}$]tetradecane ring system characteristic of the ophiobolins.[8] The synthesis described herein produces the trans BC ring juncture present in all ophiobolins. The location of substituents on the tricyclic nucleus makes **3** a potential intermediate in projected syntheses of several ophiobolins.

The known octahydronaphthalene **4**[9] was reduced with lithium in ammonia and the resulting enolate was trapped according to established procedures[10] to afford a high yield of enol ether **5**. The crude ether **5** was allowed to react with 1 equiv of *p*-bromobenzenesulfonyl azide in acetonitrile at 50 °C, followed by the addition of a small amount of water to effect hydrolysis of the intermediate imino ether.[11] The re-



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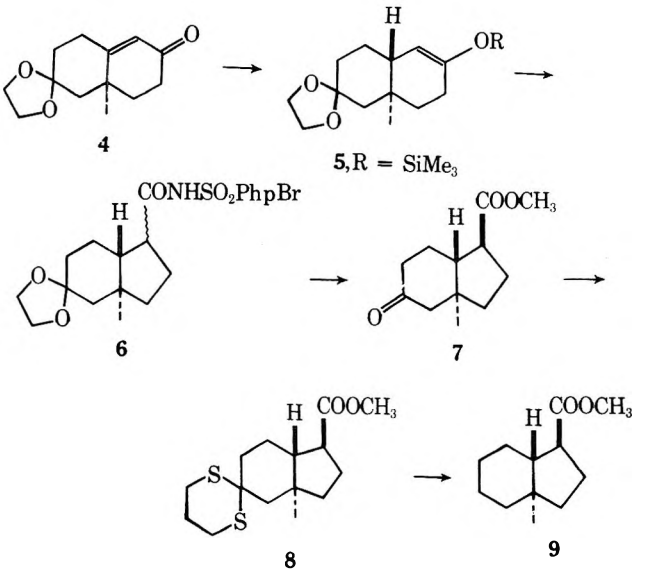

4 5, R = $SiMe_3$ 6 7 8 9

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sulting *N*-acyl sulfonamide **6** [mp 185–188 °C; NMR ($CDCl_3$) δ 0.85 (s, 3), 1.1–2.5 (m, 12), 3.87 (m, 4), 7.63 (d, 2, J = 9 Hz), 7.91 (d, 2, J = 9 Hz), 8.55 (br s, 1)] was hydrolyzed with concommitant loss of the ketal and the resulting crude keto acid was esterified to give the trans-fused hydrindan **7** in overall yield of 42% from enone **4**.[12] The structure and stereochemistry of **7** was firmly established by converting it to the known ester **9**[13] via the crystalline thioketal **8** (mp 54–57 °C). The ester **9** produced from **7** was identical (IR, ^{1}H NMR, ^{13}C NMR, VPC, TLC) with a sample of **9** prepared by an established route.[13,14]

Having established the crucial trans BC ring juncture, attention was turned to expanding the six-membered ring to an eight-membered ring via the well-known reaction between enamines and acetylenic esters.[15] It had been suggested that a trans-fused hydrindanone such as **7** should enolize predominantly away from the ring juncture.[16] This suggestion was primarily an extrapolation from results obtained with trans-fused decalones and steroidal ketones. Thus, when a mixture of keto ester **7** and morpholine was heated in refluxing tetrahydrofuran over 4A molecular sieves, crude enamino ester **10** was obtained in a 90% yield. The appearance of the vinyl proton as a doublet (J = 4.5 Hz) at δ 4.50 (benzene-d_6) in the ^{1}H NMR spectrum of **10** confirmed that enamine formation had occurred predominantly, if not exclusively, away from the ring juncture. When crude **10** was allowed to react with dimethyl acetylenedicarboxylate and the crude mixture of products was hydrolyzed with aqueous acidic methanol, a 40% yield of a mixture of 1:1 adducts between **7** and dimethyl acetylenedicarboxylate was obtained. Keto ester **7** was also obtained in an 8% yield. The mixture of adducts was 75–80% dienol **11** which was obtained in pure form by crystallization from petroleum ether [mp 114–117 °C; IR (CCl_4) 1730, 1658, 1610 cm^{-1}; UV max (MeOH) 220 nm (ϵ 7200), 264 (9100); NMR ($CDCl_3$) δ 0.93 (s, 3), 1.3–2.9 (m, 10), 3.78 (sharp m, 9), 7.08 (t, 1, J = 9 Hz), 13.0 (br s, 1); mass spectrum (70 eV) m/e 352 (M^+)].[17] The similarity between the spectral properties of **11** and those of the related cyclooctadienols **13**[18] and **14**[19] support the assigned structure.

The A ring was grafted onto dienol **11** in the following manner. The mixture of adducts from the ring expansion was hydrogenated at 45 psi over 5% palladium on alumina to give a 90% yield of β-keto ester **12** after chromatography over silica gel. Sequential treatment of **12** with sodium hydride and 1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate[20] gave a 30% yield of a *single* α,β-unsaturated ester **3** after chromatography over silica gel and recrystallization from petroleum ether [mp 120–121 °C; UV max (MeOH) 237 nm (ϵ 8700); NMR ($CDCl_3$) δ 0.82 (s, 3), 1.29 (t, 3, J = 7 Hz), 1.3–3.6 (m, 17), 3.70 (s, 3), 3.71 (s, 3), 3.74 (s, 3), 4.21 (q, 2, J = 7 Hz); exact mass calcd for $C_{24}H_{34}O_8$ 450.2254, found 450.2296].[21]

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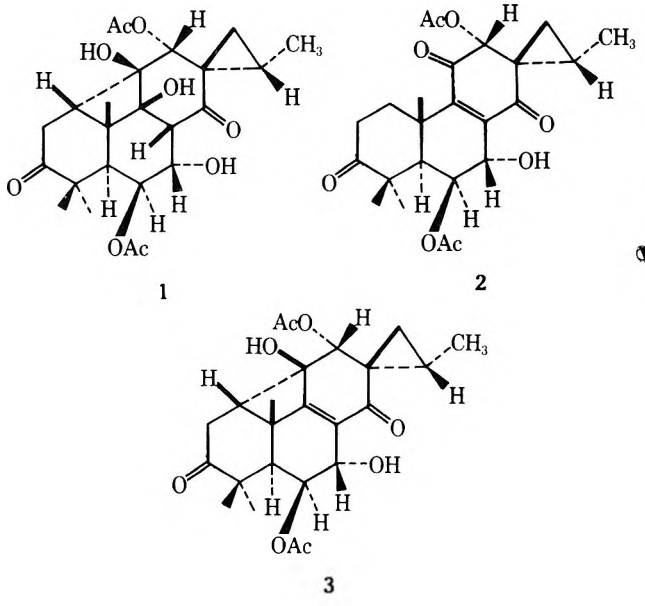
Synthesis and Structural Determination of Dehydrocyclobutatusin, a Diterpenoid with a Four-Membered Ring

Summary: Irradiation of the diterpenoid, barbatusin (**2**), produces dehydrocyclobutatusin (**3**), which contains a new four-membered ring; the structure of **3** was determined by x-ray methods.

Sir: Cyclobutatusin (**1**), a diterpenoid isolated from *Coleus barbatus*,[1,2] retains the basic spiro[2,5]octane system of bar-



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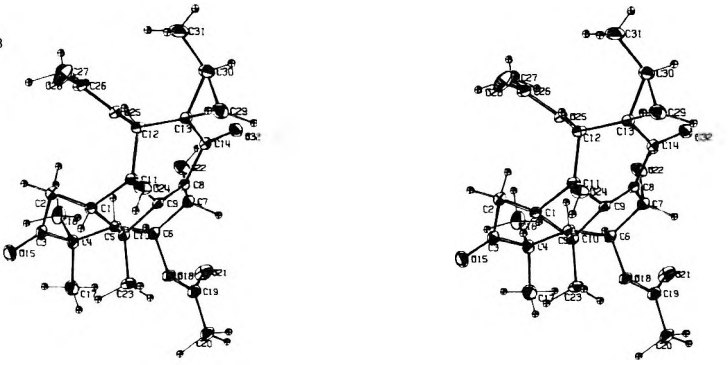

Figure 1. Stereoscopic view of a single molecule of **3**.

batusin (**2**)[2,3] but in addition has a four-membered ring formed by a bond between C(1) and C(11). These findings suggested that cyclobutatusin might be the product of a photochemically induced reaction involving a barbatusin-type precursor.[1,2] The formation of cyclobutanol derivatives upon UV irradiation of diterpenoids,[4] steroids,[5] and triterpenoids[6] has been extensively studied and this fact prompted us to examine the irradiation of barbatusin. We now wish to report the photosynthesis of a 1,11-cyclo species, dehydrocyclobutatusin (**3**), a probable precursor in the biogenesis of cyclobutatusin.

Irradiation of a benzene solution of barbatusin in the n–π^* band gave **3**, mp 176–180 °C, $C_{24}H_{30}O_8$ (M^+ 446), in 40% yield. The IR spectrum indicated the presence of hydroxyl, ester, keto, α,β-unsaturated keto, and acetyl functions (ν 3450, 1735, 1705, 1660, 1240 cm^{-1}). The NMR spectrum ($CDCl_3$, ppm) revealed the presence of three tertiary methyl groups at 4α, 4β (1.17, 1.18), and 10β (1.65), and also one secondary *C*-methyl group in the spiro side chain, d at δ 1.05 (J = 4 Hz), two acetyl functions at 2.02 (3 H, s) and 2.03 (3 H, s), two CHOAc protons at 5.75 (d of d, J_{5-6} = 4 Hz, J_{6-7} = 2 Hz) for the 6α and at 4.8 for the 12β-H, one proton at 4.62 assigned to the 7β-H (d, J_{6-7} = 2 Hz), and two hydroxyl groups (br signals at 3.40 and 3.66 with $W_{1/2}$ = 16 and 12 Hz). The two latter signal patterns collapsed following deuterium exchange (with D_2O). The UV spectrum showed an absorption maximum at 230 nm (ϵ 8475) reminiscent of that due to the α,β-unsaturated keto chromophore of barbatusin (**2**). This absorption had one half of its intensity, thus indicating the presence of one chromophore, and can thus be associated with the structural feature present in the BC ring system of structure **3**.

Dehydrocyclobutatusin which is isomeric with barbatusin readily formed an acetylated derivative, $C_{26}H_{32}O_9$, mp 127–129 °C. The presence of a hydroxyl group which resisted acetylation was indicated by examination of the NMR spectrum: the complex signal pattern at δ 3.08 ($W_{1/2}$ = 16 Hz) was assigned to that OH group and collapsed following deuterium exchange; the additional acetyl group could be observed at 2.18 (3 H, s, 7α-OAc) and the geminal CHOAc proton at 5.08 (d, J_{6-7} = 2 Hz).

The presence in **3** of the groupings shown in ring C, in association with a spirocyclopropane ring at C(13), would account for much of the above data. Furthermore the location of a tertiary OH group at C(11) was in accord with this information.

At this stage, the three-dimensional structure of dehydrocyclobutatusin was determined by the x-ray structure analysis of the crystals obtained from benzene solution. The colorless crystals appear to react with moisture forming a white surface coating. A single crystal ~0.4 × 0.2 × 0.2 mm was used to collect 1976 reflections on a Syntex $P2_1$ diffractometer (CuKα radiation). The space group is monoclinic, $P2_1$, with two molecules per unit cell: a = 8.242 (9), b = 10.816 (9), c = 12.810 (9) Å, β = 94.27 (7) °. The structure was solved by direct methods[7] and refined by full-matrix least-squares methods (for all nonzero reflections) to an R factor of 0.042.[8] Anisotropic temperature factors were used for all nonhydrogen atoms. A stereoscopic drawing of a single molecule is shown in Figure 1. The bond lengths are close to accepted values with the C(1)–C(11) distance in the four-membered ring being 1.602 (6) Å. The crystal packing is stabilized by extensive hydrogen bonding between hydroxyl oxygens O(24) and O(22) and carbonyl oxygens O(28) and O(21), respectively, in symmetry-related molecules.

The molecular mechanism responsible for the photoisomerization of barbatusin into dehydrocyclobutatusin is obviously an intramolecular γ-hydrogen transfer from C(1) to the electron deficient n–π^* excited carbonyl group at C(11) (Norrish type II process).[9] The relative ease whereby the new 1,11-cyclo species (**3**) is obtained strongly supports the assumption of a biogenetic pathway leading to cyclobutatusin (**1**) through its dehydro compound (**3**) whose double bond at C(8)–C(9) would add the elements of water from the less hindered upper side of the molecule.

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Supplementary Material Available. Tables of coordinates, temperature factors, bond lengths, bond angles, and structure factors for **3**, and the experimental details of the preparation of **3** (9 pages). Ordering information is given on any current masthead page.

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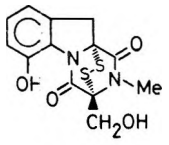
Approaches to the Resolution of Racemic Cyclic Disulfides. Application to an Epidithiodioxopiperazine

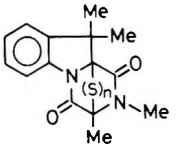
Summary: The chemical resolution of **2** has been performed via diastereomer formation (**9** and **10**) as well as via a kinetically controlled transformation; the enantiomers **11** and **12** have the same anti-reverse transcriptase activity.

Sir: Chemical resolution of racemic cyclic disulfides, devoid of convenient handles for conversion into diastereomers, has not been reported. We wish to report a method developed for the resolution of a racemic epidithiodioxopiperazine which might be of general applicability to other chiral cyclic disulfides.

Dehydrogliotoxin **1**, the sporidesmins,[1] and chaetocin[2] belong to the class of fungal metabolites containing an epi-



1

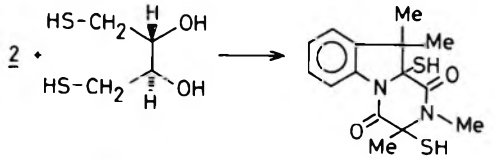


2: n = 2
3: n = 1

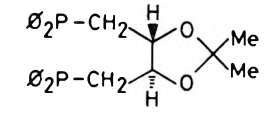
dithiodioxopiperazine ring system. The first two compounds have the *R* configuration at the bridgehead carbons and exhibit selective antiviral properties, whereas the antipodal chaetocin does not show this activity. Recently we reported a synthesis[3] of a racemic dehydrogliotoxin analogue **2**, which inhibits reverse transcriptase,[4] the RNA-dependent DNA polymerase of RNA tumor viruses, and whose activity is of the same order as that of gliotoxin. Separate examination of the enantiomers of **2** might indicate whether the antiviral activity of epidithiodioxopiperazines is related to their bridgehead configurations.

In general, resolution of **2**, which lacks a reactive handle, might be achieved[5] by crystallization, chromatographic,[6] or kinetic methods. Initially we attempted a kinetic asymmetric transformation by two routes, viz., reduction of **2** to **5** with the optically active dimercapto compound **4** (Scheme I) and partial desulfurization of **2** to **3** with the chiral phosphine **6**. When **2** was treated with 0.5 equiv of the optically active

Scheme I



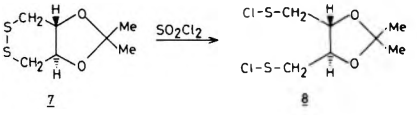
4 **5**



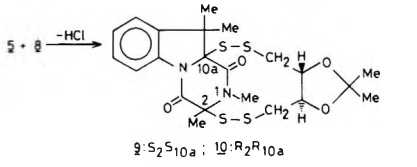
6

Cleland's reagent **4**,[7] racemic mixtures of **2** and the dithiol **5** were isolated. However, when **2** was reacted with 0.25 equiv of the diphosphine **6** [(−)-Diop[8]], a 19% enrichment[9] in one enantiomer in the isolated starting material was observed. As this enrichment was too small for our needs, we turned to resolution via covalent formation of diastereomers. The reaction scheme for the synthesis[3] of **2** proceeds via the stable intermediate **5**.[10] This could be converted into diastereomers and each transformed into **2** without racemization as will be shown below. The resolving agent was selected on the basis of the following considerations: (i) a bifunctional agent was selected, as diastereomers with a high rigidity would allow an optimal separation;[11] (ii) the minimum number of diastereomers (two) would result if this bifunctional reagent possessed an axis of symmetry. These features were present in a derivative of (−)-Diop (**6**), viz., the disulfenyl chloride **8**. This was prepared quantitatively from **7**[12] with SO_2Cl_2 and a trace of pyridine in CCl_4 (Scheme II).

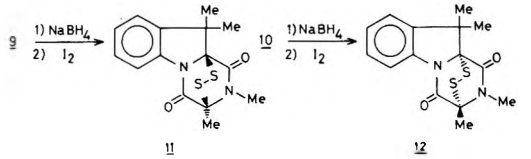
Scheme II



7 **8**



9: S_2S_{10a}; **10**: R_2R_{10a}



11 **12**

Reaction of **8** (2.1 mmol) in CCl_4 with **5** (2.1 mmol) in the presence of 2 equiv of pyridine gave, besides **2**, the diastereomeric[13] disulfides **9** and **10**. Separation by column chromatography on silica gel[14] (Merck 60 PF254) using CH_2Cl_2/CCl_4 (1:1 v/v) as eluent gave **9** and **10** (28% yield of each) whose ^1H NMR spectra were nearly identical (for the ketalic CH_3 groups: broad singlet at δ 1.40 for **9**; two singlets at 1.3 and 1.4 for **10**). Reduction of **9** or **10** with $NaBH_4$ in ethanol followed by reoxidation with I_2/pyridine in CH_2Cl_2[13] gave the enantiomers **11** {$[\alpha]^{22}D$ +477° (*c* 0.65 in $CHCl_3$)} or **12** {$[\alpha]^{22}D$ −484° (*c* 0.64 in $CHCl_3$)}, respectively, in 82% yield as well as the precursor **7** of the resolving agent. Compound

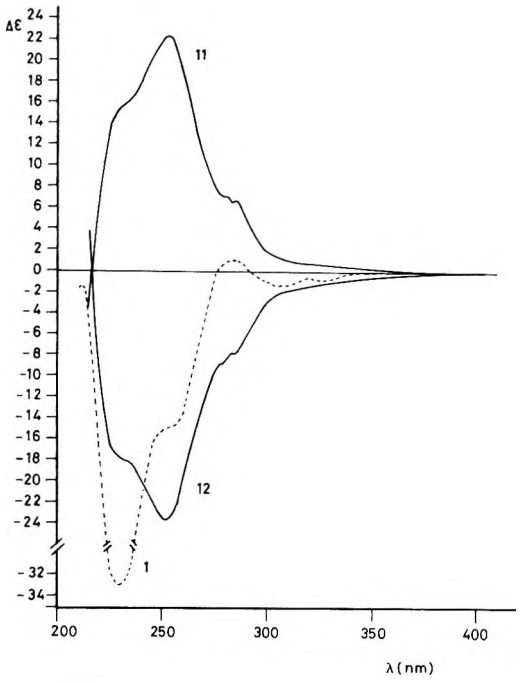


Figure 1. Circular dichroism curves of **1**, **11**, and **12**.

11 or **12** could not yet be brought to crystallization; their ^1H NMR spectra in the presence of a chiral shift reagent showed that the optical purity is higher than 90%.[9] The absolute configurations were derived from CD spectra (Figure 1). Dehydrogliotoxin (**1**) shows a negative Cotton effect at 230 nm.[15] From this the tentative conclusion is drawn that **11** possesses the *S* configuration, while **12** has the *R* configuration.[16] Surprisingly, both enantiomers were found to have the same anti-reverse transcriptase activity,[17] indicating that there is no relation between this property of epidithiodioxopiperazines and their bridgehead configurations.

Applications of this method of resolution[18] to other racemic, cyclic disulfides and to chiral compounds having two reactive functional groups is under investigation.

Acknowledgment. We are indebted to Mr. C. G. van Schagen, Landbouw Hogeschool Wageningen, for measuring the CD spectra, and Dr. E. De Clercq, Leuven, for performing the bioassays.

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(9) The ^1H NMR spectrum of racemic **2** showed two signals for the *N*-methyl as well as for the C_2-methyl group when tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) was used as chiral shift reagent; enantiomeric purity could be determined easily by integration.
(10) Dithiol **5** can also be obtained quantitatively by reduction of **2** with $NaBH_4$; see, e.g., ref 3.
(11) A possible relation between rigidity in diastereomers and their ease of separation can be deducted from Woodward's statement that separation of diastereomeric salts is more likely to succeed when the chiral centers are as close as possible in space: R. B. Woodward et al., *Tetrahedron*, **19**, 247 (1963), and footnotes on p 259.
(12) This compound is prepared in 50% overall yield from L-(+)-tartaric acid; see ref 7.
(13) In thin layer chromatography on silica gel (Merck precoated F-254 plates) compounds **2**, **9**, and **10** had R_f values of 0.35, 0.29, and 0.23, respectively, when CH_2Cl_2 was used as eluent.
(14) A layer of Na_2CO_3 was placed on top of the column to prevent acid-catalyzed deketalization of **9** and **10**.
(15) S. Safe and A. Taylor, *J. Chem. Soc. C*, 1189 (1971).
(16) The Cotton effect at 230 nm is due to an n, π^* transition of a peptide bond; see, e.g., R. Nagarajan and R. W. Woody, *J. Am. Chem. Soc.*, **95**, 7212 (1973).
(17) Details on these tests will be published elsewhere.
(18) The method outlined here meets all of the principal desirable features of resolution via diastereomeric formation as formulated by S. H. Wilen, ref 5, p 111.

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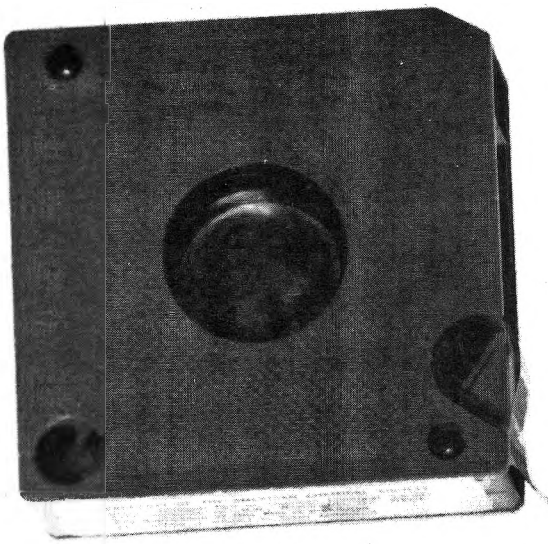

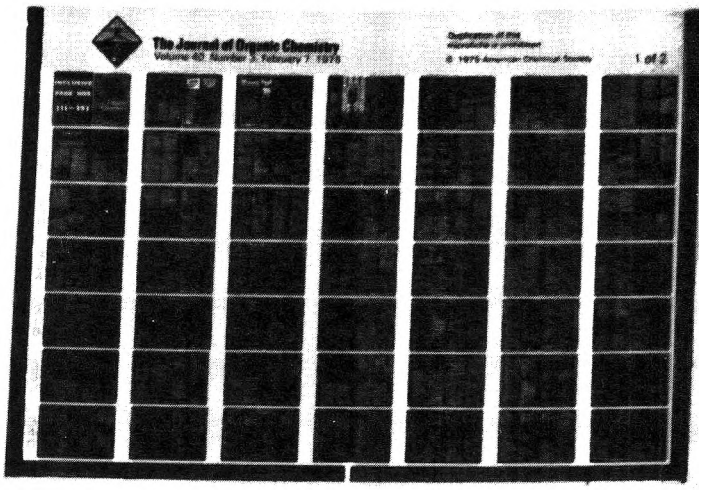

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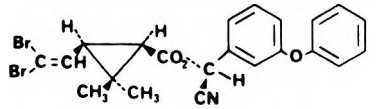
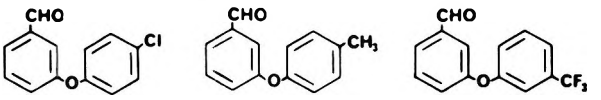
m-Phenoxybenzaldehydes

The synthetic pyrethroids are soon likely to be among the most important insecticides, because they are tremendously active, biodegradable and harmless to mammals.[1] The most active compounds, of which **NRDC 161** is an example, are esters of ***m*-phenoxybenzaldehyde cyanohydrin** or ***m*-phenoxybenzyl alcohol**.[1] At first sight, one would think that the activity must be due to the cyclopropane moiety. This, however, is not the case: Ohno *et al.*[2] have shown that quite simple esters of the ***m*-phenoxybenzaldehyde cyanohydrin** are very active. Thus, the unique insecticidal activity of these pyrethroids is due primarily to the ***m*-phenoxyphenyl moiety**.



NRDC 161

We have developed a simple method for the preparation of ***m*-phenoxybenzaldehyde**, and so we also prepared a number of *substituted* ***m*-phenoxybenzaldehydes** in the hope that these benzaldehydes will be of special interest to medicinal chemists: compounds related to the active center of pyrethroids may well show surprising medicinal activities!



References:

1) For a review, with leading references, see A. Bader, *Aldrichimica Acta*, **9**, 49 (1976).

2) N. Ohno *et al.*, *Agric. Biol. Chem.*, **38**, (4), 881 (1974).

19,175-2 ***m*-Phenoxybenzaldehyde.. 5g $7.50; 25g $23.50**

19,530-8 ***m*-(*p*-Chlorophenoxy)benzaldehyde 10g $15.50; 50g $50.00**

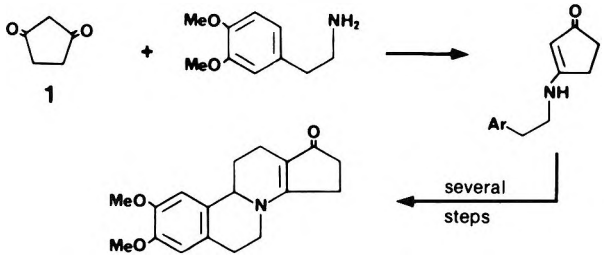
19,540-5 ***m*-(*p*-Methylphenoxy)benzaldehyde 10g $15.50; 50g $50.00**

19,539-1 ***m*-(*m*-Trifluoromethylphenoxy)benzaldehyde 5g $10.00; 25g $40.00**

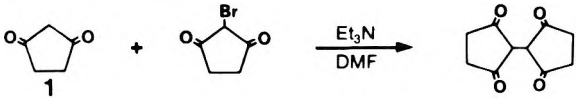
19,305-4 ***m*-Phenoxybenzaldehyde cyanohydrin 10g $15.00**

1,3-Cyclopentanedione

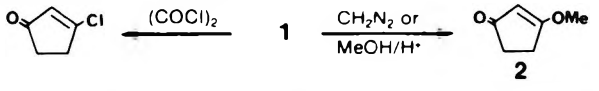
1,3-Cyclopentanedione (1) has been found to be a very useful compound with a variety of synthetic applications. For example, **1,3-cyclopentanedione** has been used as a key starting material for 8-azasteroids.[1]



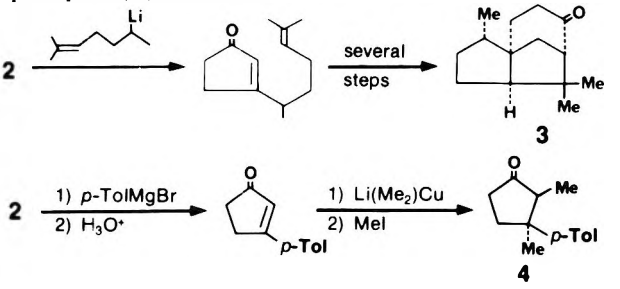
The antibacterial 2,2'-bi-(1,3-cyclopentanedione) has been synthesized by treating 2-bromo-1,3-cyclopentanedione with **1** in the presence of base.[2]



1,3-Cyclopentanedione may be conveniently modified by chlorination[3] or by O-alkylation[4] to make other useful synthetic intermediates.



The O-methylated derivative **2** has been used in Corey's synthesis of the tricyclic sesquiterpene cedrone **(3)**.[5] Compound **2** has recently been used by Posner[6] for the synthesis of *trans*-2,3-dimethyl-3-*p*-tolylcyclopentanone **(4)**. The scheme constitutes a formal synthesis of the sesquiterpene (±)-laurene.[7]



Available from stock, Aldrich offers **1,3-cyclopentanedione** to help meet your synthetic needs.

References:

1) R.E. Lyle and G.A. Heavner, *J. Org. Chem.*, **40**, 50 (1975).

2) Japan Kokai Patent, 73 99,151; *Chem. Abstr.*, **80**, 95360*f* (1974).

3) R.D. Clark and C.H. Heathcock, *J. Org. Chem.*, **41**, 636 (1976).

4) J.M. McIntosh and P.M. Beaumier, *Can. J. Chem.*, **51**, 843 (1973).

5) E.J. Corey and R.D. Balanson, *Tetrahedron Lett.*, 3153 (1973).

6) G.H. Posner and C.M. Lentz, submitted for publication in *J. Amer. Chem. Soc.*

7) J.E. McMurry and L.A. von Beraldingen, *Tetrahedron*, **30**, 2027 (1974).

17,716-4 1,3-Cyclopentanedione 1g $11.75; 5g $38.50

11,702-1 2-Methyl-1,3-cyclopentanedione 5g $18.00

19,456-5 2-Ethyl-1,3-cyclopentanedione 25g $15.00 100g $40.00