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Photolytic Formation of Isomeric Vinyl Radicals from *cis*- and *trans*-Vinyl Iodides[1,2]

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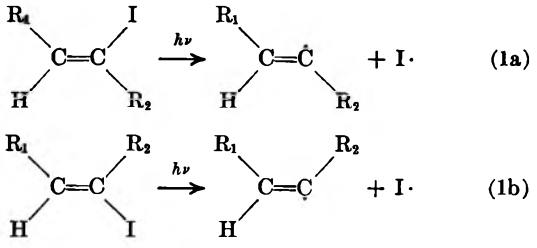
The isomeric vinyl iodides *cis*- and *trans*-4-iodo-3-heptenes have been synthesized, and their comparative solution phase photochemistry has been investigated using chloroform and pentane as solvents. Both isomers gave 3-heptyne and *cis*- and *trans*-3-heptenes as major products; the iodides isomerized; and 3,4-heptadiene was observed as a product under certain conditions. The product distributions were isomer and solvent dependent. The results are discussed in terms of the primary formation of vibrationally excited *cis*- and *trans*-3-hepten-4-yl radicals and their secondary reactions.

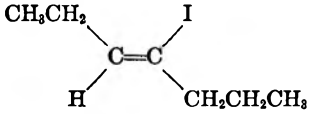
The photochemistry of vinyl iodides has received relatively little attention although these compounds are potential photolytic sources of isomeric vinyl radicals (reactions 1a and 1b). The configurational sta-



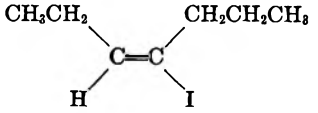
(1a)

(1b)

bility and relative chemical reactivity of such isomeric radicals are subjects of current interest,[3-10] and this prompts us to report the results of studies of the comparative solution phase photochemistry of *trans*- and *cis*-4-iodo-3-heptenes (**1** and **2**).



1 (*trans*)



2 (*cis*)

Organic monoiodides absorb light in the near-ultraviolet [$\lambda_{max} \simeq 250$ mμ ($\epsilon \sim 400$)], and photolysis in this region leads to efficient carbon–iodine bond homolysis.[11] It has been proposed that photolysis at shorter wavelengths can lead to a primary β-molecular elimination of hydrogen iodide (*e.g.*, reaction 2); however,

$$CH_3CH_2I \xrightarrow{h\nu} CH_2{=}CH_2 + HI \qquad (2)$$

the evidence is sparse, and the process seems to be relatively inefficient.[11,12] Two secondary reactions following C–I homolysis can lead to products identical with those expected from a β-molecular elimination (reactions 3 and 4). Cage disproportionation of the

$$R_3CCR_2I \xrightarrow{h\nu} \overline{R_3C\dot{C}R_2\ I\cdot} \longrightarrow R_2C{=}CR_2 + RI \qquad (3)$$

$$R_3CCR_2I \xrightarrow{h\nu} R_3C\dot{C}R_2{}^* + I\cdot \longrightarrow R_2C{=}CR_2 + R\cdot \qquad (4)$$

initially formed geminate radical pair (reaction 3) would be expected in solution when the abstracted R was hydrogen, and fragmentation of a vibrationally excited radical (reaction 4), produced from the primary scission process, might occur in vapor phase experiments. Evidence is available for both reactions for vinyl iodides and iodoalkanes.[1a,11,12]

Previous studies of vinyl iodides have been restricted to 1-iodoethylene (vinyl iodide), 2-iodopropene, and *cis*- and *trans*-1-iodopropenes. Results from the photolysis of 1-iodoethylene in carbon tetrachloride indi-

(1) (a) Photochemistry of Organic Iodides. III. Paper II: R. C. Neuman, Jr., and R. G. Wolcott, *Tetrahedron Lett.*, 6267 (1966). (b) Presented at the Pacific Conference on Chemistry and Spectroscopy, Anaheim, Calif., Oct 30–Nov 1, 1967.

(2) Support by the National Science Foundation (GP-4287 and GP-7349) is gratefully acknowledged.

(3) (a) L. A. Singer and N. P. Kong, *J. Amer. Chem. Soc.*, **89**, 5251 (1967); (b) L. A. Singer and N. P. Kong, *ibid.*, **88**, 5213 (1966).

(4) (a) E. I. Heiba and R. M. Dessau, *ibid.*, **89**, 3772 (1967); (b) E. I. Heiba and R. M. Dessau, *ibid.*, **89**, 2238 (1967).

(5) G. D. Sargent and M. W. Browne, *ibid.*, **89**, 2788 (1967).

(6) O. Simamura, K. Tokumaru, and H. Yui, *Tetrahedron Lett.*, 5141 (1966).

(7) G. M. Whitesides and C. P. Casey, *J. Amer. Chem. Soc.*, **88**, 4541 (1967).

(8) (a) R. M. Fantazier and J. A. Kampmeier, *ibid.*, **88**, 5219 (1966); (b) J. A. Kampmeier and R. M. Fantazier, *ibid.*, **88**, 1959 (1966); (c) J. A. Kampmeier and G. Chen, *ibid.*, **87**, 2608 (1965).

(9) P. S. Skell and R. G. Allen, *ibid.*, **86**, 1559 (1964).

(10) A. A. Oswald, K. Griesbaum, B. E. Hudson, Jr., and J. M. Bregman, *ibid.*, **86**, 2877 (1964).

(11) (a) J. R. Majer and J. P. Simon, *Advan. Photochem.*, **2**, 137 (1964); (b) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, pp 522–528.

(12) R. C. Neuman, Jr., *J. Org. Chem.*, **31**, 1852 (1966).

cated that C–I homolysis was the only photoreaction of the iodide and that cage disproportionation to form acetylene (analogous to reaction 3) competed with diffusive separation of the initially formed geminate vinyl radical and iodine atom.[13] Pertinent conclusions from a vapor phase study of *cis*- and *trans*-1-iodopropenes were that C–I homolysis was probably the major primary process followed by some fragmentation (analogous to reaction 4), that some molecular elimination may have occurred at wavelengths less than 2400 Å, and that the product distributions were isomer independent.[12] Less detailed results from the solution phase photolysis of *trans*-1-iodopropene[12] agreed with the data for 1-iodoethylene.[13] Vapor phase photolysis of 2-iodopropene gave both methylacetylene and allene.[14]

The solution phase photochemical studies of **1** and **2** which constitute the subject of this paper have demonstrated a marked isomer dependence of the product distribution. For this reason we feel that the following description of the syntheses of these new vinyl iodides and the bases for their isomeric assignments are necessary.

Synthesis and Structural Assignments.—The synthentic sequence used to prepare *trans*- and *cis*-4-iodo-3-heptenes (**1** and **2**) is outlined in Scheme I. The procedure was a modification of that reported for 1,1-diiodoneopentane by Barton.[15] An unsubstituted hydrazone synthesis involving the intermediate N,N-dimethylhydrazone[16] was used in place of the more difficult direct hydrazone synthesis from 4-heptanone.

SCHEME I

$$(RCH_2)_2CO + (CH_3)_2NNH_2 \longrightarrow (RCH_2)_2C{=}NN(CH_3)_2$$

$$(RCH_2)_2C{=}NN(CH_3)_2 \xrightarrow{NH_2NH_2} (RCH_2)_2C{=}NNH_2$$

$$(RCH_2)_2C{=}NNH_2 \xrightarrow{I_2,\ Et_3N,\ \text{ether}} (RCH_2)_2CI_2 \xrightarrow{-HI} RCH{=}CICH_2R$$

3 → **1** and **2**

R = CH_3CH_2

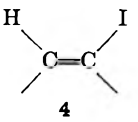
Attempts to purify 4,4-diiodoheptane (**3**) by glpc led to its efficient conversion into **1** and **2** in the ratio 4:1.[17] Sodium–liquid ammonia reduction[18] of **1** or **2** gave *trans*- or *cis*-3-heptene, respectively. Since these reductions proceed with retention of configuration,[19] the results offer confirmation of the isomeric assignments. Further proof of structure was derived from nmr and uv spectral data. The chemical shifts of the nmr resonance signals of the single vinyl proton in a series of vinyl iodides are given in Table I.[20] The cyclic compounds force a *cis* relationship between the vinyl proton and the neighboring iodine atom (**4**). The

TABLE I

CHEMICAL SHIFTS OF THE VINYL PROTON RESONANCE SIGNALS FOR A SERIES OF VINYL IODIDES[a]

Vinyl iodide	Vinyl hydrogen chemical shift, cps[b,c]
1-Iodocyclopentene[d]	−361
1-Iodocyclohexene[d]	−376
1-Iodocyclooctene[d]	−380
cis-3-Iodo-3-hexene[e]	−373
cis-4-Iodo-3-heptene (**2**)	−371
trans-3-Iodo-3-hexene[e]	−333
trans-4-Iodo-3-heptene (**1**)	−328

[a] Neat samples. [b] Reference, TMS. [c] Resonance signals were basically triplets in all cases. [d] Synthesized from the corresponding cycloalkanones. Structure proof based on microanalytical, chemical, and spectral data. Unpublished work of G. S. H. [e] Spectral data kindly furnished by Professor G. Zweifel.



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correspondence in chemical shifts between the vinyl proton of **2** and those of the cyclic iodides and the large upfield shift for the vinyl proton in **1** agree with the structural assignments. Additional confirmation is offered by the nmr data for *cis*- and *trans*-3-iodo-3-hexenes (Table I) whose structures were based on different evidence.[21,22] The C–I absorption band in the uv spectrum for *trans*-1-iodopropene (253 mμ), which has the geometry represented by **4**, is shifted by 5 mμ to a longer wavelength than that for *cis*-1-iodopropene (248 mμ).[12] Similarly, the C–I band for *cis*-4-iodo-3-heptene (**2**) (249 mμ), having the geometry of **4**, shows a 6-mμ longer wavelength shift compared with that of *trans*-4-iodo-3-heptene (**1**) (243 mμ).

Results

Solutions of **1** or **2** in chloroform or pentane were vacuum degassed and photolyzed at room temperature with stirring under nitrogen or oxygen atmospheres using the Vycor-filtered light (λ >2400 Å)[13a] of a medium-pressure mercury arc. The same quartz vessel and physical arrangement of the experimental apparatus were used in all runs, and the vapor phase region of the vessel was shielded from irradiation. Photolyzing mixtures were sampled at various time intervals, and the loss of starting material and formation of products were monitored by glpc.

The only detectable products formed from either **1** (expt 1–5) or **2** (expt 6–9) were *cis*- and *trans*-3-heptenes, 3-heptyne, 3,4-heptadiene, and the geometric isomer of the starting iodide (Table II). These products typically accounted for about 60–65% of the starting

(13) C. Roberge and J. A. Herman, *Can. J. Chem.*, **42**, 2262 (1964).

(14) R. C. Neuman, Jr., and S. Moje, unpublished work.

(15) (a) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962); (b) see also A. J. Fry and J. N. Cawse, *J. Org. Chem.*, **32**, 1677 (1967); (c) see also R. C. Neuman, Jr., and M. L. Rahm, *ibid.*, **31**, 1857 (1966).

(16) G. R. Newkome and D. L. Fishel, *ibid.*, **31**, 677 (1966).

(17) Base-catalyzed dehydrohalogenation of **3** led to the same products. Since **1** and **2** were to be purified by glpc subsequent to their preparation, we saw no need to use the base-catalyzed dehydrohalogenation for synthetic purposes since the desired elimination of HI from **3** occurred efficiently in the injector block of the gas chromatograph (see Experimental Section).

(18) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 77.

(19) M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Amer. Chem. Soc.*, **73**, 3329 (1951).

(20) The iodocycloalkenes were synthesized from the corresponding cycloalkanones. Proof of structure is based on microanalytical, chemical, and spectral data. G. Holmes, M.S. Thesis, University of California at Riverside, Riverside, Calif., 1967.

(21) G. Zweifel and C. C. Whitney, *J. Amer. Chem. Soc.*, **89**, 2753 (1967).

(22) The authors are grateful to Professor G. Zweifel for copies of the nmr and ir spectra of *cis*- and *trans*-3-iodo-3-hexenes.

TABLE II

PRODUCT DATA FOR PHOTOLYSES OF 1 AND 2[a,b]

Expt[c]	Time, min	Convn, %	Yield, %	Isomerization, %	Mol %: 3-Heptene cis	3-Heptene trans	3-Heptyne	3,4-Heptadiene	Isomerized iodide[d]
1-1 C N 3.2	10	8	62	1.0	11	10	61	0	17
	20	14	52	2.8	10	9	52	0	29
	30	18	63	3.8	11	10	54	0	26
	40	21	66	5.4	11	10	51	0	29
2-1 C N 6.3	3	1			[8]	[8]	[45]	[19]	[20]
	5	2			[8]	[8]	[50]	[14]	[20]
3-1 C N 3.2[e]	10	8	52	1.0	9	9	46	15	21
NaOH	26	22	48	2.4	11	11	46	15	17
4-1 C O 2.9	20	11	68	2.6	4	4	64	0	29
5-1 P N 2.1	10			1.9	[5]	[10]	[56]	[0]	[29]
6-2 C N 1.7	10	17	68	6.0	14	21	26	0	39
	20	27	64	9.9	13	20	26	0	41
	33	38	60	15.4	14	20	26	0	41
7-2 C N 5.0	3	1			[14]	[22]	[24]	[0]	[40]
8-2 C O 1.8	10	16	45	4.3	12	24	23	0	41
9-2 P N 3.1	10			3.5	[2]	[40]	[18]	[0]	[40]

[a] A description of the various column headings is given in the text. [b] Bracketed numbers based on assumed yields of isomerized iodide. [c] The first number in the experiment code refers to the experiment number; 1 and 2 stand for *trans*- and *cis*-4-iodo-3-heptenes, respectively; N and O stand for nitrogen and oxygen, respectively; C and P stand for chloroform and pentane, respectively; the last numbers are the molar concentrations of starting iodide × 10^2. [d] 2 in expt 1–5; 1 in expt 6–9. [e] Chloroform solution (5 ml) stirred in contact with ~2 ml of 0.1 *N* aqueous sodium hydroxide solution.

iodide which disappeared.[23] The individual mole percentages of each product, based on the total number of moles of detectable products formed, are given as the unbracketed numbers in the last five columns of Table II. The bracketed numbers in these columns are the mole percentages based on an assumed yield of isomerized iodide.

The code used in column 1 to describe the experimental conditions is explained in the footnotes of Table II. Columns 2 and 3 contain the photolysis time and corresponding per cent consumption of the starting isomeric iodide. The true over-all product balances are given in column 4, and column 5 indicates the per cent contamination of the remaining 4-iodo-3-heptene by the geometric isomer opposite that of the starting material.

Examination of the product data for expt 1 and 6 shows that their per cent yields are relatively insensitive to photolysis time or extent conversion within each experiment. This was also observed in the other experiments (with the exception of expt 2), although not all of the data have been reported. Thus, some characteristic product ratios have been summarized in Table III according to the starting vinyl iodide and the reaction conditions without reference to photolysis time or extent conversion of iodide.

Accurate analyses of the *cis*-/*trans*-3-heptene ratios were difficult because the two peaks were incompletely resolved by the gas chromatographic column. Similarly, base line resolution of 3,4-heptadiene and 3-heptyne was not accomplished. However, the large differences between the product distributions arising from 1 and 2 in comparable experiments (Tables II and III) are well outside of experimental error as determined from duplicate studies. It was necessary to monitor loss of iodide and product formation on separate glpc columns. This may have been a source of the large and somewhat random variation in the over-all yield data given in the fourth column of Table II.[23]

(23) No other products with molecular weights similar to the starting iodides or to the hydrocarbon products were detected by glpc. The origin of the low product balance is not definitely known; however, it could have been due in part to addition of S· (most often ·CCl_3) or HI to starting iodide and to experimental inaccuracies in the glpc analyses (see text).

TABLE III

SUMMARIZED PRODUCT RATIOS FOR PHOTOLYSES OF 1 AND 2[a]

Iodide	Conditions[b]	3-Heptyne/3-heptene	*cis*-3-Heptene/*trans*-3-heptene	Heptyne + heptadiene + I[c]/3-heptene
1	$CHCl_3$, N_2	~2.7	~1.1	~4
	$CHCl_3$, N_2, NaOH	~2.4	~1.0	~4
	$CHCl_3$, O_2	~9.0	~1.0	~12
	Pentane, N_2	~3.8	~0.5	
2	$CHCl_3$, N_2	~0.8	~0.7	~2
	$CHCl_3$, O_2	~0.7	~0.5	~2
	Pentane, N_2	~0.4	<0.1	

[a] Data extracted from Table II. [b] See text and Table II. [c] The symbol "I" stands for isomerized iodide.

The allene 3,4-heptadiene was detected as a reaction product only from the *trans* iodide 1 and only at low conversions (compare expt 1 and 2). However, in the presence of dilute aqueous sodium hydroxide (expt 3) it was a significant reaction product even at high conversions of starting iodide. No dark reactions occurred in the latter experiment.

The rates of photolysis of 1 and 2 in chloroform were essentially the same under nitrogen or oxygen atmospheres, and the per cent iodide isomerization and *cis*-/*trans*-3-heptene ratios (Table III) were also unaffected. However, oxygen caused a marked increase in the heptyne/heptene ratio from 1 (Table III), while the product distribution from photolysis of 2 in chloroform appears to be oxygen insensitive (Tables II and III).

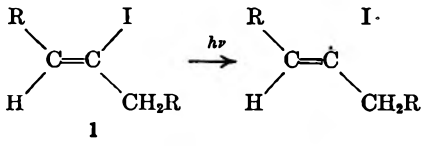
Insufficient data are available for an adequate comparison of the pentane experiments with those using chloroform. However, the product ratios in Table III show that a major difference was in the relative amounts of *cis*- and *trans*-3-heptenes formed. The relative percentage of *trans* olefin increased markedly for both 1 and 2 using pentane as solvent.

Control experiments using a chloroform light filter in addition to the Vycor filter showed no detectable differences in product distribution, rates of product

formation, or yields compared with those without the chloroform filter. The color of all of the photolyzing solutions under a nitrogen atmosphere turned light yellow with the exception of those for **1** in pentane which became purple. Under an oxygen atmosphere, all solutions rapidly turned dark purple.

Discussion

The most likely primary photochemical processes of **1** and **2** under these experimental conditions would seem to be the formation of the geminate radical pairs shown in reactions 5 and 6 (R = CH_3CH_2). Sec-



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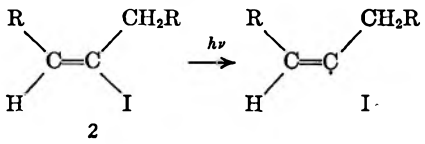

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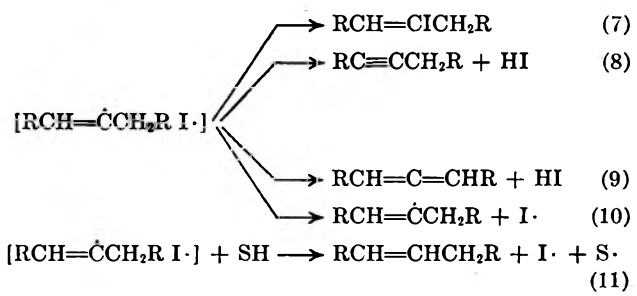
ondary reactions potentially available to the geminate pairs could include reactions 7–11 and *cis–trans* isom-



erization of the vinyl radical prior to separative diffusion of the geminate pair. Reactions 10 and 11 represent diffusion and cage scavenging, respectively. The most probable reaction of either isomeric vinyl radical subsequent to diffusion is hydrogen abstraction from solvent (reaction 12).

$$RCH{=}CCH_2R + SH \longrightarrow RCH{=}CHCH_2R + S\cdot \quad (12)$$

The similarity of the rates of formation of products and product distribution with or without an external chloroform filter suggests that initiation of detectable reactions due to photolysis of chloroform did not occur, and this was expected to be largely precluded by the use of the Vycor filter.[1a] The possible existence of chain reactions leading to the observed products also seems to be unlikely, at least in chloroform, in view of the ready availability of easily abstractable solvent hydrogen atoms.

The stability of 3,4-heptadiene in the presence of aqueous base and its disappearance at conversions above 5% in the absence of base (*vide supra*) indicate that it was destroyed by hydrogen iodide produced during the course of the photolysis of **1**. Possible reactions are represented in eq 13 and 14 shown below.

$$RCH{=}C{=}CHR + HI \longrightarrow RCH{=}CICH_2R \quad (13)$$

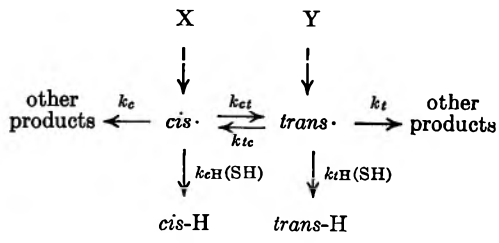
$$RCH{=}C{=}CHR + HI \longrightarrow RC{\equiv}CCH_2R \quad (14)$$

Reaction 13 could give both starting iodide and its geometric isomer, and there is an indication that the per cent yield of the isomerized iodide was slightly decreased when aqueous base was present (expt 1 and 3).[24] Similarly, if a part of the 3-heptyne arose by allene isomerization (reaction 14), the heptyne/heptene ratio would be lower in the presence of aqueous base, and a comparison of these ratios (Table III) shows such a trend.[25]

With the exception of 3,4-heptadiene, the insensitivity of the other product ratios to the extent of conversion of starting iodide and photolysis time within each experiment indicates that significant secondary reactions involving the products did not occur. In particular, a comparison of expt 2 and 7, in which product data were obtained when the per cent conversion of the starting iodide was less than one, seems to confirm that the isomer dependence of the product distribution was not due to secondary reactions in these systems, and, although HI could conceivably react with all of the products including the starting vinyl iodides,[23,24] the absence of any significant differences (with the exception of 3,4-heptadiene) between the product distributions of expt 1 and 3 suggests that this did not occur.

In previous studies of isomeric vinyl radicals, a wide range of results has been obtained for the ratio of *cis/trans* olefin arising from vinyl radical hydrogen abstraction from solvent or other hydrogen donor.[3–10] In most cases, no isomer dependence has been observed indicating that isomerization was much faster than hydrogen abstraction, but, recently, in studies by Singer[3] and Sargent,[5] the *cis/trans* olefin ratio has been found to be isomer dependent implying that the radicals produced in these cases were trapped prior to complete isomerization. If isomerically distinct vinyl radicals arise from separate sources represented by X and Y in Scheme II, the ratios of *cis/trans* olefin from

SCHEME II



either source, designated as (*cis*-H/*trans*-H)$_x$ and (*cis*-H/*trans*-H)$_y$, will be given by eq 15 and 16. Since

$$(cis\text{-H}/trans\text{-H})_x = (k_{cH}/k_{tH})\{[k_{tc} + k_{tH}(SH) + k_t)]/k_{ct}\} \quad (15)$$

$$(cis\text{-H}/trans\text{-H})_y = (k_{cH}/k_{tH})\{k_{tc}/[k_{ct} + k_{cH}(SH) + k_c]\} \quad (16)$$

these individual ratios will depend not only on the ratio k_{cH}/k_{tH} but also on the relative magnitudes of the rate constants for reactions in competition with hydro-

(24) (a) Hydrogen iodide might also add to 3,4-heptadiene to give the allyl iodide 3-iodo-4-heptene. Although no new peak was observed in glpc traces, the retention time of this compound is unknown and might be identical with that of **1** or **2**. However, it is known that addition of HI to allene yields only 2-iodopropene and 2,2-diiodopropane.[24b] If 4,4-diiodoheptane (**3**) was formed in these systems by HI addition to **1** or **2**, its major photolysis products would have been **1** and **2**.[1a] (b) K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Amer. Chem. Soc.*, **87**, 3151 (1965).

(25) The low per cent conversion in expt 2 precluded a determination of the yield of isomerized iodide. However, making the assumption that it was the same as that in expt 3 gives product distributions for these two experiments which are remarkably similar. This tends to support our proposals concerning the existence of reactions 13 and/or 14.

gen abstraction, they may vary considerably from system to system.[26] However, it becomes clear from an examination of the kinetic expressions given in eq 17 and 18 that the ratio (*cis*-H/*trans*-H)$_x$/(*cis*-H/*trans*-H)$_y$ cannot be less than unity. Based on the *a*

$$\frac{(cis\text{-H}/trans\text{-H})_x}{(cis\text{-H}/trans\text{-H})_y} = \frac{[k_{tc} + k_{t\text{H}}(\text{SH}) + k_t][k_{ct} + k_{c\text{H}}(\text{SH}) + k_c]}{k_{tc}k_{ct}} \quad (17)$$

$$\frac{(cis\text{-H}/trans\text{-H})_x}{(cis\text{-H}/trans\text{-H})_y} = \{1 + [k_{t\text{H}}(\text{SH})/k_{tc}] + (k_t/k_{tc})\}\{1 + [k_{c\text{H}}(\text{SH})/k_{ct}] + (k_c/k_{ct})\} \quad (18)$$

priori assumption that reactions 5 and 6 represent the respective primary processes of **1** and **2**, the radical sources Y and X (Scheme II) are **1** and **2**, respectively, and thus the ratio defined by eq 17 and 18 is (*cis*-/*trans*-3-heptene)$_2$/(*cis*-/*trans*-3-heptene)$_1$. However, an inspection of the data in Table III shows that this ratio was always *less* than unity under comparable reaction conditions. Although these results could indicate incorrect structural assignments of **1** and **2**, the supporting structural evidence is strong (*vide supra*). Rather, we propose that this seeming anomaly may be due to the initial production of vibrationally excited *trans*- and *cis*-vinyl radicals from **1** and **2**, respectively.

The value of D(C–I) for the vinyl iodides is probably between 55 and 60 kcal/mol,[27] while the energy of the light corresponding to their λ_{max} is on the order of 110 kcal/einstein,[28] indicating that excess vibrational energy may have remained in the vinyl radicals after C–I homolysis. This is supported by earlier observations that photolysis of methyl iodide at 2537 Å produced methyl radicals with ~32 kcal/mol of excess vibrational energy[29] and that propenyl radicals formed from vapor phase photolysis of *cis*- or *trans*-1-iodopropene (Vycor-filtered light) apparently possessed sufficient vibrational energy to fragment relatively efficiently into methyl radicals and acetylene, a process requiring energy on the order of 30 kcal/mol.[12] Although the barrier to vinyl radical isomerization seems to vary with structure, it is reasonable to assume that it is less than 15 kcal/mol in these systems,[30] and thus it is likely that the vinyl radicals initially produced from **1** or **2** had an energy content in excess of that corresponding to the inversion-transition state. If a portion of this energy found its way into the reaction coordinate for isomerization, prior to collisional deactivation, the initially formed *cis* or *trans* excited vinyl radicals could have each produced both *cis* and *trans* ground-state radicals. If the excited *trans* and *cis* radicals from **1** and **2**, respectively, partitioned to give different ground-state radical distributions such that (*cis*·/*trans*·)$_1$ was greater than (*cis*·/*trans*·)$_2$, the experimental results can be qualitatively justified if hydrogen abstraction was competitive with isomerization of the ground-state radicals. Excluding the possible occurrence of secondary reactions (*vide supra*), the different *cis*-/*trans*-3-heptene ratios from **1** and **2** support the latter contention. While no firm evidence can be cited to support the proposal that the excited radicals would partition as suggested above, the likely energy relationships $E_2 > E_1$,[31] $E(cis\cdot) > E(trans.)$,[3,5] and $[E\ (trans\cdot^*) - E_1] \cong [E(cis\cdot^*) - E_2]$[32] do not preclude such an occurrence.[33]

The apparent absence of an oxygen effect on the yields of isomerized iodide from either **1** or **2** (compare expt 1 and 4 and expt 6 and 8, Table II) indicates that they were formed by radical recombination (reaction 7) during the initial geminate encounter prior to separative diffusion (reaction 10).[33] Additionally, the absence of an apparent oxygen effect on any of the products from **2** (expt 6 and 8) implies that all were formed prior to diffusion. However, the data for **1** (expt 1 and 4), while supporting a cage disproportionation source for 3-heptyne (and presumably 3,4-heptadiene; reactions 8 and 9), indicate that a portion of the 3-heptenes was formed from scavengeable radicals. While these differences in the effect of oxygen on the product yields of **1** and **2** may be significant, it is conceivable that other unanticipated reactions were introduced by the addition of oxygen and thus we hesitate to speculate on their meaning without additional supporting data.

The significantly larger 3-heptyne/3-heptene ratios arising from **1** compared with those from **2** suggest that disproportionation was a more facile reaction for the geminate pairs produced from the former than from the latter. If it is assumed that all of the products arose from "cold" vinyl radicals, these data and our previous discussion concerning the partitioning of the excited radicals into ground-state radicals suggest that disproportionation (reactions 8 and 9) was more facile for *cis*- than for *trans*-vinyl radicals; however, we can offer no explanation for the apparent absence of 3,4-heptadiene in photolyses of **2**. While both of these products could have been formed by fragmentation of the initial vibrationally excited radicals, such processes would require on the order of 40 kcal/mol of energy[12] and, in view of our previous work,[12] seem unlikely under these experimental conditions.

Hydrogen iodide is an excellent hydrogen donor to carbon radicals, and its presence in these systems could have led to its participation in this role. Since disproportionation was a more significant process for photolyses of **1** compared with those of **2**, the differences in hydrogen iodide concentration in the respective systems might have led to some of the observed differences in product distribution. However, the similarity of the *cis*-/*trans*-3-heptene ratios from **1** in chloroform in the absence and presence of dilute aque-

(26) The rate constants k_c and k_t (Scheme II) represent, respectively, aggregates of all other possible reactions (not specifically shown) of the *cis*- and *trans*-vinyl radicals.

(27) (a) D(C–I) for methyl iodide is 56 kcal/mol,[27b] and the bond dissociation energies for vinyl carbon–X bonds are similar to those for the analogous CH_3–X bonds.[27b] (b) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).

(28) See J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, p 12.

(29) D. Lewis and G. Mains, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April, 1965, p 8S.

(30) Assuming a frequency factor of 10^{13} sec^{-1}, such a barrier corresponds to a rate constant of 10^2 sec^{-1}; see ref 3a.

(31) The relative stabilities of **1** and **2** have not been determined; however, it is generally found for simple internal alkenes of the structure $R_1CH{=}CHR_2$ that the *trans* isomer is more stable than the *cis* isomer. Additionally, the *cis* isomers of 1-halopropenes ($CH_3CH{=}CHX$) appear to be thermodynamically more stable than the *trans* isomers.[12] Both of these observations suggest that $E_2 > E_1$.

(32) This assumes the same excess energy input into **1** and **2** beyond that required to break the C–I bond.

(33) Alternative explanations involving isomerization in electronically excited states prior to homolytic scission or the direct production of vinyl radicals of the configuration opposite that of the starting iodide cannot be excluded.

ous sodium hydroxide indicates that hydrogen iodide was not involved as a free-radical hydrogen donor to the vinyl radicals. In the less reactive solvent pentane, it was observed that photolyzing solutions of **1** became iodine colored in the absence of oxygen, and this suggests that hydrogen iodide did act as a hydrogen donor. Since it was present in much lower concentrations in photolyzing pentane solutions of **2**, it apparently did not participate as seen by the absence of any iodine-color formation (see Results). The most notable difference between the chloroform experiments and those using pentane is seen in a comparison of the *cis*-/*trans*-3-heptene ratios for **1** or **2** in the two different solvents (Table III). Since the ground-state *trans*-vinyl radical is probably more stable than the ground-state *cis*-vinyl radical [$E(cis\cdot) > E(trans\cdot)$], the significantly lower *cis*-/*trans*-3-heptene ratios in pentane may reflect the poorer competition of hydrogen abstraction with isomerization in this medium of lower hydrogen-donating ability. The higher *cis*-/*trans*-3-heptene ratio from **1** compared with that from **2** could have been due to the intervention of HI as a hydrogen donor in the former case as discussed above.

Other less complicated sources of these radicals are under investigation, and it is hoped that these studies will assist in clarifying the results reported here.

Experimental Section

4-Heptanone-N,N-dimethylhydrazone.—A mixture of 240 g (4.0 mol) of anhydrous N,N-dimethylhydrazine (Matheson Coleman and Bell), 114 g (1 mol) of 4-heptanone (Matheson Coleman and Bell), and sufficient absoute ethanol to give a homogeneous solution was refluxed for 3 hr,[16] and the excess dimethylhydrazine was stripped from the reaction mixture. Vacuum distillation yielded 156 g (1.0 mol) of 4-heptanone-N,N-dimethylhydrazone: bp 55–57° (8 mm); ir 1635 cm^{-1} (C=N); nmr multiplets at τ 7.78 (2), 8.50 (2), and 9.08 (3) and singlet at 7.74 (3).

4-Heptanonehydrazone.—The purified 4-heptanone-N,N-dimethylhydrazone was refluxed for 24 hr with a fivefold molar excess of anhydrous hydrazine (Matheson Coleman and Bell) in sufficient absolute ethanol to give a homogeneous solution.[16] The excess hydrazine and resulting N,N-dimethylhydrazine were stripped from the reaction mixture along with the ethanol at 50° *in vacuo*. The crude hydrazone was not purified because such attempts led to azine formation.

4,4-Diiodoheptane.—The crude hydrazone and a twofold molar excess of triethylamine were dissolved in 100 ml of anhydrous diethyl ether, and a saturated ether solution of iodine was added dropwise with stirring over a period of about 1 hr until a dark red-brown color persisted indicating an excess of iodine.[15] After additional stirring for 1 hr the solution was decanted off the resulting triethylammonium iodide. This residue was washed with ether, and the combined solutions were washed successively with 100-ml portions of 2 *N* hydrochloric acid, water, sodium bisulfite, water, and saturated sodium bicarbonate solution and dried over anhydrous calcium carbonate (Drierite) (magnesium sulfate led to apparent decomposition of the product). The ether solvent was stripped off on a rotary evaporator. The nmr spectrum of this product showed multiplets at τ 9.0, ~8.4, and ~7.8 in the approximate ratio of 3:2:2; the uv spectrum showed λ_{max} 285 and 295 mμ (shoulder). The over-all yield from 4-heptanone was about 55%.

***cis*- and *trans*-4-Iodo-3-heptenes.**—On attempted purification of the crude 4,4-diiodoheptane by glpc using a 4 ft × 0.375 in. aluminum column packed with 20% didecyl phthalate on Chromosorb W at 110° (injector block 120°), the chromatogram showed only a partially resolved doublet with a retention time anomalously short for the diiodoalkane. The nmr spectrum of this mixture collected from the column showed two triplets corresponding to vinyl protons at τ 3.83 and 4.53 anticipated for a spectrum of a mixture of *cis*- and *trans*-4-iodo-3-heptenes.

Anal. Calcd for $C_7H_{13}I$: C, 37.52; H, 5.85; I, 56.63. Found: C, 37.45; H, 5.80; I, 56.42.

Separation of the two isomers was accomplished by lowering the column temperature to 85°. The previously purified mixture was rechromatographed at this temperature, and the separate components were collected. The shorter and longer retention time isomers **1** and **2**, respectively (see synthesis), were present in the approximate ratio 4:1. The nmr spectrum of **1** showed a triplet (1) at τ 4.55, multiplets (12) at 7.79, 8.49, and 9.08; of **2** showed a triplet (1) at 3.83, multiplets (12) at 7.80, 8.50, and 9.08. The uv spectrum of **1** showed λ_{max} 243 mμ (ϵ ~400); of **2** showed λ_{max} 249 mμ (ϵ ~400).

The identical vinyl iodides were formed by base-catalyzed dehydrohalogenation of crude 4,4-diiodoheptane.[17]

Sodium–Liquid Ammonia Reduction of 1 and 2.[18,19]—Sodium (1.5 g) was added in small pieces to liquid ammonia (20–25 ml) in a 50-ml round-bottom flask fitted with a serum cap and Dry Ice condenser and immersed in a Dry Ice–isopropyl alcohol slush. About 10 μl of **1** dissolved in 30 μl of pentane was injected into the flask, and the solution was stirred with cooling for 30 min. A 10-ml sample of pentane was added, and the reaction mixture was quenched by dropwise addition of saturated aqueous ammonium chloride solution. The pentane layer was removed, washed with water, dried over magnesium sulfate, and analyzed by flame ionization glpc on a 21 ft × 0.125 in. column of 20% SE-30 on Chromosorb W at 115°. The sole detectable olefinic product was *trans*-3-heptene. Analogous reduction of **2** gave predominantly *cis*-3-hexene. The *cis*- and *trans*-3-hexenes were identified by retention time comparison with authentic samples (*vide infra*) by mixing the known compounds with the reaction mixtures.

Analysis of Photolysis Reaction Products.—The hydrocarbon products from the photolyses of **1** and **2** were analyzed by flame ionization glpc at 115° using a 21 ft × 0.125 in. column containing 20% SE-30 Chromosorb W. The disappearance and isomerization of the vinyl iodides were followed by thermal conductivity glpc at 70° using a 6 ft × 0.125 in. column containing 20% SE-30 on Chromosorb W. The products were identified by comparison with authentic samples described below.

***cis*- and *trans*-3-Heptenes.**—*trans*-3-Heptene was a commercial sample (Matheson Coleman and Bell) and gave only a single peak on a glpc trace. Pure *cis*-3-heptene was not isolated, but its retention time was obtained from a commercial mixture of *cis*- and *trans*-3-heptenes (Matheson Coleman and Bell). Its identity was further confirmed by iodine-catalyzed photoisomerization of the *cis*–*trans* mixture in which that peak identified as *trans*-3-heptene increased simultaneously with the loss of the peak identified as *cis*-3-heptene.

3-Heptyne.—A 2-ml sample of crude 4,4-diiodoheptane in 20 ml of 10 *M* solution of potassium hydroxide in ethylene glycol was slowly heated to 180°, and the distillate was collected during the course of several hours. Purification of this distillate by glpc gave a fraction containing *cis*- and *trans*-4-iodo-3-heptenes and a fraction identified as 3-heptyne: ir 2175 cm^{-1} (w) (C≡C); nmr multiplet at τ 8.19 (4) and two overlapping multiplets at 8.6–9.5 (8).

Anal. Calcd for C_7H_{12}: C, 87.42; H, 21.57. Found: C, 87.57; H, 12.65.

3,4-Heptadiene.—Treatment of *trans*-1,2-diethyl-3,3-dibromocyclopropane[34] with magnesium metal[35] or with methyllithium in ether[36] gave as the major product a compound whose retention time fell between those of 3-heptyne and the 3-heptenes. The acetylene 3-heptyne was also formed in these syntheses. Although this compound proposed to be 3,4-heptadiene was not isolated and characterized, the synthetic origins (particularly the methyllithium preparation) are strong proof of structure. The glpc characteristics of the compound identified as 3,4-heptadiene in the photolysis experiments were identical with those of this compound.

Registry No.—**1**, 17497-50-6; **2**, 17497-51-7; 1-iodocyclopentene, 17497-52-8; 1-iodocyclohexene, 17497-53-9; 1-iodocyclooctene, 17497-54-0; *cis*-3-iodo-3-hexene, 16403-09-1; *trans*-3-iodo-3-hexene, 16403-13-7; 4-heptanone-N,N-dimethylhydrazone, 14090-58-5.

(34) W. von E. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(35) W. von E. Doering and P. M. La Flamme, *Tetrahedron*, **2**, 75 (1958).

(36) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).

Photochemical and Peroxide Induced Reductions of Benzophenone Imine with Secondary Alcohols[1]

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The photochemical reaction of benzophenone imine (I) with 2-propanol yields ammonia, benzhydrylidenebenzhydrylamine (II), and acetone. The ammonia and II are formed by a condensation reaction of benzophenone imine with benzhydrylamine (III), which is produced in the photoreduction of I with concurrent oxidation of 2-propanol to acetone. The quantum efficiency of the photoreduction of benzophenone imine relative to that of benzophenone in 2-propanol is approximately 0.03. The rate of the photochemial reaction is markedly retarded by the presence of naphthalene, an effective triplet quencher, indicating the intermediacy of a triplet species in the reaction. Reduction of benzophenone imine to benzhydrylamine with 2-butanol in *t*-butyl peroxide induced reactions also results in formation of the condensation product II.

The photochemical reduction of benzophenone in 2-propanol yielding benzpinacol (1,1,2,2-tetraphenylethylene glycol) with concurrent oxidation of the alcohol to acetone[4] suggested that benzophenone imine (I) might undergo a similar photochemical reduction yielding 1,1,2,2-tetraphenylethylenediamine (IV) as the reduction product. Recently Fisher reported that illumination through a Pyrex filter of benzophenone imine in 2-propanol with ultraviolet light (450 W, Hanovia No. 679A-36) yielded a basic product (isolated as the hydrochloride salt), purportedly benzhydrylamine, in high yields (80%) after short periods (2 hr) of illumination.[5] Our experience with this reaction had been quite different both in the efficiency of the photochemical reduction and the nature of the isolated reaction product.

After 2 hr of illumination of a solution consisting of 10 mol % I in 2-propanol sealed in a Pyrex tube, with a 450-W Hanovia No. 679A-36 lamp, comparatively small amounts of acetone (about 19–20% of theory) were formed. Approximately 28% of the theoretical amount of acetone was formed after 4.5 hr of illumination. The odor of ammonia was observed when the tubes were opened and, upon cooling, benzhydrylidenebenzhydrylamine (II) crystallized from the reaction mixtures. The ammonia and II most likely

$$\underset{\text{I}}{2(C_6H_5)_2C{=}NH} + CH_3CHOHCH_3 \xrightarrow{h\nu} CH_3COCH_3 + \underset{\text{II}}{(C_6H_5)_2C{=}NCH(C_6H_5)_2} + NH_3 \quad (1)$$

resulted from the condensation reaction of benzophenone imine with benzhydrylamine (III),[6] the photochemical reduction product of the imine in 2-propanol. Illumination of solutions of benzophenone

$$\underset{}{I} + \underset{\text{III}}{(C_6H_5)_2CHNH_2} \rightarrow \underset{}{II} + NH_3 \quad (2)$$

imine in 2-propanol by other means (see Experimental Section) also yielded ammonia, acetone, and the condensation product II. Attempts to isolate the hydrochloride salt of benzhydrylamine by saturating an ethereal solution of a reaction mixture yielded only the hydrochloride salt of the unreacted benzophenone imine. Reduction of benzophenone imine with Mg–MgI in benzene–ether solution, a mixture which reduces benzophenone to benzpinacol,[7] also yields the condensation product II[8] rather than the reductive dimer IV. Benzyhydrylamine is presumably produced as the initial reduction product in this reaction also and it reacts rapidly with unreacted benzophenone imine yielding the condensation product II. Similarly, reduction of benzophenone imine with aluminum amalgam yields largely II and III.[8]

The photochemical reduction of benzophenone imine in 2-propanol to benzhydrylamine quite possibly occurs by a mechanism similar in many respects to that of the photochemical reduction of benzophenone.[4b] Since

$$I \xrightarrow{h\nu} (C_6H_5)_2C^{*}{=}NH \longrightarrow (C_6H_5)_2\dot{C}{-}\dot{N}H \quad (3)$$

$$(C_6H_5)_2\dot{C}{-}\dot{N}H + CH_3CHOHCH_3 \longrightarrow \underset{\text{A}\cdot}{(C_6H_5)_2\dot{C}NH_2} + \underset{\text{B}\cdot}{CH_3\dot{C}OHCH_3} \quad (4)$$

$$B\cdot + I \longrightarrow CH_3COCH_3 + A\cdot \quad (5)$$

$$2A\cdot \rightleftharpoons \underset{\text{IV}}{(C_6H_5)_2C(NH_2){-}C(NH_2)(C_6H_5)_2} \quad (6)$$

$$\text{or } 2A\cdot \longrightarrow I + III \quad (7)$$

the reactions were performed in Pyrex tubes, essentially all irradiation below 300 mμ is filtered out and the photochemical reaction is caused by absorptions of light by benzophenone imine above 300 mμ. The spectrum of benzophenone imine in hexane showed an absorption at 345 mμ ($\epsilon \sim 15$) which is likely the $n \rightarrow \pi^*$ transition. This absorption maximum was shifted to 340 mμ in 2-propanol and methanol. Absorption of light by benzophenone imine would yield the excited singlet species which could decay to a triplet species in a manner analogous to that proposed for benzophenone. Abstraction of a hydrogen atom from the alcohol (reaction 4) yielding the α-aminobenzhydryl radical A· and the α-hydroxyalkyl radical B· is similar to that proposed for the benzophenone reaction as is the hydrogen atom transfer from B· to I (reaction 5) yielding acetone and another α-aminobenzhydryl radical. Al-

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(2) Taken in part from the thesis submitted by R. H. S. W. in partial fulfillment of the requirements for the Ph.D. degree from the University of Kansas, 1968.

(3) Undergraduate National Science Foundation participant, 1966–1968.

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(5) M. Fisher, *Ber.*, **100**, 3599 (1967).

(6) R. Cantarel, *Compt. Rend.*, **210**, 403 (1940).

(7) M. Gomberg and W. E. Backmann, *J. Amer. Chem. Soc.*, **49**, 236 (1927).

(8) H. Thies, H. Schonenberger, and L. H. Bauer, *Arch. Pharm.*, **293**, 67 (1960).

TABLE I

QUANTUM EFFICIENCY DETERMINATIONS

Item	Reaction mixture	Time, hr	Acetone (mmol/ml) Found	Acetone (mmol/ml) Theoretical[a]	Quantum efficiency
1	Benzophenone and 2-propanol (1:10)	2	0.352	0.349	1.01
2		2	0.372	0.349	1.07
3		2	0.354	0.349	1.02
4	Benzophenone imine (I) and 2-propanol (1:10)	9.5	0.046	1.65	0.028
5		9.5	0.051	1.65	0.031
6		19	0.093	3.29	0.028
7		19	0.110	3.29	0.033
8		30	0.185	5.19	0.035
9		30	0.178	5.19	0.035
10		60	0.333	10.38	0.032
11	Benzophenone imine, naphthalene, and 2-propanol (1:0.1:10)	8.75	~0	1.57	~0.0
12		24.75	0.019	4.29	0.0049

[a] Based on an absorption of 0.1745 mEinsteins/hr/ml of solution (see Experimental Section).

TABLE II

t-BUTYL PEROXIDE INDUCED REDUCTIONS OF BENZOPHENONE IMINE IN 2-BUTANOL AT 125°

Run	Reactants, mmol I	Reactants, mmol Peroxide	Reactants, mmol 2-Butanol	Products, mmol II	Products, mmol *t*-Butyl alcohol	Products, mmol Acetone	Products, mmol 2-Butanone
1	7.07	7.04	70.1	0.52	11.8	1.0	6.7
2	6.99	7.00	70.0	0.50	11.5	1.1	6.5

though formation of the reductive dimer IV by reaction 6 cannot be excluded, IV may be thermally unstable and disproportionation of radicals A· (reaction 7) may be the preferred route to stable products.[9] Once formed, benzhydrylamine would react with benzophenone imine yielding the observed condensation product II and ammonia.

The photoreduction of benzophenone imine in 2-propanol is considerably less efficient than that of benzophenone under similar conditions (temperature, concentration of reactants, and illumination). The quantum efficiency for the photoreduction of benzophenone in 2-propanol, measured against a benzophenone–benzhydrol actinometer,[10] was found to be very close to unity[11] (see items 1–3, Table I). Under similar conditions, the quantum efficiency for the photoreduction of benzophenone imine in 2-propanol relative to the same actinometer was approximately 0.03 (items 4–10, Table I). Although the extinction coefficient of benzophenone imine is low, the concentration of this reactant was high enough in these determinations to ensure complete absorption of the illumination. Inefficient intersystem crossing from the first excited state to the triplet state is likely responsible for the low quantum yields in these reactions. Evidence for the participation of the triplet species in these photochemical reactions is found in the observation that the rate of formation of acetone is markedly retarded by naphthalene (items 11 and 12, Table I), which can act as a triplet quencher.[10]

Reaction of benzophenone imine with 2-butanol and *t*-butyl peroxide yielded the condensation product II in small amounts. In this reaction, the radical A·, which eventually yields benzhydrylamine by the path outlined above, is produced in reaction 10, the hydrogen atom transfer reaction to benzophenone imine from the 2-hydroxy-2-butyl radicals (C·), which are formed in the reactions of the alcohol with the *t*-butoxy radicals (reaction 9). The data given in Table II indicate that

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO\cdot \quad (8)$$

$$(CH_3)_3CO\cdot + CH_3CHOHC_2H_5 \longrightarrow (CH_3)_3COH + CH_3\dot{C}OHC_2H_5 \quad (9)$$

(C· = $CH_3\dot{C}OHC_2H_5$)

$$C\cdot + I \longrightarrow A\cdot + CH_3COC_2H_5 \quad (10)$$

$$C\cdot + (CH_3)_3COOC(CH_3)_3 \longrightarrow CH_3COC_2H_5 + (CH_3)_3CO\cdot + (CH_3)_3COH \quad (11)$$

hydrogen atom transfer from C· to peroxide, producing 2-butanone by the chain sequence 9 and 11,[12] is faster than hydrogen atom transfer to benzophenone imine as evidenced by the comparatively large amount of 2-butanone formed relative to the condensation product II. In both runs, the amounts of *t*-butyl alcohol and acetone found indicate that approximately 90% of the peroxide decomposed. The amounts of 2-butanone

(9) Disproportionation products (benzhydrol and benzophenone) are also observed in the photochemical reaction of benzophenone at temperatures above 100° [E. S. Huyser and D. C. Neckers, *J. Amer. Chem. Soc.*, **85**, 3641 (1963)]. The very marked temperature dependence on the relative amounts of pinacol and benzhydrol produced in the photochemical reaction of benzophenone (essentially all pinacol at room temperature and all benzhydrol at 135°) is indicative of a process other than competition between coupling of two α-hydroxybenzhydryl radicals leading to benzpinacol and disproportionation of the radicals yielding the benzhydrol. A crude estimation of the activation energy difference for the formation of the pinacol relative to the benzhydrol is about 30 kcal/mol, a difference much larger than could be expected to exist for two bimolecular radical reactions. Somewhat more probable is that coupling occurs very rapidly yielding benzpinacol but the pinacol decomposes at a high enough rate at elevated temperatures to establish a finite concentration of α-hydroxybenzhydryl radicals which disproportionate in a slower, but irreversible, reaction. Support for thermal instability of compounds such as benzpinacol can be found in the observation that the dimethyl ether of benzpinacol decomposes readily at temperatures above 100° [G. Hartzell and E. S. Huyser, *J. Org. Chem.*, **29**, 3341 (1964)] and that benzpinacol was shown to decompose at 125° (D. C. Neckers, personal communication).

(10) W. M. Moore and M. Ketchum, *J. Amer. Chem. Soc.*, **84**, 1369 (1962).

(11) Reported quantum yield is also very near unity: J. N. Pitts, H. W. Johnson, and T. Kuwana, *J. Phys. Chem.*, **66**, 2456 (1962).

(12) E. S. Huyser and C. J. Bredeweg, *J. Amer. Chem. Soc.*, **86**, 2401 (1964).

produced are, however, somewhat larger than can be accounted for solely on the basis of the chain sequence 9 and 11 which predicts that the amount of ketone should be equivalent to the peroxide consumed. The additional ketone likely results from participation of α-hydroxyalkyl radicals C· with benzophenone imine, a reaction in which 2 mol of 2-butanone is produced for each mole of peroxide consumed.

Experimental Section

Benzophenone imine (I) was prepared by the method described by Pickard and Tobert[13] [bp 142° (2.7 mm), n^{20}D 1.1665]. 2-Propanol (Baker Analyzed Reagent Grade) was used without further purification. The ultraviolet spectrophotometric analyses were performed on a Beckman DU-2 and the gas chromatographic analyses on an F & M Model 700 gas chromatograph and traced on a Barber–Coleman recorder equipped with a Disc integrator. The photochemical sources and equipment are described in the following experiments.

Photoreduction of Benzophenone Imine in 2-Propanol.—A solution consisting of benzophenone imine and 2-propanol in a 1:10 molar ratio was sparged with nitrogen for about 20 min. The solution was placed in a Pyrex tube; the tube was sealed with a rubber septum and bound directly to a quartz thermal well through which water was passed. A 450-W Hanovia No. 679A-36 lamp placed in the thermal well was positioned such that the illumination arc was about 1 in. from the Pyrex tube containing the reaction mixture. This device allowed the photochemical reaction to occur at about 25–30°. After 2 hr of illumination, a sample of the reaction mixture was removed and the acetone content was determined by gas chromatographic analysis to be 18.5% of the theoretical amount based on complete reaction of the benzophenone imine. Another sample was removed after 4 hr and 30 min and analysis showed that approximately 27% of the theoretical amount of acetone had been formed.

At the end of the illumination, the reaction mixture had the characteristic odor of ammonia. After cooling at 0° for 2 days, benzhydrylidenebenzhydrylamine (mp 152°, lit.[14] mp 153°) crystallized from the mixture.

Illumination with a 275-W Sylvania sun lamp at 80° of a mixture consisting of 1.51 g (8.3 mmol) of benzophenone imine in 5.22 g (87.0 mmol) of 2-propanol sealed in a Pyrex tube for 72 hr yielded 0.046 g (0.80 mmol, 19% of theory) of acetone, and 0.155 g (0.43 mol, 10.3% of theory) of the condensation product II was isolated. In another reaction, illumination with the same light source for 72 hr, 1.44 g (7.9 mmol) of benzophenone imine and 5.20 g (86.6 mmol) of 2-propanol yielded 0.039 g (0.67 mmol, 17% of theory) of acetone and 0.153 g (0.44 mmol, 11% of theory) of II.

Treatment of a reaction mixture obtained in a similar manner by dissolving it in ether and saturating the solution with dry hydrogen chloride yielded a hydrochloride salt (mp 270–275° dec) the infrared spectra (Nujol mull) of which was identical with that of an authentic sample of the benzophenone imine hydrochloride. The infrared spectra of benzhydrylamine hydrochloride, which melts with decomposition in the same temperature range, was markedly different.

Quantum Efficiency Determinations.—The apparatus used for these determinations was a Rayonet photochemical reactor equipped with 16 Rayonet 3500-Å lamps and a "merry-go-round" device for quantum yield determinations. The extent of reaction of a benzophenone–benzhydrol actinometer mixture in benzene after illumination in Pyrex tubes for 5-, 10-, 15-, and 20-min intervals was measured by the spectrophotometric determination of the benzophenone remaining in the solution. A linear correlation between time and extent of reaction was observed and, assuming unity quantum efficiency for the actinometer, the reaction mixtures received 0.174 mEinsteins of irradiation/hr/ml of solution. The extent of reaction of mixtures consisting of benzophenone and 2-propanol (1:10 molar ratio) after illumination for 2 hr was determined by gas chromatographic analysis of the acetone produced per milliliter of solution. The quantum efficiency in this case was found to be very close to unity (see Table I). Determination of the extent of reactions of benzophenone imine in 2-propanol both with and without naphthalene were also performed by ascertaining the amount of acetone produced by gas chromatographic analysis of portions of the reaction mixtures.

Peroxide Induced Reductions of Benzophenone Imine in 2-Butanol.—Mixtures of benzophenone imine, 2-butanol, and *t*-butyl peroxide in the amounts shown in Table II were sealed in Pyrex tubes and heated in an oil bath at 125° for 36 hr. The solid condensation product II was allowed to crystallize from the reaction mixtures by cooling. The amounts of 2-butanone, *t*-butyl alcohol, and acetone were determined by gas chromatographic analyses of aliquotes of the supernatent liquid. The solid condensation product was isolated by filtration and weighed. The quantities of the products are given in Table I.

Registry No.—I, 1013-88-3; II, 5350-59-4; 2-propanol, 67-63-0.

(13) P. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).
(14) W. Schlenk and E. Bergmann, *Ann.*, **463**, 313 (1928).

The Anodic Oxidation of Organic Compounds. IV. Mechanism of Electrochemical Methoxylation of N,N-Dimethylbenzylamine

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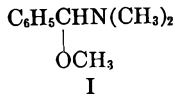
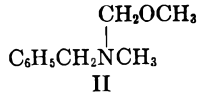
Evidence is presented that the anodic methoxylation of N,N-dimethylbenzylamine (DMB) in alkaline methanolic solution occurs by direct charge transfer of adsorbed DMB at the anode followed by the reaction of the resultant cation radical with solvent. A recent alternative proposal suggesting that electrochemically generated methoxy radicals attack DMB to give the cation radical is considered to be less tenable.

On the basis of the nature of the products formed, we proposed in a recent paper[1] that anodic methoxylation of amines probably occurs *via* discharge of adsorbed amine, followed by reaction of the resultant cation radical with solvent. The major products derived from the methoxylation of N,N-dimethylbenzylamine (DMB) at constant current in a one-compartment cell were α-methoxy-N,N-dimethylbenzylamine (I) and N-methoxymethyl-N-methylbenzylamine (II), obtained in a ratio of 1:4, respectively. The unexpected preponderance of N-methyl over N-benzyl substitution was attributed in part to the effect of adsorption of DMB on the anode prior to charge transfer. Subsequently we demonstrated[2] that the methoxylation and dimerization of the related amine, N,N-dimethylaniline, in methanolic KOH and NH_4NO_3 solution, respectively, occurred *via* a one-electron oxidation of the adsorbed amine. The subject of anodic oxidation of amines has been reviewed recently.[3]

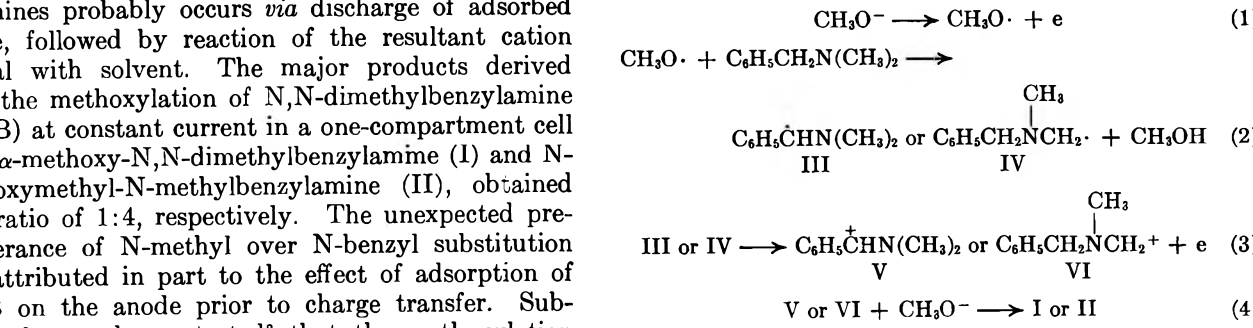


I



II

Smith and Mann[4] have reexamined the anodic methoxylation of DMB using both KOH and $KOCH_3$ electrolytes. Carrying out the reaction potentiostatically in two-compartment cells (anode and cathode compartments were separated by a fritted-glass diaphragm), they found that a 5–10% yield of methoxylation product was formed with $KOCH_3$ as electrolyte. In their hands, no methoxylated product was obtained with KOH electrolyte, but only N-methylbenzylamine and DMB, despite the use of 3–5 faradays/mol.[5] Studying current–voltage curves they found that addition of amine to a 1 *M* $KOCH_3$–CH_3OH solution failed to produce an increase in current. On the basis of these and other observations the following conclusions were made: (i) methoxide ion is necessary for methoxylation of DMB; (ii) since the limiting current for methoxide ion discharge had apparently not been exceeded the current efficiency for the amine reaction would accordingly be very low; (iii) the initial step in anodic methoxylation of aliphatic amines involves, not anodic oxidation of amine, but discharge of methoxide to methoxy radical according to eq 1–4 below.



$$CH_3O^- \longrightarrow CH_3O\cdot + e \quad (1)$$

$$CH_3O\cdot + C_6H_5CH_2N(CH_3)_2 \longrightarrow C_6H_5\dot{C}HN(CH_3)_2 \text{ (III) or } C_6H_5CH_2\dot{N}CH_2\cdot \text{ (IV)} + CH_3OH \quad (2)$$

$$\text{III or IV} \longrightarrow C_6H_5\overset{+}{C}HN(CH_3)_2 \text{ (V) or } C_6H_5CH_2\overset{+}{N}CH_2^+ \text{ (VI)} + e \quad (3)$$

$$\text{V or VI} + CH_3O^- \longrightarrow \text{I or II} \quad (4)$$

Believing that the mechanism of methoxylation of DMB could be similar to that established for N,N-dimethylaniline,[2] we have again examined the electrooxidation of DMB both potentiostatically and galvanostatically in both one- and two-compartment electrolysis cells.

Results and Discussion

Tafel plots (log current density against potential) for anodic oxidation of DMB in 0.5 *M* KOH–CH_3OH are shown in Figure 1. In the linear region (slope, 255 mV/decade) an increase in the concentration of DMB lowers the current density markedly from that of background (slope, 300 mV/decade). At more positive potentials the curves merge and become indistinguishable from background. The reaction order plots (log current density against log concentration of amine) shown in Figure 2 suggest that the electrochemical process occurring below 1.1 V is increasingly inhibited, with a limiting current being reached as the DMB concentration is increased.

While the above results provide qualitative information concerning amine adsorption, no conclusions may be drawn about a suitable mechanism of oxidation of DMB. A more direct approach to the mechanism may be taken by examination of the products formed in a series of electrolyses carried out under controlled potential conditions. The method is an extension of the technique applied by Parker and Burgert[6] to establish a mechanism for anodic cyanation of aromatic compounds.

The results of electrolysis of DMB in 0.5 *M* KOH–CH_3OH are summarized in Table I. No amine methoxylation products are observed below 1.00 V *vs.* sce (expt 1 and 2). Under the same conditions, but at potentials more anodic than 1.10 V (expt 3 and 4), amine-derived products are formed. The same prod-

(1) N. L. Weinberg and E. A. Brown, *J. Org. Chem.*, **31**, 4058 (1966).
(2) N. L. Weinberg and T. B. Reddy, *J. Amer. Chem. Soc.*, **90**, 91 (1968).
(3) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 449 (1968).
(4) P. J. Smith and C. K. Mann, *J. Org. Chem.*, **33**, 316 (1968).
(5) The formation of dealkylation product rather than ethers with KOH is believed to be caused by hydrolysis of I and II, due, at least in part, to inadequate drying of the crude product. Smith and Mann used a 3-A Molecular Sieve, while we have employed anhydrous magnesium sulfate as the desiccant.
(6) V. D. Parker and B. E. Burgert, *Tetrahedron Lett.*, 4065 (1965).

TABLE I

PRODUCT DISTRIBUTION IN ELECTROLYSIS OF DMB[a]

Expt	DMB concn, mol l.$^{-1}$	Anode potential, V *vs.* sce	Faradays mol^{-1} of DMB	Area per cent of components[e] 1[d]	DMB	I	II	5	6	7	8	9
1[b]	0.20	0.90	0.516		100							
2[b]	0.20	1.00	0.516		100							
3[b]	0.20	1.10	0.516	3.2	78.3	0.3	14.0	0.2	0.2	0.1	0.1	3.7
4[b]	0.20	1.20	0.516	2.2	84.0	1.0	9.4	1.0	1.0	0.1	0.1	1.2
5[c]	0.20	1.30	0.516		>99			+		+		
6[b,f]	1.00	1.30	1.55		35.8	0.8	41.0	0.7	2.6	2.7	0.6	15.8
7[c]	0.10	1.40	2.00	9.7	50.2		26.8	1.1	2.2	0.2	1.0	8.8
8[b]	0.50	1.85	2.00	6.5	22.0		42.2	3.4	8.6	1.7	3.1	12.5
9[c]	0.50	1.9–2.3[g]	3.00	4.9	12.1	0.7	48.5	2.3	18.0	1.8	1.2	8.3
10[b]	0.40	2.1–2.4[h]	0.50	1.0	88.7	+	6.3	+	+	+	+	4.0

[a] Electrolyses carried out in 0.5 *M* KOH–CH_3OH at 12° using Pt (10 cm²) electrodes, except for expt 10, where a pyrolytic carbon button (0.39 cm², geometrical area) replaced the Pt anode. [b] Two-compartment cell. [c] One-compartment cell. [d] Shown by retention time to be benzaldehyde. Components 5, 6, 7, and 8 are unknown. [e] Determined by gas chromatography on 0.2% SE-30 on glass beads; see Experimental Section for further detail; + value implies trace. [f] Five additional components were observed. A small amount (0.4 g) of II added to the cathode compartment was converted almost entirely into DMB. [g] Constant-current electrolysis at 1.0 A. [h] Constant-current electrolysis at 37.5 mA.

ucts are produced at both Pt and C anodes (expt 10) indicating that platinum oxides are not involved in the oxidation of DMB.[7] These experiments, taken together with the further observation that the half-wave potential of DMB (at a rotating platinum microelectrode in 0.5 *M* $LiClO_4$–CH_3CN) is 0.92 V *vs.* sce, present strong evidence that DMB is oxidized by the discharged amine mechanism (eq 5–7 and 9). Since solvent discharge occurs simultaneously, the possibility of radical abstraction of DMB cation radical (VII) cannot be ignored (eq 8).

$$\text{DMB} \xrightarrow{\text{anode}} \text{DMB (adsorbed)} \qquad (5)$$

$$\text{DMB (adsorbed)} \longrightarrow C_6H_5CH_2\overset{\cdot+}{N}(CH_3)_2 + e \qquad (6)$$

VII

$$C_6H_5CH_2\overset{\cdot+}{N}(CH_2{-}H)CH_3 + OH^- \text{ (or } CH_3O^-) \longrightarrow$$

$$\text{VI} + H_2O \text{ (or } CH_3OH) + e \qquad (7)$$

$$C_6H_5CH_2\overset{+\cdot}{N}(CH_2{-}H)CH_3 + \cdot OH \text{ (or } CH_3O\cdot) \longrightarrow \text{VI} + H_2O \text{ (or } CH_3OH) \qquad (8)$$

$$\text{VI} + CH_3OH \longrightarrow \text{II} + H^+ \qquad (9)$$

Figures 1 and 2 may be rationalized in terms of these results: below 1.1 V specific adsorption of electroinactive DMB, which is highest at less positive potentials, decreases the rate of discharge of solvent (or electrolyte) by blocking electrode sites. As the anode potential is increased the curves converge possibly owing to preferential adsorption of hydroxide ions. The effect of specifically adsorbed, uncharged, electroinactive substances on electrochemical kinetics has been reviewed by Delahay.[8]

The inflection (0.9–1.1 V) in the curves of Figure 1 could be interpreted as suggesting a change in mechanism for solvent oxidation favoring the radical-abstraction route (eq 1–4). Thus it could be argued that only above the potential of the inflection are methoxy radicals (or hydroxy radicals) formed. However, the inflection begins at about 0.9 V which is well removed from the transition potential for forming amine products. Indeed Bagotzkii and coworkers[9–12] have studied the adsorption and electrochemical kinetics of methanol oxidation on Pt in aqueous solutions and have found that there is no change of mechanism of solvent oxidation with potential. Their experimental

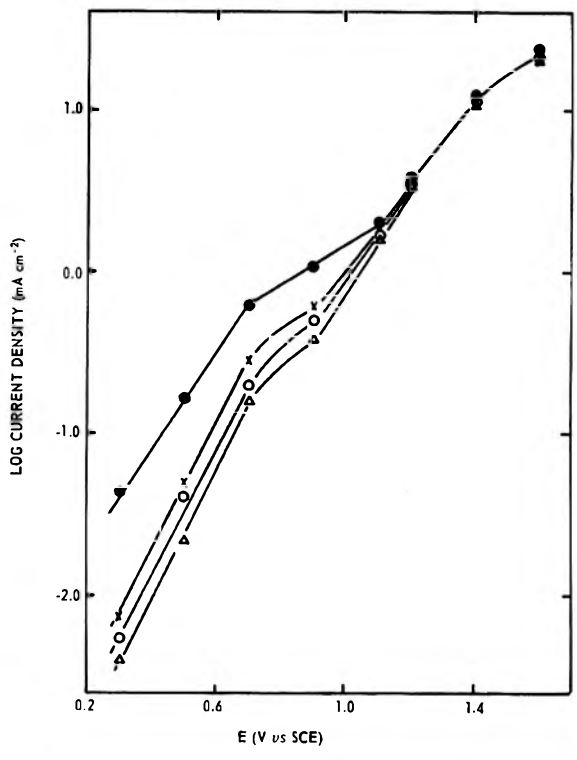


Figure 1.—Tafel plots of oxidation of DMB in 0.5 *M* KOH–CH_3OH at 12°. Concentration of DMB: ●, 0.00 *M*; ×, 0.00244 *M*; ○, 0.00476 *M*; △, 0.0130 *M*.

(7) There is considerable evidence which implicates platinum oxides (formed electrochemically on the anode surface) in certain oxidations.[3]

(8) P. Delahay, "Double Layer and Electrode Kinetics," Interscience Publishers, New York, N. Y., 1965, pp 228–233.

(9) V. S. Bagotzkii and Y. B. Vasilyev, *Electrochim. Acta*, **12**, 1323 (1967).

(10) O. A. Khazova, Y. B. Vasilyev, and V. S. Bagotzkii, *Elektrokhimiya*, **2**, 267 (1966).

(11) S. S. Beskorovainaya, O. A. Khazova, Y. B. Basilyev, and V. S. Bagotzkii, *ibid.*, **2**, 932 (1966).

(12) V. S. Bagotzkii and Y. B. Vasilyev, *Electrochim. Acta*, **11**, 1439 (1966).

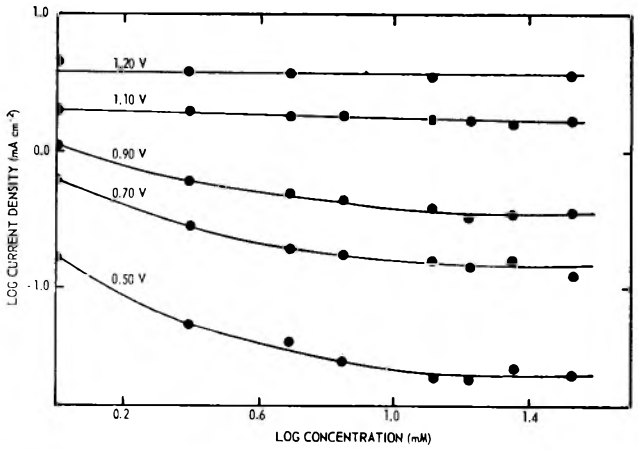


Figure 2.—Log–log plots of current density against concentration of DMB at constant potentials from 0.50 to 1.20 V *vs.* sce, in 0.5 *M* KOH–CH_3OH at 12°.

results have been explained by considering that dissociatively chemisorbed alcohol residues are chemically oxidized by adsorbed hydroxy radicals (formed as the result of discharge of hydroxide ions in alkaline solutions) in the slow step of the process.

Again in favor of the radical-abstraction route, it could be argued that the above results may be explained in terms of current density. (For example, the Kolbe reaction is known to require high current densities for successful coupling of alkyl radicals).[13] Thus at low current density (low anode potential) methoxy (or hydroxy) radicals would preferentially react with solvent rather than DMB, while at high current density (more positive anode potential) DMB would be attacked. Adsorbed amine, however, would be expected to be attacked by electrochemically generated radicals in the low current density region where coverage by DMB is greatest. A current density argument is thus in disagreement with the experimental results of Figures 1 and 2 and Table I.

The major products found in the electrolysis of DMB (Table I, in order of increasing retention time) are benzaldehyde, the ethers I and II, and an unisolated compound, peak 9, believed to be N-hydroxymethyl-N-methylbenzylamine (VIII) or the ether IX. Gas chromatographic analysis of a mixture of formaldehyde (excess) and N-methylbenzylamine showed only one high-boiling component with a retention time corresponding to peak 9. Only II could be isolated by distillation. Contrary to the observations of Smith and Mann, the yield and current efficiency for formation of amine-derived product using KOH as electrolyte is quite good. The current efficiencies for formation of the major compounds in expt 3 are estimated as follows: benzaldehyde, 15.5%; I and II, 45.7%; VIII, 12.4%.

Significantly at 1.30 V in a one-compartment cell only traces of amine-derived product are formed (expt 5). It is believed that cathodic reduction of the products I, II, and VIII (or IX) to DMB occurs almost as rapidly as these are formed. Support for this conclusion was derived from expt 6 carried out at 1.30 V using a two-compartment cell. Addition of compound II to the cathode solution provided almost pure DMB after work-up. On forcing the reaction to occur by passage of larger amounts of current (expt 7 and 9; see also ref 1) at higher potentials, amine-derived products may be formed in a one-compartment cell in good yield.

The above procedure should be helpful in establishing the mechanism(s) of oxidation in a number of other cases where voltammetric data is inconclusive, namely, the alkoxylation of olefins,[14–16] of aromatic compounds,[17–21] and of amides.[22]

Experimental Section

The electronic equipment used for controlled potential electrolyses has been described previously.[2] The constant-current electrolysis (Table I, expt 9) was carried out with a Harrison Laboratories Model 881 A (±100 V, ±1.2 A) dc power supply. Two types of glass electrolysis cells were used which allowed positioning of an aqueous saturated calomel reference (sce) close to but isolated from the anode by a small external frit separated compartment. The cells were either one-compartment (anode and cathode in the same compartment) or two-compartment cells, provided with smooth platinum electrodes (each 10 cm^2), nitrogen gas bubbler, thermometer, and magnetic stirring bar. Polarization curves and reaction order data were obtained with the one-compartment cell.

Gas chromatographic analyses were conducted with an F & M Model 5750 research gas chromatograph using stainless steel columns (10 ft × 0.25 in.) packed with 0.2% SE-30 on glass beads (mesh size 60–80). Infrared spectra were determined with a Perkin-Elmer Model 137 spectrophotometer.

Electrolysis of DMB. A.—The following is a typical description of the electrolysis and work-up procedure (Table I, expt 3). Into the anode compartment of a two-compartment cell was introduced 100 ml of 0.5 *M* KOH in distilled reagent grade methanol. An equal height of the same solution was added to the cathode and reference compartments. Freshly distilled DMB (2.70 g, 0.020 mol) was added to the anode solution and electrolysis was carried out potentiostatically at 1.10 V *vs.* sce. The cell was externally cooled at 12°. After 0.516 faradays/mol had been passed, the anode solution was concentrated at reduced pressure (10–20 mm) and 30–35° until most of the solvent had been removed. The residue was taken up in 100 ml of water and extracted with three 75-ml portions of diethyl ether; the combined organic extracts were dried over anhydrous magnesium sulfate. Filtration and reconcentration at reduced pressure below 35° provided 2.65 g of an almost colorless oil. The product distribution for this residue is shown in Table I.

B.—The crude product of expt 9, worked up in a similar manner, was distilled, and a heart-cut of a fraction with bp 40–46° (0.3–0.4 mm) was obtained. According to gas chromatographic analysis, the fraction consisted of N-methoxymethyl-N-methylbenzylamine containing about 5% the compound corresponding to peak 9. The infrared spectrum (neat) of II had characteristic bands at 1605 (w), 1595 (w), 1500 (m), 1460 (s), 1390 (m), 1370 (s), 1175 (s), 1115 (m), 1105 (s), 1070 (s), 1015 (s),

(13) A. K. Vijh and B. E. Conway, *Chem. Rev.*, **67**, 623 (1967).

(14) T. Inoue, K. Koyama, T. Matsuoka, K. Matsuoka, and S. Tsutsumi, *Tetrahedron Lett.*, 1409 (1963).

(15) T. Inoue and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **38**, 661 (1965).

(16) T. Inoue, K. Koyama, T. Matsuoka, and S. Tsutsumi, *ibid.*, **40**, 162 (1967).

(17) T. Inoue, K. Koyama, T. Matsuoka, K. Matsuoka, and S. Tsutsumi, *Kogyo Kagaku Zasshi*, **66**, 1659 (1963).

(18) T. Inoue, K. Koyama, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **37**, 1597 (1964).

(19) R. E. Juday, *J. Org. Chem.*, **22**, 532 (1957).

(20) K. Sasaki, H. Urata, K. Uneyama, and S. Nagaura, *Electrochim. Acta*, **12**, 137 (1967).

(21) K. E. Kolb and C. L. Wilson, *Chem. Commun.*, 271 (1966).

(22) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Amer. Chem. Soc.*, **88**, 4657 (1966).

930 (s), 870 (m), 743 (s), 702 (s) cm^{-1}. The nmr spectrum in CCl_4 was consistent with the structural assignment.[23]

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.53; H, 9.16; N, 8.51.

(23) The τ values for the $ArCH_2$ and NCH_2O groups were incorrectly reversed in the earlier work.[1]

Registry No.—N,N-Dimethylbenzylamine, 103-83-3; II, 13657-14-2.

Acknowledgments.—The author wishes to thank A. K. Hoffmann and T. B. Reddy for valuable discussion.

Permanganate Oxidation of N-Aryl-2-naphthylamines

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The major crystalline products from permanganate oxidation of N-aryl-2-naphthylamines are 1,1′-coupling dimers. Structures were determined by instrumental methods and by degradation to known 7-aryldibenzo[*c*,*g*]-carbazoles. Also formed are significant quantities of carbon–nitrogen coupling products, believed to be the *o*-semidines. 7-Aryldibenzo[*c*,*g*]carbazoles are formed in minor amounts. No evidence was found for stable symmetrical tetraarylhydrazines.

The oxidation of diarylamines to tetraarylhydrazines is well known from the classic work of Wieland and coworkers.[5] Wieland's views on the reversibility of

$$Ar_2NH \xrightarrow{\text{oxidn}} Ar_2NNAr_2 \rightleftharpoons 2Ar_2N\cdot \longrightarrow \text{decomposition products}$$

diarylamino radical formation and on the nature of the decomposition products have been modified by more recent work. Neugebauer and Fischer[6] have shown that no stable radicals are detected from tetraphenylhydrazine at temperatures as high as 90°. Diarylamino radicals were detected, however, when the benzene rings contained electron-supplying substituents. Contrary to Wieland's original results, the major decomposition product of tetraphenylhydrazine was shown not to be 5,10-diphenyl-5,10-dihydrophenazine.[7] The hydrazine decomposes irreversibly at 90° with a half-life of about 10 min.[8] Musso[9] recently showed the major decomposition product to be an oligomer containing an average of five diphenylamino units, formed by nitrogen–carbon coupling.

These several facets of the oxidation of diphenylamine may be considered reasonably well established. In contrast, no aspect of the oxidation of secondary naphthylamines is well understood at this time. N-Arylnaphthylamino radicals have not been identified unambiguously, and there seems to be no agreement on the products of oxidation of secondary naphthylamines.

Wieland and Süsser[10] showed that the permanganate oxidation of di-2-naphthylamine did not yield a hydrazine, and tentatively assigned to the crystalline product an *o*-semidine structure. An analogous structure was assigned by Rehner and coworkers to a crystalline product of the permanganate oxidation of N-phenyl-2-naphthylamine.[11] Somewhat later, Lieber and Somasekhara[12] oxidized a series of dinaphthylamines with potassium permanganate. Completely disregarding the previous work of Wieland[10] and Rehner,[11] and without any valid experimental evidence, they assigned symmetrical hydrazine structures to all crystalline products. The hydrazine structure has also been suggested for the oxidation product of N-phenyl-2-naphthylamine.[13] The oxidation of N-phenyl-1-naphthylamine and di-1-naphthylamine with a variety of oxidizing agents produces *p*-semidine polymers,[14] similar to those formed by decomposing tetraphenylhydrazine.[9]

The present work deals with the products resulting from permanganate oxidation of two N-aryl-2-naphthylamines.

Results and Discussion

The oxidation of N-phenyl-2-naphthylamine or di-2-naphthylamine by neutral potassium permanganate in acetone leads to the dehydrogenated 1,1′ dimer as the major crystalline product. Structure proof is shown in Scheme I.

1,1′-Bis(N-phenyl-2-naphthylamine) (**2a**) was found by nmr and infrared spectroscopy to have one amino hydrogen per phenyl-2-naphthylamine residue, *i.e.*, two amino hydrogens per molecule. 1,1′-Bis(di-2-naphthylamine) (**2b**) was too sparingly soluble for accurate nmr integration of the amine hydrogen peak. However, its infrared spectrum indicated the presence of two N–H bonds per molecule. Both dimers gave diacetates (no N–H infrared absorption band and three acetate protons per amine residue). Each oxidative dimer was degraded in excellent yield to the corresponding 7-aryldibenzo[*c*,*g*]dibenzocarbazole (**3**), which was synthesized by standard methods.

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(5) (a) H. Wieland and S. Gambarjan, *Ber.*, **39**, 1499 (1906); (b) H. Wieland, *Ann.*, **381**, 200 (1911).

(6) F. A. Neugebauer and P. H. H. Fischer, *Chem. Ber.*, **98**, 844 (1965).

(7) H. Gilman and J. J. Dietrich, *J. Amer. Chem. Soc.*, **79**, 6178 (1957).

(8) C. K. Cain and F. Y. Wiselogle, *ibid.*, **62**, 1163 (1940).

(9) H. Musso, *Chem. Ber.*, **92**, 2881 (1959).

(10) H. Wieland and A. Süsser, *Ann.*, **392**, 169 (1912).

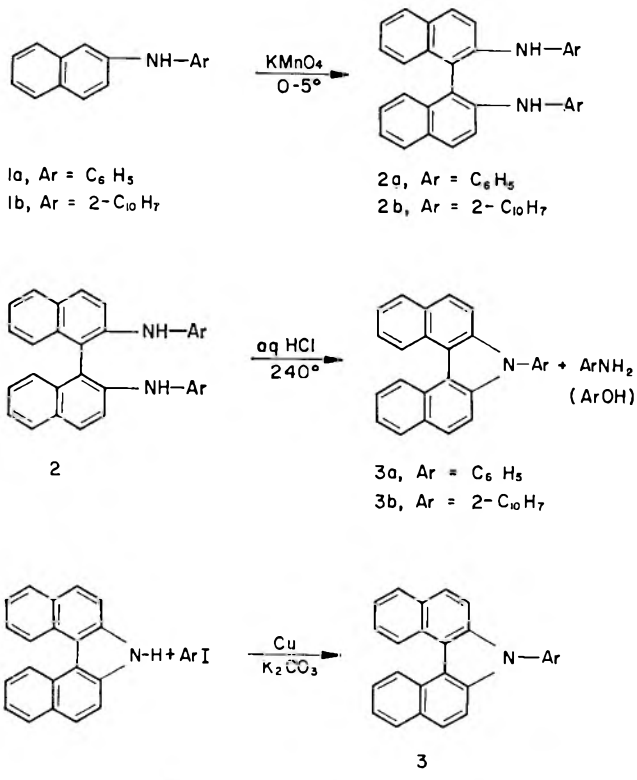
(11) J. Rehner, Jr., F. W. Banes, and S. B. Robison, *J. Amer. Chem. Soc.*, **67**, 605 (1945).

(12) E. Lieber and S. Somasekhara, *J. Org. Chem.*, **24**, 1775 (1959).

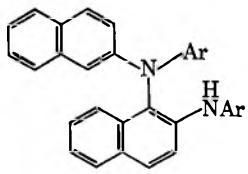
(13) See P. Schneider, *Proc. Rubber Technol. Conf., 3rd, London, 1954*, 309 (1954), footnote 29.

(14) R. L. Peeler, *Amer. Chem. Soc., Div. Petrol. Chem., Preprints*, **10** (2), D-119 (1965).

SCHEME I



Although Wieland and Süsser[10] had sound experimental evidence for eliminating a hydrazine structure for their crystalline dimer of di-2-naphthylamine (mp 273° *vs.* 282–283° in the present work), they also discarded structure **2b** without serious consideration in favor of the *o*-semidine **4b**. Rehner and coworkers[11]



4a, Ar = C_6H_5
b, Ar = 2-$C_{10}H_7$

also favored an *o*-semidine structure, **4a**, for the crystalline dimer from N-phenyl-2-naphthylamine (mp 164–165° *vs.* 168° in the present work). Their experimental evidence included the formation of aniline on hydrolysis (see Experimental Section) and the formation of a dipicrate and a monoacetate (a gray-white powder, mp 170–175°). In contrast, using their experimental conditions, we were unable to obtain a picrate and obtained a crystalline diacetate (mp 283–284°). There seems no reason to doubt that the crystalline dimers found in the present work are the same as those previously isolated. The earlier structural assignments must therefore be considered incorrect.

With 1 equiv of permanganate the amount of **1a** unreacted varied from 4 to 25% in different experiments. The yield of **2a** was always about 63% based on the amount of **1a** consumed. Several methods were used to obtain a material balance on the crude product from the oxidation of **1a**.

By utilizing the solubilities of the hydrochlorides of **1a** and **2a** in different solvents, it was possible to precipitate **2a** relatively free from the other components of the mixture by passing anhydrous hydrogen chloride through a benzene solution of the crude reaction mixture. After evaporation of the solvent, the mixture was dissolved in ether, and **1a** was likewise precipitated as the hydrochloride. The remaining material, after washing and drying, was an amorphous solid, which was found to contain a small amount of 7-phenyldibenzo[*c,g*]carbazole (**3a**) and a major fraction which will be designated as the semidine fraction **4a**. The quantities in the first column of Table I are based on crude yields of the isolated products.

TABLE I

PRODUCTS FROM THE PERMANGANATE OXIDATION OF N-PHENYL-2-NAPHTHYLAMINE

	% yield based on amine consumed	
Compd	Isolated	Nmr
2a	63	66
3a	0.5[b]	
4a[a]	32	34

[a] Semidine fraction; see text. [b] Determined by thin layer chromatography (tlc) and ultraviolet (uv) absorption.

After repeated chromatography, the semidine fraction remained amorphous. Analysis and molecular weight determination showed it to be isomeric with **2a**. The thin layer chromatogram gave a single spot with only traces of **1a**, **2a**, and **3a** discernible. A single proton resonance at τ 3.78 ($CDCl_3$) indicated one N–H bond per molecule, as did the infrared spectrum. Upon long standing, seed crystals of **4a** were finally obtained, and the amorphous material was converted (77% recovery) into a crystalline substance which had an infrared spectrum identical with that of the original amorphous fraction.

The results in the second column of Table I were obtained by integrating N–H peaks appearing at τ 4.52 (**1a**), 4.45 (**2a**), and 3.78 (**4a**) in the freeze-dried crude reaction mixture dissolved in chloroform-*d*. From the close agreement between the isolated percentages and the nmr results we conclude that no change occurred during the isolation procedure. Furthermore, the thin layer chromatograms of the crude reaction mixture and a sample reconstituted from the isolated fractions were identical.

The composition of the semidine indicates that it is a product of nitrogen–carbon coupling. The chemical shift of the amino proton—0.74 ppm downfield of **1a**—suggests an *o*-diamine structure, *i.e.*, the *o*-semidine **4a**. Attempts to synthesize **4a** by coupling **1a** with 1-iodo-N-phenyl-2-naphthylamine failed because the iodo compound could not be prepared by any of the standard methods.

The products of the oxidation of di-2-naphthylamine were isolated by crystallization, and the results in Table II probably include appreciable overlap between fractions. Again the semidine fraction **4b** was found to be isomeric with **2b** and was originally noncrystalline. By slow crystallization from benzene solution, it was possible to obtain a small quantity of a crystalline product from the semidine fraction (5% based on the semidine formed). The infrared spectra showed both the crude semidine and the crystalline product to have one N–H bond per molecule.

TABLE II

PRODUCTS FROM THE PERMANGANATE OXIDATION OF DI-2-NAPHTHYLAMINE

Compd	% yield based on amine consumed
2b	45
3b	6[b]
4b[a]	49

[a] Semidine fraction; see text. [b] By tlc and uv absorption; isolated yield 3%.

Although the structural assignments of **4a** and **4b** must be considered tentative at this point, it is evident that stable hydrazines are not formed from **1a** and **1b**. Since the thin layer chromatograms of freshly oxidized solutions give no indication of products other than **1–4**, we conclude that the half-lives of the tetraarylhydrazines must be much less than 1 hr at 25°.

The possibility of a hydrazine intermediate, however, remains. There is precedent[15] for formation of compounds **2** and **3** *via* a thermal benzidine rearrangement of a hydrazine intermediate. The yields of dibenzocarbazoles observed in the present work, however, are too low to consider this as a significant mode of reaction. The simplest rationalization of the major products appears to be formation by carbon–carbon and carbon–nitrogen radical coupling reactions.

Experimental Section

Infrared Spectra.—The frequencies and extinction coefficients (ϵ) of the fundamental N–H stretching band are given in Table III. Since all amine peaks were narrow and of equal half-width, the linear absorbance was used to calculate ϵ (M^{-1} cm^{-1}). Calculating the number of N–H bonds per molecule by $\epsilon/60$ seems well justified by the results for compounds **1a**, **2a**, and **1b**. All amine hydrogens exchanged in less than 1 min on shaking with D_2O.

TABLE III

INFRARED SPECTRA OF AROMATIC AMINES

Compd	N–H[a]	ϵ, M^{-1} cm^{-1}	N–H per molecule, $\epsilon/60$	N–D[b]
1a	3440	60.0	1.0	2540
2a	3420	122	2.0	2530
4a	3410	67	1.1	2520
1b	3440	60.7	1.0	2550
2b	3410	123	2.0	2530
4b	3400	59.6	1.0	2520

[a] Positions are given in cm^{-1}; solutions 1.25% w/v in $CDCl_3$. [b] Positions are in cm^{-1} after exchange with D_2O.

Ultraviolet Spectra.—Only minor differences were observed among the spectra of **1a**, **2a**, and **4a**. The spectra of **1b**, **2b**, and **4b** are similar also. The spectra of **3a** and **3b** are nearly identical and agree with the published[11] spectrum of **3a**. The extinction coefficient at 365 nm (2.7×10^4, 95% ethanol) was found to be somewhat higher than the published value.

Nuclear Magnetic Resonance (Nmr) Spectra.—Peak positions and integrations are summarized in Table IV. Chloroform-*d* was used as solvent. Crude reaction mixtures of **1a**, **2a**, and **4a** were analyzed by direct integration when the quantity of unreacted **1a** was small. For larger amounts of **1a** overlap between **1a** and **2a** was appreciable, and analysis was done by expanding the N–H region of the spectrum and integrating by plainimeter. Comparison with synthetic mixtures and independent determination of **1a** by gc showed a simple graphical correction to be sufficiently accurate. All peaks assigned to amine protons disappeared on shaking with D_2O and were immediately regenerated on adding H_2O.

(15) H. J. Shine and J. C. Trisler, *J. Amer. Chem. Soc.*, **82**, 4054 (1960).

TABLE IV

NMR OF AROMATIC AMINES AT 60 MC

Compd	N–H, τ[a]	Area of N–H/area of C–H	N–H per molecule
1a	4.52	0.0826	1.1
2a	4.45	0.0820	2.0
4a	3.78	0.0430	1.0

[a] *Ca.* 40% w/v in $CDCl_3$.

Chromatography.—Thin layer chromatograms on silica gel plates were developed with carbon tetrachloride or carbon tetrachloride–cyclohexane mixtures and were visualized with 260-nm light. Compounds **3a** and **3b** were determined quantitatively from reaction mixtures by removing the spot, washing out the product with ethanol, and measuring the ultraviolet absorbance at 365 nm.

Woelm neutral aluminum oxide of activity grade I was used for column chromatography with benzene as eluent unless otherwise specified. A 2-ft silicone gum rubber column was employed for gas phase chromatography.

Molecular Weights.—When solubility and availability of sample permitted, molecular weights were measured by vapor pressure osmometry (vpo). A vapor pressure osmometer, Model 302, Mechrolab, Inc., was used at 37° with benzene as solvent. Because of the low solubility of **2b**, its molecular weight was determined in toluene at 90°. Values of *m/e* were determined by mass spectrometry at 7 eV.

Materials.—N-Phenyl-2-naphthylamine (Matheson Coleman and Bell) was vacuum distilled, mp 108–109°. Di-2-naphthylamine (Aldrich Chemical Co., Inc.) was purified by chromatography over alumina, followed by recrystallization from benzene, mp 171.5–172.5°. Acetone was refluxed overnight with $KMnO_4$ and distilled prior to use as a solvent for oxidations.

7-Phenyldibenzo[*c,g*]carbazole (3a).—The standard procedure[16] was modified slightly. 7H-Dibenzo[*c,g*]carbazole[17] (1.00 g), finely divided potassium carbonate (0.54 g), iodobenzene (3.64 g), and freshly prepared[18] copper powder (0.05 g) were refluxed in 10 ml of nitrobenzene with vigorous stirring for 18 hr. After removal of nitrobenzene by steam distillation, the residue was dissolved in a minimum amount of benzene and eluted from alumina with 1:1 benzene–petroleum ether (bp 30–60°). A pale yellow glassy solid was obtained which crystallized upon stirring with a small amount of diethyl ether. Recrystallization from a diethyl ether–alcohol mixture yielded 1.11 g (87%) of 7-phenyldibenzo[*c,g*]carbazole, mp 142.5–143° (lit.[19] mp 144°).

7-(2-Naphthyl)dibenzo[*c,g*]carbazole (3b) was prepared from 7H-dibenzo[*c,g*]carbazole (0.963 g) and 2-iodonaphthalene (1.37 g) by the procedure described above. After two treatments with alumina and recrystallization from heptane–benzene the yield of **3b** was 0.766 g (54%), mp 216–217°.

Anal. Calcd for $C_{30}H_{19}N$: C, 91.57; H, 4.87; N, 3.56; mol wt, 393.5. Found: C, 91.62; H, 4.89; N, 3.50; mol wt (*m/e*), 393.

Oxidation of N-Phenyl-2-naphthylamine (1a) with Potassium Permanganate.—A solution of **1a** (0.5 mol, 109 g) in 1 l. of acetone was cooled to 0°. $KMnO_4$ (26.3 g, 1 equiv) was added in small portions during a 5-hr period to the cooled solution under a blanket of nitrogen. The solution was allowed to warm to room temperature and stand overnight. Filtration to remove MnO_2 produced a colorless solution, which was evaporated at reduced pressure. The residue was dissolved in benzene, washed with water, dried over K_2CO_3, filtered, and finally freeze dried from benzene. The freeze-dried crude mixture (101 g) was used for the operations described below.

A. **1,1′-Bis(N-phenyl-2-naphthylamine) (2a).**—To a benzene solution (200 ml) of the crude reaction mixture (11.9 g) anhydrous HCl was introduced with stirring for 20 min. The white precipitate (6.6 g) was collected by filtration and hydrolyzed by stirring in a mixture of 100 ml of benzene and 100 ml of water for 30 min. Upon evaporation of the benzene and drying, the crude yield of **2a** was 5.65 g (44% yield), mp 160–167° (oil bath).

(16) F. D. Hager, "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, p 544.

(17) J. Meisenheimer and K. Witte, *Ber.*, **36**, 4153 (1903).

(18) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1961, p 445.

(19) H. Walder, *Ber.*, **15**, 2166 (1882).

After two recrystallizations from diethyl ether, the melting point was 167.5–8.0.

Anal. Calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42; mol wt, 436.5. Found: C, 88.13; H, 5.51; N, 6.37; mol wt (vpo), 442, (*m/e*), 436.

B. N-Phenyl-2-naphthylamine (1a).—The remaining benzene solution from the HCl treatment was evaporated, and the residue was dissolved in 200 ml of diethyl ether. Anhydrous HCl was introduced with stirring for 20 min to yield 3.6 g of hydrochloride, which was hydrolyzed as before to give 3.0 g (25% yield) of **1a**, identified by mixture melting point and comparison of infrared spectrum with that of an authentic specimen.

C. Semidine Fraction 4a.—The remaining ether solution described above was washed, dried, and evaporated to give 2.9 g (24% yield) of the amorphous semidine fraction. Seed crystals were obtained by treating 0.3 g of amorphous **4a** with diethyl ether, allowing the solution to evaporate at room temperature, and leaving the residue in an open flask for 35 days. Crystallization of a larger quantity was induced by seeding 6.9 g of amorphous **4a** in the presence of 2 ml of diethyl ether for 48 hr. The resulting solid was triturated with ether and filtered to give 3.4 g of crystalline **4a**, mp 134–136°. After evaporation of the filtrate, the residue was crystallized from absolute ethanol to yield an additional 1.9 g (77% recovery) of crystalline **4a**. The infrared spectra and elemental analyses of the crystalline and amorphous materials were identical.

Anal. Calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42; mol wt, 436.5. Found: C, 87.99; H, 5.52; N, 6.35; mol wt (vpo), 440, (*m/e*), 436.

D. 7-Phenyldibenzo[*c,g*]carbazole (3a).—During column chromatography of semidine fraction **4a**, early fractions eluted with 1:1 benzene–petroleum ether were fairly rich in **3a** as shown by the uv absorption at 365 nm. Efforts to crystallize **3a** from these fractions were unsuccessful. The yield in Table I was obtained by tlc and uv absorption.

Acetylation of 1,1′-Bis(N-phenyl-2-naphthylamine) (2a).—The dimer (1.0 g) was refluxed overnight with acetic anhydride (10 ml) in acetic acid (20 ml). The cooled solution was poured into aqueous methanol, and the resulting emulsion was coagulated with calcium chloride (1.0 g). The precipitate was dried and recrystallized from benzene–hexane to give **1,1′-bis(N-phenyl-2-naphthylamine) diacetate** (0.9 g) as cubes, mp 284–285°.

Anal. Calcd for $C_{36}H_{28}N_2O_2$: C, 83.05; H, 5.42; N, 5.38. Found: C, 82.86; H, 5.25; N, 5.35.

Oxidation of Di-2-naphthylamine (1b) with Potassium Permanganate.—$KMnO_4$ (1.2 equiv, 2.4 g) was added in small quantities during 3 hr to a solution of **1b** (0.037 mol, 10 g) in 400 ml of acetone at 0° under nitrogen. At the end of the addition, the reaction mixture was allowed to warm to room temperature and stand for 1 hr. The precipitated MnO_2 was removed by filtration to give a colorless solution. Isolation of products is described below.

A. 1,1′-Bis(di-2-naphthylamine) (2b).—The acetone solution was successively reduced in volume and filtered until no more **2b** precipitated. The crude yield of **2b** was 2.8 g (28% yield). Once isolated, **2b** was sparingly soluble in most solvents. Recrystallization from xylene (1 g/25 ml, recovery 70–80%) gave colorless **2b**, mp 282–283°.

Anal. Calcd for $C_{40}H_{28}N_2$: C, 89.52; H, 5.26; N, 5.22; mol wt, 536.6. Found: C, 89.58; H, 5.32; N, 5.11; mol wt (vpo), 550, (*m/e*), 536.

B. Di-2-naphthylamine (1b).—The acetone filtrate described above was evaporated, and the residue was dissolved in benzene. The benzene solution was successively evaporated and filtered until no **1b** could be detected in the solution by gc. The yield of recovered **1b** was 3.7 g, identified by mixture melting point and infrared spectrum.

C. Semidine Fraction 4b.—Upon evaporation of the benzene filtrate described above, 3.4 g of amorphous **4b** was obtained. This was later shown to contain about 0.3 g of **3b**. Crystalline material was obtained from the semidine fraction of a large-scale run (30 g of **1b**). The semidine fraction (9.7 g) was chromatographed twice, and the center fractions (8.0 g) were stored in benzene (15 ml) under nitrogen for 2 months. White crystals (1.17 g) were removed by filtration and washed with boiling chloroform to give 0.55 g of crystalline **4b**, mp (sealed tube) 287–289° (depressed on admixture of **2b**).

Anal. Calcd for $C_{40}H_{28}N_2$: C, 89.52; H, 5.26; N, 5.22; mol wt, 536.6. Found: C, 89.56; H, 5.26; N, 5.13; mol wt (*m/e*), 536.

The crystalline substance obtained was apparently identical with the amorphous material. The amorphous fraction gave a satisfactory elemental analysis and a molecular weight of 560 by vpo and *m/e* 536. Both crystalline and amorphous materials had identical infrared spectra.

D. 7-(2-Naphthyldibenzo[c,g]carbazole (3b).—During chromatography of the 3.4 g of amorphous **4b** described above, the first two fractions (0.62 g) eluted with 1:1 benzene–petroleum ether were found to contain about 50% **3b** by uv absorption. Boiling with diethyl ether for 5 min and cooling gave **3b** in 1.9% yield (0.14 g), mp 215–216° undepressed on admixture with an authentic sample. Determination of **3b** in the crude oxidation mixture by tlc and uv absorption indicated a 6% yield based on the amount of **1b** consumed.

Acetylation of 1,1′-Bis(di-2-naphthylamine) (2b).—Under the conditions described for **2a** above, **2b** gave a diacetate (nmr) which could not be crystallized and was obtained as a gray-white powder from aqueous acetone, softening at 90–95°. The analysis suggests that it may contain a molecule of water.

Anal. Calcd for $C_{44}H_{32}N_2O_2 \cdot H_2O$: C, 82.73; H, 5.37; N, 4.38. Found: C, 82.36; H, 5.59; N, 4.40.

Reaction of 1,1′-Bis(N-phenyl-2-naphthylamine) (2a) with Concentrated Hydrochloric Acid.—The amine (2.5 g) and 10 ml of concentrated hydrochloric acid were sealed in a heavy-walled Pyrex tube. The tube was enclosed in a stainless steel pipe which was securely capped at both ends and placed in an autoclave at an initial nitrogen pressure of 1200 psi.[20] The autoclave was rocked for 6 hr at 240–250°. When cooled, the contents of the tube had separated into a brown mass and a clear acid layer, which were separated by decantation. The acid layer was neutralized, and aniline was extracted with a known volume of ether. The yield determined by gas chromatography was 98%. After drying, the solvent was evaporated to give 0.47 g of aniline (88% yield), identified by its infrared spectrum. The brown mass was dissolved in a minimum amount of ether, washed with water, and diluted to a known volume with ethanol. The ultraviolet absorption at 365 mm indicated a 94% yield of 7-phenyldibenzo-[*c,g*]carbazole (**3a**). In a separate experiment the product was purified by eluting from alumina with 1:1 benzene–petroleum ether to give 86.5% yield of **3a**, identified by comparison of melting point (143.5–144°), mixture melting point (143–144°), ultraviolet spectrum, and infrared spectrum with those of the authentic specimen described above.

From three previous attempts, a product melting at 122–123° was obtained. The mass, nmr, infrared, and ultraviolet spectra were identical with those of authentic 7-phenyldibenzo[c,*g*]carbazole. Elemental analysis and ultraviolet extinction coefficients revealed the low-melting material to be pure. The mixture melting point was 142.5–143°. The low-melting form could be converted into a solid melting at 143–144° by equilibrating the melt at 125° for 1 hr. This behavior is similar to that reported by Shine and Trisler for 7H-dibenzo[*c,g*]carbazole.[15]

Reaction of 1,1′-Bis(di-2-naphthylamine) (2b) with Hydrochloric Acid.—The procedure described above yielded 92% of **3b** as determined by uv spectroscopy. The isolated yield of **3b** was 70%, mp 214–216° undepressed on admixture with authentic **3b**. Infrared and uv spectra were identical with those of the authentic specimen. The 2-naphthylamine formed in the reaction did not survive, but was converted into 2-naphthol—60% by gc, 30% isolated and identified by mixture melting point and infrared spectrum.

Registry No.—**1a**, 135-88-6; **1b**, 532-18-3; **2a**, 17704-02-8; **2a**, diacetate, 17704-09-5; **2b**, 17704-01-7; **2b**, diacetate, 17704-10-8; **3b**, 17704-03-9; **4a**, 17704-04-0; **4b**, 17704-05-1.

(20) This procedure helps to avoid shattering of the tube, which was observed on occasion.

Reactions of Aryldiazonium Fluoroborates with Isopropyl Fluorocarbamate and with Difluoramine[1]

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The reaction of isopropyl fluorocarbamate with aryldiazonium fluoroborates, in the presence of a mild base, gave aryl azides, isopropyl fluoroformate, and diisopropyl N-fluoriminodicarboxylate. Difluoramine and benzenediazonium fluoroborate gave *o*-fluorophenyl azide, *p*-fluorophenyl azide, and benzene. Difluoramine and 2,4,6-trimethylbenzenediazonium fluoroborate gave 2,4,6-trimethylphenyl azide. The products are rationalized on the basis of fluorotriazene intermediates.

Reactions of aryldiazonium ions with nucleophilic nitrogen species generally result in direct coupling products, as in the case of amines,[2] or nitrogen displacement products, as in the case of sodium nitrite.[3] Aromatic azides are formed from coupling products to nitrogen compounds with substituents that readily undergo α elimination, such as hydroxylamine,[4] arylhydrazines,[5] sulfonamides,[6] and chloramine.[7] It was of interest to determine the effect of NF groups on diazonium reactions. Alkyl fluorocarbamates have been shown to be sufficiently acidic to form anions under mild conditions;[8] so either coupling or nitrogen displacement might be expected. Difluoramine has not been reported to give a stable anion, but its hydrogen is sufficiently labile to undergo electrophilic substitution.[9]

No reaction took place when isopropyl fluorocarbamate was added to a suspension of an aryldiazonium fluoroborate in methylene chloride; a mild base was required to effect condensation. The addition of potassium fluoride to isopropyl fluorocarbamate and benzenediazonium fluoroborate in methyl chloride at 0–5° gave a 71.5% yield of phenyl azide, an 18% yield of diisopropyl N-fluoriminodicarboxylate, and isopropyl fluoroformate, which codistilled with the solvent. The addition of ammonia to the solvent fraction gave a 61% over-all yield of isopropyl carbamate. Higher reaction temperatures resulted in increases in yields of diisopropyl N-fluoriminodicarboxylate. Similarly, *o*-nitrobenzenediazonium fluoroborate, *m*-nitrobenzenediazonium fluoroborate, and *p*-nitrobenzenediazonium fluoroborate were converted into the corresponding azides in yields of 79–98%. The use of pyridine instead of potassium fluoride to remove fluoroboric acid gave the same results.

The formation of aryl azides by this reaction represents another example of diazonium coupling to a nitrogen compound with α elimination, the first such example in which an acyl halide is eliminated. The coupling product could lose fluoride and acylium ions or, alternatively, SN2 attack by fluoride on the carbonyl carbon could give the fluoroformate and the N–F anion which would lose fluoride to give the azide (eq 1).

$$ArN_2^+BF_4^- + HNFCO_2R + base \longrightarrow ArN{=}NNCO_2R + base\cdot HBF_4 \quad (1)$$

$$ArN{=}NNCOR \longrightarrow ArN_3 + FCOR$$

Diisopropyl N-fluoriminodicarboxylate was most likely formed from the reaction of isopropyl fluoroformate with isopropyl fluorocarbamate. The acylation of N-fluorocarbamates with chloroformates has been reported[8] (eq 2).

$$ROCNHF + ROCF \longrightarrow ROCNCOR \quad (2)$$

Benzenediazonium fluoroborate, which has low solubility in common solvents, including water, was found to be very soluble in liquid difluoramine at its boiling point (−23°). No reaction took place, and the diazonium salt was recovered quantitatively when the difluoramine was removed. However, the addition of pyridine or potassium fluoride to remove fluoroboric acid resulted in the formation of *o*-fluorophenyl azide, *p*-fluorophenyl azide, and benzene. These azides, as well as the *meta* isomer, were synthesized independently by the nitrosation of the corresponding fluorophenylhydrazines and comparison of the fluorine nmr spectra of the three with that of the product showed that only the latter was absent. Yields in the difluoramine reaction were variable, and considerable amounts of tars were formed. In several instances two unidentified products were formed with ^{19}F signals indicative of NF compounds: a 1:1:1 triplet at ϕ^* −32.5[10] and a broadened singlet at ϕ^* −26.2.

Sodium fluoride was not sufficiently basic to effect the condensation of the diazonium salt with difluoramine, and the starting material was recovered. Cesium fluoride, on the other hand, gave violent decomposition even when methylene chloride was added as a diluent.

o-Fluorophenyl azide and *p*-fluorophenyl azide could be formed from the expected coupling product, 1-phenyl-3,3-difluorotriazene, by loss of fluoride ion to give a resonance-stabilized cation having carbonium

(1) This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

(2) P. Griess, *Ann.*, **121**, 258 (1862); H. Von Pechmann and L. Frobenius, *Ber.*, **28**, 170 (1895); B. F. Day, T. W. Campbell, and G. M. Coppinger, *J. Amer. Chem. Soc.*, **73**, 4687 (1951).

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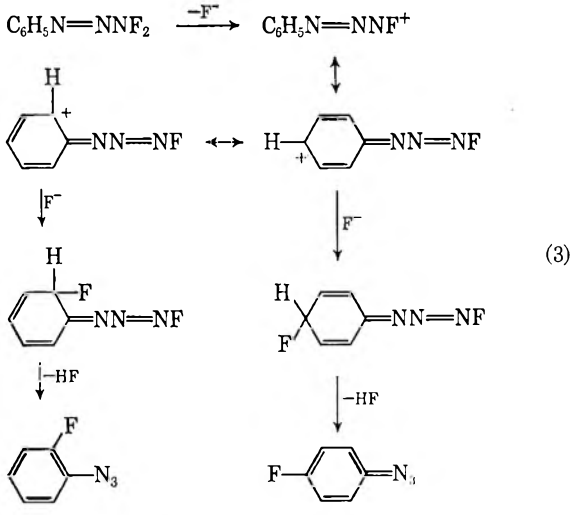
ion character at the *ortho* and *para* positions. The addition of fluoride at these positions would give semiquinoid intermediates which would give the observed fluoro azides by the elimination of HF. The absence of the *meta* isomer is consistent with this mechanism (eq 3).



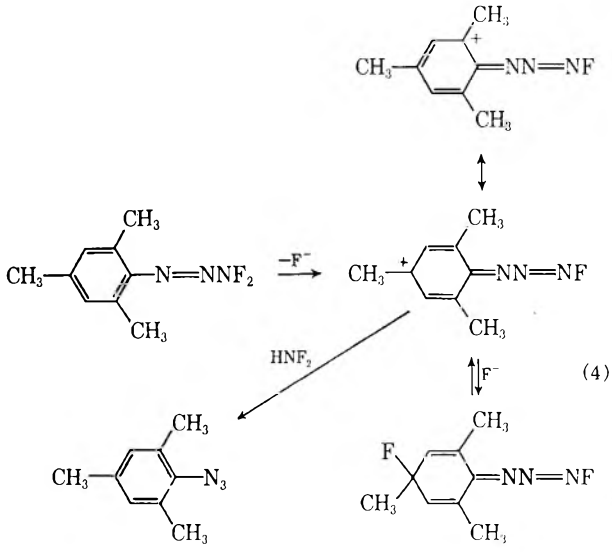
(3)

Diazonium salt reductions generally take place by a homolytic mechanism,[11] and the above difluorotriazene would be expected to react readily in this manner by loss of the stable[12] difluoramino radical. The resulting diazoaryl or aryl radicals could abstract hydrogen from difluoramine to give benzene.

Blocking the *ortho* and *para* positions of the diazonium salt with methyls should alter the above path in two ways. The diazonium coupling product should lose fluoride more readily because of methyl stabilization of positive charge in the ring. Homolytic decomposition should therefore consume a smaller portion of the intermediate. However, addition of fluoride ion to *ortho* or *para* positions in the cation cannot lead to fluoro azides without the rupture of a C–C bond; so this step should be reversible.

The reaction of 2,4,6-trimethylbenzenediazonium fluoroborate with difluoramine in the presence of potassium fluoride was found to give an 86% yield of 2,4,6-trimethylphenyl azide and a trace of mesitylene. The azide could not be distilled without decomposition, but an analytical sample for comparison was prepared independently from the diazonium salt and sodium azide. The formation of 2,4,6-trimethylphenyl azide could take place by loss of fluoride from the triazene, followed by aromatization by loss of electropositive fluorine to an available fluorination substrate, *i.e.*, difluoramine. An example of the fluorination of an anion by a neutral difluoramino compound has been reported[13] (eq 4).

The products obtained in the reactions of diazonium salts with isopropyl fluorocarbamate and with difluoramine thus indicate that nitrogen coupling takes place to give unstable fluorotriazenes, which can react



(4)

further by a variety of mechanisms, depending on substituents.

Experimental Section

Reaction of Isopropyl Fluorocarbamate with Benzenediazonium Fluoroborate.—Benzenediazonium fluoroborate[14] (5.73 g, 0.030 mol) was added to a solution of 3.63 g (0.030 mol) of isopropyl fluorocarbamate[8] in 30 ml of methylene chloride. The resulting slurry was cooled to 0°, and 6.0 g (0.104 mol) of potassium fluoride was added in small portions over a 10-min period. After the mixture was stirred an additional 2.5 hr at 0–5°, it was pressure filtered, and the solids were washed with three 10-ml portions of methylene chloride. The solvent was removed from the combined methylene chloride solutions by distillation [25° (300 mm)], and the residue was vacuum distilled to give 2.55 g (0.0214 mol, 71.3% yield) of phenyl azide, bp 49–50° (5 mm),[15] and 1.13 g (0.0055 mol, 18% yield) of diisopropyl N-fluorimmodicarboxylate, bp 68° (0.02 mm).

Anal. Calcd for $C_8H_{14}NO_4F$: C, 46.38; H, 6.77; N, 6.77; F, 9.19. Found: C, 46.14; H, 6.92; N, 7.01; F, 9.22.

The ^{19}F nmr spectrum consisted of a single peak at ϕ^* 68.7. The proton spectrum showed only isopropyl groups (doublet at δ 1.38 and septet at δ 5.10).

Isopropyl fluoroformate codistilled with the solvent, and a sample was isolated by gas chromatography (10 × 0.25 in. column of 5% Carbowax 4000 on Fluoropak 80 at 60°).

Anal. Calcd for $C_4H_7O_2F$: C, 45.28; H, 6.60. Found: C, 45.39; H, 6.85.

The infrared spectrum showed carbonyl absorption at 5.5 μ. The ^{19}F nmr spectrum consisted of an octet (J = 1.5 cps), with outer members barely detectable over background. Fluorine spectra of other fluoroformates have been reported in this region.[16] The proton spectrum consisted of a doublet (J_{HH} = 6.3 cps) of doublets (J_{HF} = 1.5 cps) at δ 1.41 for the methyls and a septet (J_{HH} = 6.3 cps) of doublets (J_{HF} = 1.5 cps) for the CH. Anhydrous ammonia was bubbled through the methylene chloride solution for several minutes. The solvent was removed under vacuum to give 1.87 g (0.0182 mol, 61% yield) of isopropyl carbamate, mp 93°.[17]

Reaction of Isopropyl Fluorocarbamate with Nitrobenzenediazonium Fluoroborates.—Potassium fluoride (1.2 g, 0.020 mol) was added during a 10-min period with stirring to a mixture of 10 ml of methylene chloride, 2.37 g (0.01 mol) of *o*-nitrobenzenediazonium fluoroborate, and 1.21 g (0.01 mol) of isopropyl fluorocarbamate at 0°. The flask was allowed to warm to room temperature, and stirring was continued for 45 min. The solution was filtered, and the precipitate was washed with 25

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ml of methylene chloride. Solvent was removed from the combined methylene chloride solutions under vacuum. The residue, an oil, was crystallized from pentane to give 1.61 g (98% yield) of *o*-nitrophenyl azide, mp 51–52° (lit.[18] mp 53°).

The identical procedure with *m*-nitrobenzenediazonium fluoroborate gave 1.40 g (85% yield) of *m*-nitrophenyl azide, mp 51–53° (lit.[19] mp 55°). Similarly, *p*-nitrobenzenediazonium fluoroborate gave 1.3 g (79% yield) of *p*-nitrophenyl azide, mp 68° (lit.[20] mp 70°). The three azides gave satisfactory elemental analyses.

The above reactions were also conducted with pyridine rather than potassium fluoride as the base. Thus, 2.37 g (0.03 mol) of pyridine was added, dropwise with stirring at 0–5°, to a stirred mixture of 3.63 g (0.03 mol) of isopropyl fluorocarbamate, 5.73 g (0.0242 mol) of *p*-nitrobenzenediazonium fluoroborate, and 30 ml of methylene chloride. The mixture was kept at 0–5°, with stirring, for 30 min. A precipitate, identified as pyridine fluoroborate by its infrared spectrum, was filtered off and washed with methylene chloride. Solvent was removed from the combined solutions to yield 4.6 g of crude *p*-nitrophenyl azide, mp 55–60°. Recrystallization from methylene chloride and pentane gave 2.5 g (63% yield) of product, mp 70°.

Starting with *o*-nitrobenzenediazonium fluoroborate, the same procedure gave 4.8 g of crude product, mp 25–40°. Recrystallization as above gave 2.2 g (55% yield) of *o*-nitrophenyl azide, mp 52–53°.

Fluorophenyl Azides.—Sodium nitrite (0.43 g, 0.0062 mol) was added dropwise to a stirred suspension of 1.0 g (0.0062 mol) of *p*-fluorophenylhydrazine hydrochloride in 5 ml of water while the reaction temperature was held at 0–5°. The mixture was kept at this temperature for 15 min, and the product was extracted with 3 ml of carbon tetrachloride. The solution was dried over sodium sulfate and was filtered. The ^{19}F nmr spectrum showed a "quintet" at ϕ^* 118.1.

The same procedure was used to prepare solutions of *o*-fluorophenyl azide and *m*-fluorophenyl azide in carbon tetrachloride, employing the corresponding fluorophenylhydrazine hydrochlorides as starting materials. The ^{19}F signal of *o*-fluorophenyl azide was an almost symmetrical multiplet at ϕ^* 127.5. That of *m*-fluorophenyl azide exhibited a general quartet profile with additional splitting of the inner members; its position was ϕ^* 112.0. The infrared spectra showed strong azide bands at 4.7 μ.

Reaction of Benzenediazonium Fluoroborate with Difluoramine.—Difluoramine was generated as described previously.[21] Explosion shields and remote handling devices are required, and air must be excluded from the system.

Pyridine (0.62 g, 0.0104 mol) was added dropwise, with stirring, to a mixture of 2.0 g (0.0104 mol) of benzenediazonium fluoroborate and 4.5 g of difluoramine at −40°. The reaction temperature was allowed to rise to −10° over a 1-hr period, and 10 ml of methylene chloride was then added. Excess difluoramine was vented off, and the remaining solution was filtered. The filtrate was kept at ambient temperature while the solvent was removed by distillation into a −80° receiver as the pressure was gradually reduced to 100 mm. The pressure was then lowered to 0.01 mm to yield 0.1 g of distillate. The ^{19}F nmr spectrum showed *p*-fluorophenyl azide (ϕ 118 ppm) and *o*-fluorophenyl azide (ϕ^* 127 ppm) in a ratio of 62:102.

In two of six similar experiments, two additional ^{19}F signals were observed, a 1:1:1 triplet (J = 46 cps) at ϕ^* −32.5 and a broadened singlet at ϕ^* −26.2. Benzene was also formed in variable amounts.

The use of potassium fluoride instead of pyridine gave similar results. Sodium fluoride, however, did not effect condensation, and the benzenediazonium fluoroborate was recovered quantitatively. The use of cesium fluoride resulted in an explosion when no diluent was used and a fume-off when methylene chloride was added.

Reaction of 2,4,6-Trimethylbenzenediazonium Fluoroborate with Difluoramine.—To a solution of 2.34 g (0.01 mol) of 2,4,6-trimethylbenzenediazonium fluoroborate[22] in 3 ml of refluxing difluoramine, 2.0 g (0.034 mol) of potassium fluoride was introduced by means of an addition tube. The mixture was stirred under reflux for 1.5 hr, and 5 ml of methylene chloride was added. Unreacted difluoramine was vented and the solution was filtered. The precipitate was washed with 50 ml of methylene chloride, and the combined solutions were stripped of solvent in a rotary evaporator. The residue consisted of 1.4 g of oil, the infrared spectrum of which indicated that it was 2,4,6-trimethylphenyl azide (86% yield) containing a trace of mesitylene. Attempted vacuum distillation of the material resulted in decomposition.

A sample of 2,4,6-trimethylphenyl azide for comparison was prepared by adding a solution of 0.28 g (0.0043 mol) of sodium azide in 5 ml of water to a solution of 1.0 g (0.0043 mol) of 2,4,6-trimethylbenzenediazonium fluoroborate in 20 ml of water at 5°. An oil separated; after 15 min it was extracted with 10 ml of methylene chloride. The solution was dried over sodium sulfate, and the solvent was removed under vacuum.

Anal. Calcd for $C_9H_{11}N_3$: C, 67.1; H, 6.83; N, 26.1. Found: C, 67.27; H, 6.74; N, 25.41.

The infrared spectrum contained peaks at μ 3.40 (w), 4.72 (s), 6.2 (w), 6.8 (m), 7.6 (m), 7.8 (m), 9.1 (w), and 11.7 (m).

Registry No.—Isopropyl fluorocarbamate, 17603-82-6; difluoramine, 10405-27-3; diisopropyl N-fluoriminodicarboxylate, 17603-84-8; isopropyl fluoroformate, 461-71-2; 2,4,6-trimethylphenyl azide, 14213-00-4.

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The Addition of N,N-Dichlorosulfonamides to Unsaturates

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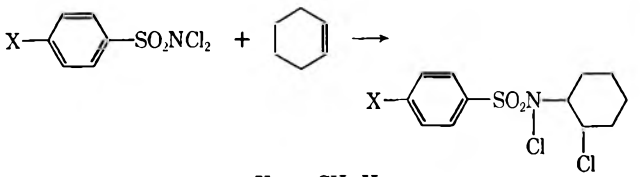
The addition of N,N-dichlorosulfonamides to olefins and conjugated dienes has been examined. The reaction of these reagents with propylene and styrene gives high yields of N-chloro-N-(β-chloroalkyl)sulfonamides which have predominantly anti-Markovnikov orientation. The reaction with isobutylene takes a different path to give 3-chloro-2-methyl-1-propene as the major product. Addition to 1,3-butadiene and chloroprene proceeds rapidly and exothermically to give high yields of 1,4 adducts. Reduction of the N-chloro adducts with sodium sulfite solution affords good yields of the corresponding sulfonamide derivatives.

In a study of the efficiency of N-chloramide derivatives as chlorinating agents, Ziegler[3] noted that N,N-dichloro-*p*-toluenesulfonamide rapidly lost about 50% of its active chlorine when treated with cyclohexene. The major product was not 3-chlorocyclohexene but an oil which was not further characterized. The major component of the oil was probably a 1:1 adduct since Thielacker[4] has reported that the addition of N,N-dichlorobenzenesulfonamide (Dichloramine B) to cyclohexene gives an 80% yield of addition product.



X = *p*-CH_3, H.

Russian workers have examined the reaction of Dichloramine B with alcohols,[5,6] carboxylic acids,[7] and phenols[8] as a method of generating hypohalite derivatives *in situ*. The reaction of these hypohalites with olefins or dienes produced chloro ether or ester derivatives.

The reaction of N,N-dichlorosulfonamides with styrene, propylene, isobutylene, 1,3-butadiene, and chloroprene has been examined. With the exception of isobutylene where chlorination is the principal reaction, good yields of 1:1 adducts are obtained. The behavior of the N,N-dichlorosulfonamides closely parallels the reactivity of the analogous N,N-dichlorocarbamates with olefins and conjugated dienes.[9]

Results

Generally, the reactions were performed by the dropwise addition of the N,N-dichlorosulfonamide in methylene chloride solution to a cooled solution of unsaturate in the same solvent. With gaseous unsaturates it was convenient to distil the reactant with nitrogen dilution into a cooled solution of the N,N-dichlorosulfonamide.

The reactions were spontaneous and quite exothermic when conjugated dienes were used. After an equimolar amount of diene had been introduced the exotherm abated. The reaction mixture was then warmed slowly to room temperature; the solvent was removed at aspirator pressure. The crude products were analyzed for isomer content by nmr spectroscopy.

The reaction with olefins was rapid, but not so exothermic as the diene reactions. Again the crude products were analyzed for isomer content by nmr spectroscopy.

An examination of the nmr spectra of the N–Cl adduct and its corresponding reduction product clearly indicates the mode of addition to the unsaturate (Table I). The chemical shift of the hydrogens on the carbon α to the sulfonamide group are very sensitive to changes in chemical environment. Upon reduction of the N-chloro function upfield shifts of approximately 0.3

$$>CH—NCl- \longrightarrow >CH—NH-$$

ppm are observed for the methylene hydrogens[9c] adjacent to the nitrogen. In addition, an increase in multiplicity of this group is observed due to coupling with the sulfonamide proton. This –CH—NH– coupling may be removed by treatment of the sample *in situ* with deuterium oxide, thereby exchanging the amide proton. The position of the hydrogens on the carbon α to the chloro group does not change significantly, shifting upfield anywhere from 0.01 to 0.20 ppm depending upon the particular compound.

Addition to Olefins.—The dropwise addition of styrene to a chilled solution of N,N-dichlorobenzenesulfonamide in methylene chloride proceeded spontaneously and exothermically to give the adduct II in nearly quantitative yield. In the nmr spectrum of II the

$$C_6H_5SO_2NCl_2 + C_6H_5CH{=}CH_2 \longrightarrow C_6H_5SO_2N(Cl)CH_2CH(Cl)C_6H_5$$
II

protons of the methylene group are nonequivalent and appear as an ABX pattern due to further coupling with the low field methine proton.

Treatment of II with aqueous sodium sulfite gave the reduction product III. Because of magnetic

$$II + Na_2SO_3 \longrightarrow C_6H_5SO_2NHCH_2CH(Cl)C_6H_5$$
III

symmetry the protons of the methylene group in III are equivalent and now appear as a triplet due to approximately equal coupling with both the methine proton and the NH proton. This signal changes to a doublet after exchange of the sulfonamide proton with deuterium oxide. The spectral data are consistent

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Table I
Nmr Parameters of N,N-Dichlorosulfonamide–Unsaturate Adducts[a]

Propylene[b]

R	N-Chloro amides[f] RSO2–NCl	CH2	CH(Cl)	CH3		Reduced N-chloro amides[g] RSO2	NH	CH2	CH(Cl)	CH3	
C_6H_5	7.72 m[d] 8.00 m	3.47 d	4.26 h	1.60 d	$J_{CH_3-CH} = 6.5$ $J_{CH_3-CH} = 6.7$	7.55 m 7.92 m	5.54 t	3.17 m[c]	4.05 h	1.44 d	$J_{CH_3-CH} = 6.5$
p-ClC_6H_5	7.57 m[e] 7.90 m	3.46 d	4.22 h	1.60 d	$J_{CH_3-CH} = 6.5$ $J_{CH_3-CH} = 6.7$	7.49 m	5.38 t	3.17 m	4.08 h	1.47 d	$J_{CH_3-CH} = 6.5$
$(CH_3)_2N$	3.03 s	3.48 dd 3.61 dd	4.25 h	1.58 s	$J_{CH_3-CH} = 6.5$ $J_{AX} = 6.0$ $J_{BX} = 6.5$ $J_{gem} = 14.0$	2.81 s	5.28 t	3.28 m	4.16 m	1.53 d	$J_{CH_3-CH} = 6.5$

Styrene

	RSO2	N-CH2Cl	CH(Cl)	C6H5		RSO2	N	CH2	CH(Cl)	C6H5	
C_6H_5	7.58 m[d] 7.89 m	3.66 dd 3.93 dd	5.15 t	7.39 m	$J_{vic} = 7.0$ $J_{gem} = 14.0$	7.49 m 7.90 m	5.67 t	3.47 t	4.92 t	7.27 m	$J_{vic} = 7.0$ $J_{NH-CH} = 6.4$
$(CH_3)_2N$	2.79 s	3.90 d	5.16 t	7.37 m	$J_{vic} = 7.1$	2.74 s	4.98 b	3.54 t	5.98 t	7.41 m	$J_{vic} = 7.0$

Butadiene

	R–SO2NCl	CH2	CH=CH	CH2Cl		R	SO2NH	CH2	CH=CH	CH2Cl	
CH_3	3.12 s	4.13 m	5.98 m	4.12 m		3.01 s	5.32 t	3.80 m	5.94 m	4.11 m	$J_{NH-H} = 6.0$
C_6H_5	7.66 m[d] 7.95 m	4.01 m	5.83 m	3.90 m		7.63 m 7.92 m	5.60 b	3.60 m	5.70 m	3.90 m	
p-ClC_6H_5	7.58 d[e] 7.93 d	3.93 m	5.86 m	4.03 m		7.54 m 7.87 m	5.10 b	3.63 m	5.73 m	3.96 m	

Chloroprene

	R–SO2NCl	CH2	C(Cl)=CH	CH2Cl		R	SO2NH	CH2	C(Cl)=CH	CH2Cl	
CH_3	3.16 s	4.23 s	6.19 t	4.27 d	$J_{vic} = 7.5$	3.02 s	5.29 b	4.02 d	6.17 t	4.24 d	$J_{vic} = 7.5$ $J_{NH-H} = 6.2$
C_6H_5	7.80 m	4.01 s	6.05 t	4.16 d	$J_{vic} = 7.3$	7.75 m 7.87 m	5.70 t	3.84 d	5.94 t	4.00 d	$J_{vic} = 7.5$ $J_{NH-H} = 6.5$
p-ClC_6H_5	7.62 d[e]	4.08 s	6.10 t	4.22 d	$J_{vic} = 7.3$	7.53 m 7.87 m	5.62 t	3.88 d	5.96 t	4.05 d	$J_{vic} = 7.5$ $J_{NH-H} = 6.5$
$(CH_3)_2N$	3.06 s	4.22 s	6.18 t	4.28 d	$J_{vic} = 7.0$	3.03 s	5.32 b	3.96 d	6.18 t	4.20 d	$J_{vic} = 7.5$ $J_{NH-H} = 6.5$

[a] Notation: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, b = broad, m = multiplet. Chemical shifts are in parts per million from TMS; coupling constants, hertz. [b] The corresponding Markovnikov adducts of propylene were identified by the characteristic methyl doublets [$CH_3CH(NClR)$] at 1.22 (R = p-ClC_6H_4), 1.12 (R = C_6H_5), and 1.37 [R = $(CH_3)_2N$] ppm. [c] On D_2O treatment the NH proton is replaced and the NH–CH coupling is removed. This simplified the methylene–methine region to an ABX system with J_{vic} = 7.3, 5.3 Hz and J_{gem} = 13.8 Hz. [d] The *ortho* protons appear at lowest field. [e] These protons appear as a typical p-disubstituted benzene pattern (AA'BB'). [f] Respective registry numbers: 17396-55-3; 17448-28-1; 17396-56-4; 17414-51-6; 17396-57-5; 17396-58-6; 17396-59-7; 17396-60-0; 17396-61-1; 17396-62-2; 17396-63-3; 17396-64-4. [g] Respective registry number: 17396-65-5; 17396-66-6; 17396-67-7; 17396-68-8; 17396-69-9; 17396-70-2; 17396-71-3; 17396-72-4; 17396-73-5; 17396-74-6; 17396-75-7; 17414-52-7.

only with the anti-Markovnikov orientation for the adduct.

The reaction of N,N-dichloro-N',N'-dimethylsulfamide[10] with styrene gave a quantitative yield of crystalline adduct. Examination of the nmr spectra of both the N-chloro adduct and its reduction product indicated that anti-Markovnikov addition had occurred.

The reaction of propylene with the N,N-dichloroamide derivatives of benzenesulfonamide, p-chlorobenzenesulfonamide, or N,N-dimethylsulfamide afforded a mixture of anti-Markovnikov (IV) and Markovnikov (V) adducts. With these reagents, the anti-Markovnikov adducts predominated in a ratio of about 85:15.

$$RSO_2NCl_2 + CH_3CH{=}CH_2 \longrightarrow RSO_2N(Cl)CH_2CH(Cl)CH_3 + RSO_2N(Cl)CH(CH_3)CH_2Cl$$

IVa–c Va–c

R = (a) C_6H_5; (b) p-Cl-C_6H_4; (c) $(CH_3)_2N$

Pure samples of the anti-Markovnikov adducts IVa and IVb were obtained by fractional crystallization. The dimethylsulfamide derivative existed as an oil at room temperature, and all attempts to obtain a pure sample of one of the isomers were unsuccessful.

In the nmr spectra of IVa and IVb the methylene groups appear as doublets, while an ABX pattern is observed for the same group in IVc. Upon reduction the methylene group of IVa changes to a complex multiplet which simplifies to an ABX pattern when the sulfonamide proton is exchanged with deuterium oxide.

When the addition to isobutylene was examined, the reaction took a completely different course. The major product did not arise from addition but from chlorination. The chlorinated product was identified as 3-chloro-2-methyl-1-propene (VI) by comparison of its ir spectrum and vpc behavior with those of an authentic sample. This product was accompanied by the formation of an equivalent amount of benzenesulfonamide.

$$(H_3C)_2C{=}CH_2 + C_6H_5SO_2NCl_2 \longrightarrow ClCH_2C(CH_3){=}CH_2 + C_6H_5SO_2NH_2 + C_6H_5SO_2NHC(CH_3)_2CH_2Cl$$

VI VII

Further, a small amount of another material was also isolated and has been assigned the structure of N-(2-methyl-3-chloropropyl-2)benzenesulfonamide

(10) V. M. Cherkasov, T. A. Dashevskaya, and L. I. Baranova, *Ukr. Khim. Zh.*, **32**, 861 (1966); *Chem. Abstr.*, **66**, 2155 (1967).

(VII). The assignment is based upon elemental analysis, the failure of VII to give a positive potassium iodide–starch test, and spectral data. In the nmr spectrum of VII, the signals for the *gem*-dimethyl and methylene groups occur as sharp singlets at 1.25 and 3.60 ppm, respectively. The N–H proton appears as a broad singlet at 5.61 while the aromatic hydrogens occur as a pair of multiplets centered near 7.61 and 8.00 ppm.

Addition to Conjugated Dienes.—In this phase of the study, butadiene and chloroprene were chosen as the conjugated diolefins for examination. In addition to the N,N-dichlorosulfonamide derivatives employed in the propylene case, a simple aliphatic sulfonamide, N,N-dichloromethylsulfonamide, was also examined.

In all of these cases the addition reactions proceeded spontaneously and exothermically to afford high yields of the corresponding 1:1 adducts (VIII). The predominant mode of addition in each case was 1,4 with a selectivity of >95%. The high selectivity for 1,4

$$CH_2{=}C(R')CH{=}CH_2 + RSO_2NCl_2 \longrightarrow RSO_2N(Cl)CH_2C(R'){=}CHCH_2Cl$$
VIII

R′ = H, Cl

addition is unusual since the addition of N,N-dichlorocarbamates to butadiene afforded significant amounts (15%) of 1,2 adducts.[9c]

The addition of N,N-dichlorobenzenesulfonamide to butadiene proceeded equally well in the dark. However, when the reaction was performed in the dark under an oxygen atmosphere, the adduct formation was inhibited.

The reduction of VIII with sodium sulfite solution proceeded smoothly to give the reduced sulfonamides (IX) in high yields.

$$\text{VIII} + Na_2SO_3 \longrightarrow RSO_2NHCH_2CH{=}CHCH_2Cl$$
IX

The structure of each of the adducts was established by nmr spectroscopy. The butadiene products (IX, R′ = H) are characterized by their nmr spectra which display proton signals (2 H apiece) for the methylene groups adjacent to chlorine and nitrogen (~4.0 ppm), respectively, and by the two-proton multiplet for the nearly equivalent olefin protons (~5.9 ppm). On reduction, the resonance position of the methylene group next to nitrogen moves upfield approximately 0.35 ppm and becomes more complicated owing to coupling with the amide proton. This coupling as well as the NH signal may be removed by treating the sample with deuterium oxide.

In the nmr spectra of the chloroprene adducts (VIII, R′ = Cl), the signal for the methylene group next to nitrogen is a broad singlet indicating the absence of an adjacent olefinic proton. The olefinic proton of the resultant internal olefin is a triplet near 6.10 ppm and is coupled to the adjacent methylene group which appears as a doublet at about 4.2 ppm. These assignments are confirmed by examining the nmr spectra of the reduction products (IX, R′ = Cl). The position of the methylene group adjacent to nitrogen moves upfield approximately 0.2 ppm and now appears as a doublet due to coupling with the amide proton. The amide proton appears as a triplet. Upon treatment with deuterium oxide this latter signal disappears, and the methylene doublet reverts to a singlet, while the multiplicity of the other signals remains unchanged. These data are consistent only with a 1,4 adduct.

Discussion

With simple olefins such as propylene and styrene, the addition of N,N-dichlorosulfonamides is predominantly anti-Markovnikov and consistent with a radical mechanism. The complete selectivity for anti-Markovnikov addition observed with styrene reflects the enhanced stability of the benzyl radical. The propylene adducts are predominantly anti-Markovnikov. The presence of some Markovnikov adduct may reflect the fact that the difference in stability of the two possible radicals is not so great that one is formed to the virtual exclusion of the other. Conversely it is possible that the Markovnikov adducts are being formed *via* a competing ionic mechanism.[11]

The propensity for isobutylene to undergo chlorination instead of addition with positive halogen compounds is well documented. Treatment of isobutylene with phenyl hypochlorite has been reported to yield[8] a large amount of chlorination product and a small percentage of adduct.

$$(CH_3)_2C{=}CH_2 + C_6H_5OCl \longrightarrow \text{VI} + C_6H_5OC(CH_3)_2CH_2Cl$$

The reaction of isobutylene with elemental chlorine has been shown to give an 87% yield of allylic chlorination product (VI) and a 13% yield of addition product.[12]

The formation of VII may arise by the interception of the chloronium ion (X) by benzenesulfonamide[13] and then subsequent proton loss as shown in Scheme I.

SCHEME I
REACTION OF ISOBUTYLENE WITH N,N-DICHLOROBENZENESULFONAMIDE

$$C_6H_5SO_2NCl_2 + (CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2C(Cl)^+{-}CH_2 + C_6H_5SO_2N^-Cl$$
X

$$X \longrightarrow \text{VI} + H^+$$

$$C_6H_5SO_2NHCl \rightleftharpoons C_6H_5SO_2NCl_2 + C_6H_5SO_2NH_2$$

$$X + C_6H_5SO_2NH_2 \longrightarrow \text{VII} + H^+$$

The data obtained, however, do not rule out the possibility of the formation of VII by reaction of X with the N-chlorobenzenesulfonamide anion to give

(11) The reaction of propylene with N,N-dichlorobenzenesulfonamide has been examined both in the dark and in the dark under an oxygen atmosphere. The nmr spectra of the crude reaction mixture in both cases are identical and are significantly different from the spectrum of the crude product obtained in this study. In both of these cases the ratio of the C–CH_3 groups for anti-Markovnikov (1.60 ppm) and Markovnikov addition products (1.09 ppm) is about 1:1; in addition, the presence of other C–CH_3 groups is also noted. The structure of these other materials has not as yet been firmly established. In any event it is apparent that the course of the reaction changes drastically when performed under nonradical conditions.

The ionic addition of N,N-dichlorobenzenesulfonamide to olefins will be reported separately.

(12) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2172 (1965).

(13) The disproportionation two molecules of N-chlorobenzenesulfonamide into N,N-dichlorobenzenesulfonamide and benzenesulfonamide has been discussed by T. Higuchi, K. Ikeda, and A. Hussain, *J. Chem. Soc., B*, 546, 549 (1967).

XI and subsequent reaction of XI with isobutylene to give VII and VIII.[14]

$$X + C_6H_5SO_2^-NCl \longrightarrow C_6H_5SO_2N(Cl)C(CH_3)_2CH_2Cl$$

$$XI + (CH_3)_2C{=}CH_2 \longrightarrow VI \text{ and } VII$$

The data obtained for the addition of N,N-dichlorosulfonamides to conjugated dienes indicate that the reaction is occurring by a radical chain mechanism. The preference for 1,4 over 1,2 addition has been observed in the reaction of N,N-dichlorocarbamates,[2c] protonated N-chlorodialkylamines,[15] and chlorine[16] with conjugated dienes. In all of these cases a radical chain mechanism has been proposed for the addition reaction. Further support for the radical mechanism is the inhibition of the reaction by oxygen.

Since radical initiations are not required for the addition to occur, the generation of the radicals may be occurring *via* a process of "spontaneous" initiation.[9c,16,17] The reaction exhibits all of the characteristics which have been observed in other "spontaneously" initiated reactions, *i.e.*, lack of initiators, mild reaction conditions, and spontaneous reaction.

Experimental Section

Nuclear magnetic resonance spectra were run on a Varian A-60 spectrometer as *ca.* 50% solutions in deuteriochloroform with tetramethylsilane as an internal standard unless otherwise noted.

Infrared spectra were recorded on a Beckman Model IR-10 infrared spectrophotomer.

Melting points were obtained using a Mel-Temp melting point apparatus and are uncorrected.

Unsaturates.—The propylene used was Research Grade obtained from the Phillips Petroleum Co. The isobutylene and butadiene were CP grade (99%) obtained from the Matheson Co. The styrene was obtained from Matheson Coleman and Bell and was distilled prior to use. The chloroprene was obtained as a 50% solution in xylene from the E. I. du Pont de Nemours and Co., Inc., Elastomer Chemicals Department, Wilmington, Del. It was separated from the xylene by fractional distillation and then used immediately.

N,N-Dichlorosulfonamides.—N,N-Dichlorobenzenesulfonamide was obtained from Matheson Coleman and Bell. Before each run the appropriate amount of reagent was dissolved in methylene chloride and filtered through a bed of Filter Aid to remove dirt and other suspended particles. The clear filtrate was then used without further purification. The N,N-dichloroamide derivatives of methyl-[18] and *p*-chlorobenzenesulfonamide[19] and N,N-dimethylsulfamide[10] were prepared according to literature procedures.

General Procedure for the Addition of N,N-Dichlorosulfonamides to Unsaturates. Propylene.—Propylene (0.3 mol) was condensed at −78° into a Pyrex pressure tube fitted with a Teflon needle valve containing a solution of 0.1 mol of N,N-dichlorosulfonamide in 100 ml of methylene chloride. The needle valve was closed and the tube warmed to 0° and maintained at that temperature for 3 hr. The excess propylene was vented, and the solvent was removed at aspirator pressure at ambient temperature. The residue was then examined for isomer content by nmr spectroscopy. Recrystallization afforded the following anti-Markovnikov adducts: $C_6H_5SO_2N(Cl)CH_2CH(Cl)CH_3$ (cyclohexane), 53%, mp 69–70°. *Anal.* Calcd for $C_9H_{11}Cl_2NO_2S$: C, 40.32; H, 4.13; N, 5.22; S, 11.96. Found: C, 40.00; H, 4.40; N, 5.45; S, 12.47. *p*-$ClC_6H_4SO_2N(Cl)CH_2CH(Cl)CH_3$ (carbon tetrachloride), 54%, mp 90–92°. *Anal.* Calcd for $C_9H_{10}Cl_3NO_2S$: C, 35.72; H, 3.33; N, 4.63; S, 10.60. Found: C, 35.66; H, 3.47; N, 4.78; S, 10.87. The N,N-dimethylsulfamide adduct, $(CH_3)_2NSO_2N(Cl)CH_2CH(Cl)CH_3$, existed as an oil at room temperature. *Anal.* Calcd for $C_5H_{12}Cl_2N_2O_2S$: C, 25.53; H, 5.14; N, 11.91; S, 13.64. Found: C, 25.53; H, 5.30; N, 11.91; S, 13.59.

Styrene (0.1 mol) was added dropwise to a stirred solution of N,N-dichlorosulfonamide (0.1 mol) in 100 ml of methylene chloride cooled to 0° in an ice–water bath. After addition was complete the solution was warmed to room temperature, and then the solvent was evaporated at aspirator pressure at ambient temperature. Recrystallization gave the following adducts: $C_6H_5SO_2N(Cl)CH_2CH(Cl)C_6H_5$, 91%, mp 69–70°. *Anal.* Calcd for $C_{14}H_{13}Cl_2NO_2S$: C, 50.92; H, 3.97; N, 4.24; S, 9.71. Found: C, 50.62; H, 4.07; N, 4.12; S, 9.80. $(CH_3)_2NSO_2N(Cl)CH_2CH(Cl)C_6H_5$, 88%, mp 63–65°. *Anal.* Calcd for $C_{10}H_{14}Cl_2N_2O_2S$: C, 40.40; H, 4.75; N, 9.42; S, 10.79. Found: C, 40.46; H, 4.99; N, 9.52; S, 10.82.

Isobutylene (0.2 mol) was slowly distilled with nitrogen dilution into a stirred solution of N,N-dichlorobenzenesulfonamide (0.1 mol) in 100 ml of methylene chloride cooled to −15°. During addition benzenesulfonamide crystallized out of solution. After addition was complete the reaction mixture was warmed to room temperature and then filtered to give 4.5 g of benzenesulfonamide, mp 149–151°. The filtrate was evaporated at reduced pressure, and the volatiles were collected in a Dry Ice–acetone trap. The residue was triturated with carbon tetrachloride to give 4.2 g of crude benzenesulfonamide, mp 140–148°.

The volatiles were distilled at atmospheric pressure to give, in addition to methylene chloride, 3.6 g of 3-chloro-2-methyl-1-propene, bp 67–70°, $n^{25}D$ 1.4245. This material was identified by comparison of its glpc retention time and ir spectrum with those of an authentic sample.

The carbon tetrachloride solution was concentrated to a small volume and then taken to the cloud point with pentane. The crude solid which crystallized was recrystallized from carbon tetrachloride–cyclohexane to give 3.0 g, 10%, of N-(2-methyl-3-chloropropyl-2)benzenesulfonamide, mp 68–69°. *Anal.* Calcd for $C_{10}H_{14}ClNO_2S$: C, 48.47; H, 5.69; N, 5.68. Found: C, 48.94; H, 5.89; N, 5.51.

Butadiene (0.1 mol) was condensed into a Pyrex pressure tube fitted with a Teflon needle valve. The tube was then connected by way of a T-joint to a nitrogen source. The butadiene container was opened and distilled with nitrogen dilution into a stirred solution of N,N-dichlorosulfonamide (0.1 mol) in 100 ml of methylene chloride cooled to −10°. The addition rate was such that the internal temperature remained between 0 and 5°. After addition was complete the solution was warmed to room temperature, and the solvent was removed at aspirator pressure at ambient temperature. The adducts were generally recrystallized from carbon tetrachloride, chloroform, or a benzene–pentane mixture. The following adducts were prepared: $C_6H_5SO_2N(Cl)CH_2CH{=}CHCH_2Cl$, 77%, mp 53–55°. *Anal.* Calcd for $C_{10}H_{11}Cl_2NO_2S$: C, 42.87; H, 3.96; N, 5.00; S, 11.44. Found: C, 43.01; H, 3.92; N, 5.13; S, 11.47. *p*-$ClC_6H_4SO_2N(Cl)CH_2CH{=}CHCH_2Cl$, 85%, mp 126–127°. *Anal.* Calcd for $C_{10}H_{10}Cl_3NO_2S$: C, 38.17; H, 3.20; N, 4.45; S, 10.20. Found: C, 38.16; H, 3.26; N, 4.61; S, 10.18. $CH_3SO_2N(Cl)CH_2CH{=}CHCH_2Cl$, 85%, mp 48–51°. *Anal.* Calcd for $C_5H_9Cl_2NO_2S$: C, 27.53; H, 4.16; N, 6.42; S, 14.70. Found: C, 27.74; H, 4.05; N, 6.46; S, 14.73.

Chloroprene.—A solution of N,N-dichlorosulfonamide (0.1 mol) in 75 ml of methylene chloride was added dropwise to a stirred solution of freshly distilled chloroprene (0.1 mol) in 25 ml of methylene chloride cooled to −10°. After addition was complete the reaction was processed as above to isolate the addition products. The following adducts were prepared: $C_6H_5SO_2N(Cl)CH_2C(Cl){=}CHCH_2Cl$, 82%, mp 49–50°. *Anal.* Calcd for $C_{10}H_{10}Cl_3NO_2S$: C, 38.17; H, 3.20; N, 4.45; S, 10.20. Found: C, 38.46; H, 3.43; N, 5.28; S, 10.61. *p*-$ClC_6H_4SO_2N(Cl)CH_2C(Cl){=}CHCH_2Cl$, 85%, mp 87–88°. *Anal.* Calcd for $C_{10}H_9Cl_4NO_2S$: C, 34.40; H, 2.60; N, 4.01; S, 9.18. Found: C, 34.89; H, 2.56; N, 4.09; S, 9.17. $CH_3SO_2N(Cl)CH_2C(Cl){=}CHCH_2Cl$, 89%, mp 72–73°. *Anal.* Calcd for $C_5H_8Cl_3NO_2S$: C, 23.78; H, 3.19; N, 5.55; S, 12.70. Found: C, 24.28; H, 3.30; N, 5.61; S, 12.80. $(CH_3)_2NSO_2N(Cl)CH_2C(Cl){=}CHCH_2Cl$, 84%, mp 38–40°. *Anal.* Calcd for C_6H_{11}-

(14) W. Thielacker, *Angew. Chem.*, **79**, 63 (1967).

(15) R. S. Neale and R. L. Hinman, *J. Amer. Chem. Soc.*, **85**, 2666 (1963).

(16) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1965), and references cited therein.

(17) C. Walling, L. Heaton, and D. D. Tanner, *J. Amer. Chem. Soc.*, **87**, 1715 (1965). There is a strong possibility that the addition to styrene also proceeds *via* a "spontaneous" initiation process although this has still to be demonstrated experimentally.

(18) A. C. Newcombe, *Can. J. Chem.*, **33**, 1250 (1955).

(19) R. R. Baxter and F. D. Chattaway, *J. Chem. Soc.*, **107**, 1814 (1915).

$Cl_3N_2O_2S$: C, 25.59; H, 3.94; N, 9.95; S, 11.39. Found: C, 25.64; H, 3.91; N, 10.65; S, 11.39.

General Procedure for the Reduction of the N,N-Dichlorosulfonamide–Unsaturate Adducts.—A solution of 0.1 mol of adduct in 100 ml of methylene chloride was vigorously stirred at ambient temperature with a solution of 0.3 mol of sodium sulfite in 150 ml of water for about 0.5 hr, or until the organic layer failed to give a positive test with potassium iodide–starch paper. The layers were then separated; the aqueous layer was extracted with methylene chloride. The organic extracts were combined and dried over sodium sulfate. The solvent was evaporated at aspirator pressure and ambient temperature to give the reduced sulfonamide. These materials were recrystallized from one or more of the following solvents or solvent pairs: benzene, carbon tetrachloride, cyclohexane, ether, and benzene–pentane. The following sulfonamides were prepared: $C_6H_5SO_2NHCH_2CH(Cl)CH_3$, 89%, mp 79–80°. *Anal.* Calcd for $C_9H_{12}ClNO_2S$: C, 46.25; H, 5.55; N, 6.00; S, 13.72. Found: C, 46.50; H, 5.55; N, 6.43; S, 13.55. p-$ClC_6H_4SO_2NHCH_2CH(Cl)CH_3$, 87%, mp 105–108°. *Anal.* Calcd for $C_9H_{11}Cl_2NO_2S$: C, 40.32; H, 4.13; N, 5.22; S, 11.96. Found: C, 40.09; H, 4.40; N, 5.26; S, 12.24. $(CH_3)_2NSO_2NHCH_2CH(Cl)CH_3$, 84%, mp 25–26°. *Anal.* Calcd for $C_5H_{13}ClN_2O_2S$: C, 29.92; H, 6.53; N, 13.95; S, 15.98. Found: C, 30.09; H, 6.69; N, 14.06; S, 15.97. $C_6H_5SO_2NHCH_2CH(Cl)C_6H_5$, 95%, mp 45–47°. *Anal.* Calcd for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.73; S, 10.84. Found: C, 56.31; H, 4.97; N, 4.61; S, 10.54. $(CH_3)_2NSO_2NHCH_2CH(Cl)C_6H_5$, 92%, mp 69–70°. *Anal.* Calcd for $C_{10}H_{15}ClN_2O_2S$: C, 45.71; H, 5.75; N, 10.66; S, 12.20. Found: C, 45.71; H, 5.83; N, 10.53; S, 12.21. $C_6H_5SO_2NHCH_2CH{=}CHCH_2Cl$, 85%, oil. *Anal.* Calcd for $C_{10}H_{12}ClNO_2S$: C, 48.88; H, 4.92; N, 5.70; S, 13.05. Found: C, 49.10; H, 4.96; N, 5.71; S, 13.38. p-$ClC_6H_4SO_2NHCH_2CH{=}CHCH_2Cl$, 78%, mp 78–79°. *Anal.* Calcd for $C_{10}H_{11}Cl_2NO_2S$: C, 42.87; H, 3.96; N, 5.00; S, 11.44. Found: C, 42.71; H, 3.88; N, 4.98; S, 11.23. $CH_3SO_2NHCH_2CH{=}CHCH_2Cl$, 87%, mp 26–27°. *Anal.* Calcd for $C_5H_{10}ClNO_2S$: C, 32.69; H, 5.49; N, 7.63; S, 17.46. Found: C, 32.51; H, 5.60; N, 7.47; S, 17.96. $C_6H_5SO_2NHCH_2C(Cl){=}CHCH_2Cl$, 81%, mp 83–84°. *Anal.* Calcd for $C_{10}H_{11}Cl_2NO_2S$: C, 42.87; H, 3.96; N, 5.00; S, 11.44. Found: C, 42.96; H, 3.93; N, 5.02; S, 11.50. p-$ClC_6H_4SO_2NHCH_2C(Cl){=}CHCH_2Cl$, 78%, mp 78–80°. *Anal.* Calcd for $C_{10}H_{10}Cl_3NO_2S$: C, 38.17; H, 3.20; N, 4.45; S, 10.19. Found: C, 37.99; H, 3.05; N, 4.47; S, 10.20. $CH_3SO_2NHCH_2C(Cl){=}CHCH_2Cl$, 84%, mp 157–158°. *Anal.* Calcd for $C_5H_9Cl_2NO_2S$: C, 27.53; H, 4.16; N, 6.42; S, 14.70. Found: C, 27.49; H, 4.33; N, 6.47; S, 14.65. $(CH_3)_2NSO_2NHCH_2C(Cl){=}CHCH_2Cl$, 84%, mp 25–26°. *Anal.* Calcd for $C_6H_{12}Cl_2N_2O_2S$: C, 29.16; H, 4.99; N, 11.34; S, 12.97. Found: C, 29.65; H, 4.90; N, 11.24; S, 13.03.

Registry No.—Tropylene, 115-07-1; styrene, 100-42-5; butadiene, 106-99-0; chloroprene, 126-99-8; isobutylene, 115-11-7; 3-chloro-2-methyl-1-propene, 563-47-3; VII, 2948-79-0; N,N-dichlorobenzenesulfonamide, 473-29-0; N,N-dichloromethylsulfonamide, 17396-47-3; N,N-dichloro-p-chlorobenzenesulfonamide, 17260-65-0; N,N-dichloro-N,N-dimethylsulfamide, 13882-13-8.

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Sulfilimines and Sulfoximines Derived from 4-*t*-Butylthiane[1,2a]

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The stereochemical course of the reactions of Chloramine-T with 4-*t*-butylthiane and of N-sulfinyl-*p*-toluenesulfonamide, *p*-toluenesulfonyl isocyanate, and *p*-toluenesulfonyl azide with 4-*t*-butylthiane 1-oxides was examined. The stereochemistry of the N-tosylsulfilimine grouping was correlated with the known configurations of the sulfoxide group in the 4-*t*-butylthiane system by N alkylation of the sulfilimine, followed by hydrolysis of the adduct salt to sulfoxide. New compounds prepared in this series include the isomeric N-tosylsulfilimines, the "free" sulfoximines, and the N-tosylsulfoximines.

The potential asymmetry at the sulfur atom in sulfilimines and sulfoximines has been established by the resolution of appropriately substituted examples.[3] A number of methods are now available for the preparation of sulfilimines and sulfoximines. Those of interest to the present work are briefly described. The well-known reaction of sulfides with chloramines, especially Chloramine-T, has been used in a typical preparation of sulfilimines by Leandri and Spinelli.[4] Recently the reactions of sulfoxides with *p*-toluenesulfonyl isocyanate[5] and N-sulfinyl-*p*-toluenesulfonamide to produce[6] sulfilimines have been described. The latter reaction is reported to proceed with inversion of configuration at the sulfur atom.[7] The most direct method for the synthesis of sulfoximines would appear to be the oxidation of sulfilimines. It is noteworthy that, at the present time, only potassium permanganate and the salts of per acids are known to effect this oxidation and, then, in the large majority of cases, only in low yield.[7b,8] A general method for the production of sulfoximines is given by the reaction of sulfoxides with hydrazoic acid (sodium azide in a mixture of sulfuric acid and chloroform).[9] Horner and Christmann[10] have obtained N-benzoyldimethylsulfoximine from the reaction of dimethyl sulfoxide and benzoyl azide under the influence of light. Very recently Kwart and Khan[11] have prepared N-benzenesulfonyldimethylsulfoximine by the use of di-

(1) (a) Part XII in the Series Chemistry of Sulfoxides and Related Compounds. (b) Part XI: C. R. Johnson, J. J. Rigau, M. Haake, D. McCants, Jr., J. E. Keiser, and A. Geertsema, *Tetrahedron Lett.*, 3719 (1968). (c) Portions of this work were presented at the Second International Symposium on Organic Sulfur Chemistry, Groningen, The Netherlands, May 1966.

(2) (a) We gratefully acknowledge support of this work by The National Science Foundation (GP 5944). (b) Alfred P. Sloan Research Fellow, 1965–1968. (c) Supported by the Economic Development Administration, Commonwealth of Puerto Rico.

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(5) C. King, *J. Org. Chem.*, **25**, 352 (1960).

(6) G. Schulz and G. Kresze, *Angew. Chem. Intern. Ed. Engl.*, **2**, 736 (1963).

(7) (a) J. Day and D. J. Cram, *J. Amer. Chem. Soc.*, **87**, 4398 (1965). (b) Shortly after this article was submitted a communication appeared describing stereospecific interconversions of optically active sulfoxides, sulfilimines, and sulfoximines [D. R. Rayner, D. M. von Schriltz, and D. J. Cram, *ibid.*, **90**, 2721 (1968)].

(8) H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 2081 (1950).

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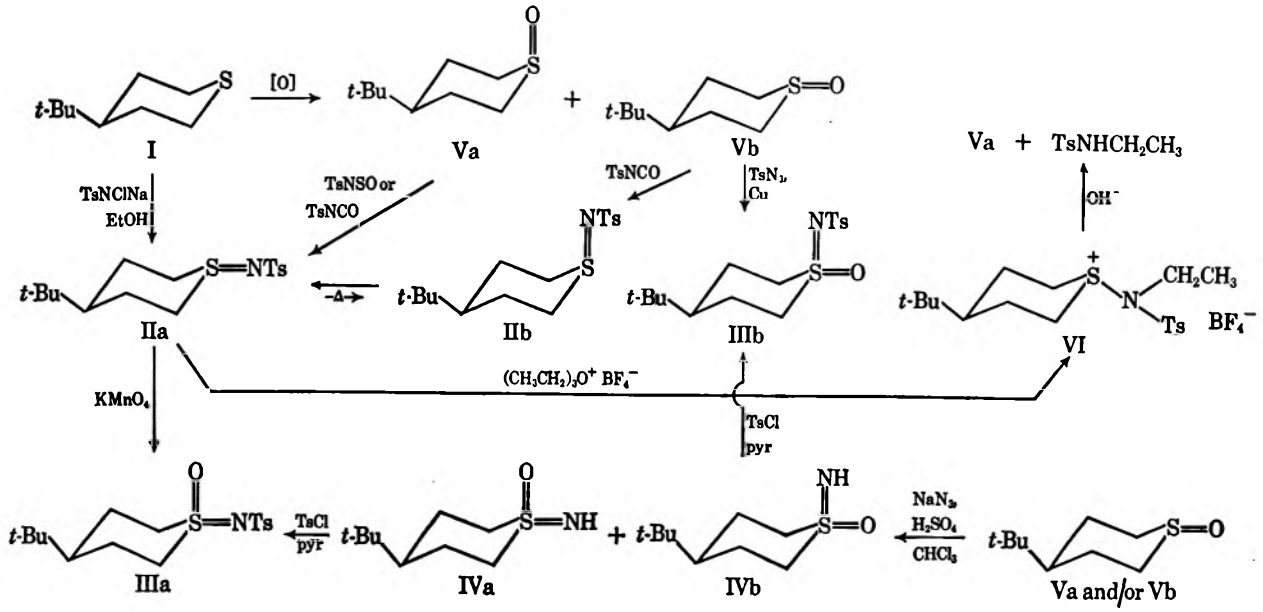
SCHEME I



methyl sulfoxide as a trap for the nitrene produced by the copper-catalyzed decomposition of benzenesulfonyl azide. In this paper we report our findings concerning the stereochemical course of certain of these reactions[12] in the 4-*t*-butylthiane system. Our results are summarized in Scheme I.

Reaction of 4-*t*-butylthiane (I) with Chloramine-T in ethanol afforded, in 95% yield, an N-*p*-toluenesulfonyl- (or N-tosyl-) sulfilimine. The *trans* structure IIa was assigned to this material based on the three lines of evidence detailed below.

(1) Alkylation[1b] of the sulfilimine with triethyloxonium fluoroborate gave, in excellent yield, the N-ethyl salt (VI). Hydrolysis of the salt with aqueous base gave the sulfoxide Va[13] and N-ethyl-*p*-toluenesulfonamide. Based on analogy with the hydrolysis of alkoxysulfonium salts[13] it can be safely suggested that this hydrolysis occurred with inversion of configuration at the sulfur atom.

(2) Oxidation of the sulfilimine with potassium permanganate gave a single sulfoximine (IIIa) which was isomeric with that (IIIb) obtained upon treatment of *cis*-4-*t*-butylthiane 1-oxide (Vb) with *p*-toluenesulfonyl azide in the presence of Raney copper. This reaction proceeded in poor yield (10%), the major material obtained being starting sulfoxide of *unaltered* configuration (Vb).

(3) The identical sulfilimine was obtained by reaction of sulfoxide Va with *p*-toluenesulfonyl isocyanate or N-sulfinyl-*p*-toluenesulfonamide. The latter reaction, which we examined in both benzene and pyridine as solvents, has been shown by Day and Cram,[14] in the case of an optically active sulfoxide, to proceed with inversion of configuration. Since the present system is relatively strain free and uncluttered, it is reasonable to assume inversion to occur here also.

Treatment of the *trans*-4-*t*-butylthiane 1-oxide (Vb) with N-sulfinyl-*p*-toluenesulfonamide in benzene afforded a single sulfilimine (IIb),[15] mp 150–151.5°, which was isomeric with that (IIa) previously obtained (mp 187–188°). After standing for 2 days at room temperature the melting point of IIb had changed to 173–175°. After recrystallization, this material had a melting point and a mixture melting point identical with those of IIa. It thus appears that the axial sulfilimine is unstable with respect to isomerization to the equatorial sulfilimine. It should be noted that insufficient difference was found in the infrared (ir) spectra of the isomers IIa and IIb to render the spectra useful for identification of the individual isomers. Qualitative ultraviolet (uv) spectroscopy revealed a relatively strong band at 228 mμ in 95% ethanol or cyclohexane for compound IIa and a corresponding absorption at 229 (95% ethanol) and 230 mμ (cyclohexane) for compound IIb.

A mixture of the isomeric "free" sulfoximines was obtained by reaction of sulfoxides Va and Vb with sodium azide and sulfuric acid in chloroform. From a 50:50 mixture of the isomeric sulfoxides Va and Vb a 53% yield of a mixture of sulfoximines consisting of 63% IVa and 37% IVb was obtained. The unreacted sulfoxide was recovered and found to consist of an equilibrium mixture of isomers Va (95%) and Vb (5%). Apparently, equilibration of the sulfoxides

(12) The stereochemical relationships of some sulfoxides, sulfilimines, and sulfoximines derived from optically active methyl-*p*-tolyl sulfoxide and the *p*-chlorophenylthiane 1-oxides have been examined by M. A. Sabol, R. W. Davenport, K. K. Andersen, *Tetrahedron Lett.*, 2159 (1968). We thank these authors for informing us of their results prior to publication.

(13) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109, 5404 (1965).

(14) Day and Cram (ref 7a) have suggested "a mechanism involving a trigonal–bipyramidal intermediate or transition state in which the entering and leaving groups occupy radial positions . . ." In the formulation of the intermediate of transition state two molecules of N-sulfinylsulfonamide were implicated. Their preliminary results, indeed, suggested that the reaction is second order in N-sulfinyl-*p*-toluenesulfonamide. However, their reaction was conducted in pyridine which catalyzes the dimerization of N-sulfinylsulfonamides: W. Wucherpfenning and G. Kresge, *Tetrahedron Lett.*, 1671 (1966).

$$RSO_2N{=}SO \xrightarrow{\text{pyridine}} RSO_2N{=}S{=}NSOR + SO_2$$

(15) A referee has suggested the possibility that the compound reported as IIb is, in actual fact, a crystalline modification of IIa. This possibility can not be entirely ruled out because of the strong similarity in the ir and uv spectra, as well as the mobility on tlc of the two materials. The two substances, however, were obtained under identical chromatographic conditions, and it would not appear likely that two different crystalline modifications would form.

TABLE I
NMR RESULTS OF SULFOXIMINE ISOMERS IVa AND IVb AT 60 MHz

Compound	Solvent	Concentration, mg/ml	N–H resonance, δ
IVa	$CDCl_3$	300	2.83
	$CDCl_3$	150	2.71
	DMSO-d_6	100	3.43
IVb	$CDCl_3$	300	2.42
	$CDCl_3$	150	2.33
	DMSO-d_6	100	3.27

under the reaction conditions occurs faster than sulfoximine production; the ratio of isomeric sulfoximines is almost independent of the isomeric composition of the starting sulfoxides. As expected, it was found that the sulfoximines, once formed, show no isomerization or decomposition when resubjected to the reaction conditions. The free sulfoximines were separated on silica gel thin layer plates developed with isopropyl alcohol, isomer IVb showing the lower R_f value. The isomers IVa and IVb were converted into the previously prepared N-tolylsulfoximines (IIIa and IIIb) on reaction with *p*-toluenesulfonyl chloride in pyridine.

An ir study of the "free" sulfoximines IVa and IVb in methylene chloride revealed an N–H band at 3328 cm^{-1}. In the nmr spectra the N–H resonance was found to be sensitive to structure and concentration (Table I).

The reaction of sulfonyl azides with 4-*t*-butylthiane and its 1-oxides under photolytic conditions gave complex reaction mixtures. The instability of the products of interest under these conditions make this approach unsuccessful. No sulfoximines or sulfilimines were isolated from these reactions.

Experimental Section

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Separation and purification of all substances were accomplished or monitored by thin layer or gas phase chromatography. Melting points were determind by the open capillary method and are uncorrected. Spectra were obtained on a Perkin-Elmer Model 621 ir spectrophotometer, a Cary-14 uv spectrophotometer, and a Varian A-60A nmr spectrometer.

The preparation of 4-*t*-butylthiane has been previously reported. The *cis*- and *trans*-4-*t*-butylthiane 1-oxides were prepared by the *t*-butyl hypochlorite oxidation method and by hydrolysis of the corresponding alkoxysulfonium salts. Synthesis of *p*-toluenesulfonyl azide was accomplished by a variation of the literature procedure.[16] N-Sulfinyl-*p*-toluenesulfonamide was prepared according to Kresze and Maschke.[17] Raney copper (Raney Catalyst Co., Inc.) and *p*-toluenesulfonyl isocyanate (The Upjohn Co., Carwin Organic Chemicals) are commercially available.

Reaction of 4-*t*-Butylthiane with Chloramine-T.—The reaction was carried out according to the general procedure of Leandri and Spinelli.[4] The product was isolated by elution from a silica gel column with chloroform, followed by ethyl acetate. The latter fraction contained the pure *trans*-**N-*p*-toluenesulfilimine** (IIa): 95%; mp 187–188°; $\nu_{CH_2Cl_2}$ 963 and 980 cm^{-1} (S=N).

Anal. Calcd for $C_{16}H_{25}NO_2S_2$: C, 58.71; H, 7.64. Found: C, 58.58; H, 7.58.

Reactions of 4-*t*-Butylthiane 1-Oxides with N-Sulfinyl-*p*-toluenesulfonamide and *p*-Toluenesulfonyl Isocyanate. A.—To 0.174 g of pure *trans*-4-*t*-butylthiane 1-oxide (Vb) dissolved in 2 ml of dry benzene was slowly added 0.235 g of the *p*-toluene-N-sulfinylsulfonamide in 2 ml of benzene. The solution was stirred at 0° for 15 min and then at room temperature overnight. The products were separated by column chromatography (silica gel–ethyl acetate). An intermediate fraction was isolated containing 27 mg (8%) of the corresponding **sulfilimine** (IIb), mp 150–151.5°, uncrystallized, which gave a single spot on tlc. Remaining fractions consisted of *p*-toluenesulfonamide and unreacted sulfoxide.

Anal. Calcd for $C_{16}H_{25}NO_2S_2$: C, 58.71; H, 7.64. Found: C, 58.44; H, 7.60.

B.—A parallel reaction with the *cis*-sulfoxide (Va) gave 6% of the corresponding sulfilimine IIa, mp 178–180°, uncrystallized. When the reaction mixture was refluxed for 10 hr, the yield increased to 8%.

C.—A reaction employing 1.00 g of *p*-toluenesulfonyl isocyanate and 0.68 g of Va in 15 ml of dry pyridine was stirred for 12 hr at room temperature. The elimination of the pyridine was partially effected by azeotropic distillation with toluene before resolving the mixture by column chromatography. Sulfilimine IIa was obtained in 13% yield.

Alkylation of Sulfilimine IIa with Triethyloxonium Fluoroborate and Hydrolysis of the Resulting Salt.—Pure *trans*-sulfilimine IIa (0.326 g, 1 mmol) was added to a solution of triethyloxonium fluoroborate (0.190 g, 1 mmol) in 10 ml of methylene chloride. The reaction was maintained at room temperature for 3 hr. The solution was filtered and anhydrous ethyl ether was added until precipitation was complete. The oily precipitate was washed with ether. Recrystallization from methylene chloride–ether afforded the pure **salt VI**: 75%; mp 175–176°; $\nu_{CH_2Cl_2}$ 811, 862, and 873 cm^{-1} (S—N).

Anal. Calcd for $C_{18}H_{30}BF_4NO_2S_2$: C, 46.50; H, 6.79. Found: C, 46.28; H, 6.43.

Hydrolysis of the pure adduct VI was effected by dissolution in water and adding 0.1 *N* sodium hydroxide to a phenolphthalein end point. The reaction mixture was extracted with methylene chloride, and the solvent was evaporated. Analysis of the reaction mixture by gas chromatography and preparative tlc (alumina–ethyl ether) revealed an almost quantitative yield of *cis*-4-*t*-butylthiane 1-oxide (Va), N-ethyl-*p*-toluenesulfonamide, and trace amounts of the parent sulfilimine IIa.

Reaction of 4-*t*-Butylthiane 1-Oxides with Hydrazoic Acid.—To 2.0 g of a 50:50 mixture of *cis*- and *trans*-sulfoxides Va and Vb in 8 ml of chloroform was added 2.73 g of sodium azide and then 3 ml of concentrated sulfuric acid. The reaction was heated at 48–55° for 60 hr. The reaction mixture was poured into a separatory funnel; water was added; and the chloroform layer was separated. The aqueous layer was again extracted with chloroform. Both the aqueous and organic layers were retained. The combined chloroform extracts were dried over sodium sulfate. Evaporation yielded 1.005 g of unreacted sulfoxides (95:5 ratio, *cis*–*trans*). Sodium hydroxide solution was added to the aqueous phase until slightly basic. The solution was extracted several times with chloroform. The combined chloroform extracts were dried over sodium sulfate. Evaporation of the chloroform provided 1.174 g of a mixture of the isomeric free sulfoximines IVa and IVb. Column chromatogaphy on silica gel with ethyl acetate followed by isopropyl alcohol gave a 1.6:1 ratio of **sulfoximine IVa**, mp 179.5–180.5°, to **sulfoximine IVb**, mp 157–157.5°. Neither isomer appears to be hygroscopic; both can be sublimed (65° at 0.1 mm) or recrystallized from ethyl acetate–hexane.

Anal. Calcd for $C_9H_{19}NOS$: C, 57.10; H, 10.12. Found (IVa): C, 56.84; H, 10.07. Found (IVb): C, 57.09; H, 10.07.

No equilibration or decomposition of the sulfoximines was found after refluxing with sodium azide–sulfuric acid–chloroform mixture at 60° for 36 hr.

Oxidation of *trans*-Sulfilimine IIa with Basic Permanganate.—To 500 ml of distilled water was added 0.46 g of potassium permanganate, 10 ml of sodium hydroxide (3%), and 0.76 g of sulfilimine IIa. The heterogeneous reaction was stirred under reflux for 2 hr. Sodium sulfite was added to destroy any remaining permanganate, and the mixture was filtered. The residue was washed with methylene chloride, and the combined filtrates were extracted with methylene chloride. The combined methylene chloride extracts were dried over sodium sulfate and evaporated. The product mixture was fractionated by chromatographic elution on silica gel with ethyl acetate. The **N-tosylsulfoximine IIIa** was recrystallized from ethyl acetate–cyclohexane: 13%; mp 167–167.5°. Unreacted sulfilimine (67%) and some *p*-toluenesulfonamide were also recovered.

(16) O. C. Dermer and M. T. Edmison, *J. Amer. Chem. Soc.*, **77**, 70 (1955); W. Lwowski and E. Scheiffele, *ibid.*, **87**, 4359 (1965).

(17) G. Kresze and A. Maschke, German Patent 1,117,566 (1961); *Chem. Abstr.*, **57**, 11110e (1962).

Anal. Calcd for $C_{16}H_{25}NO_3S_2$: C, 55.99; H, 7.34; S, 18.97. Found: C, 56.39; H, 7.47; S, 18.70.

Conversion of Sulfoximines IVa and IVb into N-*p*-Toluenesulfonyl Derivatives IIIa and IIIb.—To 3 ml of dry pyridine, 0.1 g of *p*-toluenesulfonyl chloride and 50 mg of free sulfoximine IVa were added; the mixture was stirred at room temperature for 12 hr. The mixture was poured into water and extracted with chloroform; the solvent was evaporated; and the pyridine was removed by azeotropic distillation with toluene. Column chromatography (silica gel–chloroform, then ethyl acetate) provided 92 mg (96%) of the **N-tosylsulfilimine IIIa**, identical in all respects with that obtained above by oxidation.

An analogous reaction with the free sulfoximine IVb gave the **N-tosylsulfilimine IIIb**: 95%; mp 172.5–173.5° (benzene–cyclohexane).

Anal. Calcd for $C_{16}H_{25}NO_3S_2$: C, 55.99; H, 7.34; S, 18.97. Found: C, 56.24; H, 7.37; S, 18.76.

Reaction of *trans*-4-*t*-Butylthiane 1-Oxide with *p*-Toluenesulfonyl Azide.—Following the method of Kwart and Khan, *trans*-sulfoxide Vb (80 mg), *p*-toluenesulfonyl azide (90 mg), and Raney copper (10 mg) in 5 ml of methanol were refluxed for 15 hr. Chromatography of the reaction product revealed unreacted starting sulfoxide and an N-tosylsulfoximine identical in all respects with IIIb obtained above.

Registry No.—I, 768-30-9; IIa, 17604-09-0; IIb, 17659-00-6; IIIa, 17604-10-3; IIIb, 17659-01-7; IVa, 17604-11-4; IVb, 17604-12-5; VI, 17604-13-6.

A Study of Aliphatic Sulfonyl Compounds. IX. Polar Effects in Ethylene- and 2-Propene-1-sulfonyl Chlorides[1a]

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Rates of ethanolysis of ethylenesulfonyl and 2-propene-1-sulfonyl chloride were found to be significantly faster and only slightly faster, respectively, than that of a saturated sulfonyl chloride. Although infrared and mass spectra suggest that in the case of the former there may be some allylic participation by the α double bond to give the resonance stabilized sulfonylium ion intermediate, enhancement of ethanolysis is not that great and probably is largely polar in origin. There is no evidence in the latter case for homoallylic enhancement to form the conjugated unsaturated sulfonylium ion, and the small increase in rate of ethanolysis probably is entirely due to a polar effect. From the activated state parameters of $\Delta H^* = 15.4$ and 17.7 kcal and $\Delta S^* = -7.5$ and -5.9 eu for ethanolysis of ethylenesulfonyl chloride and 2-propene-1-sulfonyl chloride, respectively, it is clear that the lower enthalpy of activation is responsible for the faster rate of ethanolysis. Alkylation of ethanolic hydrogen chloride with ethyl ethylenesulfonate is somewhat faster than with ethyl 2-propene-1-sulfonate, the former reacting at substantially the same rate as the ethyl ester of a saturated sulfonic acid. There was no spectral evidence for participation of either double bond in the case of these esters. From activated state parameters of $\Delta H^* = 21.0$ and 23.1 kcal and $\Delta S^* = +4.0$ and $+9.3$ eu, respectively, for ethyl ethylenesulfonate and 2-propene-1-sulfonate, it appears that the considerably greater increase in activation entropy in the case of the latter is more than offset by the increased enthalpy of activation. It was shown that a "polymeric vinylsulfonyl chloride" (obtained from ammonium ethylenesulfonate and phosphorus pentachloride) reported in the literature probably was only 2-chloroethanesulfonyl chloride with an impurity of ethyl ethylenesulfonate.

Previously[3-7] the steric requirements of several branched-chain sulfonyl compounds were compared by a study of the ethanolysis of saturated aliphatic sulfonyl chlorides and alkylation by the corresponding ethyl esters. However, all of the aliphatic compounds studied were saturated and were compared only with analogously branched primary alkyl halides as to steric effects; no important polar contributions could be correlated with those of alkyl halides. In other work, the polar effects of a carbonyl group in *dl*-10-camphorsulfonyl chloride[8] and of a chloro group in 3-chloro-1-propanesulfonyl chloride[9] upon ethanolysis (Table I) have been studied but these are rather special cases. Thus, in the case of the former, the halogen may be displaced by anchimeric assistance from the keto group or its hemiacetal, while in the latter the chain chlorine probably is too far removed to have a significant polar effect on sulfonyl reactivity.

TABLE I

RATES OF ETHANOLYSIS OF SELECTED SULFONYL CHLORIDES AT 84°

Sulfonyl chloride	10^3k, min^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, cal deg^{-1} mol^{-1}
Ethylene-[a]	880[a]	15.4	−7.5
dl-10-Camphor-[b]	171		
Benzene-[c]	145	16.1	−10.9
2-Propene-1-	102	17.7	−5.9
1-Octane-[d]	89		
3-Chloro-1-propane-[e]	70	8.2	−35.2
α-Toluene-[b]	63		
2,3-Dimethyl-1-butane-[f]	48		
2-Octane-[d]	14		

[a] Calculated for 84° (see Table III for experimentally determined values of k). [b] See ref 8. [c] See ref 7. [d] See ref 3. [e] See ref 9. [f] See ref 4.

In the present report the effect of unsaturation was studied in the ethanolysis of ethylene- and 2-propene-1-sulfonyl chlorides. The relative activity of the corresponding ethyl esters as alkylating agents also was investigated.

Results and Discussion

The previous studies[3-9] of the ethanolysis of aliphatic sulfonyl chlorides have led to the conclusion that substituents sterically affect alcoholysis in the same

(1) (a) From the Ph.D. Dissertation of J. Preston, University of Alabama, 1957. (b) Chemstrand Research Center, Inc., Durham, N. C.

(2) To whom inquiries should be addressed at the Department of Chemistry, The University of Mississippi, University, Miss. 38677.

(3) R. B. Scott, Jr., and R. E. Lutz, *J. Org. Chem.*, **19**, 830 (1954).

(4) R. B. Scott, Jr., and M. S. Heller, *ibid.*, **20**, 1159 (1955).

(5) R. B. Scott, Jr., and M. J. Gordon, *ibid.*, **21**, 385 (1956).

(6) R. B. Scott, Jr., and H. L. McLeod, *ibid.*, **21**, 388 (1956).

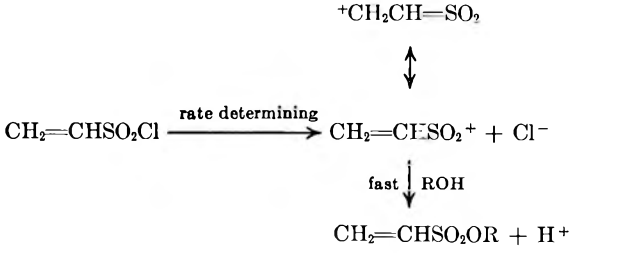
(7) R. B. Scott, Jr., and J. B. Gayle, *ibid.*, **21**, 391 (1956).

(8) J. B. Gayle, Dissertation, University of Alabama, 1953.

(9) M. J. Gordon, Dissertation, University of Alabama, 1960.

general way that they do aliphatic halides, the best analogy being drawn by considering the tetrahedral sulfo group as a pseudomethylene group, but about one-third larger.

An analogy between unsaturated sulfonyl chlorides and alkenyl chlorides also might be anticipated, *i.e.*, the analog for ethylenesulfonyl chloride being allyl chloride and for 2-propene-1-sulfonyl chloride, 4-chloro-1-butene (homoallyl chloride). Thus during solvolysis a resonance-stabilized sulfonylium ion might be expected.



Although formation of the ethylenesulfonylium ion on bombardment of the sulfonyl chloride in the mass spectrometer cannot be used to prove its existence in solution, this does provide evidence for the possibility. A large peak at *m/e* 91 in the mass spectrum[10] of ethylenesulfonyl chloride indicates fragmentation to form CH_2=CH—SO_2^+. Also, the infrared spectrum shows the double bond shifted to a slightly higher wavelength (6.20 μ) than for a normal double bond, which might be interpreted as contributing to the resonance stabilization of the sulfonylium ion, rather than simple resonance with the sulfonyl group.

However, ethylenesulfonyl chloride undergoes ethanolysis (Table I) only about ten times as fast as a saturated normal sulfonyl chloride, which is not nearly the enhancement expected[11] from appreciable resonance participation in the formation of a sulfonylium ion intermediate.

As the double bond of homoallyl halides does not participate in bimolecular displacement of their halogens, it would not be anticipated that the double bond of 2-propene-1-sulfonyl chloride would participate in a bimolecular displacement. In fact, even less evidence exists for a stabilized sulfonylium ion from this sulfonyl chloride than for one from ethylenesulfonyl chloride.[12] Thus no peak in the mass spectrum of 2-propene-1-sulfonyl chloride is noted at *m/e* 105 due to fragmentation to a sulfonylium ion, and the infrared spectrum shows no shift in the double-bond absorbance (6.09 μ). Upon ethanolysis (Table I), 2-propene-1-sulfonyl chloride reacts only about 10% faster than its saturated counterpart.

The faster rate of ethanolysis of ethylenesulfonyl chloride can be attributed to its lower enthalpy of activation ($\Delta H^* = 15.4$ kcal compared with 17.7 kcal for 2-propene-1-sulfonyl chloride) since the smaller activation entropy ($\Delta S^* = -7.5$ eu compared with -5.9 eu for 2-propene-1-sulfonyl chloride) indicates a more highly ordered activated state than is necessary for the larger molecule.

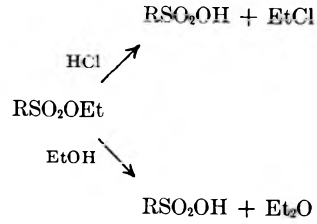
Probably the increased rates with which these unsaturated sulfonyl chlorides undergo ethanolysis simply reflect an inductive withdrawal effect of the unsaturation on the highly electronegative chlorosulfonyl group. The closer proximity of the double bond of ethylenesulfonyl chloride to the chlorosulfonyl group compared with the positions of the corresponding groups of 2-propene-1-sulfonyl chloride probably accounts for the approximately tenfold greater rate of reactivity of the former sulfonyl chloride over the latter.

Although it is perhaps an oversimplification to estimate the rate constants for ethylene- and 2-propenesulfonyl chlorides from other rate data by making some rough assumptions, it was nevertheless interesting that the estimated and determined rate constants were in good agreement.

The estimate of the rate constant for ethylenesulfonyl chloride at reflux was made by consideration of steric and polar effects. Thus as benzenesulfonyl chloride ($k = 0.14$ min^{-1}) reacts ten times as fast at 84° as 2-octanesulfonyl chloride ($k = 0.014$ min^{-1}), then ethylenesulfonyl chloride might be expected to react that much faster than an unbranched primary sulfonyl chloride ($k = 0.089$ min^{-1}). Thereby, the rate constant for ethylenesulfonyl chloride may be estimated to be 0.89 min^{-1}, assuming as a first approximation equivalence of the double bonds of the phenyl and vinyl groups. The experimental rate constant for this compound, calculated for 84° from data at lower temperatures by means of the Arrhenius equation, was 0.88 min^{-1}, agreeing very well with the estimated value and confirming the earlier prediction that this sulfonyl chloride would be quite reactive.

By a similar method an estimate of the rate constant for 2-propene-1-sulfonyl chloride was made. As a saturated sulfonyl chloride having an unbranched chain, such as 1-octanesulfonyl chloride ($k = 0.089$ min^{-1}), reacts 1.94 times as fast at 84° as one having a β-methyl group, such as 2,3-dimethylbutane-1-sulfonyl chloride[4] ($k = 0.48$ min^{-1}), it might be predicted that 2-propene-1-sulfonyl chloride will react 0.089/0.063 times as fast as α-toluenesulfonyl chloride ($k = 0.063$ min^{-1}), if it is assumed that the double bonds of allyl and tolyl groups have approximately equivalent effects. This estimated value of $k = 0.118$ min^{-1} agrees within experimental error with the observed rate constant of 0.102 min^{-1}.

Alkyl sulfonates are known to be good alkylating agents; *e.g.*, the ethyl esters are attacked by hydrogen chloride and ethanol to form free sulfonic acid and, respectively, ethyl chloride and ethyl ether. Solvolysis constitutes a minor part of the reaction when an excess of hydrogen chloride is present. Most previous solvolysis studies reported in the literature have focused



(10) The authors wish to express their appreciation to Dr. R. M. Guedin, Celanese Corp. of America, for mass spectral data.

(11) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 167, 168.

(12) It has been shown, however, that the double bond does participate in reactions with stronger bases than ethanol, this sulfonyl chloride and the isomeric 1-propene-1-sulfonyl chloride undergoing reaction with triethylamine to give the same products from ketene diethyl acetal, evidently *via* a common sulfene intermediate, CH_2=CH—CH=SO_2: W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 323 (1963).

on the alcohol moiety, except possibly in the study of aromatic substituent effects, the choice of sulfonic acid apparently being largely one of convenience. From the work of Scott and coworkers, it has become apparent that the sulfonic acid moiety also plays an important role where steric considerations are involved.[3-9]

In the present work, it is seen that unsaturation has little effect on the rates with which the ethyl esters of ethylene- and 2-propene-1-sulfonic acids alkylate refluxing ethanolic hydrogen chloride, the rates being slightly slower than that of an analogous saturated sulfonic acid ester, *e.g.*, ethyl 1-octanesulfonate (Table II). That there is no enhancement in the rate of alkylation of these esters is consistent with their mass spectra and infrared spectra. Unlike the corresponding sulfonyl chlorides, ethyl 2-propene-1-sulfonate and ethyl ethylenesulfonate have very similar mass spectra, and no resonance stabilization is indicated.

TABLE II

RATES OF ALKYLATION OF ETHANOLIC HYDROGEN CHLORIDE WITH SELECTED ETHYL SULFONATES AT 84° [a]

Ethyl sulfonate	10^3k, min^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, cal deg^{-1} mol^{-1}
1-Octane-[b]	51		
Ethylene-	47[a]	21.0	4.0
2-Propene-1-	39	23.1	9.3

[a] Calculated for 84° (see Table V for experimentally determined values of k). [b] See ref 3.

Although the activated state is much less highly ordered for ethyl 2-propene-1-sulfonate ($\Delta S^* = +9.3$ eu compared to +4.0 eu for the ethylenesulfonate), the activation energy of ethyl ethylenesulfonate is sufficiently lower ($\Delta H^* = 21.0$ kcal compared with 23.1 kcal for the 2-propene-1-sulfonate) that the smaller molecule is slightly more reactive.

During the synthesis of ethylenesulfonyl chloride from ammonium ethylenesulfonate and phophorus pentachloride, Landau obtained a high-boiling fraction which he called "possibly a polymeric vinylsulfonyl chloride."[13] From Landau's work, Kern[14] inferred this to be a dimer. No elemental analysis was reported by Landau, and the saponification equivalent reported was somewhat higher than should have been obtained for a "polymer."

Based on the evidence of mass spectra, infrared spectra, physical properties, and saponification equivalent of similar material obtained by us, it is believed that the "polymeric vinylsulfonyl chloride" reported by Landau was in fact a mixture of 2-chloroethanesulfonyl chloride and ethyl ethylenesulfonate. Formation of these substances can be attributed to any ethanol still present in the recrystallized salts of ethylenesulfonyl chloride. Facile additions of this sort are well documented.[15]

$$CH_2{=}CHSO_2ONa \xrightarrow{PCl_5} CH_2{=}CHSO_2Cl$$

$$CH_2{=}CHSO_2Cl \xrightarrow{EtOH} CH_2{=}CHSO_2OEt + HCl$$

$$CH_2{=}CHSO_2Cl \xrightarrow{HCl} ClCH_2CH_2SO_2Cl$$

(13) E. F. Landau, *J. Amer. Chem. Soc.*, **69**, 1219 (1947).
(14) W. Kern and R. C. Schulz, *Angew. Chem.*, **69**, 153 (1957).
(15) A. Lambert and J. D. Rose, *J. Chem. Soc.*, 45 (1949).

Experimental Section

Ultimate analyses were made by the Clark Microanalytical Laboratory, Urbana, Ill. Infrared spectra were determined on a Perkin-Elmer Model 21 instrument.

Sodium Ethylenesulfonate.—An aqueous solution of sodium ethylenesulfonate,[16] prepared from 46 g (1.0 mol) of ethanol by the method of Breslow,[17] *et al.*, and treated[16] to remove partially by-product sodium sulfate, was evaporated nearly to dryness under vacuum, the temperature being kept below 55°. The residual paste of salts was extracted with hot absolute ethanol, and the crystallized product was dried at 50° in a vacuum oven for 24 hr. The hard mass was crushed to a fine powder and further dried for 4 hr more. The yield of crude sodium ethylenesulfonate obtained was 107 g (82% of theory based on ethanol). Attempts to remove the ethanol more rapidly often resulted in a hard, glassy, polymeric material.

Ethylenesulfonyl Chloride.—Following a slightly modified procedure of Landau,[13] 98 g of sodium ethylenesulfonate was treated with 166 g of phosphorus pentachloride in 100 ml of chloroform. Neither Landau[13] nor Snyder[18] described the distillation of the sulfonyl chloride, but from our experience with other aliphatic sulfonyl compounds it is unlikely that either used a packed column. We used a 32 × 3 cm Vigreux column with total condensation stillhead and stabilized the distilland with potassium carbonate.[19] It was found necessary to redistil to separate the pure product: $n^{20}D$ 1.4680 (lit. $n^{20}D$ 1.4686,[13] 1.4680[18]); bp 49–50° (10 mm), from a higher boiling fraction.[20]

Ethyl Ethylenesulfonate.—Ethyl ethylenesulfonate, bp 73.5–74° (3 mm), was prepared in 40% yield from free ethylenesulfonic acid[21] and ethyl orthoformate according to a previously reported procedure:[22] $n^{28}D$ 1.4289; d^{28}_4 1.180; $n^{25}D$ 1.4295 (lit.[23] $n^{25}D$ 1.4316); $n^{20}D$ 1.4316 (lit.[24] $n^{20}D$ 1.4300); MD 30.3 (calcd 30.1). Discrepancies between these data and previously published data probably can be accounted for by the fact that previous investigators did not stabilize[19] the distilland (we used potassium carbonate) and doubtless some decomposition occurred.[3]

Attempts to prepare this compound by the reaction of ethylenesulfonyl chloride with sodium ethoxide led to a mixture of esters, probably including ethyl 2-ethoxyethanesulfonate, which could not be separated by fractional distillation.

Sodium 2-Propene-1-sulfonate.—The original synthesis of Belous,[25] *et al.*, was modified as follows. A solution of 125 g (1 mol) of sodium sulfite in 500 ml of water was heated under reflux with 121 g (1.0 mol) of freshly distilled allyl bromide for 12 hr, after which time the layer of allyl bromide had disappeared. The yield of product was 98% based on allyl bromide.

A derivative, the benzylisothiouronium 2-propene-1-sulfonate, was prepared with considerable difficulty as follows. A hot solution of 4.6 g of benzylisothiouronium chloride in 14 ml of

(16) W. F. Whitmore and E. F. Landau, *J. Amer. Chem. Soc.*, **68**, 1797 (1946).
(17) D. S. Breslow, R. R. Hough, and J. T. Fairclough, *ibid.*, **76**, 5361 (1954).
(18) H. R. Snyder, H. V. Anderson, and D. P. Hallada, *ibid.*, **73**, 3258 (1951).
(19) S. S. Rossander and C. S. Marvel, *ibid.*, **50**, 1491 (1928).
(20) The higher boiling fraction, referred to as a polymer of ethylenesulfonyl chloride by Landau, seems to have been a mixture of 2-chloroethanesulfonyl chloride, produced by HCl addition to ethylenesulfonyl chloride, and ethyl ethylenesulfonate, possibly produced from residual ethanol used in recrystallization of the salt of ethylenesulfonic acid before conversion into the sulfonyl chloride. Thus redistillation of the higher boiling fraction gave a substance [bp 73–74° (4 mm), $n^{25}D$ 1.4848, d^{25}_4 1.5169] having a saponification equivalent consistent by chance with the sulfonyl chloride or its polymer, but too high a chloride content. [*Anal.* Calcd for $(C_2H_3ClO_2S)_n$: Cl, 28.1; sapon equiv, 63.3. Found: Cl, 34.0; sapon equiv, 63.1.] The analysis is consistent with a mixture of roughly 80–90% 2-chloroethanesulfonyl chloride and 10–20% ethyl ethylenesulfonate. No attempt was made to refine this mixture, but its mass spectrum was nearly identical with that of an authentic sample of 2-chloroethanesulfonyl chloride: bp 68–70° (6 mm); $n^{25}D$ 1.4910 (lit.[16] $n^{20}D$ 1.4920).
(21) J. Preston and J. K. Lawson, Jr., *J. Polym. Sci., Part A*, **2**, 5364 (1964).
(22) J. Preston and H. G. Clark, III, U. S. Patent 2,928,859 (1960); *Chem. Abstr.*, **55**, 3522 (1961).
(23) V. V. Alder and W. E. Hanford, U. S. Patent 2,348,705 (1944); *Chem. Abstr.*, **39**, 711 (1945).
(24) S. M. McElvain, A. Jeline, and K. Rorig, *J. Amer. Chem. Soc.*, **67**, 1578 (1945).
(25) M. A. Belous and I. Ya. Postovskii, *J. Gen. Chem. USSR*, **20**, 1701 (1950).

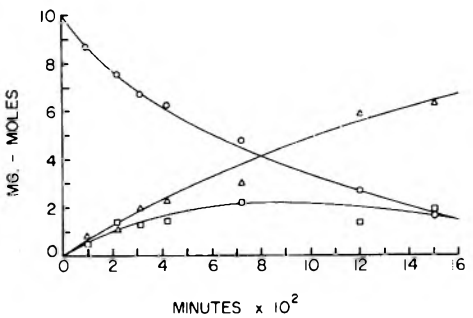


Figure 1.—Ethanolysis of ethylenesulfonyl chloride at 0°: O, CH_2=$CHSO_2Cl$; □, CH_2=$CHSO_2OH$; △, CH_2=$CHSO_2OEt$.

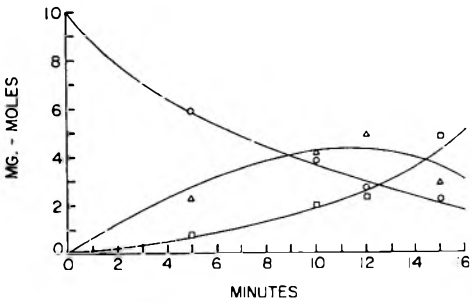


Figure 2.—Ethanolysis of 2-propene-1-sulfonyl chloride at 84°: O, CH_2=$CHCH_2SO_2Cl$; □, CH_2=$CHCH_2SO_2OH$; △, CH_2=$CHCH_2SO_2OEt$.

water was added to a hot solution of 2.9 g of sodium 2-propene-1-sulfonate in 10 ml of water; an oily layer separated which crystallized when chilled and stirred. Recrystallization from dilute ethanol gave material melting at 121–122°. Further recrystallization from acetone containing a little water gave long needles, mp 130–131°.

Anal. Calcd for $C_{11}H_{16}N_2O_3S_2$: C, 45.81; H, 5.58; N, 9.71. Found: C, 45.63; H, 5.64; N, 9.88, 9.66, 9.51.

2-Propene-1-sulfonyl Chloride.—The procedure of Belous,[25] *et al.*, was used to prepare crude 2-propene-1-sulfonyl chloride: bp 60–61° (4 mm); n^{20}D 1.4768. This material was fractionally distilled in the presence of potassium carbonate as a stabilizer through a 32 × 3 cm Vigreux column equipped with partial condensation stillhead. The heart cut had the following physical properties:[26] bp 61–62° (6.5 mm); n^{25}D 1.4743; n^{14}D 1.4788 (lit.[25] n^{14}D 1.4730); d^{25}_4 1.318; MD 30.0 (calcd 29.97).

Anal. Calcd for $C_3H_5ClO_2S$: C, 25.63; H, 3.58; Cl, 25.22; S, 22.81. Found: C, 25.58; H, 3.61; Cl, 25.56; S, 23.23.

Ethyl 2-Propene-1-sulfonate.—Ethanolic sodium ethoxide was prepared from 8.33 g (0.36 g-atom) of sodium and 200 ml of absolute ethyl alcohol. This solution was added in small increments with stirring and cooling to 46.27 g (0.33 mol) of 2-propene-1-sulfonyl chloride in 100 ml of ether. The reaction product was poured into cold water, and the ether layer was washed three times with 50-ml portions of cold 20% sodium chloride solution. The ethereal solution of ester was dried overnight with calcium chloride. After the ether had been removed under vacuum, the ester was distilled in the presence of potassium carbonate as stabilizer from a 50-ml Claisen flask having a Vigreux side arm to give a 41-g yield (82% based on sulfonyl chloride): bp 90–92° (1–2 mm); n^{20}D 1.4420. Fractional distillation through the previously described Vigreux column gave a heart cut having the following physical properties: bp 92–93° (2–3 mm); n^{25}D 1.4415; d^{25}_4 1.1442; MD 34.7 (calcd 34.67).

Anal. Calcd for $C_6H_{10}O_3S$: C, 39.98; H, 6.71; sapon equiv, 150.2. Found: C, 40.20; H, 6.67; sapon equiv, 150.3.

Determination of Rates of Ethanolysis of Sulfonyl Chlorides.—An ampoule of the sulfonyl chloride and the calculated amount of ethanol in molar proportions of 1:25 were enclosed in a flask in a constant-temperature bath at selected temperatures for 10–20 min. The ampoule was crushed, and the mixture quickly was made homogeneous by rapidly swirling the flask. Time was recorded from the crushing of the ampoule to subsequent quenching of the sample by plunging the flask into an ice slurry.

The analytical procedures for analysis of the reaction mixtures were described earlier.[7] The amount of unreacted acid chloride was obtained by determination of chloride ion produced upon saponification of the isolated acid chloride. The rate constants are summarized in Tables I, III, and IV while the distribution of products from the ethanolysis of the acid chlorides are shown in Figures 1 and 2.

TABLE III

ETHANOLYSIS OF ETHYLENESULFONYL CHLORIDE[a,b]

Temp, °C[c]	k, min^{-1}
0.0	1.12×10^{-3}
20.2	7.27×10^{-3}
35.1	2.90×10^{-2}

[a] Molar ratio of sulfonyl chloride to ethanol initially 1:25 ± 1. [b] Average value of k calculated from a least-squares solution. [c] ±0.1°.

TABLE IV

ETHANOLYSIS OF 2-PROPENE-1-SULFONYL CHLORIDE[a,b]

Temp, °C	k, min^{-1}
0.0[c]	4.32×10^{-5}
20.2[c]	5.88×10^{-4}
35.1[c]	1.52×10^{-3}
84[d]	9.92×10^{-2}

[a] Molar ratio of sulfonyl chloride to ethanol initially 1:25 ± 1. [b] Average value of k calculated from a least-squares solution. [c] ±0.1°. [d] Reflux.

The rate constants were determined by least-squares solutions of time *vs.* the logarithm of the concentration of residual sulfonyl chloride calculated on the basis of 10.00 mmol initially present. The data collected at a number of temperatures are summarized in Tables III and IV.

Determination of Rates of Alkylation of Ethanolic Hydrogen Chloride with the Ethyl Sulfonates.—The solvent for the alkylation study was an ethanolic solution of dry hydrogen chloride which is more nearly representative of the reaction product medium on ethanolysis of the sulfonyl chloride than ethanol alone, additional hydrogen chloride being used so that its concentration change would be minimized. An amount of the solution was added to the sample such that the molar proportions of ester to hydrogen chloride to ethanol were initially 1:5:50. Unreacted ester was determined by stoichiometric difference from the quantity of sulfonic acid produced; the latter was determined from differential titrations for total acid and chloride ion. Data for the esters are shown in Tables II and V.

TABLE V

RATES OF ALKYLATION OF ETHANOLIC HYDROGEN CHLORIDE BY ETHYL ETHYLENE- AND 2-PROPENE-1-SULFONATE[a,b]

Temp, °C	k, min^{-1}
Ethyl Ethylenesulfonate	
35.1[c]	3.62×10^{-4}
50.0[c]	1.86×10^{-3}
Ethyl 2-Propene-1-sulfonate	
35.1[c]	1.58×10^{-4}
50.0[c]	9.58×10^{-4}
84[d]	3.9×10^{-4}

[a] The molar proportions of ester to hydrogen chloride to ethanol initially 1:5:50 ± 2. [b] Average value of k calculated from a least-squares solution. [c] ±0.1°. [d] Reflux.

Registry No.—Ethylenesulfonyl chloride, 6608-47-5; 2-propene-1-sulfonyl chloride, 14418-84-9; benzylisothiouronium 2-propene-1-sulfonate, 17704-11-9; ethyl 2-propene-1-sulfonate, 10602-27-4.

(26) The elemental analysis reported by Belous,[25] *et al.*, was quite poor, indicating an impure product. Their material was not stabilized with potassium carbonate during the distillation and some decomposition probably occurred, accounting for physical properties which do not correspond to those found by us in the present study.

The Formation of *p*-Benzoquinones in the Oxidation of Polyphenylene Ethers

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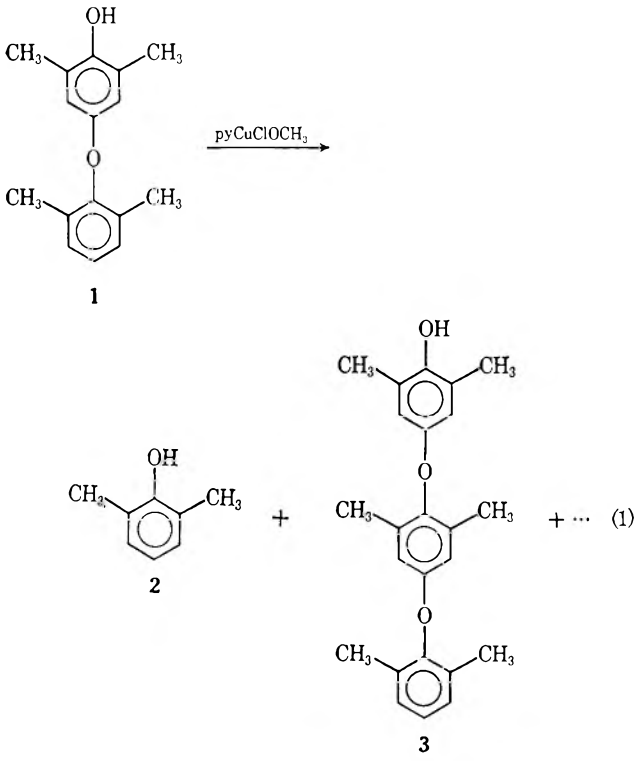
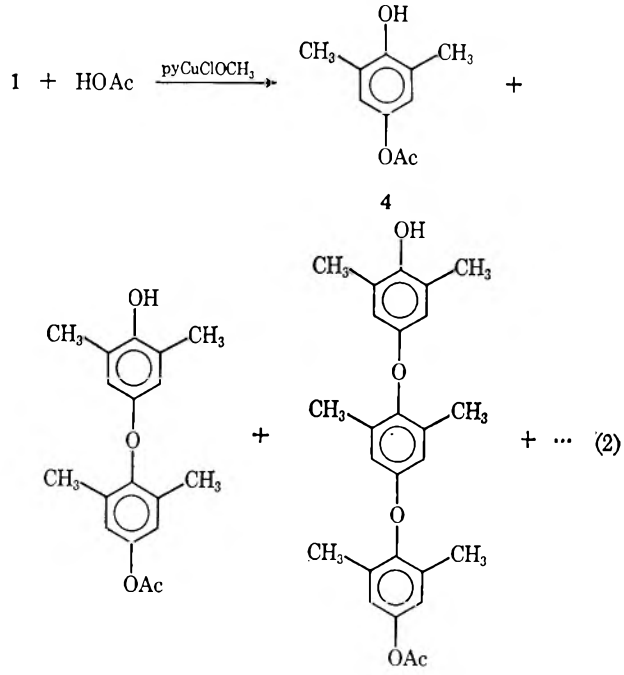
A number of oxidizing agents attack polyphenylene ethers in acetic acid solution to produce either 4-acetoxyphenols or *p*-benzoquinones. The nature of the final product depends on the ratio of oxidizing agent to polymer, since 4-acetoxyphenols are initially formed and subsequently oxidized to the benzoquinone. A mechanism is proposed for the reaction.

During the course of work on the stability of diphenyl ether group in 2,6-dimethylpolyphenylene ether,[1] an attempt was made to carry out a redistribution of the xylenol dimer, 4-(2,6-dimethylphenoxy)-2,6-dimethylphenol (**1**), in refluxing acetic acid using chloromethoxy(pyridine)copper[2] as the initiator. The expected products were 2,6-xylenol (**2**), xylenol trimer (**3**), xylenol tetramer, and higher oligomers as shown in eq 1.



Although the expected reaction did occur, vapor phase chromatography showed a second set of products which was identified by mass spectrometry and nmr spectroscopy as an analogous oligomeric series having an acetoxy group in the ultimate *para* position as shown in eq 2.

Although the formation of this series of products can be explained as the coredistribution of 4-acetoxy-2,6-dimethylphenol (**4**) with the xylenol dimer **1**, a type of reaction that had been previously demonstrated for a number of other phenols,[1,3] the origin of **4** remained to be determined. This paper reports the formation of acetoxyphenols from a number of polyphenylene ethers and their subsequent oxidation to *p*-benzoquinones.



Results and Discussion

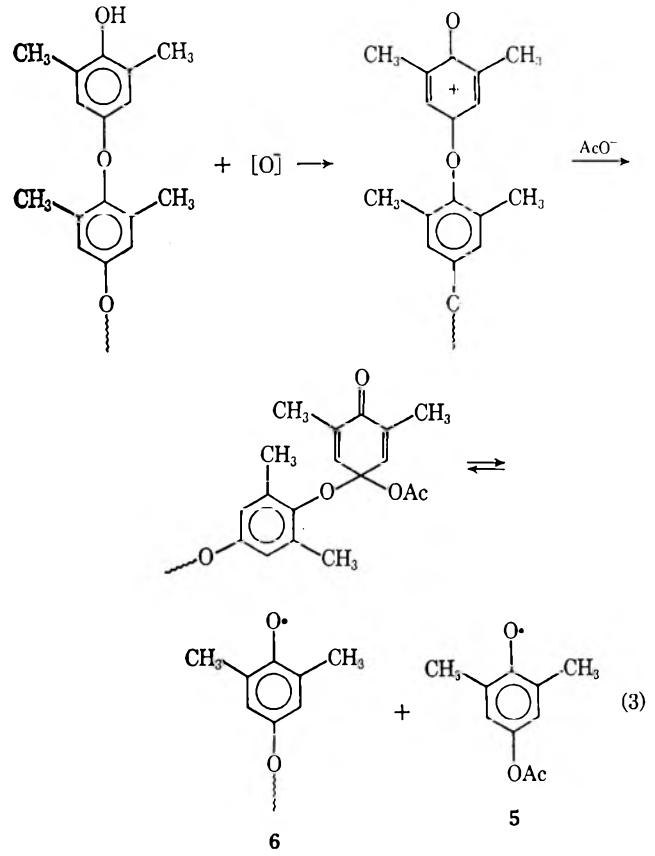
Xylenol dimer **1** readily undergoes redistribution reactions with itself to produce an oligomeric series[1,3] which severely complicated the study of the formation of **4** and its subsequent redistribution with **1**. White[4] has shown that, while poly-2,6-dimethylphenylene ether does not redistribute with itself to produce any low-molecular weight products, it readily coredistributes with a variety of phenols. These products form an oligomeric series whose ultimate group is derived from the added phenol and the remainder of each molecule from the polymer. This suggested to us that high polymer would be ideally suited for determining if acetoxyxylenol **4** is produced by a direct copper-catalyzed oxidative coupling of acetic acid and hydroxy-terminated phenylene ethers rather than from one of the redistribution products of **1**.

Poly-2,6-dimethylphenylene ether (prepared by the method of Endres[5]) was dissolved in toluene; acetic acid was added followed by chloromethoxy(pyridine)copper.[2] This mixture was refluxed until the green color of the copper complex was discharged. Vpc showed only the expected set of products (eq 2), suggesting that the acetoxyxylenol had been directly formed from acetic acid and the polymer.

Previous work[1,4] had shown that a variety of oxidizing agents such as tetramethyldiphenoquinone and benzoyl peroxide would initiate the redistribution of xylenol

(1) G. C. Cooper, A. R. Gilbert, and H. Finkbeiner, *Polymer Preprints*, **7**, 166 (1966).
(2) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966).
(3) D. A. Bolon, *ibid.*, **32**, 1584 (1967).
(4) D. M. White, *Polymer Preprints*, **7**, 178 (1966).
(5) G. F. Endres and J. Kwiatek, *J. Polym. Sci., Part A*, **58**, 593 (1962).

polymer. When experiments similar to the one described above were carried out with these two oxidizing agents, essentially identical results were obtained. The formation of 4-acetoxyxylenol can be explained in each of these cases as the attack of acetate ion on a phenonium ion formed by the oxidation of the phenolic end group of the polymer chain, as shown in eq 3. Since



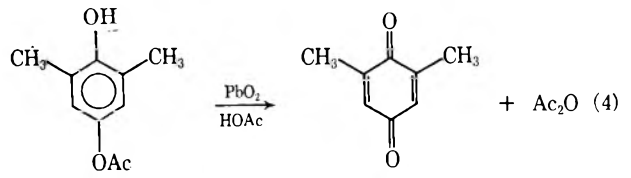
(3)

each of the products, **5** and **6**, formed in such a sequence should be capable of oxidizing phenolic end groups and the net oxidation state of the products was unchanged from that of the starting materials, it was expected that the redistribution reaction would be catalytic as in previously studied cases.[1,4] Quantitative examination of the product showed, however, that the amount of 4-acetoxyxylenol formed was only slightly greater than the number of moles of oxidizing agent used. Indeed, as the amount of oxidizing agent was increased, the yield of 4-acetoxyxylenol quickly reached a steady-state concentration suggesting that it was being formed and consumed at about equal rates. Table I shows the results obtained when lead dioxide was used to oxidize 1.0 g of polymer. Further examination of the reaction mixture showed that 2,6-dimethylbenzoquinone was being produced from the acetoxyxylenol. Since benzoquinone is in a higher oxidation state than the starting material, its formation also explains why the acetoxyxylenol formation is not catalytic.

TABLE I

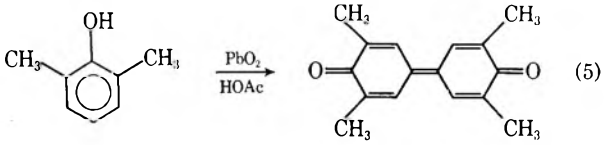
Total PbO_2, mg	4-Acetoxyxylenol, mg
200	167
400	415
600	410
800	420
1000	405

When the above reaction was repeated, except that a total of 3 g of lead dioxide were used, only 2,6-dimethylbenzoquinone was detected. In a separate experiment, acetoxyxylenol was oxidized to dimethylbenzoquinone (**7**) (eq 4).



The discovery that poly-2,6-dimethylphenylene oxide could be oxidized to 2,6-dimethyl-*p*-benzoquinone prompted an examination of other 2,6-disubstituted polyphenylene ethers. The oxidation of six different polymers using a stoichiometric amount of lead dioxide gave the *p*-benzoquinones described in Table II.

All of the polymers used in Table II were prepared by the method of Endres and Kwiatek[5] from the appropriate phenol. McNelis[6] has reported the polymerization of 2,6-dimethylphenol with lead dioxide as the oxidizing agent. If the polymer prepared in this fashion also undergoes further oxidation to benzoquinone, then it should be possible to go directly from the phenol to the benzoquinone without isolating the polymer. On attempting a reaction of 2,6-dimethylphenol with lead dioxide in acetic acid, only 3,3′,5,5′-tetramethyldiphenoquinone was produced (see eq 5).



However, when the lead dioxide oxidation of 2,6-dimethylphenol was carried out in toluene, polymerization took place readily. Acetic acid was then added and, after further oxidation, a 45% yield of 2,6-dimethylbenzoquinone was obtained.

Several other solvents have been examined for the oxidation of high polymer with lead dioxide. Under identical conditions, the lead dioxide oxidation of poly-2,6-dimethylphenylene ether gave a 54% yield of dimethylbenzoquinone in acetic acid, a 41% yield in chloroacetic acid, and a 12% yield in propionic acid. A mixture of refluxing chlorobenzene and benzoic acid gave an 18% yield of 2,6-diphenylbenzoquinone from the polymer, almost identical (19%) with that obtained in acetic acid. The oxidation in the chlorobenzene–benzoic acid mixture was much faster, but this was probably largely due to the higher temperature used.

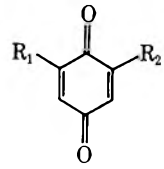
As might have been expected, phenol ethers such as 4-phenoxyphenol did not give identifiable products, no doubt because of the reactive *ortho* positions of the phenolic group. It was also shown that neither 1,4-diacetoxy-2,6-dimethylbenzene nor acetate-capped polymer react.

In addition to lead dioxide, nickel peroxide, active manganese dioxide, and manganic acetate were used in the oxidation of 4′-(2,6-dimethylphenoxy)-2′,3,5,6′-

(6) E. McNelis, *J. Org. Chem.*, **31**, 1255 (1966).

TABLE II

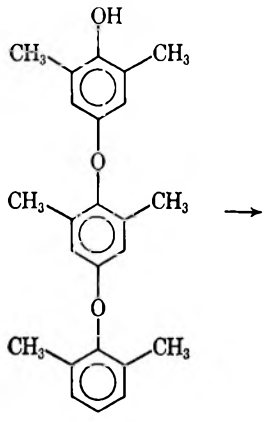
PREPARATION[a] OF



R1	R2	Registry no.	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mol wt Calcd	Mol wt Found
C_6H_5	C_6H_{11}	17603-87-1	47	100–105	81.17	6.81	81.1	7.0	266	293
i-C_3H_7	CH_3	17603-88-2	16	120–121	73.14	7.37	72.1	8.5	164	171
C_6H_5	C_6H_5	2887-97-0	19	133–135	83.06	4.64	83.0	4.7	260	265
C_6H_5	CH_3	17603-89-3	76	51–54	78.77	5.09	78.8	5.2	198	204
$C_6H_5CH_2$	CH_3	17603-81-5		*b*	79.22	5.70	79.0	5.6	212	230
CH_3	CH_3	527-61-7	62	70–72						

[a] In each case, the nmr and mass spectrum was in agreement with the assigned structure. [b] This benzoquinone is apparently a liquid and was isolated by thin layer chromatography.

tetramethyl-4-hydroxydiphenyl ether (**8**) (2,6-dimethylphenol trimer). The reaction with nickel peroxide and active manganese dioxide proceeds smoothly at acetic acid reflux temperature to produce 2 mol of 2,6-dimethylbenzoquinone, 0.5 mol of 3,3′,5,5′-tetramethyldiphenoquinone, and acetic anhydride. When xylenol trimer **8** redistributes, the terminal group appears as free xylenol (eq 6). In these experiments, the xylenol



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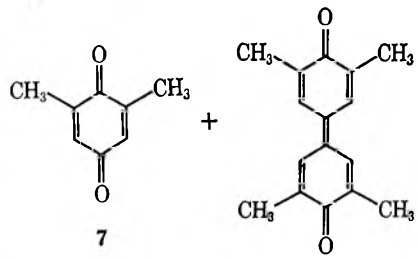


7

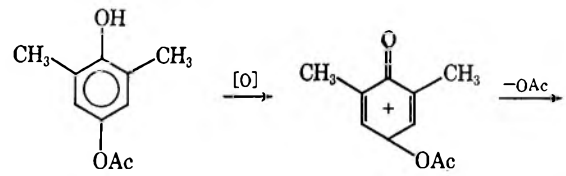
+ Ac_2O (6)

is oxidatively coupled to diphenoquinone by the manganese dioxide or nickel peroxide. Acetic anhydride formation was established by vpc and conversion into *o*-bromoacetanilide.

Manganic acetate was examined as an oxidizing agent for 2,6-xylenol trimer since it is soluble in acetic acid. The reaction of 1 g of trimer with a stoichiometric amount of manganic acetate was complete in less than 2 hr at room temperature. A 93% yield of benzoquinone was obtained.

The displacement of a phenoxy group from a hydroxypolyphenylene ether either by a phenol[1–3] or by acetate almost certainly proceeds by prior formation of a cyclohexadienone derivative as in eq 3, followed by homolytic cleavage to form two phenoxy radicals.

The oxidation of hydroquinone monoacetates to the corresponding benzoquinones can be viewed as proceeding through a similar mechanism forming first the 4,4-diacetoxycyclohexadienone as shown in eq 7 for



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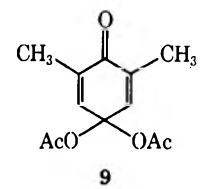

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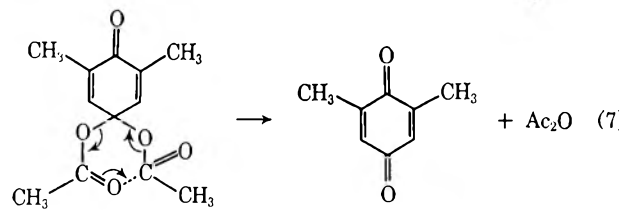
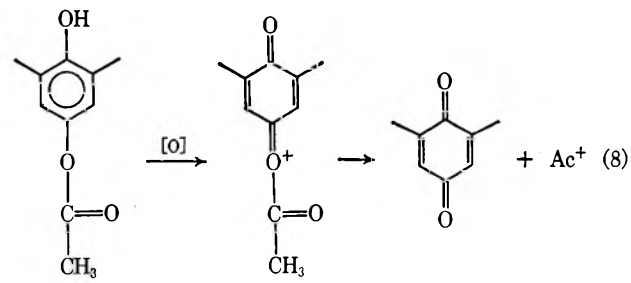


+ Ac_2O (7)

2,6-dimethyl-4-acetoxyphenol. The diacetate would then rearrange to benzoquinone and acetic anhydride.

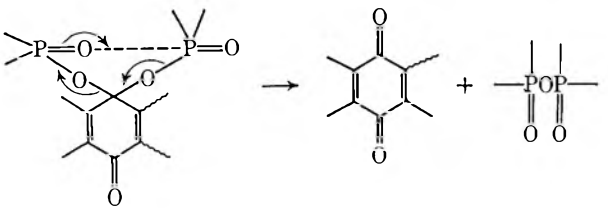
The recent work of Thanassi and Cohen[7] has shown that 4-acetoxyphenols can be oxidized by N-bromosuccinimide in acetic acid to produce the benzoquinone and acetic anhydride. Thanassi and Cohen feel that the acetic anhydride is formed by oxidation of the phenol to a phenonium ion followed by ejection of an acylium ion which combines with acetate (eq 8). In support of this view, they cite the work of Snyder and



+ Ac^+ (8)

(7) J. W. Thanassi and L. A. Cohen, *J. Amer. Chem. Soc.*, **89**, 5733 (1967).

Rapoport[8] on quinones in cell-free oxidative phosphorylation wherein it was established that neither of the oxygens of the original quinone are exchanged during the oxidation–reduction cycle. This argument has the difficulty that conditions are certainly conceivable that would require the decomposition of a diphosphate always to proceed by a route that would



leave the original oxygen intact. At present, we feel that the formation of a cyclohexadiene such as **9** followed by immediate decomposition to benzoquinone takes into account the observations made in the present study and, in addition, the fact that, while 2,2-diacetoxy-3,5-cyclohexadienones are well known,[9] the 4,4-diacetates have never been prepared.

Experimental Section

Unless listed below, all starting materials were commercially available and used as received. The nmr spectra were determined using a Varian A-60 and the mass spectra were obtained using a General Electric MS600 monopole mass spectrometer.

2,6-Dialkylpolyphenylene Ethers.—All of the polymers used were prepared by the method of Endres and Kwiatek using the appropriate phenol. The phenols in turn were prepared by conventional synthetic methods.

Oxidation of 2,6-Dimethylpolyphenylene Ether with Lead Dioxide. A.—To a refluxing suspension of 1 g of 2,6-dimethylpolyphenylene ether (μ = 0.52) in 20 ml of acetic acid was added 300 mg of lead dioxide. After 30 min, the brown color of the lead dioxide had disappeared, and an additional 700 mg of lead dioxide was added. The mixture was refluxed for 1 hr and cooled to room temperature, and 50 ml of benzene was added. The benzene solution was washed several times with water, dried over magnesium sulfate, and distilled. A total of 300 mg of 4-acetoxy-2,6-dimethylphenol, mp 93–95° (lit.[10] mp 94–95°), was obtained. The nmr spectrum showed the expected peaks, and the mass spectrum had prominent peaks at 180 (M) and 138 (M − 42) with the base peak at 43.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; mol wt, 180. Found: C, 66.4; H, 6.7; mol wt, 184.

B.—The above experiment was repeated using 3.0 g of lead dioxide. After drying the benzene extract, the solvent was removed and the residue was sublimed at 20 mm. The 2,6-dimethylbenzoquinone was recrystallized from benzene, mp 70–72° (lit.[11] mp 71–72°). The nmr and infrared spectrum were in agreement with those of authentic 2,6-dimethylbenzoquinone. The parent ion in the mass spectrum was 136, and the fragmentation agreed with the cracking pattern of 1,4-benzoquinones.

General Method of Oxidizing Polymers with Lead Dioxide.—A solution of 24 g of the polymer in 200 ml of toluene was prepared by refluxing the toluene. To the hot solution, 100 ml of glacial acetic acid was slowly added. A total of 40 g of lead dioxide was added in small portions over about a 3-hr period. The reaction mixture was cooled and poured into 600 ml of water, the toluene phase was separated, and the aqueous phase was extracted with two additional 200-ml portions of toluene. After approximately 400 ml of the toluene was distilled, the remainder was poured into 500 ml of methanol to precipitate any unreacted polymer. After filtering, the product was isolated by distillation and purified by recrystallization from *n*-hexane. Table II gives the analytical data for the 1,4-benzoquinones prepared.

Direct Polymer Preparation and Oxidation.—After preparing a solution of 10 g of 2-methyl-6-phenylphenol in 50 ml of toluene, a total of 32 g of lead dioxide was slowly added. An exothermic reaction took place and, after the mixture had cooled to room temperature, 50 ml of glacial acetic acid was added. The reaction mixture was refluxed for 12 hr and poured into 200 ml of water, and the toluene layer was removed. After extracting the aqueous phase with two 50-ml portions of toluene, the extracts were combined, dried over magnesium sulfate, and distilled to yield 5.1 g (45%) of 2-methyl-6-phenylbenzoquinone, bp 103° (0.1 mm), mp 51–54°.

Preparation of Manganese(III) Acetate, $Mn(OAc)_3 \cdot 2H_2O$.—Manganic acetate was prepared by adding 98 g of $Mn(OAc)_2 \cdot 4H_2O$ (0.4 mol) to 500 ml of glacial acetic acid. The mixture was heated to reflux and $KMnO_4$ addition was started. A total of 16 g of permanganate was added to the refluxing mixture in *ca.* 1-g portions. When the addition of the permanganate was complete (20–30 min), the solution was refluxed for an additional 25 min and cooled to 15° with an ice bath, and 85 ml of water was added. On stirring overnight, the $Mn(OAc)_3 \cdot 2H_2O$ crystallized. After filtering, the solid was washed with 100 ml of cold glacial acetic acid and air dried. The product was obtained as a red-brown powder in 90–95% yield (120–125 g). The manganese(III) content was determined by iodine or ferrous sulfate titration as 19.5–20.2% (theory 20.5%).

Oxidation of 4′-(2,6-Dimethylphenoxy)-2′,6′,3,5-tetramethyl-4-hydroxydiphenyl Ether (2,6-Xylenol Trimer) with Manganic Acetate.—A solution of 1.0 g of 2,6-xylenol trimer and 4.5 g of $Mn(OAc)_3 \cdot 2H_2O$ in 25 ml of glacial acetic acid was stirred at 30°. After 2 hr the dark color of the manganic acetate had been replaced by the pale yellow of 2,6-dimethylbenzoquinone. The reaction mixture was filtered to remove the precipitated manganous acetate and poured into 50 ml of benzene. After extracting the acetic acid by washing the solution four times with 20-ml portions of water, it was dried and the benzene was removed on a rotary evaporator. The 2,6-dimethylbenzoquinone was dissolved in 50 ml of *n*-hexane and filtered to remove the 3,3′,5,5′-tetramethyldiphenoquinone. The yield of crude 2,6-dimethylbenzoquinone was 700 mg (93%) and of diphenoquinone 188 mg (57%).

2′,3,5,6′-Tetramethyl-4-hydroxydiphenyl ether (1) and 4′-(2,6-dimethylphenoxy)-2′,3,5,6-tetramethyl-4-hydroxydiphenyl ether (8) were prepared by the redistibution of 2,6-xylenol with 2,6-xylenol polymer according to the method of White.[4]

Oxidation of 8 with Nickel Peroxide.—Nickel peroxide was prepared according to Nakagawa, *et al.*,[12] and an oxidation of xylenol trimer **8** was carried out by adding 2.78 g of nickel peroxide to a solution of 1.0 g of trimer in 25 ml of glacial acetic acid. After the mixture was refluxed for 2 hr, black nickel peroxide was replaced by a pale green solid. After filtering off the solid, it was washed with 100 ml of benzene; the benzene was added to the acetic acid solution; and the mixture was extracted three times with 25-ml portions of water. After drying over magnesium sulfate, the benzene was removed on a rotary evaporator, and the product was sublimed at 20 mm. The yield of crude 2,6-dimethylbenzoquinone was 186 mg (25%).

Manganese Dioxide.—The manganese dioxide was prepared by dissolving 20 g of potassium permanganate, 15 g of sodium bicarbonate, and 20 g of potassium carbonate in 400 ml of water. On the addition of 100 ml of 95% ethanol, the temperature rose to 50°. The mixture was vigorously stirred until the temperature had dropped to 25°, at which point the manganese dioxide was filtered off. After slurrying in a solution of 20 g of potassium carbonate in 400 ml of water, the product was again filtered, washed with 400 ml of water, and dried by pulling air through the filter cake for 10 min. The filter cake was then powdered and dried at 110° for 3 hr.

Oxidation of 8 with Manganese Dioxide.—Manganese dioxide (1.5 g) was added to a solution of 1.0 g of xylenol trimer **8** in 25 ml of glacial acetic acid. After 2 hr at reflux, the manganese dioxide had dissolved and the work-up was as described for nickel peroxide. The yield of crude 2,6-dimethylbenzoquinone was 718 mg (96%).

(8) C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, **89**, 1269 (1967).
(9) G. Billek, J. Swoboda, and F. Wessely, *Tetrahedron*, **18**, 909 (1962).
(10) E. Zbiral, F. Wessely, and E. Lahrmann, *Monatsh. Chem.*, **91**, 331 (1960).
(11) G. R. Bacon and D. J. Munro, *J. Chem. Soc.*, 1339 (1960).
(12) K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).

Oxidation of 4-Acetoxy-2,6-dimethylphenol (4) with Lead Dioxide.—A solution of 600 mg of **4** in 10 ml of glacial acetic acid was heated with 700 mg of lead dioxide until a pale yellow homogeneous solution was obtained. Vpc analysis showed essentially quantitative conversion into 2,6-dimethylbenzoquinone.

Acknowledgments.—The authors wish to thank Dr. Hans-Dieter Becker for a gift of nickel peroxide and Dr. John B. Bush, Jr., for a gift of manganese dioxide.

The Synthesis of 2-Methyl-3-vinyl-1,4-naphthoquinones[1]

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Chlorobiumquinone, previously isolated from *Chlorobium thiosulfatophilum* and characterized as a 2-methyl-3-vinylmultiprenyl-1,4-naphthoquinone, is unique among natural multiprenylquinones in being a vinyl- rather than an allylquinone. Various approaches to the synthesis of 2-methyl-3-vinyl-1,4-naphthoquinones have been studied, and two general syntheses have been developed, both constructing the substituted vinyl side chain *via* the Wittig reaction. A primary requirement for both methods was a protecting protocol for the 1,4-oxygen functions which would be inert to the ylide yet would allow generation of the quinone without destruction of the vinyl group. Such functionality was provided by the 1-pivalate ester–4-methyl ether. These groups do not react with the ylide, and removal of the ester with lithium aluminum hydride and oxidation of the 1-hydroxy-4-methoxy compound with ferric chloride gave quinone while leaving the vinyl side chain intact. One synthesis proceeded *via* 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate which was converted into its triphenylphosphonium salt and thence to vinyl derivative by generation of the naphthalenic ylide and reaction with a carbonyl component. The other synthesis utilized the 3-naphthaldehyde, prepared from the chloromethyl compound and potassium 2-propanenitronate, in reaction with the appropriate ylide. To avoid isomers, some secondary ylides were prepared by alkylation of primary ylides. The relative advantages and disadvantages of both methods are considered. The separate, isomeric vinyl compounds were obtained, and *cis* and *trans* stereochemical assignments were made by relating their nmr absorptions to those of unambiguous synthetic models. Various vinyl substitution patterns can be easily distinguished from the ultraviolet absorption of the resulting 2-methyl-3-vinyl-1,4-naphthoquinones.

We have reported the isolation and structure determination of chlorobiumquinone (I), a novel 2-methyl-3-vinylmultiprenylnaphthoquinone isolated from the anaerobic, photosynthetic sulfur bacterium, *Chlorobium thiosulfatophilum*, strain PM.[5,6] Chlorobiumquinone is unique[7] among the menaquinones, ubiquinones, and plastoquinones found in nature in that it has a double bond conjugated with the ring moiety and the side chain contains one carbon less than the multiples of five found in all other natural multiprenylquinones. Hence, chlorobiumquinone may be visualized as menaquinone-7 (II),[8] which also occurs in *C. thiosulfatophilum*, minus the 1′-methylene, rather than as a double-bond isomer.

Our interest in the chemistry of chlorobiumquinone, especially as it relates to a possible role for the quinone in photosynthesis and oxidative phosphorylation in *C. thiosulfatophilum*[9] and the fact that vinylquinones are a little studied class of compounds (except for their use in polymerizations) have led us to develop general methods for the synthesis of vinylnaphthoquinones, which is the subject of this paper.

The syntheses reported in the literature have been designed for the preparation of vinylhydroquinone diesters or diethers with vinyl moieties bearing no substitutents, the object being the preparation of monomers from which a redox polymer might be obtained.[10]

Most of the vinylhydroquinones and vinylhydroquinone derivatives have been prepared by (1) synthesis and decarboxylation of a 2,5-dihydroxy cinnamic acid, (2) reduction of the ketone moiety of an acetylhydroquinone diacetate and dehydration of the resulting alcohol, or (3) metalation or formation of the Grignard reagent of a hydroquinone diether followed by reaction with ethylene oxide or acetaldehyde and dehydration of the resulting alcohol. The reverse of 3, formation of the diether of a 2,5-dihydroxybenzaldehyde followed by reaction with methyllithium or a Grignard reagent, is also known. In only one case did the vinyl group contain a substituent and that was an α-methyl group.[11]

Several 2-hydroxy-3-(1-alkenyl)-1,4-naphthoquinones (IV) have been prepared by heating 2-hydroxy-1,4-naphthoquinone (III) with a variety of straight-chain, aliphatic aldehydes and hydrochloric acid in acetic acid.[12] Under these conditions 1,4-naphthoquinones (V) do not yield (1-alkenyl)-1,4-naphthoquinones (VI) but give instead pigments of the anthocyanidin type,[13] VII. By moderating the conditions, however, 2-methyl-1,4-naphthoquinone (VIII) was successfully condensed with acetaldehyde and hydrogen bromide to afford 2-methyl-3-(1-bromoethyl)-1,4-naphthoquinone

(1) Sponsored in part by Grant AI-04888 from the National Institutes of Health, U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow.

(3) Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Buenos Aires, Argentina.

(4) National Science Foundation Undergraduate Research Participant.

(5) B. Frydman and H. Rapoport, *J. Amer. Chem. Soc.*, **85**, 823 (1963); menaquinone-7 also was isolated.

(6) R. Powls and E. R. Redfearn [*Biochem. J.*, **102**, 3c (1967)] also have isolated chlorobiumquinone and menaquinone-7 from *C. thiosulfatophilum*.

(7) A quinone detected spectrophotometrically in *Sarcina lutea* also may be of this type: D. H. L. Bishop, K. P. Pandya, and H. K. King, *ibid.*, **83**, 606 (1962).

(8) IUPAC–IUB Commission on Biochemical Nomenclature Tentative Rules, *Arch. Biochem. Biophys.*, **118**, 505 (1967).

(9) I. Chmielewska [*Biochem. Biophys. Acta*, **39**, 170 (1960)] has postulated the intermediacy of a vinylquinone in the mechanism of the quinone's role in oxidative phosphorylation.

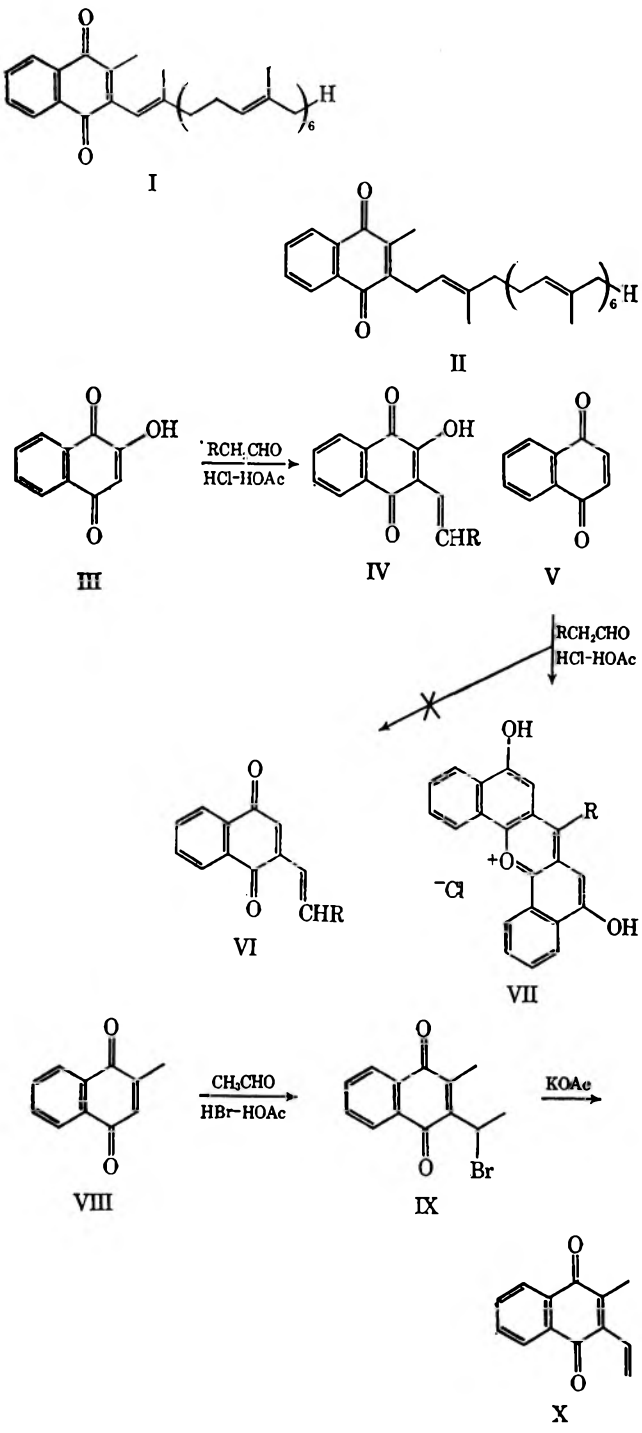
(10) For a review of the synthesis of vinylhydroquinones, see H. C. Cassidy and K. A. Kun, "Polymer Reviews," Vol. 11, Interscience Publishers, New York, N. Y., 1965, Chapter 2.

(11) J. M. Bruce and P. Knowles, *J. Chem. Soc., C*, 1627 (1966).

(12) S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1163, 1168 (1936).

(13) M. Fieser and L. F. Fieser, *ibid.*, **63**, 1572 (1941).

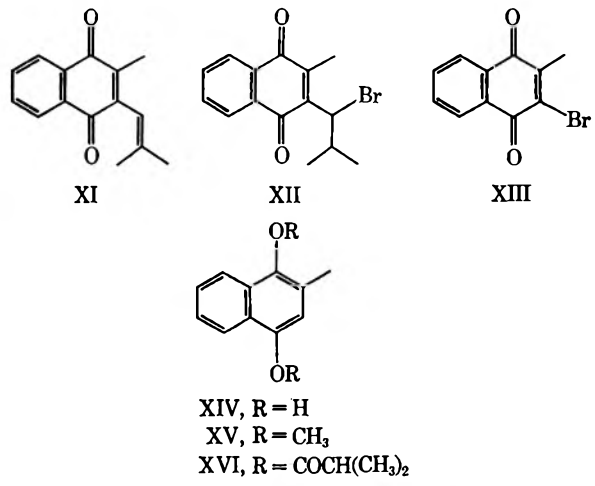
SCHEME I



(IX) which was dehydrohalogenated to 2-methyl-3-vinyl-1,4-naphthoquinone (X).[14] See Scheme I.

While some of these methods are not applicable to the preparation of β,β-dialkylvinylnaphthoquinones of the chlorobiumquinone type, others held promise, and suitable modifications were studied, as well as new methods.

Direct Introduction of the Vinyl Side Chain.—We first investigated those reactions which would allow direct introduction of a vinyl side chain or of a vinyl side chain precursor. Our initial goal was the synthesis of 2-methyl-3-(2-methyl-1-propenyl)-1,4-naphthoquinone (XI) which contains many of the features present in I. Following the method used for the preparation of 2-methyl-3-vinyl-1,4-naphthoquinone (X), isobutyraldehyde was condensed with 2-methyl-1,4-naphthoquinone (VIII), but no 2-methyl-3-(1-bromo-2-methylpropyl)-1,4-naphthoquinone (XII) could be isolated. The only product was a small amount of 2-methyl-3-bromo-1,4-naphthoquinone (XIII).[15]



A second approach which was investigated for the direct introduction of the entire vinyl side chain was alkenylation with an α,β-unsaturated diacyl peroxide. The preparation of 2-methyl-3-(1-hexadecenyl)-1,4-naphthoquinone by this method has been reported;[16] however, parallel reactions with other α,β-unsaturated acyl peroxides were reported to fail.[16,17] We carried out the reaction with β,β-dimethylacryloyl peroxide and 2-methyl-1,4-naphthoquinone (VIII). No alkenylation product was obtained and only starting quinone was recovered.

Our third approach was to introduce the vinyl side chain precursor by preparing the acyl derivative which could then be reduced and dehydrated. This was first attempted by acylating 1,4-dimethoxy-2-methylnaphthalene[18] (XV) with isobutyryl chloride and aluminum chloride. Acylation occurred, as indicated by the nmr signals for one isobutyryl group, but it had entered the unsubstituted ring since the C-3 proton signal was undiminished. Fries rearrangement of 2-methyl-1,4-naphthalenediol diisobutyrate (XVI) also failed.

Building the Vinyl Side Chain on a Substituted Naphthohydroquinone.—Inability to introduce the vinyl side chain directly led us to approach the synthesis by first inserting a functionalized carbon at C-3 and then building the vinyl side chain on this carbon. As a model, the 2-aminoethyl compound XIX was prepared, since success in eliminations with this compound could be translated to secondary and tertiary amines for the corresponding substituted vinyl derivatives. The 2-aminoethyl compound XIX was prepared from 3-chloromethyl-1,4-dimethoxy-2-methylnaphthalene (XVII) by treatment with aqueous sodium cyanide to give the nitrile XVIII followed by lithium

(14) G. Manecke and W. Storck, *Ber.*, **94**, 300 (1961).

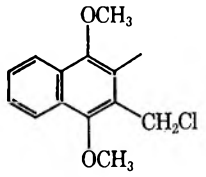
(15) R. H. Thomson [*J. Chem. Soc.*, 1196 (1953)] has reported that formaldehyde, acetaldehyde, and benzaldehyde react with 2-methyl-1,4-naphthoquinone to give 3-(1-chloroalkyl) derivatives whereas propionaldehyde, 2-naphthaldehyde, and 2-formylthiophene instead gave only traces of 2-methyl-3-chloro-1,4-naphthoquinone.

(16) L. F. Fieser and A. E. Oxford, *J. Amer. Chem. Soc.*, **64**, 2060 (1942); L. F. Fieser, U. S. Patent 2,398,418 (1946).

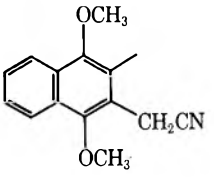
(17) L. F. Fieser, M. T. Leffler, and coworkers, *J. Amer. Chem. Soc.*, **70**, 3175, 3195 (1948).

(18) S. Ansbacher, E. Fernholz, and M. A. Dolliver, *ibid.*, **62**, 155 (1940).

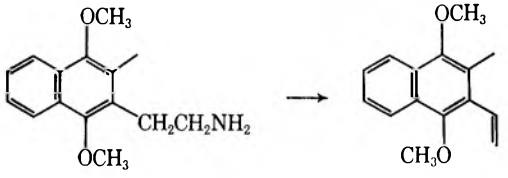
aluminum hydride reduction to amine XIX. Exhaustive methylation to the quaternary methiodide followed by heating in alkali gave a good yield of 1,4-dimethoxy-2-methyl-3-vinylnaphthalene (XX). However, ether



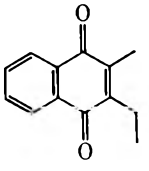
XVII



XVIII



XIX XX



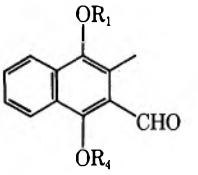
XXI

cleavage with acidic reagents[19] proceeded in very poor yield and subsequent oxidation gave the vinylquinone X in only 10% yield from dimethoxy compound XX. Significant by-products in this reaction were 2-methyl-1,4-naphthalenediol (XIV) and the ethylquinone XXI, which may be considered as a tautomer of the intermediate 2-methyl-3-vinyl-1,4-naphthohydroquinone. Loss of the entire vinyl side chain in such ether-cleaving reactions has been observed previously[19] with benzohydroquinones; however, conversion into the ethylquinone has not been heretofore reported.

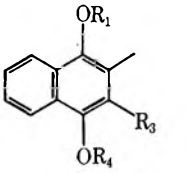
Although this Hofmann elimination approach was abandoned because of its complexity and the poor yield in the ether cleavage step, it clearly established that a protecting protocol other than methylation–demethylation had to be developed for a successful, general synthesis of vinylquinones.

Synthesis of Vinyl Side Chain Using Wittig Reaction.—The failures and limitations of the various methods considered above directed our attention to the use of the Wittig reaction. This method has been used to prepare a number of vinyl-1,4-dimethoxybenzenes,[19,20] but conversion into the corresponding quinones was thwarted at the ether cleavage stage. Thus the problem became one of finding protecting groups compatible with the Wittig reagent and removable without destruction of the vinyl side chain. Approaches both through the naphthaldehyde and the naphthalenic ylide were explored in detail.

A. *Via* **the Naphthaldehyde.**—Three protected derivatives of 1,4-dihydroxy-2-methyl-3-naphthaldehyde (XXIIa)[21] were prepared and tested for their efficacy in the Wittig reaction and for ease in subsequent conversion into quinone. These were the diacetate XXIIc, the 4-methyl ether 1-acetate XXIId, and the 4-methyl ether 1-pivalate XXIIe. Acetylation of the dihydroxyaldehyde XXIIa by heating with acetic anhydride and either sulfuric acid or sodium acetate or pyridine led to excellent yields of the tetraacetate XXIII. Although treatment with methanol–HCl or



XXIIa, R_1 = H; R_4 = H
b, R_1 = CH_3CO; R_4 = H
c, R_1 = CH_3CO; R_4 = CH_3CO
d, R_1 = CH_3CO; R_4 = CH_3
e, R_1 = $(CH_3)_3CCO$; R_4 = CH_3



XXIII, R_1 = CH_3CO; R_4 = CH_3CO; R_3 = $CH(OCOCH_3)_2$
XXIV, R_1 = CH_3CO; R_4 = H; R_3 = H
XXV, R_1 = CH_3CO; R_4 = CH_3; R_3 = H
XXVI, R_1 = CH_3CO; R_4 = CH_3; R_3 = CH_2Cl
XXVII, R_1 = H; R_4 = CH_3; R_3 = H
XXVIII, R_1 = $(CH_3)_3CCO$; R_4 = CH_3; R_3 = H
XXIX, R_1 = $(CH_3)_3CCO$; R_4 = CH_3; R_3 = CH_2Cl

acetic acid did convert this tetraacetate into diacetate XXIIc, the product always contained the difficultly removed 1-acetoxy compound XXIIb. A superior preparation of the pure aldehyde diacetate XXIIc directly from dihydroxy aldehyde XXIIa was then found using milder acetylation conditions.

To prepare the 4-methoxyaldehyde acetate XXIId, 2-methyl-1,4-naphthalenediol 1-acetate (XXIV)[22] was methylated with dimethyl sulfate. The 1-hydroxy-4-methoxy-2-methyl-1-naphthol acetate (XXV) formed was always accompanied by some of the dimethoxy compound (XV). This troublesome side product could be removed by treatment with Claisen alkali which hydrolyzed the ester and removed the resulting 4-methoxy-2-methyl-1-naphthol (XXVII) as its salt; reacetylation gave XXV. This separation was avoided by direct conversion of 2-methyl-1,4-naphthalenediol into the same 4-monomethyl ether XXVII in practically quantitative yield using methanol and hydrogen chloride.[23] Conversion of XXV into the aldehyde then followed by chloromethylation to XXVI and transformation of the chloromethyl to an aldehyde group using 2-nitropropane and potassium *t*-butoxide in *t*-butyl alcohol. These conditions reduced deacetylation to <20%, but reacetylation was still necessary for a good yield of the 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde acetate (XXIId).

Esterification of the 4-monomethyl ether XXVII with pivalic acid in trifluoroacetic anhydride[24] gave the pivalate ester XXVIII. Because of limited solubility, chloromethylation was carried out using formalin–acetic acid saturated with hydrogen chloride, and the

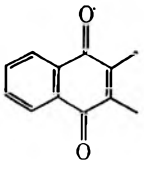
(19) L. I. Smith and J. J. Baldwin, *J. Org. Chem.*, **27**, 1770 (1962).
(20) M. Hashimoto, K. Uno, and H. G. Cassidy, *J. Polym. Sci., Part A-1*, **5**, 998 (1967).
(21) L. I. Smith and I. M. Webster, *J. Amer. Chem. Soc.*, **59**, 662 (1937).
(22) B. R. Baker, T. H. Davies, L. McElroy, and G. H. Carlson, *ibid.*, **64**, 1096 (1942); B. R. Baker and G. H. Carlson, *ibid.*, **64**, 2657 (1942).
(23) Patterned after the procedure M. Tishler, L. F. Fieser, and N. L. Wendler [*ibid.*, **62**, 1982 (1940)] used to prepare the monoethyl ether.
(24) R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965).

chloromethyl derivative XXIX was converted into 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde pivalate XXIIe with potassium 2-propanenitronate in the usual way.

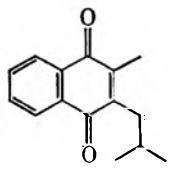
Construction of the vinyl side chain was now undertaken first with the diacetate aldehyde XXIIc by adding to its suspension in tetrahydrofuran 1 equiv of the ylide, isopropylidenetriphenylphosphorane, and refluxing the mixture for several hours. Analysis of aliquots by nmr indicated a substantial loss of acetyl groups while the aldehydic proton signal remained. To simplify product analysis, lithium aluminum hydride was added at the conclusion of the reaction (indicated by the disappearance of the ylide) to remove all ester groups and reduce any remaining aldehyde, which surprisingly was converted into a methyl rather than a hydroxymethyl group. The hydroquinones were then oxidized with silver oxide, and the mixture of quinones was analyzed by glpc.

Three quinones, 2,3-dimethyl-1,4-naphthoquinone (XXX), 2-methyl-3-(2-methyl-1-propenyl)-1,4-naphthoquinone (XI), and 2-methyl-3-isobutyl-1,4-naphthoquinone (XXXI), were obtained in the ratio of 4:1:2. When the ratio of ylide to naphthaldehyde XXIIc was increased to 3:1, the product ratio now changed to 2:3:5 for dimethyl-, 2-methyl-1-propenyl-, and isobutylquinones. An authentic sample of the isobutylquinone (XXXI) was prepared by the reaction of 2-methyl-1,4-naphthoquinone (VIII) and diisovaleryl peroxide.

The source of the isobutylquinone XXXI is not clear. Using a mixture of methylene chloride and tetrahydrofuran, in which the starting diacetate aldehyde XXIIIc is completely soluble or carrying out the reaction at 0° caused no change in the product ratio. Also, the action of lithium aluminum hydride on the vinylquinone XI or on the corresponding vinylhydroquinone diacetate under the conditions of the isolation procedure followed by silver oxide oxidation gave only recovered vinylquinone XI and no isobutylquinone XXXI. However, lithium aluminum hydride must be involved in some way in its formation, since treatment of the reaction mixture with Claisen alkali and then silver oxide gave the vinylquinone XI in 60% yield and no isobutylquinone XXXI.



XXX

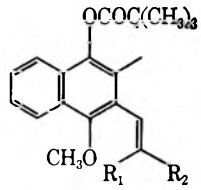


XXXI

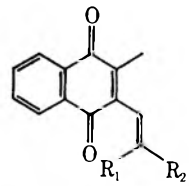
As a method for synthesizing vinylquinones, this procedure may be useful when the ylide is readily available since the diacetate aldehyde XXIIc is easily obtained. However, the reaction of one or both of the ester groups with the Wittig reagent, necessitating the use of at least 3 equiv of ylide, makes this procedure prohibitively expensive with difficultly available ylides.

On the assumption that the 4-acetoxy group might be the major source of the ester–ylide reaction, the same procedure was applied to XXIId in which the 4-methoxy group has replaced the acetoxy, but the results were essentially the same. Clearly, a much more hindered ester was required, and we turned to the 1-pivaloyloxy-4-methoxyaldehyde XXIIe.

When XXIIe was treated with isopropylidenetriphenylphosphorane, reaction occurred rapidly and practically quantitatively to give the corresponding 4-methoxy-2-methyl-3-(2-methyl-1-propenyl)-1-naphthol pivalate (XXXIIa). The pivaloyl group was removed with lithium aluminum hydride, and the intermediate naphthol was oxidized to the vinylquinone XI in 88% over-all yield from aldehyde XXIIe. Again, this procedure applied to XXIIe and *n*-butylidenetriphenylphosphorane gave a *cis–trans* mixture (the stereochemistry of these compounds is treated in detail in a later section) of the vinylquinone XXXIIIa in good yield. Clearly, an excellent protecting pattern—1-pivaloyloxy-4-methoxy—had been found which allows synthesis of vinylquinones in high yield with respect to naphthaldehyde and ylide.



XXXIIa, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_2CH_2CH_3$
c, $R_1 = CH_3$; $R_2 = CH_2CH_2CH_3$
d, $R_1 = R_2 = CH_2CH_3$
e, $R_1 = H$; $R_2 = C_6H_5$
f, $R_1 = CH_3$; $R_2 = n\text{-}C_6H_{13}$
g, $R_1 = CH_3$; $R_2 = CH_2(CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2)_3H$



XXXIIIa, $R_1, R_2 = H, CH_2CH_2CH_3$
b, $R_1, R_2 = CH_3, CH_2CH_2CH_3$
c, $R_1, R_2 = H, C_6H_5$
d, $R_1, R_2 = CH_3, n\text{-}C_6H_{13}$
e, $R_1, R_2 = CH_3, CH_2(CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2)_3H$

To extend the scope of this synthesis, we next investigated its application to unsymmetrical secondary ylides, since this would be needed for the synthesis of chlorobiumquinone (I) and presumably other natural vinylquinones. For this purpose, a secondary alkyltriphenylphosphonium halide would be needed. Six such compounds have been reported in the literature, prepared by heating triphenylphosphine and the halide, neat. Two of these (cyclopentyl,[25] and cyclohexyl[25,26]) offer no complications, since only one salt can be formed; the obtention of isomers is possible with the others (isopropyl,[27] 2-butyl,[26,28] 2-octyl,[28] and α-phenylethyl[26]).

(25) A. Moercker, *Org. Reactions*, **14**, 270 (1965).
(26) H. J. Bestmann and O. Kratzer, *Ber.*, **96**, 1899 (1963).
(27) (a) U. H. M. Fagerlund and D. R. Idler, *J. Amer. Chem. Soc.*, **79**, 6473 (1957); (b) G. Wittig and D. Wittenberg, *Ann.*, **606**, 1 (1957).
(28) C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963).

We pursued the synthesis of 2-pentyltriphenylphosphonium bromide by heating triphenylphosphine and pure 2-bromopentane,[29] and the best yield of phosphonium salt was obtained with excess phosphine at 170° in a sealed tube for 48 hr. However, glpc showed the recovered bromopentane to be a 2:1 mixture of 2- and 3-bromopentanes, and this was true also for lower temperature and shorter time reactions where conversion into salt was less.

This result strongly suggested that the phosphonium salt was also a mixture, and this was established as the case by conversion into ylide and reaction with the 1-pivaloyloxy-4-methoxyaldehyde XXIIe as above. The product was a mixture of *cis*- and *trans*-2-methyl-1-pentenylhydroquinones XXXIIc and 2-ethyl-1-butenylhydroquinone XXXIId. Again, when the triphenylphosphonium salt of 6,10,14-trimethyl-2-pentadecyl bromide[30] was used similarly and the reaction carried through to quinone, at least four products were isolated by tlc, and none was the vinylquinone which would have resulted from unrearranged bromide.

This formation of rearranged bromide undoubtedly occurs by elimination and readdition of hydrogen bromide. For example, when 2-bromopentane was heated at 170° for 24 hr, a 1:9 mixture of 3- and 2-bromopentanes was obtained; in the presence of 10 mol % triphenylphosphine or pentylphosphonium salt, the isomer ratio became 1:2. In both cases, hydrogen bromide and olefin also were formed. Similar observations obtained with 2-bromooctane, but in no case was any primary bromide or its phosphonium salt formed. The phosphonium salt, once formed, appears to be stable to these conditions since the triphenylphosphonium salts of 3- and 2-bromopentanes, heated with 2-bromooctane, gave only octenes and bromooctanes.

Attempts to prepare phosphonium salts under milder, nonrearranging, conditions failed. The same results were obtained with 2-iodopentane at 130°, and the 2-pentyl tosylate gave entirely olefin and no phosphonium salt. Clearly, this direct formation of phosphonium salts from secondary halides is useful only when no other secondary or tertiary isomers are possible.

An alternative route to 2-alkylphosphonium salts is available by alkylation of the *n*-alkylidenephosphorane. This can be quite successfully accomplished with iodomethane with which we alkylated *n*-butylidenetriphenylphosphorane to pure 2-pentyltriphenylphosphonium iodide;[31] we also prepared other secondary phosphonium salts in this way. The only drawback to this method might be residual primary salt which was not converted into ylide and which would lead to a difficultly removed impurity; however, care in the stoichiometry should eliminate this possibility.

Alkylation with other than iodomethane leads to mixtures because of dehydrohalogenation of the haloalkane. Formation of the tertiary salt by transylidation followed by alkylation of the secondary ylide is also a possibility.[32] In tetrahydrofuran at 25°, alkylation

$$RCH{=}P(C_6H_5)_3 \xrightarrow{R'X}$$

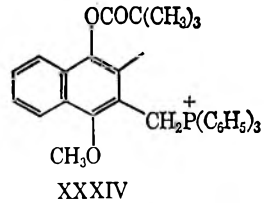
$$RCH\overset{R'}{\underset{|}{}}\overset{+}{P}(C_6H_5)_3,\ RCH_2\overset{+}{P}(C_6H_5)_3,\ RC\overset{R'}{\underset{R'}{}}\overset{+}{P}(C_6H_5)_3,$$

of ethylidenetriphenylphosphorane with either 1-bromopropane or 1-bromobutane led to 80% the secondary and 20% the regenerated primary phosphonium salt; no tertiary salt was formed. The distribution between secondary and primary could be easily determined by the ratio of the α-methinyl proton peak at about δ 5 to the α-methylene proton absorption at about δ 4. Although this method results in a mixture,[33,34] it may have useful applications where the alkylating group is large, making for a ready separation of the salts or the subsequent products.

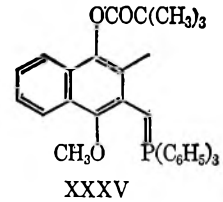
In summary, the preparation of vinylnaphthoquinones *via* 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde pivalate (XXIIe) and an alkylidenetriphenylphosphorane is an excellent method. No difficulties are encountered when the alkylidene group is primary or secondary, if no isomeric secondary structures are possible for the latter. Other pure secondary ylides may be prepared if the branching group is methyl, *via* alkylation with iodomethane. However, for larger branching group mixtures are encountered.

B. *Via* the Naphthalenic Ylide.—Because of the slight limitation in scope of potential side chains and the fact that in many cases the corresponding aldehyde or ketone would be readily available, the alternate approach using the naphthalenic ylide was investigated. Treatment of 4-methoxy-2-methyl-3-chloromethyl-1-naphthol pivalate (XXIX) with triphenylphosphine in refluxing benzene gave the naphthylmethyl salt XXXIV in quantitative yield. The naphthalenic ylide XXXV was generated by adding butyllithium to a suspension of this salt in toluene, and the addition of benzaldehyde caused immediate reaction at room temperature; an essentially quantitative yield of the styrylnaphthalene XXXIIe was isolated.

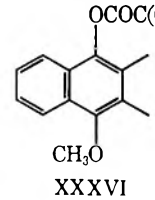
With 2-octanone and ylide XXXV reaction was much slower. The course of the reaction could be followed by titration of aliquots with standard benzaldehyde solutions to disappearance of the orange–red ylide color; 72 hr at 110° was required for complete consumption of ylid. The reaction product consisted of the desired



XXXIV



XXXV



XXXVI

(29) J. Cason and J. S. Correia, *J. Org. Chem.*, **26**, 3645 (1961).

(30) Prepared from 6,10,14-trimethyl-2-pentadecanone [S. J. DiMari, C. D. Snyder, and H. Rapoport, *Biochemistry*, **7**, 2301 (1968)] by reduction to the alcohol and conversion into the bromide *via* the tosylate.

(31) H. J. Bestmann and F. Seng, *Tetrahedron*, **21**, 1373 (1965).

(32) S. Tripett, *Advan. Org. Chem.*, **1**, 83 (1960); D. Seyferth and G. Singh *J. Amer. Chem. Soc.*, **87**, 4156 (1965).

(33) H. J. Bestmann and E. Kranz, *Angew. Chem.*, **79**, 95 (1967).

(34) The recent alkylation of α-lithiophosphonic acid bisamides may offer some advantage: E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5652 (1967).

2-methyl-1-octenylnaphthohydroquinone XXXIIf in about 30% yield, but the 2,3-dimethyl compound XXXVI was isolated as well.

This undoubtedly results from aldol-type condensation of the less reactive ketone, catalyzed by ylide and liberating water or hydroxide ion, which in turn reacts with ylide to give the dimethyl compound XXXVI and triphenylphosphine oxide.[35] To test this interpretation, 2-octanone-d_5-1,1,1,3,3 was prepared[36] and used in the condensation with naphthalenic ylide XXXV. The 2,3-dimethyl compound XXXVI now obtained contained about 70% deuterium in the C-3 methyl, as would be anticipated if two atoms of deuterium were incorporated from the ketone.

With 6,10,14-trimethyl-2-pentadecanone, a 21% yield of the vinyl compound XXXIIg was obtained, and again the 2,3-dimethyl compound XXXVI was formed. The amount of the latter compound fluctuated in the various condensations, but it could not be eliminated. Apparently, it will always be formed to some extent when less reactive ketones, which can self-condense, are used. Although this leads to a decreased yield, no vinylhydroquinone by-products are formed, and the naphthalenic ylide procedure is a good method for synthesizing the vinyl side chain when the carbonyl component is available.

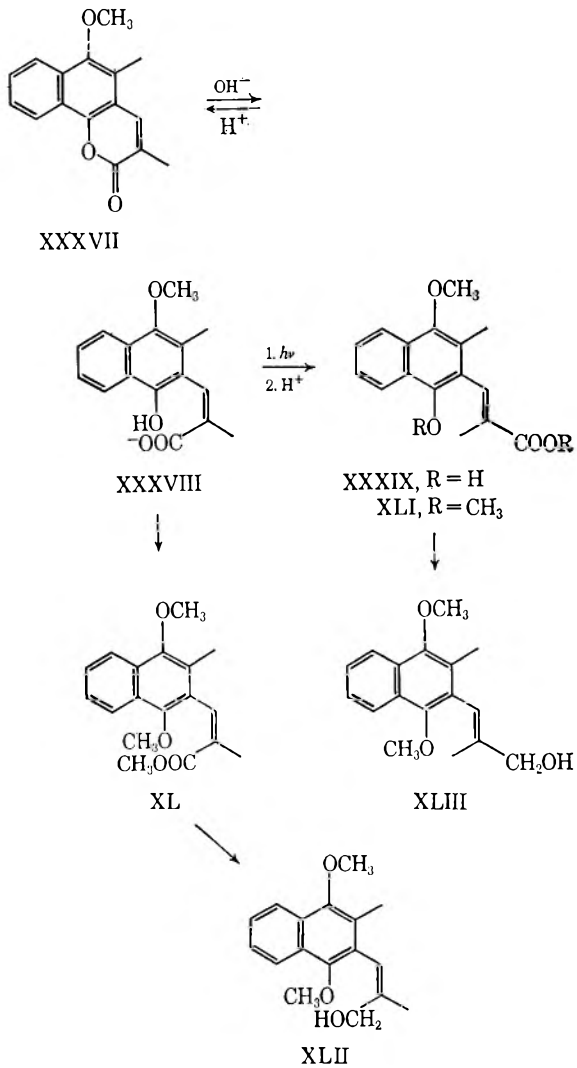
Stereochemistry.—In all of the syntheses described above where *cis* and *trans* isomers are possible, both isomers were indeed found and definitive stereochemistry was assigned on the basis of nmr spectra.

For the β-monosubstituted compound, 1-pentenylhydroquinone XXXIIb, stereochemical assignment relied on the splitting constants for the vinyl protons. By glpc, the synthetic olefinic product was separated into two fractions in the ratio 2:3, the first of which in the vinyl proton region of the nmr shows an AB quartet, J = 11 Hz, with the doublet due to the β-vinyl proton split into triplets, J = 7 Hz, by the adjacent methylene. The second fraction had a similar pattern with J = 17 Hz. From these values and by comparison with the spectra of *cis*- and *trans*-isoeugenos,[37] the isomer (J = 11 Hz) eluted first is assigned the *cis* configuration and the isomer (J = 17 Hz) eluted second the *trans*. In addition, the signals due to the *n*-propyl group are shifted upfield to lower δ values in the *cis* isomer relative to the *trans*, as would be expected if the *cis*-alkyl group is shielded by being held in the π-electron cloud of the aromatic ring.

Since the stereochemical assignments for the β,β-dialkylvinyl compounds would rest solely on the interaction with the aromatic nucleus, an unassailable isomeric pair was needed as models. These were derived from the coumarin XXXVII with its fixed, *trans*-vinyl methyl. Ring opening with alkali led to the salt XXXVIII which on acidification quantitatively recyclized to the coumarin. However, if this salt was irradiated with a low-pressure mercury lamp,[38] nmr analysis revealed the appearance of a second vinyl methyl group which grew to 70% of the total. This represents the *trans* acid XXXIX which can be isolated by acidification whereas the *cis* acid immediately reverts into coumarin. Therefore, a pure sample of each isomer can be readily obtained.

These isomerically pure acids (salts), XXXVIII and XXXIX, were then methylated under mild conditions,[39] a single, pure isomer of the 1,4-dimethoxy methyl ester (XL and XLI) being obtained in each case thus establishing stereochemical integrity. The methyl ester XL contains a *trans*-methyl group which appears at δ 2.15, whereas the methyl ester XLI contains a *cis*-methyl appearing at δ 1.8. Each isomer was reduced to the corresponding allylic alcohol (XLII and XLIII) and the *trans*-methyl signal in XLII appears at δ 2.08 while the *cis*-methyl signal in XLIII is at δ 1.58. Thus shielding by the aromatic ring current for the *cis*-methyl is established in each case, $\Delta\delta_{trans-cis}$ being 0.35 for the methyl esters and 0.50 for the allylic alcohols. See Scheme II.

SCHEME II



The 2-methyl-1-propenylhydroquinone XXXIIa shows two vinyl methyl signals, one at δ 1.95 (*trans* to ring) and the other at δ 1.55 (*cis* to the ring) ($\Delta\delta_{trans-cis}$

(35) G. Wittig, W. Böll, and K. Krück [*Ann.*, **95**, 2514 (1962)] have observed similar behavior in the condensation of cyclopentanone with methoxymethylenetriphenylphosphorane.

(36) Following the procedure of A. C. Cope and D. M. Gale, *J. Amer. Chem. Soc.*, **85**, 3747 (1963).

(37) H. Rottendorf, S. Sternhell, and J. R. Wilmshurst, *Aust. J. Chem.*, **18**, 1759 (1965); G. P. Newsoroff and S. Sternhell, *ibid.*, **19**, 1667 (1966).

(38) F. A. Haskins and H. J. Gorz, *Arch. Biochem. Biophys.*, **81**, 204 (1959).

(39) R. Kuhn and H. Trischmann, *Ber.*, **94**, 2258 (1961).

0.40), completely consistent with the above correlation. In the other vinylhydroquinone compounds (XXXIIc and f) the isomers were separated by glpc, and in each instance the isomer eluted first has a vinyl methyl signal at δ 1.95 and therefore is the *cis* isomer (*trans* methyl). The second fraction has its vinyl methyl at δ 1.55 and thus is the *trans* isomer. Signals due to the other β-alkyl groups show similar shifts.

The 3-styrylhydroquinone XXXIIe is tentatively assigned *trans* stereochemistry by analogy with the stilbenes where the vinyl protons appear as singlets at δ 6.55 and 7.10 for the *cis* and *trans* isomers, respectively. In XXXIIe all vinyl and aromatic absorption falls in a multiplet from δ 7.1 to 7.8; however, there is a sharp singlet at δ 7.15 which is presumably due to the *trans* vinyl protons. The remaining vinylhydroquinone (2,6,10,14-tetramethyl-1-pentadecenyl-) XXXIIg, was separated into isomers at the quinone stage.

Preparation and Properties of the Vinylnaphthoquinones.—In every case, the pivaloyl group was removed by reductive cleavage with lithium aluminum hydride to the hydroquinone 4-monomethyl ethers. A single isomer was obtained each time, and the nmr spectra were essentially unchanged except that the pivalate signal was absent, showing maintenance of stereochemistry during this removal. Oxidation to the quinones was then easily accomplished with ferric chloride in aqueous acetonitrile or ethanol–ether, as required for solubility.

The nmr spectra of the vinylquinones are similar to those of the pivalate esters and hydroquinone monomethyl ethers from which they were derived, showing the same distinctive vinyl methyl resonances which allow stereochemical assignment and show that no isomerization had occurred in the conversion. The *cis*- and *trans*-2,6,10,14-tetramethyl-1-pentadecenylvinylquinones XXXIIIe were separated by tlc at this stage and assigned stereochemistry on the same nmr basis.

In their uv absorption all the vinylnaphthoquinones are similar; however there are sufficient differences to allow all of the various substitution patterns to be distinguished. All types (unsubstituted, β-mono-, and β,β-disubstituted) have their most intense absorption around 250 nm. The unsubstituted and β-monosubstituted compounds then have a lesser peak at ~280 nm and a still weaker maximum at 330 nm. The *trans*-β-monosubstituted compound shows the longest wavelength absorption of the group with another peak at 365 nm, probably the result of substitution which still allows coplanarity and full conjugation between vinyl and naphthoquinone chromophores. In the β,β-disubstituted compounds (*cis* and *trans* isomers identical) the 280-nm peak is shifted hipsochromically to a shoulder at 264 nm, this effect probably being the result of decreased planarity between the naphthoquinone and the β,β-disubstituted vinyl group. The four types of uv absorptions are shown in Figure 1.

In their mass spectra, both the *cis*- and *trans*-2-methyl-1-pentenylvinylnaphthoquinones (XXXIIIb) give identical fragmentation patterns. The molecular ion, *m/e* 254, is also the base peak. Other strong peaks are at *m/e* 239 (M − 15), 225 (M − 29), and 211 (M − 43), probably arising from loss of alkyl groups from the vinyl side chain.

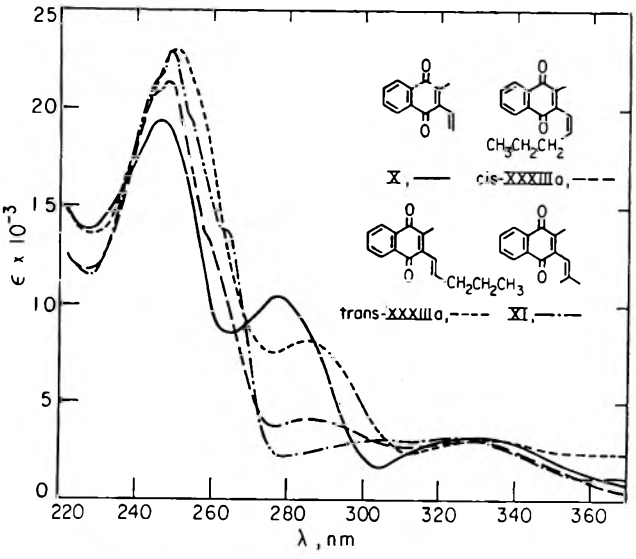


Figure 1.—Ultraviolet absorption spectra of 2-methyl-3-vinyl-1,4-naphthoquinone (X), *cis*-2-methyl-3-(1-pentenyl)-1,4-naphthoquinone (*cis* XXXIIIa), *trans*-2-methyl-3-(1-pentenyl)-1,4-naphthoquinone (*trans* XXXIIIa), and 2-methyl-3-(2-methyl-1-propenyl)-1,4-naphthoquinone (XI) in isooctane.

Experimental Section[40]

2-Methyl-3-vinyl-1,4-naphthoquinone (X) was prepared by heating 3-(1-bromoethyl)-2-methyl-1,4-naphthoquinone (IX) with sodium acetate in glacial acetic acid to 120–125° as previously described:[14] mp 79.5–80.5° (lit.[14] mp 81–82°); λ_{max} 330 nm (ϵ 3300), 278 (10,400), 246 (19,400); nmr (CCl_4) δ 5.57 (d, J = 2 Hz), 5.7 (t, J = 2 Hz), 6.0 (d, J = 2 Hz) ArC=CH_2; 6.45 (d, J = 11 Hz), 6.74 (d, J = 11 Hz) ArCH=C.

β,β-Dimethylacryloyl Peroxide.—A solution of 2.4 g of β,β-dimethylacryloyl chloride, bp 60–61° (30 mm) [lit.[41] bp 59–61° (30 mm)], dissolved in 8 ml of ether was converted into β,β-dimethylacryloyl peroxide in 50% yield following the general procedure for the preparation of diacyl peroxides.[17]

2-Methyl-1,4-naphthalenediol Diisobutyrate (XVI).—Boron trifluoride was bubbled through a suspension of 5 g of 2-methyl-1,4-naphthalenediol (XIV) in 30 ml of isobutyric acid cooled in an ice bath. When the internal temperature reached 80° (several minutes) and the hydroquinone dissolved, the solution was poured onto crushed ice and allowed to stand overnight at 0°. The upper aqueous layer was decanted, and the remaining oil crystallized on addition of ethanol. Recrystallization from ethanol gave 4 g (44%) of 2-methyl-1,4-naphthalenediol diisobutyrate (XVI), mp 75° (lit.[18] mp 73–74°).

3-Cyanomethyl-1,4-dimethoxy-2-methylnaphthalene (XVIII).—To a solution of 2.2 g (33 mmol) of potassium cyanide in 8 ml of water was added 5.5 g (22 mmol) of 3-chloromethyl-1,4-dimethoxy-2-methylnaphthalene (XVII)[42] dissolved in 27 ml of 95% ethanol. The solution was heated on a steam bath for 45 min; the ethanol was evaporated; and the residue was diluted fivefold with water and allowed to stand at 0°. The resulting

(40) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California at Berkeley; uv spectra were obtained in isooctane unless otherwise noted on a Cary 14 spectrophotometer; nmr spectra were obtained on a A-60 Varian Associates instrument in deuteriochloroform unless otherwise stated with internal TMS, δ 0; all evaporations were *in vacuo* using a rotary evaporator, and all reactions were carried out in a nitrogen atmosphere. Glpc analyses were performed on a 5 ft × 1/4 in. column, 5 or 10% SE-30 on acid-washed, DMCS-treated (60–80 mesh) Chromosorb P, at 200–250° and a flow rate of 60–100 ml of He/min. Preparative work was performed on a 8 ft × 3/8 in. column, 10% SE-30 on acid-washed, DMCS-treated (60–80 mesh) Chromosorb P, at 200–250° and a flow rate of 200 ml of He/min. Glpc analysis of alkyl halides and olefins was carried out on a 10 ft × 1/4 in. column, 10 or 20% polypropylene glycol on (60–80 mesh) Chromosorb P, at 60–100° and a flow rate of 60 ml of He/min. Some exploratory experiments were performed by J. H. Supple and O. Muscio, to whom we are grateful.

(41) L. I. Smith and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **71**, 2671 (1949).

(42) L. I. Smith, S. Wawzonek, and H. C. Miller, *J. Org. Chem.*, **6**, 229 (1941).

crystals were filtered, washed with water, dried, and recrystallized from petroleum ether to give 4 g (75%) of 3-cyanomethyl-1,4-dimethoxy-2-methylnaphthalene (XVIII), mp 105°.

Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.7; N, 5.8. Found: C, 74.4; N, 5.8.

3-(2-Aminoethyl)-1,4-dimethoxy-2-methylnaphthalene (XIX).—A solution of 4 g (17 mmol) of 3-cyanomethyl-1,4-dimethoxy-2-methylnaphthalene (XVIII) in 60 ml of ether was added slowly to a stirred suspension of 4 g (0.105 mol) of lithium aluminum hydride in 60 ml of ether. Stirring was continued an additional 15 min, and excess hydride was destroyed with ice followed by 200 ml of a 25% solution of sodium bitartrate in water. The solution was extracted three times with 200-ml portions of ether, and the combined ether extracts were washed with 1.5 *N* hydrochloric acid. After being made alkaline with 30% aqueous sodium hydroxide, the acid washes were extracted with ether, and the combined ether phase was washed free of alkali, dried, and evaporated to give 2.9 g (72% yield) of 3-(2-aminoethyl)-1,4-dimethoxy-2-methylnaphthalene (XIX).

The hydrochloride was recrystallized from absolute ethanol, mp 270°.

Anal. Calcd for $C_{15}H_{20}O_2NCl$: N, 5.0. Found: N, 4.9.

1,4-Dimethoxy-3-(2-dimethylaminoethyl)-2-methylnaphthalene Methiodide.—A solution of 5.3 g (21 mmol) of 3-(2-aminoethyl)-1,4-dimethoxy-2-methylnaphthalene (XIX) in 300 ml of absolute ethanol containing 25 ml of iodomethane and 24 g of anhydrous potassium carbonate was refluxed for 6 hr, 25 ml of iodomethane was added, and the solution was refluxed for 24 hr. Then 25 ml of iodomethane and 24 g of anhydrous potassium carbonate were added, and the solution was refluxed for 24 hr. The resulting suspension was evaporated, the residue was dissolved in water and cooled to 0°, and the crystals which formed were removed. Recrystallization from ethanol gave 3.7 g (43%) of 1,4-dimethoxy-3-(2-dimethylaminoethyl)-2-methylnaphthalene methiodide, mp 265°.

Anal. Calcd for $C_{18}H_{26}O_2NI$: C, 52.1; H, 6.3; N, 3.4; I, 30.6. Found: C, 52.0; H, 6.3; N, 3.2; I, 30.3.

1,4-Dimethoxy-2-methyl-3-vinylnaphthalene (XX).—A solution of 3.7 g of 1,4-dimethoxy-3-(2-dimethylaminoethyl)-2-methylnaphthalene methiodide in 490 ml of ethanol and 300 ml of 30% aqueous potassium hydroxide was refluxed for 2 hr. The ethanol was evaporated; the remaining solution was extracted with ether; and the ether extracts were washed with water, dried, and evaporated. The residue was crystallized from methanol to give 1.3 g (62% yield) of 1,4-dimethoxy-2-methyl-3-vinylnaphthalene (XX): mp 42°; $\lambda_{max}^{C_2H_5OH}$ 290–295 nm (sh), 243 (ε 58,000); nmr (CS_2) δ 5.5 (d, J = 3 Hz), 5.67 (t, J = 3 Hz) 5.95 (d, J = 3 Hz) ArC=CH_2; 6.75 (d, J = 11 Hz), 7.05 (d, J = 11 Hz) ArCH=C.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.9; H, 7.2.

3-Ethyl-2-methyl-1,4-naphthoquinone (XXI) and 2-Methyl-3-vinyl-1,4-naphthoquinone (X).—A mixture of 200 mg (0.9 mmol) of 1,4-dimethoxy-2-methyl-3-vinylnaphthalene (XX) and 1.2 g (10.5 mmol) of pyridine hydrochloride was heated at 220° for 8 min, after which it was cooled, diluted with 5 ml of water, and extracted with ether. The ether extract was dried and evaporated, and the residue was dissolved in 20 ml of ether; 1 g of anhydrous sodium sulfate and 1 g of silver oxide were added, and the mixture was shaken in the dark for 30 min, filtered, and the ether evaporated. Chromatography on Decalso and elution with isooctane gave (fraction 1) 30 mg (15% yield) of starting material and (fractions 2–5) 20 mg (14%) of impure 3-ethyl-2-methyl-1,4-naphthoquinone (XXI): mp 72–73° after crystallization from methanol (lit.[43] mp 72–72.6°); λ_{max} 327 nm (ε 3100), 268 (17,000), 259 (16,900), 248 (18,600), 243 (23,600). Fractions 5–7 gave on evaporation 30 mg which was crystallized from acetone giving 15 mg (10%) of 2-methyl-3-vinyl-1,4-naphthoquinone (X).

1,4-Dimethoxy-2-methyl-3-naphthaldehyde.—To a solution of 10.2 g (0.45 g-atom) of sodium dissolved in 300 ml of anhydrous ethanol was added 54 ml (0.6 mol) of 2-nitropropane followed by a solution of 7.5 g (0.03 mol) of 3-chloromethyl-1,4-dimethoxy-2-methylnaphthalene (XVII) in 600 ml of absolute ether. After 24 hr at 25° the solvent was evaporated; the residue was dissolved in water and extracted with ether; the ether extract was washed, dried, and evaporated; and the residue was crystallized from ethanol giving 3 g (43%) of 1,4-dimethoxy-2-methyl-3-naphthaldehyde: mp 92–93°; $\lambda_{max}^{C_2H_5OH}$ 285–292 nm (sh), 258 (ε 43,000); nmr (CS_2) δ 3.85 (s, OCH_3), 4.0 (s, OCH_3), 10.7 (s, ArCHO).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.8; H, 6.2.

1,4-Dihydroxy-2-methyl-3-naphthaldehyde (XXIIa) was prepared by treatment of 2-methyl-1,4-naphthalenediol (XIV) with zinc cyanide and hydrogen chloride in ether as previously described:[21] mp 159.5–161° (lit.[21] mp 158–160°).

1,4-Dihydroxy-2-methyl-3-naphthaldehyde 1-Acetate (XXIIb).—A suspension of 9.6 g (33.6 mmol) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde diacetate (XXIIc) in 70 ml of 50% aqueous acetic acid was refluxed for 90 min to give a clear yellow solution. Cooling gave 7.4 g (90% yield) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde 1-acetate (XXIIb), mp 126–127°.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.8; H, 5.0. Found: C, 68.9; H, 5.3.

1,4-Dihydroxy-2-methyl-3-naphthaldehyde Tetraacetate (XXIII).—A suspension of 1.4 g of 1,4-dihydroxy-2-methyl-3-naphthaldehyde (XXIIa) in 4 ml of pyridine–acetic anhydride (1:1) was heated at reflux for 30 min. The solution was poured into water and extracted with chloroform which was washed, dried, and evaporated. The crystalline residue was recrystallized twice from methanol to give 1 g (23%) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde tetraacetate (XXIII), mp 169–171°.[44]

Anal. Calcd for $C_{20}H_{20}O_8$: C, 61.9; H, 5.2. Found: C, 61.8; H, 5.0.

1,4-Dihydroxy-2-methyl-3-naphthaldehyde Diacetate (XXIIc).—A solution of 13.5 g (67 mmol) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde (XXIIa) in 10 ml of pyridine and 12 ml of acetic anhydride was stirred at 25° for 1 hr. The precipitate which formed was removed, washed with water, and dissolveed in methylene chloride. Evaporation of the dried methylene chloride and crystallization of the residue twice from chloroform–petroleum ether gave 12.7 g (65%) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde diacetate (XXIIc): mp 202–204°;[45] nmr δ 2.45–2.52 (s, s, s, 2 $ArOCOCH_3$, $ArCH_3$), 10.5 (s, ArCHO).

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 66.8; H, 4.9.

2-Methyl-1,4-naphthalenediol 1-acetate (XXIV) was prepared by selective hydrolysis of 2-methyl-1,4-naphthalenediol diacetate[46] in methanolic ammonia in the manner described:[22] mp 124–125° (lit.[22] mp 124.5–125.8°).

4-Methoxy-2-methyl-1-naphthol (XXVII). A. O^4 Methylation of (XIV).—A solution of 50 g of 2-methyl-1,4-naphthalenediol (XIV), dissolved in 500 ml of methanol containing 20 g of hydrogen chloride, was stirred at room temperature for 24 hr. Threefold dilution with water caused the product to precipitate as a mass of fine needles. The mixture was extracted with ether, washed, dried, and evaporated giving 50 g (98%) of 4-methoxy-2-methyl-1-naphthol (XXVII), mp 101–102.5° (lit.[22] mp 101–103°). Glpc showed the product to be >95% pure, the chief impurity being 1–2% 1,4-dimethoxy-2-methylnaphthalene (XV).

B. Methylation of XXIV and Hydrolysis to XXVII.—A suspension of 50 g (0.23 mol) of 2-methyl-1,4-naphthalenediol 1-acetate (XXIV) in 246 g (1.95 mol) of dimethyl sulfate was cooled at 0° and stirred vigorously as a solution of 193 g (3.5 mol) of potassium hydroxide in 200 ml of water was added dropwise over 90 min. Toward the end of the reaction the oily organic layer solidified, and it was removed, washed, and dried to give 50 g of solid. By glpc it consisted of 80–85% 4-methoxy-2-methyl-1-naphthol acetate (XXV) and 10–15% 1,4-dimethoxy-2-methylnaphthalene (XV).

The solid was dissolved in 500 ml of pentane and cooled to 0°, Claisen' salkali (200 ml) was added slowly with stirring, and the two-phase system was allowed to warm to room temperature. Repeated washing with pentane removed all the 1,4-dimethoxy-2-methylnaphthalene (XV). Cooling to 0° and neutralizing by dropwise addition of concentrated hydrochloric acid followed by extraction with ether which was washed, dried, and evaporated gave 30 g (70% yield) of 4-methoxy-2-methyl-1-naphthol (XXVII), mp 102–103°.

(43) L. F. Fieser and F. C. Chang, *J. Amer. Chem. Soc.*, **64**, 2043 (1942).

(44) J. Madinaveitia [*Rev. Acad. Cienc* (Madrid), **31**, 617 (1934)] reports an unspecified acetate derivative of 1,4-dihydroxy-2-methyl-3-naphthaldehyde with mp 168°.

(45) G. Carrara and G. Bonacci [*Gazz. Chem. Ital.*, **73**, 225 (1943)] report mp 154–155° for the aldehyde diacetate. We have found the following melting points in this series: aldehyde, 159–161°; O^1-monoacetate, 126–127°; diacetate, 202–204°; and tetraacetate, 169–171°.

(46) R. J. Anderson and M. S. Newman, *J. Biol. Chem.*, **103**, 405 (1933).

4-Methoxy-2-methyl-1-naphthol Acetate (XXV).—A mixture of 40 g of 4-methoxy-2-methyl-1-naphthol (XXVII) and 5 g of anhydrous sodium acetate was suspended in 80 ml of acetic anhydride and heated to 100° for 1 hr. The hot solution was then poured onto crushed ice, and the resulting solid was washed, dried, and crystallized from methanol to give 46 g (95%) of 4-methoxy-2-methyl-1-naphthol acetate (XXV): mp 68.5–70° (lit.[22] mp 67–68°); nmr δ 2.22, 2.32 (s, s, $ArCH_3$, $ArOCOCH_3$), 3.8 (s, $ArOCH_3$), 6.5 (s, C-3), 7.3–7.8 (m, C-5, -6, -7), 8.05–8.3 (m, C-8).

3-Chloromethyl-4-methoxy-2-methyl-1-naphthol Acetate (XXVI).—A suspension of 4.6 g (20 mmol) of 4-methoxy-2-methyl-1-naphthol acetate (XXV) in 15 ml of 36% formalin and 20 ml of concentrated hydrochoric acid was stirred in an ice bath, and hydrogen chloride was bubbled through at a rate such that the internal temperature did not rise above 10°. After 1 hr, the ice bath was removed, and hydrogen chloride addition was continued for 12 hr. The mixtue was poured onto ice, and the resulting solid was dried and crystallized twice from ether–hexane to give 3.6 g (65%) of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol acetate (XXVI), mp 103–103.5°.

Anal. Calcd for $C_{15}H_{15}ClO_3$: C, 64.7; H, 5.4; Cl, 12.6. Found: C, 64.7; H, 5.2; Cl, 13.0.

1-Hydroxy-4-methoxy-2-methyl-3-naphthaldehyde acetate (XXIId) was prepared from the corresponding chloromethyl compound XXVI, using the 2-nitropropane procedure described in the preparation of 1,4-dimethoxy-2-methyl-3-naphthaldehyde, except that potassium *t*-butoxide in *t*-butyl alcohol was used and the reaction was conducted at 35°. The partially deacetylated naphthol aldehyde was acetylated in acetic anhydride–pyridine and an 82% yield of 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde acetate (XXIId) was obtained: mp 99–100°.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.7; H, 5.5. Found: C, 69.4; H, 5.4.

4-Methoxy-2-methyl-1-naphthol Pivalate (XXVIII).—A solution of 13.5 g (0.13 mol) of pivalic acid in 84 g (0.40 mol) of trifluoroacetic anhydride was added to 25 g (0.13 mmol) of 4-methoxy-2-methyl-1-naphthol (XXVII). After 4 hr at room temperature, benzene was added, and the solution was poured into ice water and extracted with benzene which was washed with 10% aqueous sodium hydroxide and then with water. Evaporation of the benzene and crystallization of the residue from hexane gave 29 g (80% yield) of 4-methoxy-2-methyl-1-naphthol pivalate (XXVIII), mp 90.5–91°.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4. Found: C, 75.1; H, 7.3.

3-Chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate (XXIX) was prepared by chloromethylation of the naphthol pivalate XXVIII in the same manner as described for the chloromethyl acetate XXVI at 40° in acetic acid–HCl instead of aqeuous HCl. A 90% yield of chloromethyl compound was obtained: mp 92–93° from cyclohexane.

Anal. Calcd for $C_{18}H_{21}ClO_3$: C, 67.4; H, 6.6; Cl, 11.1. Found: C, 67.0; H, 6.7; Cl, 11.1.

1-Hydroxy-4-methoxy-2-methyl-3-naphthaldehyde pivalate (XXIIe) was prepared from the chloromethyl compound and 2-nitropropane as described for the corresponding acetate XXIId. The naphthaldehyde pivalate was obtained in 97% yield: mp 81–82° after sublimation at 80° (6 μ).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 71.9; H, 6.9.

Reaction of 1,4-Dihydroxy-2-methyl-3-naphthaldehyde Diacetate (XXIIc) with Isopropylidenetriphenylphosphorane.—Butyllithium in hexane (3.0 ml, 1.6 *N*) was added to a suspension of 1.87 g (4.85 mmol) of isopropyltriphenylphosphonium bromide[23a] in 20 ml of tetrahydrofuran. The ylide solution was stirred 90 min; 13 ml (2.5 mmol) was removed and added dropwise to a suspension of 0.7 g (2.45 mmol) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde diacetate (XXIIc) in 20 ml of tetrahydrofuran; the solution was refluxed 3.5 hr; 0.3 g (8.0 mmol) of lithium aluminum hydride was added; and the mixture was refluxed an additional 3 hr. It was cooled to 0°; wet ether was added followed by saturated aqueous ammonium chloride; the ether phase was removed; the aqueous phase was extracted with several portions of ether; and the combined extracts were washed and dried. Silver oxide was then added to the ether, and the suspension was stirred for 30 min, filtered, and evaporated to give a mixture of quinones. Glpc analysis showed three peaks at 12.6, 24.2, and 29 min in the ratio of 4:2:1 based on peak areas. The assignments based on uv, nmr, tlc, and glpc comparison with authentic samples are 12.6 min ≡ 2,3-dimethyl-1,4-naphthoquinone (XXX), 24.2 min ≡ 3-isobutyl-2-methyl-1,4-naphthoquinone (XXXI), and 29 min ≡ 2-methyl-3-(2-methyl-1-propenyl)-1,4-naphthoquinone (XI).

3-Isobutyl-2-methyl-1,4-naphthoquinone (XXXI) was prepared as described for similar compounds.[17] This material has been reported[16] as melting at 123°. However, we find it to be a clear yellow oil, molecularly distilling at 60° (5 μ): nmr (CCl_4) δ 0.92 (d, Ar—C—$CH(CH_3)$—CH_3), 2.5 (d, Ar—CH_2—CH<); mass spectrum *m/e* 228 (M^+).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.8; H, 6.9.

2-Methyl-3-(2-methyl-1-propenyl)-1,4-naphthalenediol Diacetate.—Zinc dust (2 g) and pyridine (1 ml) were added to a solution of 2 g of 2-methyl-3-(2-methyl-1-propenyl)-1,4-naphthoquinone (XI) dissolved in 20 ml of acetic anhydride, which was stirred 20 min at 0° and then at room temperature for 24 hr. Acetic acid (20 ml) was added; the mixture was heated to reflux and filtered; the precipitate was washed with hot acetic acid; and the combined filtrates poured onto crushed ice. The product solidified and was crystallized from ethanol–water to give 1.95 g (70% yield) of 2-methyl-2-(2-methyl-1-propenyl)-1,4-naphthalenediol diacetate: mp 161–161.5°; nmr δ 1.54 (d, *J* = 1 Hz, *cis* ArC=C—CH_3), 1.9 (d, *J* = 2 Hz, *trans* ArC=C—CH_3), 6.0 (b, ArCH=).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.0; H, 6.4. Found: C, 72.8; H, 6.2.

4-Methoxy-2-methyl-3-(2-methyl-1-propenyl)-1-naphthol Pivalate (XXXIIa).—Butyllithium (4.6 ml, 1.3 *N*, 6 mmol) was added dropwise to a stirred suspension of 2.32 g (6 mmol) of isopropyltriphenylphosphonium bromide in 20 ml of tetrahydrofuran, and after 2 hr this solution was added dropwise to 1.5 g (5 mmol) of 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde pivalate (XXIIe) in 6 ml of tetrahydrofuran. The solution was stirred for 1 hr and evaporated. Then the residue was chromatographed on silica gel, eluting with benzene, to give 1.5 g (92% yield) of 4-methoxy-2-methyl-3-(2-methyl-1-propenyl)-1-naphthol pivalate (XXXIIa), pure by tlc and glpc: nmr (CCl_4) δ 1.55 (d, *J* = 1 Hz, *cis* ArC=C—CH_3), 1.95 (d, *J* = 1 Hz, *trans* ArC=C—CH_3), 6.2 (b, ArCH=).

***cis*- and *trans*-4-methoxy-2-methyl-3-(1-pentenyl)-1-naphthol pivalates (XXXIIb)** were prepared from *n*-butyltriphenylphosphonium bromide[47] and 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde pivalate (XXIIe) in the same manner as described for the preparation of 4-methoxy-2-methyl-3-(2-methyl-1-propenyl)-1-naphthol pivalate (XXXIIa). A mixture of 1.55 g (88% yield) was obtained of *cis*- and *trans*-4-methoxy-2-methyl-3-(1-pentenyl)-1-naphthol pivalates. The *cis* and *trans* isomers were present in a ratio of 2:3 and were separated by glpc: R_T *cis* 35 min, *trans* 55 min.

cis **XXXIIb**: nmr (CCl_4) δ 0.83 (t, *J* = 7 Hz, CH_2CH_3), 5.72 (t, *J* = 7 Hz), 5.9 (t, *J* = 7 Hz), *trans* ArC=C—H, 6.38 (d, *J* = 11 Hz, ArCH=C).

trans **XXXIIb**: nmr (CCl_4) δ 0.95 (t, *J* = 7 Hz, CH_2CH_3); 5.92 (t, *J* = 5 Hz), 6.2 (t, *J* = 5 Hz) *cis* ArC=CH—; 6.45 (d, *J* = 17 Hz, ArCH=C).

***cis*- and *trans*-4-methoxy-2-methyl-3-(2-methyl-1-pentenyl)-1-naphthol pivalates (XXXIIc)** were prepared from 2-pentyltriphenylphosphonium iodide and 1-hydroxy-4-methoxy-2-methyl-3-naphthaldehyde pivalate (XXIIe) in the same manner as described for 4-methoxy-2-methyl-3-(2-methyl-1-propenyl)-1-naphthol pivalate (XXXIIa). A mixture of 1.6 g (85% yield) was obtained of *cis*- and *trans*-4-methoxy-2-methyl-3-(2-methyl-1-pentenyl)-1-naphthol pivalates. The *cis* and *trans* isomers were present in a ratio of 1:1 and were separated by glpc: R_T *cis* 30 min, *trans* 42 min.

cis **XXXIIc**: nmr (CCl_4) δ 0.78 (t, *J* = 7 Hz, CH_2CH_3), 1.95 (d, *J* = 1 Hz, *trans* ArC=C—CH_3), 6.15 (b, ArCH=C).

trans **XXXIIc**: nmr (CCl_4) δ 1.0 (t, *J* = 7 Hz, CH_2CH_3), 1.55 (d, *J* = 1 Hz, *cis* ArC=C—CH_3) 6.15 (b, ArCH=C).

2- and 3-Pentyltriphenylphosphonium Bromides.—A mixture of 20 g (76 mmol) of triphenylphosphine and 11.5 g (76 mmol) of 2-bromopentane[29] was sealed in a glass tube in a nitrogen atmosphere and heated at 170° for 48 hr. The tube was cooled to room temperature; the contents were dissolved in ethanol and decolorized with carbon; and the salt was precipitated by addition of ether. Solution in ethanol and reprecipitation by

(47) R. Mechoulam and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 4386 (1958).

addition of ether gave 18 g (57%) of a mixture of 2- and 3-pentyltriphenylphosphonium bromides: mp 208–211°; nmr δ 0.75–2.0 (t, J = 6 Hz, CH_3–C-5), 1.6 (d, J = 7 Hz, $\geqslant P^+$—C-(CH_3)<, m, $\geqslant$P—C—CH_2—), 4.7–5.25 (b, $\geqslant$P—CH<), 7.65–8.3 (m, Ph_3P^+—).

Anal. Calcd for $C_{23}H_{26}BrP$: C, 66.8; H, 6.3. Found: C, 66.3; H, 6.3.

Glpc analysis of the unreacted bromopentane showed two distinct peaks (R_T 60 and 64 min) in the ratio of 2:1, shown to be 2- and 3-bromopentanes.

2-Pentyltriphenylphosphonium Iodide.—Butyllithium in hexane (18.5 ml, 1.6 N, 0.3 mol) was added dropwise to a suspension of 12 g (30 mmol) of n-butyltriphenylphosphonium bromide in 90 ml of tetrahydrofuran. The solution was stirred for 2 hr, and then the clear red supernatant was added dropwise to a solution of 0.85 g (60 mmol) of iodomethane in 10 ml of tetrahydrofuran. Reaction was immediate, and a white solid precipitated from solution. The solvent was evaporated after stirring for 1 hr, and the residue was purified by solution in ethanol and precipitation with ether to give 7.5 g (53%) of 2-pentyltriphenylphosphonium iodide: mp 172–173° (lit.[31] mp 172°); nmr δ 0.8–2.0 (t, J = 6 Hz, 5-CH_3; two d, J = 7 Hz, —P^+CHCH_3, —P⁺—C—CH_2CH_2), 4.6–5.05 (b, —P^+—CH), 7.65–8.2 (m, Ph_3P^+—).

Alkylation of Ethylidenetriphenylphosphorane with n-Bromobutane.—Butyllithium (6.3 ml, 10 mmol, 1.6 N) in hexane was added dropwise to a suspension of 3.71 g (10 mmol) of ethyltriphenylphosphonium bromide[27b] suspended in 20 ml of tetrahydrofuran. The mixture was stirred 1 hr; the suspended salts were added to settle; and the clear orange-red supernatant was added to a solution of 3 ml of n-bromobutane in 10 ml of tetrahydrofuran. Complete loss of ylide color required 3 hr as a white precipitate formed. The mixture was evaporated to dryness; the residue was dissolved in chloroform, filtered, and again evaporated to dryness; and the residue was triturated with ether to give a white solid. Comparison of the nmr signals due to the α-methylene protons of ethyltriphenylphosphonium bromide at δ 3.5–4.0 and the α-methinyl proton of 2-pentyltriphenylphosphonium bromide at δ 4.6–5.2 indicated that the product was 20% ethyl salt and 80% 2-pentyl salt.

Triphenylphosphonium salt of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate (XXXIV) was prepared from triphenylphosphine and 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate (XXIX) in refluxing benzene, giving 9 g (77% yield) of the triphenylphosphonium salt of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate, mp 185–186° (d).

Anal. Calcd for $C_{36}H_{36}ClO_3P$: C, 74.2; H, 6.2; Cl, 6.1. Found: C, 74.0; H, 6.4; Cl, 6.0.

4-Methoxy-2-methyl-3-(2-styryl)-1-naphthol Pivalate (XXXIIe).—To a suspension of 2.9 g (5 mmol) of triphenylphosphonium salt of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate (XXXIV) in 15 ml of toluene stirred under nitrogen was added butyllithium (3.3 ml, 1.5 N, 5 mmol) in hexane. The resulting orange-red solution was stirred for 1 hr and 0.5 ml (5 mmol) of benzaldehyde was added. After 1 hr, the solvent was evaporated, and the residue was chromatographed on silica gel, eluting with benzene, to give 1.7 (90% yield) of 4-methoxy-2-methyl-3-(2-styryl)-1-naphthol pivalate pure by tlc: nmr (CCl_4) δ 7.1–7.75 (11 H, m, C-5, -6, -7, -8, Ar—CH=CH—Ph).

***cis*- and *trans*-4-Methoxy-2-methyl-3-(2-methyl-1-octenyl)-1-naphthol Pivalates (XXXIIf).**—To a suspension of 8.74 g (15 mmol) of triphenylphosphonium salt of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate (XXXIV) in 50 ml of toluene was added 8.5 ml (1.6 N, 13.5 mmol) of butyllithium in hexane. The resulting orange-red solution was stirred 1 hr at 25° and then was centrifuged. To the clear supernatant 1.54 g (12 mmol) of 2-octanone was added and the solution was heated at reflux for 72 hr. The solvent was evaporated, and the residue was chromatographed on silica gel, eluting with benzene–hexane (1:1). Initial fractions contained 800 mg (3.05 mmol) of triphenylphosphine and intermediate fractions contained 1.45 g (3.6 mmol, 30% yield) of a mixture of *cis*- and *trans*-4-methoxy-2-methyl-3-(2-methyl-1-octenyl)-1-naphthol pivalates in a ratio of 35:65. The isomers were separated by glpc: R_T *cis* 65 min, *trans* 113 min.

cis **XXXIIf**: nmr (CCl_4) δ 0.78 (t, J = 5 Hz, ArC=C($C)_5$-CH_3), 1.95 (d, J = 1 Hz, *trans* ArC=C—C—CH_3), 6.15 (b, ArCH=).

trans **XXXIIf**: nmr (CCl_4) δ 0.95 (t, J = 5 Hz, ArC=C($C)_5$-CH_3), 1.55 (d, J = 1 Hz, *cis* ArC=C—CH_3), 6.2 (b, ArCH=).

The last fractions contained 700 mg (2.5 mmol) of 2,3-dimethyl-4-methoxy-1-naphthol pivalate (XXXVI) pure by tlc and glpc: nmr (CCl_4) δ 2.15 (s, 2-$ArCH_3$), 2.32 (s, 3-$ArCH_3$).

2-Octanone-1,1,1,3,3-d_5.—A solution of 500 mg of anhydrous potassium carbonate in 25 ml of deuterium oxide and 12 ml of 2-octanone were refluxed for 24 hr; the organic phase was then removed; and fresh K_2CO_3–D_2O was added to it. Three such exchanges were carried out after which the organic layer was distilled to give 10 ml of 2-octanone-1,1,1,3,3,d_5, bp 170–171.5°. The signals present in the nmr spectrum of 2-octanone at δ 2.05 (s, CH_3CO—) and 2.38 (t, J = 6 Hz, —$COCH_2$—) were absent.

***cis*- and *trans*-4-Methoxy-2-methyl-3-(2,6,10,14-tetramethyl-1-pentadecenyl)-1-naphthol Pivalates (XXXIIg).**—The triphenylphosphonium salt of 3-chloromethyl-4-methoxy-2-methyl-1-naphthol pivalate (XXXIV) was converted into ylide and then treated with 6,10,14-trimethyl-2-pentadecanone as previously described. The solution was refluxed for 72 hr; the solvent was evaporated; and the residue was chromatographed on silica gel, eluting with benzene–hexane (1:1). Triphenylphosphine was eluted first. Intermediate fractions contained a 21% yield of a mixture of *cis*- and *trans*-4-methoxy-2-methyl-3-(2,6,10,14-tetramethyl-1-pentadecenyl)-1-naphthol pivalates: nmr (CCl_4) δ 1.56 (*cis* ArC=C—CH_3), 1.95 (*trans* ArC=C—CH_3), 6.15–6.28 (b, ArCH=).

The last fraction contained a small amount of 2,3-dimethyl-4-methoxy-1-naphthol pivalate (XXXVI), pure by glpc and tlc.

1,4-Dihydroxy-α,2-dimethyl-3-naphthaleneacrylic Acid δ-Lactone 1-Propionate.—A suspension of 500 mg (2.5 mmol) of 1,4-dihydroxy-2-methyl-3-naphthaldehyde (XXIIa) and 275 mg (3 mmol) of sodium propionate in 1 g (7.5 mmol) of propionic anhydride was heated at 195° (bath temperature) for 8 hr; the solution was cooled; water was added; and the the solid organic phase was removed, ground, and washed with water. Crystallization from absolute ethanol gave 470 mg (63% yield) of 1,4-dihydroxy-α,2-dimethyl-3-naphthaleneacrylic acid δ-lactone 1-propionate: mp 184.5–185.5°; nmr δ 2.2 (d, ArC=CCH_3).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 73.0; H, 5.4.

1,4-Dihydroxy-α,2-dimethyl-3-naphthaleneacrylic Acid δ-Lactone.—A suspension of 7.5 g (25 mmol) of 1,4-dihydroxy-α,2-dimethyl-3-naphthaleneacrylic acid δ-lactone 1-propionate in 125 ml of absolute ethanol containing 3 g of sodium was refluxed for 2 hr; the solution was then cooled in an ice bath, diluted with water, neutralized with concentrated hydrochloric acid, and evaporated. The residue was washed with water to give 1,4-dihydroxy-α,2-dimethyl-3-naphthaleneacrylic acid δ-lactone: mp 224–227°; nmr (DMSO) δ 2.12 (d, ArC=CCH_3).

α,2-Dimethyl-4-hydroxy-1-methoxy-3-naphthaleneacrylic Acid δ-Lactone (XXXVII).—To a suspension of the crude 1,4-dihydroxy-α,2-dimethyl-3-naphthaleneacrylic acid δ-lactone in 19.5 g (155 mmol) of dimethyl sulfate was added dropwise over 30 min a solution of 13.0 g (233 mmol) of potassium hydroxide in 30 ml of water. The solid was removed, washed with water, and dried to give 4.0 g (63% yield) of α,2-dimethyl-4-hydroxy-1-methoxy-3-naphthaleneacrylic acid δ-lactone: mp 163–164.5° after crystallization from absolute ethanol; nmr δ 2.15 (d, ArC=CCH_3), 3.8 (s, $ArOCH_3$).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.6; H, 5.5. Found: C, 75.3; H, 5.5.

***trans*-4-Hydroxy-1-methoxy-α,2-dimethyl-3-naphthaleneacrylic Acid (XXXIX).**—A solution of 3 g (12 mmol) of α,2-dimethyl-4-hydroxy-1-methoxy-3-naphthaleneacrylic acid δ-lactone (XXXVII) in 250 ml of 3 N methanolic potassium hydroxide was irridiated for 48 hr with a low-pressure mercury lamp with a Vycor filter. The contents were then diluted with water, cooled in an ice bath, neutralized with concentrated hydrochloric acid, and extracted with ether. The residue from the combined, washed, dried, and evaporated ether extracts was taken up in ether and washed with 1% aqueous sodium bicarbonate. The combined bicarbonate washes were extracted with ether, and the combined ether extracts were washed with water and evaporated, leaving a residue which was sublimed at 100° (20 μ) to give 500 mg (16%) of recovered lactone XXXVII.

The combined bicarbonate extracts were acidified with hydrochloric acid and extracted with ether. Evaporation of the combined ether extracts left a residue which was chromatographed on silica gel, eluting with ether–hexane (1:1). The fractions containing the acid were pooled and evaporated. Crystallization from chloroform gave 400 mg (12.5% conversion) of *trans*-α,2-dimethyl-4-hydroxy-1-methoxy-3-naphthaleneacrylic acid

(XXXIX): mp 140° dec (very sensitive to rate of heating); nmr (DMSO) δ 1.72 (d, ArC=CCH$_3$).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9. Found: C, 70.5; H, 5.4.

Methyl *cis*-1,4-Dimethoxy-α,2-dimethyl-3-naphthaleneacrylate (XL).—A solution of 508 mg (2 mmol) of 4-hydroxy-α,2-dimethyl-1-methoxy-3-naphthaleneacrylic acid δ-lactone (XXXVII) and 2.3 g (16 mmol) of iodomethane in 7 ml of N,N-dimethylformamide was stirred with 2 g (6.3 mmol) of barium hydroxide octahydrate for 50 hr at 25°. Volatiles were then evaporated, and the remainder was diluted with water and extracted with ether. The combined ether layers were washed and evaporated to give a yellow oil which was purified by preparative glpc on 10% SE-30 to yield 580 mg (96% yield) of methyl *cis*-1,4-dimethoxy-α,2-dimethyl-3-naphthaleneacrylate: nmr δ 2.15 (d, J = 2 Hz, ArC=CCH$_3$), 6.75 (b, ArCH=).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 72.2; H, 6.9.

Methyl *trans*-1,4-Dimethoxy-α,2-dimethyl-3-naphthaleneacrylate (XLI).—The *trans*-methyl ester was prepared exactly as described for the *cis*-methyl ester above. Purification by preparative glpc on 10% SE-30 gave a 63% yield of methyl *trans*-1,4-dimethoxy-α,2-dimethyl-3-naphthaleneacrylate: mp 45–46°; nmr δ 1.8 (d, J = 2 Hz, ArC=CCH$_3$), 7.62 (b, ArCH=).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 71.7; H, 6.8.

***cis*-1,4-Dimethoxy-2-methyl-3-(2-methyl-1-propen-3-ol)naphthalene (XLII).**—A solution of 100 mg (0.33 mmol) of methyl *cis*-1,4-dimethoxy-α,2-dimethyl-3-naphthaleneacrylate (XL) dissolved in 20 ml of ether was added slowly to a solution of 100 mg (2.5 mmol) of lithium aluminum hydride in 15 ml of ether maintained at −15°. After addition was complete, the solution was stirred 1 hr at −15° and then treated with wet ether followed by saturated aqueous ammonium chloride. Extraction with ether which was then washed and evaporated left an oil, purified by preparative tlc on Kiesel gel G (eluting with ether–hexane, 1:1) and sublimed at 60° (20 μ) to give *cis*-1,4-dimethoxy-2-methyl-3-(2-methyl-1-propen-3-ol)naphthalene: mp 69–70°; nmr δ 2.08 (d, J = 1 Hz, ArC=CCH$_2$), 3.8 (s, ArOCH$_3$, =CCH$_2$O), 6.15 (b, ArCH=).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4. Found: C, 74.6; H, 7.5.

***trans*-1,4-Dimethoxy-2-methyl-3-(2-methyl-1-propen-2-ol)naphthalene (XLIII).**—Prepared from 100 mg (0.33 mmol) of methyl *trans*-1,4-dimethoxy-α,2-dimethyl-3-naphthaleneacrylate (XLI) exactly as described for the *cis* isomer. Purification by tlc (Kiesel gel G, eluting with ether–hexane, 2:1) and sublimation at 75° (20 μ) gave *trans*-1,4-dimethyl-2-methyl-3-(2-methyl-1-propen-2-ol)naphthalene: mp 49–50°; nmr δ 1.58 (d, ArC=CH$_3$), 4.25 (b, =C—CH$_2$O), 6.45 (b, ArCH=).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4. Found: C, 74.7; H, 7.1.

Conversion of Pivalate Esters into Quinones. A. Removal of Pivaloyl Group.—A solution of 1 mmol of the 4-methoxy-1-naphthol pivalate in 5 ml of ether was added dropwise to 145 mg (3.5 mmol) of lithium aluminum hydride in 5 ml of ether. After being refluxed for 1 hr, the solution was cooled to 0°; wet ether followed by saturated aqueous ammonium chloride was added; the ether layer was removed; and the aqueous phase was extracted several times with ether. Evaporation of the combined, washed, and dried ether extracts left the 4-methoxy-1-naphthol.

B. Oxidation of the 4-Methoxy-1-naphthol to Quinone.—A solution of 680 mg (2.5 mmol) of ferric chloride hexahydrate in 40 ml of 50% aqueous acetonitrile was added to a solution of 1 mmol of the 4-methoxy-1-naphthol in 40 ml of 50% aqueous acetonitrile. The solution was stirred for 15 min, diluted with two volumes of water, and extracted several times with ether. Evaporation of the combined, washed, and dried ether extracts left the quinone.

This procedure was used for the 4-methoxy-1-naphthols with shorter chains, soluble in the 50% aqueous acetonitrile. For the longer chain methoxynapththols, insoluble in this medium, an ether–ethanol mixture (1:1) was used as solvent, and 30% aqueous ferric chloride was added.

The following quinones were prepared by the above procedure.

2-Methyl-3-(2-methyl-1-propenyl)-1,4-naphthoquinone (XI): 88% yield from pivalate ester; mp 42–43° after chromatography on silica gel, eluting with benzene–hexane (1:1), and crystallization from methanol at −20°; λ_{max} 315 nm (broad) (ϵ 3300), 264 (sh), (14,000), 249 (23,000); nmr δ 1.58 (d, J = 1 Hz, *cis* ArC=CCH$_3$), 1.98 (d, J = 1 Hz, *trans* ArC=CCH$_3$), 6.08 (b, CH=C).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.6; H, 6.1.

***cis*-2-Methyl-3-(2-methyl-1-pentenyl)-1,4-naphthoquinone (XXXIIIb):** 50% yield from pivalate ester; mp 79–80° after chromatography on silica, eluting with hexane–ether (19:1), and sublimation at 50° (10 μ); λ_{max} 315 nm (broad) (ϵ 3200), 265 (sh) (13,000), 249 (23,000); nmr (CCl$_4$) δ 0.8 (t, J = 7 Hz, —CH$_2$CH$_3$), 1.95 (d, J = 2 Hz, *trans* ArC=CCH$_3$), 5.85 (b, ArCH=); mass spectrum m/e 254 (M$^+$), 239, 225, 221.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.2; H, 7.3.

***trans*-2-Methyl-3-(2-methyl-1-pentenyl)-1,4-naphthoquinone (XXXIIIb):** 60% yield from pivalate ester; mp 64.5–66° after sublimation at 50° (10 μ); λ_{max} 315 nm (broad) (ϵ 3150), 265 (sh) (13,500), 249 (23,000); nmr (CCl$_4$) δ 1.0 (t, J = 7 Hz, —CH$_2$CH$_3$), 1.55 (d, J = 1 Hz, *cis* ArC=CCH$_3$), 5.95 (b, ArCH=); mass spectrum m/e 254 (M$^+$), 239, 225, 221.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 79.8; H, 7.1.

***cis*-4-Methoxy-2-methyl-3-(1-pentenyl)-1-naphthol** was oxidized to quinone which was chromatographed on silica gel, eluting with ether–hexane. The quinone so obtained contained 10% of the *trans* isomer (R_F *cis* 0.28, *trans* 0.34 on tlc, Kiesel gel G, 15% butyl ether in hexane) which was removed by crystallization from methanol. Pure ***cis*-2-methyl-3-(1-pentenyl)-1,4-naphthoquinone (XXXIIIa)** had mp 68.5–69°; λ_{max} 330 nm (ϵ 3000), 285 (4400), 250 (21,200); nmr (CCl$_4$ δ 0.86 (t, J = 6 Hz, —CH$_2$CH$_3$), 5.65 (t, J = 5 Hz), 5.85 (t, J = 5 Hz) ArC=CH; 6.1 (d, J = 10 Hz, ArCH=).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.0; H, 6.8.

***trans*-2-Methyl-3-(1-pentenyl)-1,4-naphthoquinone (XXXIIIa),** purified by tlc (Kiesel gel G, benzene), remained an oil: λ_{max} 365 nm (ϵ 2300), 330 (3150), 285 (8150), 250 (23,000); nmr (CCl$_4$) δ 1.0 (t, J = 7 Hz, —CH$_2$CH$_3$), 6.3 (s, ArCH=), 6.35 (t, J = 6 Hz, ArC=CH).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.0; H, 6.8.

2-Methyl-3-(2-styryl)-1,4-naphthoquinone (XXXIIIc) crystallized from methanol and had mp 97–98°; λ_{max} 400 nm (ϵ 8150), 280 (24,200).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.2; H, 5.2. Found: C, 83.3; H, 5.4.

***cis*-2-Methyl-3-(2-methyl-1-octenyl)-1,4-naphthoquinone (XXXIIId):** oil; λ_{max} 315 nm (broad) (ϵ 3200), 265 (sh) (13,500), 249 (22,400); nmr (CCl$_4$) δ 0.75 (t, J = 5 Hz, —CH$_2$CH$_3$), 1.9 (d, J = 1 Hz, *trans* ArC=CCH$_3$), 5.88 (b, ArCH=).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2. Found: C, 81.2; H, 8.0.

***trans*-2-Methyl-3-(2-methyl-1-octenyl)-1,4-naphthoquinone (XXXIIId):** oil; λ_{max} 315 nm (broad) (ϵ 3150), 265 (sh) (13,500), 249 (23,000); nmr (CCl$_4$) δ 0.92 (t, J = 5 Hz, —CH$_2$CH$_3$), 1.55 (d, J = 1 Hz, *cis* ArC=CCH$_3$), 5.95 (b, ArCH=).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2. Found: C, 81.4; H, 8.1.

2-Methyl-3-(2,6,10,14-tetramethyl-1-pentadecenyl)-1,4-naphthoquinone (XXXIIIe) was obtained as an oily *cis–trans* mixture which was separated by tlc on Kiesel gel G, developing with butyl ether–hexane, 1:12 (R_F *cis* 0.84, *trans* 0.92).

***cis* XXXIIIe:** λ_{max} 315 nm (broad) (ϵ 3300), 263 (sh) (14,100), 248 (23,100); nmr (CCl$_4$) δ 1.95 (d, J = 1 Hz, *trans* ArC=CCH$_3$), 5.87 (b, ArCH=).

Anal. Calcd for $C_{30}H_{44}O_2$: C, 82.5; H, 10.2 Found: C, 81.9; H, 10.1.

***trans* XXXIIIe:** λ_{max} 315 nm (broad) (ϵ 3300), 263 (sh) (13,600), 248 (23,100); nmr (CCl$_4$) δ 1.55 (d, J = 1 Hz, *cis* ArC=CCH$_3$), 6.0 (b, ArCH=).

Anal. Calcd for $C_{30}H_{44}O_2$: C, 82.5; H, 10.2. Found: C, 82.1; H, 10.0.

Registry No.—X, 5571-10-8; XI, 17827-37-1; XVIII, 17838-73-2; XIX HCl, 17827-38-2; 1,4-dimethoxy-3-(2-dimethylaminoethyl)-2-methylnaphthalene methiodide, 17827-57-5; XX, 17827-39-3; 1,4-dimethoxy-2-methyl-3-naphthaldehyde, 17827-40-6; XXIIb,

17827-41-7; XXIIc, 17827-42-8; XXIIa, 17827-43-9; XXIId, 17827-44-0; XXIIe, 17827-45-1; XXIII, 17827-56-4; XXVI, 17827-46-2; XXVIII, 17827-47-3; XXIX, 17827-48-4; XXXI, 2397-62-8; 2-methyl-2-(2-methyl-1-propenyl)-1,4-naphthalenediol diacetate, 17827-58-6; XXXIIa, 17827-59-7; XXXIIb (*cis*), 17831-10-6; XXXIIb (*trans*), 17831-11-7; XXXIIc (*cis*), 17831-12-8; XXXIIc (*trans*), 17831-13-9; 2-pentyltriphenylphosphonium bromide, 17827-53-1; 3-pentyltriphenylphosphonium bromide, 7333-53-1; XXXIIe, 17827-51-9; XXXIIf (*cis*), 17831-25-3; XXXIIf (*trans*), 17831-15-1; 2-octanone-1,1,1,3,3-d_5, 17827-52-0; XXXIIg (*cis*), 17831-26-4; XXXIIg (*trans*), 17831-27-5; 1,4-dihydroxy-α,2-dimethyl-3-naphthaleneacrylic acid δ-lactone 1-propionate, 17838-75-4; 1,4-dihydroxy-α,2-naphthaleneacrylic acid δ-lactone, 17838-76-5; XXXIIIa (*cis*), 17831-16-2; XXXIIIa (*trans*), 17831-17-3; XXXIIIb (*cis*), 17831-18-4; XXXIIIb (*trans*), 17831-19-5; XXXIIIc, 17827-50-8; XXXIIId (*cis*), 17831-09-3; XXXIIId (*trans*), 17831-08-2; XXXIIIe (*cis*), 17838-74-3; XXXIIIe (*trans*), 17831-14-0; XXXIV chloride, 17866-64-7; XXXVII, 17827-55-3; XXXIX, 17831-20-8; XL, 17831-21-9; XLI, 17831-22-0; XLII, 17831-24-2; XLIII, 17831-23-1

N-Alkyl Substituents as Competition Reaction Sites in the α Alkylation of Tertiary Amines[1a]

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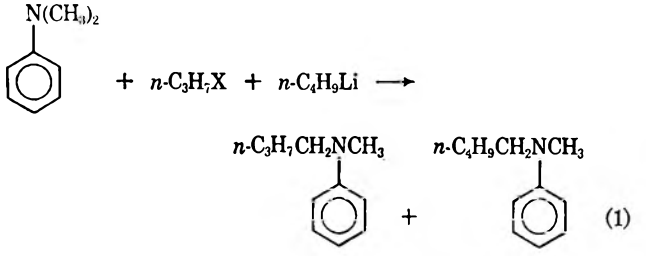
The direct α butylation of tertiary amines with *n*-butyllithium and 1-iodobutane was investigated by inter- and intramolecular competition reactions. Structure changes at the α position in the reacting amine were used as the competition variables. The intermolecular competition of N,N-dimethylaniline with N,N-diethylaniline, N-methyldiphenylamine, N-methyl-N-ethylaniline, triethylamine, or triethylenediamine showed that reactivity per α hydrogen was significantly greater for methyl than for ethyl groups. This effect of alkyl structure was much greater than the conjugative or resonance effects caused by increasing or decreasing the number of aromatic rings attached to nitrogen. Intramolecular competition in N-methyl-N-ethylaniline and in N-methyl-N-(2-butyl)aniline extended the reactivity order to methyl > ethyl > *sec*-butyl or primary > secondary > tertiary. The quantitative alkyl reactivity ratios closely parallel hydrocarbon acidities and σ^* values for cumulative inductive effects. A model is therefore suggested for the reaction transition state which is compatible with previous α alkylation results and with two other simultaneously occurring reactions, halogen–metal interchange and Wurtz coupling.

The direct α-carbon alkylation of tertiary amines takes place when these amines are used as solvents for the reaction of organolithium reagents with alkyl or aryl halides[2] (eq 1). Either the bromo- or iodoalkanes



(1)

will participate in the reaction, but the former are less reactive while the latter also undergo extensive halogen–metal interchange.[3]

Trialkylamines[4] as well as N-alkylanilines[2,3,5] can undergo substitution. However, the reaction is limited to an α-alkyl position as demonstrated with triethylamine[4] and N,N-diethylaniline.[5]

These observations seemed to be in agreement with a simple mechanism involving metalation of the amine at an α-alkyl site followed by a "Wurtz" coupling with the available halide. Metalation studies of both N,N-dimethylaniline[6] and triethylamine[4] failed to confirm such a pathway, although the aniline reactivity was in reasonable agreement with hydrogen–deuterium exchange data.[7] A second route for product formation, amine quaternization with a subsequent Stevens rearrangement, was also eliminated in these same studies.

Although the reaction is described as a *direct* α alkylation because of the initial lack of a cogent mechanism, it seemed desirable to attempt to clarify this situation. Since steric effects and the relative reactivity of alkyl groups are closely related in many cases to the type of species involved as intermediates or in transition states, we have investigated the competition of α reaction sites in direct alkylation of tertiary amines. In order to ascertain comparability of steric factors as well as group reactivity, both inter- and intramolecular competition reactions were considered.

Results

The direct α-substitution reaction of tertiary amines was carried out on compounds or mixtures of compounds in which two nonequivalent positions were available for competitive alkylation. *n*-Butyllithium and 1-iodobutane were used so that the alkyl group

(1) (a) Presented in part before the Division of Organic Chemistry, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstracts S161; A. R. Lepley and W. A. Khan, *Chem. Commun.*, 1198 (1967). This work was supported by U. S. Public Health Grants GM-09136 and GM-13987 from the National Institute of General Medical Sciences. (b) Department of Chemistry, Marshall University, Huntington, W. Va. (c) Department of Chemistry, Queen's University of Belfast, Belfast 9, Northern Ireland.

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substituting for an α hydrogen was limited to butyl in all reactions; *cf.* eq 1. Gas chromatography (gc) of the ice-quenched reaction mixtures was used to determine product retention ratios and to isolate preparative samples. The gc data were compared with retention ratio values of available or independently synthesized compounds to establish tentative product identifications, Table I. The final product structural assignments were based on the infrared spectra and proton magnetic resonance (pmr) chemical shifts, Table II, of the materials separated by preparative gc. The quantitative evaluation of relative and absolute product yields was made by gc, using an internal standard method,[8] and from pmr integral ratios, Table III.

TABLE I

GAS CHROMATOGRAPHIC RETENTION RATIOS[a] OF REACTANTS, PRODUCTS, AND STANDARDS IN THE INTER- AND INTRAMOLECULAR COMPETITIVE TERTIARY AMINE α-ALKYLATION REACTIONS

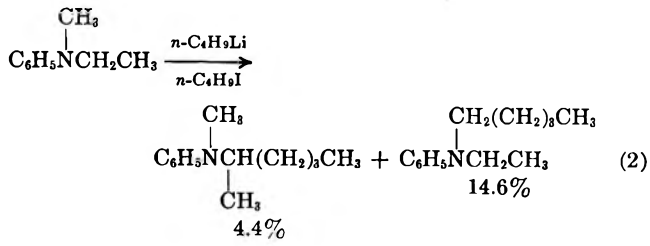
	Retention ratios		
	Calibration, deg		
Compound	100	185	Reaction products
Triethylamine	0.194		
Octane	0.400		0.402
Aniline[b]	1.000[c]		
N,N-Diethyl-2-hexylamine	1.42		1.42
N,N-Dimethylaniline	2.04	0.146	
N-Methyl-N-ethylaniline		0.194	
N,N-Diethylaniline		0.208	
N-Methyl-N-(2-butyl)aniline		0.330	
N-Methyl-N-(1-pentyl)aniline		0.524	0.525
N-Ethyl-N-(1-pentyl)aniline		0.615	0.618
N-Methyl-N-(2-hexyl)aniline		0.622	0.618
N-Ethyl-N-(2-hexyl)aniline[d]		0.694	0.695
N-Methyldiphenylamine		0.946	
N-(2-Butyl)-N-(1-pentyl)aniline		0.961	0.959
Benzhydryldimethylamine[b]		1.00[e]	
o-(Diethylamino)biphenyl[d]		1.27	
N-(1-Pentyl)diphenylamine		2.70	2.73

[a] 0.25 in. × 10 ft column of 20% GE-SF96 on 40–60 mesh Chromosorb W, 160–170 cc/min of He flow at indicated temperatures; retention ratio variation ±0.2–1% of reported values. [b] Standard for quantitative analysis. [c] Standard for retention ratio at 100°; retention time, 9.1 ± 0.4 min; peak width at half-height, 0.86 ± 0.03 min. [d] Alternate standards for quantitative analysis and retention ratios; values measured with respect to these compounds are scaled to benzhydryldimethylamine as a primary standard. [e] Standard for retention ratio at 185°; retention time, 14.6 ± 0.7 min; peak width at half-height, 1.07 ± 0.05 min.

The several tertiary amines needed for product identification were synthesized in 30–40% yield by the reaction of a secondary amine and an alkyl halide. N-Methylaniline reacted with 2-bromobutane or 2-bromohexane to form N-methyl-N-(2-butyl)aniline[9] and N-methyl-N-(2-hexyl)aniline, respectively. N-Ethyl-N-(1-pentyl)aniline was prepared from N-ethylaniline and 1-bromopentane, while the more sterically hindered N-(2-butyl)-N-(1-pentyl)aniline was formed from N-(2-butyl)aniline and 1-bromopentane.

Intermolecular competition in the α-alkylation reaction was run with a mixture of N,N-dimethylaniline and of an equimolar amount of a second tertiary amine acting as the solvent and reactants, Table III. The gc of the reaction mixture showed two products in all cases except that of triethylenediamine, where only the product of N,N-dimethylaniline butylation was observed. Gc retention ratios on these products were generally adequate for identification as confirmed by the infrared and pmr spectra. However, with N-methyl-N-ethylaniline, the isomeric products were not separated but their distribution was determined by pmr analysis of the product from the intermolecular competition reactions; see below. The over-all yields of α-tertiary amine alkylation were determined by comparison with a known amount of added gc standard. The relative amounts of the competition products were determined by the ratios of peak areas. All data were reduced to absolute yields and compared both on the basis of products from each amine and in terms of the number of α protons for the individual reactants, Table III.

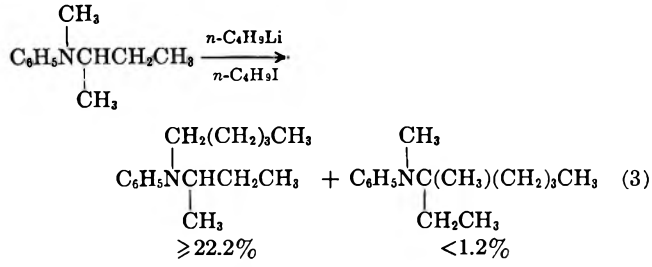
Intramolecular competition reactions were carried out with N-methyl-N-ethylaniline or N-methyl-N-(2-butyl)aniline. In both cases only a single peak for products was evident from gc. As before, no other peaks were evident from other reactions with the amine nor was there a multiplicity of peaks in the region of interest. Thus the product mixture was readily collected. In the case of N-methyl-N-ethylaniline (eq 2), the difference in retention ratios for N-methyl-N-(2-hexyl)aniline and N-ethyl-N-(1-pentyl)aniline was



(2)

much less than that required for peak resolution;[3] *cf.* Table I. However, quantitative analysis of the two product mixture was possible by pmr or preparative gc samples. The methyl and methine on nitrogen peaks of the first of the compounds was adequately separated from the overlapping methylene on nitrogen bands of the second to give readily determined integral ratios which allowed calculation of the yields.

N-Methyl-N-(2-butyl)aniline gave predominantly N-(2-butyl)-N-(1-pentyl)aniline on α alkylation, eq 3.



(3)

The over-all yield of products was 23.4% for the reaction. Qualitative features of the pmr and ir spectra from preparative gc samples were essentially identical with those of N-(2-butyl)-N-(1-pentyl)aniline except for a very weak pmr singlet at 2.65 ppm. Such a pmr singlet is characteristic[10] of a NCH_3 group on an aniline with steric inhibition of conjugation

(8) A. R. Lepley, *Anal. Chem.*, **34**, 2365 (1962).

(9) T. C. van Hoek, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **77**, 559 (1958).

(10) A. R. Lepley and V. C. Dohm, *Proc. W. Va. Acad. Sci.*, **39**, 382 (1967).

TABLE II

PROTON MAGNETIC RESONANCE SPECTRA OF TERTIARY AMINES ASSOCIATED WITH THE INTER- AND INTRAMOLECULAR COMPETITIVE α-ALKYLATION REACTIONS

		Chemical shift[a]							
		CH_3		CH_2			CH		H
Compound	Registry no.	C	NAr	C, C	C, N	C, NAr	C, C, N	C, CN	ArN Ar
N-(2-Butyl)-N-(1-pentyl)aniline	17692-89-6	1.11 m (16)[b]		1.11 m (16)[b]		3.05 m (2)		3.71 q[c] (1)	6.69 m (3) 7.14 m (2)
N,N-Diethylaniline	91-66-7	1.08 t (6)				3.21 q (4)			6.53 m (3) 7.01 m (2)
N,N-Dimethylaniline	121-69-7		2.78 s (6)						6.61 m (3) 7.09 m (2)
N,N-Diethyl-2-hexylamine	17692-90-9	0.97 t 1.05 m } (18)[b]		1.05 m (18)[b]	2.41 m (5)[e]		2.41 m (5)[e]		
N-Ethyl-N-(2-hexyl)aniline	3299-40-9	1.10 t 1.15 m } (15)[b]		1.15 m (15)[b]		3.16 q (2)		3.7 m (1)	6.62 m (3) 7.03 m (2)
N-Ethyl-N-(1-pentyl)aniline	17693-26-4	1.08 t 1.17 m } (12)[b]		1.17 m (12)[b]		3.28 q 3.18 m } (4)[d]			6.59 m (3) 7.08 m (2)
N-Methyl-N-(2-butyl)aniline	17693-27-5	1.02 m (8)[b]	2.61 s (3)	1.01 m (8)[b]				3.71 q[c] (1)	6.66 m (3) 7.07 m (2)
N-Methyldiphenylamine	91-00-9		3.16 s (3)						6.96 m (10)
N-Methyl-N-ethylaniline	613-97-8	1.05 t (3)	2.78 s (3)			3.29 q (2)			6.60 m (3) 7.09 m (2)
N-Methyl-N-(2-hexyl)aniline	17693-29-7	1.10 m (12)[b]	2.59 s (3)	1.10 m (12)[b]				3.78 m (1)	6.63 m (3) 7.05 m (2)
N-Methyl-N-(1-pentyl)aniline	3299-39-6	1.30 m (9)[b]	2.82 s (3)	1.30 m (9)[b]		3.21 t (2)			6.58 m (3) 7.06 m (2)
Triethylamine	121-44-8	0.93 t (9)			2.43 q (6)				
Triethylenediamine	280-57-9				2.60 s (12)				

[a] All shifts are δ values relative to tetramethylsilane in parts per million (ppm); splitting, s singlet, t triplet, q quartet, m multiplet; J values are 6.9 ± 0.1 cps unless otherwise indicated; values in parentheses are relative integrated peak ratios in compound. [b] Total of CH_3 and CH_2 protons attached only to other carbon atoms in particular compound. [c] Probably sextet inadequately amplified, more complex splitting not evident. [d] Total of all CH_2 protons attached to NAr in a particular compound. [e] Total of all CH_2 and CH proton attached to N of aliphatic amine; *cf.* ref 4.

TABLE III

INTERMOLECULAR COMPETITION IN α BUTYLATION OF N,N-DIMETHYLANILINE WITH OTHER TERTIARY AMINES

						Yield/α-H		
	Over-all	Competition product yields			α-H in B,[b]			Ratio of
Competing amine	% yield	% A[a]	% B[b]	Ratio of B/A	N	% A/6	% B/N	(B/N)/(A/6)
Triethylenediamine (TED)	5.8	5.8	<0.1		12	0.97		
Triethylamine	22.0	13.1	8.9	0.69	6	2.2	1.5	0.68
N,N-Diethylaniline	21.1	15.2	5.9	0.39	4	2.5	1.5	0.58
N-Methyl-N-ethylaniline	31.0	18.8	12.2[c]	0.65	5	3.1	2.4	0.78
N-Methyldiphenylamine	29.6	19.5	10.1	0.52	3	3.3	3.4	1.04

[a] A, N-methyl-N-(1-pentyl)aniline from reaction with N,N-dimethylaniline. [b] B, product from reaction with the competing amine. [c] N-Ethyl-N-(1-pentyl)aniline plus N-methyl-N-(2-hexyl)aniline; relative amounts of the two products were determined in intramolecular competition experiments; see text.

between nitrogen and the aromatic ring. Although we were unsuccessful in attempts to synthesize N-methyl-N-(3-methyl-3-heptyl)aniline, the pmr band at 2.65 ppm was quite reasonable for this product. Further support of this assignment was seen in the 2.61-ppm location for the NCH_3 singlet of N-methyl-N-(2-butyl)aniline, which was absent in the separated products as determined by gc. Analysis of the pmr integrals for the products indicated a maximum possible yield of 1.2% for N-methyl-N-(3-methyl-3-heptyl)-aniline which corresponded to a minimum of 22.2% for N-(2-butyl)-N-(1-pentyl)aniline.

The several intramolecular competition yields were converted to a comparable scale by dividing the yields by the number of α hydrogens per group and normalizing them with respect to the methyl hydrogen value. This gave the relative values 1.0, 0.45, and <0.13 for the methyl, ethyl, and *sec*-butyl groups, respectively.

Discussion

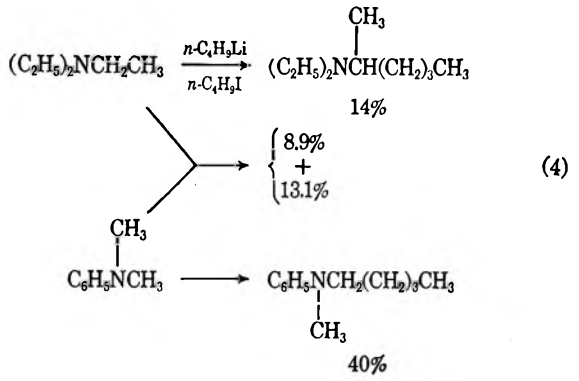
Several factors influencing the α alkylation of tertiary amines were apparent from the chosen set of compounds for inter- and intramolecular competition. These include group reactivity at the α position, steric effects in this position and in the tertiary amine as a whole, and conjugative effects on the amine nitrogen. These qualitative and quantitative factors and the mechanisms of analogous reactions aided in the formulation of a model for the transition state of α-amine alkylation. In particular, comparisons of measured yields were made with the ease of carbanion formation from hydrocarbons and with carbene insertion selectivity on hydrocarbons. These results, in conjunction with reaction routes in metalation, Wurtz coupling, and halogen–metal interchange were used in model development.

Complexes readily form between tertiary amines and organolithium reagents.[11] The insolubility of the triethylenediamine–*n*-butyllithium complex[12] probably accounts for the very low yields in the competition reaction involving this amine.

(11) J. F. Eastham and G. W. Gibson, *J. Amer. Chem. Soc.*, **85**, 2171 (1963); Z. K. Cheema, G. W. Gibson, and J. F. Eastham, *ibid.*, **85**, 3517 (1963); F. A. Settle, M. Hagerty, and J. F. Eastham, *ibid.*, **86**, 2076 (1964); T. L. Brown, R. L. Gerteis, D. A. Bafus, and J. A. Ladd, *ibid.*, **86**, 2135 (1964).

(12) C. G. Screttas and J. F. Eastham, *ibid.*, **87**, 3276 (1965).

Triethylamine alone[4] undergoes α alkylation much less readily than dimethylaniline,[5] eq 4. The larger value for competition may well be associated with the



(4)

milder reaction in dialkylanilines[3,5] than in triethylamine, where significantly higher yields, up to 25%, were achieved when lower temperatures were used to control the vigorous initial reaction.[4]

A comparison of compounds with equal numbers of ethyl and methyl groups as in N,N-diethylaniline and N,N-dimethylaniline decreased the ratio of A/B seen with triethylamine by 0.30. This change was small with respect to the exponentially related effect in steric requirements with thermodynamic stabilities in going from an ethyl to a phenyl group.[13] A distinct major variation normally observed in conjunction with these two groups is decreased basicity with conjugation. A factor of 6 decrease in pK_b occurs when going from a trialkylamine to the comparable dialkylaniline.[14] The availability of the lone pair on nitrogen is directly associated with organolithium–amine complex formation. Participation of base in related organometallic reactions including Wurtz coupling has recently been reported in tetrahydrofuran solutions involving an RLi–solvent complex.[15] The extent of structural effects on complexes or other reaction intermediates should be clearly distinguishable from normal statistical variations in the number of each type of reaction site as given by the yield per equivalent α hydrogen; see Table III.

Methyl group reactivity with structure variation was evident from the methyldiphenylamine and dimethylaniline competition. The yields per α hydrogen were within 0.1. In the range 3.3–3.4, this represents 3% which is comparable with the gc reproducibility and hence the optimum precision. It should be noted, however, that a 1:1 reactivity ratio occurred in this case where a pK_b decrease from phenyl to diphenyl is to the order of 4.[16]

Yields per α hydrogen for N,N-diethylaniline and triethylamine remained significantly lower than the competitive methyl results. The normalized ratio displayed an increased reactivity for the all alkyl compound.

Intramolecular competition in N-methyl-N-ethylaniline helped to place the intermolecular competition of this compound with dimethylaniline in perspective, eq 2. The ratio of reaction, although similar to the previous B/A value, was slightly less than that of diethylaniline *vs.* dimethylaniline. Reduction of these values to the per cent α H gave 2.5 and 1.1 for methyl and ethyl, respectively.[17] Both these absolute ethyl and methyl yields and their ratio, B/A = 0.45, were lower than in the intermolecular experiments. Application of the intramolecular reaction distribution to the intermolecular competition with dimethylaniline gave the distribution from N-methyl-N-ethylaniline alone of % B/*N* as 3.1 on methyl and 1.4 on ethyl. Since a 3.1% A/6 value for dimethylaniline was also obtained in this experiment, a 1:1 ratio for methyl group reactivity in the two compounds was maintained and ethyl results were consistent with other ethyl substituted compounds.

The 2-butyl group was compared only in intramolecular competition, eq 3. Per cent yield per α hydrogen for the methyl group in this case gave B/3 of 3.7.[17] The very low value for the 2-butyl group might be cause for suggesting appreciable steric hindrance at this tertiary carbon atom. However, the methyl reactivity is quite comparable with that in most of the intermolecular experiments. Since there is no obvious reason to assume that the alkylation reaction process differs in mechanism for the methyl and ethyl groups, it may well be considered to be similar in this case as well. Based on the statistical α-hydrogen activity as normalized to 1.0 for methyl, the order of substitution ease for the three groups was methyl > ethyl > *sec*-butyl or more generally primary > secondary > tertiary.

For irreversible reactions, the relative reactivities of groups from competition processes are equivalent to the ratios of rate constants when comparable ratios of product yields are present at all times; *i.e.*, the reaction orders are the same. The intramolecular values normalized to the methyl group then compose a short set of relative rates, k/k^0. *Qualitatively*, the order (decreasing) of structural class reactivities is not comparible with carbene insertion (increasing) reactions,[18] but is comparable with hydrocarbon acidities.[19]

Although dimethylaniline ring and alkyl group acidities have been studied,[7] the alkyl carbon attached to nitrogen has such a low acidity that in general only the effect of nitrogen on aromatic ring protons has been considered. Alkyl structural effects are more completely available, particularly with respect to the groups of interest, for the α positions of alkyl-

(13) The relative values from cyclohexane conformer studies are ΔG^* of 1.8 and 3.1 for ethyl and phenyl, respectively: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 44.

(14) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. Ltd., London, 1965.

(15) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **88**, 5668 (1966).

(16) N-Alkyldiphenylamines have not been reported, but the decrease from aniline or N-alkylated anilines to diphenylamine is of this order of magnitude.[14]

(17) Since only a single tertiary amine was employed in the reaction mixture for intramolecular competition and yet the same quantities of *n*-butyllithium and 1-iodobutane were used as in the intermolecular cases, it was necessary to divide B/*N* values by 2 to obtain these values which are comparable with those in Table III.

(18) α dehydrohalogenation of the alkyl halide participating in the reaction could give a carbene; however, the order of CH insertions called for by the reactivity ratios is the reverse of that required for this reaction: J. Hine, "Divalent Carbon," Ronald Press Co., New York, N. Y., 1964, Chapter 7; W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 252.

(19) A. I. Shatenshtein, *Tetrahedron*, **18**, 95 (1962).

benzenes.[19,20-23] While the absolute magnitude of these values greatly exceeds that of CH_3 in N,N-dimethylaniline, the qualitative order primary > secondary > tertiary is in agreement both for lithium[20,21] and cesium[22,23] cyclohexylamides.

The quantitative α-alkylation results are in best agreement with the more ionic cesium base as an attacking reagent in hydrogen abstraction, Table IV. As suggested by Streitwieser and Young,[23] results of this type should be predominantly carbanionic in character. Inductive effects must then play a major role and the log k/k^0 may well relate to σ^* for the collective groups if the C_6H_5N effect is assumed to be constant. Although the three groups considered here constitute too small a set for statistical treatment, a quantitative direct proportionality with the inductive constant does seem to hold.

TABLE IV

α-PROTON EXCHANGE IN ALKYLBENZENES AND RELATIVE REACTION RATES OF α ALKYLATION IN TERTIARY ANILINES

	Alkylbenzenes[a]		N-Alkylanilines[b]		
Group	Li^+, k/k^0	Cs^+, k/k^0 [d]	k/k^0	Log k/k^0	σ^* [c]
CH_3	1.0[e]	1.0	1.0	0.0	0.0
CH_2	0.11[f]	0.49	0.45	−0.35	−0.10
CH	0.008[g,h]	0.13[g]	>0.16	>−0.79	−0.20[g,i]

[a] From proton-exchange studies using lithium or cesium cyclohexylamide. [b] α-Alkylation data from this work. [c] Calculated by additivity of inductive effects neglecting NC_6H_5 and/or C_6H_5 as constants in the reactions considered; *cf.* J. E. Leffler and E. Grunwald, "Rates and Equilibria in Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, pp 222, 224. [d] Reference 23. [e] Reference 20. [f] Reference 21. [g] Value for isopropyl. [h] *sec*-Butyl value may be calculated as 0.003 from the data of ref 22, assuming the same primary isotope effect as in ref 21. [i] *sec*-Butyl value is −0.215 by the method in footnote *c*.

Previous alkylation studies,[3-5] metalation experiments,[6] and the measured acidities in dimethylaniline[7] indicate that metalation is not important on the N-alkyl group. The current structural data and their relationship to carbanionic character are not in conflict with this evidence. A carbanionic intermediate indicates the existence of a thermodynamic state of some stability with respect to the over-all reaction profile, *i.e.*, a definite species. The carbanionic character in the α-alkylation process, however, is based on a kinetic relationship. Thus the transition state rather than any intermediate species is under consideration. Certain simple analogs may help us to construct a model for this state.

The transition states for the related reactions, metalation, halogen–metal interchange, and Wurtz coupling aided in the construction of a model for α alkylation. Streitwieser in his extensive studies of reaction kinetics for hydrocarbon acidities has found a four-membered-ring transition state,[21,22] where M is cesium or lithium and R is cyclohexylamide, to be in best agreement with the kinetic data.

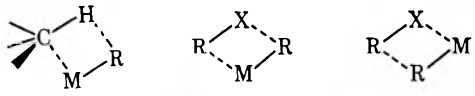
(20) A. Streitwieser, Jr., D. E. Van Sickle, and W. S. Langeworthy, *J. Amer. Chem. Soc.*, **84**, 244 (1962).

(21) A. Streitwieser, Jr., and D. E. Van Sickle, *ibid.*, **84**, 249 (1962).

(22) A. Streitwieser, Jr., R. A. Caldwell, R. G. Lawler, and G. R. Ziegler, *ibid.*, **87**, 5399 (1965).

(23) A. Streitwieser, Jr., and W. R. Young, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, O 19.

Similar states represent the halogen–metal interchange and Wurtz coupling. In terms of the simpler four-membered ring, these are



metalation interchange coupling

Rather than ionic species, these models seem to be reasonable transition states in such solvents as ethers or tertiary amines. However, the participation of additional RLi in any of the states may not be evident since the $(RLi)_2$–solvent complex may mask this secondary role as Screttas and Eastham[15] have pointed out in considering literature data on the Wurtz reaction.

Both halogen–metal interchange and Wurtz coupling compete with α alkylation of tertiary amines. Our earlier studies[3,5] indicated that a complex between the base and amine was involved in the alkylation, and that the group forming the carbon–carbon bond came with equal ease from either the alkyl halide or organolithium reagent even when halogen–metal interchange was limited. A transition state in which halogen–metal interchange occurs on the amine complex is then a strong possibility. This intermediate can either undergo exchange and then dissociate, or be involved in alkylation. Alternatively the complex might participate in Wurtz coupling or α alkylation.

The close relationship between coupling and interchange suggests that a simpler model may relate to both. If the groups of interest occupy the corners of a tetrahedron, slight variations in the attractive forces could give either of these reactions or interchange followed by coupling. Now if we have the lithium atom associated with nitrogen of the amine in such a fashion that the α hydrogen and carbon form a second approximate tetrahedron having a common R---R edge with the first, a transition state allowing α alkylation is generated. The carbanionic character relationship to this model would indicate that the CH bond is considerably weakened in the configuration for reaction. Although such a model seems exceedingly complex, the use of Fisher–Taylor–Hirshfelder space filling models shows that, if reaction of the alkyl halide occurs on the amine complex, the α N-alkyl hydrogens are very near the alkyl groups from halide or lithium compound. This is particularly true in the tetrahedral conformation.

Much more information is needed on both α alkylation and competing reactions of the other partcipating reagents to justify this model. However, the model provides a fundamental basis for further understanding of these several reactions. The stereochemical implications represented by such a transition state may well furnish the means of clarifying this situation. While some of this stereochemistry may be

in evidence in the current inter- and intramolecular competition results, a more extensive study including organometallic and halide structures is needed for a thorough analysis.

Experimental Section[24]

Physical Constants.—Proton magnetic resonance (pmr) spectra were measured on a Varian A-60 spectrometer as 20% v/v solutions in carbon tetrachloride with approximately 1% tetramethylsilane as an internal standard and are reported as δ values in parts per million. Infrared measurements were made on the pure liquids using a Perkin-Elmer Model 137 spectrophotometer. Wavelengths are given in microns; intensities relative to the most intense peak (*) as equivalent to 100% are s = strong 76–100%, m = medium 51–75%, w = weak 26–50%, and vw = very weak 10–25% (very weak bands are given only when quite sharp and characteristic). Refractive indices were measured with a Bausch and Lomb Abbé refractometer. Ethylbenzene was used as the standard in determining specific gravities with a Fisher–Davidson gravitometer.

Gas Chromatography.—Retention ratios, resolution, and product yields were determined using an internal standard method.[3,8] An F & M Model 500 gas chromatograph was used with 0.25 in. × 10 ft column of 20% GE-SF96 on 40–60 mesh Chromosorb W. The flow rate was maintained between 160 and 170 cc/min of helium for analyses at either 100 or 185°. Retention ratio reproducibility was ±0.2–1.0% of the reported values with the lower value applying at only very high retention ratios. Quantitative analyses were accomplished by adding 1.0 ml of the organic layer from a reaction mixture to a accurately weighed amount of the appropriate standard. The mixture was shaken well and a specific volume (usually 25–50 μl) was injected into the gas chromatograph. Areas of peaks, calculated from peak heights and peak widths at half-height, were used to determine the weight of product formed and its yield.[3]

Chemicals.—Methyl- and dimethylanilines, N-methyldiphenylamine, 1-iodobutane, 2-bromobutane, and 1-bromopentane were obtained from Eastman. Ethyl- and diethylanilines, N-methyl-N-ethylaniline, triethylamine, triethylenediamine, and 2-bromohexane were products of Matheson Coleman and Bell. N-(2-Butyl)aniline was from Chemicals Procurement Laboratories. Monofree dimethyl- and diethylanilines and triethylamine were dried over sodium wire before use. Commercial N-methyl-N-ethylaniline was purified using benzoyl chloride in the Schotten–Baumann reaction, dried over KOH, distilled, and stored over sodium wire; material treated in this fashion did not give an immediate precipitate formation with *n*-butyllithium. The active lithium content of *n*-butyllithium (Foote Mineral, 20% in hexane) was determined by the double titration method[25] before use. Benzhydryldimethylamine,[26] N,N-diethyl-2-hexylamine,[4] N-ethyl-N-(2-hexyl)aniline,[5] *o*-(diethylamino)biphenyl,[26] N-methyl-N-(1-pentyl)aniline,[5] and N-(1-pentyl)diphenylamine[26] were available from previous studies.

N-Methyl-N-(2-hexyl)aniline.—N-Methylaniline (5.4 ml, 50 mmol) was mixed with 5.9 ml (40 mmol) of 2-bromohexane and heated on a steam bath in a sealed flask for 2 days. The reaction mixture was treated with concentrated sodium hydroxide solution; the oil was separated; and the aqueous solution was extracted twice with ether. The oil and ether extracts were combined and washed several times with water. The ether solution, which showed gc peaks for starting amine and product, was evaporated to remove the solvent. The residue was shaken well with benzoyl chloride and aqueous sodium hydroxide. This mixture was poured into ice water and extracted with ether; the product was removed from the combined ether layers by repeatedly extraction with 2 *N* hydrochloric acid. The acid solution was cooled in ice and made strongly alkaline with sodium hydroxide. The separated oil and several ether extracts of this aqueous solution were dried over sodium sulfate and distilled. The pure product, 2.3 g, 30% yield, was collected at 73° (0.3 mm).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.38; H, 11.21; N, 7.46.

The infrared spectrum had bands at 3.30 w, 3.39 s, 3.49 m, 6.25 s, 6.36 w, 6.67 s*, 6.88 w, 7.20 w, 7.41 w, 7.58 m, 8.00 vw, 8.17 w, 8.29 w, 8.38 w, 8.66 vw, 8.83 m, 9.20 vw, 9.34 vw, 9.65 w, 10.08 w, 10.79 vw, 11.60 vw, 13.32 s, 14.08 vw, and 14.48 m μ.

N-Ethyl-N-(1-pentyl)aniline.—N-Ethylaniline (12.6 ml, 0.1 mol) was mixed with 12.1 g (80 mmol) of 1-bromopentane and treated as in the preparation of N-methyl-N-(2-hexyl)aniline. Distillation gave 9.3 g (61% yield) of a chromatographically pure product: bp 74° (0.1 mm); $n^{21.5}D$ 1.5221, d^{20}_4 0.911.

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.57; H, 11.06; N, 6.97.

Infrared analysis showed bands at 3.29 w, 3.40 s, 3.49 m, 6.27 s, 6.38 w, 6.67 s*, 6.82 w, 7.19 w, 7.30 m, 7.40 m, 7.70 vw, 7.89 m, 8.08 vw, 8.21 w, 8.41 m, 8.62 w, 9.08 w, 9.30 vw, 9.61 w, 10.04 w, 11.6 vw, 11.8 vw, 12.6 vw, 13.39 s, and 14.46 m μ.

N-Methyl-N-(2-butyl)aniline.[9]—Freshly distilled N-methylaniline (44 g, 0.41 mol) was mixed with 54 g (0.40 mol) of 2-bromobutane and heated at 120° for 36 hr. The mixture was made strongly alkaline with potassium hydroxide solution. The oil which separated and several ether extracts of the aqueous solution were combined and dried over sodium sulfate. The solvent was stripped off and the reaction product was refluxed with 25 ml of acetic anhydride for 2 hr. The mixture was poured into about 480 ml of ice cold 4 *N* hydrochloric acid. The acid layer was extracted with ether for several days in a continuous extractor. The acid layer was made alkaline with sodium hydroxide and repeatedly extracted with ether. The latter ether solution was washed with water, dried over sodium, and distilled. Gas chromatographically pure product, 20 g, 31% yield, distilled at 61–62° (0.1 mm) [lit. 121° (20 mm)[9]], $n^{21.5}D$ 1.5360, d^{20}_4 0.934, and had a gc retention ratio of 0.475 *vs.* N-ethyl-N-(2-hexyl)-aniline as a standard.

The infrared spectrum had bands at 3.30 vw, 3.37 m, 3.48 w, 3.58 vw, 6.27 s, 6.39 w, 6.67 s*, 6.89 w, 7.21 w, 7.42 w, 7.59 m, 7.78 w, 7.79 w, 8.27 w, 8.39 vw, 8.66 vw, 8.87 m, 8.95 w, 9.10 vw, 9.48 vw, 9.68 vw, 9.83 vw, 10.09 w, 10.44 vw, 10.91 vw, 11.5–11.6 vw, 13.33 s, 14.09 vw, and 14.48 m μ.

N-(2-Butyl)-N-(1-pentyl)aniline.—N-(2-Butyl)aniline (14.9 g, 0.1 mol) was mixed with 22.6 g (0.15 mol) of 1-bromopentane and heated at 100° in a sealed flask for 2 days. The reaction mixture was then cooled, treated with concentrated sodium hydroxide solution, and extracted with ether. Since gc analysis of this ether solution showed a small amount of starting amine, the ether was evaporated and the residue was shaken with benzoyl chloride and sodium hydroxide solution. The mixture was poured into ice water and extracted with ether; the combined ether layers were extracted with several portions of 6 *N* hydrochloric acid. This acid solution was washed once with ether and then made strongly alkaline with sodium hydroxide. The amine was picked up in ether, washed with water, and dried over anhydrous sodium sulfate. Pure N-(2-butyl)-N-(1-pentyl)-aniline, 8.7 g, 40% yield, distilled at 90–93° (0.1 mm), $n^{21.5}D$ 1.5140, d^{20}_4 0.898, and had a retention ratio of 1.376 relative to N-ethyl-N-(2-hexyl)aniline.

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.48; N, 6.39. Found: C, 82.21; H, 11.55; N, 6.27.

Infrared analysis showed bands at 3.30 vw, 3.38 s, 3.49 m, 6.28 s, 6.38 vw, 6.67 s*, 6.88 w, 7.20 w, 7.28 w, 7.42 w, 7.76 w, 7.97 w, 8.09 vw, 8.23 vw, 8.49 w, 8.63 vw, 8.81 w, 9.10 vw, 9.61 w, 10.04 vw, 13.38 m, 13.8 vw, and 14.48 m μ.

General Procedure for Competitive α-Substitution Reactions.—Equimolar amounts (50 mmol) of dried monofree N,N-dimethylaniline and a second tertiary amine were mixed in a dry glass stoppered 100-ml round-bottomed flask containing a Teflon-coated stirring bar and cooled to −10° in an ice–salt bath. In the case of intramolecular competition reactions, no N,N-dimethylaniline was used but 0.1 mol of a tertiary amine with two different reactive alkyl sites was employed.

n-Butyllithium, 20 mmol of 1.6 *N* in hexane,[25] was added rapidly with stirring and cooling to the amine mixture. This solution was allowed to reach bath temperature, approximately 5 min, and 20 mmol of 1-iodobutane was added, either rapidly or over a 5-min period in the case of an immediate vigorous reaction. The reaction was continued by allowing slow melting of the cooling bath. After about 1 hr, the mixture had attained room temperature and the bath was removed. After 1.5 hr the temperature reached 32° and this temperature ±2° was maintained during the remainder of the reaction period; over-all reaction time was 2 hr.

The reaction was terminated by adding crushed ice with rapid

(24) Analyses were performed by Crobaugh Laboratories, Cleveland, Ohio. Melting and boiling points are uncorrected.

(25) H. Gilman and A. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944); H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).

(26) A. R. Lepley, A. G. Giumanini, A. B. Giumanini, and W. A. Khan, *J. Org. Chem.*, **31**, 2051 (1966).

stirring. The reaction mixture was allowed to stand for 15 min and then 1.0-ml samples of the organic layer were withdrawn for qualitative and quantitative gc analysis. The products were isolated by preparative gc and characterized by their gc retention ratios and infrared and pmr spectra. Comparisons of these properties for the products were made with those of synthetic materials. In intermolecular competition reactions, N,N-dimethylaniline, *n*-butyllithium, and 1-iodobutane were common reagents.

Intermolecular Competition Reactions. A. Triethylenediamine.—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 5.7 g (50 mmol) of triethylenediamine and the mixture was treated with 13 ml of 1.6 *N* (20 mmol) *n*-butyllithium. 1-Iodobutane (2.3 ml, 20 mmol) was added slowly to control the vigorous reaction which was accompanied by the immediate formation of a precipitate. The reaction was continued for 2 hr as described above and quenched with ice, and the organic phase was analyzed by gc at 100 and 185°; see Table III.

B. Triethylamine.—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 7.0 ml (50 mmol) of dry triethylamine. *n*-Butyllithium (13 ml, 20 mmol) was added to the cooled mixture with stirring. 1-Iodobutane (2.3 ml, 20 mmol) was added slowly over a period of 5 min since the reaction was very vigorous on rapid addition. On slow addition, the reaction proceeded controllably and was completed as described in the general procedure. The organic products reported in Table III were determined by gc analysis at 100° using aniline as a standard and at 185° with a benzhydryldimethylamine reference.

C. N,N-Diethylaniline.—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 8.0 ml (50 mmol) of anhydrous monofree N,N-diethylaniline and 13 ml (20 mmol) of *n*-butyllithium. 1-Iodobutane (2.3 ml, 20 mmol) was added rapidly and the reaction was carried out as in the general procedure. After 2 hr, the reaction was quenched and the organic phase was analyzed by quantitative gc at 185° using benzhydryldimethylamine as the internal standard. Two product peaks were observed, Table III.

D. N-Methyl-N-ethylaniline.—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 7.3 ml (50 mmol) of purified anhydrous N-methyl-N-ethylaniline and 13 ml (20 mmol) of *n*-butyllithium. After stirring briefly, 2.3 ml (20 mmol) of 1-iodobutane was added. When the reaction mixture was worked up as described in the general procedure, two product peaks (Table III) were observed in the gc of the organic phase at 185° with retention ratios of 0.525 and 0.618 using benzhydryldimethylamine as a standard.

E. N-Methyldiphenylamine.—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 9.0 ml (50 mmol) of N-methyldiphenylamine and 13 ml (20 mmol) of *n*-butyllithium. 1-Iodobutane (2.3 ml, 20 mmol) was added rapidly and the reaction was carried out following the general procedure. The reaction was quenched after 2 hr, and the organic phase was analyzed by gc at 185°. The two product peaks observed (Table III) were determined using *o*-(diethylamino)biphenyl as an internal standard.

Intramolecular Competition Reactions. A.—N-Methyl-N-ethylaniline (14.7 ml, 0.1 mol) was mixed with 13 ml of 1.6 *N* (20 mmol) *n*-butyllithium at −10°. 1-Iodobutane (2.3 ml, 20 mmol) was added rapidly and the reaction was carried out according to the general procedure. The reaction was quenched after 2 hr and the organic phase when examined by gc at 185° showed only one product peak with a retention ratio of 0.618 *vs.* benzhydryldimethylamine as an internal standard. This peak corresponded to a 19.0% yield of $C_{13}H_{21}N$ products. Preparative gc was used to collect this material for infrared and pmr analysis. The infrared spectrum corresponded to that of N-ethyl-N-(1-pentyl)aniline except for very weak bands at 7.58 and 8.83 μ which are characteristic of two medium-intensity bands in N-methyl-N-(2-hexyl)aniline. In the pmr spectrum, δ values of the NCH_3 singlet at 2.59 ppm and NCHRR′ multiplet centered at 3.78 ppm in N-methyl-N-(2-hexyl)aniline were adequately separated from the NCH_2R overlapping quartet ($J = 6.9 \pm 0.1$ cps) of ethyl and multiplet of *n*-pentyl (centered respectively at 3.28 and 3.18 ppm) in N-ethyl-N-(1-pentyl)aniline to allow quantitative determination of the two isomeric products. The absence of a NCH_3 singlet at 2.78 ppm showed the separated product to be free of starting N-methyl-N-ethylaniline. The ratios of products as determined from pmr integral ratios was 3.3:1.0 methyl to ethyl position reaction for yields of 14.6% N-ethyl-N-(1-pentyl)aniline and 4.4% N-methyl-N-(2-hexyl)-aniline.

B. N-Methyl-N-(2-butyl)aniline.—N-Methyl-N-(2-butyl)-aniline (12.2 ml, 75 mmol) combined with 10 ml of 1.6 *N* (15 mmol) *n*-butyllithium and 1.6 ml (14 mmol) of 1-iodobutane was rapidly added to the mixture at −10°. The reaction was carried out as before and quenched after 2 hr, and the organic phase was examined using N-ethyl-N-(2-hexyl)aniline as a gc standard at 185°. Only one product peak was observed with a retention ratio of 1.37 relative to this standard. The infrared spectrum of a preparative gc sample was comparable with that of N-(2-butyl)-N-(1-pentyl)aniline but the pmr spectrum had a very weak singlet at 2.65 ppm. The integral ratio of this singlet and the $NCHR_2$ multiplet centered at 3.71 ppm was used for quantitative analysis indicating a maximum of 1.2% N-methyl-N-(3-methyl-3-heptyl)aniline in the over-all yield of 23.4%. The bulk of the product, at least 22.2%, was N-(2-butyl)-N-(1-pentyl)aniline.

Synthesis and Reactions of N-*p*-Tolylsulfonyl-N′-cyclohexylcarbodiimide

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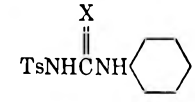
The synthesis of the title compound (**2a**) is described, and its reactions with several nucleophiles are described. Amino acid esters underwent addition–cyclization with **2a** giving imidazolidones, while cyclohexylamine and sodium azide afforded a guanidine and tetrazole, respectively. The condensation of N-carbobenzyloxyglycine with **2a** required a high temperature and gave only pyrolysis products.

Carbodiimides (**1**) are of considerable interest because of their use as agents in peptide synthesis[1] and more recently as oxidizing agents in dimethyl sulfoxide solution.[2] Our interest in sulfonylcarbodiimides (**2**) derived from the expectation that this highly polar diimide might have interesting uses in peptide chemistry. Ulrich[3] and coworkers have reported most completely on the synthesis of sulfonylcarbodiimides and some of their reactions. Using the Ulrich thiourea phosgenation procedure we have synthesized N-*p*-toluenesulfonyl-N′-cyclohexylcarbodiimide (TsCC) (**2a**) from the corresponding thiourea (**3a**) in 65% yield.

$$\underset{\mathbf{1}}{RN{=}C{=}NR'} \qquad \underset{\mathbf{2a}}{RSO_2N{=}C{=}NR'}$$

R = 4-$CH_3C_6H_4$; R′ = cyclohexyl



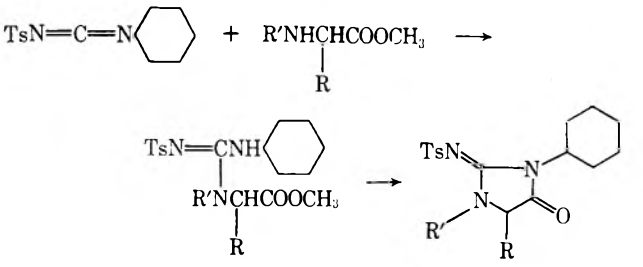
3a, X = S
b, X = O
Ts = 4-$CH_3C_6H_4SO_2$

(1) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
(2) K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); **87**, 5661, 5670 (1965).
(3) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Tetrahedron*, **22**, 1565 (1966).

TsCC is a white crystalline solid and is quite stable at 5° under anhydrous conditions over a period of at least 3–4 months. The urea (**3a**) was most conveniently prepared from *p*-toluenesulfonamide and cyclohexyl isothiocyanate. Alternatively, *p*-toluenesulfonyl isothiocyanate could be prepared by the method of Hartke[4] followed by treatment with cyclohexylamine to form **3a**, but the procedure was more lengthy. Even less rewarding was the attempt to convert the urea **3b** into **3a** with phosphorus pentasulfide.

When TsCC was allowed to react with molar equivalents of N-carbobenzyloxyglycine and L-phenylalanine methyl ester, the product corresponded to the combination of only the amino ester with TsCC. The same compound was obtained in the absence of the glycine derivative. It has been assigned the imidazolidone structure **5a** (Scheme I) on the basis of spectral data

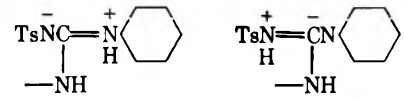
SCHEME I



4a, R = $C_6H_5CH_2$; R′ = H
b, R = R′ = H
c, R = H; R′ = CH_3

5a, R = $C_6H_5CH_2$; R′ = H
b, R = R′ = H
c, R = H; R′ = CH_3

and elemental analysis and by analogy to a report[5] which showed that glycine *p*-nitrophenyl ester hydrobromide slowly reacted with dicyclohexylcarbodiimide to give an imidazolidone. When this reaction mixture was worked up immediately after the TsCC had been consumed, a gummy product showing two NH absorptions and a carbonyl peak at 30-cm^{-1} higher frequency than that in **5a** was isolated. This material also showed an nmr peak at δ 3.59 ppm corresponding to a methyl ester and was undoubtedly the intermediate **4a** in which cyclization had not yet occurred. When **4a** was heated in methanol solution, **5a** was formed in excellent yield. It was interesting to note that **4a** showed $[\alpha]^{27}D$ + 49.3°, but that the cyclic product **5a** was completely racemic whether formed at room temperature or above. Enolization of the carbonyl function in **5a** must therefore be occurring. Since the infrared carbonyl absorption was of the expected intensity, a ferric chloride test for enol content was negative and **5a** was insoluble in dilute alkali; the enolization equilibrium was apparently established very rapidly but strongly favored the carbonyl form. Alternative structures **6** and **7** can be visualized for the intermediate ester and imidazolidone, respectively. The spectral data are also consistent with these structures, but we feel that **4a** and **5a** are to be preferred. Certainly **4a** can be considered thermodynamically more stable than **6** since the resonance form **8** which contributes to **4a** should be considerably more stable than the corresponding **9**, which has a positive charge

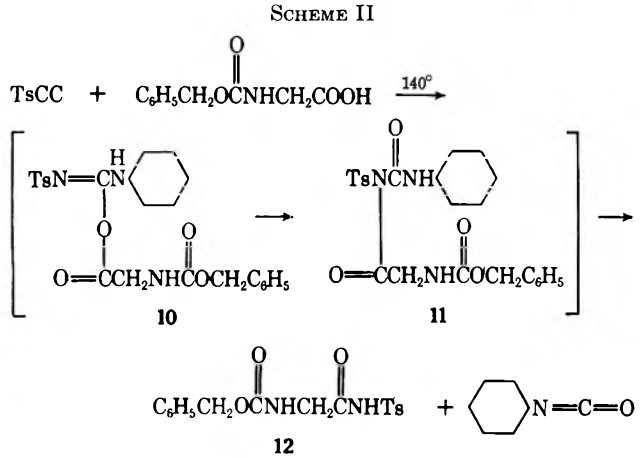


8 **9**

close to the electronegative tosyl group.[6] The same argument holds for the stability relationship between **5a** and **7**. If we accept the intermediacy of the ester **4a**, it seems extremely unlikely that the ring closure to imidazolidone might occur at the nitrogen atom having the *lower* nucleophilicity, giving **7**. For these reasons, we assign the structure **5a** to the imidazolidone.[7] When glycine and sarcosine are allowed to react with TsCC, imidazolidones **5b** and **5c** were formed. The N-methyl compound **5c** showed an intense azomethine absorption within 8 cm^{-1} of this same absorption peak in **5a**. Since **5c** *must* have an *exo*-azomethine grouping, this similarity between **5a** and **5c** supports the *exo*-azomethine structure for **5a**.

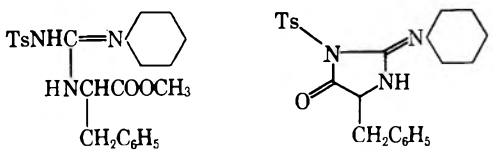
In a further attempt to make use of TsCC in amino acid couplings, we examined the conditions necessary to cause it to react with N-carbobenzyloxyglycine. No reaction occurred in methylene chloride, and the higher boiling solvents dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) could not be used because TsCC was slowly consumed by them even in the absence of N-carbobenzyloxyglycine. When the two reactants were fused at *ca.* 140°, an almost quantitative yield of N-(N-carbobenzyloxyglycyl)-*p*-toluenesulfonamide (**12**) was obtained. Cyclohexylisocyanate was formed simultaneously and isolated as N,N′-dicyclohexylurea after reaction with cyclohexylamine. To explain these results we propose that the expected intermediate **10** formed and rearranged rapidly[1] to the acylurea **11**. The pyrolysis of **11** (Scheme II) at 140°

SCHEME II



10 **11**

12



6 **7**

(4) K. Hartke, *Arch. Pharm.*, **299**, 174 (1966).

(5) D. F. TeTar, R. Silverstein, and F. F. Rogers, *J. Amer. Chem. Soc.*, **88**, 1024 (1966).

(6) In ref 3, Ulrich and coworkers established the position of the N–H proton in a similar system by chemical shift analogy with N-sulfonyl-N′-alkylureas. In **4a**, strong absorption by the aromatic protons in the δ 7.22–7.82-ppm region overlaps the absorption of NH protons and thus makes the detection of N–H absorption difficult. Lack of absorption of >8.5 ppm in **4a** makes probable the absence of an N–H proton adjacent to the tosyl group.

(7) For a discussion of a sulfonylamidine structural investigation, see S. J. Angyal and W. K. Warburton, *Aust. J. Sci. Res.*, **4A**, 93 (1951).

might then afford the observed products.[8] It would be most interesting if the O-acylurea **10** could be isolated, but attempts to carry out the reaction at lower temperatures or in the presence of catalysts failed.

In 1963, Aumueller[9] suggested that TsCC might be intermediate in the formation of N,N′-bis-*p*-tolyl-N″-cyclohexylguanidine when cyclohexyl isocyanide reacted with Chloramine-T in aqueous acetone solution. We have found that TsCC is very rapidly hydrated in this medium[10] giving the urea **3b**. TsCC was also converted very readily into the guanidine **13** and tetrazole **14** by reaction with cyclohexylamine and sodium azide, respectively. Both of these compounds showed the characteristic strong absorption (*ca.* 1610 cm^{-1}) for the tosylimino group. The ease with which these derivatives were formed is consistent with the electrophilic character of the central carbon atom of TsCC.

It occurred to us that this enhanced electrophilicity might cause TsCC to have some utility as an oxidizing agent in DMSO solution since dicyclohexylcarbodiimide (DCC) has been used in this medium. The proposed mechanism[2] of this reaction requires an intermediate formed by addition of the nucleophilic oxygen atom of DMSO to the central electrophilic carbon of DCC. Thus we might expect TsCC to form such an intermediate quite readily because of its enhanced electrophilicity. We examined the oxidation of benzhydrol to benzophenone and found that oxidation proceeded readily both in the presence and absence of acid catalysis. Yields, however, were not high even in the presence of excess TsCC. As previously mentioned, we have observed that both DMSO and DMF destroy TsCC rapidly at room temperature. These rapid side reactions may explain the low oxidation yields.

Experimental Section

All melting points were determined on a Nalge hot stage and are uncorrected. Infrared spectra were obtained with Perkin-Elmer grating spectrophotometers, Models 237B or 257, in KBr or NaCl cells. Nmr spectra were obtained on a Varian Associates Model A-60 or HA-100 spectrometer using tetramethylsilane as internal standard. Tlc analyses were carried out on Eastman precoated silica gel sheets, Type 6060, with fluorescent indicator. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

N-*p*-Toluenesulfonyl-N′-cyclohexylthiourea (3a).—To a solution of 8.56 g (0.05 mol) of *p*-toluenesulfonamide in 35 ml of aqueous sodium hydroxide containing 2.0 g (0.05 mol) of NaOH was added a solution of 7.06 g (0.05 mol) of cyclohexyl isothiocyanate in 20 ml of acetone. The mixture was stirred magnetically and refluxed in an oil bath maintained at 63 ± 2° for 15 hr. A small amount of insoluble material was filtered; the filtrate was concentrated to *ca.* 10 ml *in vacuo* and acidified with concentrated HCl. The precipitated thiourea was filtered, washed with a little cold water, and recrystallized from 75% aqueous EtOH to give 9.5 g (61%), mp 173–175°, of pure product in two crops: ir (Nujol) 3318 (NH), 1375, 1160 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 8:11 (d, 1, J = 8 Hz, NHC_6H_{11}), 7.87–7.29 (q, J_{AB} = 8 Hz, *p*-tolyl), 4.06 (s, broad, 1, –CH–NH–), 1.95–1.01 (m, 10, cyclohexyl).

N-*p*-Toluenesulfonyl-N′-cyclohexylcarbodiimide (TsCC) (2a).—To a stirred suspension of 8.3 g (26.6 mmol) of N-*p*-toluenesulfonyl-N′-cyclohexylthiourea in 30 ml of dry chlorobenzene was added a solution of 3.0 g (30 mmol) of phosgene in 20 ml of dry chlorobenzene during 30 min at 3–5° and the mixtue was stirred at room temperature for 3 hr. A tlc (C_6H_6–$CHCl_3$, 1:1) plate indicated the complete absence of thiourea in the reaction mixture. It was refluxed for 2 hr during which time a slow stream of dry nitrogen was bubbled through the clear solution to expel unreacted phosgene. The chlorobenzene was removed *in vacuo* to give a viscous oil to which 25 ml of pentane was added. The solution was evaporated at room temperature to give 7.3 g (100%) of slightly impure TsCC. Crystallization from a mixture of 250 ml of pentane and 20 ml of benzene at 0–5° yielded 6.2 g (83%), mp 55–56°, of a white powder which was recrystallized from pentane to give 4.75 g (65%) of pure TsCC: mp 56–57°; ir ($CHCl_3$) 2180 (N=C=N), 1332, 1160 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 7.88–7.00 (q, 4, J_{AB} = 8 Hz, *p*-tolyl), 3.70 (s, 1), 2.40 (s, 3, Ar–CH_3), 1.96–1.00 (m, 10 H).

Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.42; H, 6.52; N, 10.07; S, 11.50. Found: C, 60.78; H, 6.75; N, 9.74; S, 11.38.

1-Cyclohexyl-2-*p*-toluenesulfonimido-4-benzyl-5-imidazolidone (5a). In the Presence of Carbobenzyloxyglycine.—To a stirred solution of 617 mg (3.44 mmol) of freshly prepared L-phenylalanine methyl ester and 720 mg (3.44 mmol) of carbobenzyloxyglycine in 15 ml of methylene chloride was added 1.07 g (3.84 mmole) of TsCC in one lot, and the solution was stirred 3 hr at room temperature. A tlc plate (C_6H_6–$CHCl_3$, 3:7) indicated the complete absence of TsCC in the reaction mixture. Evaporation of the solvent *in vacuo* yielded 2.06 g of a gum which was dissolved in 50 ml of ethyl acetate, and the solution was washed with 1 *N* NaOH (two 10-ml portions) and water (two 10-ml portions) and dried. Removal of solvent furnished 1.36 g of a sticky mass which on crystallization from aqueous methanol yielded 961 mg (66%) of **5a** as colorless cubes, mp 185–189°. Two recrystallizations from methanol furnished an analytical sample: mp 193–194.5°; ir ($CHCl_3$) 3372 (NH), 1700 (C=O), 1612 cm^{-1} (SO_2N=C); nmr ($CDCl_3$), δ 8.17 (s, 1, NH), 7.90–7.32 (q, 4, J_{AB} = 8 Hz, *p*-tolyl), 7.24 (s, 5, $C_6H_5CH_2$), 4.37 (t, 1, J = 5 Hz, O=C–CH–), 3.16 (d, 2, J = 5 Hz, –CH–CH_2–C_6H_5), 2.47 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{23}H_{27}N_3O_3S$: C, 64.93; H, 6.40; N, 9.88; S, 7.52. Found: C, 64.90; H, 6.42; N, 10.05; S, 7.51.

Isolation of Intermediate 4a.—A freshly prepared solution of 303.6 mg (1.7 mmol) of L-phenylalanine methyl ester, $[\alpha]^{27}D$ +13.7 (c 5, $CHCl_3$), in 6 ml of chloroform was added to 474 mg (1.7 mmol) of TsCC, and its rotation was observed at various intervals. After 5 min the observed rotation was +6.40° and did not change on standing for 720 min. On the assumption that the reaction was complete, $[\alpha]^{27}D$ +49.3° was calculated. Removal of solvent *in vacuo* at room temperature yielded a gum: ir ($CHCl_3$) 3420, 3320 (NH), 1735 (ester C=O), 1595 cm^{-1} (SO_2 N=C); nmr ($CDCl_3$), δ 3.59 (s, 3, $COOCH_3$). The gum was dissolved in 12 ml of methanol and gently refluxed for 12 hr. Removal of solvent furnished a white solid which was twice crystallized from methanol to give white cubes, mp 192–194°, identified as **5a** by ir, tlc, and mixture melting point.

1-Cyclohexyl-2-*p*-toluenesulfonimido-5-imidazolidone (5b).—TsCC (1.12 g, 4 mmol) was allowed to react with 4 mmol of glycine methyl ester prepared from 502 mg of the hydrochloride using 0.8 ml of triethylamine in 15 ml of methylene chloride. The product was obtained by the procedure outlined for **5a**: yield, 1.20 g (90%); mp 203–205° after crystallization from methanol. Recrystallization from aqueous methanol furnished an analytical sample of **5b** as colorless needles: mp 205–206°; ir ($CHCl_3$) 3360 (NH), 1755 (C=O), 1615 cm^{-1} (SO_2N=C); nmr ($CDCl_3$), δ 7.91–7.23 (m, 5, *p*-tolyl and NH), 4.08 (d, J = 1 Hz, O=C–CH_2–NH), 2.41 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{16}H_{21}N_3O_3S$: C, 57.30; H, 6.31; N, 12.53; S, 9.54. Found: C, 57.33; H, 6.55; N, 12.51; S, 9.60.

1-Cyclohexyl-2-*p*-toluenesulfonimido-3-methyl-5-imidazolidone (5c).—To a suspension of 580 mg (4.15 mmol) of sarcosine methyl ester hydrochloride in 15 ml of dry methylene chloride was added 0.64 ml of triethylamine. The mixture was stirred for 30 min at room temperature, and to this clear solution 1.20 g (4.30 mmol) of TsCC was added. After stirring for 20 min the solvent was removed *in vacuo*, and the residue was worked up as described in the above experiment to yield 1.59 g of a gum. It was dissolved in 20 ml of methanol, and the solution was refluxed for 18 hr. The methanol was evaporated to a volume of *ca.* 8 ml and then allowed to cool. The crystalline product was filtered, washed with a little methanol, and dried (weight,

(8) F. Zetzsche, H. E. Meyer, H. Overback, and H. Lindlar [*Chem. Ber.*, **71**, 1512, 1516 (1963)] reported that 2-benzamidopyridine was formed when N,N′-bis(2-pyridyl)carbodiimide and benzoic acid were fused at *ca.* 200°. This result parallels that just discussed.

(9) R. Aumueller, *Angew. Chem. Intern. Ed. Engl.*, **2**, 616 (1963).

(10) It has been reported that TsCC also hydrates readily in dioxane–water mixtures; *cf. Chem. Abstr.*, **64**, 19506*a* (1966).

1.14 g). From the mother liquors another 0.07 g of the compound was obtained: total yield, 1.21 g (74%); mp 179–181°. Recrystallization from methanol provided an analytical sample as colorless needles: mp 180–181°; ir ($CHCl_3$) 1754 (C=O), 1620 cm^{-1} (SO_2N=C); nmr ($CDCl_3$) δ 7.93–7.22 (q, 4, J_{AB} = 8 Hz, *p*-tolyl), 4.00 (s, 3, NCH_3), 2.42 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{17}H_{23}N_3O_3S$: C, 58.44; H, 6.64; N, 12.03; S, 9.16. Found: C, 58.61; H, 6.92; N, 11.96; S, 9.30.

N-(N-Carbobenzyloxyglycyl)-*p*-toluenesulfonamide (12).—A mixture of 418 mg (2 mmol) of carbobenzyloxyglycine and 556 mg (2 mmol) of TsCC was stirred for 90 min at 140 ± 2° under anhydrous conditions. The melt was allowed to attain room temperature; the solid cake was broken up and extracted with 20 ml of refluxing hexane for 15 min. After cooling, the precipitated product was filtered, washed with a little hexane, and dried to give 740 mg of a powder, mp 134–136°. It was dissolved in 25 ml of benzene treated with a pinch of charcoal and filtered. The filtrate was concentrated to *ca.* 10 ml and diluted with an excess of hexane. The precipitate was filtered and recrystallized from benzene–hexane giving 527 mg (73%) of pure **12** as a white solid: mp 139–140°; ir ($CHCl_3$) 3420 (NH), 1720–1700 (C=O); nmr (DMSO-d_6), δ 7.94–7.36 (q, 4, J_{AB} = 8 Hz, *p*-tolyl), 7.35 (s, 5, $C_6H_5CH_2O$), 5.05 (s, 2, C_6H_5–CH_2–O–), 3.74 (d, 2, J = 6 Hz, –CH_2–NH–), 2.40 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{17}H_{18}N_2O_5S$: C, 56.35; H, 5.01; N, 7.73; S, 8.83. Found: C, 56.19; H, 4.96; N, 7.80; S, 8.76.

To the hexane extracts of the reaction mixture, cyclohexylamine was added. Within a short time a white precipitate formed and was filtered, washed with little hexane, and dried to give 340 mg (76%) of a white solid, mp 234–235°. This was identified as N,N'-dicyclohexylurea by mixture melting point and ir spectrum.

Reaction of TsCC with Aqueous Acetone.—A solution of 53 mg (0.19 mmol) of TsCC in 1 ml of acetone and 0.15 ml of water was stirred at room temperature. After stirring for 2 hr the tlc (C_6H_5–$CHCl_3$; 3:7) spot corresponding to TsCC had disappeared; however, stirring was continued for another 6 hr. Upon addition of 5 ml of water, a white precipitate was formed and filtered, yield 52 mg (93%). Recrystallization from aqueous acetone gave white needles, mp 175–177°, identified as **3a** by tlc and mixture melting point.

N,N'-Dicyclohexyl-N''-*p*-toluenesulfonylguanidine (13).—To a stirred solution of 99 mg (1 mmol) of cyclohexylamine in 5 ml of methylene chloride was added 278 mg (1 mmol) of TsCC. After the mixture was stirred for 1 hr at room temperature, a tlc plate (C_6H_6–$CHCl_3$; 1:1) indicated the complete absence of TsCC. Evaporation of solvent *in vacuo* furnished 376 mg (100%) of a white amorphous solid, mp 160–165°, which was crystallized from benzene–hexane to give 345 mg (94%) of the guanidine **13**, mp 164–166°. Recrystallization from benezne–hexane yielded an analytical sample of **13** as fine needles: mp 165–166°; ir ($CHCl_3$) 3444 and 3320 (NH), 1590 cm^{-1} (SO_2N=C).

Anal. Calcd for $C_{20}H_{31}N_3O_2S$: C, 63.64; H, 8.28; N, 11.13; S, 8.47. Found: C, 63.66; H, 8.10; N, 11.47; S, 8.77.

1-Cyclohexyl-5-*p*-toluenesulfonimido-2(4)-H-tetrazole (14).—A mixture of 834 mg of TsCC, 195 mg (3 mmol) of sodium azide, and 20 ml of dimethoxyethane was stirred for 12 hr at room temperature. To this suspension 1 ml of water was added, and stirring was continued for another 2 hr. Evaporation of the solvent *in vacuo* gave a white solid which was dissolved in 15 ml of 1 *N* sodium hydroxide. The solution was filtered, the filtrate was acidified with concentrated HCl, and the precipitate was filtered, washed with cold water, and dried to give 920 mg (96%) of crude tetrazole **14**. Two recrystallizations from chloroform furnished an analytical sample: mp 232–233°; ir (Nujol) 3120 (NH), 1628 cm^{-1} (SO_2N=C).

Anal. Calcd for $C_{14}H_{19}N_5O_2S$: C, 52.33; H, 5.94; N, 21.79; S, 9.96. Found: C, 52.28; H, 5.94; N, 22.07; S, 10.24.

Oxidation of Benzhydrol Using TsCC. A. Pyridinium Trifluoroacetate[2] As Catalyst.—A reaction medium was prepared by adding 3 ml of DMSO to a mixture of 0.16 ml of dry pyridine and 0.08 ml of trifluoroacetic acid in 3 ml of benzene. To 184 mg (1 mmol) of benzhydrol, 3 ml of this mixture was added followed by 556 mg (2 mmol) of TsCC. The mixture was stirred for 36 hr at room temperature in a stoppered flask. Tlc analysis (C_6H_6–$CHCl_3$, 1:1) of the reaction mixture indicated that after 8 hr there was no further progress of the oxidation. The reaction mixture was diluted with 30 ml of ether and washed successively with water (three 10-ml portions), 1 *N* NaOH (two 10-ml portions), and water (one 10-ml portion) and dried. Removal of solvent *in vacuo* furnished 139 mg of an oil which showed at least four spots on a tlc plate. Two of these spots had the same R_f as benzhydrol and benzophenone. The total mixture was dissolved in 5 ml of benzene–hexane (1:1) mixture, treated with decolorizing carbon, and filtered, and the filtrate was evaporated *in vacuo* to yield 70 mg of an oil. This was dissolved in 1 ml of ethanol and treated with a slight excess of ethanolic 2,4-dinitrophenylhydrazine containing HCl. After 2 hr at room temperature, the orange 2,4-dinitrophenylhydrazone (DNP) was filtered, washed, and dried: yield, 39 mg; mp 242–244°. There was no depression in melting point when on admixture the authentic 2,4-DNP of benzophenone.

B. Without Catalyst.—To a stirred solution of 834 mg (3 mmol) of TsCC in 5 ml of DMSO was added 552 mg (3 mmol) of benzhydrol. The stirring was continued for 22 hr at room temperature; however, tlc analysis indicated that no further oxidation occurred after 4 hr. The mixture was diluted with 50 ml of ether and worked up as described in part A to give 668 mg of an oil containing a small amount of solid. Upon acidification the sodium hydroxide washing gave 346 mg (39%) of the urea **3a**. The oily product was found by tlc to be a mixture of at least four compounds. It was chromatographed on an alumina column (6.6 g, Woelm "neutral" alumina, activity I), and the column was developed by successive elution with hexane and ether. The first hexane eluate (260 ml) was evaporated *in vacuo* to give 345 mg of an oil. A tlc (C_6H_6 solvent) of this oil indicated the presence of two close spots, the major one corresponding to benzophenone. The oil was dissolved in 15 ml of ether, washed with water (two 5-ml portions), and dried, and the solvent was removed to give 290 mg of a liquid: ir (liq film) 1655 cm^{-1} (C=O). It was converted into its 2,4-DNP giving 250 mg (23%) of impure 2,4-DNP which on crystallization from acetic acid furnished 150 mg (14%) of pure 2,4-DNP, mp 243–244°, identified as in part A.

Registry No.—**2a**, 5287-13-8; **3a**, 5530-82-5; **4a**, 17703-97-8; **5a**, 17719-27-6; **5b**, 17703-94-5; **5c**, 17703-95-6; **12**, 17719-28-7; **13**, 908-18-9; **14**, 17703-98-9.

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Reaction of N,N′-Biisomaleimide with Butylamine. Amine-Catalyzed *cis–trans* Isomerization

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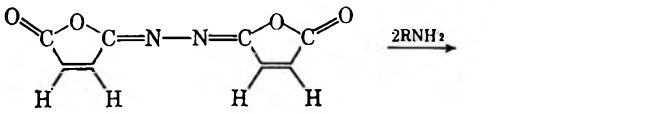
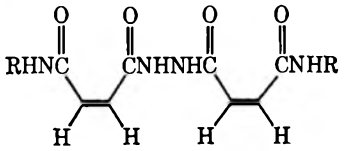
Reactions of N,N′-biisomaleimide with *n*-, *sec*-, and *t*-butylamine in dimethyl sulfoxide solution produce the anticipated ring-opened adducts, but different geometric isomers were obtained. An amine-catalyzed *cis–trans* isomerization is believed to have taken place. In the presence of a primary or a secondary amine, but not a tertiary amine, the N,N′-biisomaleimide–butylamine adducts were found to undergo simultaneous complexation and isomerization. Using a given butylamine as catalyst, the extent of isomerization decreases in the order N,N′-biisomaleimide–*n*-butylamine adduct > N,N′-biisomaleimide–*sec*-butylamine adduct > N,N′-biisomaleimide–*t*-butylamine adduct. When different butylamines were used as catalysts, the extent of isomerization for a given adduct decreases in the order *n*-butylamine > *t*-butylamine. Because of the small differences in basicity among these butylamines, our results suggest that steric interactions are responsible for the differences in the extent of isomerization. The occurrence of complexation during the isomerization provides a useful correlation for understanding the catalytic behavior of these amines. The mechanism proposed by Nozaki and Ogg for an acid- or salt-catalyzed isomerization of maleates to fumarates is extended to include amine-catalyzed isomerizations.

It was recently reported by Hedaya and his collaborators[1,2] that N,N′-biisomaleimide (I), similar to other isomaleimides,[3] reacts readily with nucleophiles to yield ring-opened adducts illustrated by II. These



I



II

IIa, R = *n*-Bu
b, R = *sec*-Bu
c, R = *t*-Bu

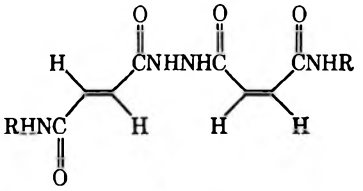
adducts were suggested to assume a *cis* configuration with respect to the carbon–carbon double bond. Reactions of I with aliphatic amines were shown in the present work to form in certain instances different geometric isomers. An amine-catalyzed *cis–trans* isomerization is believed to have taken place.

The base-catalyzed isomerization of maleic acid and its esters has received only limited attention. Meerwein and Weber[4] found that potassium in ether converted methyl maleate into methyl fumarate. Tanatar[5] and Pfeiffer[6] reported the isomerization of maleic acid to fumaric acid by means of ammonia and pyridine, respectively. Clemo and Graham[7] investigated systematically the catalytic action of various amines and found that only primary and secondary amines were effective; tertiary amines, even though they were stronger bases than many primary and secondary amines, did not lead to isomerization. It was concluded that organic bases are only effective as catalysts when they contain amino or imino hydrogen. A mechanism was proposed by these authors involving the formation of a coordinate link between the hydrogen atom of the base and the carbonyl oxygens of the maleic ester. Isomerization occurs as a result of rotation about the electron-deficient double bond.

We have examined the amine-catalyzed *cis–trans* isomerization of various N,N′-biisomaleimide–butylamine adducts. The catalytic activity of the three isomeric butylamines and the extent of isomerization of various adducts with a given amine were investigated. We have also studied the complexation of amine with these adducts and the correlation of the complex formation with the isomerization. A reconsideration of the mechanism for an amine-catalyzed isomerization is presented.

Results and Discussion

Reaction of N,N′-biisomaleimide (I) with *n*-butylamine in dimethyl sulfoxide (DMSO) solution at 25° was found to yield products consisting of both *cis–cis* adduct (IIa) and *cis–trans* adduct (IIIa). Under the same reaction conditions either *sec*-butylamine or *t*-butylamine produced only the corresponding *cis–cis* adduct IIb and IIc, respectively.



IIIa, R = *n*-Bu
b, R = *sec*-Bu
c, R = *t*-Bu

Amines are known to effect the isomerization of maleic acid and its esters to the fumaric forms.[4–7] This leaves unanswered, however, the question of why isomerization did not occur in the reactions involving either *sec*-butylamine or *t*-butylamine.

The isomerization of these adducts by various butylamines was investigated using the nmr method. Figure 1 shows the nmr spectra in the ethylenic proton regions of three N,N′-biisomaleimide–butylamine ad-

(1) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.*, **31**, 1311 (1966).
(2) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1317 (1966).
(3) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).
(4) H. Meerwein and J. Weber, *Ber.*, **58**, 1266 (1925).
(5) S. Tanatar, *J. Russ. Phys. Chem. Soc.*, **43**, 1742 (1911).
(6) P. Pfeiffer, *Ber.*, **47**, 1592 (1914).
(7) G. R. Clemo and S. B. Graham, *J. Chem. Soc.*, 213 (1930).

ducts after being heated at 60° for 10 min in the presence of 0.5 mol of *n*-butylamine/mol of adduct. The *cis*-ethylenic protons, which exhibit a singlet signal in DMSO solution, are observed as an AB quartet (J_{AB} = 13 Hz) in the presence of *n*-butylamine. This phenomenon is associated with a complexation of the hydrazide group of the adduct with the *n*-butylamine. Of specific interest, however, is the observation that all three of these adducts (IIa, b, and c) show absorption characteristic of *trans*-ethylenic protons (collapsed AB quartet, about 6.9 ppm) after being heated for 10 min with *n*-butylamine.

The results are summarized in Table I. It is seen that the extent of isomerization noticeably increased when the butyl group in the adduct was changed from *t*-butyl to *sec*-butyl to *n*-butyl.

TABLE I

ISOMERIZATION OF N,N'-BIISOMALEIMIDE–BUTYLAMINE ADDUCTS CATALYZED BY *n*-BUTYLAMINE IN DMSO SOLUTION

	Conditions			
Adduct	*T*, °C	*t*, min	%	%
IIa	60	10	75	25
IIb	60	10	83	17
IIc	60	10	86	14

The relative extents of isomerization of IIb by different butylamines were determined in a similar manner.

As seen in Table II, 85% isomerization was observed on treatment with 0.5 mol of *n*-butylamine for 10 min at 100° while only 8% isomerization occurred on treatment with *t*-butylamine under the same conditions.

TABLE II

CATALYTIC ACTIVITIES OF SOME BUTYLAMINES IN THE ISOMERIZATION OF IIb

	Conditions			
Catalyst	*T*, °C	*t*, min	%	%
n-Butylamine	100	10	15	85
t-Butylamine	100	10	92	8

The ionic intermediate proposed by Clemo and Graham[7] seems not to be present in our system. Our data suggest that only the carbonyl of the hydrazide group participates during the isomerization.

In DMSO solution, the amide protons of IIb were observed as a doublet at 8.66 ppm. Addition of 0.5 mol of *t*-butylamine shifted the absorption due to the amide protons to 10.72 ppm, but did not change either the multiplicity (d, J = 8 Hz) or the relative intensity. In contrast, the addition of *t*-butylamine caused a disappearance of the 11.7-ppm hydrazide signal, and in its place was observed a singlet at 8.68 ppm having double the original intensity. This absorption is believed to result from a rapid exchange of the hydrazide protons with the protons of the added amine and indicates a complex of the type shown by IV or V.

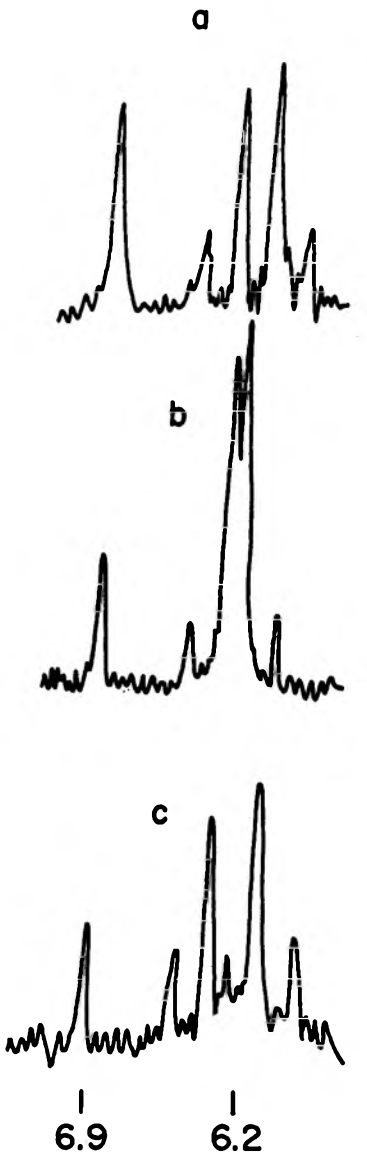
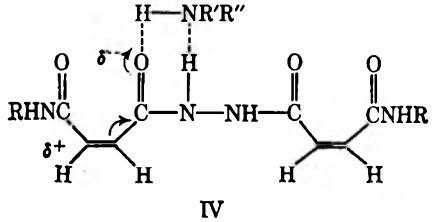
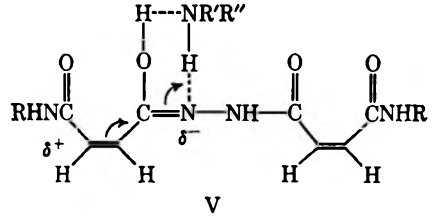


Figure 1.—Nmr spectra of (a) IIa, (b) IIb, and (c) IIc in DMSO solution containing *n*-butylamine measured after 10 min at 60°.



IV

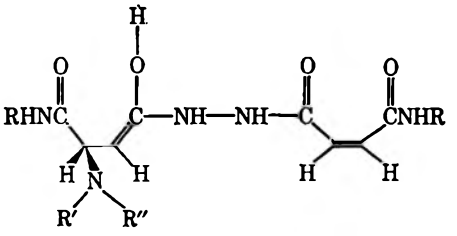


V

Infrared spectral changes were also consistent with these postulated complexes. The NH stretching absorption at 3170 cm^{-1} was converted into a very broad band extending from 3430 to 2520 cm^{-1} on addition of *t*-butylamine. This type of change has previously been

ascribed to the occurrence of a chelated hydroxy group through hydrogen bonding.[8]

Let us assume that the initial step of an amine-catalyzed isomerization involves a nucleophilic attack of amine at the *cis*-ethylenic double bond to generate an intermediate VI where R′ is alkyl and R″ is alkyl or hydrogen. This is analogous to the initial step in the Nozaki and Ogg mechanism for the acid- or salt-catalyzed isomerization of maleic acid and its esters.[9] We would then predict that the catalytic activities of the butylamines should parallel their nucleophilicities.



VI

A correspondence generally exists between the order of basicities and the order of nucleophilicities for a group of nucleophiles having the same attacking atom.[10] Thus the following order of catalytic activities would be expected for these amines (the pK_b values are in parentheses): *n*-butylamine (3.39) > *sec*-butylamine (3.44) > *t*-butylamine (3.55). Although the order is consistent with our observations, it is doubtful that the small differences in basicities between these three primary amines could account fully for our results. Additionally, the data shown in Table I cannot be satisfactorily explained in terms of nucleophilicity of the *n*-butylamine.

It is conceivable that the initial attack at the *cis*-ethylenic double bond could be hindered substantially when bulky species are involved. The dependence of rate of isomerization on the bulkiness of the neighboring butyl groups in a *cis–cis* adduct is consistent with the data shown in Table I. This result suggests that the incoming butylamine molecules encounter steric interactions of different degrees with the butyl groups present in the *cis–cis* adducts during the formation of the intermediate VI. Following this line of reasoning one would expect that the rates of isomerization of a given adduct should also be different when amines of different steric nature are employed as catalysts. This consideration is in agreement with the results shown in Table II. *n*-Butylamine was found to be a much more effective catalyst than *t*-butylamine in spite of their relatively close base strength. This observation is parallel to the result found in the reaction of amines with alkyl halides.[11] The effect of steric hindrance on the catalytic activity of a cyclic secondary amine was also observed by Janssen[12] in the isomerization of maleic acid based polyesters.

Isomerization of these adducts could also be catalyzed by a secondary amine, but not by a tertiary amine regardless of the base strength. Such behavior is similar to that of maleic acid and its esters.[7]

(8) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1068 (1949).

(9) K. Nozaki and R. Ogg, Jr., *ibid.*, **63**, 2583 (1941).

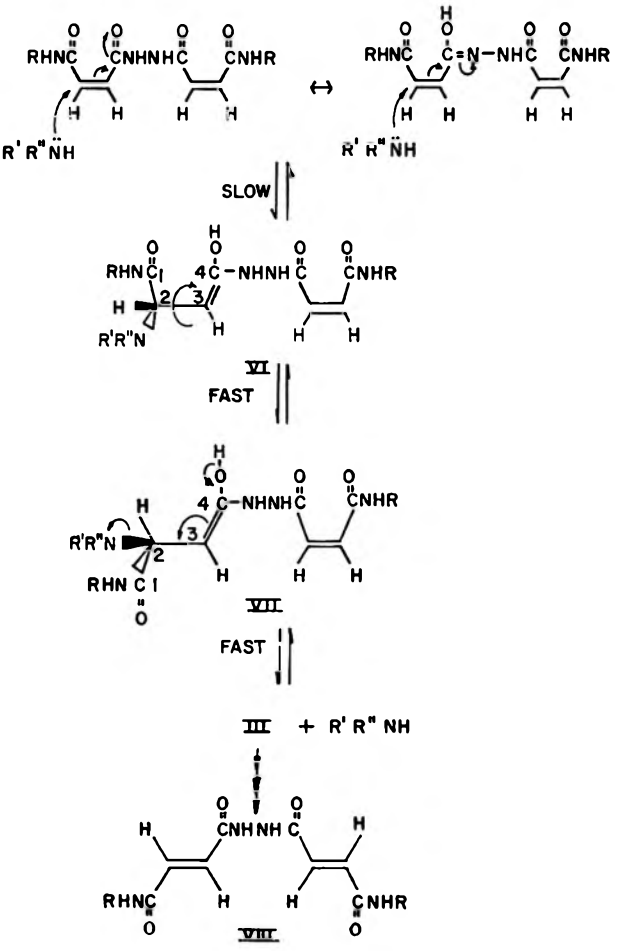
(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 259.

(11) H. C. Brown and N. R. Eldred, *J. Amer. Chem. Soc.*, **71**, 445 (1949).

(12) B. Janssen, *Chimia*, **19**, 154 (1965).

In our view, the mechanism postulated by Nozaki and Ogg[9] can be extended to include an amine-catalyzed isomerization with some modifications. As illustrated by Scheme I, the initial step, which is believed to be

SCHEME I



the rate-determining step, involves a 1,4 addition of amine at the conjugated double bonds to generate the intermediate VI. In VI, bond 1–2 can rotate freely about the axis of bond 2–3 forming either a *trans* conformer, VII, or a *gauche* conformer (such as VI) with respect to bond 3–4. A *trans–cis* adduct, III, results when a rapid elimination of amine from the unstable intermediate VII occurs. An elimination of amine from a *gauche* conformer would regenerate the original *cis–cis* adduct, II. Further isomerization of III would form eventually the *trans–trans* adduct VIII.

Intermolecular hydrogen bonding to give complexes such as IV and V probably results in a polarization of the maleic carbon–carbon double bond, and thus would be expected to facilitate greatly nucleophilic addition to this unsaturated site. This consideration appears to explain the ease with which the isomerization can proceed under appropriate conditions. The actual rate of addition of amine to the double bond in this system, however, is strongly influenced by steric considerations.

Experimental Section

Instrumental.—A Varian Model A-60 instrument was used for the nmr measurements. Tetramethylsilane and DMSO (J. T. Baker, redistilled) were employed as the internal standard and solvent, respectively. For infrared spectra, a Perkin-Elmer

Model 221 was used with either potassium bromide pellets or DMSO solution in KBr cells. Melting points were taken with a Thomas–Hoover capillary apparatus and were corrected.

N,N'-Biisomaleimide (I) was prepared according the procedures previously described.[6] The crude product was recrystallized from dimethylformamide to yield a yellow solid (61%), mp 260° (lit.[1] mp 260°).

Anal. Calcd for $C_4H_2NO_2$: C, 50.00; H, 2.08; N, 14.58. Found: C, 50.19; H, 2.29; N, 14.41.

Reaction of N,N'-Biisomaleimide (I) with *n*-Butylamine.—Into a 50-ml three-necked flask, equipped with a condenser, thermometer, nitrogen inlet, rubber cap, and a magnetic stirrer was placed 1.92 g (0.01 mol) of I and 10 ml of redistilled DMSO. While under cooling with an outside water bath, 1.61 g (0.022 mol) of *n*-butylamine was introduced into the reaction vessel with a syringe. An exothermic reaction occurred immediately and an orange solution was obtained. The reaction was allowed to proceed at room temperature for 23 hr. The white solid formed in the flask was collected by filtration. It was washed successively with dimethoxyethane and ether and was dried under vacuum: white solid, mp >335°; yield 0.82 g (24.3%). This product was shown to be the *cis–trans* adduct IIIa: nmr (DMSO, 100°), δ 8.7 (s, 2, hydrazide), 8.18 (t, 2, J = 5 Hz, amide), 6.93 (s, 2, *trans*-ethylene), and 6.23 (s, 2, *cis*-ethylene); ir (KBr), 1625 cm^{-1} (medium, amide–amide I), 1591 (very strong, hydrazide–amide I), 1556 (strong, amide–amide II), 1473 (strong, hydrazide–amide II), and 996 (medium, *trans*-disubstituted ethylene).

Anal. Calcd for $C_8H_{13}O_2N_3$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.56; H, 7.75; N, 16.75.

The above filtrate was poured into 50 ml of water and the pinkish solid which precipitated was collected, washed with an acetone–ether mixture, and dried under vacuum: pale yellow solid; mp 150°; yield 3.02 g (65.1%). This product was assigned to be the *cis–cis* adduct IIa: nmr (DMSO, 70°), δ 11.4 (s, 2, hydrazide), 8.81 (t, 2, J = 5 Hz, amide), 6.17 (s, 4, *cis*-ethylene); ir (KBr), identical with that of IIIa except no 996-cm^{-1} absorption was observed.

Anal. Calcd for $C_8H_{13}O_2N_3$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.55; H, 7.57; N, 16.47.

The aqueous solution was combined with the acetone–ether washings and concentrated to less than 5 ml with a rotating evaporator. The solution was diluted with a small amount of acetone and was poured into 50 ml of ether. A reddish brown, resinous material was obtained: yield 0.061 g (1.8%). This resinous material exhibits in the nmr weak ethylenic proton signals but a broad signal at about 8 ppm which is presumably due to the presence of various amido and amino protons.

Reaction of N,N'-Biisomaleimide (I) with *sec*-Butylamine.—The reaction was carried out in the same manner as described above. There was no insoluble product formed by the end of the reaction. Two fractions of product were obtained. The DMSO-soluble, water-insoluble fraction was a greenish yellow solid, mp 204°, yield 3.16 g (93.3%). This product was shown to be the *cis–cis* adduct IIb: nmr (DMSO, 70°), δ 11.4 (s, 2, hydrazide), 8.66 (d, J = 8 Hz, 2, amide), and 6.19 (s, 4, *cis*-ethylene); ir (KBr), 1625 cm^{-1} (medium, amide–amide I), 1596 (very strong, hydrazide–amide I), 1555 (strong, amide–amide II), and 1493 (strong, hydrazide–amide II).

Anal. Calcd for $C_8H_{13}O_2N_3$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.13; H, 7.78; N, 16.53.

The water-soluble, ether–acetone-insoluble fraction was a reddish brown, resinous substance, yield 0.041 g (1.2%).

Reaction of N,N'-Biisomaleimide (I) with *t*-Butylamine.—The reaction was carried out in the same manner as described above. There was no insoluble product formed by the end of reaction. Two fractions of products were isolated. The DMSO-soluble, water-insoluble fraction was a greenish yellow solid, mp 222°, yield 3.08 g (91.1%). This product was shown to be the *cis–cis* adduct IIc: nmr (DMSO, 100°), δ 8.6 (broad s, 4, hydrazide and amide), and 6.20 (s, 4, *cis*-ethylene); ir (KBr), 1625 cm^{-1} (medium, amide–amide I), 1590 (very strong, hydrazide–amide I), 1556 (strong, amide–amide II), and 1490 (strong, hydrazide–amide II).

Anal. Calcd for $C_8H_{13}O_2N_3$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.00; H, 7.80; N, 16.18.

The water-soluble, ether–acetone-insoluble fraction was a reddish brown, resinous material, yield 0.034 g (1%).

Isomerization Measurement.—Appropriate amounts of a *cis,cis*-N,N'-biisomaleimide–butylamine adduct and an amine were dissolved in dimethyl sulfoxide and transferred into a thin-walled nmr tube which was sealed under an argon atmosphere. The tube was then placed in the nmr cavity which was preheated to the desired temperature, and held for 10 min. The spectra of the ethylenic proton regions were immediately recorded. Amounts of the *cis*- and *trans*-ethylenic protons were determined by both area integration and weighing.

Registry No.—I, 6990-21-2; IIa, 17954-86-8; IIb 17954-87-9; IIc, 17954-88-0; IIIa, 17954-89-1.

Acknowledgment.—We are indebted to Professor E. J. Corey of Harvard University and to Professor D. J. Cram of the University of California at Los Angeles for helpful discussions.

Azabicyclic Alcohols. V. Synthesis and Stereochemistry of the 1-Azabicyclo[3.2.1]octanols

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Both epimers of the 1-azabicyclo[3.2.1]octan-3-, -4-, and -6-ol isomers have been synthesized and their stereochemistry has been assigned. The alcohols were obtained by reductions of their corresponding ketones, except for the *exo*-6-hydroxy isomer, which was obtained by Raney nickel catalyzed epimerization of the *endo* isomer, or (together with its epimer) by cyclodehydration of 3-piperidylethylene glycol. Attempts to prepare this *exo* alcohol by oxidative epimerization of the *endo* isomer were unsuccessful. Unexpectedly, several condensation products with the oxidized solvent were formed. Structures of two of these products have been assigned as 7-ethylidene- and 7-ethyl-1-azabicyclo[3.2.1]octan-6-ols (**15** and **16**), respectively.

We have been investigating the synthesis and stereochemical correlations of pharmaceutically useful azabicyclic alcohol epimers. Previous papers in this series have discussed fused bicyclic, bridgehead nitrogen systems.[1] We now report the results of a study of the 1-azabicyclo[3.2.1]octanols, a bridged bicyclic system that differs from its fused analogs in that inversion of the nitrogen atom is no longer possible. Apart from presumably unstable carbinolamines, there are three pairs of epimeric secondary 1-azabicyclo[3.2.1]-octanols, of which only a 6-ol isomer (*cf.* **4**) of unknown configuration has been previously reported.[2]

The six isomers have been synthesized; their stereochemistry has been assigned. Pertinent physical data are listed in Table I. As expected on the basis of their molecular geometry, none of these isomers shows any infrared absorptions below 2850 cm^{-1} (Bohlmann bands) which are characteristic of two or more C–H bonds being *trans* diaxial to a nitrogen electron pair.[3]

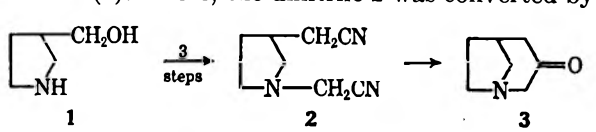
TABLE I

PHYSICAL DATA FOR THE 1-AZABICYCLO[3.2.1]OCTANOLS

Compound	Mp, °C	Glpc retention time, min[a]	pK_a[b]	Nmr, carbinol H τ[c]	Nmr, carbinol H W, cps[d]
3-OH; A (**5**)	175–177	5.0	10.30	6.27	10
3-OH; B (**6**)	132–135	5.4	9.55	6.13	22
4-OH; A (**10**)	180–182	6.4	10.04	6.27	21
4-OH; B (**11**)	184–185	6.7	10.35	6.19	10
6-OH; A (**13**)	177–179	3.7[e]	10.30	5.54	18[f]
6-OH; B (**14**)	157–159	4.0[e]		5.76	12[g]

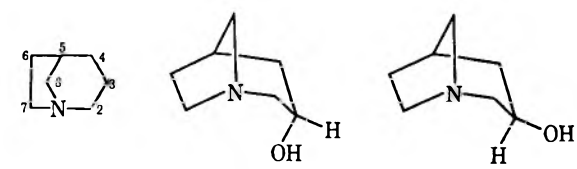
[a] From the air peak on a 10 ft × 1/4 in. column of 13% Carbowax 20M on 60–80 mesh Gas-Chrom P at 230° and a helium flow rate of 110 ml/min. [b] Ionic strength, 0.0050 μ. [c] In 20% $CDCl_3$ solution, from TMS as internal standard. [d] Width of the carbinol proton multiplet at one-half the peak height. [e] From the air peak on a 5 ft × 1/4 in. column of 4% QF-1 on 60–80 mesh Chromosorb W at 135° and a helium flow rate of 55 ml/min. [f] Quintet. [g] Quartet.

1-Azabicyclo[3.2.1]octan-3-ols.—These were obtained from the corresponding ketone **3**, which was synthesized in four steps from the known 3-pyrrolidinemethanol (**1**). Here, the dinitrile **2** was converted by a Thorpe condensation into an iminonitrile, which was not isolated, but was hydrolyzed and decarboxylated directly to the ketone.



1 **2** **3**

The structure of **3**, established by its method of synthesis, is confirmed from the fact that it was hydrogenolyzed to 1-azabicyclo[3.2.1]octane (**4**), the ir spectrum of which was identical with that obtained by hydrogenolysis of the corresponding 4-one and 6-one analogs.[4] Reduction of **3** with lithium aluminum hydride gave a 40:60 mixture of epimeric alcohols, designated A and B according to their order of glpc elution. Hydrogenation of **3** over platinum dioxide gave epimer A (**5**), while reduction with sodium in ethanol–benzene gave epimer B (**6**), each greater than 95% epimerically pure.



4 **5** **6**

The stereochemistry of these alcohols may be assigned by analogy to reductions of the isosteric 3-tropinone system.[5,6] Thus, catalytic hydrogenation would be expected to occur more readily from the less hindered *exo* side of the molecule, giving rise to the axial alcohol (**5**), while a thermodynamically controlled sodium in ethanol reduction should give a predominance of the more stable equatorial hydroxyl isomer (**6**). Relative glpc retention times (Table I) and pK_a values correspond to those previously observed for epimeric axial and equatorial alcohol pairs.[7,8]

These assignments are confirmed by the dilute solution ir spectral data, given in the Experimental Section, which reveal that the axial hydroxyl epimer has a symmetrical free O–H stretching band envelope, of greater extinction coefficient and smaller half band width than that of its equatorial hydroxyl epimer, which has an unsymmetrical band.[9] It may be noted that the O–H stretching maximum occurs at the same

(1) Paper IV: H. S. Aaron, C. P. Rader, and G. E. Wicks, Jr., *J. Org. Chem.*, **31**, 3502 (1966).

(2) L. H. Sternbach and S. Kaiser, *J. Amer. Chem. Soc.*, **74**, 2215 (1952).

(3) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(4) L. P. Reiff and H. S. Aaron, *Tetrahedron Lett.*, 2329 (1967).

(5) L. C. Keagle and W. H. Hartung, *J. Amer. Chem. Soc.*, **68**, 1608 (1946); A. Nickon and L. F. Fieser, *ibid.*, **74**, 5566 (1952).

(6) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

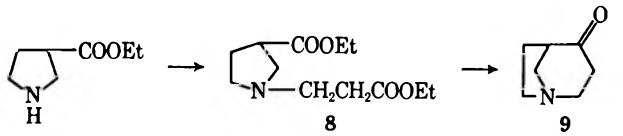
(7) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964), and references cited therein.

(8) (a) C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *ibid.*, **30**, 1536 (1965); (b) H. S. Aaron and C. P. Rader, *ibid.*, **29**, 3426 (1964).

(9) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967).

frequency in both epimers, in exception to a general rule[9,10] that the axial epimer will absorb at the higher frequency. Nmr spectra showed a half band width of the carbinol proton signal of epimer A to be 10 cps, which suggests an equatorial hydrogen (axial alcohol), while that of epimer B (22 cps) is typical of a strongly coupled axial hydrogen, hence equatorial alcohol.[7,8a] The observation that the equatorial carbinol hydrogen (epimer A) absorbs at higher field than that of its axial epimer is unusual.[11]

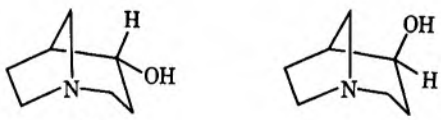
1-Azabicyclo[3.2.1]octan-4-ols.—The parent ketone (**9**) was synthesized[12] by a Dieckmann condensation of **8**, obtained in turn from the known ethyl 3-pyrrolidinecarboxylate (**7**). Compound **9** was reduced



7 8 9

both chemically and catalytically under a variety of conditions to mixtures of epimeric alcohols, as given in the Experimental Section. In every case, epimer A was obtained as the predominant product. The pure epimers were obtained by column chromatography on basic alumina.

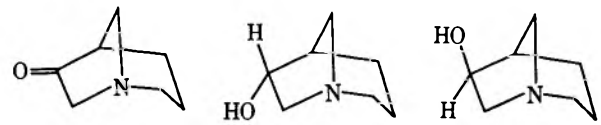
The structure of the ketone **9** was established by its method of synthesis, and by its hydrogenolysis to 1-azabicyclo[3.2.1]octane.[4] The stereochemistry of its derived alcohols may be assigned as **10** (epimer A) and **11** (epimer B) from the reduction data, since for steric reasons, the equatorial alcohol (**10**) would be expected to predominate by either a chemical reduction or a catalytic hydrogenation route. It may be noted



10 11

that the relative glpc (Carbowax) retention times (Table I), which are very close for these two epimers, are the reverse of that usually observed for an axial–equatorial alcohol pair. Structures **10** and **11**, however, are confirmed by their pK_a values[8b] and their nmr spectral data (Table I). Both the relative chemical shifts and half band widths of the carbinol protons are in agreement with these assignments.[11,13]

1-Azabicyclo[3.2.1]octan-6-ols.—Catalytic hydrogenation or hydride reduction of 1-azabicyclo[3.2.1]-octan-6-one (**12**) gave the known 6-ol isomer, apparently epimerically pure. The configuration of this alcohol is assigned as *endo* (**13**), based on the assumption that



12 13 14

these reductions should all take place from the relatively unhindered *exo* side of the molecule.[14]

Attempts to epimerize the *endo* alcohol with aluminum isopropoxide or sodium ethoxide under equilibrating conditions[6,15] were unsuccessful. The latter reaction, however, led to some interesting and unusual results. Glpc analysis of the product revealed four major components, which were separated by chromatography on alumina. None proved to be the *exo* alcohol **14**. The major component was the *endo* alcohol **13**. Two of the products were assigned from their spectral data and elemental analyses as 7-ethylidene- and 7-ethyl-1-azabicyclo[3.2.1]octan-6-ols (**15** and **16**), respectively. The structure of the fourth component was not established. The relative configurations of **15** and **16** are depicted as deduced below. Compound **15** apparently was obtained as a near equal mixture of *cis* and *trans* isomers, judging from the appearance in the nmr of two (split) methyl peaks of slightly different chemical shift. It appears that **15** and **16** are the products of a

15 16

sequence of reactions, which start with an air oxidation of the ethanol solvent to acetaldehyde, followed by an aldol condensation with the ketone **12**, and subsequent dehydration (to **17**) and reduction.

17 18

To confirm these structural assignments, the parent ketone **12** was treated with acetaldehyde. The main product was an α,β-unsaturated ketone, **17**, which upon reduction with sodium borohydride gave the identical product (**15**) isolated above. From this mode of synthesis and by analogy to reductions of **12**, compound **15** would be expected to have an *endo*-hydroxyl group. Catalytic hydrogenation of **15** gave a saturated amino alcohol **18**, isomeric with **16**. The stereochemistry of **18** is assigned on the basis that catalytic hydrogenation of **15** should proceed from the less hindered *exo* side of the molecule, while the configuration of the hydroxyl group, of course, would remain unchanged. The configuration of **16**, therefore, is assigned as the C-7 epimer of **18** on the assumption that the configuration at C-6, shown above to be the same in **15** and **18**, should also be the same in **16**,

(10) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959).

(11) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962).

(12) First synthesized by C. A. Feit and coworkers at Regis Chemical Co., Chicago, Ill., under a U. S. Army Chemical Research and Development Contract. An additional quantity subsequently was prepared in our laboratory from **7**, obtained from Regis. Some of the physical data for **8** and **9** were supplied by Regis.

(13) N. C. Franklin and H. Feltkamp, *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965).

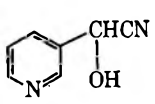
(14) By analogy, the isosteric tropan-6-one molecule is stereospecifically reduced to the 6-α-ol isomer: H. S. Aaron and L. P. Reiff, *J. Heterocycl. Chem.*, **5**, 423 (1968).

(15) M. Balasubramanian and N. Padma, *Tetrahedron*, **19**, 2135 (1963).

since **15** appears to be the precursor of **16** in the reaction from which both were isolated. Further experimentation to establish unequivocally the stereochemistry of these condensation products was not pursued. Based upon these results, the unidentified higher boiling impurities often observed in sodium and alcohol reductions of azabicyclic ketones[4,8a] suggest that side reactions with oxidized solvent may commonly occur under these conditions.

The desired *exo* alcohol (**14**) was finally obtained by a Raney nickel catalyzed epimerization of the *endo* isomer.[16] The configurational assignments of the epimeric alcohols **13** and **14** are supported by the nmr data (Table I), which reveal the carbinol proton signal of **13** to be considerably broader than that of **14**. Inspection of Dreiding models indicates that the orientation of this proton relative to that of the two protons at C-7 is the same in both isomers. Thus, no difference in the band widths of the epimeric carbinol proton signals due to coupling with these protons would be expected. To a first approximation, therefore, the difference in the band widths of the two carbinol proton signals should be due to the difference in coupling constants between them and the C-5 proton. The dihedral angle between the carbinol proton in **13** and the proton at C-5 is about 30°, whereas in **14** this angle is approximately 100°. In general, the magnitude of the coupling constant between vicinal protons is a function of their dihedral angle, being a maximum near 0 and 180°, and a minimum near 90°.[17] It would be expected, therefore, that **13** would have the larger coupling constant between the protons at C-6 and C-5, and thus have the larger carbinol proton band width.

Just prior to the preparation of **14** by the epimerization reaction, above, a synthesis which did not proceed through the ketone **12** was carried out. Here, 3-pyridinecarboxaldehyde cyanohydrin (**19**) was hydrolyzed and esterified to ethyl 3-pyridylglycolate (**20**). The latter was hydrogenated (rhodium on alumina) and reduced (lithium aluminum hydride) to 3-piperidylethylene glycol, which was cyclodehydrated[18] in poor yield to an impure mixture of **13** and **14**, which appeared (ir, after collection by glpc) to be mainly **14**. Optimum conditions for this synthesis were not established, however, in view of the success of the alternate method.



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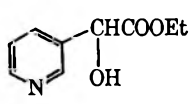

20

Experimental Section

The following instrumentation was used, unless otherwise indicated. Nmr analyses were obtained on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard. Ir spectra were obtained on a Perkin-Elmer 237B grating spectrophotometer. Glpc analyses were carried out on a 10 ft × 0.25 in. column of Carbowax 20M, 13% on Gas-Chrom P, at the indicated temperatures and helium flow rates. Reductions and hydrogenations were carried out as previously described.[19] Picrates were prepared in ether and recrystallized from the indicated solvents. Melting and boiling points are uncorrected.

3-Hydroxymethyl-1-pyrrolidineacetonitrile.—3-Pyrrolidinemethanol[20] (**1**), 24 g (0.24 mol), was treated with sodium bisulfite, formaldehyde, and potassium cyanide essentially as described for the synthesis of pyrrolidineacetonitrile,[21] except that the product was extracted with chloroform and dried over potassium carbonate, to give 22 g (66%) of product: bp 105–106° (0.05 mm); ir (neat) 3350 (OH) and 2235 cm^{-1} (weak, CN).

Anal. Calcd for $C_7H_{12}N_2O$: C, 60.0; H, 8.6; N, 20.0. Found: C, 59.6; H, 8.8; N, 19.4.

1,3-Pyrrolidinediacetonitrile (**2**).—An ice-cold solution of 22 g (0.16 mol) of 3-hydroxymethyl-1-pyrrolidineacetonitrile and 45 g of *p*-toluenesulfonyl chloride in 200 ml of pyridine was placed in the refrigerator overnight, then concentrated under reduced pressure at room temperature. The residual oil was dissolved in chloroform, washed with 5% sodium hydroxide solution, then concentrated to give 35 g (77%) of tosylate, a viscous brown oil that could not be induced to crystallize [ir (neat) 2230 (CN) and 1360, 1160 cm^{-1} (SO_2 of tosylate)]. This product was stirred with 23 g of sodium cyanide in 200 ml of dimethyl sulfoxide for 1 hr at room temperature, then 2 hr at 92°, then cooled, diluted with 500 ml of water, and extracted twice with 300 ml of chloroform. The chloroform solution was washed with water and brine, then dried, concentrated, and distilled to give 15 g of **2**, a slightly yellowish oil, bp 120–123° (0.16 mm), which gave a single glpc peak (1.5 min) on a 5-ft column of LAC 446 at 175°. Its ir spectrum showed an intense band at 2245 cm^{-1} (CN) and lacked bands characteristic of the tosylate.

1-Azabicyclo[3.2.1]octan-3-one (**3**).—Compound **2** (14 g, 0.093 mol) was added dropwise over 3 hr to are fluxing slurry (drying tube) of 31 g of potassium *t*-butoxide (MSA Research Corp.) in 700 ml of sodium-dried benzene. The mixture was refluxed for an additional hour, then allowed to stir overnight at room temperature, cooled, and acidified with 10 ml of sulfuric acid in 25 ml of water. After distillation of most of the benzene, the solution was again cooled, and 200 ml of 50 vol % sulfuric acid was added. The remaining benzene was removed as an azeotrope, and the solution was refluxed for 3 hr, then set aside for 48 hr before the work-up was completed. The solution was cooled, brought to pH 12 with 20% sodium hydroxide solution, filtered, and extracted with chloroform. The chloroform solution was dried and concentrated, and the residual brown oil was distilled to give 5.5 g (47%) of **3**, a waxy hygroscopic white solid, which solidified during the distillation, and only an approximate bp 89° (4 mm) was obtained. The product showed a single glpc peak (4.8 min, 210°, 100 ml/min) and melted at 83–87° after two recrystallizations from pentane: ir (neat) 1720 cm^{-1} (C=O). Its picrate was obtained as orange needles from ethanol and orange prisms from ethyl acetate–hexane: mp 197–198° dec.

Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.1; H, 4.0; N, 15.8. Found: C, 44.3; H, 4.2; N, 15.7.

1-Azabicyclo[3.2.1]octan-3-ol, Axial Alcohol, Epimer A (**5**).—An ethanol solution of the ketone **3** was hydrogenated over platinum dioxide for 0.5 hr, filtered, and concentrated under reduced pressure to give **5**, mp 175–177°, which contained (glpc) only a trace, if any, of epimer B. A dilute solution showed these ir data:[9,22] $\nu_{OH}^{CCl_4}$ 3624 cm^{-1}; $\Delta\nu_{1/2}$ 16 cm^{-1}; ϵ 76; α/β 1.0. Its picrate melted at 230–232° dec (isopropyl alcohol).

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.5. Found: C, 43.8; H, 4.6.

1-Azabicyclo[3.2.1]octan-3-ol, Equatorial Alcohol, Epimer B (**6**).—A benzene solution of the ketone **3** was reduced with sodium in ethanol as described,[19] except that chloroform was used for the final extraction. The product was obtained as a yellow oil, which contained about 3% epimer A. It was taken up in hot hexane and cooled to give a yellow solid, mp 127–134°, from which pure **6** was collected by preparative glpc as a white solid, mp 132–135°. A dilute solution showed these ir data:[9,22]

(16) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

(17) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 84.

(18) H. S. Aaron, O. O. Owens, P. D. Rosenstock, S. Leonard, S. Elkin, and J. I. Miller, *J. Org. Chem.*, **30**, 1331 (1965).

(19) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *ibid.*, **29**, 2252 (1964).

(20) Y.-H. Wu and R. F. Feldkamp, *ibid.*, **26**, 1519 (1961).

(21) R. H. Reitsma and J. H. Hunter, *J. Amer. Chem. Soc.*, **70**, 4009 (1948).

(22) Recorded by C. P. Ferguson on a Perkin-Elmer 521 grating spectrophotometer.

$\nu_{OH}^{CCl_4}$ 3624 cm^{-1}; $\Delta\nu_{1/2}$ 26.5 cm^{-1}; ϵ 58; α/β 0.64. Its picrate melting point, 198–205°, did not sharpen on recrystallization from acetone–pentane.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.5; N, 15.7. Found: C, 43.8; H, 4.5; N, 15.7.

1-Azabicyclo[3.2.1]octane (4) by Hydrogenolysis of 3.—The ketone **3**, 0.1 g in 5 ml of 0.2 *N* hydrochloric acid, was hydrogenated over 0.05 g of platinum dioxide at 3 atm of hydrogen for 1 hr and worked up in the usual manner.[19] The product (**4**) was obtained as a soft, hygroscopic solid of strong ammoniacal odor, which gave a single glpc peak (0.9 min, 220°, 120 ml/min). Its ir spectrum contained no carbonyl or hydroxyl absorption, and was identical with that obtained by hydrogenolysis of the corresponding 4-one and 6-one analogs. It spicrate melted at 280–284° dec (methanol) (lit.[23] mp 294–295°).

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.9; H, 4.7; N, 16.5. Found: C, 45.7; H, 4.7; N, 16.6.

A chloroplatinate was prepared, mp 214–216° dec (lit.[23] mp 215–215.5°).

1-Azabicyclo[3.2.1]octan-4-one (9).[12]—Ethyl 3-pyrrolidinecarboxylate (**7**)[20] (18 g, 0.13 mol) and ethyl acrylate (16 g, 0.16 mol) were refluxed for 3 hr in 125 ml of ethanol, then concentrated to give (according to the cognate procedure of Leonard)[24] 30 g (99%) of diethyl pyrrolidine-3-carboxylate-1-β-propionate (**8**). The undistilled product gave a single glpc peak (11.5 min, 237°, 110 ml/min) and was used directly in the next step. An earlier sample, prepared at Regis, had bp 93–97° (0.08 mm), n^{30}D 1.4529.

Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.7; N, 5.8. Found: C, 59.0; H, 8.8; N, 5.7.

The diester **8** was converted into **9** by the Dieckmann procedure,[24] except potassium isopropoxide in toluene (potassium *t*-butoxide, at Regis) was used for the condensation. The product (**9**), which was difficultly distilled owing to its tendency to solidify in the condenser, gave a single glpc peak (3.6 min, 245°, 120 ml/min) and was obtained as a waxy solid: 9.5 g (61%); mp 84–86°; bp 116° (*ca.* 27 mm); ir ($CHCl_3$, Infracord) 1700 (CO), with a shoulder at 1690 cm^{-1}; picrate mp 233–235°.

Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.1; H, 4.0; N, 15.8. Found: C, 43.9; H, 4.0; N, 15.5.

1-Azabicyclo[3.2.1]octan-4-one Reductions.—Catalytic hydrogenations of the ketone **9** gave the following percentages of epimer A (**10**) in an A/B mixture: ruthenium on carbon in acid, 66%; rhodium on carbon in acid, 76%; platinum dioxide in ethanol, 89%. Palladium on carbon in acid and ruthenium on carbon in ethanol gave little or no reduction, while platinum dioxide in acid gave only the hydrogenolysis product (**4**).[4] Lithium aluminum hydride and sodium in ethanol–benzene reductions gave 74 and 82%, respectively, of epimer A in an A–B mixture.

Epimeric 1-Azabicyclo[3.2.1]octan-4-ols (10 and 11).—A mixture (5.0 g) of the epimeric alcohols, obtained from hydrogenation of **9** over ruthenium on carbon, was dissolved in a little chloroform, then chromatographed on 500 g of neutral alumina (Woelm) which had been packed in chloroform. The progress of the separation was monitored by glpc, and the eluent, containing the indicated product, was collected in the following order: 4 l., chloroform (epimer A); 5 l., chloroform–methanol (9:1) (A and B mixture); and 4 l., methanol (epimer B). In addition, some of the hydrochloride of epimer B was obtained as a chloroform-insoluble brown gum on evaporation of the methanol fraction. Therefore, the column was washed with 2 l. of 5% sodium hydroxide solution, from which an additional quantity of epimer B was eventually recovered. The eluent fractions were evaporated and the respective residues recrystallized from hexane to give epimer A (**10**), 1.4 g of white needles, mp 180–182°, and epimer B (**11**), 0.2 g of white crystals, mp 184–185°. A mixture melting point was undepressed. Picrates (from isopropyl alcohol) melted at 244.5–246° (A) and 220–221° (B), respectively. A mixture of these two picrates melted at 230–235°.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.8; H, 4.5. Found for epimer A: C, 43.5; H, 4.3. Found for epimer B: C, 43.9; H, 4.6.

1-Azabicyclo[3.2.1]octan-6-one (12) Reductions. *endo*-1-Azabicyclo[3.2.1]octan-6-ol (13).—The ketone **12** was prepared[25] as described.[2] Hydrogenation over palladium on carbon in aqueous acid or ethanol or ruthenium on carbon in aqueous acid gave little or no reduction, while use of platinum dioxide produced considerable hydrogenolysis product (**4**), isolated by preparative glpc and identified by ir analysis.[4] Reduction with lithium aluminum hydride, or hydrogenations over platinum dioxide in ethanol, or rhodium on carbon in ethanol or 0.2 *N* hydrochloric acid gave the *endo* alcohol **13**, mp 177–179° (cyclohexane) (lit.[2] mp 177–179°), apparently epimerically pure, as judged from the identity of these ir spectra. The picrate melted at 224–225.5° (lit.[2] mp 224–226°). A tosylate, mp 107–109° (hexane), was prepared by the Schotten–Baumann procedure at 10°.[26]

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.8; H, 6.8; S, 11.4. Found: C, 59.6; H, 6.8; S, 11.4.

***exo*-1-Azabicyclo[3.2.1]octan-6-ol (14).**—An aqueous slurry of sponge nickel catalyst (Davison Chemical Co.) was washed by decantation with distilled water until neutral, then three times each with ethanol and benzene. The residual alcohol was distilled as an azeotrope from the benzene suspension of the catalyst, and 1 g of the resultant slurry was added to 0.5 g of the *endo* epimer (**13**) in 40 ml of benzene, then refluxed (drying tube) for 24 hr, filtered, and concentrated. Glpc analysis revealed the product to consist of a 60:40 mixture of the ketone **12** and what proved to be the *exo* alcohol (**14**). The epimeric alcohols have identical retention times on Carbowax, but partially separated on QF-1. A third of this solution was chromatographed on 12 g of basic alumina (Woelm, grade IV) using successively hexane, ether, and methanol for elution. The ketone was obtained from the ether fraction. The methanol fraction was concentrated, and the residue was crystallized from cyclohexane to give 26 mg of the *exo* alcohol (**14**), mp 157–159°, mass spectrum mol wt 127.137 amu (theory 127.140 amu). Its ir spectrum differed from that of the *endo* epimer, most notably by the absence of a strong band at 1100 cm^{-1} and the appearance of a new band at 1040 cm^{-1} (probably C–O). A picrate was obtained as small orange prisms, mp 240–241.5° (from ethyl acetate–cyclohexane), mmp 213–223° (with **13** picrate).

Reduction of 1-Azabicyclo[3.2.1]octan-6-one (12) with Sodium in Ethanol. Attempted Epimerization of 13.—The ketone **12** (5. g, 0.04 mol) in 80 ml of ethanol was added dropwise over 1 hr with stirring to 10 g of freshly cut sodium in 80 ml of sodium-dried benzene, then refluxed for 1 hr with stirring. The remaining sodium was then destroyed by the addition of 40 ml of ethanol. Additional ketone (0.5 g) was added, and the solution was refluxed for 16 hr. Water (100 ml) was added, and the aqueous phase was extracted with five 100-ml portions of chloroform. The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give 4.9 g of a viscous brown oil, which was found (glpc) to contain four major components, designated B (smallest), C (largest), D, and E, in order of increasing retention time. (A small amount of a product, observed as component A in an earlier small scale run, was not observed in this experiment.) When the product mixture was triturated with hot benzene–cyclohexane, the major portion dissolved and left a solid residue (1.0 g), which appeared to be mainly the hydrochloride of **13**. The solution was concentrated under reduced pressure to 3.0 g of a brown oil, which was chromatographed on 250 g of basic alumina (Woelm, IV), prepared in benzene, and eluted with ether (1300 ml) and methanol (800 ml), respectively. The eluent was collected in 100-ml fractions, concentrated, and analyzed by glpc. The order of elution from the column was A, (position determined from the previous run), D, B, E, and C. Although most of the fractions consisted of mixtures, each component was obtained essentially pure by evaporation of selected fractions. Component C was found (glpc, ir, melting point, and picrate) to be identical with the *endo* alcohol **13**, obtained by hydrogenations of **12** above. Component D was recrystallized from cyclohexane to give 7-ethylidene-1-azabicyclo[3.2.1]octan-6-ol (assigned *endo*), **15**: mp 91.5–93°; mass spectrum mol wt 153 (theory 153); ir (CCl_4) 3627 (O—H), 3012 (weak, vinylic C—H), 1688 (HC=C, *exo* to a five-membered ring), 1450 (CH_2 and CH_3), and 1380 cm^{-1} (CH_3); nmr (20% $CDCl_3$) τ 8.28 and 8.31 (two d of near equal intensity, 3, J = 7 cps for each, C=CH—CH_3),

(23) V. Prelog, S. Heimbach, and E. Cerkonikov, *J. Chem. Soc.*, 677 (1939).

(24) N. J. Leonard, S. Swann, and J. Figueras, *J. Amer. Chem. Soc.*, **74**, 4620 (1952).

(25) Synthesized by Dr. A. Y. Garner and coworkers, Monsanto Research Corp., Dayton, Ohio, from intermediates supplied by Mr. F. F. Frulla and coworkers, Olin–Mathieson Chemical Corp., New Haven, Conn., under U. S. Army Research and Development Contracts.

(26) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 784.

cis/trans), 8.1 (m, 5, CH_2 and CH not adjacent to N), 7.0 (m, 4, CH_2 adjacent to N), 5.68 (s, 1, OH), 5.28 (m, 1, CH—OH), and 4.73 (q, 1, J = 7 cps, C=CH—CH_3). A picrate was obtained as bright yellow needles, mp 172.5–175° (from ethyl acetate–benzene).

Anal. Calcd for $C_{15}H_{18}N_4O_8$: C, 47.1; H, 4.8; O, 33.5. Found: C, 47.0; H, 4.9; O, 33.4.

Component E was recrystallized from hexane to give 0.09 g of needles, assigned as 7-(*exo*)ethyl-1-azabicyclo[3.2.1]octan-6-(*endo*)ol (**16**): mp 95–96°; ir (CCl_4) 3628 (O—H), 1465 (CH_3 and CH_2), and 1385 cm^{-1} (CH_3). A picrate was obtained as iridescent yellow needles, mp 192–194° (from ethyl acetate–benzene).

Anal. Calcd for $C_{15}H_{20}N_4O_8$: C, 46.9; H, 5.3; O, 33.3. Found: C, 47.0; H, 5.2; O, 33.6.

Component B was purified by sublimation (60–75°, 0.015 mm) to give 5 mg of a waxy solid, mp 100–132°, which showed OH, CH_2, and CH_3 bands in the ir spectrum. However, insufficient material was available for further purification and characterization.

Hydrogenation of 7-Ethylidene-1-azabicyclo[3.2.1]octan-6-ol (15).—Component D (**15**), 0.10 g in 5 ml of ethanol, was hydrogenated over 0.05 g of platinum dioxide at 40 psig for 0.5 hr, filtered, and concentrated to give 0.09 g of an oil which solidified on standing overnight. The oily crystals were triturated under hexane to give a product assigned as 7-*endo*-ethyl-1-azabicyclo-[3.2.1]octan-6-*endo*-ol (**18**): mp 85–90°; ir (CCl_4) 3630 cm^{-1} (OH), no olefinic stretching absorption. The compound gave a single glpc peak of identical retention time with **16**. However, their ir spectra differed in the fingerprint region. Its picrate melted at 213.5–215°.

Anal. Calcd for $C_{15}H_{20}N_4O_8$: C, 46.9; H, 5.3; O, 33.3. Found: C, 46.6; H, 5.2; O, 33.1.

7-Ethylidene-1-azabicyclo[3.2.1]octan-6-one (17).—Compound **12** (0.5 g, 0.004 mol) with 0.35 g (0.008 mol) of acetaldehyde was kept in a pressure bottle in a 53° oven for 7 days and at room temperature for 21 days, then concentrated under reduced pressure. Glpc analysis (227°, 43 ml/min) revealed a small amount of **12**, three minor unidentified components (possibly acetaldehyde selfcondensation products), and a major component of longer retention time, **17**, whose ir (neat, sample collected by glpc) spectrum showed strong bands at 1732 (C=O) and 1660 cm^{-1} (conjugated C=C). Attempts to crystallize the product were not successful, even after chromatography over basic alumina with ether. A picrate was obtained as yellow plates, mp 160–161° (from ethyl acetate–benzene).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.4; H, 4.2; O, 33.7. Found: C, 47.7; H, 4.2; O, 33.4.

7-Ethylidene-1-azabicyclo[3.2.1]octan-6-ol (15).—Crude **17**, 0.40 g (0.0025 mol), was added to 0.10 g (0.0026 mol) of sodium borohydride in 5 ml of water plus 1 drop of 20% sodium hydroxide solution, then placed on the steam bath for 0.5 hr. Concentrated ammonium hydroxide solution (1 ml) was added, and the product was extracted with chloroform, which was dried ($MgSO_4$) and concentrated. Glpc analysis revealed a single volatile component, mp 85–91° (as collected from the column), whose ir spectrum was identical with that of **15**, obtained above as component D.

3-Pyridinecarboxaldehyde Cyanohydrin (19).—3-Pyridinecarboxaldehyde (Aldrich Chemical Co.), 22 g (0.21 mol), was treated with hydrochloric acid and aqueous potassium cyanide as described for the 5-methyl analog.[27] The product was filtered and used as the moist precipitate in the next step. In another run, a 92% yield of **19**, mp 38–52°, was obtained as unstable white crystals, which yellowed on standing and had the odor of hydrogen cyanide.

Ethyl 3-Pyridylglycolate (20).—The crude **19** was refluxed with 100 ml of concentrated hydrochloric acid for 18 hr, then concentrated, and finally dried on the steam bath under reduced pressure for 1 hr. The salt mixture thus obtained (37 g) was refluxed (drying tube) with 125 ml of ethanol and 2.5 ml of sulfuric acid for 18 hr, concentrated, cooled, and made basic with saturated sodium carbonate solution. The product was extracted with chloroform, dried ($MgSO_4$), concentrated, and distilled to give 19 g (50% over-all) of **20**: bp 86° (0.05 mm); $n^{25}D$ 1.5156. Its picrate was obtained as yellow needles, mp 103–104° (methanol).

Anal. Calcd for $C_{15}H_{14}N_4O_{10}$: C, 43.9; H, 3.4; O, 39.0. Found: C, 43.8; H, 3.2; O, 38.5.

Registry No.—3-Hydroxymethyl-1-pyrrolidineacetonitrile, 17604-26-1; **2**, 17604-27-2; **3**, 17604-28-3; **3** picrate, 17604-29-4; **4**, 279-92-5; **5**, 17628-91-0; **5** picrate, 17629-14-0; **6**, 17628-92-1; **6** picrate, 17629-15-1; **8**, 17604-85-2; **9**, 17604-77-2; **9** picrate, 17604-78-3; **10**, 17629-13-9; **10** picrate, 17628-84-1; **11**, 17628-85-2; **11** picrate, 17628-93-2; **13**, 17628-86-3; **14**, 17628-87-4; **14** picrate, 17628-88-5; **15**, 17628-89-6; **15** picrate, 17628-90-9; **16**, 17603-93-9; **17**, 17604-71-6; **17** picrate, 17604-72-7; **18**, 17604-73-8; **19**, 17604-74-9; **20**, 17604-75-0; **16** picrate, 17603-94-0; **18** picrate, 17603-95-1; **20** picrate, 17604-76-1.

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Heterocyclic Studies. 29. Photoisomerization of 2,3-Dihydro-1,2-diazepine Ketones and Carbinols to 1,2-Diazabicyclo[3.2.0]-6-heptenes[1]

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Irradiation of the 2,3-dihydrodiazepinones (**1**) and the carbinols (**3**) gives in high yields the 1,2-diazabicyclo-[3.2.0]-6-hepten-4-ones (**2**) and -4-ols (**4** and **5**), respectively. The major photoalcohols in each case were shown by nmr analysis to be the *exo* isomers. The *endo* alcohols were the minor photoproducts of **3** and were obtained exclusively on reduction of the ketones (**2**) with $NaBH_4$. The alcohols and tosylates are thermally stable, and elimination reactions have not been observed. Hydrogenation of derivatives of the *endo* alcohols gives mainly the *endo*-phenyldiazabicyclo[3.2.0]heptanols; in the *exo* alcohol series, equal amounts of *exo*- and *endo*-phenyl compounds are obtained. The rates of the photocyclization of the diazepinones (**1**) at 313 or 390 mμ decrease in the order R = $CH_3 \cong CH_2CH_2CN > H \gg COC_6H_5 \cong COCH_3$. Under the same conditions at 313 mμ, the reverse order of substituent effects is obtained with the diazepinols **3**: R = $COCH_3 \cong COC_6H_5 > CH_3 \cong H$.

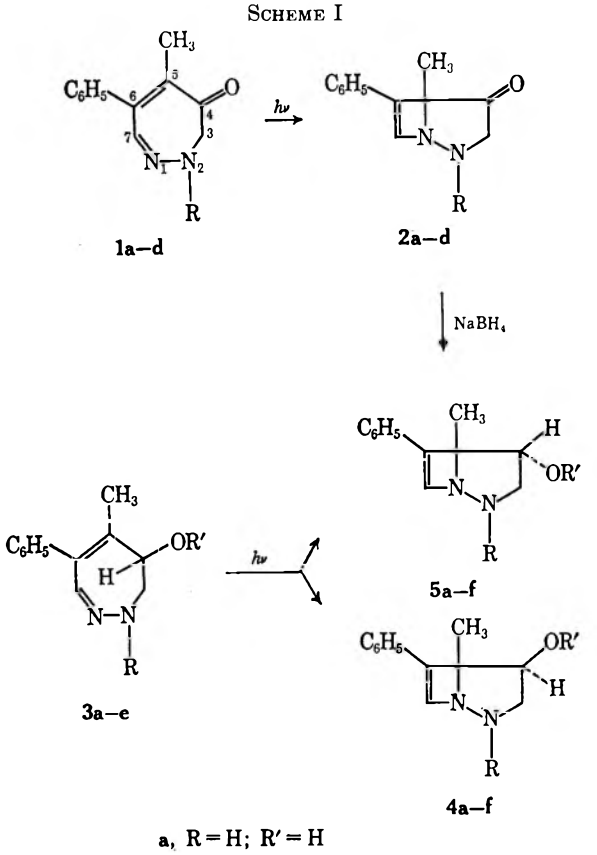
The photocyclization of seven-membered cyclic dienes and dienones to bicyclo[3.2.0]heptene derivatives is a generally useful reaction and has been applied to a variety of carbocyclic[3] and heterocyclic[4] systems. As noted previously,[5] the diazepine ketones **1** and carbinols **3** readily undergo this photocyclization to give the bicyclic ketones **2** and alcohols **4** and **5** (Scheme I). We now report the results of a study of several aspects of this cyclization and the novel bicyclic products.

For preparative purposes, exposure of the ketones **1**, which absorb strongly in the 400-mμ region, to sunlight in Pyrex vessels is the most satisfactory procedure for photocyclization. Cyclization of the colorless carbinols **3** requires higher frequency radiation and these reactions were carried out with a 200-W medium-pressure arc in a quartz envelope, usually with a Corex filter.

Under optimum conditions, essentially complete conversion into the photoisomers was achieved with small amounts of impurities. In kinetic experiments described in a later section, good isosbestic points were observed when the photocyclization was followed spectrophotometrically. From the acetyl ketone **1c**, the crystalline bicyclic ketone **2c** was isolated in yields of 80–90% in gram-scale runs. Ketones **2a** and **b** were obtained as unstable oils; a crystalline hydrochloride was obtained from **2a**.

The structure of the photoketones **2** was apparent from spectral data and several interconversions. All of the compounds showed singlet methyl peaks at δ 1.63–1.72, AB methylene patterns with $|J_{gem}| = 18$ Hz, and a singlet one-proton peak at 6.73–6.78. The ketone carbonyl band in **2c** appeared at 1767 cm^{-1} (CCl_4). The acetyl ketone **2c** was obtained both by cyclization of **1c** and by acetylation of **2a**. The semicarbazone of **1a** also underwent cyclization, and subsequent acetylation gave the N-acetyl bicyclic semicarbazone, also obtained from **2c**. Finally, isomerization of the photoketones **2a** and **b** on warming regenerated the respective diazepinones.

SCHEME I



a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = $COCH_3$; R′ = H
d, R = COC_6H_5; R′ = H
e, R = $COCH_3$; R′ = $COCH_3$
f, R = $COCH_3$; R′ = $SO_2C_7H_7$

With the bicyclic alcohols **4a–e**, the possibility of stereoisomers arises, and two isomeric alcohols were in fact obtained in unequal amounts by photocyclization of the diazepinols. These mixtures could be separated by crystallization or chromatography, and, as discussed below, the major cyclization product in each case was shown to be the *exo* alcohol and the minor product the *endo* isomer. Reduction of the bicyclic ketones **2a–d** with sodium borohydride gave cleanly single products which were identical with the minor photocyclization products, providing a convenient source of the *endo* alcohols.

The bicyclic alcohols **4a** and **5a** were stable, high-

(1) Supported by Grant GP-5219 from the National Science Foundation.

(2) On leave, 1967–1968, from the Laboratoire de Chimie Organique II, Faculté des Sciences, Université de Caen, France.

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(5) A preliminary note of some of this work has appeared: *Chem. Commun.*, 468 (1965).

TABLE I

NMR DATA FOR BICYCLIC ALCOHOLS AND KETONES

Compd	R	R′	δ, ppm ($CDCl_3$) 3ex	3en	4en	J, Hz 3ex-3en[a]	3ex-4en	3en-4en	CH_3	H-7
exo Alcohols (Major Photoisomers)										
4a	H	H	3.23	3.86	4.48	−13.5	0	3.0		
4b	CH_3	H	3.17	3.80	4.52	−12.5	0	4.1	1.78	6.50
4c	Ac	H	4.58	3.82	4.58	−13.5	0	3.6	1.72	6.40
4d	Bz	H	4.71	4.00	4.58	−13.5	0	4.0	1.64	6.45
4e	Ac	Ac	4.69	3.85	5.66	−14	0	4.5	1.59	6.45
4f	Ac	Tos	4.54	3.73	5.25	−15	0	4.5	1.70	6.40
endo-Alcohols (Hydride Series)										
5a[b]	H	H								
5b	CH_3	H	3.46	3.07	4.45	−11.5	8.7	10.3	1.79	6.70
5c	Ac	H	4.59	3.46	4.00	−11.3	6.3	8.5	1.69	6.57
5d	Bz	H	4.79	3.67	4.09	−10.7	6.5	9.0	1.62	6.64
5e	Ac	Ac	4.91	3.47	5.01	−11.7	7.4	8.75	1.77	6.66
5f	Ac	Tos	4.55	3.45	4.66	−11.7	7.1	8.7	1.66	6.56
Ketones										
2b	CH_3		3.13	4.33		−18			1.70	6.78
2a	H		3.53	4.35		−18			1.63	6.73
2c	Ac		4.71	4.39		−18.5			1.72	6.78

[a] Negative value assumed for all J_{gem}; opposite sign from J_{vic} shown by calculation in **5e** and **5f**. [b] Compound insoluble in $CDCl_3$. [c] Spin decoupling of the spectrum of the N-acetyl alcohol **5c** with an irradiating frequency of −74 Hz caused the upfield multiplet to collapse to a doublet, δ 3.46, J = 8.5 Hz.

melting solids. The nmr spectra of the alcohols and several derivatives (Table I) contained methyl, phenyl and vinyl singlets very similar in position to those in the ketone spectra and three-proton ABX or ABC multiplets for the $-CH_2CHOR$ protons. Acetylation of the alcohols **4a** and **5a** or the N-acetyl alcohols **4c** and **5c** gave diacetyl derivatives also obtained by cyclization of the N-acetyl-4-acetoxydiazepine, and tosylates were also prepared from **4c** and **5c** in the usual way. The interconversions of individual isomers in each series established configurational correlation of the major photocyclization products and hydride reduction products.

Preliminary study of the chemical properties of these compounds revealed no obvious differences in reactivity of the two isomeric series and no notable instability or susceptibility to rearrangement or elimination. The alcohols were unchanged on prolonged refluxing in ethanol; some decomposition of **4a** occurred in refluxing butanol but the diazepinol **3a** was not detected. Alkaline hydrolysis of the diacetyl derivative **4e** gave first the N-acetyl alcohol **4c** and then **4a**. The N-acetyl tosylates in both series were unaffected by treatment with aqueous acetone or acetic acid–sodium acetate at 50°; higher temperatures did lead to decomposition. An attempt to methylate **4a** by the Clarke–Eschweiler method (HCHO–HCO_2H, 90°) caused extensive decomposition, and correlation of configuration of the N-methyl alcohol **4b** with the other *exo* alcohols rests on nmr data.

The isomer distributions in the photocyclization of several of the diazepinols were determined by area measurement of the C-7 (vinyl) proton peaks and other well-separated peaks for the two isomers in the nmr spectra of the total photolysis product mixtures (Table II). The relatively minor differences in amounts of the

TABLE II

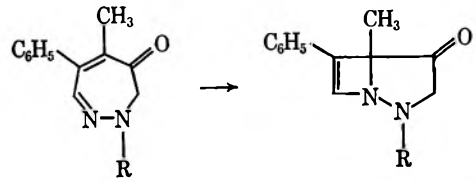
ISOMER DISTRIBUTION IN PHOTOCYCLIZATION OF DIAZEPINOLS

Compd	Diazepinol R	R′	Per cent isomer Major (*exo*)	Minor (*endo*)
3a	H	H	78	22
3b	CH_3	H	80	20
3c	$COCH_3$	H	65	35
3d	COC_6H_5	H	60	40
3e	$COCH_3$	$COCH_3$	65	35

Table III

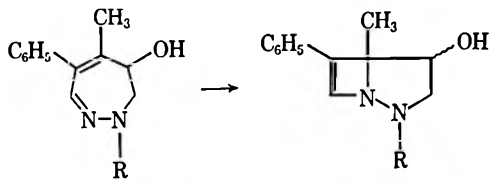
Cyclization of Diazepines at 313 mμ

Ketones



		Methanol solution						Hexane solution					
R	R′	Absorption maxima of diazepinone, λ, mμ (ε)	Concn × 10⁴, mol/l.	k_1 × 10³, min^{-1}	$t_{1/2}$, min	n × 10³, mol min^{-1} $l.^{-1}$	% diazepine at equilibrium	Absorption maxima of diazepinone, λ, mμ (ε)	Concn × 10⁴, mol/l.	k_1 × 10³, min^{-1}	$t_{1/2}$, min	n × 10³, mol min^{-1} $l.^{-1}$	% diazepine at equilibrium
CH_3		410 (4400) 315 (5000)	1.46	38	18	410	18	406 (3480) 321 (4220)	1.70	35	19	450	27
$(CH_2)_2CN$[a]		406 (3900) 315 (5150)	1.40	39	17	410	13	402 (3040) 316 (4640)	1.55	30	23	340	25
H		398 (2900) 312 (5020)	1.43	28	25	280	6	388 (2050) 310 (4530)	1.59	17	40	200	47
COC_6H_5		393 (2860) 298 (7160)	1.00	9.6	72	69	9	399 (2700) 330, 297 (5330, 6770)	1.20	6.9	100	60	37
$COCH_3$		393 (2240) 315 (5520)	1.30	8.7	80	81	5	399 (2100) 326, 314 (5000, 4940)	1.43	7.3	95	75	50
Semicarbazone, R = H		345 (6700) 305 (7300)	0.99	5.8	120	41							
Semicarbazone, R = $COCH_3$		360 (8300) 298 7100)	0.74	3.6	190								

Carbinols

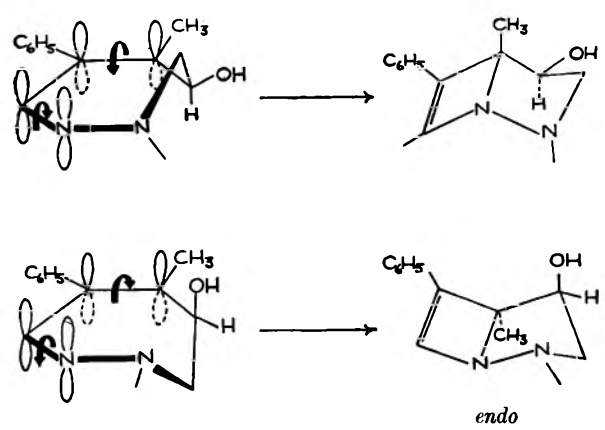


CH_3	H	320 (6150)	1.17	2.1	330	17		316 (5300)	1.36	2.6	270	25
H	H	306 (4650)	1.55	1.1	660	13		299 (4380)	1.64	0.8	840	10
COC_6H_5	H	313 (8240)	0.87	41	17	250		316 (8620)	0.83	41	17	240
$COCH_3$	H	308 (5820)	1.23	44	16	390		309 (4610)	1.56	32	22	350
$COCH_3$	$COCH_3$	312 (7160)	1.00	35	20	250		316 (7220)	1.00	33	21	240

[a] W. J. Theuer and J. A. Moore, *J. Org. Chem.*, **32**, 1602 (1967). The bicyclic product from this diazepinone was not characterized.

two isomers reflect very small energy differences in the transition states for the two modes of cyclization, which must arise by disrotatory movement of the C-5–C-6 and C-7–N-1 bonds from opposite faces of the ring, as shown in Scheme II. The cyclizations are arbitrarily represented in these drawings as proceeding from two

Scheme II



endo

different nonplanar conformations of the diazepinol. As discussed below (*cf.* Table III), cyclization of the NH and NCH_3 alcohols **3a** and **3b**, which give the highest *exo*/*endo* ratio (4:1), is slower by a factor of 20–40 than the photocyclization of the N-acyl alcohols **3c–e** which give more nearly equal amounts of the two isomers. Thus the degree of stereoselectivity in these cyclizations seems clearly to be inversely related to the rate or efficiency of the photocyclization process. The significance of this relationship, and the extent to which the ground-state geometry of **3** determines the product structure, cannot be assessed until more is known about the photochemical mechanism.

It should be mentioned that, in representing the (racemic) *exo* and *endo* alcohols formed in the photocyclization by the single projection structures **4** and **5**, and in naming these compounds, the same configuration of the ring junction at C-5 is implied for both epimers. This cannot be the case, however, since the configuration at C-4 does not change during the cyclization. As illustrated in Scheme II for the (4*S*) enantiomer, the *exo*-bicyclic alcohol has the (4*S*,5*R*) configuration, while the *endo* epimer is (4*S*,5*S*).

In assigning the configuration of the hydride reduction products and the major photoisomers, the direction of attack of hydride on the ketones **2a–d** was first considered. The same alcohol (**5c**) was also obtained exclusively on reduction of **2c** with diisocampheylborane, confirming that the highly selective isomer formation in these reductions stems from steric approach ("steric strain") control.[6,7] The question then depends upon the relative steric importance of the ethylenic bridge and the adjacent axial methyl group.

The parent bicyclo[3.2.0]heptanone is reduced by hydride reagents to the *endo* alcohol,[8] but information about the stereochemistry of substituted bicyclo-[3.2.0]-6-heptenols is rather sketchy. Photocyclization of 2,4-cycloheptadienol[9] and the 2,6,6-trimethyl derivative (eucarvol)[10] have been reported to proceed in good yield, but the stereochemistry of the bicyclic alcohols was not specified. Several dimethylbicyclo-[3.2.0]-6-hepten-2-ones have been reduced with lithium aluminum hydride to give sterically homogeneous alcohols, but again the configuration has not been definitely established.[11] Reduction of bicyclo[3.2.0]-3,6-heptadien-2-one with $LiAlH_4$ gives nearly equal amounts of the *exo*- and *endo*-dienols. With a more bulky reagent, conjugated addition of hydride predominates, but *endo*-bicyclo[3.2.0]-6-hepten-2-ol was isolated as a minor product.[12] In view of these limited data, assignment of stereochemistry from the course of reduction of the ketones **2**, containing two substituents and two heteroatoms, seemed unjustified.

Stereochemistry of Alcohols.—A firm basis for the hydroxyl configurations was provided by analysis of the C-3 and C-4 protons in the nmr spectra of **4a–f** and **5a–f** (Table I). In the spectra of the major photoisomers (**4**), one of the coupling constants was zero in each case, and all values of δ and J could be measured directly from the spectra. In the hydride isomers **5** the signals for these protons contained three spin–spin interactions; exact values of δ_{3ex}, δ_{3en}, and J_{gem} for the hydride isomers were obtained from the AX spectra of the 4-deuterio compounds prepared from **2a–d** with $NaBD_4$. In the spectra of the N-acetyl esters **5e** and **5f**, one proton was sufficiently deshielded to permit analysis by the standard calculation for ABX spectra,[13] but the A and B lines overlapped heavily because of the very small value of $(\delta_A - \delta_B)$ and required reference to 100-MHz spectra.[14]

Identification of peaks due to the 3-*exo*,3-*endo* and 4 protons in the N-acetyl photoisomers (**4c–f**) follows the assignments $|J|_{gem}$ = 12–14 Hz and J_{cis} = 3.6–4.5 > J_{trans} = 0 Hz. On the basis that **4** represents the *exo* series, H_{3en} is then upfield from H_{3ex} in **4c–f**, as usually found with *exo* and *endo* protons at C-5 and C-6 in norbornenes.[15–19] However, the reverse chemical-shift relationship of H_{3en} and H_{3ex} is seen in the NH and $N-CH_3$ derivatives **4a** and **b**. The chemical shifts of these protons are influenced by three factors: (a) the diamagnetic anisotropy of the double bond (as noted above, H_{3en} should experience positive shielding because of its position above the plane of the double bond),[19] (b) proximity to OH or OR at C-4, and (c) the effect of N-acyl or N-methyl at N-2.

In these folded molecules, the N-2 substituent must assume an *exo* configuration to avoid nonbonding interactions with the C-6–C-7 bridge,[20] and any difference due to proximity of the carbonyl group in the N-acyl derivatives *vs.* $N-CH_3$ would therefore be reflected more strongly in H_{3ex} than in H_{3en}. This conclusion is borne out by the relatively small differences in δ_{3en} in N-acyl and N-methyl derivatives in both series. In each pair of epimeric alcohols, the H_{3en} signal in the *endo* isomer, *i.e.*, the proton *cis* to the hydroxyl group, is at 0.33–0.6-ppm higher field than H_{3en} in the *exo* isomer. In the epimeric 2-norbornenols, the corresponding difference in H_{3en} in the *endo* and *exo* alcohols is 0.45 ppm, with the signal in the *endo* isomer again at higher field.[17]

The signals of the 3-*exo* protons in the diazabicyclo[3.2.0] alcohols, however, are strongly dependent on the substituent at N-2, and the $N-CH_3$ group in both hydride and photoisomers is seen to cause a large diamagnetic shielding of H_{3ex} in **4b** and **5b** which outweighs the influence of the 6,7 double bond and causes H_{3ex} to resonate at higher field than H_{3en} in the NH and $N-CH_3$ *exo* alcohols. In the N-acetyl and N-benzoyl compounds, the deshielding of H_{3ex} by the adjacent carbonyl and the shielding of H_{3en} by the double bond are mutually reinforcing, leading to a difference $\delta_{3ex} - \delta_{3en}$ of 1.1 ppm in the *endo* alcohols and 0.7 ppm in the *exo* epimers. These differences between *exo* and *endo* C-3 protons in the two series may be compared to differences of 1.1 and 0.5 ppm in the *exo* and *endo* C-3 protons in *endo*- and *exo*-2-norbornenol, respectively.[17]

A similar effect of the N-2 substituent is observed also in one of the H-3 chemical shifts of the ketones **2a–c**, whereas the other signal remains practically unchanged throughout the three compounds. The *exo* and *endo* assignments of these protons is of necessity based entirely on this parallel behavior to the alcohols, in the absence of additional data from coupling constants.

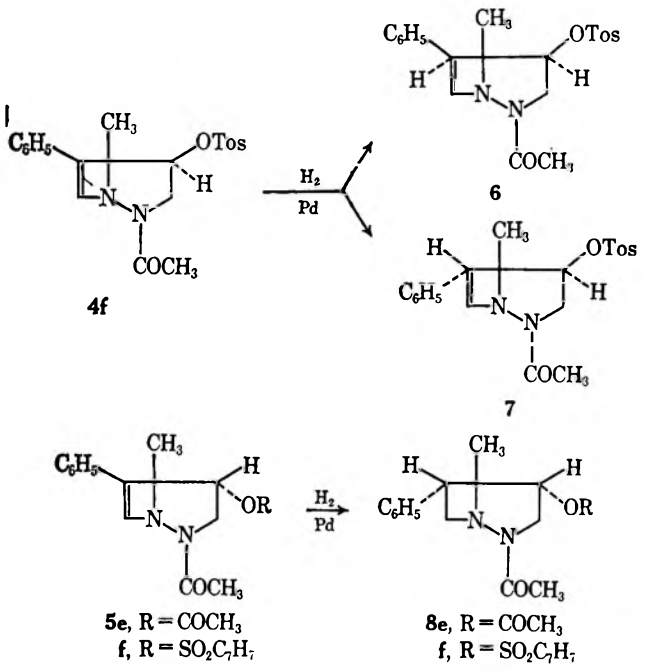
Final confirmation of the alcohol configurations was achieved in the hydrogenation of the epimeric N-acetyl tosylates and acetates. Catalytic reduction of the *exo*-tosylate **4f** gave a mixture of two dihydro compounds **16** and **7**. The nmr spectrum of the total product showed no vinyl protons. The signals due to the six secondary and tertiary protons were hopelessly mixed in four overlapping ABC patterns, but there were two clear methyl singlets at δ 0.91 and 1.55 ppm with an area ratio of 55:45. These isomers were not separated, but analysis corresponded to **6** or **7**. The higher field signal is assigned to the methyl group of the *exo*-phenyl

(6) H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965).
(7) H. C. Brown and V. Varma, *ibid.*, **88**, 2871 (1966).
(8) S. Winstein, F. Gadient, E. T. Stafford, and P. E. Klinedinst, *ibid.*, **80**, 5895 (1958).
(9) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *ibid.*, **84**, 1220 (1962).
(10) O. L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).
(11) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965); R. L. Cargill and D. M. Pond, *ibid.*, **31**, 2414 (1966).
(12) P. R. Story and S. R. Fahrenholz, *J. Amer. Chem. Soc.*, **87**, 1624 (1965).
(13) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 132.
(14) We are indebted to Dr. G. Reddy, Central Research Department, E. I. du Pont de Nemours and Co., Inc., for the 100-MHz spectra and for helpful discussions.
(15) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963).
(16) P. Laszlo and P. R. Schleyer, *ibid.*, **86**, 1171 (1964).
(17) J. C. Davis, Jr., and T. V. Van Auken, *ibid.*, **87**, 3900 (1965).
(18) F. A. L. Anet, H. H. Lee, and J. L. Sudmeier, *ibid.*, **89**, 4431 (1967).
(19) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).
(20) There was no indication of splitting in the $N-COCH_3$ methyl peaks arising from population of two "invertomers."

isomer **6**, in which methyl and phenyl groups are eclipsed and the methyl group is strongly shielded by the aromatic ring. This result shows that in hydrogenation of the *exo*-tosylate there is negligible discrimination of the two sides of the 6 7 double bond.

Hydrogenation of either the *endo*-tosylate or *endo*-acetate, on the other hand, led to greater than 90% one isomer, in which the C-5 methyl peak appeared at 1.50 and 1.18, respectively. These products must be the *endo*-phenyl compounds **8e** and **8f** (Scheme III).

Scheme III



The spectrum of the dihydro acetate **8e** contained acetyl peaks at 1.61 and 2.16 ppm which are assigned to the *endo*-$OCOCH_3$ and $-N-COCH_3$, respectively, the acetoxy methyl group evidently experiencing considerable shielding from the juxtaposed *endo*-phenyl ring. In the hydrogenation of the *endo* alcohol derivatives, therefore, approach to the catalyst surface occurs exclusively on the *outer* face of the four-membered ring because of crowding on the inside of the bicyclic system.

Rates of Photocyclization.—In the initial experiments on solar photocyclization of the diazepine ketones, it was noted that the reaction was appreciably faster with the 2-methyl derivative **1b** than with the 2-acetyldiazepinone **1c**. These diazepinones and diazepinols comprise a fairly extensive series of compounds in which the reacting cyclic diene chromophore is modified by a variety of substituents. This situation is one that cannot readily be achieved with carbocyclic compounds, and prompted us to study the effect of substituents on the photoreaction in somewhat more detail.

The electronic spectra of the ketones and carbinols are quite similar in the ultraviolet, with maxima at 230–240 and 300–315 mμ. The ketone spectra also contain a third maximum at 390–410 mμ, and it is presumably this latter band which enables photocyclization of the ketones to proceed rapidly in Pyrex vessels in ordinary daylight. In order to compare directly the effect of substituents in the carbinols and ketones, the relative rates of photocyclization were measured in a simple apparatus in which solutions of the diazepines of the same initial transmittance at the 300–315-mμ absorption maximum were irradiated under standardized conditions. The source was a 100-W medium-pressure mercury arc with glass and solution filters which provided irradiation primarily by the 3126–3132-Å band, and prevented absorption of the ketones at the longer wavelength maximum.[21]

Data on the disappearance of the diazepines with time were plotted as first-order reactions (Table III). Since the transmittance of the solutions increased during the reaction, these plots became nonlinear after about one half-life; rate constants were measured from the initial slopes. For convenience in measurement, the irradiations were carried out with a fixed initial optical density of 0.72–0.74 at the wavelength of the main absorption maximum in the 300–315-mμ region. Because of variations in the extinction coefficient of these maxima, the initial diazepine concentrations differed from compound to compound; in order to compare the number of moles of diazepine reacting in a given time, the quantity n mol/l. min was derived by dividing one-half of the initial concentration by $t_{1/2}$.

Cyclization of the diazepinols **3a–e** was complete under these irradiation conditions, but an equilibrium was reached with 8–18% of the diazepine in the case of the ketones **1** in methanol; in hexane solution cyclization was even less complete, and proceeded only to the extent of 50% with the N-acetyl ketone **1c**. The same equilibrium compositions were reached when solutions of the bicyclic ketones, obtained by unfiltered irradiation, were exposed to the 313-mμ source. The rate of the reverse reaction was measured directly for the crystalline bicyclic ketones **2c** and **2d** in hexane and the values of k_{-1}, 72×10^{-4} min^{-1} for **1c** and 42×10^{-4} min^{-1} for **1d**, agreed very well with those calculated, 73×10^{-4} and 41×10^{-4}, respectively, from the rate k_1 of the forward reaction and the measured equilibrium concentrations.

$$\text{diazepine} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{bicyclic ketone}; \quad k_{-1} = K_{eq}/k_1$$

The concentrations of diazepinones given in Table III thus represent a true photoequilibrium due to excitation of the bicyclic ketones. It is not surprising that a significant reverse reaction occurs, since these ketones possess strong end absorption at 315 mμ (*e.g.*, **2a**, ϵ_{315} 2400; **2c**, ϵ_{315} 900). With the N-methyl bicyclic ketone **2b**, but not the other compounds, the reverse reaction occurs at a measurable rate in the dark at 25°; the rate of the dark reaction in methanol ($k_1 = 21 \times 10^{-3}$ sec^{-1}) was about one-fourth that of the photoreaction. In hexane, the dark reaction of **2b** was 30-fold slower, indicating a polar transition state. The lability of the bicyclic system in **2b**, which appears to stem from the presence of an electron-releasing N-2 alkyl group, invites comparison with the rapid cleavage of 5-methoxybicyclo[3.2.0]-6-hepten-2-one in alcohol solution, attributed to the bridgehead methoxy group.[9]

Although the rate of the reverse photoisomerization of the bicyclic ketones is considerably enhanced in hexane, as seen in Table III, the solvent polarity has a

(21) K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *J. Amer. Chem. Soc.*, **84**, 1016 (1962).

negligible effect on the rate of the diazepine cyclizations. A significant decrease in the photocyclization rate of the ketone was observed, however, in 10^{-2} *M* methanolic HCl. The rates of the –NH and NCH_3 diazepinones **1a** and **1b** were reduced to 12 and 23%, respectively, of the values in methanol; a somewhat smaller decrease to 40 and 25% of the methanol rate was observed with the acyl ketones **1c** and **1d**. The larger effect of acid on **1a** and **b** is in line with the higher basicity of the latter.

A similar comparison of the rates of cyclization of the three ketones **1a**, **b**, and **c** was also made by irradiation at the long wavelength maximum (393–408 mμ) using the same source with a narrow band-pass filter (T_{max} 390 mμ); the light intensity was about one-tenth that available in the 313-mμ runs. Rates and values of *n* mol/l. min are given in Table IV. In this series, the maxima and extinction coefficients differ considerably, and there is a correspondingly large difference in the ratios of k_1 and *n*.

TABLE IV

CYCLIZATION OF DIAZEPINONES AT 390 mμ

Ketone	λ_{max}, mμ (ε)	Concn × k_1 × 10^3, 10^4, mol/l.	10^3, min^{-1}	$t_{1/2}$, min	$n \times 10^8$, mol min^{-1} l. $^{-1}$
1b (R = CH_3)[a]	410 (4400)	1.60	3.6	190	42
1b (R = CH_3)[b]	406 (3480)	2.10	3.1	220	47
1a (R = H)[a]	398 (2860)	2.46	2.0	340	36
1c (R = Ac)[a]	393 (2240)	3.08	0.35	1980	7.8

[a] Methanol solution. [b] Hexane solution.

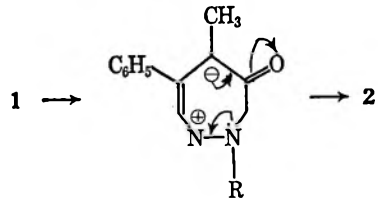
As shown in Table V, the ratios of *n* mol/l. min for three diazepinones in methanol at the two wavelengths correspond tolerably well, considering the limitations of the photolysis procedure. This correspondence and the fact that the rates of disappearance of the diazepinones at 390 and 313 mμ were proportional to the source intensity lead us to feel that the variation in values of *n* mol/l. sec for the differently substituted diazepines reflects, at least approximately, the relative quantum efficiencies.

TABLE V

COMPARISON OF DIAZEPINONE CYCLIZATIONS AT 313 and 390 mμ

Ratio of *n*	313 mμ	390 mμ
1b/1a	1.42	1.17
1b/1c	5.0	5.4
1a/1c	3.5	4.6

Perhaps the most striking result in these comparisons of photochemical reactivity is the opposite effect of substitution at N-2 in the ketones and carbinols. It is evident from the rate-retarding effect of acyl substitution and of acid that electron release by N-2 in the ketone series enhances the photochemical efficiency. The facilitation of photocyclizations of this type by methoxyl groups situated at the terminus of the reacting diene system is familiar in the photochemistry of cycloheptadienones,[9] cycloheptatrienones (tropolone α- and γ-methyl ethers),[3a] and cycloheptatrienes.[22] The role of an electron-donating group at N-2 in these cyclizations can be viewed in terms of a polar excited state as shown in **9**.



9

The opposite effect of acyl substitution at N-2 in the diazepine carbinols **3** was unexpected, and cannot be explained with the data now available. If excitation of the alcohols at 313 mμ involves an n → π* transition of the C=N group, cyclization *via* an excited state having a *reverse* polarity from that depicted in **11** could conceivably benefit by electron withdrawal at N-2. It is entirely possible, however, and perhaps more likely that the differences in photochemical efficiency in the acyldiazepinols arises from the operation of different excitation processes in the acyl derivatives and the nonacylated compounds **3a** and **b**.

Experimental Section[23,24]

2-Acetyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-one (2c).—A solution of 0.60 g of the 2-acetyldiazepinone **1c**[25] in 600 ml of methanol was placed in a 2-l. shallow wide-bottomed Brewster fermentation flask (Pyrex), and the flask was placed in direct October sunlight for 3 hr. The nearly colorless solution was evaporated and the solid residue was crystallized from ether–hexane to give 0.53 g (88%) of colorless prisms of **2c**: mp 122–123°; ν^{KBr} 1767, 1678 cm^{-1}; nmr, see Table I.

Anal. Calcd for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.22; H, 5.89; N, 11.29.

A solution of 73 mg of the unsubstituted diazepinone **1a** in 10 ml of methanol was exposed to sunlight in a Pyrex erlenmeyer flask for 2 hr and then evaporated to give **5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-one (2a)** as a yellow oil. This oil was treated with acetic anhydride and pyridine and the resulting product (**2c**) was crystallized to give pale yellow crystals, mp 119–120°, identical (ir) with material obtained by irradiation of **1c** (above).

The **semicarbazone** of the acetyl bicyclic ketone **2c** was prepared in the usual way[25] and recrystallized from methanol to give white prisms: mp 189–191°; λ_{max}^{MeOH} 250, 278 mμ.

Anal. Calcd for $C_{15}H_{17}O_2N_5$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.01; H, 5.78; N, 23.21.

Hydrochloride of 1a.—To an 87-mg sample of the unsubstituted bicyclic ketone **2a** was added 1.8 ml of 6 *N* HCl and then 0.5 ml of concentrated HCl. Tan crystals separated which were collected and washed with a small volume of cold water to give 93 mg of the hydrochloride, mp 136–137 dec. Recrystallization from methanol containing a trace of HCl gave tan prisms: mp 139–140°; λ^{KBr} 1760 cm^{-1}.

Anal. Calcd for $C_{21}H_{13}ON_2Cl$: C, 60.88; H, 5.53; N, 11.84. Found: C, 60.48; H, 5.36; N, 11.58.

Semicarbazone of 1a.—A solution of 30 mg of the semicarbazone of diazepinone **1a** in 36 ml of methanol was irradiated in a cylindrical Pyrex cuvette (1 cm thick × 5 cm diameter) for 2.5 hr with a Hanovia 510C1 xenon arc. Evaporation of the solution gave 28 mg of white prisms of **2a semicarbazone**: mp 136–137° (to yellow melt); λ_{max}^{MeOH} 253, 281 mμ. On crystallizing the melt or recrystallization of the product from methanol, the diazepinone semicarbazone, mp and mmp 188–190°, λ_{max}^{MeOH} 305, 350 mμ, was obtained. The bicyclic semicarbazone, mp 136°, was also ob-

(22) G. W. Borden, O. L. Chapman, R. Swindell, and T. Tezuka, *J. Amer. Chem. Soc.*, **89**, 2979 (1967).

(23) General procedures are given in paper XXII of this series.[24]

(24) J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.*, **31**, 52 (1966).

(25) J. A. Moore and J. Binkert, *J. Amer. Chem. Soc.*, **81**, 6029 (1959).

tained by irradiation of **1a** followed by treatment with semicarbazide acetate. Acetylation gave the acetyl bicyclic semicarbazone, mp 189–190°, identical with that prepared from **2c**.

2-Benzoyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-one (2d).—A solution of 300 mg of the 2-benzoyldiazepinone **1d** in 300 ml of methanol was irradiated in sunlight for 2 hr and evaporated. The light yellow solid was recrystallized to give 150 mg of nearly colorless crystals, mp 112–114°. Repeated crystallization caused some yellow color to appear; this compound appeared to be significantly more sensitive to heat than the acetyl derivative.

Anal. Calcd for $C_{19}H_{16}O_2N_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.77; H, 5.26; N, 9.12.

5-Methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-*endo*-ol (5a).—A solution of 65 mg of diazepinone **1a** in 20 ml of methanol was irradiated (xenon lamp) until nearly colorless and evaporated to an oil. The oil was dissolved in 4 ml of ethanol, and a solution of 38 mg of $NaBH_4$ in 2 ml of water–ethanol (1:2) was added. The solution became turbid and a white precipitate separated. After stirring for 1 hr, several drops of glacial acetic acid was added and the mixture was diluted with water. The colorless solid was collected in two crops to give a total of 60 mg of **5a**, mp 208–214°. Recrystallization from ethanol gave glistening white plates, mp 215–220° dec.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.20; H, 6.95; N, 13.72.

Acetylation gave the **N,O-diacetyl** derivative, **5e**, mp 124–125°, identical mixture melting point and ir) with that obtained by acetylation of the N-acetyl *endo* alcohol (*vide infra*).

5-Methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-*exo*-ol (4a).—A solution of 250 mg of the diazepinol **3a**[25] in 250 ml of methanol was placed in two semicylindrical quartz cuvettes and irradiated at room temperature, with a slow stream of nitrogen, using a 200-W Hanovia medium-pressure arc with Corex filter. The uv spectrum of the original solution had λ_{min} 280 mμ, λ_{max} 306 mμ (ϵ 5000); after 260 min the spectrum had λ_{max} 273 mμ (14,000), λ 306 mμ (ϵ 1200), and the irradiation was discontinued and the solution evaporated.

Crystallization of the residue gave a first crop of 23 mg of the *endo* alcohol, **5a**, mp 217–221° dec (one spot, tlc), and as a second crop, 106 mg of the *exo* isomer, mp 167–170° dec. The tlc of the second crop showed the presence of a slower spot representing about 10–20% *endo* alcohol. The oily mother liquor from the second crop showed a major tlc spot corresponding to *exo* alcohol and three smaller spots corresponding to the diazepinol **1a**, *endo* isomer and one other compound. Recrystallization of the first crop from methanol gave large prisms of *endo* alcohol **5a**, mp 220–225° dec; the ir spectrum contained 29 bands at the same position and relative intensities as those in the spectrum of **5a** obtained by reduction of the ketone. Recrystallization of the second crop from methanol gave 8 mg of **5a**, mp 210–213°, and then 60 mg of *exo* alcohol, **4a**, mp 166–169° (one spot, tlc). Further crystallization from methanol–ether gave rhombs, mp 168–171°. A sample was sublimed for analysis.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.79; H, 7.00; N, 13.93.

Acetylation of 40 mg of the *exo* alcohol (0.3 ml of Ac_2O, 0.3 ml of C_5H_5N, 16 hr, 20°) gave 48 mg of the ***exo*-O,N-diacetyl** derivative **4e**: mp 145–146°; ν^{KBr} 1740, 1665 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 66.79; H, 5.98; N, 9.66.

2-Acetyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-*endo*-ol (5c).—A solution of 114 mg of the 2-acetyl bicyclic ketone **2c** in 9 ml of ethanol was treated with 56 mg of $NaBH_4$ dissolved in 1 ml of water. After 1 hr, 1 ml of acetic acid was added and the solution was evaporated, treated with water, and extracted with ether; evaporation of the washed ($NaHCO_3$) and dried ether solution gave 93 mg of **5c** as a colorless oil which showed one spot on tlc: ν^{CCl_4} 3400, 1670 cm^{-1}. Material prepared in this way was used for nmr. On one occasion, crystals, mp 75–80° dec, were obtained on evaporation of a carbon tetrachloride solution; this sample contained chlorine, and analysis indicated a solvate.

Anal. Calcd for $(C_{14}H_{16}N_2O_2)_3 \cdot CCl_4$: C, 58.24; H, 5.45; N, 9.48. Found: C, 58.39; H, 5.52; N, 9.53.

Acetylation of the oil (Ac_2O, pyridine) gave an oil which crystallized from ether, giving the ***endo*-N,O-diacetyl** derivative **5e**: mp 124–125°; ν^{KBr} 1770, 1675 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 66.92; H, 6.33; N, 9.87.

The ***endo*-N-acetyl tosylate 5f** was obtained by treatment of 130 mg of **5c** with 130 mg of *p*-toluenesulfonyl chloride in 1 ml of pyridine for 24 hr. After pouring into ice, 125 mg of beige solid, mp 165–170° dec, was collected and recrystallized from benzene and then ethanol to give 100 mg of **5f**, mp 170° dec.

Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.39; H, 5.66; N, 7.03.

2-Acetyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-*exo*-ol (4c).—A solution of 250 mg of the 2-acetyldiazepinol in 200 ml of methanol was irradiated at 0° using a 200-W Hanovia medium-pressure mercury arc with Pyrex filter. After 30 min, the uv spectrum showed no further change, and the solution was evaporated and the residue was crystallized from benzene, giving 100 mg of white crystals, mp 158–165°. Several recrystallizations from benzene gave white prisms of **4c**, mp 167–168°.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.27; H, 6.79; N, 11.43.

The mother liquor from the first crop of **4c** was evaporated to an oily residue (130 mg) which showed two spots on tlc (alumina coating, ether solvent). The slower moving spot corresponded to the crystals from the first crop (*exo* isomer). The two zones containing the separate spots [as shown by a control plate (I_2) and subsequent separate spotting of the zones] were scraped from the plate and eluted with methanol. After dilution to equal volumes, the eluates from the upper and lower zones showed A_{270} 1.07 and 0.50, respectively, corresponding to 68% *endo* and 32% *exo* alcohol. Nmr examination of this mother liquor mixture gave values of 72 and 28%, respectively. Assuming that the first crop of crystals was 90% *exo* isomer, the ratio of *exo*/*endo* in the total reaction mixture would be *ca.* 60:40. The value of 65:35 determined by nmr analysis of the total mixture (Table II) is undoubtedly more accurate because of mechanical losses in the above isolation.

Acetylation of the N-acetyl-*exo* alcohol gave the **O,N-diacetyl** derivative, mp 146–147°, identical with that obtained by acetylation of the *exo* alcohol **4a**.

The ***exo*-N-acetyl tosylate 4f** was obtained as described for **5f** as a viscous oil which crystallized after several days. Recrystallization from benzene–hexane and then methanol–water gave **4f** as white crystals, mp 144–145°.

Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.67; H, 5.93; N, 6.94.

2,5-Dimethyl-6-phenyl-2,3-dihydro-4H-1,2-diazepin-4-ol (3b).—A solution of 700 mg of the 2-methyldiazepinone (**1b**) in 70 ml of ethanol was treated with 140 mg of sodium borohydrides and allowed to stand 2 hr. Acetic acid was added and the solution was evaporated. The ether solution of the residue was washed, dried and concentrated to give 320 mg of white crystals of **3b**, mp 110°; recrystallization from methanol–water gave needles, mp 114–116°.

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.12; H, 7.50; N, 13.29.

2,5-Dimethyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-ol. *endo* Isomer (5b).—A solution of 0.37 g of 2-methyldiazepinone **1b** in 650 ml of ethanol was irradiated in sunlight for 30 min. The nearly colorless solution was then treated with 0.1 g of $NaBH_4$ and the solution kept in the sunlight for 2 more hr to avoid reverse reaction. After adding a few drops of acetic acid, the solution was evaporated to a solid residue. Addition of 10 ml of water gave a clear solution. At pH 7 some turbidity developed, but the compound remained dissolved. The aqueous solution was evaporated and the residue was extracted with hot benzene. The dried benzene solution was concentrated to give a white crystalline solid, mp 153–158°. Recrystallization from benzene gave 290 mg of **5b**, mp 158°.

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.40; H, 7.19; N, 12.77.

***exo* Isomer (4b).**—A methanol solution of 0.26 g of the 2-methyldiazepinol **3b** was irradiated with a 450-W Hanovia medium-pressure lamp for 65 min and then evaporated to dryness. Tlc (silica, ether–methanol 1%) showed two spots; the larger spot (*exo* alcohol) was faster moving. The slower, small spot corresponded to the *endo* alcohol. The composition of the mixture was determined by nmr and the material was then chromatographed on 6 g of silicic acid. Initial fractions eluted with ether contained brown oil; fractions eluted with ether–2% methanol contained exclusively *exo* alcohol; the nmr spectrum of material from these fractions was used for detailed analysis. Evaporation gave a solid residue; recrystallization from carbon tetrachloride gave crystals, mp 145–147°; analytical data were not obtained.

2-Benzoyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-ol (4d and 5d).—A solution of 306 mg of the 2-benzoyldiazepinol (**3d**) was irradiated as described for the N-acetyl derivative. After evaporation and nmr analysis of the crystalline residue, the mixture was triturated with ether and the insoluble material (85 mg), together with the first crop of crystals from the ether (25 mg), was recrystallized from benzene to give 98 mg of the *exo* isomer (major product by nmr), mp 174–176°. Recrystallization from ethanol gave colorless crystals of **4d**, mp 174–175°; a satisfactory analysis was not obtained.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 73.57; H, 6.55; N, 8.75.

The 200 mg of solid remaining after removal of 25 mg of **4d** from the ether-soluble fraction was crystallized several times from ethanol to give 67 mg of the *endo*-N-benzoyl alcohol **5d**, mp 188–189°.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.75; H, 5.93; N, 9.02.

Photocyclization of 4-Acetoxy-2-acetyl-5-methyl-6-phenyl-2,3-dihydro-4H-1,2-diazepine (3e).—A solution of 286 mg of **3e**[24] in 200 ml of methanol was irradiated as described for **3c** and after removal of solvent and nmr analysis, the solid mixture was crystallized from ether–hexane. The first crop of crystals, 130 mg, mp 145–150°, was recrystallized from ether to give the *exo*-acetate **4e**, mp 149–150° (major product). From the more soluble fractions, a sample of the *endo*-acetate **5e**, mp 125–126°, was isolated.

4-Acetoxy-2-benzoyl-5-methyl-6-phenyl-2,3-dihydro-4H-1,2-diazepine was prepared in 83% yield by acetylation of the N-benzoyl alcohol **3d** (acetic anhydide, pyridine, 90°, 2 hr) and crystallized from ethanol, mp 162–163°.

Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.32; H, 5.85; N, 7.89.

Irradiation of this compound was qualitatively similar to that of **3e**; the bicyclic products were not isolated.

2-Acetyl-5-methyl-6-*endo*-phenyl-1,2-diazabicyclo[3.2.0]-heptan-4-*endo*-yl Acetate (8e).—A solution of 130 mg of N-acetyl *endo*-acetate **5e** in 10 ml of ethanol was injected into a flask containing 20 ml of ethanol and 30 mg of 10% palladium on charcoal serving as the hydrogenation vessel in an Brown hydrogenation apparatus (Delmar Scientific Co.). After passing in hydrogen generated from $NaBH_4$ until uptake ceased, the solution was filtered and concentrated to a solid residue. Recrystallization from ether–hexane gave 120 mg of crystals, mp 100°. Further recrystallization gave 80 mg of **8e**, mp 107°.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.88; H, 7.30; N, 9.60.

2-Acetyl-5-methyl-6-*endo*-phenyl-1,2-diazabicyclo[3.2.0]heptan-4-*endo*-yl *p*-toluenesulfonate (8f) was obtained by hydrogenation of **5f** as described above. The nmr spectrum of the crude product contained peaks corresponding to about 10% the *exo*-phenyl isomer. Several recrystallizations from benzene–hexane gave pure **8f**, mp 166–167°.

Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.99; H, 6.04. Found: C, 63.28; H, 5.84.

A mixture of 6-*endo* and 6-*exo* isomers of **2-acetyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]heptan-4-*exo*-yl *p*-toluenesulfonate** was prepared by similar hydrogenation of the *exo*-tosylate **4f**. Evaporation of the filtered solution gave a colorless oil whose nmr spectrum showed methyl peaks corresponding to two isomers in a ratio of 55:45. A hexane solution of the oil crystallized on scratching to give a white solid, mp 105–108°; the nmr spectrum resembled that of the oil. Further crystallization gave a mixture of the *exo*- and *endo*-phenyl-4-*exo* tosylates **6** and **7**, mp 111–119°.

Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.99; H, 6.04. Found: C, 63.60; H, 6.31.

Determination of Isomer Ratios in Diazepinol Cyclizations.—Solutions of 200-300 mg of the diazepinols **3a–e** in 250 ml of Spectrograde methanol were irradiated with a 200- or 400-W medium-pressure lamp until A_{315} was constant; the time required varied from 10 min for **3e** to 100 min for **3a** (*cf.* Table III). The solutions were then evaporated to an oily or solid residue; after removal of all solvent at 0.1 mm, the residues, except for that from **3a**, were dissolved completely in 1.5–2.0 ml of $CDCl_3$. The mixture from **3a** was dissolved in acetic acid.

The nmr spectra of these mixtures contained negligible peaks for the diazepinols. The scans were made at 250 sweep width over a 27-Hz region containing the H-7 signals of the photoalcohols (6.4–6.8 ppm). Areas of the peaks from each isomer were calculated from height and $W_{1/2}$ (about 2 Hz) for each scan, and the average values were used to derive the ratios given in Table I. The same procedure was applied also to the N-CH_3 or N-$COCH_3$ peaks in the mixtures from **3b**, **3c** and **3e**. The ratios from these measurements differed by less than 2% from those calculated from the H-7 peaks.

4-*exo*-*d*-4-*endo* Alcohols.—Reductions of the bicyclic ketones **2b**, **2c**, and **2d** were carried out using 400-mg samples of **2** and 80 mg of $NaBD_4$ (Merck Sharp and Dohme) by the procedures described for the $NaBH_4$ reductions. The ir spectra of these 4-*d* alcohols showed several distinct differences from those of the 4-^{1}H compounds in the 800–1200-cm^{-1} region. The spectra (KBr) contain about eight to ten strong or medium bands in this region, and most of these differed in position and relative intensity. In the spectra of the 4-*d* derivatives of **4b**, **4c**, and **4d**, there were strong bands at 1120–1150 and 820–860 cm^{-1} which were either extremely weak or shifted by as much as 50 cm^{-1} in the spectra of the 4-^{1}H compounds.

Photocyclization Rate Comparison. Apparatus.—A Hanovia 100-W utility lamp with U-shaped quartz arc tube 616A-13 was mounted horizontally. Directly in front of the lamp were placed in sequence a Pyrex heat shield, a 1-cm Pyrex cuvette with circulating water, a 7-54 Corning glass filter, and a 1-cm Pyrex cuvette containing a filter solution of 145 g/l. of $NiSO_4$ and 44.5 g/l. of $CoSO_4$. The uncollimated beam was passed through a 1.3 × 1 cm shuttered aperture in a box with a removable lid. The solution to be irradiated was placed in a standard 1-cm quartz cuvette mounted about 1 cm from the aperture. A stirring bar was placed in the cell and positioned over a rotating magnetic stirrer. The temperature inside the box was maintained at 24–25° by means of a circulating air stream. The lamp output with this filter system was measured by the standard potassium ferrioxalate system[26] to be $I_0^i = 7.6 \times 10^{14}$ quanta/sec.

For irradiation at the long wavelength maximum of the ketones (Table IV), the same lamp was used with heat shield and water-cooled cuvette and a narrow band pass (CS-5-62) filter with 30% transmittance at 390 mμ. The intensity I_0^i was 9.8×10^{13} quanta/sec.

Procedure.—A solution of the diazepine was diluted in the quartz cuvette with the appropriate solvent (Spectrograde methanol or hexane) to a measured optical density of 0.72–0.75. The cuvette was then placed in the holder and irradiated for appropriate time intervals; optical density was measured with a Cary Model 14 spectrophotometer. In general, ten readings were made during the first half-life time. For all ketones except the 2-acetyldiazepinone **1c**, the reaction was followed using the 390–410-mμ maximum, and concentrations were derived directly. For the 2-acetyl ketone **1c** and the 2-unsubstituted and 2-methyldiazepinols **3a** and **3b**, the concentrations were calculated by measurements of the maxima of the diazepine at 300–315 mμ and of the bicyclic product at 260–270 mμ. For the remaining diazepinols **3c, d,** and **e**, the bicyclic alcohol absorption at 315 mμ was neglected.

Registry No.—**1a**, 1706-26-9; **1a**·HCl, 17838-72-1; **1a** semicarbazone, 17827-16-6; **1b**, 4084-21-3; **1c**, 4134-95-6; **1c** semicarbazone, 17827-19-9; **1d**, 17827-20-2; **2a**, 17827-21-3; **2a** semicarbazone, 17827-22-4; **2b**, 17827-23-5; **2c**, 3988-19-0; **2c** semicarbazone, 17827-25-7; **2d**, 17827-26-8; **3a** (*exo*), 17827-63-3; **3a** (*endo*), 17827-64-4; **3b** (*exo*), 17827-65-5; **3b** (*endo*), 17827-66-6; **3c** (*exo*), 17827-67-7; **3c** (*endo*), 17827-68-8; **3d** (*exo*), 17827-69-9; **3d** (*endo*), 17827-70-2; **3e** (*exo*), 17827-71-3; **3e** (*endo*), 17827-72-4; **4a**, 17831-28-6; **4b**, 17831-30-0; **4c**, 17831-29-7; **4d**, 17831-31-1; **4e**, 17831-32-2; **4f**, 17831-33-3; **5a**, 17831-34-4; **5b**, 17831-35-5; **5c**, 17831-36-6; **5d**, 17831-37-7; **5e**, 17831-38-8; **5f**, 17831-39-9; **6**, 17831-40-2; **7**, 17831-41-3; **8e**, 17831-42-4; **8f**, 17831-43-5; 4-acetoxy-2-benzoyl-5-methyl-6-phenyl-2,3-dihydro-4H-1,2-diazepine, 17827-27-9.

(26) C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc.* (London), **A235**, 518 (1956).

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1,3-Dipolar and Diels–Alder Cycloaddition Reactivity of Lumisantonin[1]

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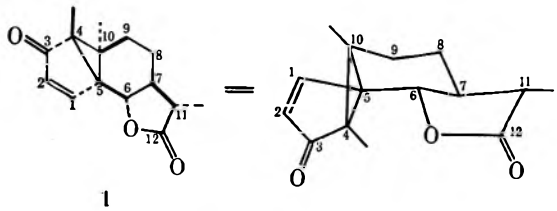
Some double-bond derivatives of lumisantonin (**1**) were prepared by its 1,3-dipolar and Diels–Alder cycloaddition reactions. Benzonitrile oxide, α,N-diphenylnitrone, and diazomethane afforded the corresponding 1:1 adducts **2**, **3a**, **3b**, and **4**, respectively, but diphenylnitrilimine, phenyl azide, and tosyl azide did not give any adduct. The pyrolysis and photolysis of **4** afforded 1-methyl lumisantonin (**5**) and 1,2-methylene lumisantonin (**6**), respectively; **6** was surprisingly stable on heating at 250°. The Diels–Alder reactions with cyclopentadiene, furan, isoprene, and myrcene were investigated, but only cyclopentadiene gave the corresponding 1:1 adduct **8a**. In the reactions with isoprene and myrcene, pyrolumisantonin was produced in very low yields as a by-product.

Although a number of double-bond derivatives of santonins and their derivatives have been reported,[2] only little about those of lumisantonin (**1**) has been known.[3] In aiming to prepare some double-bond derivatives of **1**, its 1,3-dipolar and Diels–Alder cycloaddition reactions were investigated. As the 1,3 dipoles were utilized, benzonitrile oxide, α,N-diphenylnitrone, diazomethane, diphenylnitrilimine, and phenyl and tosyl azide, the former three gave the corresponding adducts, **2**, **3a**, **3b**, and **4**, respectively, but the latter



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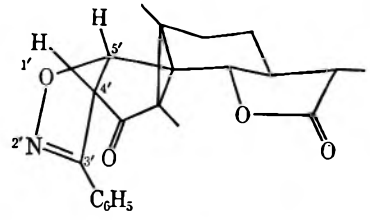

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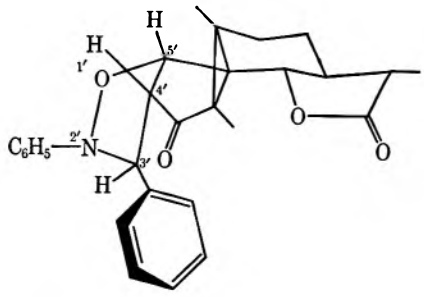
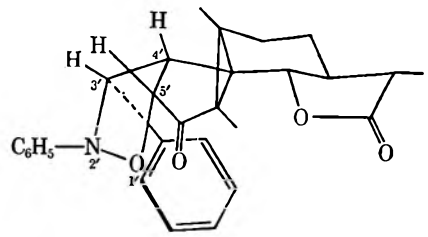


3a



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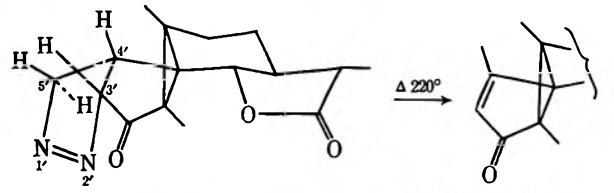
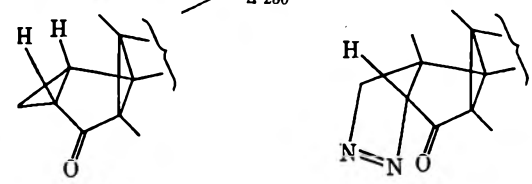
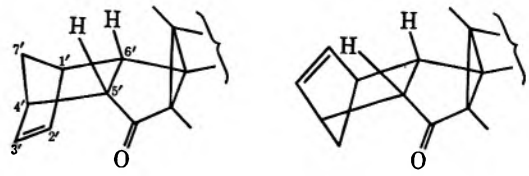


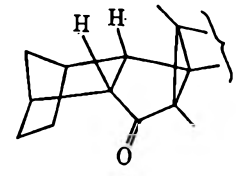
4 **5**



6 **7**



8a **8b**



9

(1) Part III in the series of "Studies on the Reactions of Isoprenoids." Part II: T. Sasaki and S. Eguchi, *Bull. Chem. Soc. Jap.*, **41**, 2453 (1968).

(2) See, for example, J. B. Hendrickson and T. L. Bogard, *J. Chem. Soc., B*, 1678 (1962).

(3) For pioneering works on lumisantonin and its stereochemistry, see (a) D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger, and L. J. Krebaum, *Helv. Chim. Acta*, **40**, 1732 (1957); (b) W. Cocker, K. Crowley, J. Edwards, T. B. H. McMurry, and E. R. Stuart, *J. Chem. Soc.*, 3416 (1957); (c) D. H. R. Barton, P. de Mayo, and M. Shafiq, *ibid.*, 140 (1958); (d) D. H. R. Barton, and P. T. Gilham, *ibid.*, 4596 (1960); (e) D. H. R. Barton, J. T. Pinhey, and R. J. Wells, *ibid.*, 2518 (1964).

three did not. The pyrolysis and photolysis of **4** afforded 1-methyl lumisantonin (**5**) and 1,2-methylene lumisantonin (**6**), respectively.

In the Diels–Alder reactions, cyclopentadiene, furan, isoprene, and myrcene were applied as the diene, in which only cyclopentadiene gave the corresponding Diels–Alder adduct **8a** in a low yield.

Results and Discussion

The reaction of lumisantonin (**1**) with benzonitrile oxide was carried out by refluxing an ethereal solution of **1** and benzohydroxamoyl chloride[4] in the presence of triethylamine. Purification of the reaction products afforded a 1:1 adduct in a 51% yield as colorless needles which exhibited infrared absorption bands at 1770 (γ-lactone), 1710 (cyclopentanone conjugated with a cyclopropane), 1602 and 710 (phenyl) cm^{-1}. Assuming principally the occurrence of a β side addition of benzonitrile oxide to **1** because of the presence of C-10 α-methyl group in **1**, the structure was assigned as **2** based on the nmr data which had signals at τ 4.41 and 5.71 (a pair of d, J = 6.5 Hz, assignable to protons at 4′ and 5′ positions of a oxazoline ring), and those at τ 2.07–2.70 (5 H, m, phenyl protons), 6.14 (1 H, d, J = 8.2 Hz, C-6 H), 8.65 (3 H, d, J = 6.5 Hz, C-11 methyl protons), 8.73 and 8.78 (each 3 H, s, C-4 and C-10 methyl protons).

Reaction of **1** with α,N-diphenylnitrone in refluxing benzene afforded two kinds of 1:1 adducts, **3a** and **3b**, in 24 and 8% yields, respectively. The nmr spectrum of the main product **3a** had two doublets at τ 4.83 (J = 9.0 Hz) and 4.92 (J = 6.0 Hz), assignable to 3′ and/or 5′ protons, and a quartet at τ 6.52 (J = 9.0 and 6.0 Hz) assignable to 4′ proton besides signals due to two phenyl protons at τ 2.40–2.81 (10 H, m) and three methyl protons at τ 8.72 (3 H, d, J = 6.5 Hz, C-11 methyl protons), 8.99 and 9.33 (each 3 H, s, C-10 and C-4 methyl protons). The fact that the chemical shift of C-4 methyl protons was considerably higher than those of **2** and **1**[5] may be explained by a diamagnetic anisotropy of 3′-phenyl ring[6] supporting the structure **3a**. The structure of the minor product, therefore, could be assumed reasonably to be **3b** which was supported by the nmr signals at τ 2.30–2.88 (10 H, m, two phenyl ring protons), 3.61 (1 H, slightly broad s, C-5′ H of a oxazolidine ring), 5.63 (1 H, d, J = 5.8 Hz, C-3′ H of a oxazolidine ring), 6.47 (1 H, d, J = 8.5 Hz, C-6 H), 6.57 (1 H, d, J = 5.8 Hz, C-4′ H of a oxazolidine ring), 8.72 (3 H, d, J = 5.5 Hz. C-11 methyl protons), 9.00 and 9.42 (each 3 H, s, C-10 and C-4 methyl protons).[7]

Contrary to benzonitrile oxide and α,N-diphenylnitrone, diazomethane reacted very smoothly with **1** even at room temperature to give a 1:1 adduct (**4**) almost quantitatively, the structure of which was assigned from the following spectral evidence: 1-pyrazoline structure has been shown by the infrared absorption band of N=N stretching frequency at 1560 cm^{-1} and by the lack of NH band, and a typical azoalkane n–π^* ultraviolet absorption at 322 mμ (ϵ 535).[8] In the nmr spectrum of **4**, the signal due to 3′ proton appeared at τ 4.60 in a doublet (J = 8.0 Hz) which was further split into a quartet (J = 2.5 and 1.5 Hz) by the long-range coupling with 5′-methylene protons, those of 5′ protons at τ 4.92 and 5.14 as AB portions of an ABX pattern, in which a X portion due to 4′ proton appeared at τ 7.18 in a broad quartet.[8] The signals due to C-6 H and three methyl protons appeared at τ 6.30 (1 H, d, J = 10.3 Hz), 8.61, 8.64, and 8.74 (9 H, s), respectively, at the similar positions to those of **1** and **2**. This structure was also supported by its pyrolytic decomposition to 1-methyl lumisantonin (**5**); **4** on heating at 210–220° for several minutes yielded a brownish mass which was purified on a silica gel column to give needles with a melting point of 155–157° in a 54% yield. This compound was characterized as 1-methyl lumisantonin (**5**) by the analytical and the spectral data. The infrared absorption bands at 1768, 1688, and 1595 cm^{-1} and the ultraviolet absorption maxima at 215.5 mμ (ϵ 6182) and 257 (3448) were compatible with the structure **5**. The nmr spectrum had signals at τ 4.27 (1 H, q, J = 1.5 Hz) assignable to C-2 H, and 7.81 (3 H, d, J = 1.5 Hz) assignable to C-1 methyl protons, besides those due to C-6 H at τ 6.12 (d, J = 10.0 Hz) and three methyl groups at C-4, C-10, and C-11 at τ 8.77 (s), 8.83 (s), and 8.72 (d, J = 6.0 Hz), respectively. In the above pyrolysis, no trace of a cyclopropane derivative **6** could be isolated, and the minor possibility that **6** had been produced at first as an intermediate in the decomposition, followed by its rearrangement to **5**, was excluded by the fact that **6** was stable in the pyrolytic conditions.[9] This compound **6**, on the other hand, was obtainable in a 50% yield on the photolytic decompositions of **4** at 20°. The presence of a cyclopropane structure in **6** was indicated by its nmr spectrum, which had the signals at τ 8.34–9.20 in a complex multiplet for four protons.

It should be mentioned here that the formation of **5** on pyrolysis and **6** on photolysis both from **4** might supply an example of decomposition of 1-pyrazoline that might proceed *via* a dipolar intermediate on pyrolysis and *via* a diradical intermediate on photolysis.[10]

1-Methyl lumisantonin (**5**) had been treated also with diazomethane to examine its reactivity in the cycloadditions. However, an adduct **7** melting at 229–232° dec was produced in a very low yield, suggesting considerable steric hinderance of C-1 methyl

(4) M. H. Benn, *Can. J. Chem.*, **42**, 2313 (1964), and references cited therein.

(5) The chemical shifts of C-4 and/or C-10 methyl protons have been reported as τ 8.77 and/or 8.88: J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).

(6) An inspection of the Drieding stereomodel indicated obviously that the carbonyl group hindered sterically a free rotation of 3′-phenyl ring.

(7) A larger steric hindrance for a free rotation of 3′-phenyl ring with a lactone ring in **3b** was suggested by the Dreiding model inspection, and this steric hindrance may cause to lower **3b**'s yield more than **3a**'s. The higher chemical-shift values of C-4 methyl protons might be ascribable to a diamagnetic anisotropy of the 3′-phenyl ring.

(8) For spectral properties of 1-pyrazolines, see R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Amer. Chem. Soc.*, **88**, 3959 (1966), and references cited therein. The observed geminal coupling constant of 5′-methylene protons in **4** was *ca.* 16 Hz.

(9) Compound **6** was stable and unchanged on heating *in vacuo* even at 250° for 2 hr, though **1** has been known to decompose on heating at 200°; see ref 3a.

(10) In extrusion reactions of nitrogen from 1-pyrazoline, two different intermediates (nitrogen-free diradical and dipolar or ionic) have been postulated depending on reaction conditions and on the substituents: (a) B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press Ltd., Oxford, 1967, pp 116–134; (b) D. E. McGreer and W-S. Wu, *Can. J. Chem.*, **45**, 461 (1967); (c) R. J. Crawford and L. H. Ali, *J. Amer. Chem. Soc.*, **89**, 3909 (1967); and references cited in 10a–c.

group for cycloadditions.[11] 1-Pyrazoline structure of **7** was evidenced by its spectral data (see Experimental Section). The stability of 1-pyrazoline structure in **4** and **7** might come from their characteristic ring system, even though they have an enolizable hydrogen at the 3′ position.[12]

Diphenyl nitrilimine, known as a 1,3 dipole of nucleophilic character,[13] did not react with **1** at all. This lower reactivity might come from the steric hindrance of bulky phenyl group as observed in the reaction of α,N-diphenylnitrone with **1**. Since organic azides are known to be 1,3 dipoles of rather electrophilic character and their reactivity toward some strained olefins are relatively higher,[13] **1** was treated with phenyl azide and tosyl azide, but no addition had occurred.

The Diels–Alder reaction of **1** with cyclopentadiene was carried out by heating a mixture of **1** and dicyclopentadiene in a sealed tube at 180–185° for 24 hr. The product was purified on a silica gel column to afford a 1:1 adduct in a 28% yield. The structure was assigned as the *endo* isomer **8a** rather than the *exo* isomer **8b** from its nmr spectrum; a comparison of the chemical shifts due to two methyl groups at C-4 and C-10 (τ 9.05 and 8.86) of this adduct with those (τ 8.85 and/or 8.90) of a dihydro derivative **9**, indicated the presence of a diamagnetic shift due to a double bond for one of the two methyl groups. In **8a**, C-4 methyl protons are held in the shielding cone of the double bond, whereas in **8b**, both methyl protons at C-4 and C-10 are remote from the double bond and thus the signal at τ 9.05 could be assignable to C-4 methyl protons, supporting the assigned *endo* structure **8a**.[14]

Diels–Alder reactions of **1** with furan (at 100° for 3 days), isoprene (at 145° for 40 hr), and myrcene (at 150° for 64 hr) were all unsuccessful, recovering the starting **1**. In the latter two reactions, however, a compound with a melting point of 126–128° was isolated in low yields in addition to the recovered **1** by chromatography. This product was identical with the known pyrolumisantonin[3a] by the mixture melting point determination and the perfect superimposition of the infrared spectrum with an authentic sample's.

As a conclusion, it can be stated that lumisantonin is a good 1,3 dipolarophile with nucleophilic 1,3 dipoles involving no bulky substituents, but its dienophilic reactivity seems to be considerably low.

Experimental Section[15]

Reaction of 1 with Benzonitrile Oxide.—To a refluxing mixture of 248 mg (1.00 mmol) of lumisantonin (prepared from α-santonin by the method of Arigoni, *et al.*[3a]) and 187 mg (1.20 mmol) of benzhydroxyamoyl chloride[4] in 20 ml of ether was added slowly a solution of triethylamine (140 mg) in 10 ml of ether in *ca.* 0.5 hr. Refluxing was continued for further 2 hr, and the reaction mixture was washed with water, dried over anhydrous sodium sulfate, and dried up to give a white solid which was purified on a silica gel (Mallinckrodt, 100 mesh) column. The first fractions eluted with chloroform gave 100 mg of diphenylfuroxan, mp 115–117° (from ethanol, lit.[16] mp 115°), and the second fractions gave 50 mg of the recovered **1**. The third fractions afforded 185 mg (51%) of **2**, mp 263–265° (from chloroform–*n*-hexane).

Anal. Calcd for $C_{22}H_{23}O_4N$: C, 72.31; H, 6.34; N, 3.83. Found: C, 71.92; H, 6.22; N, 3.58.

Reaction of 1 with α,N-Diphenylnitrone.—A mixture of 248 mg (1.00 mmol) of **1** and 197 mg (1.00 mmol) of α,N-diphenylnitrone[17] in 10 ml of benzene was refluxed for 15 hr, and the crude products were chromatographed on a silica gel column. From the fractions eluted with chloroform, 34 mg (8%) of **3b** was obtained as needles (from chloroform–*n*-hexane): mp 201–203°; ir (KBr), 1763 (γ-lactone), 1725 (cyclopentanone), 1601, 1590, 765, and 700 (phenyl) cm^{-1}.

Anal. Calcd for $C_{28}H_{29}O_4N$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.52; H, 6.55; N, 3.07.

From the fractions eluted with chloroform–methanol (2% methanol v/v), 105 mg (24% yield) of **3a** was obtained as needles (chloroform–*n*-hexane): mp 210–212°; ir (KBr), 1770 (γ-lactone), 1725 (cyclopentanone), 1600, 760, and 700 (phenyl) cm^{-1}.

Anal. Calcd for $C_{28}H_{29}O_4N$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.53; H, 6.66; N, 2.97.

Reaction of 1 with Diazomethane.—To a solution of **1** (496 mg, 2.0 mmol) and a few drops of triethylamine in a minimum amount of chloroform (*ca.* 3 ml) was added an ethereal solution of diazomethane (prepared from 2.0 g of nitrosomethylurea in 100 ml of ether). The mixture was kept standing in a dark place at room temperature for 24 hr. Large needle crystals were separated which was almost pure **4**, melting at 203–207° dec, and amounted to 560 mg (97%). An analytical sample was recrystallized from chloroform–ether: mp 207–208° dec; ir (KBr), 1770 (γ-lactone), 1728 (cyclopentanone), and 1560 (N=N) cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_3N_2$: C, 66.64; H, 6.99; N, 9.72. Found: C, 67.04; H, 7.02; N, 10.06.

Pyrolysis of 4.—Heating of 300 mg of **4** in a longer test tube (25-cm length and 1.5-cm diameter) at 210–220° completed nitrogen extrusion in a few minutes, and the resulting dark brown mass was purified on a silica gel column. From the fraction eluted with chloroform, 140 mg (54% yield) of 1-methyl luminsantonin **5** was obtained as needles (from methanol), mp 155–157°.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.97.

Photolysis of 4.—Irradiation of a suspension of 320 mg (1.11 mmol) of **4** in 200 ml of ether at room temperature (*ca.* 20°) through a quartz cooling jacket with a 100-W high-pressure mercury lamp (UM-102, Ushio Denki Co., Tokyo) caused an evolution of nitrogen. It was completed in *ca.* 3 hr; at the end of this period the suspension became to a clear solution which was dried up to give a yellowish residue. Purification on a silica gel column using chloroform as an eluent afforded 143 mg (50% yield) of **6** as plates (from chloroform–*n*-hexane): mp 253–256° (the crystal form changed at *ca.* 200°); uv max (EtOH) 273 mμ (ϵ 126); ir (KBr) 3055 (cyclopropane C–H), 1770 (γ-lactone), and 1710 (cyclopentanone conjugated with cyclopropanes) cm^{-1}; nmr τ 6.44 (1 H, d, J = 9.0 Hz, C-6 H), 8.34–9.20 (complex m, superimposed with the signals of three methyl groups but total area for this region corresponded to 9 H + 4 H = 13 H; this indicated the presence of 4 H attached to a cyclopropane), 8.72 (d, J = 7.5 Hz), 8.76 (s) (each *ca.* 3 H and assignable the former to C-11 methyl protons and the latter to C-10 methyl protons), and 8.92 (*ca.* 3 H, s, C-4 methyl protons).

(11) A nonbonded interaction of C-1 methyl with C-10 methyl in the product as well as C-1 methyl's steric hindrance for the approach of a attacking molecule may cause lower the yield.

(12) A facile isomerization of 1-pyrazolines to 2-pyrazolines is known as a general trend of 1-pyrazolines with an active hydrogen at the 3 position; see also ref 13a.

(13) (a) For a recent review, see R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, pp 806–878; (b) R. Huisgen, H. Knupfer, R. Sustman, G. Wallbillich, and V. Weberndörfer, *Ber.*, **100**, 1580 (1967).

(14) In the Diels–Alder reactions of a cyclic dienophile with cyclic dienes, the *endo*-addition rule is well established; see ref 13a, pp 910–912.

(15) All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Yanagimoto C. H. N. Corder Model MT-1. Infrared spectra were recorded on a Jasco Model IR-S infrared spectrophotometer and ultraviolet spectra, on a Jasco Model ORD/UV-5 spectrophotometer. Nmr spectra were obtained in $CDCl_3$ with a Varian A-60 or a Hitachi H-6013 spectrometer and are reported in τ values relative to tetramethylsilane as an internal standard and singlet peaks are designated as s, doublet as d, triplet as t, quartet as q, and multiplet as m.

(16) H. Reinbolt, *Ann.*, **451**, 164 (1927).

(17) A. H. Wragg and T. S. Stevens, *J. Chem. Soc.*, 461 (1959).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.86; H, 8.10.

Reaction of 5 with Diazomethane.—A mixture of 290 mg (1.11 mmol) of **5** and a few drops of triethylamine in 3 ml of chloroform was treated with an excess of diazomethane in ether, and the mixture was kept standing in a dark place for 1 week at room temperature. After removal of the excess diazomethane and the solvent, the residue was chromatographed on a silica gel column. Fractions eluted with chloroform afforded 190 mg of the starting **5**, and the fractions eluted with ethyl acetate gave 65 mg (21.5% yield) of the adduct **7** as fine needles from chloroform–*n*-hexane: mp 229–232° dec; ir (KBr) 1780 (γ-lactone), 1710 (cyclopentanone), and 1557 (N=N) cm^{-1}; nmr τ 4.60–5.50 (3 H, these signals were very weak because of low solubility in $CDCl_3$, 1-pyrazoline ring protons), 6.45 (1 H, d, J = 10.0 Hz, C-6 H), 8.69, 8.76, and 8.93 (each 3 H, s, three methyl protons at C-1, C-4, and/or C-10), and 8.80 (3 H, d, J = 7.0 Hz, C-11 methyl protons).

Anal. Calcd for $C_{17}H_{22}O_3N_2$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.95; H, 7.73; N, 9.41.

Reaction of 1 with Diphenylnitrilimine.—To a solution of 496 mg (2.00 mmol) of **1** and 450 mg (2.00 mmol) of benzphenylhydrazidoyl chloride[18] in 25 ml of benzene was added 0.5 ml of triethylamine, and the mixture was stirred for 15 hr at 40°. After being washed with water and dried over sodium sulfate, the mixture was evaporated to dryness, which, on purification by chromatography, gave 300 mg of the starting **1** (mp 155–157°) but no other crystalline products.

Reactions of 1 with Phenyl and Tosyl Azides.—**1** was treated with an equimolar amount of phenyl[19] and tosyl azide[20] in benzene solution at 40° for 2 weeks, and the product was examined on tlc, only a spot corresponding to the starting **1** being observed, which was recovered in 80–90% yield.

Reaction of 1 with Cyclopentadiene.—A mixture of 496 mg (2.00 mmol) of **1**, 200 mg (1.5 mmol) of dicyclopentadiene, and 10 mg of hydroquinone was heated at 180–185° for 24 hr in a sealed tube (under reduced pressure of 30 mm). The product was purified on a silica gel column, using chloroform as an eluent. The first fractions gave the excessd icyclopentadiene, and the second fractions afforded 175 mg (28% yield) of **8a** as needles from chloroform–*n*-hexane: mp 198–200°; ir (KBr) 1770 (γ-lactone), 1713 (cyclopentanone), and 1640 (as shoulder, double bond) cm^{-1}; uv max (MeOH) 283 mμ (ε 72); nmr τ 3.81 and 4.01 (each 1 H, AB q, J = 5.5 Hz, each peak was further split into doublet, J = 3.0 Hz) assignable to C-2′ and C-3′ H, 6.40 (1 H, broad s, C-4′ H, superimposed with the signal due to C-6 H), 6.50 (1 H, d, J = 10 Hz, C-6 H), 6.84 (1 H, broad s, C-1′ H), 7.18 and 7.28 (2 H, AB q, J = 5.0 Hz, C-1 and C-2 H = C-5′ and C-6′ H), 8.76 (3 H, d, J = 7.0 Hz, C-11 methyl protons), 8.86 and 9.05 (each 3 H, s, C-10 and C-4 methyl protons).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.88; H, 8.25.

Hydrogenation of 8a.—A mixture of 94 mg (0.30 mmol) of **8a** and 300 mg of prereduced Pd–C (10%) in 20 ml of ethyl acetate was hydrogenated at 21° for 5 hr. After work-up product was recrystallized from dichloromethane–*n*-hexane to afford 74 mg (79% yield) of **9** as prisms: mp 208–210°; ir (KBr) 1770 (γ-lactone) and 1720 (cyclopentanone) cm^{-1}; nmr τ 6.30 (1 H, d, J = 9.6 Hz, C-6 H), 7.05 (1 H, broad s, C-4′ H), 7.47 (3 H, broad unsymmetrical s, C-1′, C-1, and C-2 H), 8.75 (3 H, d, J = 6.0 Hz, C-11 methyl protons), 8.85 and 8.90 (each 3 H, s, C-4 and/or C-10 methyl protons).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.36; H, 8.88.

Reactions of 1 with Furan, Isoprene, and Myrcene.—An equimolar amount of **1** and furan, isoprene, and myrcene was heated in the presence of a catalytic amount of hydroquinone in a sealed tube at 100° for 3 days, 145° for 40 hr, and 150° for 64 hr, respectively. After work-up and chromatography on a silica gel column the product was only the starting **1**, respectively, but in the reactions with isoprene and myrcene, pyrolumisantonin was also obtained in 3–13% yields as needles (from *n*-hexane), mp 126–128° (lit.[3a] mp 126–127°), which was identified with an authentic sample by no depression of a mixture melting point and a superimposition of the infrared spectra.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.69; H, 7.30.

Registry No.—**1**, 467-41-4; **2**, 17668-46-1; **3a**, 17603-79-1; **3b**, 17658-99-0; **4**, 17603-80-4; **5**, 17668-48-3; **6**, 17668-47-2; **7**, 17668-49-4; **8a**, 17668-50-7; **9**, 17668-51-8.

Acknowledgments.—We wish to thank Nippon Shinyaku Co., Ltd., for the generous supply of santonin.

(18) R. Huisgen, M. Seidel, G. Wallbillicht, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).

(19) R. O. Lindsay and C. F. H. Allen, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 710.

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The Crystal Structure of Photoisopyrocalciferyl *m*-Bromobenzoate[1]

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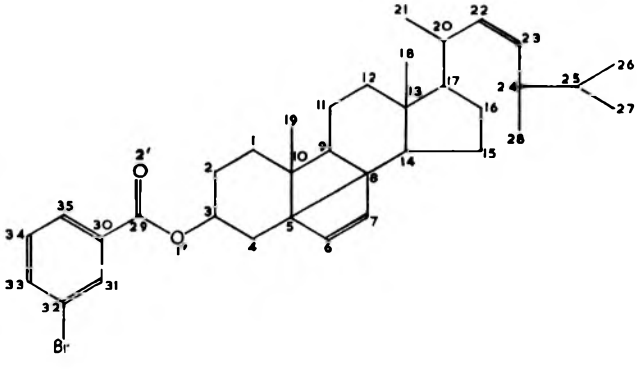
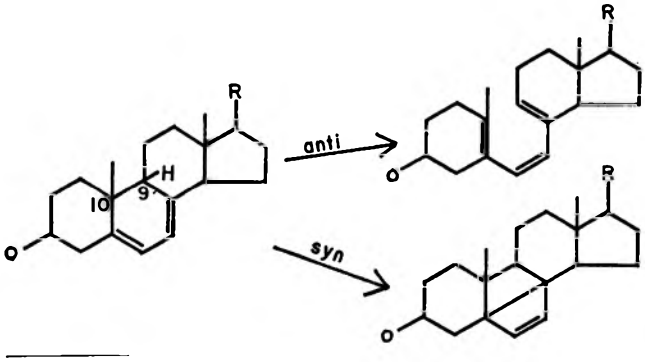
The molecular structure of photoisopyrocalciferol has been determined by a crystallographic investigation of the *m*-bromobenzoate ester. The unit cell is described by space group $P2_1$ with dimensions *a* 21.20, *b* 7.38, *c* 10.34 Å, β 92.77° containing two $C_{35}H_{47}O_2Br$ molecules. The B ring of the sterol nucleus is in the form of two fused four-membered rings, one of which contains a double bond. The cyclobutene ring is *cis* to the C-19 methyl group on one side of the cyclobutane ring, while on the opposite side the A and C rings are attached in *cis* configuration. The sterol configuration may be described as 3β-OH, 9β-H, 10β-CH_3, 13β-CH_3, and 17β-C_9H_{17}.

The structural formula of photoisopyrocalciferyl *m*-bromobenzoate was proposed by Dauben and Fonken,[2] and it has been confirmed by this analysis. Photoisopyrocalciferol is a member of the vitamin D series



of sterols derived from ergosterol.[3] If calciferol is heated at 188° in a sealed tube a 1:1 mixture of pyrocalciferol and isopyrocalciferol is produced.[4] The latter compounds contain the conjugated diene structure as does ergosterol.[5]

Ultraviolet irradiation of these pyro compounds gives, respectively, photopyrocalciferol and photoisopyrocalciferol.[6] The compounds with the conjugated diene bonds in the B ring undergo rearrangement when irradiated with ultraviolet light. The products which form depend on the configuration at C-9 and C-10.[2] When the C-9 and C-10 substituents are in the *anti* configuration, in particular 8α-H, 10β-CH_3 in ergosterol and 9β-H, 10α-CH_3 in lumisterol, irradiation induces ring opening between C-9 and C-10 to form the triene precalciferol now believed to be the precursor of calciferol in its formation from ergosterol. In the case of the two *syn* isomers, 9α-H, 10α-CH_3 in pyrocalciferol and 9β-H, 10β-CH_3 in isopyrocalciferol, the irradiation products are those formed by ring closure with a single bond across the B ring between C-5 and C-8 and with a double bond in the position between C-6 and C-7.



Dauben and Fonken have proposed the structures of the photo compounds based on chemical and spectroscopic studies.[2] The present study was undertaken to determine the stereochemistry of photoisopyrocalciferol by independent means.

Experimental Section

The crystals used in this study were kindly supplied by Dr. Dauben and Dr. Bauman. They prepared crystals of the ester of photoisopyrocalciferol and *m*-bromobenzoic acid with mp 94.0–94.5°. *Anal.* Calcd for $C_{35}H_{47}O_2Br$: C, 72.52; H, 8.17; Br, 13.79. Found: C, 72.23; H, 8.17; Br, 13.58. The crystals form flat colorless needles with the long dimension parallel to the *b* axis (Table I). The *a* axis is perpendicular to the flat sides of the crystals. Weissenberg photographs show monoclinic symmetry with systematic absences only of the type 0*k*0 for *k* odd. For assymmetric molecules the only space group possible is $P2_1$. Quartz-calibrated photographs of the *h*0*l* and *hk*0 were used to determine the cell dimensions. Multifilm equiinclination Weissenberg photographs of the layers *h*0*l* through *h*6*l* were taken with Cu Kα radiation. The intensities of the reflections were measured by visual comparison with an intensity standard. Absorption corrections were not made. The reflection intensity cut off sharply at high angles indicating large thermal motions or possible radiation damage to the crystals. A fresh crystal was chosen for each long exposure to minimize the effects of the latter.

TABLE I

a, Å	21.20 ± 0.04
b, Å	7.38 ± 0.01
c, Å	10.34 ± 0.02
β	92.77 ± 0.25°
Space group	$P2_1$
Molecules per unit cell	4
Measd *d*, g/ml	1.17
Calcd *d*, g/ml	1.19
Observed reflections	1342

Determination of the Structure.—The structure was determined by heavy-atom electron-density methods followed by nine cycles of least-squares refinement. The listing of atomic parameters, isotropic temperature factors, and observed and calculated structure factors has been deposited with the American Documentation Institute.[7] The final $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.205$.

(1) This investigation was supported by U. S. Public Health Service Grants A-5382 and GM 10941-02 and by a special postdoctoral fellowship 1-F3-GM-28,496-01.

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(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y. 1959, Chapter 4.

(4) P. Busse, *Z. Physiol. Chem.*, **214**, 211 (1933).

(5) A. Windaus and J. Naggatz, *Ann.*, **542**, 204 (1939); A. Windaus and K. Bucholz, *Z. Physiol. Chem.*, **256**, 273 (1938).

(6) K. Dimroth, *Ber.*, **70**, 1631 (1937).

(7) Document NAPS-00022 from ASIS National Auxiliary Publications Service, % CCM Information Sciences, Inc., 22 West 34th Street, New York, N. Y. 10001; remit $1.00 for microfiche or $3.00 for photocopies.

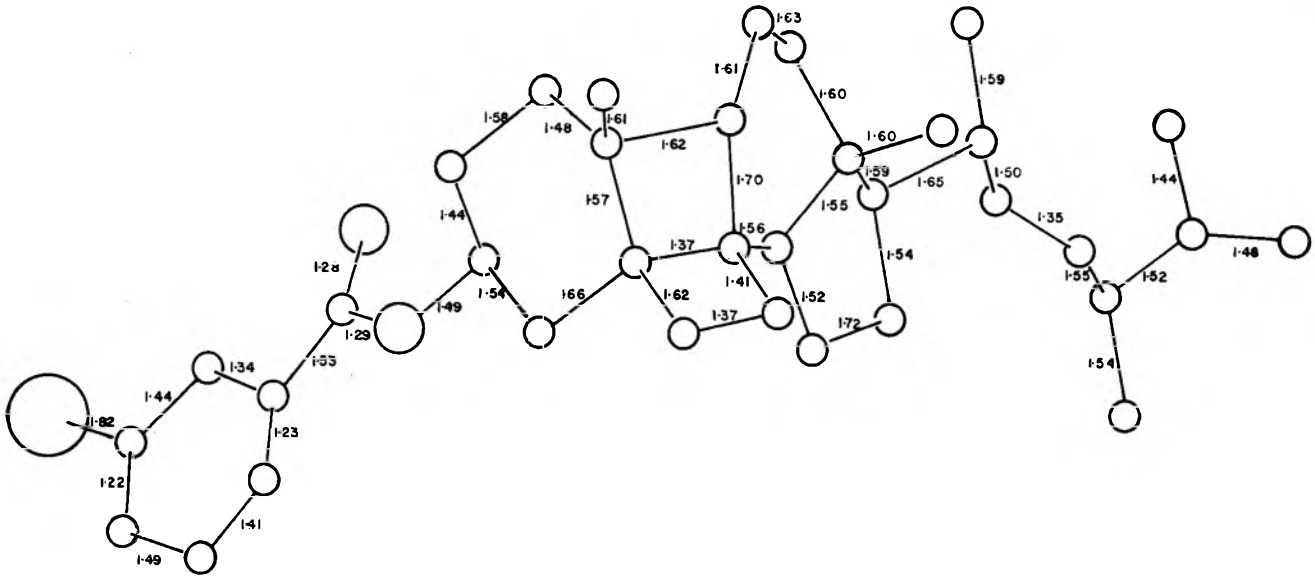

Figure 1a.—The bond distances in photoisopyrocalciferyl *m*-bromobenzoate.

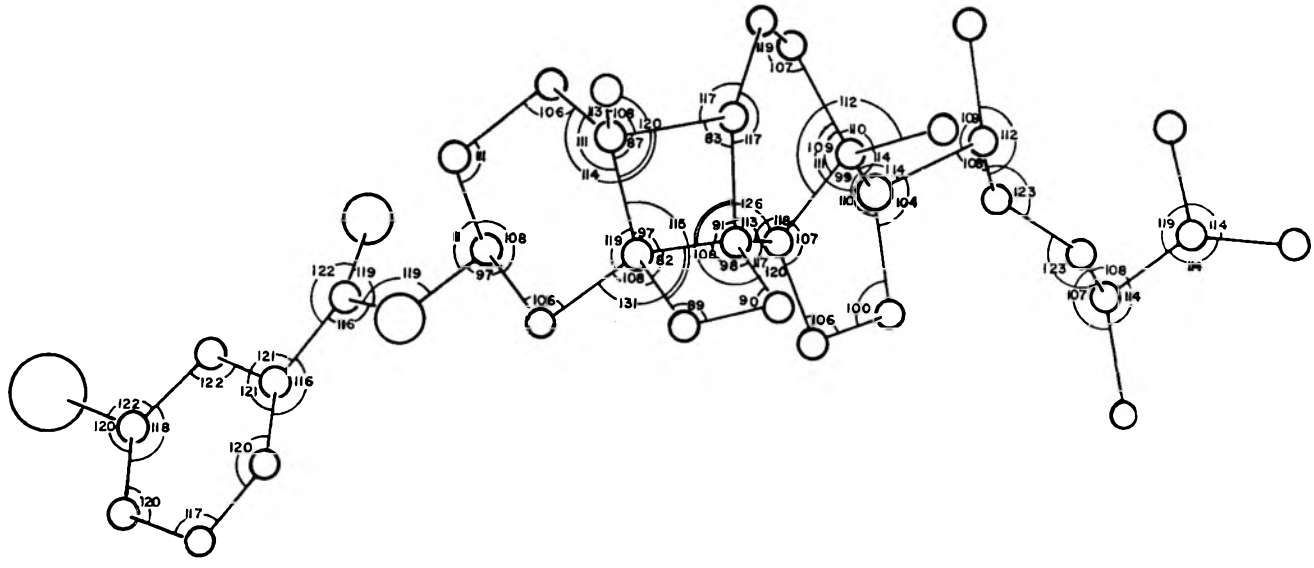

Figure 1b.—The bond angles in photoisopyrocalciferyl *m*-bromobenzoate.

The isotropic temperature factors fall in the range 2.9–11.6 with the lower values for carbon atoms in the sterol framework and the highest values for Br (11.2) and C-26 (11.6 Å²). No dispersion corrections were applied to the Br scattering which may be an explanation for this high value. The large value for C-26 may be caused by large thermal motions of this methyl group at the end of the carbon side chain. The over-all temperature factor determine by intensity statistics is 7.2. From the determined positional standard deviations the expected average standard deviation for a carbon–carbon bond length is 0.05 Å, and the average standard deviation for a bond angle about a carbon atom is 4° (see Figures 1a and b).

Discussion

The rearrangement of atoms is in agreement with the structure proposed by Dauben and Fonken.[1] The configuration of the sterol nucleus is 3β-OH, 9β-H, 10β-CH_3, 13β-CH_3, and 17β-C_9H_{17}. The novel feature of this sterol is the system of two fused four-membered rings, one of which contains a double bond. One of these rings containing C-5, C-8, C-9, and C-10 joins ring A and ring C in *cis* configuration giving a right-angle bend in the over-all shape of the molecule. On the opposite side of the cyclobutane ring the C-19 methyl group and the cyclobutene ring are in *cis* configuration. The bromobenzoate phenyl group is planar within a maximum deviation of 0.04 Å. The plane of the carboxyl group is tilted 8° with respect to the plane of the bromobenzene ring. The A ring shows the chair configuration with the oxygen atom attached to C-3 in the equatorial position as has been found for calciferol.[8] The cyclobutane ring and the cyclobutene ring make an angle of 110°. The angles about the C-5–C-8 bond show distortions up to 20° from tetrahedral owing to the necessary bending of this bond. The four-membered rings appear to be twisted out of square shape by as much as 8°. Such a distortion places the atoms in the cyclobutene double bond more distant from the C-19 methyl group, and it allows ring A to adopt a less strained chair arrangement. Ring C which is usually in the chair form in this series of sterols is in this case flattened with C-9 lying in the plane of atoms C-8, C-11, C-12, and C-14 in order to

(8) D. C. Hodgkin, B. M. Rimmer, D. D. Dunitz, and K. N. Trueblood, *J. Chem. Soc.*, **83**, 4945 (1963).

accommodate the strained B ring system. In the D ring C-13 lies 0.66 Å out of the plane of the other four atoms. The ethylene group in the side chain is found to be planar. Examination of the intramolecular distances leads to the conclusion that the packing of molecules in the crystal is determined by the bulk and shape of the molecules, and it is not influenced by specific interactions between molecules.

Registery No.—Photoisopyrocalciferyl *m*-bromobenzoate, 17448-36-1.

Acknowledgments.—We are indebted to Dr. Dorothy C. Hodgkin who made available the facilities of the Chemical Crystallography Laboratory at Oxford and offered much encouragement and many suggestions for the completion of this work. For the earlier computational work we are indebted to the Control Data Corporation, Minneapolis, Minn., and to the Numerical Analysis Center of the University of Minnesota. The final calculations were completed through the kind offer of the facilities of the Computing Laboratory of Oxford University.

Reactions of 1,2-Dichloroperfluorocycloalkenes and Perfluorocycloalkenes with Various Trivalent Phosphines

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The reactions of trivalent phosphines with certain 1,2-dichloroperfluorocycloalkenes or perfluorocycloalkenes give the corresponding phosphobetaines in fair to excellent yields. Ample physical data are presented to substantiate the assigned structures. This includes ir, ^{19}F and ^{31}P nmr, and analytical data. Although the literature is voluminous with possible mechanistic paths of various nucleophiles with the above type olefins, there exists no proof of the suggested first intermediates involved. This paper describes the isolation and experimental results of the initial 1:1 adduct of triphenylphosphine and perfluorocyclobutene, as well as discussing a plausible mechanism for the formation of the phosphobetaine. The betaine 4,4,5,5-tetrafluoro-2-(triphenylphosphoranylidene)cyclobutane-1,3-dione undergoes several crystal structure changes and two melts before its final melting solid. This interesting and novel polymorphism is discussed.

When trialkyl phosphites and 1,2-dichlorohexafluorocyclopentene (DCHFC) are heated together, the corresponding tetraalkyl perfluoro-1-cycloalken-1,2-ylenediphosphonates are formed as the major products.[1] Owing to the extreme reactivity of trivalent phosphorus compounds towards electron-deficient olefins, we considered the possibility of preparing phosphobetaines by treating 1,2-dichloroperfluorocycloalkenes and perfluorocycloalkenes with trivalent phosphines. This was based on our previous work involving the reaction of certain tertiary amines with DCHFC, which gave nitrogen betaines under hydrolytic conditions,[2] and some unreported work involving the reaction of 1-chloro-2-methoxyhexafluorocyclopentene with triphenylphosphine. In the latter case the phosphobetaine was obtained in fair yields.

Our experimental approach was devised from a recent communication which illustrates the use of acetic acid and water for the preparation of the betaine 1-(3,3,4,4-tetrafluoro-2-hydroxy-5-oxo-1-cyclopenten-1-yl)pyridinium hydroxide, inner salt.[3] By adopting this procedure for our own work we were able to prepare various phosphobetaines in fair to excellent yields depending on the particular olefinic substrate.

Reactions Studied.—Although the reaction of several tertiary phosphines are included in this paper, only triphenylphosphine was extensively investigated with all of the halo olefins studied in this paper. These olefins include 1,2-dichlorooctafluorocyclohexene, 1,2-dichlorohexafluorocyclopentene, 1,2-dichlorotetrafluorocyclobutene, perfluorocyclohexene, perfluorocyclopentene, and perfluorocyclobutene. In the 1,2-dichloro series an interesting but not altogether unexpected trend was observed. The cyclobutene derivative was by far the most reactive, followed by the cyclopentene as depicted in Figure 1. The cyclohexene derivative does not give any phosphobetaine under these reaction conditions. Instead, only triphenylphosphine oxide and tars are found. Even under more strenuous conditions, using an auto-clave at temperatures above 125° under a slight nitrogen atmosphere, identical results were observed. In the perfluoro series a similar trend was observed, where perfluorocyclobutene and perfluorocyclopentene reacted readily, and perfluorocyclohexene remained unreacted. No effort was made to compare the reactivities of the 1,2-dichloro and perfluoro cyclic olefins.

A plausible explanation for this observed deviation can be rationalized from Table I.[4] This shows a noticeable reduction of the double-bond strain in cyclohexene. By applying this reasoning to the perhalo olefins it becomes apparent why the six-membered cyclic compounds are less reactive than the corresponding four-, five-, and seven-membered compounds. Although this

TABLE I

Ring size	Excess strain of cyclo olefin, kcal/mol
C_3	54.3
C_4	
C_5	5.9
C_6	0
C_7	5.2

(1) A. W. Frank, *J. Org. Chem.*, **30**, 3663 (1965).

(2) F. H. Megson, M. T. Beachem, and R. F. Stockel, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 11P.

(3) S. E. Ellzey, Jr., and W. A. Guece, *J. Org. Chem.*, **31**, 1300 (1966).

(4) N. S. Zefirov and V. I. Sokolov, *Russ. Chem. Rev.*, **36** (2), 90 (1967).

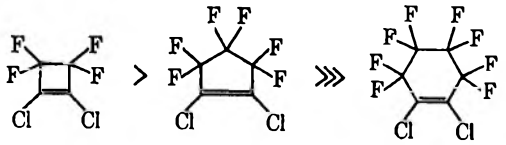


Figure 1.

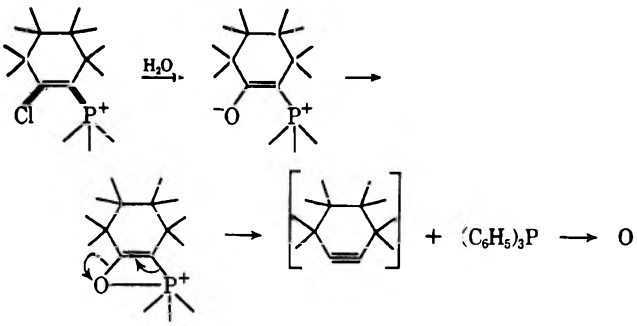


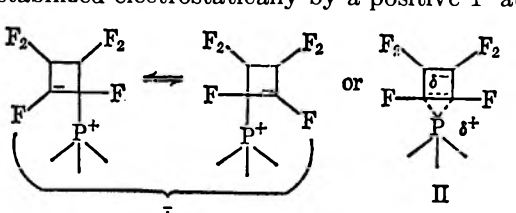
Figure 2.

order is in contrast to the scheme of *I* strain,[5] a number of cyclic systems have been studied which show this trend.[6,7]

An alternate possibility which cannot be ruled out because of the observed facts involves the intervention of a intramolecular Wittig reaction.[8] In this case the six-membered ring, more so than the other homologs, is ideally set up sterically and electronically for this possibility. This would lead to an extremely reactive cyclohexyne intermediate as illustrated in Figure 2, which would result in a variety of products. Thus far trapping experiments have failed to reveal the presence of this species.

During the course of this study we were able to isolate under anhydrous conditions a 1:1 adduct of perfluorocyclobutene and triphenylphosphine. Recent investigators have been trying to prove that that carbanions are the first formed intermediates in the reactions of nucleophiles with perhalo olefins. In certain cases it appears that the stability of the postulated initial intermediate carbanion influences the reaction path,[9] while in other examples this apparently is not so important as other factors.[10] However, the formation of a carbanion as the first step has been a hypothesis up to the present time, and no experimental proof existed.

The 1:1 adduct which we have succeeded in isolating can perhaps be best explained by an equilibrating 1,3-dipolar species I, although a nonclassical structure II cannot be excluded. We feel that this lends credibility to the carbanion mechanism. In a sense this is a carbanion stabilized electrostatically by a positive P atom.



I II

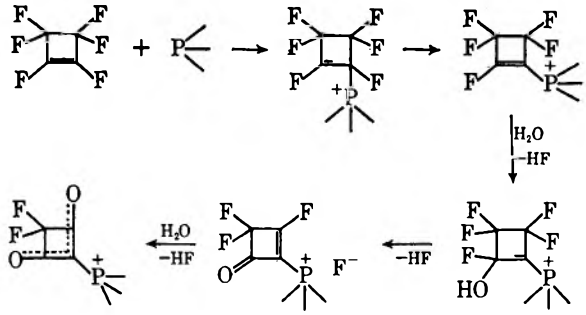


Figure 3.

Structure assignment of the adduct is based on analytical results and ir and nmr spectroscopic data. The ^1H spectrum [$(CH_3)_4Si$ as the internal standard] shows only aromatic absorption. The ^{31}P spectrum [$(CH_3CH_2)_3PO_4$ as the internal standard] shows a broad peak at -5.6 ppm, which is in the correct region for a tetravalent positively charged phosphorus atom.[11] In fact this value is very close to that found for the phosphobetaine product of this adduct. The ^{19}F nmr spectrum (CCl_3F as the internal standard) shows two clusters of peaks at ϕ 86.1 and 124.2. Using allyl trifluoroacetate as an internal standard the H:F(86.1):F(124.2) ratio is 15:4:2. These multiplets give symmetrical spin-coupling patterns, but the coupling constants could not be measured because of their complexity.

Further probes in the area of ^{19}F nmr studies are currently in progress. These include low-temperature examination and a study involving computer analysis. We hope to report shortly on these findings as soon as meaningful information is ascertained.

Supplementary proof is derived from the analysis of $C_{22}H_{15}F_6P$ (*Anal.* Calcd: C, 62.26, H, 3.53; P, 7.31. Found: C, 62.75; H, 3.55; P, 7.50.) and the ir spectrum. The latter gives strong bands[12] at 7.0, 13.22, and 14.54 μ due to P-phenyl, and strong bands at 8 μ due to the CF_2 absorption. There was no absorption centered around 1665 cm^{-1} due to the O=C=C=C=O functional group.[13] Final support is the ease in which the 1:1 adduct readily reacts with water to give the phosphobetaine II.

Analogously, tributylphosphine and butylidiphenylphosphine give the corresponding betaines with DCHFC in comparable yields as indicated in Table II p. 4396.

Reaction Mechanism.—The 1:1 adduct supports an addition–elimination path similar to that of other nucleophiles studied using this substrate. However, in this instance the addition product happens to be isolable as has been found with some alicyclic perhalo olefins. Even when excess phosphine is present the major product is still the phosphobetaine. This is in sharp contrast to other nucleophiles studied on these halo olefin substrates. With perfluorocycloalkenes, the products are 1,2 disubstituted.[14,15] The same types

(5) H. C. Brown, *Rec. Chem. Progr.*, **14**, 83 (1953).
(6) K. Ziegler and H. Froitzheim-Kühlhorn, *Ann.*, **589**, 157 (1954).
(7) J. G. Traynham and M. F. Sehnert, *J. Amer. Chem. Soc.*, **78**, 4024 (1956).
(8) A. Maercker, *Org. Reactions*, **14**, 378 (1965).
(9) J. D. Park, J. R. Lacher, and J. R. Dick, *J. Org. Chem.*, **31**, 1116 (1966).
(10) D. J. Burton and R. L. Johnson, *Tetrahedron Lett.*, 2681 (1966).
(11) K. Moedritzer, L. Maier, and L. C. D. Groenevegh, *J. Chem. Eng. Data*, **7**, 310 (1962).
(12) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964.
(13) R. F. Stockel, M. T. Beachem, and F. H. Megson, *J. Org. Chem.*, **30**, 1629 (1965).
(14) J. D. Parks, M. L. Sharrah, and J. R. Lacher, *J. Amer. Chem. Soc.* **71**, 2337 (1949).
(15) R. F. Stockel, M. T. Beachem, and F. H. Megson, *Can. J. Chem.*, **42**, 2880 (1964).

TABLE II

PHYSICAL DATA ON PHOSPHOBETAINES

Compound	Yield, %	Mp, °C	Ir,[a] μ	Nmr[b]		Anal., % C	H	P
A, 4,4-Difluoro-2-(triphenylphosphoranylidene)-cyclobutane-1,3-dione	42[c]	228–229	5.68	^{31}P −4.1 ppm	Calcd	69.47	3.94	8.15
	60[d]		6.03	^{19}F φ +118.4	Found	69.29	4.10	8.18
$C_{22}H_{15}F_2O_2P$			6.16					
B, 4,4,5,5-Tetrafluoro-2-(triphenylphosphoranylidene)cyclopentane-1,3-dione	81[e]	173–174	5.85	^{31}P −10.2 ppm	Calcd	64.18	3.48	7.20
	75[f]		5.98	^{19}F φ +128.3	Found	64.1	3.46	7.18
$C_{23}H_{15}F_4O_2P$			6.10					
C, 4,4,5,5-Tetrafluoro-2-(butyldiphenylphosphoranylidene)cyclopentane-1,3-dione	72[g]	148–149	5.82	^{31}P −12.8 ppm	Calcd	61.46	4.63	7.56
			5.95	^{19}F φ +128.5	Found	61.46	4.68	7.61
$C_{21}H_{19}F_4O_2P$			6.08					
D, 4,4,5,5-Tetrafluoro-2-(tributylphosphoranylidene)cyclopentane-1,3-dione	60[h]	68–69	5.75	^{31}P −21.7 ppm	Calcd	55.13	7.28	8.38
			5.85	^{19}F φ +128.4	Found	54.90	7.31	8.37
$C_{17}H_{27}F_4O_2P$			6.08					

[a] Mineral oil mulls on a Perkin-Elmer Model 317 spectrophotometer. [b] Varian HR-60 compounds were measured as 10% solutions, F in $CFCl_3$, and P in $(Et)_3PO_4$ as internal standards. [c] Reactants: triphenylphosphine and 1,2-dichlorotetrafluorocyclobutene. [d] Reactants: triphenylphosphine and perfluorocyclobutene. [e] Reactants: triphenylphosphine and 1,2-dichlorohexafluorocyclopentene. [f] Reactants: triphenylphosphine and perfluorocyclopentene. [g] Reactants: butyldiphenylphosphine and 1,2-dichlorohexafluorocyclopentene. [h] Reactants: tributylphosphine and 1,2-dichlorohexafluorocyclopentene.

of disubstituted products are observed with 1,2-dichlorofluorocycloalkenes when the nucleophiles are phosphorus, sulfur, and arsenic,[16] but otherwise these latter types of olefins give 1,3,3-trisubstituted derivatives.[17,18] The reason for this difference with phosphines is probably due to electronic and steric factors. Once the initial addition–elimination is complete C-2 becomes susceptible to attack by water because of the positive phosphorus atom. Furthermore this course of events are probably the only possibility that could occur because additional attack by phosphine would be inhibited at C-1 or C-2 due to steric hindrance. Finally water reacts a second time at C-4 to give the final stable phosphobetaine. See Figure 3.

Recent studies indicate that once the initial carbanion is formed elimination can occur at two different sites.[19,20] The mode of elimination depends on the effect which the α substituents have on the stability of the carbanion.[9,21] In our studies, the elimination of the halogen vicinal to the phosphorus atom appears to be the predominant leaving group. This is actually what one would predict.

Physical Data.—Nuclear magnetic resonance confirms the assigned structures of the betaines prepared. The ^{31}P signal in all cases is of the right field strength expected from a tetravalent phosphorous atom.[11] Furthermore the ^{19}F nmr complements the proposed structure by indicating the equivalency of the fluorine atoms due to the molecules symmetry.

The ir spectra are also diagnostic because of the characteristic O=C=C=C=O system.[13] In each case three bands are evident as shown in Table II. Actually, four bands should be present due to the two C=O and two C=C bands; however, one of these centered around 8 μ is not observed owing to C—F absorption. Other bands observed were due to P-phenyl, 7.0, 13.22, and 14.54 μ;[12] however, in the case of the tributyl derivative the band at 6.82 μ is blocked out by the mineral oil.

The microanalyses for C, H, and P were all satisfactory.

The ability of a compound to exist in at least two distinctly different crystalline phases is actually a common occurrence in organic chemistry. However, unlike most polymorphic compounds, crystals of B in Table I show two phases stable below the melting point, and two quite different phases are obtained on cooling the melt. Table III lists transition temperatures for the polymorphs of B. Further microscopic investigation is in progress with similar type compounds.

TABLE III

Polymorphic form	Transition temp, °C
1 → 2	164–168
2	178–179, melts
3 → 4	124.0–124.5
4	181–182, melts

Experimental Section

General Procedure for the Preparation of Betaines.—Equivalent amounts of phosphine and halo olefin (usually 0.1 mol were used) were added to 100 ml of glacial acetic acid and 10 ml of water. (Similar results are obtained with commercial DMF). The solution was refluxed from 8–15 hr. After the reflux 300 ml of water was added, which caused precipitation. The precipitate was then recrystallized from methanol–water.

The Preparation of the 1:1 Adduct of Perfluorocyclobutene and Triphenylphosphine.—Into a three-necked flask equipped with a Dry Ice–acetone condenser was added 20 g (excess) of perfluorobutene. Then with stirring 26 g (0.1 mol) of triphenylphosphine dissolved in 150 ml of ethyl ether which was added to the flask. A white precipitate immediately was formed. This was filtered off and washed with more ethyl ether. Approximately 42 g of the adduct was isolated.

Registry No.—I, 17447-55-1; Table II—A, 17447-51-7; B, 17447-52-8; C, 17447-53-9; D, 17447-54-0.

Acknowledgment.—The authors wish to acknowledge the assistance of Dr. J. E. Lancaster and Mrs. M. Neglia for the fluorine, phosphorus, and hydrogen nmr spectra. The authors are also grateful to Dr. A. Mohan for his helpful discussions concerning the perfluorocyclobutene–triphenylphosphine adduct and to Mr. R. E. Stevens for the microscopic analysis.

(16) W. R. Cullen, D. S. Dawson, and P. S. Dhaliwal, *ibid.*, **45**, 683 (1967).
(17) J. D. Park, C. M. Snow, and J. R. Lacher, *J. Amer. Chem. Soc.*, **73**, 2342 (1951).
(18) A. L. Henne and K. A. Latif, *J. Indian Chem. Soc.*, **30**, 809 (1953).
(19) A. B. Clayton, J. Roylance, D. R. Sayers, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 7358 (1965).
(20) W. J. Feast, D. R. A. Perry, and R. Stephens, *Tetrahedron*, **22**, 433 (1966).
(21) J. D. Park, R. J. McMurtry, and R. Sullivan, *J. Org. Chem.*, **33**, 33 (1968).

Oxidation of s-Dodecahydrotriphenylene with Peroxytrifluoracetic Acid–Boron Fluoride and the Photoisomerization of the Resulting Cyclohexadienones[1]

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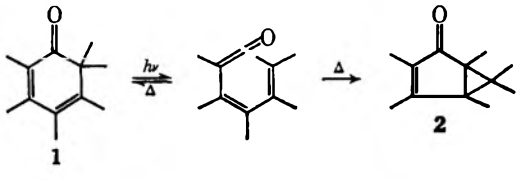
Received June 24, 1968

Oxidation of symmetrical dodecahydrotriphenylene (**3**) with peroxytrifluoroacetic acid and boron fluoride etherate at 0° afforded cross-conjugated cyclohexadienone **4** rather than the anticipated conjugated dienone **5**. At −65°, however, both dienones were produced. Dienone **5** isomerized to **4** unusually rapidly (when compared with similar hexaalkyl-2,4-cyclohexadienones) in the presence of trifluoroacetic acid. Irradiation of cross-conjugated dienone **4** in methanol gave the bicyclo[3.1.0]hexenone **9**, but in ether **4** or **9** were further converted into the conjugated dienone **5**. Possible reasons for the difference between the photochemical behavior of these fused ring dienones and that of the related hexaalkyldienones are discussed.

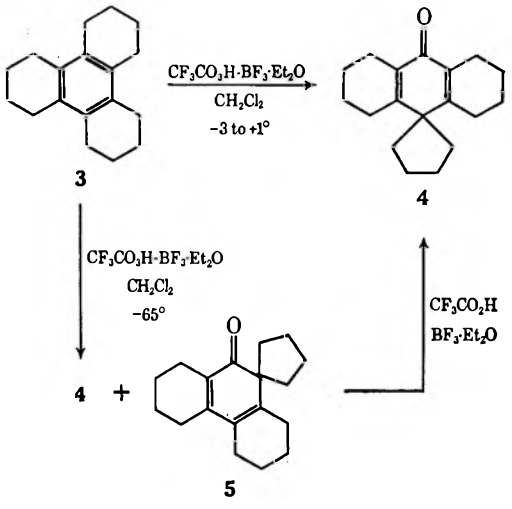
Peroxytrifluoroacetic acid–boron fluoride has proved to be an excellent electrophilic oxidizing agent which can convert aromatic compound directly into phenols,[3] alkenes into ketones[1] and certain aromatics into 2,4-cyclohexadienones.[4] In the present work, our goal was to extend this reaction to the preparation of a 6-spiro-2,4-cyclohexadienone, and to investigate its photoisomerization. It is now known[5] that hexamethyl-2,4-cyclohexadienone (**1**) photoisomerizes to a ketene which, in the absence of a strong nucleophile, thermally



rearranges either to the starting dienone or to a bicyclo-[3.1.0]hexenone (**2**). These thermal reactions of the diene–ketene are influenced, amongst other factors, by the substituents, although our present state of knowledge about the reaction does not permit many predictions. We were interested in determining whether the spirodienone **5** behaved photochemically in a manner analogous to that of the hexamethyl- (and hexaethyl-[4b]) dienones.

Oxidation Studies.—s-Dodecahydrotriphenylene (**3**) is readily available through the trimerization of cyclohexanone.[6] A methylene chloride solution of **3** was oxidized at −3 to +1°, using a more than 100% excess of peroxytrifluoroacetic acid and 47% boron fluoride etherate. Under these conditions, all of the starting material was consumed, which simplified product isolation. There was obtained in 45% yield a crystalline product, mp 115–117°, which was not the desired 6-spiro compound, but whose structure is considered to be that of the 4-spiro-2,5-dienone **4**.[7]

SCHEME I



The structure of **4** follows from its analysis, spectral properties, and mode of formation (Scheme I). Spectroscopic data are summarized in Table I.

TABLE I

SPECTRAL PROPERTIES OF THE DIENONES

Compd	Nmr spectra: Chemical shift[a]	Assignment[b]	Ir spectra[c]: $\nu_{C=O}$, cm^{-1}	$\nu_{C=C}$, cm^{-1}	Ultraviolet spectra[d]: λ, mμ	ε
4	7.79	Allylic methylenes	1655	1627	253	18,300
	8.17	Spiro ring methylenes			280 (sh)	6,800
	8.40	Nonallylic methylenes in six-membered rings				
5	7.78	Allylic methylenes	1644	1580	332	5,100
	8.37	All remaining protons				

[a] Measured in CCl_4, relative to TMS as an internal reference. [b] All areas are consistent with the assignments. [c] Measured in CCl_4 solution; calibrated against polystyrene. [d] In methanol.

The ultraviolet absorption maximum and conjugated C=O and C=C absorptions in the infrared spectrum are consistent with the assigned structure and are typical for 2,5-cyclohexadienones.[8] In particular, the uv maximum appears at much shorter wavelength than would be expected for the anticipated 2,4-cyclohexadienone **5**. The uv maximum of **4** does appear, however, at a slightly higher wavelength than has been reported for other 2,5-cyclohexadienones,[8] but this can

(1) Paper X in a series on oxidations with peroxytrifluoracetic acid–boron fluoride; for paper IX, see H. Hart and L. Lerner, *J. Org. Chem.*, **32**, 2669 (1967).

(2) Taken from the M.S. Thesis of D. C. L., Michigan State University, 1967.

(3) C. A. Buehler and H. Hart, *J. Amer. Chem. Soc.*, **85**, 2177 (1963); H. Hart and C. A. Buehler, *J. Org. Chem.*, **29**, 2397 (1964); H. Hart, C. A. Buehler, A. J. Waring, and S. Meyerson, *ibid.*, **30**, 331 (1965).

(4) (a) A. J. Waring and H. Hart, *J. Amer. Chem. Soc.*, **86**, 1454 (1964); (b) H. Hart, P. M. Collins, and A. J. Waring, *ibid.*, **88**, 1005 (1966); (c) H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966); (d) P. M. Collins and H. Hart, *J. Chem. Soc.*, 895 (1967); (e) H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, **32**, 2448 (1967).

(5) J. Griffiths and H. Hart, *J. Amer. Chem. Soc.*, **90**, 3297 (1968).

(6) C. Mannich, *Chem. Ber.*, **40**, 153 (1906).

(7) Named spiro[1,2,3,4,5,6,7,8,9,10-decahydroanthracen-10-one-9,1′-cyclopentane]; see "Definitive Rules for Nomenclature of Organic Chemistry," *J. Amer. Chem. Soc.*, **82**, 5545 (1960).

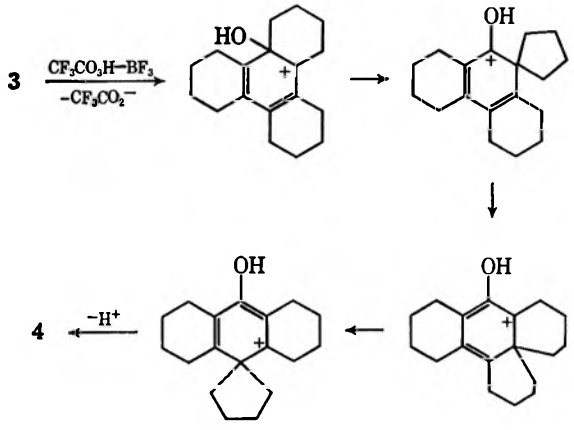
(8) A. J. Waring, *Advan. Alicyclic Chem.*, **1**, 184 (1966).

readily be accounted for by comparison with model compounds.[9-12]

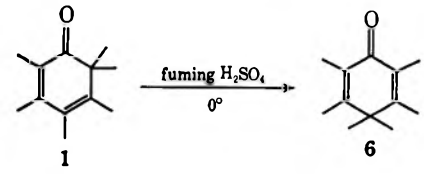
The nmr spectrum of **4** consists of three rather broad and unstructured bands, equal in area. The lowest field band (τ 7.79) is assigned to the allylic methylene protons.[13] The high-field band (τ 8.40) is due to the remaining protons in the six-membered ring, whereas the protons in the spiro five-membered ring appear at τ 8.17.[14]

This the first case we have observed where the major product of aromatic oxidation is a 2,5- rather than a 2,4-cyclohexadienone. Even hexaethylbenzene, which is closely related structurally to **3**, but without the "ears" pinned back, gave only the conjugated dienone.[4b] It is likely that **4** is formed by a sequence of three Wagner–Meerwein rearrangements as shown in Scheme II. Normally the carbonium ion from the first of

SCHEME II



these migrations would be expected to lose a proton to give conjugated dienone **5**. With hexamethyl-2,4-cyclohexadienone, further rearrangement to the 2,5-dienone is not observed under oxidation conditions, although the rearrangement can be brought about by concentrated (and more rapidly by fuming) sulfuric acid.[12] For some reason, in the present instance, further migrations occur in preference to proton loss.

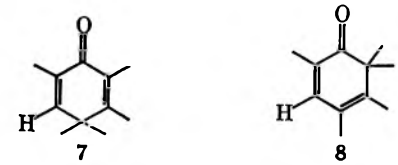


To provide support for this mechanism, the oxidation was carried out at a lower temperature, with the hope that the conjugated dienone might be isolated. When **3** was oxidized at -67 to $-65°$, there was obtained, in addition to unchanged **3** and 2,5-dienone **4**, a third product which proved to be the desired conjugated dienone **5**. It was isolated by preparative thin layer chromatography, and, though the yield was not determined, substantial amounts were produced.

The structure of **5** follows from its spectral properties (see Table I), mode of formation, and reactions. Elemental analysis and mass spectrum confirm that the product is an isomer of **4**. The uv and ir data are typical for a 2,4-cyclohexadienone.[8] In the nmr spectrum, the spiro five-membered ring protons have shifted upfield relative to their position in the spectrum of **4**.[15] Thus there are only two broad bands centered at τ 7.78 and 8.37, assigned to the allylic protons and all the remaining methylene protons, respectively.

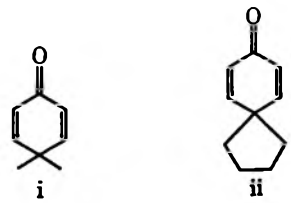
To seek evidence that protonated **5** is an intermediate in the formation of **4** when the oxidation is performed at 0° or above, samples of **5** were treated, in separate experiments, with either boron fluoride etherate or trifluoroacetic acid in methylene chloride at room temperature. Rearrangement of **5** → **4** was complete in 3 hr and in 20 min, respectively. Thus protonic acids are more effective than Lewis acids in bringing about the rearrangement, and the results are consistent with the proposed Scheme II.

At the moment, we have no satisfactory explanation for the fact that **5** rearranges to a cross-conjugated dienone so much more rapidly than **1** or its hexaethyl analog. The only related observation is the formation of **7** (7% yield) as a minor product during the oxidation of pentamethylbenzene.[4d] Presumably the precursor is **8**, one of the major oxidation products.



Photochemical Studies.—Since it was difficult to obtain appreciable quantities of the conjugated spirodienone **5** directly from the oxidation of s-dodecahydrotriphenylene (*vide supra*), we first studied the photoisomerization of the more readily available cross-conjugated dienone **4**. Irradiation of **4** in methanol using a Vycor filter lead to a smooth and steady decrease in the absorption at 253 mμ and the appearance of three new maxima. The photoproduct is considered

(9) The maxima of i and ii appear at 234.5[10] and 242 mμ,[11] respectively. The difference, 7.5 mμ, is attributed to the spiro ring.[8] If this value is added



to 246 mμ reported[12] for **6**, one predicts a λ_{max} of 253.5 mμ for a tetraalkylspirodienone such as **4**. Agreement with the experimental value (Table I) is excellent.

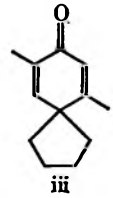
(10) E. W. Garbisch, *J. Org. Chem.*, **30**, 2109 (1963).

(11) S. Winstein and R. Baird, *J. Amer. Chem. Soc.*, **84**, 788 (1962).

(12) H. Hart and D. W. Swatton, *ibid.*, **89**, 1874 (1967).

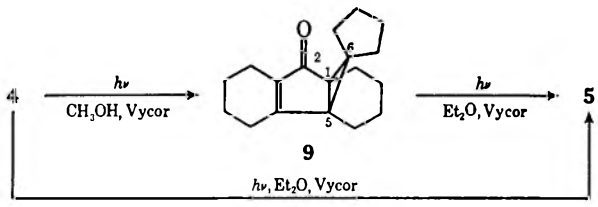
(13) D. W. Mathieson, "Interpretation of Organic Spectra," Academic Press, New York, N. Y., 1965, pp 51–58.

(14) The spiro protons in ii appear as a weakly split singlet at τ 8.17 (S. Winstein, private communication); similarly, those in iii occur as a narrow band at τ 8.13 (P. J. Kropp, private communication).



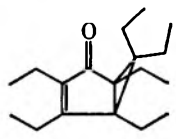
(15) A similar upfield shift, from τ 8.79 to 8.89, is observed in the *gem*-dimethyl group of **1** relative to **6**.

SCHEME III



to be **9**, spiro[tetracyclo[7.4.1.0^{1,9}0^{3,8}]tetradec-3-en-2-one-14,1′-cyclopentane] (Scheme III).

The structure of **9** rests on its spectral properties, method of synthesis, and further conversions. The mass spectrum showed a parent peak at *m/e* 256, consistent with formulation of **9** as an isomer of **4**. The carbonyl and carbon–carbon double bond bands at 1685 and 1639 cm^{-1}, respectively, may be compared with similar bands at 1680 and 1638 cm^{-1} reported for the closely related **10**.[4b] The ultraviolet spectrum of **9** [λ_{max} 240 mμ (ε 6440), 275 (2735), and 330 (580)]



10

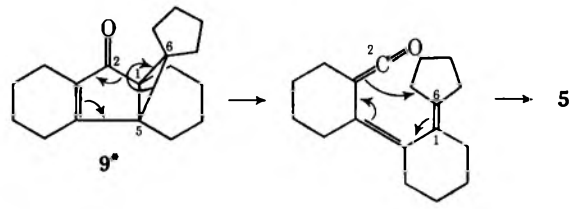
also closely resembles that of **10** [λ_{max} 239 mμ (ε 5300), 270 (2660), 332 (850)]. The nmr spectrum of **9** was complex and not helpful in the structural assignment. The formation of **9** from **4** has ample precedent.[16]

Compound **9** was relatively inert to further irradiation in methanol; *i.e.*, it was a simple matter to obtain **9** in high yield from **4** without having to be overcautious about the irradiation time. Irradiation of **9** in ether, however, proceeded smoothly; the bands at 240 and 275 mμ diminished in intensity, and the band at 330 mμ grew and shifted slightly. The reaction was worked up after the band at 332 mμ reached maximum intensity. The crystalline product was the conjugated dienone **5**. The same product was obtained by irradiation of **4** in ether, and, if this photoisomerization was monitored by uv, **9** could be detected as an intermediate. The structure of **5** was established by comparison with an authentic sample prepared by the low temperature oxidation of *s*-dodecahydrotriphenylene.

Continued irradiation of **5** in ether resulted in a gradual decay of the band at 332 mμ until eventually the only remaining band of any significance had a maximum at 205 mμ. The product had ir bands at 1720 and 1705 cm^{-1}. The ir data suggest that the product was an acid,[17] probably from reaction of the diene–ketene with water present in the ether used as solvent.

The contrast between the photochemical reactions in the hexamethyldienone series (**1**, **2**, and **6**) and the fused ring series (**4**, **5**, and **9**) is striking. Whereas the conjugated dienone **1** is converted into bicyclic ketone **2**, the analogous ketone **9** is under similar conditions, converted into the conjugated dienone **5**. The reasons for this difference are not yet clear, but several features of the reactions are worth noting. Whereas the conversion **1** → **2** is favored by polar solvents,[4b,5] the reverse type of reaction, **9** → **5**, proceeds only very slowly in methanol and is particularly favored by nonpolar solvents. The effect is sufficiently large that the photolysis of **4** to either **9** or **5** can be controlled by choice of solvent.

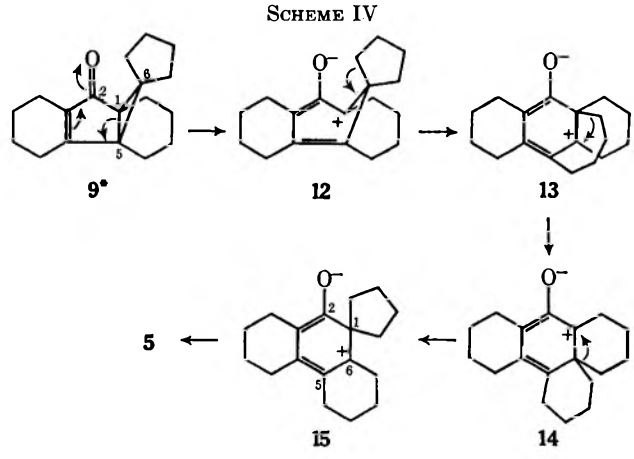
There are several alternative mechanisms which one can envision for the photochemical conversion of **9** → **5**. Perhaps the most plausible is the isomerization of an excited state of **9** (**9***) to a ketene (**11**), followed by cyclization to **5**.[18] The closure of highly substituted diene–ketenes such as **11** to 2,4-cyclohexadienones in



nonpolar solvents is particularly facile,[5,19] whereas their reaction with nucleophiles can be quite slow.[5,19] In this mechanism the 5,6 bond of the three-membered ring in **9*** is broken. Thus atoms 6 and 1 interchange positions during the reaction (*i.e.*, in **9**, atom 2 is connected to atom 1, whereas, in **5**, atom 2 is connected to atom 6). It is not essential that the ketene be a discrete intermediate to accomplish the same result; cleavage of the 5,6 bond followed by acyl migration and rebonding has the same net effect.

There are several examples in the literature where the exocyclic bond (5,6) of a bicyclo[3.1.0]hexenone breaks in a photochemical reaction,[16,20,21] but much more frequently it is the endocyclic or 1,5 bond which breaks.[16] If this were to happen with **9**, one could envision the sequence given in Scheme IV to complete the

SCHEME IV



reaction. Three Wagner–Meerwein rearrangements follow the initial ring opening (**9*** → **12**). Atoms 2, 1, and 6 which are joined consecutively in **9** remain in the

(16) For a general discussion, see P. J. Kropp in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, Inc., New York, Chapter 1.

(17) K. Nakanishi, "Practical Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1964, p 43.

(18) For a related example, see J. S. Swenton, E. Saurborn, R. Srinivasan, and F. I. Sonntag, *J. Amer. Chem. Soc.*, **90**, 2990 (1968). In a low temperature study, we have observed a ketene from the irradiation of a tetramethylbicyclo[3.1.0]hexenone; unpublished observation of J. Griffiths and H. Hart.

(19) J. D. Hobson, M. M. Al Holly, and J. R. Malpass, *Chem. Commun.*, 764 (1968).

(20) H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, **84**, 4527 (1962).

(21) B. Miller and H. Margulies, *ibid.*, **89**, 1678 (1967).

same sequence throughout the mechanistic scheme. Thus one could, by a carbon-labeling experiment, distinguish between these alternatives. Only carbon labeling will do, however; the spiro ring in **9** becomes the spiro ring in **5** by either path. Thus the labeling experiment will be quite difficult indeed.

It will be noted that the first intermediate (**12**) in the latter mechanism contains five sp^2 hybridized carbons in a bridged system with six-, seven-, and nine-membered rings. Two of these carbons are at bridgehead positions. Although models of **12** (and **13**, which at first glance also seems unduly strained) can be constructed we currently are inclined to favor a mechanism in which bond 5,6 (rather than 1,5) is broken. One reason for this preference (other than that it is simpler) is that the reaction is favored by nonpolar solvents; this would seem to be inconsistent with the dipolar intermediates **12**–**15**. It may be the strain in **12**, as contrasted with the corresponding intermediate derived from **2**, which causes the two bicyclo[3.1.0]hexenones to exhibit different photochemical behavior.[12,22]

Experimental Section

General Procedures.—Spectra were determined as follows: ir, CCl_4 solution, Unicam SP200; uv, CH_3OH solution, Unicam SP800; nmr, CCl_4 solution, Varian HA-100; mass spectra, CEC21-103C operating at 70 V. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are uncorrected. Analysis by tlc involved 1 × 4 in. microscope slides coated with Brinkmann silica gel H as the adsorbent, eluted with $CHCl_3$ and developed with iodine vapor. Separations by preparative tlc used 8 × 8 in. glass plates coated with Brinkmann silica gel PF_{254}, 2 mm thick, eluted with $CHCl_3$.

Oxidation of s-Dodecahydrotriphenylene (3).[23]—To a cooled, vigorously stirred solution of s-dodecahydrotriphenylene (**3**, 4.59 g, 1.9 × 10^{-2} mol) in 200 ml of methylene chloride was simultaneously added (1) a solution of peroxytrifluoroacetic acid prepared by dissolving trifluoroacetic anhydride (9.0 g, 4.3 × 10^{-2} mol) in 15 ml of methylene chloride, cooling to 0°, and with vigorous stirring adding 1.1 ml of 98% hydrogen peroxide until a homogeneous solution was obtained; (2) 20 ml of distilled 47% boron fluoride etherate. The temperature was maintained at −3 to +1°. Slow addition of the oxidant and acid catalyst was completed after 1.5 hr and the reaction was stirred for an additional 1.5 hr, during which time the temperature rose to 20°. The reaction mixture was analyzed by tlc and it was determined that all of **3** had reacted. The reaction mixture was hydrolyzed with water (200 ml) and the organic layer was successively extracted with two 200-ml portions of water, two 200-ml portions of saturated sodium bicarbonate solution, and two 200-ml portions of water, dried (Na_2SO_4), and concentrated. The residue was dissolved in 20 ml of methanol, concentrated to 5–10 ml, and cooled overnight. Crystallization afforded 2.21 g (45%) of **spiro[1,2,3,4,5,6,7,8,9,10-decahydroanthracen-10-one-9,1′-cyclopentane]**, **4**, mp 115–117°, as colorless crystals. Spectral properties are given in Table I. The compound showed a parent peak in the mass spectrum at *m/e* 256. In several experiments it was necessary to treat the methanol solution with Norit, as the solution was dark and did not lighten during work-up.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found: C, 84.26; H, 9.26.

Low Temperature Oxidation of 3.—To a cooled, vigorously stirred solution of **1** (4.74 g, 1.97 × 10^{-2} mol) in 175 ml of methylene chloride was simultaneously added (1) a solution of peroxytrifluoroacetic acid, made by dissolving trifluoroacetic anhydride (8.7 g, 4.15 × 10^{-2} mol) in 15 ml of methylene chloride, cooling to 0°, and with vigorous stirring adding 98% hydrogen peroxide (2.9 g, 8.3 × 10^{-2} mol) until a homogeneous solution was obtained; (2) 15 ml of distilled 47% boron fluoride etherate. The temperature was maintained at −67 to −65° using a Dry Ice–acetone bath. Addition of the oxidant and acid catalyst was completed in 35 min after which the reaction mixture was immediately hydrolyzed by pouring into 750 ml of cold saturated sodium bicarbonate solution. The organic layer was successively washed with two 300-ml portions of water, two 200-ml portions of saturated sodium bicarbonate solution, and two 200-ml portions of water and dried (Na_2SO_4). The reaction mixture was analyzed by tlc and shown to consist of three components. A portion of the reaction mixture was separated by preparative tlc and the three components were identified. Two were shown to be unreacted **3** and dienone **4** by comparison of tlc R_f values and ir and nmr spectra with those of authentic samples. The third component, obtained as pale yellow crystals, mp 69–71° (MeOH), was **spiro[1,2,3,4,5,6,7,8,9,10-decahydrophenanthrene-10-one-9,-1′-cyclopentane]**, **5**. Spectroscopic data are given in Table I. The compound showed a parent peak in the mass spectrum at *m/e* 256.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found: C, 84.35; H, 9.44.

The Acid-Catalyzed Isomerization of 5 to 4. A. With Trifluoroacetic Acid.—To a stirred solution of **5** (100 mg, 3.9 × 10^{-4} mol) in 30 ml of methylene chloride was added 2 ml of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 45 min. The reaction was monitored by tlc after 5, 10, and 20 min, at which time no detectable trace of **5** could be observed. The mixture was hydrolyzed with 150 ml of water, extracted with two 50-ml portions of saturated sodium bicarbonate solution and two 50-ml portions of water, dried (Na_2SO_4), and concentrated. The residue was dissolved in 5 ml of methanol. Tlc analysis of the methanol solution indicated the presence of only one compound. Crystallization afforded 71.4 mg of **4**. The melting point and spectral properties of the rearrangement product were identical with those of authentic material.

B. With Boron Fluoride Etherate.—To a stirred solution of **5** (100 mg, 3.9 × 10^{-4} mol) in 30 ml of methylene chloride was added 3 ml of distilled 47% boron fluoride etherate. The reaction mixture was stirred at room temperature and monitored by tlc. After 3 hr, no detectable trace of **5** could be observed. The reaction mixture was hydrolyzed with 150 ml of water, the layers were separated, and the organic layer was extracted with two 50-ml portions of water, dried (Na_2SO_4), and concentrated. The residue was dissolved in 5 ml of methanol and analysis of the methanol solution by tlc indicated the presence of only one compound. Crystallization afforded 56.9 mg of **4**, with melting point and spectral properties identical with those of authentic material.

General Photolysis Procedure.—All irradiations were conducted with a Hanovia Type S 200-W mercury vapor lamp placed in a quartz water jacket which was fitted into a Pyrex container of slightly larger diameter. The effective volume of the intervening space, which held the solution being irradiated, was 450 ml. The solution could be agitated with a moderate flow of nitrogen. A Vycor filter was fitted between the lamp and the quartz jacket. The entire system was immersed in a dewar flask filled with cold (15°) water.

Irradiation of 4 in Methanol.—A solution of **4** (691.6 mg, 2.70 mmol) in 400 ml of methanol was irradiated and the reaction was followed by decay of the 253-mμ band. Reaction was complete in 50 min. Overphotolysis for several hours brought about no significant change in the spectrum. The methanol was evaporated, affording 672 mg (97%) of a slightly colored transparent oil which showed only a single spot on tlc, with a different R_f from that of **4**. The product is considered to be **spiro[tetracyclo[7.4.1.0^{1,9}0^{3,8}]tetradec-3-en-2-one-14,1′-cyclopentane]**, **9**.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found: C, 83.11; H, 9.29.[24]

The compound showed a parent peak at *m/e* 256. It had principle ir bands (liquid film) at 1685 and 1639 cm^{-1} and a uv spectrum with maxima [mμ (ε)] at 211 (5950), 240 (6440), 275 (2735), and 330 (580). The nmr spectrum consisted of a broad complex between τ 7 and 9, with principle peaks centered at

(22) We thank one of the referees, who encouraged the somewhat expanded mechanistic discussion presented here, over that in the original manuscript.

(23) Prepared according to ref 6. The nmr spectrum of **3** showed two broad singlets centered at τ 7.55 and 8.3 with areas in the ratio 1:1. These correspond to the benzylic and remaining alicyclic methylenes, respectively.

(24) Analytical samples were purified by tlc or column chromatography; despite several attempts, we could not get a sample which gave an entirely satisfactory carbon analysis.

τ 8.02, 8.43, 8.38 (sh), and 8.72. The peaks overlapped too much to obtain accurate integrations.

Irradiation of 9 in Ether.—A solution of 9 (448.9 mg, 1.78 mmol) in 350 ml of anhydrous ether was irradiated. The photolysis was followed by the appearance of a maximum at 332 mμ, which reached maximum intensity in 2 hr. The ether was evaporated and the residue was dissolved in methanol and concentrated to a volume of 5 ml. On cooling, crystals (347 mg, 77%) of spiro[1,2,3,4,5,6,7,8,9,10-decahydrophenanthren-10-one-9,1′-cyclopentane] (**5**) separated, mp 69–70°. The compound was identical (ir, nmr) with material obtained from the low temperature oxidation of **3**. No other photoproduct was detected (tlc).

Irradiation of 4 in Ether.—A solution of **4** (770.7 mg, 3.00 mmol) in 400 ml of anhydrous ether was irradiated, the reaction being followed by the decay of a maximum at 253 mμ and the appearance of a new band at 332 mμ. After 4.9 hr the latter band reached maximum intensity, and the reaction was terminated. The ether was evaporated, and the residue, taken up in 15 ml of methanol, showed no unreacted **4** and only one product (tlc). The solution was concentrated to 5 ml, cooled, and afforded 438.4 mg (57%) of dienone **5**, identical (melting point, ir, nmr) with an authentic sample. During the photolysis, maxima attributable to **9** appeared, then decayed.

Irradiation of 5.—A solution of **5** (107 mg, 0.42 mmol) in 300 ml of ether was irradiated through a Pyrex filter with a 200-W Hanovia Type S mercury lamp. The photolysis, followed by the disappearance of the band at 332 mμ, was complete in 6.2 hr. Evaporation of the solvent gave an oil different (ir, uv, tlc) from **9**. The oil, which had characteristic ir bands at 3500, 1720, 1705, and 1452 cm^{-1} and λ_{max}^{MeOH} 205 mμ (ϵ 12,300) in the uv, was an acid which was not further characterized.

Dark Reactions.—A solution of dienone **4** (14 mg) in either 5 ml of methanol or 3 ml of ether was stored in the dark for 27 and 36 days, respectively. Analysis by tlc showed that no reaction had occurred, and evaporation of the solvent afforded quantitative recovery of the starting material. Similarly, a solution of **9** (15 mg) in 3 ml of ether kept in the dark for 15 days gave a quantitative recovery of unchanged starting material.

Registry No.—**3**, 1610-39-5; **4**, 17790-43-1; **5**, 17790-44-2; **9**, 17790-45-3; peroxytrifluoroacetic acid–boron fluoride, 17790-46-4.

Acknowledgment.—We are indebted to the National Science Foundation for financial support.

Nitrogen Photochemistry. *syn* and *anti* Isomers of Semicarbazones[1-4]

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The *syn* and *anti* sets of isomers of several different phenyl ketone semicarbazones have been isolated, and the structural formulas have been assigned. Evidence is presented which demonstrates that the phenyl ring is restricted from rotation in the *syn*-phenyl isomers of the semicarbazones as shown by a diminished amount of conjugation of the phenyl group with the imine double bond. The *syn*-phenyl isomers also have a decreased thermal stability, and, with these isomers, the nmr data clearly portrays that one of the hydrogens of the ureido group is strongly shielded by the phenyl ring confirming the structural assignments.

Although the existence of *syn* and *anti* isomers of semicarbazones has been recognized for some time, there are few cases where both isomers of a semicarbazone have been isolated. In these instances, the structural assignments given are open to question. However, from these earlier experiments certain facts have been learned. The early works of Heilbron and Wilson[6] and of Wilson and Macaulay[7] have clearly demonstrated that *syn* and *anti* isomers of semicarbazones exist and can be interconverted by the agency of ultraviolet light.

Another significant contribution to the history of semicarbazones is the work of Ramart-Lucas and Bruzau.[8] Semicarbazones of phenyl ketones were categorized into two types by means of their uv spectra characteristics, *i.e.*, the "forme absorbante" and the "forme transparente." The phenyl ketone semicarbazones studied had uv spectra which nearly superimposed on one of two general type absorption curves (curves a and b, Figure 1). The "forme absorbante" refers to those semicarbazones which absorb at longer wavelengths. Acetophenone, *p*-methylacetophenone, *p*-methoxyacetophenone, and deoxybenzion semicarbazones have uv spectra approximating that of curve a; and α,α-dimethyldeoxybenzoin, β-phenyl-*p*-methylpropiophenone, and β-phenyl-*p*-methoxypropiophenone semicarbazones have spectra similar to that of curve b. The semicarbazone of α-methyldeoxybenzoin is composed of two isomeric forms which were separated by fractional crystallization from the reaction solution. One of the isomers has an uv absorption spectrum similar to that of curve a in Figure 1, and the other to curve b. A conjugated phenylimine structure of the semicarbazone was postulated for the compounds absorbing with longer wavelengths, and either of two nonconjugated cyclic structures were proposed for the other.

A third important contribution to the background of semicarbazones is the nmr studies of Karabatsos, Graham, and Vane.[9] The nmr spectra were obtained from solutions made by dissolving the crystalline isomer mixtures in trifluoroacetic acid. No separation of the isomers was attempted. The relative chemical shielding of the protons on positions adjacent to the semicarbazone substituent (H_α on I) was measured. The necessary assumption was made that the H_α protons *syn* to the ureido group are more shielded than those *anti* to it. The mixtures of isomeric semicarba-

(1) Presented before the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract No. S181.

(2) Taken in part from the Ph.D. Dissertation of D. V. Rao, University of North Dakota, 1965.

(3) Taken in part from the senior thesis of D. D. Hammargren, University of North Dakota, 1967.

(4) This investigation was supported in part by a Public Health Service Research Grant GM 01012-13 from the National Institute of General Medical Sciences, U. S. Public Health Service.

(5) Author to whom requests for reprints should be addressed

(6) I. M. Heilbron and F. J. Wilson, *J. Chem. Soc.*, **101**, 1482; *Chem. Abstr.*, **7**, 331 (1913).

(7) F. J. Wilson and R. M. Macaulay, *J. Chem. Soc.*, **125**, 841 (1924).

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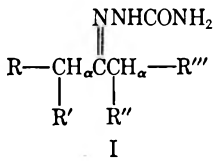
zones all exhibited two absorption bands for the H_α protons, and the relative concentrations of the isomers present in solution could be determined by measuring relative absorption peak areas.

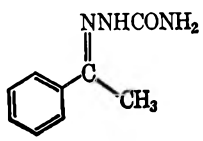


I

Thus, it was evident, on tracing the background of semicarbazone chemistry, that there was a need for the actual isolation of the semicarbazone isomers, and the correlation of the uv spectra studies with the later nmr work. Then more positive statements could be made about the structure of the semicarbazones.

The only structure which is in common to the nmr work of Karabatsos, *et al.*,[9] and the uv spectral work of Ramart-Lucas and Bruzau[8] is acetophenone semicarbazone. Potentially it was a structure which could give the proper answer to the cause of the two types of uv spectra of the phenyl ketone semicarbazones and augment the nmr structural assignments.

The melting point of the crystals (II) which result in the preparation of the semicarbazone from the aceto-



II

phenone and semicarbazide hydrochloride is sharp. These give evidence of being homogenous on analysis with thin layer chromatography. The nmr study of Karabatsos, *et al.*,[9] assigned the concentration of the minor isomer at 10% in a trifluoroacetic acid solution of the crystals. However, since the nmr spectrum was obtained in an acid solution, the major isomer might have equilibrated. As a consequence, isolation of the minor isomer from II was not promising and not attempted.

Hence it was desirable to enrich the acetophenone semicarbazone crystals with the second isomer before attempting the isolation. The uv spectrum of II showed that these were of the longer wavelength absorbing type, *i.e.*, "forme absorbante," in confirmation of the work of Ramart-Lucas and Bruzau[8] (curve a, Figure 1). The second isomer was presumed to be the "forme transparente" or of the shorter wavelength absorbing type (curve b, Figure 1). This is the ideal situation in which the optical pumping principle operates, and irradiation with uv light of the appropriate wavelengths was expected to produce an increased concentration of the second isomer.

Since the irradiation was to be done in liquid solution, the limited solubility of acetophenone semicarbazone in organic solvents was one of the principal problems. Although it was soluble in 95% ethanol, irradiation of this solution produced the undesirable product III, and, as a consequence, ethanol could not be used as a solvent.[10] Anhydrous tetrahydrofuran was chosen

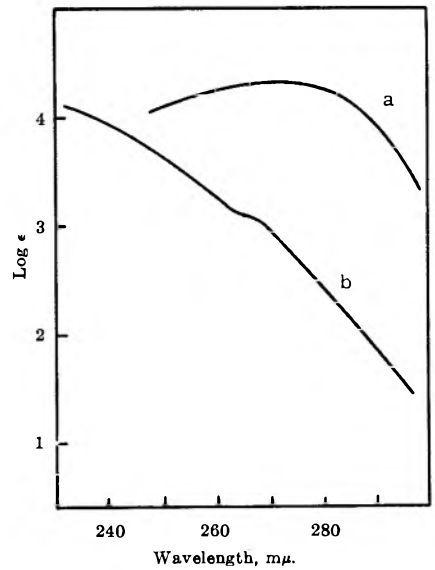
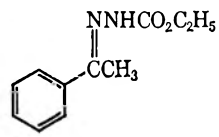


Figure 1.—General shapes of ultraviolet absorption spectra of the two types of phenyl ketone semicarbazones found by Ramart-Lucas and Bruzau.[8] Curve a is the "forme absorbante" and curve b is the "forme transparente."



III

as an alternate because it was one of the better solvents for the semicarbazone though admittedly poor. Because the phenyl ketone semicarbazones have only one principal uv absorption band (Figure 1) and the medium-pressure mercury arc lamps have a diminished amount of light emmision close to 2000 Å where both isomers absorb equally well, the optical pumping irradiations were done without filters.

The acetophenone semicarbazone irradiation solution gave a white crystalline compound (IV) in high yield. This photoproduct gave the correct carbon, hydrogen, and nitrogen analysis for an acetophenone semicarbazone and had the proper molecular weight. The photoproduct readily hydrolyzed to acetophenone with aqueous HCl, and it was converted into the 2,4-dinitrophenylhydrazone of acetophenone by the 2,4-dinitrophenylhydrazine reagent solution. The photoproduct isomerized to the starting semicarbazone at its melting point and upon exposure to anhydrous hydrogen chloride when dissolved in an ether solution. It was more soluble in organic solvents than II. From these data, it was obvious that the photoproduct was chemically not very far removed from the starting material, and that it most probably was the desired isomer of the starting material.

The uv spectrum of IV is exhibited in Figure 2. The photoproduct clearly has a more transparent uv spectrum than the starting material II, and, as expected, the spectrum conformed to the second of the two types (curve b, Figure 1) of uv spectra observed by Ramart-Lucas and Bruzau.[8]

The interpretation of the uv spectra was instrumental in the assignment of the appropriate stereo-

(10) This product can be formed in the solution by heat in the absence of light.

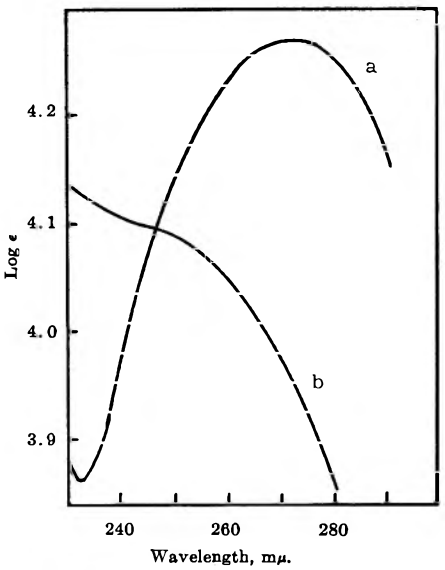
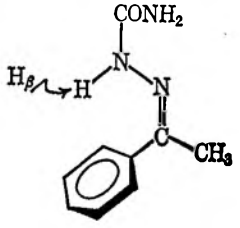


Figure 2.—The ultraviolet spectra of (a) the starting material and (b) the photoproduct of acetophenone semicarbazone.

chemistry to the two isomers. The difference in the absorption between the two isomers is essentially that of the same magnitude difference between the uv maxima of styrene and benzene. This implies that, in the shorter wavelength absorbing isomer IV, the imine bond is not conjugated with the aromatic ring. The uv spectrum of IV can be explained on the basis of steric hindrance. In a study of molecular models, a restricted rotation of the phenyl group in the *syn*-phenyl acetophenone semicarbazone model (IV) was apparent. The π orbital of the imine bond is nearly perpendicular to the π orbitals of the phenyl ring in the model. This



IV

is expected to result in a diminished amount of resonance interaction of the two π-bonded systems, and the molecule should have a uv maximum at a shorter wavelength than the *anti*-phenyl isomer. This is true of the photoproduct; as a consequence, its structure is most probably *syn*-phenyl acetophenone semicarbazone.

syn-Phenyl acetophenone semicarbazone IV should be less stable thermodynamically than the *anti*-phenyl semicarbazone because of steric strain. The equilibration with anhydrous HCl in an ether solution provides the more stable II. This, together with the conversion of the photoproduct IV into starting material II at its melting point, clearly portrays the photoproduct as the least stable of the two isomers. This correlates nicely with the predicted lesser stability of the *syn*-phenyl isomer and supplements the structural assignments based on uv spectral data.

By further observing molecular models of the *syn*-phenyl isomer of acetophenone semicarbazone IV, it was obvious that the ureido group position is such that the NH hydrogen of the NNHCO group (H_β) should be directly over the aromatic ring and immersed in or near the π electrons of the ring. This is a condition in which the proton is expected to be heavily shielded. The same proton in the *anti*-phenyl form does not have such shielding (see structure II). This was expected to influence position of the H_β band on the nmr spectra of the two isomers.

The expectations in regard to the nmr spectra did indeed materialize. The H_β proton of the starting semicarbazone II occurs at δ 9.38 and the H_β of the *syn*-phenyl semicarbazone is δ 7.82, at a difference of 1.56 units. Thus the nmr data further supplements the stereochemical assignments made on the basis of the uv spectral and stability data.

The only remaining feature of acetophenone semicarbazone chemistry to be discussed is the stereochemical assignments made by Karabatsos, *et al.*[9] In trifluoroacetic acid solution it was stated that the *syn*-phenyl isomer IV was present to the extent of 90% and the *anti*-phenyl form at 10%. The hydrogen-bonded structure V was suggested to account for the unexpected results. This assignment was made on the basis that the H_α hydrogens *syn* to the ureido group are *always* more shielded than the H_α hydrogens which are *anti* to it. This assignment we now believe to be open to question.

In tetrahydrofuran, the H_α hydrogens of *anti*-phenyl acetophenone semicarbazone II are shielded slightly more than the *syn*-phenyl form IV. This unexpected result can be attributed to the shielding effect of the phenyl ring on the H_α hydrogens in the *syn*-phenyl isomer. The ring is held in a fairly rigid position, and the H_α protons are affected by the shielding zone of the phenyl ring. This shielding by the aromatic ring is somewhat more pronounced than that of the ureido group. This is most probably true in trifluoroacetic acid solutions also. To check this, *anti*-phenyl acetophenone semicarbazone was dissolved in trifluoroacetic acid, and the sample was allowed ample time to equilibrate. The mixture was quenched by pouring it into water, and the precipitated solid consisted of the *anti*-phenyl isomer of acetophenone semicarbazone as the predominant product. This is a strong indication that the major isomer present in trifluoroacetic acid is the *anti*-phenyl isomer and not the *syn*-phenyl form as previously assigned.[9]

Table I summarizes the nmr data for other semicarbazone isomers isolated in our laboratories. The H_β protons exhibited a chemical shift in the order of $1\frac{1}{2}$ δ units. In every case the compounds which now could be assigned the *syn*-phenyl form on the basis of the uv spectra have the most shielded H_β proton. Since benzophenone semicarbazone must have the *syn*-phenyl form by virtue of its structure, it acts as a standard for the shielded H_β proton. The position of its resonance absorption is in the same vicinity as the other *syn*-phenyl isomers.

Although the two benzaldehyde semicarbazones provide the expected relative chemical shifts of the H_β protons in the nmr spectra, the absolute values are at a lower field than expected. The *anti*-phenyl isomer proton resonance frequency is at lower field possibly because of the relative shielding ability of the hydrogen in comparison with other substituents attached opposite on the imine group.

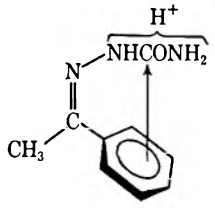
TABLE I
SEMICARBAZONE NMR BANDS

	Semicarbazone	Hβ (δ)	Hα (δ)
1	Benzaldehyde (*syn*-phenyl)	9.09[a,c]	
2	(*anti*-phenyl)	10.33[a,c]	
3	Acetophenone (*syn*-phenyl)	7.82[b,c]	2.20[b,c]
4	(*anti*-phenyl)	9.38[b,c]	2.21[b,c]
5	α-Methyldeoxybenzoin (*syn*-phenyl)	7.67[a,d]	4.02[b,d]
6	(*anti*-phenyl)	9.50[a,d]	4.83[b,c]
7	Deoxybenzoin (*anti*-phenyl)	9.85[a,c]	4.29[b,c]
8	Benzophenone	7.87[b,c]	

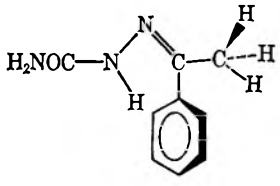
[a] Recorded in DMSO. [b] Recorded in DMSO-d_6. [c] Recorded at ambient temperature. [d] Recorded at 40°.

The reason for the *syn*-phenyl isomer proton resonance being at lower field is more complex. In view of the fact that the difference in the uv spectra of benzaldehyde semicarbazone isomers (Figure 3) is less pronounced than that of either the two isomers of acetophenone or α-methyldeoxybenzoin semicarbazones, the implication is strong that both the ureido group and the third substituent on the imine group, *i.e.*, the hydrogen in this case, are instrumental in restricting the movement of the phenyl ring in the *syn*-phenyl isomers (VI). This is further implied by the fact that the H_α's are shielded in the *anti*-phenyl isomer of acetophenone semicarbazone, a measure of the interaction of the methyl group with the π orbitals of the aromatic ring. When the third substituent is small such as a hydrogen atom in the case of *syn*-phenyl benzaldehyde semicarbazone, the phenyl ring has less restriction to movement, and this allows more resonance interaction of the aromatic ring with the amine bond.

The photochemical conversion of *anti*-phenyl benzaldehyde semicarbazone into the *syn*-phenyl isomer is complicated by a competing side reaction. Products which incorporate solvent molecules are found in the reaction solution. This implies a second reaction pathway occurring where the imino hydrogen atom is lost to the medium.



V



VI

Experimental Section

The nmr spectra were done on an A-60 machine and the uv spectra were made using a Bausch and Lomb Spectronic 505. The melting points are uncorrected. The photochemical lamps used were 140 and 550-W medium-pressure Hanovia mercury arc lamps. The yields are corrected for recovered starting material.

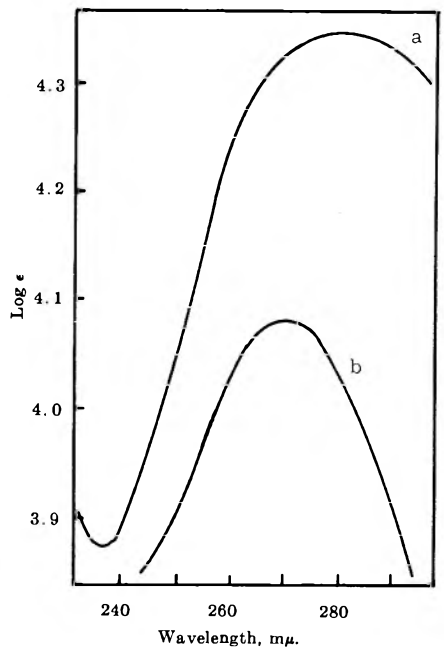


Figure 3.—The ultraviolet spectra of (a) the starting material and (b) the photoproduct of benzaldehyde semicarbazone.

Irradiation of Acetophenone Semicarbazone II in Tetrahydrofuran.—Acetophenone semicarbazone (5.0 g), mp 217–218°, in 200 ml of anhydrous tetrahydrofuran was placed in a quartz round-bottomed flask provided with a condenser and an inlet tube for nitrogen. The solution was deoxygenated for 5 min with a nitrogen stream and then irradiated with a 140-W mercury arc lamp for 24 hr. A white crystalline solid IV separated upon cooling which showed two spots on thin-layer chromatography. The solvent was carefully distilled off and the crystalline solid thus obtained also showed two spots on tlc. These two fractions were combined and continually extracted (24 hr) on a steam bath with a Soxhlet extracter using Skellysolve B as the solvent. The white solid that precipitated out from Skellysolve B was recrystallized from aqueous alcohol to give 2.3 g (85.1% yield), provided an analytical sample: mp 173.5–174.5°; λ_{max} (95% ethanol) 240 mμ (ε 12,640); ir (chloroform) 2.81, 2.94, and 5.94 μ. A corresponding dark reaction gave only recovered starting material.

Anal. Calcd for $C_9H_{11}N_3O$: C, 60.99; H, 6.26; N, 23.71. Found: C, 60.96; H, 6.31; N, 23.52; mol wt (by Rast method), 190.

Hydrolysis of Photoproduct IV from Acetophenone Semicarbazone.—The photoproduct (100 mg) was refluxed with 25 ml of 10% HCl for 1.5 hr. The solution was cooled and extracted several times with ether. After drying over anhydrous $MgSO_4$, the ether solution was evaporated to give a colorless liquid with an odor resembling that of acetophenone. It was recognized as acetophenone by comparing its retention time with an authentic sample by vpc.

To an alcoholic solution of the liquid was added a few drops of 2,4-dinitrophenylhydrazine solution. This resulted in the separation of an orange crystalline solid. It was filtered and washed with alcohol, mp 249–250°. Mixture melting point with the 2,4-dinitrophenylhydrazone of an authentic sample of acetophenone was undepressed.

Treatment of Photoproduct IV from Acetophenone Semicarbazone with Anhydrous Hydrogen Chloride.—The photoproduct (100 mg) was dissolved in 10 ml of anhydrous ethanol, and a gentle stream of anhydrous hydrogen chloride was bubbled through the solution. A white crystalline solid slowly settled out (0.5 min) which was filtered and washed with a few milliliters of aqueous alcohol, mp 200–201°. Mixture melting point with an authentic sample of acetophenone semicarbazone II was undepressed.

Irradiation of Benzaldehyde Semicarbazone in Tetrahydrofuran.—Benzaldehyde semicarbazone (3.0 g) in 200 ml of anhydrous tetrahydrofuran was irradiated for 24 hr with a 140-W lamp. The resulting solution showed two spots on tlc, one corresponding to the starting material. The filtrate was further concentrated and cooled in the refrigerator, and the precipitated

solid was filtered. Partial melting occurred at about 140° and the semisolid resolidified. The latter crystals had mp 217–218°. The former crystals were dissolved in hot ethanol, and the first crop of crystals that separated out was shown to be a mixture by tlc. The second and third crops were shown to be pure by tlc. They were combined and dissolved in tetrahydrofuran to which Skellysolve B was added dropwise resulting in a precipitation of 0.5 g of a white solid (yield 71.4%). In a previously heated silicone oil bath a small sample of this solid in a capillary was introduced. It melted, then slowly resolidified, and melted at 217–218°: λ_{max} (95% ethanol) 275 mμ (ε 11,860); ir 2.87, 3.05, and 5.94 μ. A corresponding dark reaction produced only starting material.

Anal. Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.82; N, 25.80. Found: C, 58.60; H, 5.69; N, 26.21.

The hydrolysis of the photoproduct of benzaldehyde semicarbazone with aqueous HCl to benzaldehyde and the isomerization of the initially prepared semicarbazone was accomplished in the same manner as described for acetophenone semicarbazone.

Preparation of the Two Semicarbazones of α-Methyldeoxybenzoin.—This was accomplished through the published procedures of Ramart-Lucas and Bruzau.[8]

Acetophenone Semicarbazone in Trifluoroacetic Acid.—Acetophenone semicarbazone (1.2 g) was dissolved in 10.4 g of trifluoroacetic acid. The solution was allowed to stand for 2 hr and then was poured into an ice–water mixture. The white precipitate was filtered immediately with a Büchner funnel, washed with an ice–sodium bicarbonate solution and later with water. The air-dried white solid melted at 194–197°. After recrystallization from 95% ethanol three times, it had the melting point of 201.5–202.0° and the mixture melting point with the starting material was undepressed.

Registry No.—Table I, **1**, 17539-52-5; Table I, **2**, 17539-53-6; Table I, **3**, 17539-54-7; Table I, **4**, 17539-55-8; Table I, **5**, 17539-56-9; Table I, **6**, 17539-57-0; Table I, **7**, 17539-58-1; Table I, **8**, 14066-73-0.

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Reactions of Ynamines

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Reactions of ynamines with acidic carbon compounds such as malononitrile and ethyl cyanoacetate gave cyanoenamines, whereas acidic nitrogen compounds such as arylsulfonamides gave saturated amidines. The condensation of several arylsulfonylimides with ynamines and electrocyclic opening of the adducts led to unsaturated amidines while 2-pyridal-*p*-toluenesulfonimide gave a pyrrocoline. Reactions of diphenylketene and dimethylketene with ynamines furnished aminocyclobutenone and four-membered cyclic enol ether products. Similarly, sulfenes and ynamines formed cyclic sulfones. Aryl isocyanates and ynamines gave 4-amino-2-quinolones and 2-amino-4-quinolones. An example of a 1,3 dipolar addition and a reaction with tetraphenylcyclopentadienone, which gave a pentaphenylaniline, are also described.

Ynamine chemistry has been investigated only in the last 4 years and remains largely unexplored. During the course of our studies in this area, preparative methods for this new class of compounds became available,[2–8] and some reactions of these compounds were described.[9–11] This report presents further aspects of ynamine chemistry.

Two of the ynamines used in this work have not been described previously. N,N-dipropylheptynylamine (**1**) was prepared by a displacement reaction from an acetylenic ether,[5] whereas N,N-diethylcarbomethoxyethynylamine (**2**) was obtained from N,N-diethyltrichlorovinylamine, butyllithium, and methyl chlorocarbonate.

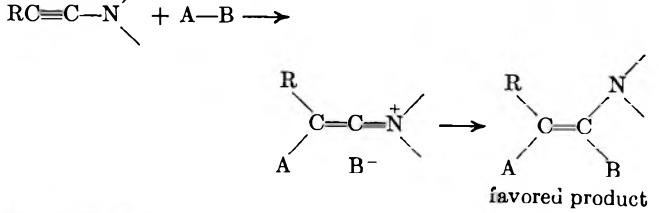
$$CH_3(CH_2)_4C{\equiv}COC_2H_5 \xrightarrow{(C_3H_7)_2NLi} CH_3(CH_2)_4C{\equiv}CN(C_3H_7)_2$$

1

$$Cl_2C{=}CN(C_2H_5)_2 \xrightarrow[ClCO_2CH_3]{BuLi} CH_3O_2CC{\equiv}CN(C_2H_5)_2$$

2

Since electrophilic substitution adjacent to a carboxyl group often presents a serious synthetic obstacle, formal activating derivatives of carboxylic acids, such as ynamines, are of potential synthetic interest. However, ynamines do not parallel enamines in their broad utility for substitution reactions.[12] In contrast to the formation of aliphatic imonium salts, which one obtains on nucleophilic reactions of enamines, energetically less favorable allenic imonium functions are generated by electrophilic attack on ynamines. Thus one can expect ynamines to be less reactive toward monofunctional electrophiles than enamines and to undergo preferentially reactions in which addition takes place at positions α and β to the nitrogen. Ynamines should thus be good substrates for reactions with di-



(1) Alfred P. Sloan Fellow.
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(9) For a summary, see H. G. Viehe, *Angew. Chem.*, **79**, 744 (1967).
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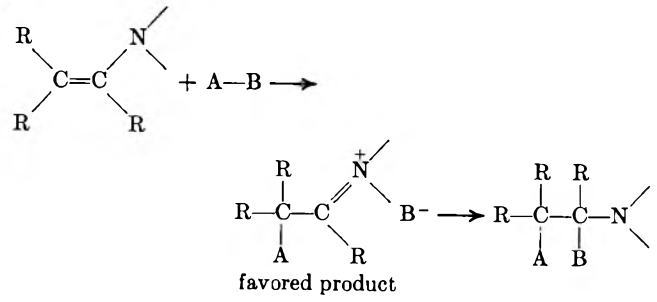
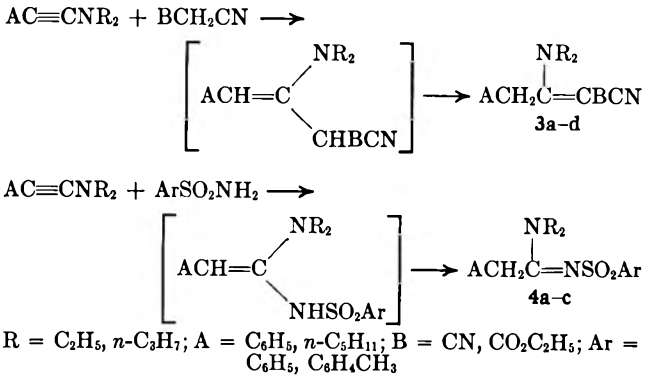
(12) For a summary of enamine chemistry with 630 references, see M. E. Kuehne in "Enamines: Their Synthesis, Structure and Reactions," A. G. Cook, Ed., Marcel Dekker, Inc., New York, N. Y., 1968.



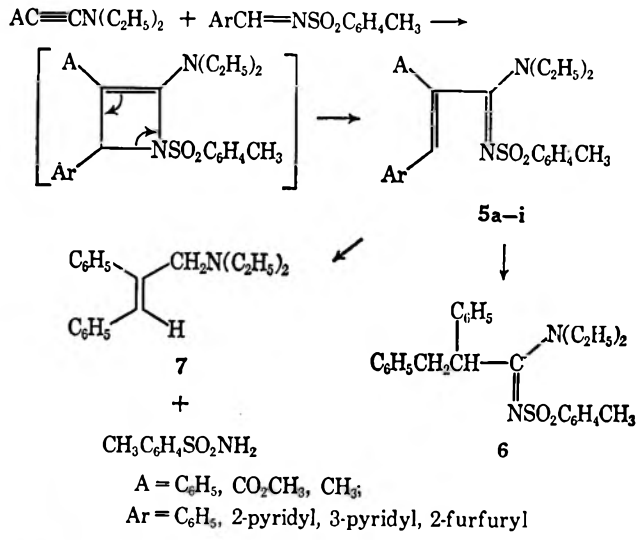
polar or electrically opposing bifunctional molecules, particularly if a concerted addition to the acetylenic system is possible.

The hydration and addition of amines and alcohols to ynamines under acid catalysis has already been described.[9,13] We have found that acidic carbon and nitrogen species will add spontaneously to ynamines to give ketone-related enamines and amidine derivatives, respectively. Thus ethyl cyanoacetate and malononitrile added readily to phenyl- and pentyl-substituted ynamines to give vinylogous cyanamides, **3a–d**, through double-bond rearrangement of the initially formed enamines. Similarly, benzene and *p*-toluenesulfonamides gave adducts which rearranged to arylsulfonamidines, **4a–c**.



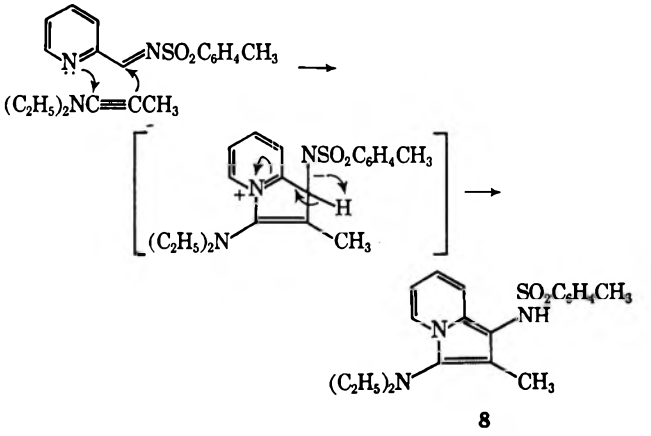
Ketones and imines have also been found to react with ynamines, particularly in the presence of Lewis acids such as boron trifluoride.[9] Substituted amides and amidines were thus obtained, presumably by rearrangement of initially formed four-membered-ring adducts. Arylsulfonylimines[14] showed an expected greater reactivity with ynamines and led to the corresponding unsaturated arylsulfonamidines **5a–i**. The structures of these products were established by catalytic and chemical reductions. While the phenylynamine-derived product **5a** was stable to refluxing acid or alkali and resistant to hydrogenation at atmospheric pressure, its stilbene double bond was reduced over a palladium catalyst at 850 psi, giving the saturated sulfonamidine **6**. Lithium aluminum hydride reduction of the sulfonamidine group in **5a** led to the aminomethyl-*cis*-stilbene **7** and *p*-toluenesulfonamide.

The formation of a *cis*-stilbene system in **5a** is especially interesting since it indicates that opening of



the initially formed four-membered-ring adduct may follow the Woodward–Hoffmann[15] selection rules for electrocyclic transformations. (The required *trans* arrangement of the aryl and sulfonyl substituents on the four-membered ring can be assumed.)

A remarkable departure from the reaction path followed by the other sulfonimides was found with the 2-pyridalsulfonimide in its reaction with the methyl-substituted ynamine. Here, formation of a pyrrocoline **8**

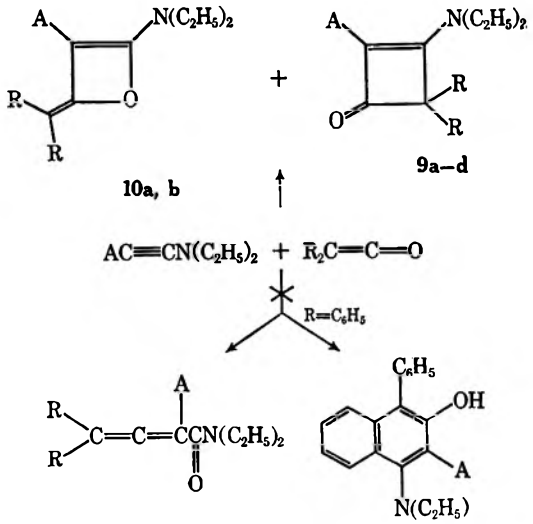


indicates that the relative nucleophilicities of the nitrogens in the pyridalsulfonimide, rather than in a zwitterionic cyclization precursor, may govern the course of the reaction. This result would then be a direct reflection of the preferred concerted addition reactions of ynamines. Formation of a pyrrocoline from the least polarized ynamine is consistent with this postulate.

The addition of diphenylketene to ynamines led to both of the possible four-membered-ring cyclization products, **9a–c** and **10a, b**. Allenic amide structures, which could have arisen from opening of the heterocyclic adducts **10** in analogy to the opening found with cyclic sulfonamides (above) were excluded by the absence of characteristic allenic absorption in the infrared. Ultraviolet, infrared, and nuclear magnetic resonance spectra also excluded aminophenol structures analo-

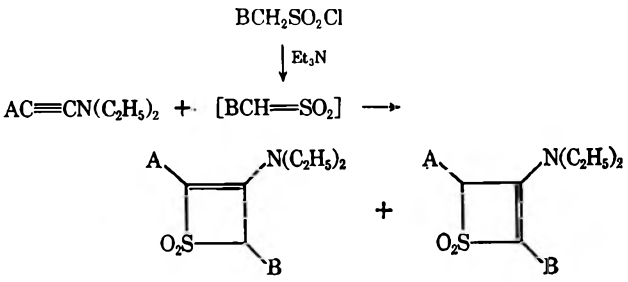
(13) J. Ficini and C. Barbara, *Tetrahedron Lett.*, 6425 (1966).
(14) G. Kresze and R. Albrecht, *Angew. Chem.*, **74**, 781 (1962).
(15) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965). Of two possible conrotatory cyclobutene openings one expects to favor the process which avoids eclipsing of initial *trans* substituents.

gous to the quinolones formed with aryl isocyanates (below). An aminocyclobutenone **9d** was also obtained with dimethylketene and N,N-diethylphenylethynylamine.



A = C_6H_5, CO_2CH_3, CH_3; R = C_6H_5, CH_3

Analogous to the addition of ketenes, sulfenes were also found to give adducts with ynamines. The four-membered cyclic sulfonamide structures **11a–e** and **12a, b** were assigned on the basis of nmr spectra. Double-bond isomerization from type **11** to **12** was only observed in the products derived from the methyl-substituted ynamine.

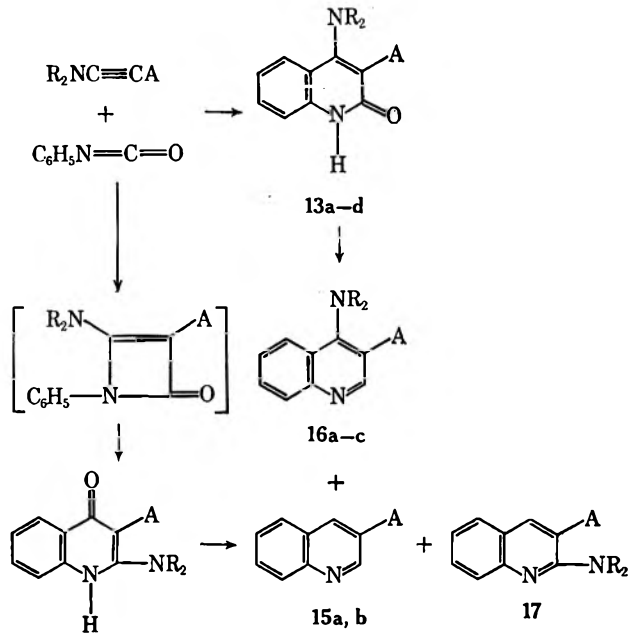


A = C_6H_5, CO_2CH_3, CH_3; B = H, C_6H_5

In contrast to the preceding reactions, ynamines reacted with phenyl isocyanate to give 4-amino-2-quinolones **13a–d** by 1,4 addition as well as 2-amino-4-quinolones **14a, b** by initial 1,2 addition, subsequent opening of the four-membered-ring adduct, and cyclization to the 4-quinolone products. The relative extent of 1,4 *vs.* 1,2 addition was found to depend on solvent polarity. Thus 2-quinolone formation was favored in acetonitrile while more 4-quinolone isomer was produced in benzene.[16] Infrared absorption at 1755 cm^{-1}, which was seen in the course of the reactions, may be assigned to the intermediate unsaturated four-membered lactams.

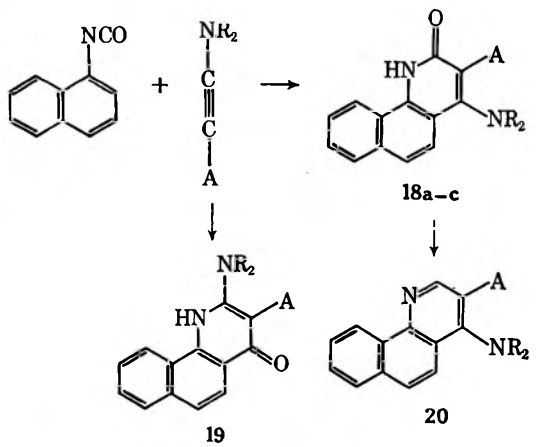
Structural assignments for the aminoquinolones were based on complete reductions with lithium aluminum hydride to the quinolines **15a, b**, common to each isomer pair, as well as partial reductions to the respective aminoquinolines **16a–c** and **17**. The 4-aminoquinolines **16a–c** displayed an nmr singlet at δ 8.5–8.7 for the C-2 proton, downfield[17] from the other aromatic proton signals, while the isomeric 4 proton of the 2-aminoquinoline **17** was found at 7.6.[17] In the quinolines **15a, b** the C-2 proton was again seen downfield, but as a doublet.

The isomeric aminoquinolones could also be differentiated by infrared spectra, which showed strong maxima at 1640, 1600, and 900 cm^{-1} for the 4-amino-2-quinolones **13a–c** *vs.* 1615 and 1570 cm^{-1} for the 2-amino-4-quinolones **14a, b**. The ultraviolet spectra of the isomeric compounds could be consistently distinguished by their general shapes but showed the same positions and relative intensities of maxima.



A = C_6H_5, C_5H_{11}, CO_2CH_3, CH_3; R = C_2H_5, C_3H_7

The reaction of 1-naphthyl isocyanate and ynamines also led to 1,4-addition products **18a–c** in acetonitrile, and a rearranged 1,2-addition product **19** could be isolated from a reaction in cyclohexane. Reduction of the benzo-2-quinolone **18a** with lithium aluminum hydride gave the desoxyproduct **20** with an nmr singlet at δ 8.56. The 1,4-addition products **18a–c** could again be cor-



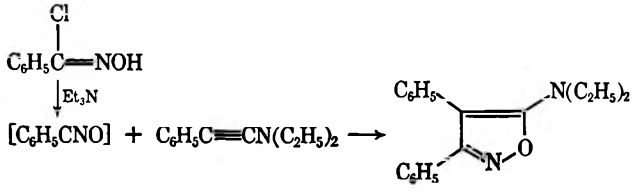
A = C_5H_{11}, CO_2CH_3, CH_3; R = C_2H_5, C_3H_7

(16) Recently,[11] the addition of phenyl isocyanate to two ynamines was reported to give the 4-amino-2-quinolones **13a** and **d**. However, the products obtained correspond in physical properties to our 2-amino-4-quinolones **14a** and **b**.

(17) R. F. M. White in "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 143.

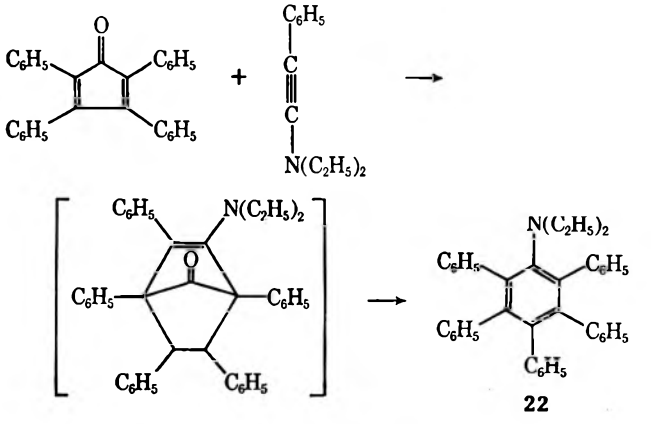
related by infrared spectra (1625, 1600, and 850 cm^{-1}) and differentiated from the isomer **19** (1600 and 1545 cm^{-1}).

Additions of 1,3 dipolar species to ynamines were described during the course of our work.[18] A further example, leading to compound **21**, is found in the reaction of benzonitrile oxide with the phenyl-substituted ynamine.



21

The phenyl-substituted ynamine was also found to undergo a Diels–Alder addition to tetraphenylcyclopentadienone. The corresponding decarbonylation product **22** was isolated in low yield.



22

Experimental Section

The proton magnetic resonance (pmr) spectra were recorded on a Varian Associates Model A-60 spectrometer as 10% solutions in carbon tetrachloride or deuterated chloroform. Chemical shifts for the compounds are reported as δ (parts per million) relative to tetramethylsilane (TMS), internal or external. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 237B infrared spectrometer. Solids were recorded as potassium bromide discs and liquids as films on sodium chloride plates. Ultraviolet (uv) spectra were recorded on a Perkin-Elmer Model 202 spectrometer, and extinction coefficients were determined on a Cary 14 spectrometer. All reported melting points are corrected, but boiling points are uncorrected. All reactions were carried out in a nitrogen atmosphere.

Preparation of Ynamines.—The N,N-diethylphenylethynylamine used in the following reactions was prepared by the method of Ficini.[3]

The N,N-dipropylpentylethynylamine, **1**, previously unreported, and the N,N-dipropylethylethynylamine were prepared from the corresponding acetylenic ethyl ethers by the method of Montijin.[5] The N,N-dipropylpentylethynylamine had the following physical constants: bp 93–94° (4.7 mm); ir 2240 cm^{-1}. This amine could be hydrolyzed to the N,N-dipropylamide of heptanoic acid by dilute aqueous acid. The amide was compared with an authentic sample by matching ir spectra.

Preparation of N,N-Diethylcarbomethoxyethynylamine (2).—N,N-diethyl-1,2,2-trichlorovinylamine,[19] 5.0 g (23 mmol), was cooled to −15° under a nitrogen atmosphere, and *n*-butyllithium (50 mmol) in hexane (diluted with one-third volume of dry ether) was added dropwise at −10°. The mixture was left at room temperature for 45 min, then cooled to −10°, and methyl chloroformate, 2.16 g, in 5 ml of dry ether was added dropwise while the temperature of the reaction mixture was kept at −10°. After addition of methyl chloroformate, the mixture was left at room temperature for 45 min. Centrifugation and distillation of the centrifugate gave 2.5 g (70% yield) of the ynamine: bp 91° (2.5 mm); ir 2200, 1695 cm^{-1}; nmr (neat with external TMS) δ 1.20 (t, 6 H), 2.97 (q, 4 H), 4.35 (s, 3 H).

Reaction of N,N-Diethylphenylethynylamine with Malononitrile.—A solution of 0.51 g (3.0 mmol) of the ynamine in 2 ml of dry acetonitrile was added dropwise to a stirred solution of 0.2 g (3.0 mmol) of malononitrile in 10 ml of dry acetonitrile, and the mixture was stirred for 22 hr. The solvent was removed under vacuum, and recrystallization of the residue from ethyl acetate–petroleum ether (bp 30–60°) gave 0.3 g (51% yield) of adduct **3a**, mp 110–111°. A reaction in dry benzene gave a 10% yield: ir 1575, 2175, 2200 cm^{-1}; λ_{max}^{EtOH} 208, 293 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.23 (t, 6 H), 3.60 (q, 4 H), 4.00 (s, 2 H), 7.33 (m, 5 H).

Anal. Calcd for $C_{15}H_{17}N_3$: C, 74.07; H, 7.55; N, 18.51. Found: C, 73.98; H, 7.32; N, 18.25.

Reaction of N,N-Dipropylpentylethynylamine with Malononitrile.—This reaction was carried out under the conditions of the previous reaction, except that benzene was used as a solvent. Distillation of the reaction mixture gave a light brown oil, bp 110° (0.005 mm). This compound, **3b**, 3.35 g (84% yield), was homogeneous by thin layer chromatography (tlc) on Eastman silica gel plates in dichloromethane and also in benzene: ir 2200, 2210, 1565 cm^{-1}; λ_{max}^{EtOH} 210, 295 mμ; nmr (in $CDCl_3$ with internal TMS at sweep width of 250 cps) δ 0.75–2.50 (m, 21 H), 2.50 (m, 2 H), 3.47 (t, 4 H).

Anal. Calcd for $C_{16}H_{27}N_3$: C, 73.51; H, 10.41. Found: C, 73.44; H, 10.66.

Reaction of N,N-Diethylphenylethynylamine with Ethyl Cyanoacetate.—This reaction was carried out in acetonitrile and gave a 42% yield of the product **3c** which crystallized from ethyl acetate–petroleum ether (bp 30–60°): mp 74–75°; ir 1690, 1560, 2205 cm^{-1}; λ_{max}^{EtOH} 210, 307 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.2 (m, 9 H), 3.55 (q, 4 H), 4.2 (q, 2 H), 4.4 (s, 2 H), 7.3 (m, 5 H).

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.39; H, 7.75; N, 9.80. Found: C, 71.54; H, 7.79; N, 9.60.

Reaction of N,N-Dipropylpentylethynylamine with Ethyl Cyanoacetate.—This reaction was carried out in dry benzene to give a 51% yield of product **3d**: bp 105° (0.005 mm); ir 1695, 1535, 2205 cm^{-1}; λ_{max}^{EtOH} 220, 311 mμ; nmr (in $CDCl_3$ with external TMS) δ 0.8–1.6 (m, 24 H), 2.78 (m, 2 H), 3.43 (t, 4 H), 4.11 (q, 2 H).

Anal. Calcd for $C_{18}H_{32}N_2O_2$: C, 70.09; H, 10.46; N, 9.08. Found: 70.31; H, 10.54; N, 8.95.

Reaction of N,N-Diethylphenylethynylamine with *p*-Toluenesulfonamide.—A solution of 0.5 g (3.0 mmol) of the ynamine in 5 ml of dry acetonitrile was added dropwise to a solution of 0.5 g of *p*-toluenesulfonamide in 20 ml of dry acetonitrile. The mixture was stirred for 72 hr, and the solvent taken off under a vacuum. Recrystallization of the residue from ethyl acetate–petroleum ether (bp 30–60°) afforded 0.82 g (80% yield) of N-*p*-toluenesulfonyl-N′,N′-diethylphenylacetamidine (**4a**): mp 134–135°; ir 1555, 1280, 1145 cm^{-1}; λ_{max}^{EtOH} 250 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.00 (pentet, 6 H), 2.35 (s, 3 H), 3.35 (m, 4 H), 4.40 (s, 2 H), 7.0–7.5 (m, 7 H), 7.83 (d, 2 H).

Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C, 66.33; H, 7.03; N, 8.14; S, 9.32. Found: C, 66.11; H, 6.95; N, 7.90; S, 9.26.

Attempts to reduce this N-*p*-toluenesulfonyl-N′,N′-diethylphenylacetamidine in dry dioxane with palladium on charcoal and hydrogen at atmospheric pressure or with platinum dioxide in dry ethanol failed.

Reaction of N,N-Dipropylpentylethynylamine with *p*-Toluenesulfonamide.—This reaction was carried out in dichloromethane and gave a 79% yield of the N-*p*-toluenesulfonyl-N′,N′-dipropylheptamidine (**4b**): bp 190° (0.001 mm); ir 1550, 1275 (SO_2 *as*), 1150 cm^{-1} (SO_2 *s*); λ_{max}^{EtOH} 248 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.90 (t, 9 H), 1.35 (m, 12 H), 2.39 (s, 3 H), 2.88 (t, 2 H), 3.30 (q, 4 H), 7.25 (d, 2 H), 7.90 (d, 2 H).

Anal. Calcd for $C_{20}H_{34}N_2O_2S$: C, 65.53; H, 9.35; N, 7.64; S, 8.73. Found: C, 65.37; H, 9.52; N, 8.16; S, 8.91.

Reaction of N,N-Diethylphenylethynylamine with Benzenesulfonamide.—This reaction, carried out in dry acetonitrile, gave a 67% yield of the N-benzenesulfonyl-N′,N′-diethylphenylacetamidine (**4c**), mp 68–69°, after recrystallization from cyclohexane–ethyl acetate: ir 1550, 1270 (SO_2 *as*), 1145 cm^{-1} (SO_2 *s*);

(18) R. Fuks, R. Buijle, and H. G. Viehe, *Angew. Chem.*, **78**, 594 (1966).
(19) A. J. Speziale and L. R. Smith, *J. Amer. Chem. Soc.*, **84**, 1868 (1962).

λ_{max}^{EtOH} 247 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.00 (pentet, 6 H), 3.35 (m, 4 H), 4.42 (s, 2 H), 7.30 (m, 8 H), 7.90 (m, 2 H).

Anal. Calcd for $C_{18}H_{22}N_2O_2S$: C, 65.51; H, 6.72; N, 8.49; S, 9.72. Found: C, 65.74; H, 6.56; N, 8.28; S, 9.72.

Reaction of N,N-Diethylphenylethynylamine with Benzal *p*-Toluenesulfonimide.[14]—A solution of 0.50 g (3.0 mmol) of the ynamine in 5 ml of dry benzene was added dropwise to a stirred solution of the benzal *p*-toluenesulfonimide, 0.78 g (3.0 mmol) in 20 ml of dry benzene. The mixture was stirred for 20 hr. Evaporation of the solvent under a vacuum and recrystallization of the solid from ethyl acetate gave 0.93 g (75% yield) of product **5a**, mp 163–164°. With acetonitrile as a solvent a yield of 70% was obtained: ir 1540, 1280, 1145 cm^{-1}; λ_{max}^{EtOH} 247 mμ; nmr (in $CDCl_3$ with external TMS) δ 0.72 (t, 3 H), 1.16 (t, 3 H), 2.35 (s, 3 H), 3.33 (q, 4 H), 6.63 (s, 1 H), 7.1–7.3 (m, 12 H), 7.71 (d, 2 H).

Anal. Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.20; H, 6.53; N, 6.48; S, 7.40. Found: C, 72.18; H, 6.74; N, 6.37; S, 7.48.

Reaction of N,N-Diethylcarbomethoxyethynylamine with Benzal *p*-Toluenesulfonimide.[14]—This reaction was carried out in benzene to give a 60% yield of product **5b**, mp 113–114°, which was recrystallized from ethyl acetate. With acetonitrile as the reaction medium an 18% yield was obtained: ir 1725, 1610, 1525, 1140 cm^{-1}; λ_{max}^{EtOH} 253 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.16 (m, 6 H), 2.36 (s, 3 H), 3.2–3.7 (q and s, 7 H), 6.78 (s, 1 H), 7.1–7.85 (m, 9 H).

Anal. Calcd for $C_{22}H_{26}N_2O_4S$: C, 63.74; H, 6.32; N, 6.76; S, 7.74. Found: C, 64.00; H, 6.28; N, 7.00; S, 7.82.

Reaction of N,N-Diethylmethylethynylamine with Benzal *p*-Toluenesulfonimide.[14]—This reaction was carried out in benzene and gave a 95% yield of product **5c**, mp 142–143°, which was recrystallized from ethyl acetate: ir 1535, 1275, 1150 cm^{-1}; λ_{max}^{EtOH} 252 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.18 (t, 6 H) 2.11 (s, 3 H), 2.33 (s, 3 H), 3.45 (m, 4 H), 6.21 (s, 1 H), 7.0–7.9 (m, 9 H).

Anal. Calcd for $C_{21}H_{26}N_2O_2S$: C, 68.27; H, 6.82; N, 7.58; S, 8.68. Found: C, 68.25; H, 7.01; N, 7.69; S, 8.69.

Reaction of N,N-Diethylphenylethynylamine with 2-Pyridal *p*-Toluenesulfonimide.[14]—This reaction was carried out in dry benzene and gave a 54% yield of product **5d**, mp 145–146°, after recrystallization from ethyl acetate–petroleum ether (bp 30–60°): ir 1530, 1280, 1145 cm^{-1}; λ_{max}^{EtOH} 235, 295 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.68 (t, 3 H), 1.16 (t, 3 H), 2.35 (s, 3 H), 3.40 (m, 4 H), 6.70 (s, 1 H), 7.25 (m, 11 H), 7.83 (d, 2 H).

Anal. Calcd for $C_{25}H_{27}N_3O_2S$: C, 69.26; H, 6.28; N, 9.69; S, 7.38. Found: C, 68.98; H, 6.15; N, 9.47; S, 7.40.

Reaction of N,N-Diethylcarbomethoxyethynylamine with 2-Pyridal *p*-Toluenesulfonimide.[14]—This reaction was carried out in dry benzene to give a 41% yield of product **5e**, mp 132–133°, after recrystallization from ethyl acetate: ir 1735, 1620, 1550, 1280, 1150 cm^{-1}; λ_{max}^{EtOH} 215, 250 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.18 (t, 6 H), 2.35 (s, 3 H), 3.58 (m, 4 H), 3.65 (s, 3 H), 6.88 (s, 1 H), 7.16 (m, 4 H), 7.73 (m, 4 H).

Anal. Calcd for $C_{21}H_{25}N_3O_4S$: C, 60.71; H, 6.07; N, 10.12; S, 7.70. Found: C, 60.69; H, 6.26; N, 9.92; S, 7.58.

Reaction of N,N-Diethylmethylethynylamine with 3-Pyridal *p*-Toluenesulfonimide.—This reaction was carried out in dry benzene to give a 72% yield of product **5f**, mp 168–169°, after recrystallization from ethyl acetate: ir 1540, 1275, 1145 cm^{-1}; λ_{max}^{EtOH} 247 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.16 (t, 6 H), 2.13 (s, 3 H), 2.33 (s, 3 H), 3.41 (m, 4 H), 6.21 (s, 1 H), 7.23 (m, 3 H), 7.66 (m, 3 H), 8.50 (s, 2 H).

Anal. Calcd for $C_{20}H_{25}N_3O_2S$: C, 64.67; H, 6.78; N, 11.31; S, 8.61. Found: C, 64.79; H, 6.53; N, 11.04; S, 8.38.

Reaction of N,N-Diethylmethylethynylamine with 2-Pyridal *p*-Toluenesulfonimide.[14]—A solution of 0.33 g (3.0 mmol) of the ynamine in 5 ml of dry acetonitrile was added dropwise to a stirred solution of 0.78 g (3.0 mmol) of 2-pyridal-*p*-toluenesulfonimide in 20 ml of dry acetonitrile, cooled to 5°. The ynamine was added dropwise over a 30-min period, and the mixture stirred another 2 hr at 5° and 16 hr at room temperature. The solvent was removed under a vacuum, and the black–green oil was treated with Florisil and dichloromethane to give, after recrystallization from ethyl acetate–petroleum ether (bp 30–60°), 0.5 g (45% yield) of product **8**: mp 120–121°; ir 3300, 1345, 1150 cm^{-1}; λ_{max}^{EtOH} 235 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.86 (t, 6 H), 1.73 (s, 3 H), 3.06 (q, 4 H), 6.4–6.6 (m, 3 H), 7.3–7.7 (m, 3 H), 7.16 (d, 3 H), 7.60 (d, 2 H), 8.00 (m, 1H).

Anal. Calcd for $C_{20}H_{25}N_3O_2S$: C, 64.67; H, 6.78; N, 11.31; S, 8.62. Found: C, 64.57; H, 6.93; N, 11.03; S, 8.80.

The singlet at δ 6.58 disappeared when the solvent was CH_3OD, indicating exchange of the N–H hydrogen of the sulfonamide.

Reaction of N,N-Diethylmethylethynylamine with 2-Furfural *p*-Toluenesulfonimide.[14]—This reaction was carried out in dry benzene and gave a 65% yield of product **5g**, mp 127–128°, after recrystallization from ethyl acetate: ir 1530, 1280, 1150 cm^{-1}; λ_{max}^{EtOH} 257 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.16 (t, 6 H), 2.18 (s, 3 H), 2.36 (s, 3 H), 3.36 (m, 4 H), 6.00 (s, 1 H), 6.40 (m, 2 H), 7.16 (d, 2 H), 7.45 (s, 1 H), 7.75 (d, 2 H).

Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.32; H, 6.71; N, 7.77; S, 8.88. Found: C, 63.03; H, 6.86; N, 7.74; S, 8.62.

Reaction of N,N-Diethylcarbomethoxyethynylamine with 2-Furfural *p*-Toluenesulfonimide.[14]—This reaction was carried out in dry benzene and gave a 57% yield of the adduct **5h**, mp 146–147°, after recrystallization from ethyl acetate: ir 1550, 1620, 1720 cm^{-1}; λ_{max}^{EtOH} 222, 245, 325 mμ; nmr (in $CDCl_3$ with external TMS) δ 1.20 (m, 6 H), 2.38 (s, 3 H), 3.50 (m, 4 H), 3.73 (s, 3 H), 6.46 (s, 1 H), 6.63 (m, 1 H), 7.1–8.0 (m, 6 H).

Anal. Calcd for $C_{20}H_{24}N_2O_5S$: C, 59.40; H, 5.98; N, 6.93; S, 7.91. Found: C, 59.14; H, 5.93; N, 6.72; S, 8.02.

Reaction of N,N-Diethylmethylethynylamine with 2-Naphthal *p*-Toluenesulfonimide.—This reaction was carried out in dry benzene and gave a 94% yield of product **5i**: mp 137–138°; ir 1535, 1275, 1145 cm^{-1}; λ_{max}^{EtOH} 213, 248, 294 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.20 (t, 6 H), 2.20 (s, 3 H), 2.31 (s, 3 H), 3.43 (m, 4 H), 6.36 (s, 1 H), 7.1–7.9 (m, 11 H).

Anal. Calcd for $C_{25}H_{28}N_2O_2S$: C, 71.41; H, 6.71; N, 6.66; S, 7.61. Found: C, 71.24; H, 6.80; N, 6.84; S, 7.63.

Catalytic Reduction of the N-*p*-Toluenesulfonyl-N′,N′-diethylstilbylformamidine (5a).—A solution of 0.1 g (0.22 mmol) of the formamidine in 20 ml of dry ethanol was shaken with 15 mg of 10% palladium on charcoal under 850 psi of hydrogen for 24 hr. The catalyst was filtered, and the solvent taken off under vacuum. Recrystallization of the residue from ethyl acetate–petroleum ether (bp 30–60°) gave 30 mg of the dihydro compound **6**: mp 125–126°; ir 1550, 1260, 1135 cm^{-1}; λ_{max}^{EtOH} 210, 252 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.78 (m, 6 H), 2.35 (s, 3 H), 3.33 (m, 6 H), 5.95 (t, 1 H), 7.1–7.9 (m, 14 H).

Attempts to reduce the formamidine at atmospheric pressure failed. The starting material was recovered in all cases.

The compound was also stable to refluxing 10% aqueous hydrochloric acid and 10% sodium hydroxide.

Anal. Calcd for $C_{26}H_{30}N_2O_2S$: C, 71.85; H, 6.96; N, 6.45; S, 7.38. Found: C, 72.01; H, 7.22; N, 6.33; S, 7.43.

Lithium Aluminum Hydride Reduction of N-*p*-Toluenesulfonyl-N′,N′-diethylstilbylformamidine (5a).—A solution of 0.1 g (0.22 mmol) of the formamidine in 20 ml of dry dioxane was refluxed for 48 hr with 60 mg of lithium aluminum hydride. The excess lithium aluminum hydride was hydrolyzed with a few drops of 50% sulfuric acid. The mixture was then made basic and extracted with three 20-ml portions of dichloromethane. The extract was dried over magnesium sulfate, and the solvent was removed under vacuum. Distillation of the remaining oil gave 50 mg (83% yield) of the amine **7**, bp 83–88° (block temperature) at 0.005 mm. The hydrobromide salt was crystallized from isopropyl alcohol: mp 176–177°; ir spectrum (hydrobromide salt) 2475–2560 cm^{-1}; λ_{max}^{EtOH} 225 mμ (ε 22,000), 270 (13,000);[20] nmr (in CCl_4 with external TMS) (free amine) δ 1.06 (t, 6 H), 2.30 (q, 4 H), 3.20 (s, 2 H), 6.51 (s, 1 H), 6.8–7.2 (m, 10 H).

Anal. Calcd for $C_{19}H_{24}BrN$: C, 65.89; H, 6.98; N, 4.05; Br, 23.08. Found: C, 66.12; H, 6.94; N, 4.07; Br, 23.30.

The solution was then made acidic and extracted with three 20-ml portions of chloroform. This extract was dried over magnesium sulfate, and after removal of the solvent gave 23 mg of *p*-toluenesulfonamide, mp 134–137°, identical with the known compound by mixture melting point and ir spectrum.

Reaction of N,N-Diethylphenylethynylamine with Diphenylketene.—A solution of 0.51 g (3.0 mmol) of the ynamine in 2 ml of dry benzene was added dropwise to a stirred solution of 0.58 g (3.0 mmol) of diphenylketene in 15 ml of dry benzene. The mixture was stirred for 24 hr. Evaporation of the solvent and crystallization of the residue from ethyl acetate gave 0.7 g (64% yield) of 2,2-diphenyl-3-N,N-diethyl-4-phenylcyclobutenone **9a**, mp 192–193°. With acetonitrile as a solvent the same yield was obtained: ir 1743, 1608, 1585 cm^{-1}; λ_{max}^{EtOH} 272 mμ;

(20) For a comparable uv absorption of *cis*-stilbene see M. Calvin and H. W. Alter, *J. Chem. Phys.*, **19**, 765 (1951).

nmr (in $CDCl_3$ with internal TMS) δ 0.44 (t, 3 H), 1.01 (t, 3 H), 3.35 (m, 4 H), 7.43 (m, 15 H).

Anal. Calcd for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81. Found: C, 85.06; H, 6.68; N, 3.84.

Attempts to isomerize this cyclobutenone to the aminonaphthol with BF_3 etherate, *p*-toluenesulfonic acid, or methanolic hydrochloric acid failed. The starting cyclobutenone was recovered in all cases.

Reaction of N,N-Diethylcarbomethoxyethynylamine with Diphenylketene.—This reaction was carried out in dry benzene for 2 hr and gave a 15% yield of the cyclobutenone **9b**, mp 216–217° (turned blue at the melting point), after recrystallization from ethyl acetate: ir 1755, 1685, 1612 cm^{-1}; λ_{max}^{EtOH} 247, 275 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.45 (t, 3 H), 1.38 (t, 3 H), 3.39 (q, 2 H), 3.68 (s, 3 H), 4.14 (q, 2 H), 7.36 (s, 10 H).

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.66; H, 6.64; N, 4.01. Found: C, 75.80; H, 6.51; N, 4.01.

Crystallization of the ethyl acetate soluble material from carbon tetrachloride–petroleum ether (bp 30–60°) gave a 53% yield of the cyclic ether **10a**: mp 114–115°; ir 1720, 1625 cm^{-1}; λ_{max}^{EtOH} 265 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.90 (t, 3 H), 1.17 (t, 3 H), 3.37 (m, 4 H), 3.82 (s, 3 H), 7.43 (s, 10 H).

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.66; H, 6.64; N, 4.01. Found: C, 75.29; H, 6.41; N, 4.04.

Reaction of N,N-Diethylmethylethynylamine with Diphenylketene.—This reaction gave an 11% yield of the substituted cyclobutenone **9c**, mp 116–117°, which was crystallized from ethyl acetate–petroleum ether (bp 30–60°): ir 1740 cm^{-1}; λ_{max}^{EtOH} 228, 287 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.48 (t, 3 H), 1.31 (t, 3 H), 1.85 (s, 3 H), 3.33 (m, 4 H), 7.30 (s, 10 H).

Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.39; H, 7.74; N, 4.67.

Recrystallization of the ethyl acetate–petroleum ether (bp 30–60°) soluble material from ligroin (bp 90–120°) gave a 27% yield of the cyclic ether **10b**: mp 88–89°; ir 1620 cm^{-1}; λ_{max}^{EtOH} 215, 271 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.98 (t, 6 H), 2.11 (s, 3 H), 3.30 (q, 4 H), 7.33 (s, 10 H).

When this reaction was carried out in dry acetonitrile at −27° only the cyclic ether was obtained in 48% yield.

Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.75; H, 7.32; N, 4.51.

Reaction of N,N-Diethylphenylethynylamine with Dimethylketene.—Dimethylketene was generated by pyrolysis of tetramethylcyclobutanedione and trapped in dry tetrahydrofuran at −75°. The ynamine, 0.5 g (3.0 mmol), was added dropwise to the stirred solution of the dimethylketene at 0°. The mixture was then warmed to room temperature and stirred for an additional 2 hr. The solvent was removed under vacuum, and the mixture was chromatographed on 35 g of neutral alumina with these solvents: (1) benzene; (2) benzene–30% dichloromethane; and (3) benzene–40% dichloromethane. The 30% fraction gave 0.12 g (17% yield) of substituted cyclobutenone **9d**: bp 103° (0.05 mm); mp 51–52°; ir 1725 cm^{-1}; λ_{max}^{EtOH} 210, 280 mμ; nmr (in $CDCl_3$ with external TMS) δ 1.06 (t, 6 H), 1.30 (s, 6 H), 3.33 (q, 4 H), 7.20 (s, 5 H).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.23; H, 8.95; N, 5.53.

Reaction of N,N-Diethylphenylethynylamine with Phenylsulfene.—A solution of benzylsulfonyl chloride, 0.57 g (3.0 mmol), in 5 ml of dry tetrahydrofuran was added dropwise to a stirred solution of triethylamine, 0.39 g, and the ynamine, 0.51 g (3.0 mmol), in 20 ml of dry tetrahydrofuran. The mixture was stirred for 20 hr, and the triethylamine hydrochloride was filtered. Evaporation of the solvent under vacuum and crystallization of the residue from ethyl acetate afforded 0.40 g (42% yield) of product **11a**: mp 143–144°; ir 1620, 1275, 1100 cm^{-1}; λ_{max}^{EtOH} 227, 272 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.88 (t, 6 H), 3.06 (q, 4 H), 5.72 (s, 1 H), 7.44 (m, 10 H).

Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.70; H, 6.47; N, 4.28; S, 9.77. Found: C, 69.96; H, 6.49; N, 4.09; S, 9.48.

Reaction of N,N-Diethylcarbomethoxyethynylamine with Phenylsulfene.—This reaction was carried out in benzene to give a 32% yield of product **11b**, mp 185–186°, after recrystallization from ethyl acetate. With tetrahydrofuran as a solvent the reaction gave a 16% yield of the product: ir 1615, 1710, 1283, 1170 cm^{-1}; λ_{max}^{EtOH} 222, 279 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.86 (t, 3 H), 1.26 (t, 3 H), 3.08 (q, 2 H), 3.82 (s, 3 H), 4.00 (q, 2 H), 5.65 (s, 1 H), 7.43 (m, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.24; H, 6.19; N, 4.54; S, 10.37. Found: C, 58.08; H, 6.19; N, 4.60; S, 10.24.

Reaction of N,N-Diethylmethylethynylamine with Phenylsulfene.—This reaction was carried out in dry benzene and gave a 54% yield of product **12a**, mp 108–109°, after recrystallization from isopropyl alcohol: ir 1635, 1255, 1085 cm^{-1}; λ_{max}^{EtOH} 236, 247 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.03 (t, 6 H), 1.66 (d, 3 H); 3.16 (q, 4 H), 4.63 (q, 1 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.38; H, 7.22; N, 5.28; S, 12.06. Found: C, 63.14; H, 7.21; N, 5.17; S, 11.98.

Reaction of N,N-Diethylcarbomethoxymethylethynylamine with Sulfene.—Methanesulfonyl chloride, 0.34 g (3.0 mmol), in 5 ml of dry benzene was added dropwise to a stirred solution of the ynamine, 0.46 g (3.0 mmol), and 0.3 g of triethylamine in 20 ml of dry benzene. The mixture was stirred for 20 hr, and the triethylamine hydrochloride was filtered. Evaporation of the solvent under vacuum and crystallization of the residue from ethyl acetate gave 0.21 g (30% yield) of product **11c**, mp 144–145°. With dioxane as the reaction solvent a yield of 23% was obtained: ir 1700, 1625, 1285, 1125 cm^{-1}; λ_{max}^{EtOH} 277 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.28 (t, 6 H), 3.43 (q, 2 H), 3.78 (s, 3 H), 3.98 (q, 2 H), 4.41 (s, 2 H).

Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.51; H, 6.35; N, 5.86.

Reaction of N,N-Diethylphenylethynylamine with Sulfene.—This reaction was carried out in dry tetrahydrofuran and gave a 60% yield of product **11d**, mp 132–133°, after recrystallization from ethyl acetate: ir 1640, 1270, 1115 cm^{-1}; λ_{max}^{EtOH} 229, 284 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.00 (t, 6 H), 3.15 (q, 4 H), 4.43 (s, 2 H), 7.40 (s, 5 H).

Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.39; H, 6.70; N, 5.73.

Reaction of N,N-Diethylmethylethynylamine with Sulfene.—This reaction was carried out in dry tetrahydrofuran and gave a 66% yield of an oil, bp 120–125° (block temperature) at 0.001 mm, which was a 1:1 mixture of double-bond isomers, **11e** and **12b** (the mixture was not formed by thermal rearrangement, since the nmr spectra before and after distillation showed the same 1:1 ratio): ir 1610, 1640, 1265, 1100 cm^{-1}; λ_{max}^{EtOH} 204, 240 mμ; nmr (in CCl_4 with external TMS) δ 1.18 (t, 6 H); 1.50 (d, 1.5 H), 1.83 (s, 1.5 H), 3.21 (q, 4 H), 4.18 (d, 1 H), 4.53 (q, 0.52 H), 5.08 (s, 0.53 H); mass spectrum, *m/e* 189 (molecular ion), 96, 68 (major ions).

Reaction of N,N-Diethylphenylethynylamine with Phenyl Isocyanate.—A solution of 0.50 g (3.0 mmol) of the ynamine in 2 ml of dry acetonitrile was added dropwise to a stirred solution of 0.36 g (3.0 mmol) of phenyl isocyanate in 10 ml of dry acetonitrile. The mixture was stirred for 19 hr, and the white precipitate was filtered. Recrystallization from isopropyl alcohol–ethyl acetate gave 0.15 g (17% yield) of the carbostyril **13a**: mp 238–239°; ir 1640, 3450 cm^{-1}; λ_{max}^{EtOH} 233, 275, 335 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.00 (t, 6 H), 2.90 (q, 4 H), 7.40–7.90 (m, 9 H), 12.00 (s, 1 H).

No additional carbostyril could be obtained even after chromatography on Florisil.

When the reaction was carried out in nitromethane and dichloromethane the yields of **13a** were 15 and 9%, respectively.

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.15; H, 6.90; N, 9.59. Found: C, 77.72; H, 6.73; N, 9.57.

A solution of 0.51 g of the ynamine in 5 ml of dry benzene was added dropwise to a stirred solution of 0.36 g of phenyl isocyanate in 25 ml of dry benzene. The temperature of the reaction was kept at 45° during the addition, and the mixture was stirred at room temperature for 24 hr after the addition. The precipitated solid **14a** was filtered and recrystallized from ethanol: 0.25 g (28% yield); mp 258–259°; ir 1620, 1575 cm^{-1}; λ_{max}^{EtOH} 230, 267, 325 mμ.

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.15; H, 6.90; N, 9.59. Found: C, 78.30; H, 6.94; N, 9.86.

Reaction of N,N-Dipropylpentylethynylamine with Phenyl Isocyanate.—This reaction was carried out for 96 hr in dry acetonitrile to give a 50% yield of the carbostyril **13b** which recrystallized from ethyl acetate–petroleum ether (bp 30–60°): mp 119–120°; ir 1650, 3450 cm^{-1}; λ_{max}^{EtOH} 223, 282, 355, 373 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.95 (t, 9 H), 1.67 (m, 10 H), 2.95 (s, 2 H), 3.30 (t, 4 H), 7.50–8.10 (m, 3 H), 9.50 (d, 1 H), 13.70 (s, 1 H).

Anal. Calcd for $C_{20}H_{30}N_2O$: C, 76.37; H, 9.62; N, 8.90. Found: C, 76.09; H, 9.80; N, 9.17.

Reaction of N,N-Diethylcarbomethoxyethynylamine with Phenyl Isocyanate.—This reaction was run in dry acetonitrile for 20 hr to give a 51% yield of the carbostyril **13c**, which crystallized from ethyl acetate: mp 191–192°; ir 1735, 1650, 1605 cm^{-1}; λ_{max}^{EtOH} 233, 330 mμ; nmr (in $CDCl_3$ with internal TMS) δ, 1.16 (t, 6 H), 3.35 (q, 4 H), 4.00 (s, 3 H), 7.0–7.50 (m, 3 H), 7.83 (d, 1 H), 12.95 (s, 1 H).

Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.82; H, 6.62; N, 10.22. Found: C, 65.71; H, 6.52; N, 10.13.

Reaction of N,N-Diethylmethylethynylamine with Phenyl Isocyanate.—This reaction was carried out under the same conditions and gave a 63% yield of carbostyril **13d**, which crystallized from ethyl acetate: mp 122–123°; ir 1640 cm^{-1}; λ_{max}^{EtOH} 215, 271 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.08 (t, 6 H), 2.30 (s, 3 H), 3.33 (q, 4 H), 7.0–8.0 (m, 4 H), 12.85 (s, 1 H); (in hexamethylphosphortriamide) δ 11.83 (sharp s) for NH.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.78; H, 7.83; N, 12.17.

The reaction of the N,N-diethylmethylethynylamine with phenyl isocyanate in benzene gave a 31% yield of the 2-N,N-diethylamino-3-methyl-4-quinolone **14b**: mp 294–295° (from ethanol); ir 1620, 1580 cm^{-1}; λ_{max}^{EtOH} 230, 263, 324 mμ; nmr in hexamethylphosphortriamide showed the N–H at δ 11.50 as a very broad singlet.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.06; H, 7.87; N, 12.25.

Recrystallization of the alcohol-soluble material gave a 20% yield of the 3-methyl-4-N,N-diethyl-2-quinolone **13d**, mp 122–123°, from ethyl acetate.

Reaction of N,N-Dipropylpentylethynylamine with α-Naphthyl Isocyanate.—This reaction was carried out in dry acetonitrile for 5 hr. A 66% yield of the addition product **18a** was obtained. The compound recrystallized from ethyl acetate: mp 199–201°; ir 1625, 3260 cm^{-1}; λ_{max}^{EtOH} 232, 282 355, 373 mμ; nmr (in $CDCl_3$ with internal TMS) δ 0.95 (t, 9 H), 1.67 (m, 10 H), 2.95 (s, 2 H), 3.30 (t, 4 H), 7.50–8.10 (m, 5 H), 9.50 (d, 1 H), 13.70 (s, 1 H).

Anal. Calcd for $C_{24}H_{32}N_2O$: C, 79.08; H, 8.86; N, 7.70. Found: C, 79.06; H, 8.60; N, 7.87.

Reaction of N,N-Diethylcarbomethoxyethynylamine with α-Naphthyl Isocyanate.—This reaction was carried out under the same conditions and gave a 92% yield of the adduct **18b**, mp 250–251°, which was recrystallized from dichloromethane–ethyl acetate: ir 1620, 1735 cm^{-1}; λ_{max}^{EtOH} 230, 283 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.20 (t, 6 H), 3.40 (q, 4 H), 4.08 (s, 3 H), 7.4–7.90 (m, 5 H), 9.06 (m, 1 H), 12.92 (s, 1 H).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.09; H, 6.32; N, 8.78.

Reaction of N,N-Diethylmethylethynylamine with α-Naphthyl Isocyanate.—This reaction was carried out in dry acetonitrile for 24 hr and gave a 73% yield of product **18c**, mp 199–200°, after recrystallization from ethyl acetate: ir 3140, 1625 cm^{-1}; λ_{max}^{EtOH} 240, 285, 355, 372 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.11 (t, 6 H), 2.41 (s, 3 H), 3.36 (q, 4 H), 7.4–8.0 (m, 5 H), 9.15 (d, 1 H), 12.90 (s, 1 H), (in hexamethylphosphortriamide with external TMS) δ 12.5 (broad singlet, 1 H).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19; N, 9.99. Found: C, 76.62; H, 7.65; N, 9.56.

Alternatively, this reaction was run in cyclohexane to give an immediate precipitate of the 3-methyl-4-N,N-diethylamino-7,8-benzo-2-quinolone (**18c**). Removal of the solvent under vacuum gave a yellow oil, which, on heating at 100° for 3 hr and cooling gave 0.12 g of 2-N,N-diethyl-3-methyl-7,8-benzo-4-quinolone (**19**) [mp 210–211°, ir 1600, 1545 cm^{-1}; λ_{max}^{EtOH} 225, 246, 275 mμ; nmr (in hexamethylphosphortriamide with external TMS) δ 11.0 (broad singlet, 1 H)] after recrystallization from ethanol. A mixture of compounds **19** and **18c** melted at 165–185°.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19; N, 9.99. Found: C, 77.21; H, 7.40; N, 9.86.

Reduction of 3-Methyl-4-N,N-diethyl-2-quinolone.—A solution of 2.0 g (8.7 mmol) of the 2-quinolone **13d** in 60 ml of dry dioxane was refluxed with 1 g of lithium aluminum hydride for 24 hr. The excess lithium aluminum hydride was hydrolyzed with a few drops of 50% sulfuric acid; the dioxane was taken off under vacuum and 15 ml of 10% NaOH solution was added. The basic solution was then extracted with three 20-ml portions of dichloromethane; the extract was dried over magnesium sulfate; and concentrated to an oil. Chromatography of this oil, 1.8 g, on 40 g of neutral alumina, activity I, with (1) petroleum ether–20% dichloromethane, (2) dichloromethane, and (3) dichloromethane–20% chloroform as solvents gave, in fraction 1, an oil that was a mixture of 3-methylquinoline **15a** and 3-methyl-4-N,N-diethylaminoquinoline **16a**. This oil was distilled to give 0.3 g of 3-methylquinoline **15a**, bp 74–76° (block temperature) at 1 mm. This quinoline formed a picrate, mp 186–187° (lit.[21] mp 187°), after recrystallization from ethanol: ir 2700, 1625, 1555, 1315 cm^{-1}; λ_{max}^{EtOH} (picrate) 210, 229, 233, 360 mμ; nmr (in CCl_4 with external TMS) (free amine) δ 2.11 (t, 3 H), 6.7–7.1 (m, 4 H), 7.91 (d, 1 H), 8.45 (d, 1 H).

Anal. Calcd for $C_{16}H_{12}N_4O_7$: C, 51.62; H, 3.25; N, 15.05. Found: C, 51.34; H, 3.67; N, 14.26.

The second fraction of 0.2 g, bp 57–61° (block temperature) at 0.005–0.001 mm, was 3-methyl-4-N,N-diethylaminoquinoline **16a**. It formed a perchlorate salt, which crystallized from ethanol: mp 237–240°; ir (perchlorate salt) 3250, 1115 cm^{-1}; λ_{max}^{EtOH} 208, 230, 265, 388 mμ; nmr (in CCl_4 with external TMS) (free amine) δ 0.90 (t, 6 H), 2.21 (s, 3 H), 3.18 (q, 4 H), 7.2–7.5 (m, 2 H), 7.8–8.1 (m, 2 H), 8.45 (s, 1 H).

Anal. Calcd for $C_{14}H_{19}ClN_2O_4$: C, 53.41; H, 6.09; N, 8.90; Cl, 11.27. Found: C, 53.27; H, 5.87; N, 8.78; Cl, 11.41.

Reduction of 3-Methyl-2-N,N-diethylamino-4-quinolone with Lithium Aluminum Hydride.—Reduction of quinoline **14b** with lithium aluminum hydride in refluxing N-ethylmorpholine for 6 hr gave 2-N,N-diethylamino-3-methylquinoline (**17**). This quinoline could be separated by tlc on silica gel with chloroform–ethanol (98:2) as the eluent. The 2-N,N-diethylamino-3-methylquinoline formed a perchlorate which was recrystallized from ethanol: mp 188–189°; ir (perchlorate salt) 3400, 1635, 1100 cm^{-1}; λ_{max}^{EtOH} 215, 253, 340 mμ; nmr (in CCl_4) (free amine) δ 1.15 (t, 6 H), 2.38 (s, 3 H), 3.33 (q, 4 H), 7.2–7.9 (m, 5 H).

Anal. Calcd for $C_{14}H_{19}ClN_2O_4$: C, 53.41; H, 6.09; N, 8.90. Found: C, 53.94; H, 6.22; N, 8.53.

Reduction of the quinolone **14b** in dioxane gave only 3-methylquinoline **15a**.

Reduction of 3-Phenyl-4-N,N-diethylamino-2-quinolone with Lithium Aluminum Hydride.—This reduction gave a mixture that could be separated by tlc on silica gel with dichloromethane–ethanol (49:1) as the eluent. The 3-phenyl-4-N,N-diethylaminoquinoline **16b** was recrystallized from petroleum ether (bp 30–60°): mp 117–118°; λ_{max}^{EtOH} 229, 276, 355 mμ; nmr (in $CDCl_3$ with internal TMS) δ 1.00 (t, 3 H), 3.00 (q, 4 H), 7.2–8.1 (m, 9 H), 8.66 (s, 1 H).

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.80; H, 7.13; N, 9.80.

Reduction of 3-Pentyl-4-N,N-dipropylamino-2-quinolone with Lithium Aluminum Hydride.—This reduction gave an oil that on distillation gave 3-pentylquinoline **15b**, bp 69–72° (block temperature) at 0.005–0.001 mm. This oil formed a picrate, which was recrystallized from ethanol: mp 155–156°; ir (picrate) 2550–2750 cm^{-1}; λ_{max}^{EtOH} 210, 230, 235, 362 mμ; nmr (in CCl_4) (free base) δ 0.8–1.8 (m, 9 H), 2.71 (t, 2 H), 7.4–8.1 (m, 5 H), 8.53 (d, 1 H).

Anal. Calcd for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.32; H, 4.95; N, 13.23.

Distillation of the remaining oil gave the 3-pentyl-4-N,N-dipropylaminoquinoline: bp 80–82° (block temperature) at 0.001 mm; λ_{max}^{EtOH} 229, 262 mμ; nmr (in CCl_4, external TMS) δ 0.83 (t, 9 H), 1.1–1.8 (m, 10 H), 2.75 (t, 2 H), 3.21 (t, 4 H), 7.3–8.1 (m, 4 H), 8.65 (s, 1 H). A hydrobromide formed in ethyl acetate: mp 133°.

Reduction of 3-Methyl-4-N,N-diethylamino-7,8-benzo-2-quinolone with Lithium Aluminum Hydride.—Reduction of this quinolone gave 3-methyl-4-N,N-diethylamino-7,8-benzoquinoline (**20**) in essentially quantitative yield. This quinoline formed a hydrobromide salt, which was recrystallized from isopropyl alcohol: mp 215–216°; ir (salt) 2700–2800 cm^{-1}; λ_{max}^{EtOH} 211, 233, 270 mμ; nmr (in CCl_4 with external TMS) (free base) δ 0.91 (t, 6 H), 2.30 (s, 3 H), 3.16 (q, 4 H), 7.4–8.0 (m, 5 H), 8.56 (s, 1 H), 9.16 (m, 1 H).

Anal. Calcd for $C_{18}H_{21}BrN_2$: C, 62.55; H, 6.13; N, 8.11; Br, 23.13. Found: C, 62.29; H, 6.03; N, 8.20; Br, 23.37.

Reaction of N,N-Diethylphenylethynylamine with Benzonitrile Oxide.—A solution of 1 ml of triethylamine in 10 ml of anhydrous ether was added dropwise to a stirred solution of 0.43 g of phenylchlorohydroxamic acid and 0.45 g of N,N-diethylphenylethynylamine in 20 ml of anhydrous ether. The triethylamine hydrochloride was filtered, and the residue on crystallization from petroleum ether (bp 30–60°) afforded 0.47 g (42% yield) of the

(21) W. P. Untermohlen, Jr., *J. Org. Chem.*, **18**, 544 (1953).

1,3 dipolar cycloaddition product **21**: mp 87–88°; ir 1615, 775 cm^{-1} (N–O); λ_{max}^{EtOH} 245, 293 mμ; nmr (in CCl_4 with external TMS) δ 1.1 (t, 6 H), 3.2 (q, 4 H), 7.23 (m, 10 H).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.15; H, 6.90; N, 9.59. Found: C, 77.93; H, 6.87; N, 9.35.

Reaction of N,N-Diethylphenylethynylamine with Tetraphenylcyclopentadienone.—Tetraphenylcyclopentadienone, 0.5 g (1.5 mmol), and the ynamine, 0.25 g (1.5 mmol), in 3 ml of dry diglyme were heated in a sealed tube at 180° for 12 hr. Filtration of the mixture and recrystallization of the solid from toluene gave 50 mg (7% yield) of pentaphenyl-N,N-diethylaniline (**22**): mp 326–328; nmr (in $CDCl_3$ with internal TMS) δ 0.55 (t, 6 H), 2.5 (q, 4 H), 6.80 (m, 15 H), 7.10 (10 H).

Anal. Calcd for $C_{40}H_{35}N$: C, 90.69; H, 6.66; N, 2.64. Found: C, 90.90; H, 6.55; N, 2.90.

2-Naphthal- and 3-Pyridalsulfonimides.—The 2-naphthal-*p*-toluenesulfonimide was prepared in 90% yield according to the method of Kresze.[14] This sulfonimide was recrystallized from ethyl acetate and had mp 114–115°.

Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.89; H, 4.89; N, 4.53; S, 10.34. Found: C, 69.69; H, 5.04; N, 4.57; S, 10.33.

The 3-pyridal-*p*-toluenesulfonimide was prepared in the same manner in 40% yield and had mp 131–132° after recrystallization from ethyl acetate–petroleum ether (bp 30–60°).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.99; H, 4.65; N, 10.77; S, 12.29. Found: C, 59.53; H, 4.78; N, 10.30; S, 11.99.

Registry No.—**1**, 17691-74-6; **2**, 17691-75-7; **3a**, 17691-76-8; **3b**, 17691-77-9; **3c**, 17691-78-0; **3d**, 17691-79-1; **4a**, 17691-80-4; **4b**, 17691-81-5; **4c**, 17691-82-6; **5a**, 17692-75-0; **5b**, 17692-86-3; **5c**, 17692-87-4; **5d**, 17692-88-5; **5e**, 17692-76-1; **5f**, 17693-46-8; **5g**, 17693-47-9; **5h**, 17693-48-0; **5i**, 17693-49-1; **6**, 17693-50-4; **7**, 17692-77-2; **7** HBr, 17692-78-3; **8**, 17691-83-7; **9a**, 17691-84-8; **9b**, 17691-85-9; **9c**, 17691-86-0; **9d**, 17691-87-1; **10a**, 17691-88-2; **10b**, 17691-89-3; **11a**, 17691-90-6; **11b**, 17691-91-7; **11c**, 17691-92-8; **11d**, 17691-93-9; **11e**, 17691-94-0; **12a**, 17691-95-1; **12b**, 17691-96-2; **13a**, 17691-97-3; **13b**, 17691-98-4; **13c**, 17691-99-5; **13d**, 17692-00-1; **14a**, 17692-01-2; **14b**, 17692-02-3; **15a**, 612-58-8; **15b**, 17692-04-5; **15b** picrate, 17692-05-6; **16a**, 17692-06-7; **16a** perchlorate, 17692-07-8; **16b**, 17692-08-9; **17** perchlorate, 17692-09-0; **18a**, 17692-10-3; **18b**, 17692-11-4; **18c**, 17692-12-5; **19**, 17692-79-4; **20** HBr, 17692-80-7; **21**, 17692-81-8; **22**, 17692-82-9; 3-pentyl-4-N,N-dipropylaminoquinoline, 17692-83-0; 3-pentyl-4-N,N-dipropylaminoquinoline HBr, 17743-99-6; 2-naphthal *p*-toluenesulfonimide, 17692-84-1; 3-pyridal *p*-toluenesulfonimide, 17692-85-2; **15a**, picrate, 17693-31-1.

Formation of Pyrazoles from 3,3-Disubstituted 2,4-Pentanediones. Evidence of a Novel Claisen–Cope Type of Rearrangement

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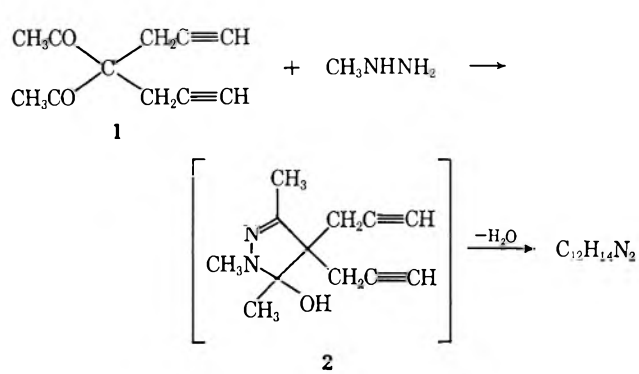
Received May 28, 1968

Reaction of monosubstituted hydrazines with 3,3-disubstituted 2,4-pentanediones having one or more allylic or propargylic groups at C-3 afforded high yields of pyrazoles bearing, respectively, 5-$CH_2CH(R)CH{=}CH_2$ or 5-$CH_2C(R){=}C{=}CH_2$ substituents. All evidence points to formation of an intermediate 5-methylene pyrazoline whose allylic or propargylic groups undergo a novel type of Claisen–Cope rearrangement, becoming attached to the enaminic methylene group with synchronous pyrazole formation. Treatment of 3-allyl-3-(2-propynyl)-2,4-pentanedione (**17**) with methylhydrazine leads to condensation and propargyl → allene rearrangement even at 0° and the relative rearrangement rates of allyl to propargyl were about 1.6:1 under the conditions studied. Similar reaction of methylhydrazine with 3-benzyl-3-methyl-2,4-pentanedione (**13**) produced the *exo*-methylene enamine **14** which was relatively stable under its conditions of formation. The enamine **14** underwent thermal rearrangement at 175° to 5-(2-phenylethyl)-1,3,4-trimethylpyrazole (**16**), evidently by a different type of process.

While the reaction of 3,3-disubstituted 2,4-pentanediones with hydrazine to give isopyrazoles is well known,[1,2] reaction of such substituted diketones with substituted hydrazines is imperfectly understood. Bis-2,4-dinitrophenylhydrazones[3–5] and bisphenylhydrazones[6] are usually formed, although 1:1 addition[7] and lack of reaction[8] have also been reported. Condensations with monoalkylhydrazines have apparently not been studied.

Reaction of 3,3-di(2-propynyl)-2,4-pentanedione (**1**) with methylhydrazine (*ca.* 1:1 mol ratio) in refluxing ethanol containing aqueous acetic acid gave a 72% yield of a crystalline base, $C_{12}H_{14}N_2$, corresponding to a loss of 1 mol of water from the hypothetical carbinolamine **2**.[9] The infrared (ir) spectrum of the product



(1) I. I. Grandberg, A. P. Krasnoshchek, A. N. Kost, and G. K. Faizova *J. Gen. Chem. USSR*, **33**, 2521 (1963).

(2) K. Auwers and F. Bergmann, *Ann.*, **472**, 287 (1929).

(3) M. F. Ansell, W. J. Hickinbottom, and A. A. Hyatt, *J. Chem. Soc.*, 1592 (1955).

(4) T. A. Favorskaya, A. V. Marshueva, and T.-Y. Hsü, *J. Gen. Chem. USSR*, **30**, 2499 (1960).

(5) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).

(6) A. E. Favorskii and A. S. Onishchenko, *J. Gen. Chem. USSR*, **11**, 1111 (1941).

(7) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Amer. Chem. Soc.*, **80**, 6533 (1958).

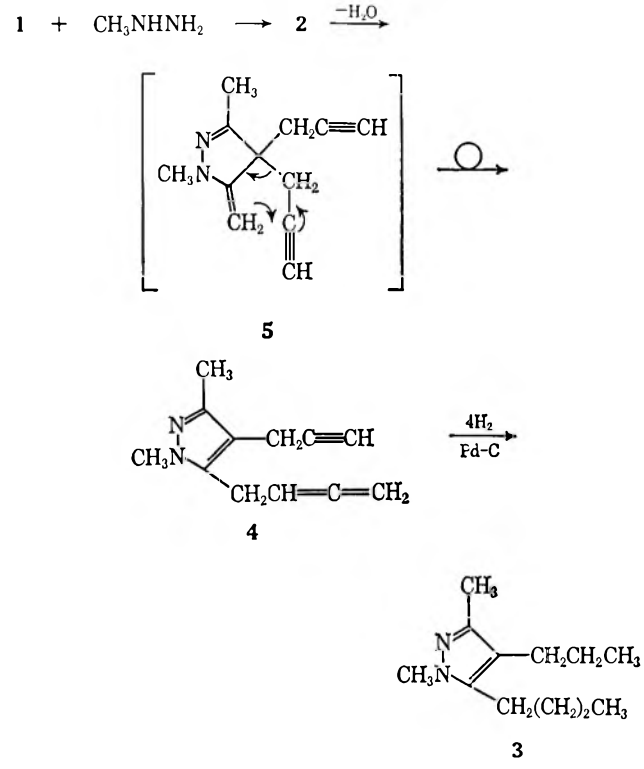
(8) G. T. Morgan and C. J. A. Taylor, *J. Chem. Soc.*, **127**, 797 (1925).

(9) P. Bouchet, J. Elguero, and R. Jacquier [*Tetrahedron*, **22**, 2461 (1966)] describe preparation of a related carbinolamine by reduction of the corresponding 5-pyrazolone.

indicated propargyl and cyclic C=CC=N functions and, most interestingly, the presence of an allenic group (5.1, 11.58 μ). The latter was shown by the nmr spectrum to be a butadienyl group $H_2C{=}C{=}CHCH_2$— giving three multiplets at δ 3.29–3.45 (CH_2), 4.59–4.84 ($=CH_2$), and 4.94–5.39 ppm (=C—H) and the presence of one propargyl and two methyl groups was also evident. A maximum at about 225 mμ (ϵ 814) was seen in the uv, while the mass spectrum showed a parent peak at 186. The appearance of an unconjugated allene group together with evident aromatization to a pyrazole (ir, uv, nmr) indicates that a cyclic migration–rearrangement of one propargyl group has taken place.

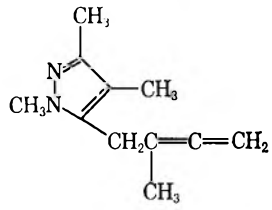
Catalytic reduction of $C_{12}H_{14}N_2$ required 4 mol of hydrogen and produced a base, identified by spectral and combustion analyses as 5-butyl-1,3-dimethyl-4-propylpyrazole (**3**). This information, along with the spectral data of $C_{12}H_{14}N_2$, indicates the structure of the product to be that of 5-(2,3-butadienyl)-1,3-dimethyl-4-(2-propynyl)pyrazole (**4**).[10]

The formation of a 2,3-butadienyl side chain in **4** suggests the occurrence of a new variant of the Claisen–Cope rearrangement involving the intermediate enamine **5** as follows.



In similar fashion, methylhydrazine reacted with 3-(2-butynyl)-3-methyl-2,4-pentanedione giving only **6** (*ca.* 98% yield) with no evidence of the acetylenic isomer **7**. When the diketone **1** was treated with the less basic phenylhydrazine, the same rearrangement occurred, giving **8**.

Since Claisen rearrangements of olefinic functions are better known than those involving propargyl groups,



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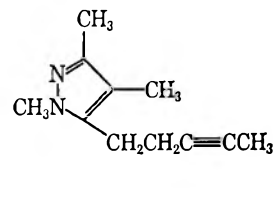

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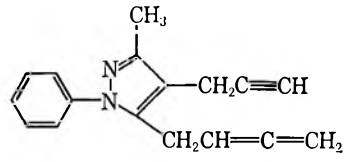
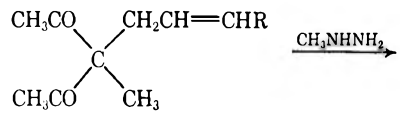
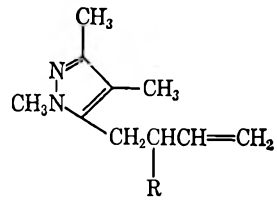


8

reaction of methylhydrazine with 3-allyl-3-methyl-2,4-pentanedione (**9**) and with 3-crotyl-3-methyl-2,4-pentanedione (**10**) was investigated. Smooth formation of pyrazoles **11** and **12** occurred with the exclusive appearance of the product (**12**) of crotyl inversion in-



9, R = H
10, R = CH_3



11, R = H
12, R = CH_3

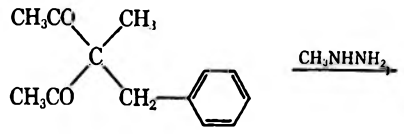
dicating the occurrence of a cyclic intramolecular rearrangement mechanism. Of additional interest was the reaction of methylhydrazine with 3-benzyl-3-methyl-2,4-pentanedione (**13**), since the expected enamine **14** should be potentially capable of (a) benzyl cleavage[11,12] by an ionic or radical mechanism and (b) Claisen rearrangement to the 5-*o*-tolyl product **15**. Action of methylhydrazine on **13** in refluxing ethanol, in fact, afforded **14** in 60% yield with no evident products of benzyl cleavage. When **14** was heated to 170–175°, however, an exothermic reaction occurred producing **16** in 85% yield. No trace of the hypothetical Claisen product **15** could be detected. It is thus apparent that migration of benzyl groups involves a process qualitatively distinct from the rearrangement of allylic or propargylic groups.

The present allylic and propargylic rearrangements are evidently facilitated by enamine electron donation from a C-5 methylene group and can be visualized as involving a six-membered cyclic transition state whose energy is decreased by synchronous formation of a stable pyrazole ring. While it might seem, *a priori*,

(10) The spectroscopic data of **3** and **4** do not preclude alternative attachment of the C_3 and C_4 chains at pyrazole positions C-5 and C-4, respectively. In the absence of known reference derivatives for comparison our structural assignment is based upon a consideration of the structures of the possible pyrazole products and of their known intermediate precursors.

(11) Y. Makisumi, *Tetrahedron Lett.*, 6413 (1966). The possibility that thermal rearrangement of an allyloxypyrazole occurs by a dissociation–recombination process rather than by a concerted mechanism has also been considered by O'Brien and Gates.[12]

(12) D. F. O'Brien and J. W. Gates, Jr., *J. Org. Chem.*, **31**, 1538 (1966).



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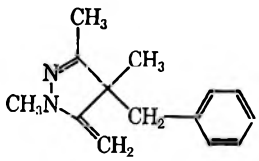

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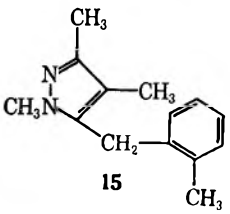

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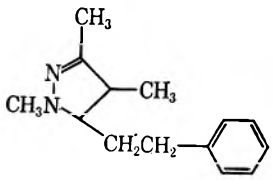
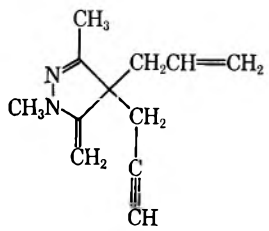


16

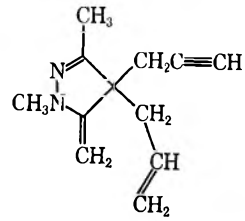
difficult to accommodate such a transition state to linear propargyl and allenyl groups, similar propargylic rearrangements have been observed, although at temperatures higher than those presently employed.[13-15]

Since both propargyl and allyl groups rearrange readily under our present conditions, the reaction of methylhydrazine with 3-allyl-3-(2-propynyl)-2,4-pentanedione (**17**) was studied in order to obtain some idea of the relative abilities of the two groups to rearrange. When the diketone **17** was treated with methylhydrazine at room temperature, vpc analysis of the reaction mixture at intervals showed concurrent formation of the products of allyl (**18**) and propargyl (**19**) rearrangement in the approximately constant ratio of 1.6:1. An ir spectrum of the reaction mixture after 23 hr showed strong bands corresponding to **18** (C≡C—H at 3.05 μ), to **19** (>C=C=C< at 5.15 μ), and to the enamine **20** (C=CH_2 at 6.1 μ), and the composition of the mixture, estimated from its nmr spectrum, was **18** (41%), **19** (34%), and **20** (25%). Upon refluxing the mixture for 1 hr in ethanol, a decrease in **20** with a corresponding increase in **19** was observed. Both **18** and **19** were thermally stable at the temperature (175°) of the gas chromatograph; hence the product ratio of 1.6:1 evidently represents a ratio of rate constants.[16] Final verification of the intermediate enamine (**20**) was obtained by repeating the reaction at 0° after which the pure picrate (**21**) of **20** was readily isolated. While structural assignments of **18** and **19** are made without recourse to independent syntheses, it would be difficult to postulate the formation of other products from **20**.

Although the ability of the propargyl group to compete so well with allyl in the rearrangement is surprising, consideration of the rotational modes of allyl and propargyl groups suggests an explanation. In orientation **20a** leading to propargyl rearrangement the rigid propargyl group can swing out of the bond-forming

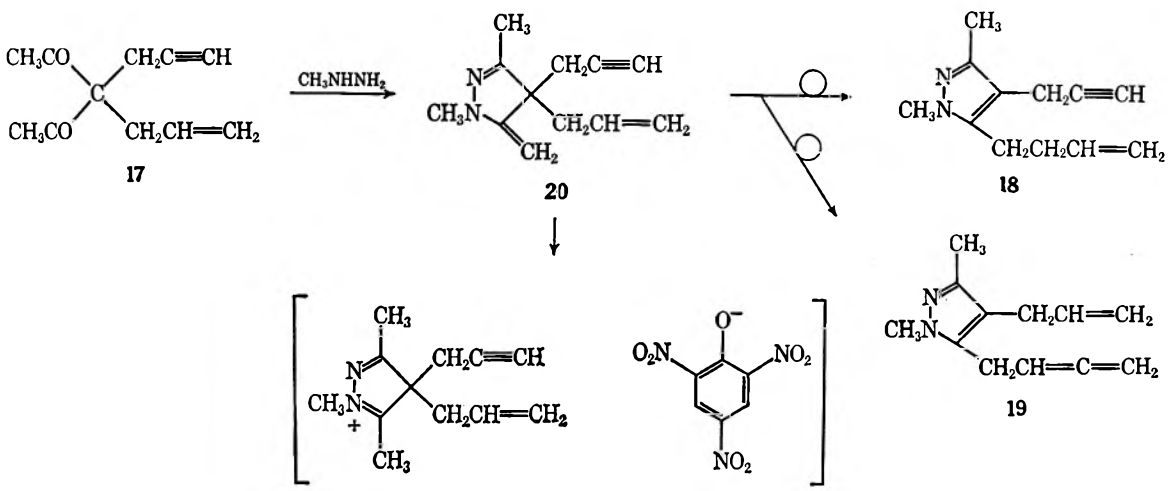


20a



20b

position only by rotation about the propargylpyrazoline sp^3 bond at C-4, while rotation about the linear C—C≡C axis has no effect upon sp availability. Allyl rearrangement orientation (**20b**), however, requires correct rotational orientation about the two sp^3 bonds of the more flexible allyl group. Therefore, it may be argued that any steric disadvantages existing for propargylic Claisen–Cope rearrangement should be mitigated by an entropy factor favoring propargyl.



17 **20** **18** **19** **21**

While Claisen-type rearrangements of allyl derivatives of pyrazoles[12] and of other nitrogen heterocycles[17,18] have been reported, formation of heteroaromatic systems *via* a carbon to carbon Claisen–Cope-type

(13) D. K. Black and S. R. Landor, *J. Chem. Soc.*, 6784 (1965).
(14) R. Gardi, R. Vitalli, and P. P. Castelli, *Tetrahedron Lett.*, 3203 (1966).
(15) B. S. Thyagarajan, K. K. Balasubramanian, and R. Brima Rao, *ibid.*, 1393 (1963).

(16) Since vpc analysis of the final reaction product gave no indication of *ca.* 25% enamine (**20**), it is evident that part of the **18** and **19** measured result from decomposition of **20** in the chromatograph. Hence the 1.6:1 ratio represents a composite ratio for temperature ranging between 25 and 175°.
(17) J. K. Elwood and J. W. Gates, Jr., *J. Org. Chem.*, **32**, 2956 (1967).
(18) B. S. Thyagarajan, *Advan. Heterocycl. Chem.*, **8**, 143 (1967).

rearrangement appears to be novel as does the migration of allyl groups to an enaminic β carbon from a site other than nitrogen.[19] The present rearrangement of propargylic groups under extremely mild conditions is seemingly without precedent.[20]

Pyrazoles with allenic substitution have apparently not been described in the literature. The present reaction provides a synthetic route to such C-5 allenic derivatives and to other unsymmetrically substituted pyrazoles.

Experimental Section

Nuclear magnetic resonance spectra were determined with Varian A-60 and HA-100 instruments employing TMS as the internal reference. An Aerograph Model 202B dual-column gas chromatograph was used for vpc analysis. Ordinary molecular weight determinations were performed by a modification of the thermistor method of Neumayer.[21] All melting points are corrected.

Preparation of 3,3-Disubstituted 2,4-Pentanediones.—Stepwise alkylation of 2,4-pentanedione by the method of Johnson, *et al.*,[22] proved highly effective in preparing 3,3-di(2-propynyl)-2,4-pentanedione (**1**),[23] 3-allyl-3-methyl-2,4-pentanedione (**9**),[1] 3-benzyl-3-methyl-2,4-pentanedione (**13**),[1] and other starting 3,3-disubstituted 2,4-pentanediones.

3-(2-Butenyl)-3-methyl-2,4-pentanedione (**10**) had bp 58° (0.75 mm). *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.70; H, 9.65.

3-(2-Butynyl)-3-methyl-2,4-pentanedione had bp 76° (1.8 mm). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.07; H, 8.44.

3-Allyl-3-(2-propynyl)-2,4-pentanedione (**17**) had bp 98° (5.8 mm). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.81; H, 7.99.

5-(2,3-Butadienyl)-1,3-dimethyl-4-(2-propynyl)pyrazole (**4**).—A solution of 3,3-di(2-propynyl)-2,4-pentanedione (2.64 g, 0.015 mol), methylhydrazine (0.78 g, 0.017 mol), glacial acetic acid (0.025 ml), and water (5 ml) in 75 ml of ethanol was refluxed for 3.5 hr, then evaporated under a stream of nitrogen. Crystallization of the residue from hexane at −80° gave 2.02 g (72.3%) of **4** as pale yellow crystals: mp 40–40.5°; ir (KBr) 3.05 (C≡C—H), 3.35, 3.41 (CH_3, CH_2), 4.73 (C≡C), 5.1 (C=C=C), 6.4 (C=C—C=N), 7.25 (C—CH_3), 11.5 μ (=CH_2 allene wagging); nmr ($CDCl_3$) δ 1.94 (t, 1, J = 2.8 Hz, C≡C—H), 2.20 (s, 3, CH_3—C=N), 3.62 (d, 2, J = 2.8 Hz, CH_2C≡C), 3.29–3.45 (m, 2, CH_2—C=C=C<), 3.70 (s, 3, CH_3—N<), 4.59–4.84 (m, 2, H_2C=C=C<), 4.94–5.39 (m, 1, —CH=C=C<); *m/e* 186 (parent), 147 (loss of $CH_2C{\equiv}CH$), 132 (loss of CH_3 from 147), 51 (C_4H_3 ion). *Anal.* Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04; mol wt, 186. Found: C, 77.12; H, 7.58; N, 14.85; mol wt, 182.

Compound **4** was sensitive to air at room temperature and sintered to a dark gum unless stored under nitrogen. Upon treatment with HCl in pentane, **4** gave a monohydrochloride, mp 112–114° (from ethyl acetate). *Anal.* Calcd for $C_{12}H_{15}N_2Cl$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.55; H, 7.04; N, 12.98.

The salt possessed an ir spectrum similar to that of **4** but with NH^+ bands at 3.83 and 3.95 μ. The nmr spectrum was essentially that of **4** with an additional proton (exchangeable) appearing at δ 14.6.

5-Butyl-1,3-dimethyl-4-propylpyrazole (**3**).—A solution of 2.0 g (0.0107 mol) of **4** in 50 ml of ethanol was hydrogenated at 25° (*ca.* 760 mm) in the presence of 5% Pd on carbon (0.1 g) causing uptake of about 4 mol of hydrogen. Distillation of the crude product gave 0.88 g of **3**: bp 155° (12 mm); *m/e* 194 (parent); ir (KBr) 6.35 μ (C=C—C=N); nmr ($CDCl_3$) δ 0.71–1.12 (t, 6, $CH_3CH_2CH_2$, $CH_3CH_2CH_2CH_2$), 1.12–1.70 [m, 6, >(CH_2)CC(=C)—, >(CH_2CH_2)CC=C<], 2.15 (s, 3, CH_3—C=N), 2.26–2.72 [m, 4, >(CH_2)C=C(CH_2)<], 3.69 (s, 3, CH_3—N<). The picrate of **3**, recrystallized from methanol, melted at 91.5–93° and gave the following analysis. *Anal.* Calcd for $C_{18}H_{25}N_5O_7$: C, 51.06; H, 5.95; N, 16.54. Found: C, 51.00; H, 5.99; N, 16.58.

5-(2-Methyl-2,3-butadienyl)-1,3,4-trimethylpyrazole (**6**).—Methylhydrazine (2.4 g, 0.052 mol) and 3-(2-butynyl)-3-methyl-2,4-pentanedione (6.64 g, 0.04 mol) were allowed to react as described previously, employing a 7.5-hr reflux period. The residue product was dissolved in ethyl ether and dried ($MgSO_4$), and ether was removed to give a product which crystallized on standing. Recrystallization from pentane (cooling to −80°) gave 5.6 g of pure **6** (100% purity by vpc): mp 41.5–43°; nmr ($CDCl_3$) δ 1.61 (t, 3, J = 3 Hz, CH_3C=C=CH_2), 1.89 (s, 3, CH_3C=C<), 2.15 (s, 3, CH_3C=N—), 3.20 [t, 2, J = 3 Hz, —(CH_2)C=C=CH_2], 3.69 (s, 3, CH_3—N), 4.58 [sextet, 2, J = 3 Hz, H_2C=C=C(CH_3)CH_2—]; ir (KBr) 3.44, 3.5 (CH_3, CH_2), 5.10 (C=C=C), 6.35 (C=C—C=N), 7.24 (C—CH_3), 11.65 μ (C=C=CH_2 wagging). *Anal.* Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.89. Found: C, 74.79; H, 9.35; N, 15.96. A second crop of product, 1.4 g (96.3% purity by vpc), brought the total yield to 98.0%.

5-(2,3-Butadienyl)-3-methyl-1-phenyl-4-(2-propynyl)pyrazole (**8**).—Phenylhydrazine (11.9 g, 0.11 mol) and **1** (17.6 g, 0.10 mol) were allowed to react as above but employing butanol as the solvent with a reflux period of *ca.* 13 hr. An ether solution of the stripped residue was dried ($MgSO_4$) and chromatographed on alumina giving 20.45 g of crude **8** which crystallized from pentane on cooling to −80°. The solid (11.3 g, 45.3%) melted near room temperature to a red oil which was recrystallized (pentane) to give 5.3 g of pure **8**: ir (NaCl) 3.0 (C≡C—H), 3.25 3.4 (C—H), 4.7 (C≡C), 5.1 (C=C=C), 6.25, 6.65, 6.95 (C=C—C=N, phenyl C=C), 7.22 (C—CH_3), 11.78 (C=C=CH_2), 13.1, 14.4 μ (monosubstituted phenyl). *Anal.* Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.30; H, 6.55; N, 11.41.

5-(3-Butenyl)-1,3,4-trimethylpyrazole (**11**).—3-Allyl-3-methyl-2,4-pentanedione (15.4 g, 0.1 mol) and methylhydrazine (5.06 g, 0.11 mol) were allowed to react under conditions identical with those described in the preparation of **4** giving, after evaporation of volatiles, an oil. An ether solution of the latter was dried ($MgSO_4$) and chromatographed on alumina giving 13.0 g (71.4%) of **11**: ir 6.05 (C=CH_2), 6.35 μ (C=C—C=N).

A 1.64-g (0.01 mol) portion of **11** yielded 3.34 g (85%) of a recrystallized (ethanol) picrate: mp 140.5–142.5°; nmr ($CDCl_3$) δ 2.04 (s, 3, CH_3C=C<), 2.39 (s, 3, CH_3C=N—), 2.15–2.57 [skewed quartet, 2, >(CH_2)C=C<], 2.68–3.00 (t, 2, >CH_2C=N<), 4.05 (s, 3, CH_3N<), 8.8 (s, 2, C_6H_2—), 15 (s, 1, exchangeable). *Anal.* Calcd for $C_{16}H_{19}N_5O_7$: C, 48.85; H, 4.87; N, 17.80. Found: C, 49.17; H, 4.69; N, 17.54.

5-(2-Methyl-3-butenyl)-1,3,4-trimethylpyrazole (**12**).—Methylhydrazine (1.5 g, 0.033 mol) and 3-crotyl-3-methyl-2,4-pentanedione (**10**, 5.0 g, 0.03 mol) were treated as before, employing butanol as solvent with a reflux period of 3.5 hr. The reaction residue was distilled under reduced pressure giving 3.25 g of **12** in the main fraction (95.7% by vpc), bp 64–65° (0.6 mm), and an additional 1.0 g in the forerun and in a final fraction as estimated by vpc. The total yield was 82.2%. The following spectral data were obtained: nmr ($CDCl_3$) δ 1.00 (d, 3, J = 6.5 Hz, CH_3C<), 1.88 (s, 3, CH_3C=C<), 2.14 (s, 3, CH_3C=N—), 2.49 (d, 2, CH_2CN<), 2.4–2.6 (m, 1, tertiary H), 3.68 (s, 3, CH_3—N), 4.77–5.15 (m, 2, CH_2=C<), 5.5–6.08 (m, 1, —HC=C<); ir (KBr) 6.10 (C=CH_2), 6.35 (C=C—C=N), 10.05 (=CH *trans* wagging), 10.94 μ (=CH_2 wagging). The picrate, mp 103.5–104.5° (from ethanol), gave the following analysis. *Anal.* Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19. Found: C, 50.17; H, 5.16; N, 17.26.

4-Benzyl-5-methylene-1,3,4-trimethyl-2-pyrazoline (**14**).—A mixture of methylhydrazine (5.06 g, 0.11 mol), 3-benzyl-3-methyl-2,4-pentanedione (20.4 g, 0.10 mol), acetic acid (1.0 ml), water (25 ml), and ethanol (200 ml) was refluxed for 4 hr, after which volatiles were removed giving 20.9 g of crude **14** as residue. A 5.0-g portion of the latter was dissolved in ether and chromatographed on an alumina column giving 3.1 g (60.5%) of pure **14**: nmr ($CDCl_3$) δ 1.17 (s, 3, CH_3C<), 1.86 (s, 3, CH_3C=N), 2.73 (s, 2, C_6H_5—CH_2), 2.89 (s, 3, CH_3—N), 3.67 (d, 2, J = 12 Hz, =CH_2), 7.11 (s, 5, C_6H_5); ir (KBr) 6.1

(19) R. K. Hill and N. W. Gilman, *Tetrahedron Lett.*, 1421 (1967).

(20) Propargyl → allenyl migration of **20** → **19** is actually observable, by ir analysis, after 17 hr at 0°.

(21) J. J. Neumayer, *Anal. Chim. Acta*, **20** (6), 519 (1959).

(22) A. W. Johnson, E. Markham, and R. Price, *Org. Syn.*, **42**, 75 (1962).

(23) K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.* (Weinheim), **295**, 627 (1962).

μ (N—C=CH_2). *Anal.* Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found: C, 78.12; H, 8.29.

5-(2-Phenylethyl)-1,3,4-trimethylpyrazole (16).—A 10.0-g sample of **14** was placed in a small distillation flask and heated to 172° under nitrogen. An exothermic reaction occurred with increase of the temperature to 210°, whereupon the heat was removed and the temperature fell to 165° in 17 min. An ether solution of the cooled residue was chromatographed (alumina) giving 8.5 g (85.0%) of pure **16**: bp 120–125° (0.15 mm); nmr ($CDCl_3$) δ 1.80 (s, 3, CH_3—C=C<), 2.14 (s, 3, CH_3—C=N—), 2.80 (s, 4, —CH_2—CH_2), 3.51 (s, 3, CH_3—N), 7.02–7.40 (m, 5, C_6H_5); ir (KBr) 13.32, 14.35 μ (monosubstituted phenyl). *Anal.* Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.40; H, 8.58; N, 13.20.

Reaction of Methylhydrazine with 3-Allyl-3-(2-propynyl)-2,4-pentanedione (17). A. In Refluxing Ethanol.—Methylhydrazine (5.06 g, 0.11 mol) and **17** (17.8 g, 0.1 mol) were allowed to react under the usual rearrangment conditions, but employing *ca.* a 15-hr reflux period. The solvent was evaporated, and a 16.5-g portion of the resulting oil (18.3 g) was chromatographed (ether elution) on alumina giving 14.6 g of **18** containing some of the allenic isomer (**19**) as indicated by absorption at 5.1 and 11.75 μ. Additional ir bands appeared at 3.0 (≡CH), 3.4 (C—H), 4.7 (C≡C), 6.4 (C=C—C=N), 7.2 (C—CH_3), 10.05 μ (=CH—), and 10.45 (=CH_2). A sample of product was converted into a picrate, mp 88–93° (51.2%), which, on recrystallization from ethanol, gave the picrate, mp 93.5–95.5°, of pure **18** showing no allenic absorption in the ir and nmr spectra: nmr ($CDCl_3$) δ 2.13 (t, 1, J = 2.8 Hz, H—C≡C), 2.47 (s, 3, CH_3—C=N), 2.44 (m, 2, CH_2—CH=CH), 2.90 (t, 2, J = 7.5 Hz, CH_2—CH_2CH=CH—), 3.41 (d, 2, J = 2.8 Hz, CH_2C≡C), 4.06 (s, 3, CH_3—N), 4.9–5.4 (m, 2, CH_2=C), 5.46–6.1 (m, 1, C=CH—), 8.90 (s, 2, C_6H_2), 14.08 (s, 1, exchangeable). *Anal.* Calcd for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.87; H, 4.48; N, 16.73.

Free **18** was isolated from its picrate by stirring 1.0 g of the latter with excess aqueous–ethereal HCl for 15 min followed by basification with NaOH and recovery by ether extraction. The yield of pure **18**, a yellow oil, was 410 mg (90.8%): ir (NaCl) 3.0 μ (≡C—H), 4.7 (C≡C), 6.07 (C=CH_2), 6.36 (C=C—C=N).

From a similar reaction of methylhydrazine with **17**, a reaction product was obtained, as above, consisting of **18** and **19**. A vpc analysis (5% Carbowax on 60–80 mesh Chromosorb W. AW, column temperature 175°) revealed peaks at 6.2 min (35.9% area) and 8.1 min (57.8% area). Enrichment of the mixture with pure **18** (from picrate, above) caused enlargement of the major (57.8%) peak. A sample of the minor (35.9%) component was collected by preparative vpc and shown to be the allenic isomer (**19**) by the following ir (KBr) data: 3.35, 3.42 (CH_3, CH_2), 5.11 (C=C=C), 6.4 (—C=C—C=N—), 7.25 (C—CH_3), 11.85 μ (allenic =CH_2).

The thermal stability of 5-(3-butenyl)-1,3-dimethyl-4-(2-propynyl)pyrazole (**18**) was tested by heating a sample at 172–175° for a 1-hr period followed by vpc and ir analyses. Although a pure sample of 4-allyl-5-(2,3-butadienyl)-1,3-dimethylpyrazole (**19**) was not available, a mixture containing *ca.* 66.5% **19** and 28.9% **18** was recovered from a mixture of the corresponding picrates and similarly subjected to the thermal treatment. Neither **18** nor the **19** + **18** mixture showed any change in ir or vpc following thermal treatment.

B. In Ethanol at Room Temperature.—The above-described reaction of methylhydrazine and **17** was performed at room temperature with subsequent vpc analysis (5% Carbowax 1540 on 60–80 mesh Chromosorb W. AW, column temperature 175°) of the mixture at 0-, 1-, 2-, 3-, 4-, 5-, 6-, and 23-hr intervals. The t = 0 sample showed substantial formation of **18** (7.1 min peak) and **19** (5.5 min peak) in an area ratio of about 1.62:1 which remained essentially constant as **18** and **19** increased over the 23-hr interval. At the end of the reaction, the mixture was rapidly evaporated at *ca.* 25° under reduced pressure. Infrared analysis showed, in addition to **18** and **19**, a C=O band (5.85 μ) and strong enamine absorption at 6.1 μ. Column chromatography (alumina) of an ether solution removed most of the carbonyl component with essentially no effect upon the other constituents as indicated by ir analysis. An nmr spectrum of the mixture showed the enamine **20** as a distinct singlet at δ 3.05 (CH_3—N<). Compound **19** showed a distinct multiplet at 4.59–4.76 (C=C=CH_2), and the corresponding integrals enabled the following estimate of composition: **20** (25%); **19** (34%); **18** (41%, by difference).

A sample of the chromatographed reaction product was refluxed in ethanol for 1 hr, and, after removing solvent, the ir spectrum was again determined. The enaminic 6.1-μ band was still present although notably weaker than before reflux, while a corresponding intensification of the allene (5.1, 11.8 μ) bands had occurred.

C. In Ethanol at 0°.—The above reaction was repeated at 0°, storing the mixture under nitrogen for a 17-hr period. Evaporation of volatiles left 19.0 g of material showing a strong enamine band (6.1 μ). Alumina chromatography afforded a 16.3-g fraction of oil showing very weak allenic absorption (5.1 μ) and and intense band at 6.1 μ. Treatment of 5.64 g (0.03 mol) of the material with picric acid (7.60 g, 0.03 mol) in ethanol at 0° gave 9.95 g of a crude picrate, mp 105–119°. A 1.75-g portion of the latter was recrystallized twice from ethanol giving 0.5 g (22.7%) of the pure picrate **21**: mp 135–136°; nmr (CD_3COCD_3); δ 2.44 (s, 3, CH_3—C=N—N), 2.73 (t, 1, J = 2.7 Hz, C≡C—H), 2.91 (s, 3, CH_3—C=N<), 2.98–3.12 (m, 2, CH_2—CH=CH), 3.20 (m, 2, CH_2C≡C), 4.16 (s, 3, CH_3—N), 5.02–5.6 (m, 3, CH=CH_2), 8.60 (s, 2, C_6H_2); ir (KBr) 3.03 (≡C—H), 6.1 (C=N, C=C), 6.44, 7.35 (NO_2), 7.05 (N—CH_3), 7.18 μ (C—CH_3). *Anal.* Calcd for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59; N, 16.78. Found: C, 51.93; H, 4.29; N, 16.70.

Registry No.—**3**, 17512-04-8; **3** picrate, 17512-05-9; **4**, 17512-06-0; **4** HCl, 17512-07-1; **6**, 17512-08-2; **8**, 17528-40-4; **10**, 17512-09-3; **11** picrate, 17512-10-6; **12** picrate, 17512-11-7; **14**, 17512-12-8; **16**, 17512-13-9; **17**, 17512-14-0; **18**, 17528-41-5; **18** picrate, 17528-42-6; **19**, 17512-15-1; **21** picrate, 17528-43-7; 3-(2-butynyl)-3-methyl-2,4-pentanedione, 17512-16-2; **12**, 17512-17-3.

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The Reactions of Cyanoacetic Acid with 2,6-Diphenyl-4-pyrone

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Cyanoacetic acid reacts with 2,6-diphenyl-4-pyrone (**1**) under neutral conditions to give a salt (**2**), and under basic conditions to give 4-(cyanomethylene)-2,6-diphenyl-4H-pyran (**4**). In hot acetic anhydride the same reactants give 1,3-dicyano-1,3-bis(2,6-diphenyl-4H-pyranylidene-4)acetone (**7**). A proof of structure and a proposal for the formation of **7** is given.

The product obtained by the reaction of 2,6-diphenyl-4-pyrone (**1**) and cyanoacetic acid in ethyl acetate has been assigned structure **2a** on the basis of the electronic and nmr spectra. The electronic spectrum of **2a** is almost identical with that of 2,6-diphenyl-4-hydroxypyrylium perchlorate (**2b**) (see Table I), and the nmr spectrum of **2a** shows the methylene protons as a singlet at τ 6.49 (2 H), the protons at the 3,5 positions of the pyrylium ring as a singlet at 3.18 (2 H), the hydroxyl proton at −4.6 (1 H), and the aromatic protons as a multiplet at 2.2–2.8 (10 H).

Table I

Electronic Spectra[a]

Compound no.	λ_1	λ_2	λ_3	λ_4	λ_5
	λ_{max}, mμ (ε × 10⁻³)				
1	263 (20.6)			340 (12.4)	
2a	252 (21.5)		280 (25.3)		
2b	252 (20.2)		282 (24.5)		
3		270 (15.0)	280 (14.5)	327 (7.4)	~350 (6.0)
4	253 (18.5)	261 (18.6)	288 (21.3)	341 (23.6)	
			293 (20.9)		
5	232 (24.8)		274 (35.7)	392 (32.4)	537 (87.0)
6		262 (12.6)	366 (17.6)	406 (32.0)	422 (28.4)
7			333 (38.5)	465 (54.7)	480 (57.5)
8	257 (30.2)	~295 (8.7)		409 (21.4)	
9	263 (15.0)		376 (12.1)	460 (57.6)	
10a	259 (19.9)	308 (15.7)	388 (24.1)	~415 (14.7)	
10b	259 (20.5)	316 (20.2)	390 (34.4)	400 (35.5)	
11	256 (15.2)	318 (22.0)	386 (28.0)		~406 (17.0)
12	258 (15.8)	333 (20.9)	393 (35.4)		~420 (30.0)
13a	260 (12.4)		378 (32.3)		
13b	250 (18.0)		388 (46.3)		
14	258 (53.0)		280 (64.7)		
15	235 (37.8)		275 (42.0)	400 (52.5)	575 (77.0)
17	230 (21.0)		268 (26.4)	379 (27.2)	543 (120.8)

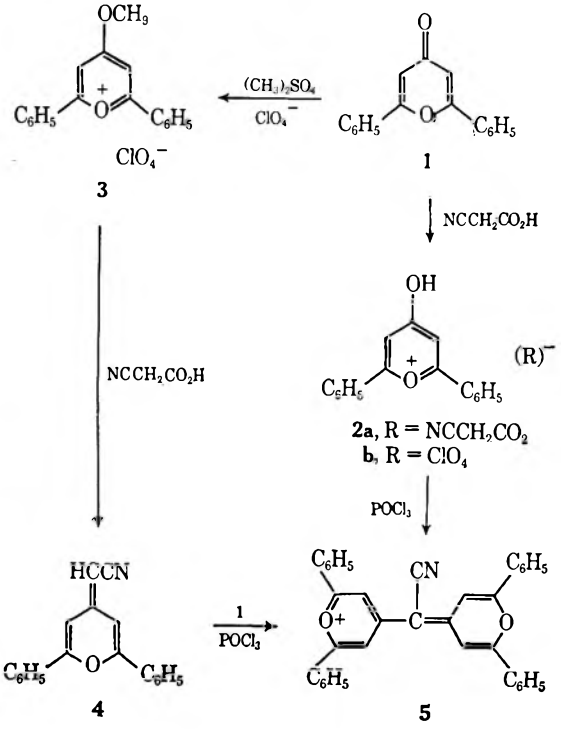
[a] All spectra were determined in acetonitrile using a Cary Model 15 spectrophotometer.

Thermolytic decomposition of **2a** in the heated inlet of the mass spectrometer occurs to give **1**, acetonitrile, and carbon dioxide.

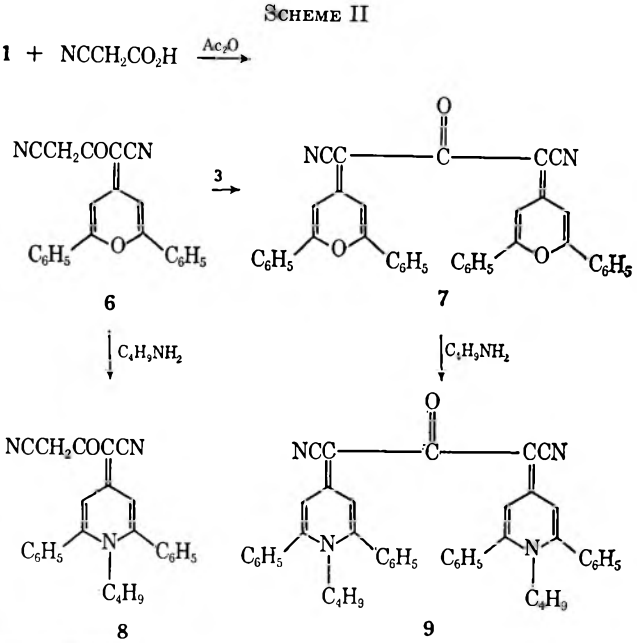
Treatment of **2a** with phosphorus oxychloride gave the dye **5**. Dimethyl sulfate converts **1** into the pyrylium salt **3**[1] which was isolated as the perchlorate, and reaction of **3** with cyanoacetic acid under basic conditions gave **4**. A mixture of **4**, **1**, and phosphorous oxychloride gave the dye **5**. These reactions are summarized in Scheme I.

The pyrone **1** and cyanoacetic acid react in acetic anhydride at reflux temperature to give **6**. A similar compound has been prepared from 2,6-dimethyl-4-pyrone and cyanoacetic acid.[2] To demonstrate the presence of a reactive methylene group in **6**, the latter compound was condensed with an equivalent of **3** under basic conditions to give **7**. The reaction of **6** and **7** with *n*-butylamine gave **8** and **9**, respectively, a reaction which is typical of 4-dehydro-4H-pyrans.[2,3] These reactions are illustrated in Scheme II.

Scheme I



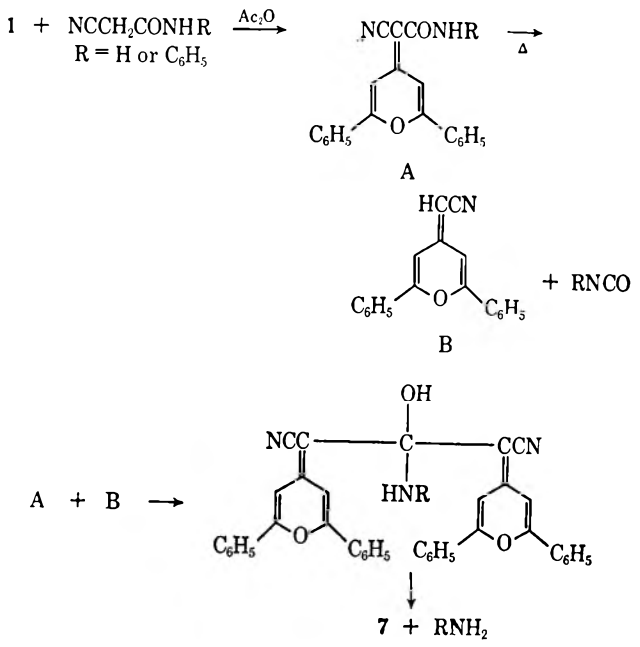
Scheme II



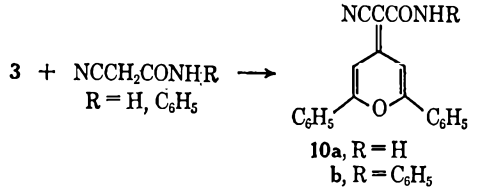
(1) G. Traverso, *Ann. Chim.* (Rome), **46**, 821 (1956).
(2) S. Yamamara, K. Kato, and H. Herato, *Tetrahedron Lett.*, 1637 (1967).
(3) F. Eiden, *Naturwissenshaften*, **47**, 61 (1960); *Arch. Pharm.* (Weinheim), **295**, 607 (1962).

Cyanoacetamide and cyanoacetanilide both react with **1** in boiling acetic anhydride to give **7**. One possible route to **7** from these components is shown in Scheme III.

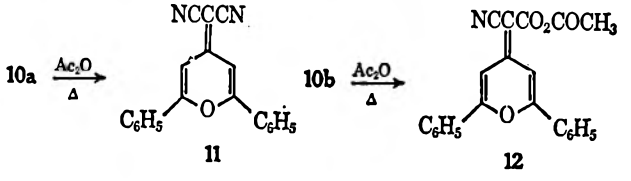
SCHEME III



As a test of the reaction sequence shown in Scheme III, the compounds **10a** and **10b** were prepared by the reaction of **3** with cyanoacetamide and cyanoacetanilide, respectively. However, it was found that



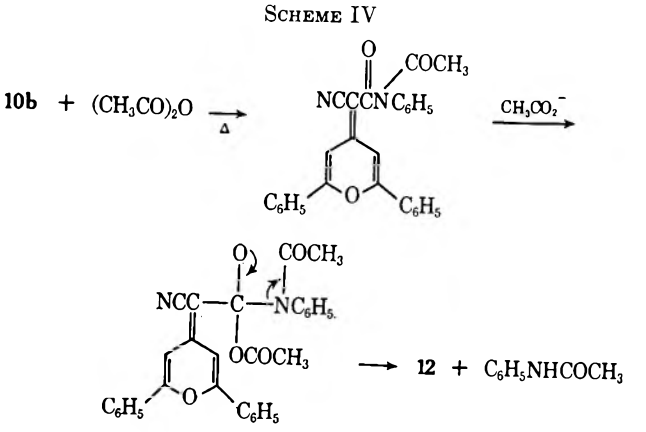
heating **10a** in acetic anhydride gave **11** rather than **7**, and **10b** under the same conditions gave **12**. Compound **11** is known and is probably formed by the dehydration of the amide group of **10a**.



The structure of **12** was established by the electronic spectrum which is similar to that of **10a**: the infrared (ir) spectrum shows strong absorption at 5.65 and 5.78 μ which is assignable to the anhydride function; and mass spectrometric data show a parent peak at m/e 357 and a fragmentation typical of an anhydride group. The probable reaction path leading to **12** is shown in Scheme IV.

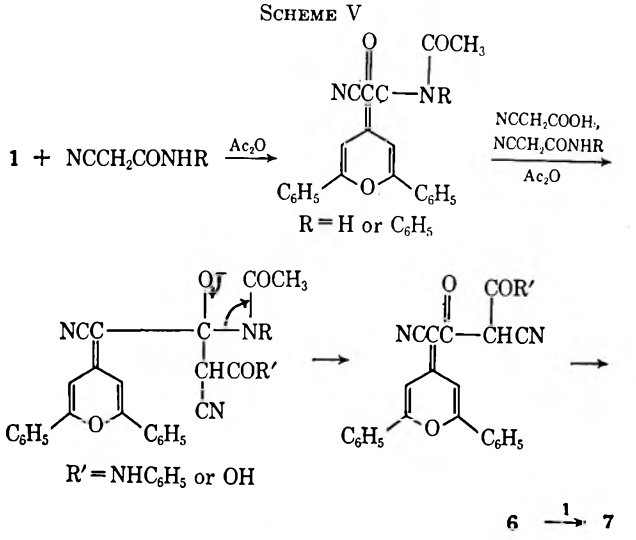
If an equivalent of cyanoacetic acid or cyanoacetanilide is heated with **10b** in acetic anhydride, the product is **6** rather than **12**. This result is due to either the stronger nucleophilic character of cyanoacetic acid and cyanoacetanilide compared with that of acetate or to a favorable equilibrium.

SCHEME IV



On the basis of the data presented above, the reaction path outlined in Scheme III has been shown to be wrong, and that presented in Scheme V is consistent with the experimental data.[4]

SCHEME V



Compounds **10a** and **10b** were converted into the pyridinium salts **13a** and **13b** by means of *n*-butylamine.

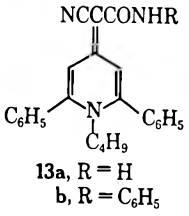
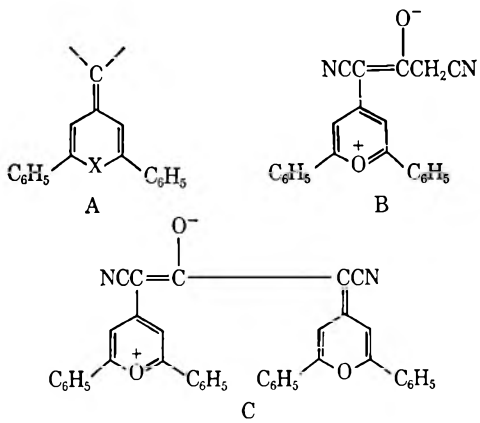


Table I contains the absorption spectra of the compounds described in this paper. All of the compounds with the exception of **1**, **2**, and **5** contain the conjugated system A. The basic absorption pattern of the compounds of type A is similar but modified by substituents in the following manner. The long-wavelength band of **4** (341 mμ) is shifted to about 388 mμ, and shoulders appear at about 415 mμ in **10a** and **10b**. The corresponding nitrogen analogs **13a** and **13b** absorb again at about 388 mμ, but no shoulders were observed. The

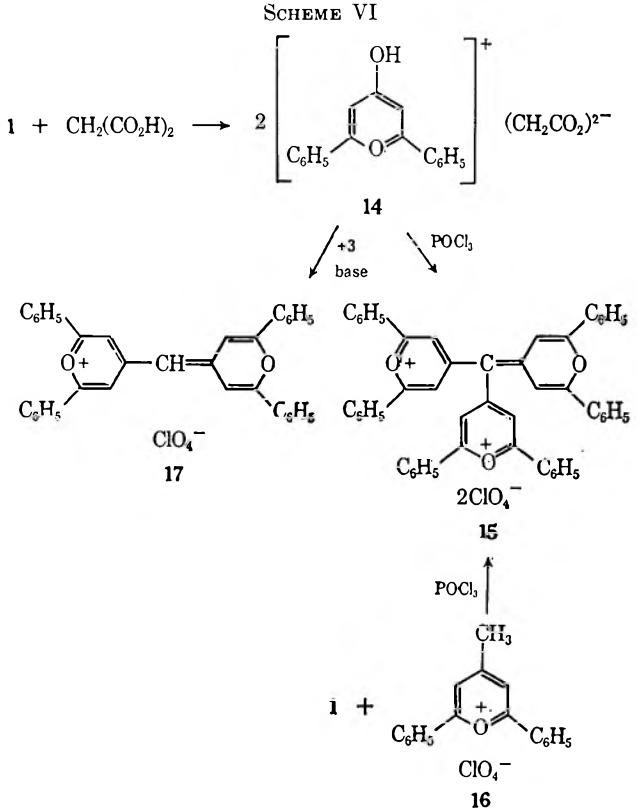
(4) A referee has suggested another process for the formation of **6** through the formation of 1,3-dicyanoacetone from cyanoacetic acid or cyanoacetanilide and acetic anhydride. Dicyanoacetone and **1** would give **6**. We were unable to isolate dicyanoacetone from the reaction of cyanoacetic acid with acetic anhydride, but this does not prove that dicyanoacetone is not an unstable intermediate.

ketones **6** and **7** show absorption at 422 and 480 mμ, which may arise from the charged species B and C, respectively. The nitrogen homologs of **6** and **7** show absorption at 409 and 460 mμ, respectively, again suggesting some contribution from a dipolar form. The spectrum of **12** is similar to **11**, indicating that the same basic structure is present in both compounds.



The reaction of 2,6-diphenyl-4-pyrone (**1**) has been extended to malonic acid. In a similar fashion to cyanoacetic acid, malonic acid reacts with **1** in ethyl acetate to give di(4-hydroxy-2,6-diphenylpyrylium) malonate (**14**). With phosphorous oxychloride, **14** yields the dye **15** which may also be obtained from **16** and **1** in the presence of phosphorous oxychloride.

Scheme VI



The magenta dye **17** is formed by the reaction of **14** with **3** under basic conditions. These reactions are summarized in Scheme VI above.

Experimental Section[5]

4-Hydroxy-2,6-diphenylpyrylium Cyanoacetate (2a).—A solution of 5 g (0.02 mol) of **1** and 1.7 g (0.02 mol) cyanoacetic acid in 75 ml of ethyl acetate was refluxed for 15 min. The mixture was cooled, and the solid was collected and recrystallized from ethyl acetate to give an 80% yield of product: mp 141°; mass spectrum thermally decomposes in the heated inlet (235°) to **1**, CO_2, and CH_3CN.

Anal. Calcd for $C_{20}H_{13}NO_4$: C, 72.2; H, 4.5; N, 4.2. Found: C, 72.2; H, 4.3; N, 4.2.

4-Hydroxy-2,6-diphenylpyrylium Perchlorate (2b).—A solution of 5 g of **1** in 50 ml of acetonitrile was mixed with 3 ml of 70% perchloric acid, and the precipitate was collected and recrystallized from acetonitrile, giving a 94% yield of **2b**: mp 237–238°.

Anal. Calcd for $C_{17}H_{13}ClO_6$: C, 58.6; H, 3.7; Cl, 10.6. Found: C, 58.7; H, 3.7; Cl, 10.4.

4-Methoxy-2,6-diphenylpyrylium Perchlorate (3).—A mixture of 15 g of **1** and 35 ml of dimethyl sulfate was heated on the steam bath for 3 hr and cooled, and ether (100 ml) was added. The precipitate was collected, washed with ether, and dissolved in methanol. The addition of 7 ml of 70% perchloric acid caused **3** to separate, and the solid was collected and recrystallized from acetonitrile; yield 83%; mp 257–258°.

Anal. Calcd for $C_{18}H_{15}ClO_5$: C, 59.7; H, 4.1; Cl, 9.7. Found: C, 59.3; H, 4.5; Cl, 9.9.

4-(Cyanomethylene)-2,6-diphenyl-4H-pyran (4).—A solution of 3.6 g (0.01 mol) of **3**, 2 g of cyanoacetic acid, and 4 ml of N,N-diisopropylethylamine in 30 ml of acetonitrile was heated under reflux for 2 hr, poured into water, and the precipitate collected and crystallized from alcohol and then acetic acid: yield 45%; mp 145–150°; *m/e* 271, 242, 215, 105, 102, 77.

Anal. Calcd for $C_{19}H_{13}NO$: C, 84.1; H, 4.8; N, 5.2. Found: C, 84.7; H, 4.7; N, 5.4.

4-[Cyano-(2,6-diphenyl-4H-pyran-4-yl)methylidene]-2,6-diphenylpyrylium Perchlorate (5). A.—A solution of 2.0 g of **2** in 4 ml of phosphorous oxychloride was heated for 3 hr at 95–100°. The reaction mixture was poured into methanol, and 2 ml of 70% perchloric acid was added. The precipitated dye was collected and extracted with methanol in a Soxhlet extractor. The dye **5** crystallized from the extract: yield 33%; mp 321–322°.

Anal. Calcd for $C_{36}H_{24}ClNO_6$: C, 71.8; H, 4.0; N, 2.3. Found: C, 71.4; H, 4.1; N, 2.2.

B.—Alternatively, a mixture of 1.4 g of **4** and 1.4 g of **1** in 5 ml of phosphorous oxychloride was treated in the same manner to give **5** in 77% yield.

4-(Cyanoacetylcyanomethylene)-2,6-diphenyl-4H-pyran (6).—A solution of 5.0 g (0.02 mol) of **1** and 3.0 g (0.035 mol) of cyanoacetic acid in 15 ml of acetic anhydride was heated at 90–95° for 3 hr and then cooled to give **6**: mp 261–262° from 1,2,3-trichloropropane; yield 75%; *m/e* 338, 298, 105, 102, 77.

Anal. Calcd for $C_{22}H_{14}N_2O_2$: C, 78.0; H, 4.3; N, 8.3. Found: C, 77.9; H, 4.5; N, 8.1.

The mother liquors were concentrated, and the solid which was obtained was recrystallized from N,N-dimethylformamide, giving 1 g of **7**.

1,3-Dicyano-1,3-bis(2,6-diphenyl-4H-pyranylidene-4)acetone (7). A.—A solution of 1.7 g of **6** and 1.8 g of **3** in 30 ml of acetonitrile was heated to reflux, and 2.0 ml of N,N-diisopropylethylamine was added. After 2 hr at 90–95°, the mixture was cooled and **7** was collected and recrystallized from N,N-dimethylformamide: mp 344–345°; yield 86%; *m/e* 568, 298, 270, 105, 77.

Anal. Calcd for $C_{39}H_{24}N_2O_3$: C, 82.4; H, 4.2; N, 4.9. Found: C, 82.1; H, 4.5; N, 5.1.

B and C.—A solution of 5.0 g of **1** and 3.5 g of cyanoacetanilide (or 2.5 g of cyanoacetamide) in 30 ml of acetic anhydride was heated at reflux for 4 hr. The mixture was cooled, and the solid was collected and recrystallized to yield 78% from cyanoacetanilide and 69% from cyanoacetamide.

1-*n*-Butyl-4-(cyanoacetylcyanomethylene)-2,6-diphenyl-1,4-dihydropyridine (8).—A solution of 2.0 g of **6** and 4 ml of *n*-

(5) The mass spectra were obtained by using either a 60° sector-type mass spectrometer, or a Consolidated Electrodynamics Model 21-110B mass spectrometer. The heated inlet was of the type described by V. J. Caldecourt [*Anal. Chem.*, **27**, 1670 (1955)] but constructed entirely of glass. The compounds which were not volatile in the heated inlet system were analyzed *via* the direct probe of the CEC 21-110B.

butylamine in 10 ml of ethoxyethanol was heated to 90–95° for 3 hr. The solvent was evaporated, methanol was added to the residue, and the product **8** was collected and recrystallized from butyl alcohol: yield 72%; mp 295–296°; *m/e* 393, 392, 364, 350, 337, 77.

Anal. Calcd for $C_{26}H_{23}N_3O$: C, 79.3; H, 5.8; N, 10.7. Found: C, 79.5; H, 5.9; N, 10.9.

1,3-Dicyano-1,3-bis(2,6-diphenyl-1-*n*-butyl-1,4-dihydropyridylidene-4)acetone (**9**).—A mixture of 1.0 g of **7** and 6 ml of *n*-butylamine was heated under reflux for 2 hr. The excess butylamine was removed by vacuum distillation, the residue was dissolved in methanol, and the product was precipitated by the addition of 3 ml of acetic acid in 10 ml of water. The solid was collected and recrystallized from acetonitrile giving a 50% yield of **9**, mp 310°.

Anal. Calcd for $C_{47}H_{42}N_4O$: C, 81.9; H, 6.1; N, 8.1. Found: C, 82.0; H, 6.3; N, 8.3.

4-(Cyanocarbamoylmethylene)-2,6-diphenylpyran (**10a**).—A solution of 14.5 g of **3** and 7.2 g of cyanoacetamide in 100 ml of acetonitrile was heated to reflux and 12 ml of N,N-diisopropylethylamine was added. The product which separated immediately was collected and recrystallized from 1,2,3-trichloropropane: yield 95%; mp 290°; *m/e* 314, 298, 105, 77. This compound slowly decomposed in the heated inlet system to **4** and **11**.

Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.4; H, 4.5; N, 8.9. Found: C, 76.1; H, 4.3; N, 8.9.

4-(Cyanophenylcarbamoylmethylene)-2,6-diphenylpyran (**10b**).—The compound was prepared by the method described for **10a** and was recrystallized from chlorobenzene: yield 93%; mp 240°; *m/e* 390, 298, 105, 77.

Anal. Calcd for $C_{26}H_{18}N_2O_2$: C, 80.0; H, 4.6; N, 7.2. Found: C, 80.0; H, 4.6; N, 7.1.

4-(Cyanocarbamoylmethylene-1-*n*-butyl-2,6-diphenyl-1,4-dihydropyridine (**13a**) **and 4-Cyanophenylcarbamoylmethylene-2,6-diphenyl-1,4-dihydropyridine** (**13b**).—These compounds were prepared from **10a** and **10b**, respectively, by the method described for the preparation of **9**. Compound **13a** was recrystallized from methanol and melted at 194–195°: yield 71%. This compound thermally decomposed in the heated inlet system to 1-butyl-4-cyanomethylidene-2,6-diphenyl-1,4-dihydropyridine and cyanic acid.

Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.2; H, 6.2; N, 11.4. Found: C, 77.9; H, 6.5; N, 11.5.

Compound **13b** was recrystallized from ethanol and melted at 185–186°: yield 84%. This compound thermally decomposed to the same dihydropyridine derivative as **13a** plus phenyl isocyanate.

Anal. Calcd for $C_{30}H_{27}N_3O$: C, 80.6; H, 6.0; N, 9.4. Found: C, 80.8; H, 6.0; N, 9.3.

4-(Dicyanomethylene)-2,6-diphenyl-4H-pyran (**11**). **A.**—A solution of 4.0 g of **10a** in 24 ml of acetic anhydride was heated for 18 hr, the mixture was cooled, and the solid was collected and recrystallized from nitromethane, giving a 74% yield of **11**: mp 267°; *m/e* 296, 267, 240, 105, 102, 77.

Anal. Calcd for $C_{20}H_{12}N_2O$: C, 81.0; H, 4.0; N, 9.5. Found: C, 81.4; H, 4.0; N, 9.5.

B.—A solution of 7.0 g of **3** and 2 g of malononitrile in 50 ml of acetonitrile was heated to reflux, and 5.0 ml of N,N-diisopropylethylamine was added. The mixture was chilled, and the solid was collected and recrystallized giving a 70% yield of **11**.

4-(Cyanoacetoxycarbonylmethylene)-2,6-diphenyl-4H-pyran (**12**).—A solution of 4.0 g of **10b** and 25 ml of acetic anhydride was heated to reflux for 16 hr and cooled, and the solid was collected and recrystallized from acetonitrile: yield 59%; mp 229–230°; *m/e* 357, 315, 298, 271, 105, 102, 77, 43.

Anal. Calcd for $C_{22}H_{15}NO_4$: C, 74.0; H, 4.2; N, 3.9. Found: C, 74.2; H, 4.0; N, 4.1.

Di(4-hydroxy-2,6-diphenylpyrylium) Malonate (**14**).—A mixture of 10 g of **1**, 4.2 g of malonic acid, and 200 ml of ethyl acetate was heated for 5 min on a steam bath and cooled, and the solid was collected and recrystallized from ethyl acetate: yield 98%; mp 125°. This compound thermally decomposed to **1** and acetic acid.

Anal. Calcd for $C_{37}H_{28}O_8$: C, 73.1; H, 4.7. Found: C, 73.4; H, 4.9.

***meso*-(2,6-Diphenylpyrylium-4)bis(2,6-diphenylpyrylium-4)monomethinecyanine Diperchlorate** (**15**). **A.**—A solution of 3 g (0.005 mol) of **14** and 3 ml of phosphorous oxychloride was heated on a steam bath for 2 hr, and 15 ml of ethyl alcohol was added to the reaction mixture. The mixture was chilled, 3 ml of 70% perchloric acid was added, and the solid was collected and recrystallized from acetonitrile: yield 47%; mp 315°; explodes.

Anal. Calcd for $C_{52}H_{36}Cl_2O_{11}$: C, 68.6; H, 3.9; Cl, 7.9. Found: C, 68.2; H, 4.1; Cl, 7.9.

B.—A mixture of 2.5 g (0.01 mol) of **1**, 1.73 g (0.005 mol) of 4-methyl-2,6-diphenylpyrylium perchlorate (**16**), and 9 ml of phosphorous oxychloride was heated for 2 hr on a steam bath, diluted with 100 ml of methanol, and chilled, and the solid was collected and recrystallized to give a 56% yield of product.

Bis(2,6-diphenylpyrylium)monomethinecyanine Perchlorate (**17**).—A mixture of 3 g (0.005 mol) of **14**, 3.5 g (0.01 mol) of **3**, 2 ml of N,N-diisopropylethylamine, and 25 ml of acetonitrile was refluxed for 3 hr and cooled, and the solid was collected and recrystallized from acetonitrile: yield 51%; mp 310–311°.

Anal. Calcd for $C_{35}H_{25}ClO_6$: C, 72.8; H, 4.3; Cl, 6.2. Found: C, 72.8; H, 4.6; Cl, 6.1.

Registry No.—**1**, 1029-94-3; **2a**, 17605-20-8; **2b**, 17539-76-3; **3**, 17539-77-4; **4**, 17539-78-5; **5**, 17558-09-7; **6**, 17533-57-2; **7**, 17533-58-3; **8**, 17533-59-4; **9**, 17533-60-7; **10a**, 17558-05-3; **10b**, 17533-61-8; **11**, 17533-62-9; **12**, 17558-06-4; **13a**, 17533-63-0; **13b**, 17605-21-9; **14**, 17558-07-5; **15**, 17558-08-6; **17**, 17558-10-0; cyanoacetic acid, 372-09-8.

Intermediates in the Hantzsch Thiazole Synthesis

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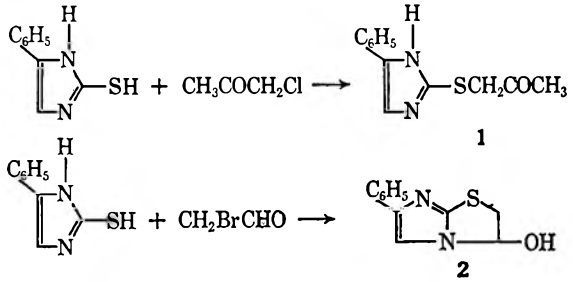
The reaction of N-methyl-*p*-dimethylaminothiobenzamide (**3**) with a number of α-halo ketones and one α-halo aldehyde gave stable 4-hydroxythiazolinium salts (**4**) which could be subsequently dehydrated to the thiazolium salts (**5**). When the intermediates were also substituted in the 5 position, both possible diastereoisomeric forms were detected by nmr spectroscopy. The effects of acidification and temperature variation on the nmr spectra indicated that the diastereoisomeric 4-hydroxythiazolinium salts are in dynamic equilibrium *via* the open-chain α-thio ketone.

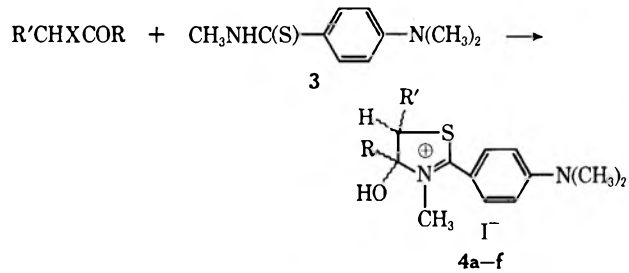
The reaction of a thioamide or a thiourea with an α-halocarbonyl compound in the Hantzsch synthesis usually proceeds smoothly to yield the desired thiazole.[1] Although the reaction has been postulated to be stepwise, reports of the isolation of intermediates in this reaction have been infrequent. In some early examples[2] intermediates of varying stability were isolated by working at low temperatures. These substances were characterized solely by elemental analysis (before the advent of spectroscopic techniques) and were always assumed to be the open-chain α-thio ketones (for example, see ref 3).

Recently, Kochergin and Shchukina[4] isolated an intermediate from the reaction of chloroacetone with 2-mercapto-4-phenylimidazole which was shown by both chemical evidence and ir spectroscopy to be 2-acetonylmercapto-4-phenylimidazole (**1**). However, the analogous reaction[5] between bromoacetaldehyde and 2-mercapto-4-phenylimidazole unexpectedly afforded the cyclized intermediate 2,3-dihydro-3-hydroxyimidazo[2,1-*b*]thiazole (**2**). Both **1** and **2** could be dehydrated in acidic media to the corresponding thiazole derivatives.



In a series of papers by Murav'eva and Shchukina,[6] the isolation of hydroxythiazolines from the reaction between α-halo ketones and a variety of thioureas is reported. The use of a reagent bearing a basic center or the addition of a base to the reaction mixture was recognized as necessary to prevent the acid-catalyzed elimination of the elements of water from the intermediates. Since the publication of this work, a number of similar intermediates have been isolated from analogous reactions.[7,8] It is interesting to note that in each of these cases[3-8] only one intermediate, either the α-thio ketone or the hydroxythiazoline, was isolated from the reaction mixture.

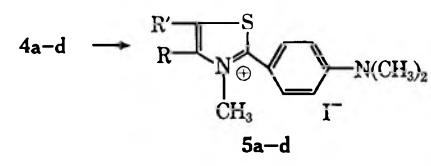
In the present work, the reaction of N-methyl-*p*-dimethylaminothiobenzamide (**3**) with a number of α-halo ketones and one α-halo aldehyde was found to give stable 4-hydroxy-2-thiazolinium derivatives **4a–f**, which were isolated as the iodide salts.



4a–f

a, R = CH_3; R′ = H
b, R = CH_3; R′ = n-C_4H_9
c, R = n-C_5H_{11}; R′ = H
d, R = C_2H_5; R′ = CH_3
e, R = p-BrC_6H_4; R′ = H
f, R = H; R′ = n-C_5H_{11}

The 4-hydroxy-2-thiazolinium salts were stable in neutral and basic media, but they could be dehydrated to the thiazolium salts **5a–d** by treatment with methanolic hydrogen chloride. Dehydration could also be accomplished, although less conveniently, by treatment with methanesulfonyl chloride containing sulfur dioxide in the presence of collidine.[9]



5a–d

The reaction of **3** with 3-bromo-2-pentanone yielded a mixture of the intermediate (**4d**) and the thiazolium

(1) R. H. Wiley, D. C. England, and L. L. Behr, *Org. Reactions*, **6**, 367 (1951).

(2) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 496.

(3) A. R. Todd, F. Bergel, and Karimullah, *Ber.*, **69B**, 217 (1936).

(4) P. M. Kochergin and M. N. Shchukina, *J. Gen. Chem. USSR*, **26**, 483 (1956).

(5) P. M. Kochergin and M. N. Shchukina, *ibid.*, **26**, 3233 (1956).

(6) (a) K. M. Murav'eva and M. N. Shchukina, *Zh. Obshch. Khim.*, **30**, 2327 (1960); *Chem. Abstr.*, **55**, 9376*a* (1961). (b) K. M. Murav'eva and M. N. Shchukina, *ibid.*, **30**, 2334 (1960); *Chem. Abstr.*, **55**, 9376*g* (1961). (c) K. M. Murav'eva and M. N. Shchukina, *ibid.*, **30**, 2340 (1960); *Chem. Abstr.*, **55**, 9377*b* (1961). (d) K. M. Murav'eva and M. N. Shchukina, *ibid.*, **30**, 2344 (1960); *Chem. Abstr.*, **55**, 9377*e* (1961). (e) K. M. Murav'eva and M. N. Shchukina, *Dokl. Akad. Nauk SSSR*, **126**, 1274 (1959); *Chem. Abstr.*, **54**, 498*g* (1960).

(7) A. Takamizawa, K. Hirai, T. Ishiba, and Y. Matsumoto, *Chem. Pharm. Bull. Jap.*, **15**, 731 (1967).

(8) B. M. Regan, F. T. Galysh, and R. N. Morris, *J. Med. Chem.*, **10**, 649 (1967).

(9) G. G. Hazen and D. W. Rosenberg, *J. Org. Chem.*, **29**, 1930 (1964).

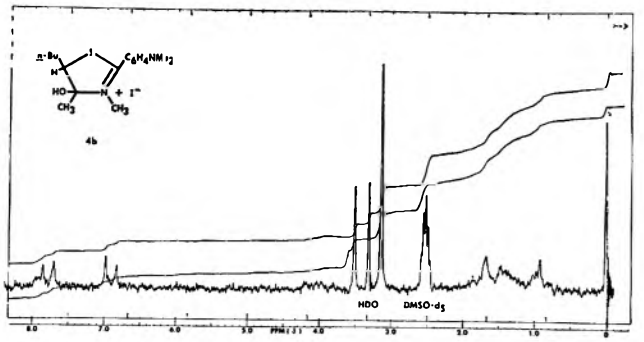


Figure 1.—The nmr spectrum of 5-*n*-butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4b**) at 60 MHz in DMSO-d_6.

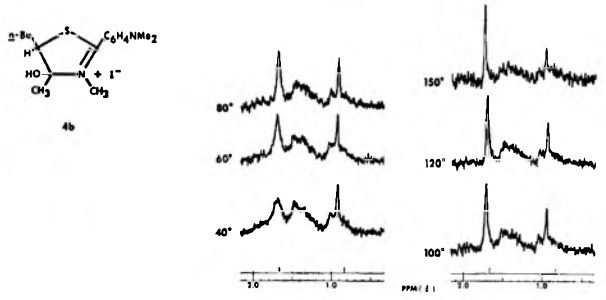


Figure 2.—The partial 60-MHz nmr spectrum of 5-*n*-butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4b**) at various temperatures in DMSO-d_6.

salt (**5d**). The mixture was readily resolved by crystallization.

The importance of the quaternary nitrogen in stabilizing the intermediates was shown by the fact that replacement of **3** by *p*-dimethylaminothiobenzamide in the reaction with 3-bromo-2-heptanone resulted in a normal Hantzsch reaction with no evidence of formation of a stable intermediate.

The cyclic nature of the intermediates was established by means of nmr and ir spectra, and, in those cases where diastereomers were possible, both forms were detected and the existence of a dynamic equilibrium between them, *via* the open-chain keto form, could be observed. The absence of carbonyl and NH absorptions coupled with the presence of hydrogen-bonded –OH bands in the ir spectrum indicated the cyclized rather than the open-chain structure for the intermediates. The nmr spectrum of **4b** in dimethyl sulfoxide-d_6 (DMSO-d_6) (Figure 1) showed, in addition to the expected aromatic, *n*-butyl and N-methyl resonances, a broadened singlet at δ 1.67 (relative area 3) assigned to the ring methyl, and a multiplet at 4.17 (relative area 1) assigned to the ring methine group. The chemical shift of the methyl group was inconsistent with an acetyl moiety and thus excluded the ketonic structure. The –OH proton was not visible owing to exchange with the D_2O present in the solvent.

Attention was focused on the broadening of the 4-methyl peak in **4b**. A variable-temperature experiment was performed on this compound with the results shown in Figure 2. The broad methyl peak sharpened with increasing temperature until at 150°, the peak had the same width at half-height exhibited by other sharp singlets in the spectrum. No other peaks were affected by the increase in temperature.

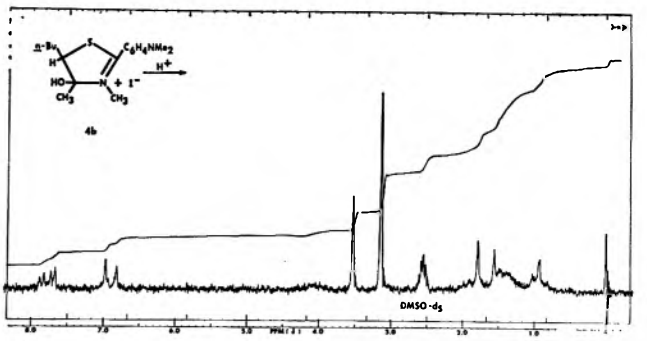


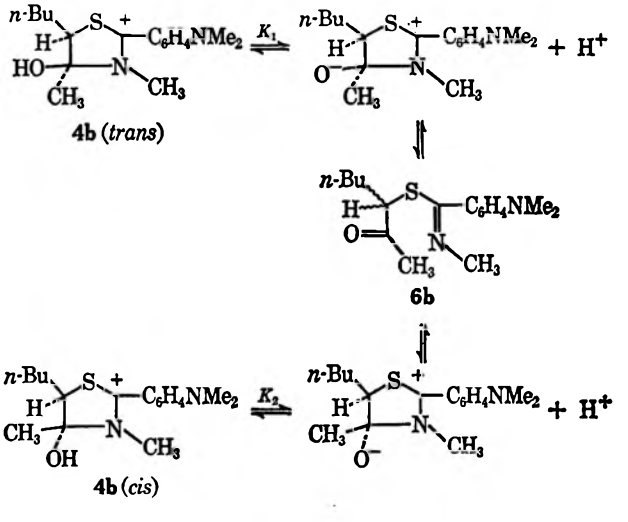
Figure 3.—The nmr spectrum of 5-*n*-butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4b**) at 60 MHz in DMSO-d_6 after the addition of 1 drop of trifluoroacetic acid.

The effect on the nmr spectrum of adding trifluoroacetic acid to a solution of **4b** in DMSO-d_6 is shown in Figure 3. The most striking change observed in the spectrum after acidification was the appearance of two separate methyl singlets at δ 1.57 and 1.80 symmetrically located about the position of the broad singlet which was present before acidification.

The sharpening of the methyl peak indicated an equilibrium which affected the environment of this group. The addition of acid effectively retarded the rate of the equilibrium responsible for the original broadening, and allowed the observation of the individual species participating.

These observations may be accounted for by the equilibria outlined in Scheme I.

SCHEME I



The equilibrium between *cis* **4b** and *trans* **4b** (*cis* and *trans* are defined with reference to the orientations of the 4-methyl and 5-*n*-butyl groups), which proceeds *via* the open-chain ketone **6b**, is sufficiently slow on the nmr time scale to cause broadening of the 4-methyl signal in untreated DMSO-d_6 solution. Raising the temperature of the sample increases the rate of equilibration, thereby sharpening the methyl signal. In the proposed scheme, the addition of acid is postulated to shift the equilibria (K_1 and K_2) to the left and thus to retard the interconversion of the two isomers. The 4-methyl signals of both *cis* **4b** and *trans* **4b** are therefore detectable in the nmr spectrum. Since the chemical shift of the dimethylamino group does not change after

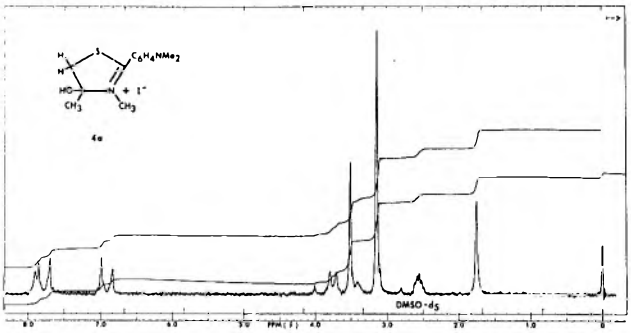
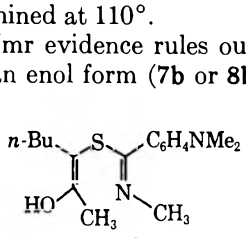


Figure 4.—The 60-MHz nmr spectrum of 2-(*p*-dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (**4a**) in DMSO-d_6.

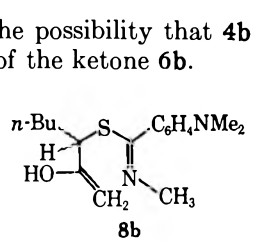
the addition of trifluoroacetic acid, **4b** is not protonated in this medium. This is probably a consequence of unfavorable resonance interaction in the conjugate acid of **4b**.

Further evidence in agreement with the proposed explanation was obtained by examining the nmr spectrum (Figure 4) of the simple analog **4a**. The absorption of the 4-methyl group at δ 1.75 appeared as a sharp singlet which was uneffected by either temperature variation or acidification. The slow equilibrium between enantiomers was evidenced in the room temperature spectrum by the appearance of the absorption of the C-5 methylene protons as an AB quartet centered at δ 3.75 which coalesced when the spectrum was determined at 110°.

Nmr evidence rules out the possibility that **4b** may be an enol form (**7b** or **8b**) of the ketone **6b**.



7b



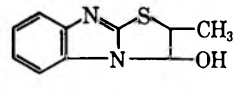
8b

Although enolization of carbonyl groups causes a paramagnetic shift of vicinal methyl groups,[10] the magnitude of such a shift (δ +0.17) is not sufficient to account for the observed shift of δ +0.41 from the normal acetyl resonance. In addition, the proton involved in the enolization would be rapidly exchangeable with D_2O; however, no evidence of the rapid exchange of the proton at C-5 was found.[11] No vinyl proton resonance was observed in the nmr spectrum of any compounds in the present series. Further, the AB quartet of the C-5 methylene protons in compound **4a** is consistent only with the cyclic 4-hydroxy compound. Finally, the nmr spectrum of the structurally related 3-methylmercapto-2-heptanone (prepared by treating 3-bromo-2-heptanone with sodium methyl mercaptide) gave no evidence of enolization.

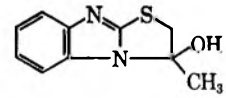
The existence of equilibria of the kind outlined in Scheme I may account for the acid-catalyzed rearrangements of 2-imino-3-phenyl-4-thiazolines to 2-anilinothiazoles observed by Murav'eva and Shchukina,[6c] since the 2-anilinothiazoles can readily arise from the authors on the rearrangement of 4-hydroxy-2-acyliminothiazolidines[6d,e] induced by acetylation agents may also be accounted for by the intermediacy of an open-chain compound.

In the work described by Fefer and King[12] a series of *para*-substituted phenacyl halides was condensed with 2-thioimidazolidine and the resulting intermediates were isolated. The Hammett σ values of the substituent on the phenacyl halides were correlated with the presence or absence of carbonyl absorption in the ir spectra of the reactive intermediates. The authors postulated that these results were evidence of enolization induced by unfavorable resonance interactions. The present work, however, shows that enolization of ketonic intermediates of this type is not demonstrable. The results of Fefer and King may be more adequately explained by the proposed equilibria between open-chain and cyclic intermediates.

Alper and Taurins[13] have recently described the preparation, chemical properties, and nmr spectra of 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**9**) and the 3-methyl analog (**10**) along with other related compounds. On the basis of the nmr



9



10

spectrum in DMSO-d_6 acidified with trifluoroacetic acid, **9** was shown to be a mixture of the *cis*- and *trans*-alcohols, which could not be separated by thin layer chromatography. The nmr spectrum of **10** indicated that in solution the cyclic structure and the tautomeric open-chain α-mercapto ketone are present in a 1:2 ratio.

The nmr spectra of **9** and **10** in DMSO-d_6, in the absence of acid, were investigated in these laboratories to determine whether equilibria were involved similar to those in the present work.[14] The nmr spectrum of **9** exhibited a significant temperature dependence, and at 180°, the pair of methyl doublets of the diastereomeric alcohols coalesced to a single doublet. Complete coalescence of the C-2 and C-3 protons did not occur even at 190°. This is not unexpected because the methyl doublets have a smaller chemical-shift difference ($\Delta\delta$ = 0.02) than either the C-2 or C-3 protons ($\Delta\delta$ = 0.48, and 0.17, respectively), and the coalescence temperature is a function of the lifetimes of the protons at both sites and the chemical shift differences between these sites.[15] The nmr spectrum of **10** was also temperature dependent as the AB quartet and singlet arising from the C-2 methylene protons of the cyclic and open-chain forms coalesced to a single sharp resonance at 150°. The same behavior was noted for the methyl signals of both isomers. These results are consistent with those obtained with our compounds, and support the proposal that the hydroxythiazoline open-chain form. The observations by the same

(10) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 91.

(11) The proton at C-5 did exchange after prolonged standing in DMSO-d_6/D_2O solution, but this is thought to be due to the proximity of the ring sulfur. See P. Beak and E. McLeister, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. P127.

(12) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).

(13) A. E. Alper and A. Taurins, *Can. J. Chem.*, **45**, 2903 (1967).

(14) We are indebted to Dr. A. Taurins for kindly supplying us with these samples.

(15) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 218.

intermediates in the Hantzsch synthesis are in equilibrium with the corresponding α-thio ketones.

Experimental Section

Melting points were determined using a Thomas–Hoover apparatus and are corrected. Nmr spectra were obtained on Varian A-60 and HA-100 spectrometers. Tetramethylsilane (δ 0) was used as an internal reference standard. Ir spectra were determined in potassium bromide using a Beckman IR-8 spectrophotometer.

4-Hydroxy-2-thiazolinium Salts (4a–e). 3,4-Dimethyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-2-thiazolinium Iodide (4a).—A suspension of N-methyl-4-dimethylaminophenylthiobenzamide[16] (**3**) (6.0 g, 0.03 mol) in methanol (25 ml) containing chloroacetone (4.5 g, 0.05 mol) was shaken at room temperature for 6 days. The solution was evaporated and the residue was partitioned between water (75 ml) and ether (50 ml). Addition of excess potassium iodide (15 g) to the aqueous layer gave the product as the iodide salt: yield 10.3 g (90%); mp 157–158° (recrystallization from ethanol–ether raised this to 164°); ν_{max} 3170 (OH), 1605 (C=N).

When the reaction was performed at 100° for 1 hr in dimethylformamide, the same product was obtained in 80% yield.

Anal. Calcd for $C_{13}H_{19}IN_2OS$: C, 41.27; H, 5.06; I, 33.55; N, 7.41; O, 4.23; S, 8.48. Found: C, 41.09; H, 5.11; I, 33.27; N, 7.60; O, 4.29; S, 8.40.

5-*n*-Butyl-3,4-dimethyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-2-thiazolinium Iodide (4b).—The thioamide (**3**) was shaken with 3-bromo-2-heptanone in methanol as described above and the iodide salt, mp 130–133°, was obtained in 78% yield (recrystallization from methanol–ether raised the melting point to 134–135°): ν_{max} 3180 (OH), 1605 (C=N).

When the reaction was performed in refluxing ethanol a less pure product was formed.

Anal. Calcd for $C_{17}H_{27}IN_2OS$: C, 47.01; H, 6.27; N, 6.45. Found: C, 47.37; H, 6.20; N, 6.59.

4-*n*-Amyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium Iodide (4c).—1-Bromo-2-heptanone (6.5 g, 0.033 mol) was added to a suspension of **3** (6.0 g, 0.03 mol) in 25 ml of methanol. The temperature rose spontaneously to 50° and the solution was allowed to stand for 2 days. The methanol was evaporated and the residue was dissolved in water. The aqueous solution was neutralized with ammonium hydroxide and treated with excess potassium iodide: yield 11.1 g (85%); mp 145° (from methanol–ether); ν_{max} 3150 (OH), 1604 (C=N).

Anal. Calcd for $C_{17}H_{27}IN_2OS$: C, 47.01; H, 6.27; I, 29.22; N, 6.45; O, 3.68; S, 7.28. Found: C, 47.26; H, 6.28; I, 29.49; N, 6.38; O, 3.70; S, 7.44.

3,5-Dimethyl-2-(*p*-dimethylaminophenyl)-4-ethyl-4-hydroxy-2-thiazolinium Iodide (4d) and 3,5-Dimethyl-2-(*p*-dimethylaminophenyl)-4-ethylthiazolium Iodide (5d).—A solution of **3** (44.7 g, 0.23 mol) and 2-bromo-3-pentanone (58.8 g, 0.36 mol) in ethanol (150 ml) was refluxed for 4 hr. The ethanol was evaporated and the residue was dissolved in water. The solution was neutralized to pH 7 and potassium iodide (57 g) was added to precipitate a mixture of the thiazolinium and thiazolium salts (90 g). The mixture was crystallized from chloroform–ether and methanol–ethyl acetate to give the less soluble thiazolium salt (**5d**): mp 198–200°; yield 25 g, 28%; ν_{max} 1610 (C=N).

Anal. Calcd for $C_{15}H_{21}IN_2S$: C, 46.39; H, 5.45; I, 32.68; N, 7.22; S, 8.26. Found: C, 46.22; H, 5.46; I, 32.64; N, 7.23; S, 8.16.

The 4-hydroxy-2-thiazolinium salt (**4d**) was obtained from the mother liquors: yield 9 g (9%); mp 148–150° (from methanol–ether); ν_{max} 3190 (OH), 1610 (C=N).

Anal. Calcd for $C_{15}H_{23}IN_2OS$: C, 44.34; H, 5.70; N, 6.90. Found: C, 44.78; H, 5.61; N, 7.04.

4-(*p*-Bromophenyl)-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium Iodide (4e).—A solution of *p*-bromophenacyl bromide (2.8 g, 0.01 mol) and **3** (1.9 g, 0.01 mol) in dimethylformamide (10 ml) was heated at 100° for 40 min. The solution was evaporated and the residue was extracted with hot water. The product separated on addition of potassium iodide: yield 1.5 g (32%); mp 164–165° (from methanol); ν_{max} 3160 (OH), 1612 (C=N).

Anal. Calcd for $C_{18}H_{20}BrIN_2OS$: C, 41.63; H, 3.88; Br, 15.39; I, 24.44; N, 5.40. Found: C, 41.65; H, 4.11; Br, 15.23; I, 24.42; N, 5.42.

5-*n*-Amyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium Iodide (4f).—A solution of **3** (6.0 g, 0.02 mol) and α-bromoheptaldehyde (6.0 g, 0.02 mol) was refluxed in methanol (50 ml) for 5 hr. The solution was evaporated and the residue was dissolved in water. The aqueous solution was washed with ether, neutralized with ammonia, and treated with potassium iodide (5 g). The thiazolinium salt melted at 108–115° after recrystallization from methanol–ether: yield 4.5 g (54%); ν_{max} 3200 (OH), 1602 (C=N).

Anal. Calcd for $C_{17}H_{27}IN_2OS$: C, 47.00; H, 6.27; I, 29.22; N, 6.45. Found: C, 46.95; H, 6.07; I, 29.04; N, 6.65.

Dehydration of the 4-Hydroxy-2-thiazolinium Salts. 2-(*p*-Dimethylaminophenyl)-3,4-dimethylthiazolium Iodide (5a).—2-(*p*-Dimethylaminophenyl)-3,4-dimethyl-4-hydroxy-2-thiazolinium iodide (7.7 g, 0.02 mol) was dissolved in 100 ml of saturated methanolic hydrogen chloride and the solution was allowed to stand for 1 day. The methanol was evaporated and the residue was dissolved in water and filtered clear. The filtrate was neutralized with ammonium hydroxide and an excess of potassium iodide was added to give the thiazolium salt: mp 212–213° (from ethanol–ether); yield 4.3 g (63%); ν_{max} 1605 (C=N).

Anal. Calcd for $C_{13}H_{17}IN_2S$: C, 43.34; H, 4.76; N, 7.78. Found: C, 43.28; H, 5.05; N, 7.81.

5-*n*-Butyl-2-(*p*-dimethylaminophenyl)-3,4-dimethylthiazolium Iodide (5b).—The dehydration of the 4-hydroxy compound was performed by refluxing for 20 min in methanolic hydrogen chloride. The solution was evaporated, the residue was dissolved in water, and the aqueous solution was neutralized with ammonium hydroxide. Addition of potassium iodide caused the precipitation of the product: mp 119–120° (from methanol–ethyl acetate); yield 70%; ν_{max} 1594 (C=N).

Anal. Calcd for $C_{17}H_{25}IN_2S$: C, 49.04; H, 6.05; I, 30.48; N, 6.73; S, 7.70. Found: C, 49.34; H, 6.30; I, 30.77; N, 6.59; S, 7.86.

4-*n*-Amyl-2-(*p*-dimethylaminophenyl)-3-methylthiazolium Iodide (5c).—4-*n*-Amyl-2-(*p*-dimethylaminophenyl)-4-hydroxy-3-methyl-2-thiazolinium iodide (0.47 g, 0.002 mol) was dissolved in dimethylformamide (5 ml) containing 1.6 ml of collidine. Methanesulfonyl chloride (0.8 ml) containing 4% sulfur dioxide was added in portions at 20–25°, and the mixture was allowed to stand for 1 hr. Dilution with water gave a brown solid which was crystallized from methanol–ethyl acetate to give 0.8 g, mp 123–130°. The analytical sample obtained by repeated recrystallization from the same solvents had mp 134°, ν_{max} 1600 (C=N).

Anal. Calcd for $C_{17}H_{25}IN_2S$: C, 49.04; H, 6.05; I, 30.48; N, 6.73; S, 7.70. Found: C, 48.99; H, 6.31; I, 30.43; N, 6.71; S, 7.44.

3-Methylthio-2-heptanone.—Methanethiol (2.4 g, 0.05 mol) was added to a solution of sodium ethoxide (from 1.2 g of sodium) in 40 ml of ethanol. 3-Bromo-2-heptanone (10.0 g, 0.05 mol) was added dropwise with stirring, and the mixture was refluxed for 2 hr. The precipitated sodium bromide was removed by filtration, and the filtrate was fractionated to yield 2-methylthio-2-heptanone: bp 72–75° (20 mm); ν_{max} (in chloroform) 1700 (C=O).

Anal. Calcd for $C_8H_{16}OS$: C, 59.96; H, 10.06; O, 9.98; S, 20.00. Found: C, 59.92; H, 10.21; O, 9.70; S, 20.23.

5-*n*-Butyl-2-(4-dimethylaminophenyl)-4-methylthiazole.—A solution of 3-bromo-2-heptanone (3.9 g, 0.02 mol) and *p*-dimethylaminothiobenzamide (3.6 g, 0.02 mol) in *n*-butyl alcohol (20 ml) was heated at 100° for 2 hr. The solution was evaporated and the residue was crystallized from ether, giving the thiazole hydrobromide, mp 160–165° dec. The salt was dissolved in water and basified, giving the free base: mp 50–51.5° (from petroleum ether; ν_{max} 1608 (C=N). Recrystallization from petroleum ether (bp 30–60°) raised the melting point to 50–51.5°.

Anal. Calcd for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.08; N, 10.21; S, 11.68. Found: C, 69.75; H, 8.23; N, 10.41; S, 11.65.

Registry No.—**4a,** 17790-29-3; **4b** (*trans*), 17796-66-6; **4b** (*cis*), 17797-05-6; **4c,** 17790-30-6; **4d,** 17790-31-7; **4e,** 17790-32-8; **4f,** 17790-33-9; **5a,** 17790-34-0; **5b,** 17790-35-1; **5c,** 17790-36-2; **5d,** 17790-37-3; 3-methylthio-2-heptanone, 17790-38-4; 5-*n*-butyl-2-(4-dimethylaminophenyl)-4-methylthiazole, 17790-39-5;

(16) D. L. Garmaise, C. H. Chambers, and R. C. McCrae, submitted for publication.

5-*n*-butyl-2-(4-dimethylaminophenyl)-4-methylthiazole hydrobromide, 17790-40-8.

Acknowledgments.—The authors wish to thank Mrs. Ruth Stanaszek for assistance in determining the nmr spectra, Mr. Victor Rauschel and coworkers for elemental analyses, and Mr. William Washburn for some ir spectra. Helpful discussions with Dr. Milton Levenberg of these laboratories and Professor Peter Beak of the University of Illinois are appreciated.

A One-Step Synthesis of 5-Hydroxy-1,3-benzoxathiol-2-ones from Quinones and Thiourea

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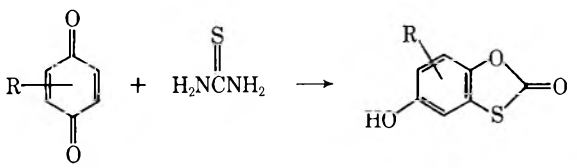
Received May 10, 1968

A wide variety of 5-hydroxy-1,3-benzoxathiol-2-ones were prepared in excellent yields by a one-step synthesis from readily available quinones and thiourea. Depending on the nature of the substituents and the reaction conditions, the intermediate S-(2,5-dihydroxyaryl)thiouronium salts and 5-hydroxy-2-imino-1,3-benzoxathioles could also be readily isolated. Reactions of thiourea with unsubstituted, disubstituted, or trisubstituted quinone gave only one end product. However, monosubstituted quinones gave one or more of the three possible isomeric end products, the 4-, 6-, and 7-substituted 5-hydroxy-1,3-benzoxathiol-2-ones. The directive influence of the substituent groups on the addition of thiourea and their effect on the ease of cyclization of the resulting thiouronium salts are described.

Although several methods have been reported in the literature[1,2] for the synthesis of 5-hydroxy-1,3-benzoxathiol-2-ones, these methods are, in general, characterized by low yields or by cumbersome preparative procedures.

In this paper we describe a method whereby a wide variety of 5-hydroxy-1,3-benzoxathiol-2-ones can be prepared rapidly and in excellent yields by a one-step synthesis from readily available quinones and thiourea.

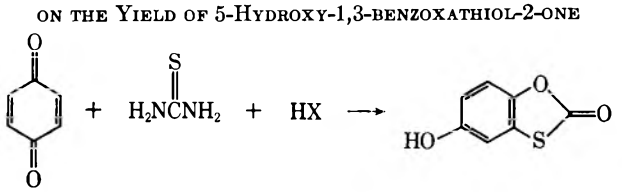


In general, the procedure consists in mixing a solution of thiourea in aqueous hydrochloric acid with a solution of a quinone in glacial acetic acid and heating for 1 hr on a steam bath. The product, which crystallizes from solution on cooling, is essentially pure. As can be seen from Table I, the reaction is best run with a large excess of thiourea and aqueous hydrochloric acid. Good results are also obtained with sulfuric or trifluoroacetic acid. When a weak acid such as acetic acid is used, the yield is considerably lower, and the product is generally contaminated with colored impurities which are difficult to separate. No product is formed in the absence of acid.

These observations strongly suggest that the reaction involves a 1,4 addition of thiourea to the protonated quinone, giving first an intermediate S-(2,5-dihydroxyaryl)thiouronium salt (**1**), which cyclizes to a second intermediate, 5-hydroxy-2-imino-1,3-benzoxathiole (**2**). This, in turn, is hydrolyzed to the final 5-hydroxy-1,3-benzoxathiol-2-one (**3**) (Scheme I). The formation of each intermediate, and the final product, during the course of the reaction can be readily detected and followed by thin layer chromatography (tlc). Several of the thiouronium salts (Table II) and imino salt were isolated and characterized. Upon being heated in strong aqueous acid, they were rapidly and quantitatively converted into the corresponding products.

TABLE I

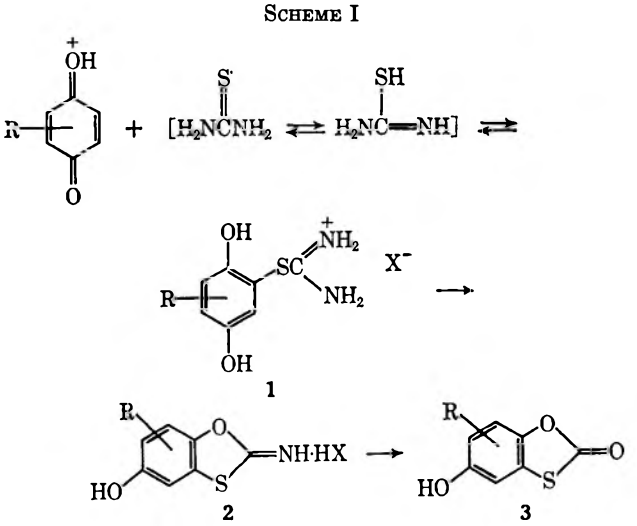
EFFECTS OF AMOUNT OF ACIDS, THIOUREA, AND QUINONES ON THE YIELD OF 5-HYDROXY-1,3-BENZOXATHIOL-2-ONE



Acid	Molar ratio	Benzoquinone[a] molar ratio	Thiourea[b] molar ratio	Yield, %
...	...	1.0	1.5	0
HCl	3.0	1.0	1.5	92
HCl	1.0	1.0	1.5	60
HCl	0.5	1.0	1.5	21
HCl	3.0	2.0	1.0	10
H_2SO_4	3.0	1.0	1.5	94
CF_3CO_2H	10.0	1.0	1.5	85
HOAc	10.0	1.0	1.5	45

[a] Solution in HOAc. [b] Solution in aqueous 2 *N* HCl or H_2SO_4

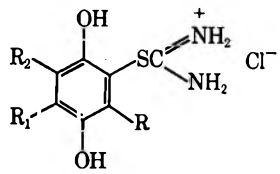
SCHEME I

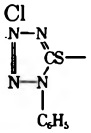


(1) H. Burton and S. B. David, *J. Chem. Soc.*, 2193 (1952).
(2) H. Fiedler, *Chem. Ber.*, **95**, 1771 (1962).

TABLE II

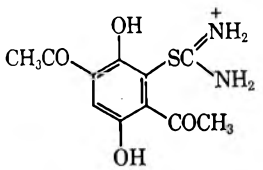
S-(2,5-DIHYDROXYARYL)THIOURONIUM CHLORIDES



R	R_1	R_2	Registry no.	Mp, dec, °C[a]	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
H	H	H	6274-93-7	156	38.2	4.1	14.5	38.3	4.0	14.2
H	H	Ph	17630-82-9	112	52.6	4.4	10.8	52.4	4.6	11.0
H	H	CH_3 [b]	17630-83-0	121	40.9	4.7	13.6	40.5	4.5	13.8
H	CH_3	H [b]	17630-84-1							
H	H	PhS	17630-85-2	160	47.5	4.0	19.5	47.5	3.9	19.3
H	H	CH_3CO	17630-86-3	195	41.2	4.2	12.2	41.1	4.3	12.2
H	H	OCH_3 [b]	17630-87-4	170	38.3	4.4	12.8	37.9	4.3	13.2[c]
H	OCH_3	H [b]	17630-88-5							
H	H	Cl	17630-89-6	140	33.0	3.1	11.0	32.7	3.2	11.0
H	Cl	H [b]	17630-90-9	145	33.0	3.1	11.0	33.3	3.2	11.3
Cl	H	H [b]	17630-91-0							
H	CH_3	CH_3	17630-92-1	110	43.5	5.3	12.8	43.5	5.4	12.5
CH_3	CH_3	H	17658-48-9	198	43.5	5.3	12.8	43.8	5.6	12.9
Cl	H	Cl	17630-93-2	160	29.3	2.4	11.1	29.0	2.8	10.8
	H	H	17630-94-3	149	42.4	3.3	16.2	42.3	3.4	16.0

[a] The temperature at which the salt turned color was taken as the decomposition point. [b] Isomeric mixtures as analyzed by nmr spectroscopy. [c] Analytically pure samples were not obtained.

Contrary to previous reports,[1,3] the thiouronium salts do not decompose to colored products when heated in strong acid. Only when the salts were heated in weak acids or failed to undergo cyclization (*e.g.*, **4** and **5**) did we observe extensive decomposition.



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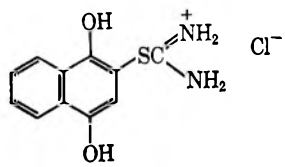
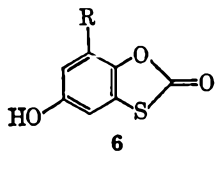


5

Reactions of thiourea with an unsubstituted, a disubstituted, or a trisubstituted quinone gave only a single product (Table III). No difficulty was encountered in controlling the reaction in order to obtain the monoaddition product with thiourea. However, when a monosubstituted quinone was used, the reaction was more complex. Depending on the nature of the substituent, one or more of the three possible isomers (**6**–**8**) is obtained. The results of this study, listed in Table IV, show that, when R is $-C_{18}H_{37}$ and $-C_8H_{17}$, the thiourea adds *meta* to the substituents to give exclusively the 7-substituted 5-hydroxy-1,3-benzoxathiol-2-one (**6**). With groups such as CH_3, C_6H_5S, and C_6H_5, a small amount (3–10%) of the 6-substituted isomer (**7**) is also obtained. If the position *meta* to these substituents is blocked, as in 2,6-dimethylbenzoquinone, the yield is considerably lower (Table III).



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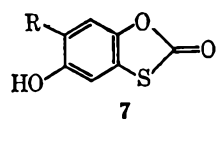

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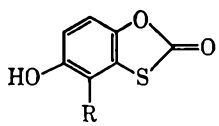
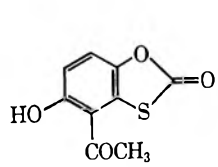


8

The reaction of thiourea with 2-acetylquinone, which contains an electron-withdrawing group, also gave a mixture of two isomeric products, shown by nmr and vpc to consist of 83% **9** and 17% **10**. The formation of these isomers was conveniently followed by tlc. The thiouronium chloride (**11**) was converted completely into its cyclized product (**9**), when the reaction mixture was heated on a steam bath for 40 min, while the thiouronium chloride (**12**) remained practically unchanged. Only upon prolonged heating was **12** converted into product **10**. This striking difference



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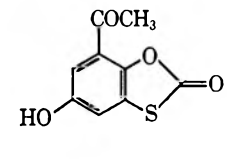

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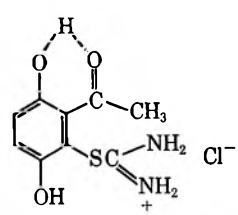

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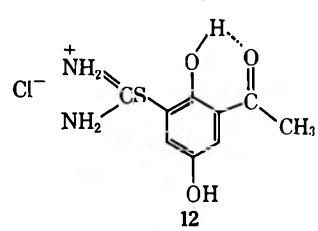
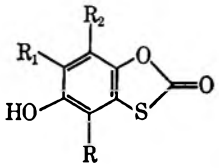


12

(3) M. Schubert, *J. Amer. Chem. Soc.*, **69**, 712 (1947).

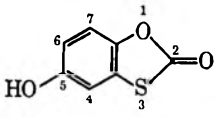
TABLE III
UNSUBSTITUTED, DISUBSTITUTED, AND TRISUBSTITUTED 5-HYDROXY-1,3-BENZOXATHIOL-2-ONES



R	R_1	R_2	Registry no.	Mp (lit.[a]), °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
H	H	H		174–175 (175–176)	92	50.0	2.4	19.0	49.9	2.7	19.0
H	CH_3	CH_3	17631-06-0	164–165	73	55.1	4.1	16.4	55.1	4.2	16.1
CH_3	CH_3	H	7735-65-1	145–146 (147–147.5)	38[b]	55.1	4.1	16.4	55.3	4.2	16.2
CH_3	H	CH_3		205–206 (205–206)	95	55.1	4.1	16.4	55.1	4.4	16.6
Cl	H	Cl		174–175 (177–178)	90	35.5	0.9	13.5	35.3	1.0	13.5
Cl	Cl	H		161–162 (162–162.5)	87	35.5	0.9	13.5	35.5	1.1	13.8
Ph	H	Ph	17630-96-5	181–182	98	71.2	3.7	10.0	71.3	4.0	10.3
CH_3	CH_3	CH_3	17630-97-6	159–160	72	57.1	4.8	15.2	56.9	4.7	15.2
CH_3	H	$CH(CH_3)_2$		156.5–157.5 (158.5–159)	96	58.9	5.4	14.3	58.8	5.3	14.5
CH_3CO	H	CH_3		217–218	82	53.6	3.6	14.3	53.6	3.9	14.0

[a] Reference 2. [b] A large amount of 2,5-dimethyl-4-chlorophenol was also isolated.

TABLE IV
MONOSUBSTITUTED 5-HYDROXY-1,3-BENZOXATHIOL-2-ONES

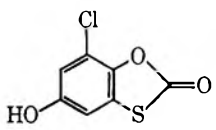


R	Registry no.	Mp, °C	Yield, %[a]	Coupling constant,[b] cps	Product ratio, %[c]	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
7-Ph		176–177	90	2.5	93	63.9	3.3	13.1	63.8	3.4	13.1
6-Ph	7735-69-5	144–145	3	<1.0	7				63.8	3.3	13.0
7-CH_3	17631-00-4	164–165	82	2.5	90	52.7	3.3	17.6	52.4	3.4	17.4
6-CH_3	17631-01-5	143–144	7	<1.0	10				52.4	3.0	17.3
4-CH_3CO		187–188	79	9.0	83	51.4	2.9	15.3	51.6	2.9	15.6
7-CH_3CO		209–210	11	2.6	17				51.5	2.7	15.3
7-Cl		180–181	53	2.5	62				41.5	1.6	15.6
6-Cl		128–130	25	<1.0	20	41.5	1.5	15.8	41.6	1.7	16.1
4-Cl				9.0	18						
7-PhS	17630-67-0	167–168	96	2.3	97	56.5	2.9	23.2	56.4	3.0	23.4
6-PhS	17630-68-1	118–119	2	<1.0	3						
7-*n*-$C_{18}H_{37}$	17630-69-2	122–123	96	2.5	100	71.4	9.6	7.6	71.5	9.7	7.7
7-*n*-C_8H_{17}	17630-70-5	108–109	99	2.5	100	64.2	7.2	11.4	64.3	7.2	11.4

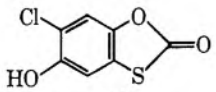
[a] Isolated yield. [b] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 85. [c] Product ratio of isomeric mixture as analyzed by nmr spectroscopy and vpc.

in reactivity, which made the separation of the cyclized products easy, may be attributed to hydrogen bonding between the carbonyl oxygen and the hydroxyl group of the thiouronium salts.

With a quinone containing a substituent such as chloro, which can withdraw as well as donate electrons, all three isomeric products were obtained. Of these, only the 7-chloro isomer (**13**) was obtained in a pure



13



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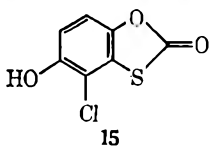
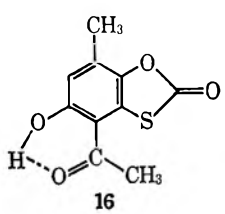


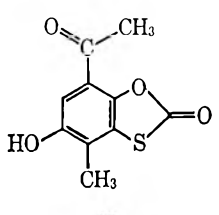
15

condition. The position of the chloro substituent in the ring was established by nmr spectroscopy, and the amount of each isomer present in the mixture was determined by nmr spectroscopy and vpc to be in the ratio of 62% **13**, 20% **14**, and 18% **15**.

Although reaction of thiourea with 2-acetyl-5-methylbenzoquinone would theoretically yield two isomeric products, only one product, identified as the 4-acetyl-5-hydroxy-1,3-benzoxathiol-2-one (**16**), was iso-



16

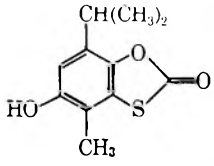


17

lated in excellent yield. This result again demonstrates the directive influence of the methyl and acetyl groups. Structure assignment of the product was made in favor of the intramolecularly hydrogen-bonded **16** over **17** on the basis of its nmr spectrum, which shows that the chemical shift of the hydroxyl proton is far downfield

at 12.4 ppm, indicative of hydrogen bonding. The very slight upfield shift on changing temperature from 35 to 60° and the absence of any shift on dilution suggest an intramolecular hydrogen bond, a phenomenon which is possible only for compound **16**.

The addition of thymoquinone to thiourea afforded only the 5-hydroxy-7-isopropyl-4-methyl-1,3-benzoxathiol-2-one (**18**). That the other isomer (**19**) was not formed probably results from the steric effect of the isopropyl group. This is further supported by the



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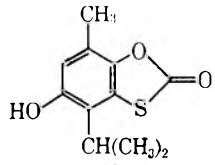

19

observation that, when 3-bromothymoquinone or 2,5-di-*t*-butylbenzoquinone was used, no reaction occurred. Instead, the quinones were reduced quantitatively to their respective hydroquinones. This procedure was also useful for reducing duroquinone to durohydroquinone.

The observations made in this study indicate that, in general, strong electron-donating groups direct the addition of thiourea primarily *meta* and secondarily *para* to the substituents. Electron-withdrawing groups, on the other hand, direct *ortho* to the substituents. Addition is sterically excluded at the *ortho* position by bulky substituents such as the isopropyl or *t*-butyl groups. It is interesting to note that these reactions somewhat resemble the Thiele acetylation of quinones,[4] in that they are both acid-catalyzed reactions, and that they both give only monoaddition products. However, they differ from each other in the orientation effects of strong electron-donating groups and in the distribution of isomers.[5]

Experimental Section

All melting points were taken on a Thomas–Hoover Unimelt apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord spectrometer. Nuclear magnetic resonance spectra were determined with a Varian A-60 spectrometer in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts are reported in parts per million relative to an internal tetramethysilane standard. Thin layer chromatography (tlc) was run on silica gel plates containing a uv indicator and developed in a solvent mixture of equal volumes of ethyl acetate and chloroform. Vapor phase chromatography (vpc) was done on a 0.25 in. × 10 ft column of 20% OV-17 on 80–100 mesh Anakdrom ABS, with a helium flow of 70–75 cc/min. Samples were run as trimethylsilyl derivatives, and product ratios were determined by a comparison of peak areas. Unless specified otherwise, all reagents were Eastman Kodak Co. chemicals.

Preparation of *S*-(2,5-Dihydroxyaryl)thiouronium Chlorides. General Procedure.—To a solution of 0.15 mol of thiourea in 100 ml of 2 *N* hydrochloric acid was added, with stirring, a solution of 0.1 mol of quinone in 50–100 ml of glacial acetic acid. The mixture was stirred for 30 min at room temperature. If the thiouronium chloride did not precipitate at this point, concentrated hydrochloric acid was added to the mixture. The precipitated salt was removed by suction filtration and washed with a little cold 2 *N* hydrochloric acid. The salt was purified by dissolving it in cold water, filtering the solution, and reprecipitating it with concentrated hydrochloric acid. Pertinent data concerning these compounds are reported in Table I. Most of these salts have no definite melting point; they decompose without melting over a wide range of temperatures. Their structures are confirmed by elemental and spectral analyses.

4,7-Dichloro-5-hydroxy-2-imino-1,3-benzoxathioles and 4,7-Dimethyl-5-hydroxy-2-imino-1,3-benzoxathioles.—To a solution of 5.7 g (0.075 mol) of thiourea in 30 ml of 2 *N* hydrochloric acid was added 8.9 g (0.05 mol) of 2,5-dichlorobenzoquinone in 100 ml of glacial acetic acid. The mixture was stirred for 30 min at room temperature, then heated slowly in a water bath to 50–55°. The precipitated thiouronium salt redissolved to give a clear, faintly yellow solution. After about a 10-min stirring at this temperature, a mass of white solid crystallized out of solution. Stirring was continued for 20 min more, until tlc indicated that the thiouronium salt had been completely converted into the imino product. The solid was collected by suction and washed with alcohol to remove the small amount of 4,7-dichloro-5-hydroxy-1,3-benzoxathiol-2-one present in the reaction product: yield, 7.5 g (64%); mp 213–214° dec. Its ir and nmr spectra were consistent with the structure.

Anal. Calcd for $C_7H_3Cl_2NO_2S$: C, 35.6; H, 1.3; S, 13.6. Found: C, 35.3; H, 1.5; S, 13.9.

Similarly, 4,7-dimethyl-5-hydroxy-2-imino-1,3-benzoxathiole hydrochloride salt was prepared in a yield of 81%, mp 116° dec.

Anal. Calcd for $C_9H_{10}ClNO_2S$: C, 46.7; H, 4.7; S, 13.8. Found: C, 46.9; H, 4.6; S, 13.7.

Preparation of Unsubstituted, Disubstituted, and Trisubstituted 5-Hydroxy-1,3-benzoxathiol-2-ones. General Procedure.—To a solution of 0.15 mol of thiourea in 100 ml of 2 *N* hydrochloric acid was added, with stirring, a solution of 0.1 mol of quinone in 50–70 ml of glacial acetic acid. The mixture was stirred at room temperature for 30 min, during which time a mass of crystalline thiouronium salt precipitated (with most of the quinones). Upon heating on a steam bath, the salt redissolved to give a clear solution. The mixture was heated for 1 hr, then chilled in an ice bath until crystallization was complete. The solid was collected, washed with water, and dried. For elemental analysis, the product was recrystallized from ethanol–water.

Compounds prepared by this procedure are reported in Table III. The structures were confirmed by elemental and nmr spectral analyses or by comparison of the melting point and infrared spectra with those of known authentic samples.

S-(2,5-Dihydroxy-4,6-dimethylphenyl)thiouronium Chloride and 4,6-Dimethyl-5-hydroxy-1,3-benzoxathiol-2-one.—To a stirred solution of 5.7 g (0.075 mol) of thiourea in 50 ml of 2 *N* hydrochloric acid was added, at room temperature, 6.8 g (0.05 mol) of 2,6-dimethylbenzoquinone[6] dissolved in 50 ml of glacial acetic acid. The mixture was stirred for 30 min, during which time a mass of crystalline white needles precipitated. The solid was collected by filtration and dried to give 4.7 g (38%) of a product which was identified by elemental analysis and infrared and nmr spectroscopy as the S-(2,5-dihydroxy-4,6-dimethylphenyl)thiouronium chloride. The purified colorless salt became orange at 198° and, after progressive darkening, decomposed to a black solid at 245°.

Anal. Calcd for $C_9H_{13}ClH_2O_2S$: C, 43.5; H, 5.3; S, 12.8. Found: C, 43.8; H, 5.6; S, 12.9.

The filtrate from the isolation of the thiouronium salt was mixed with an equal volume of concentrated hydrochloric acid. The resulting precipitate was collected and recrystallized from ethanol–water to give 2.6 g (33%) of white needles, mp 80–81°. Its infrared and nmr spectra were identical with those of an authentic sample of 4-chloro-2,6-dimethylphenol, and a mixture melting point was not depressed.

A 2.0-g (0.008 mol) sample of S-(2,5-dihydroxy-4,6-dimethylphenyl)thiouronium chloride prepared as just described was suspended in a mixture of 20 ml of 2 *N* hydrochloric acid and 20 ml of glacial acetic acid. The slurry was heated for 2 hr. The hot solution was diluted with 25 ml of water and allowed to stand at room temperature. The crystals which separated were collected and dried to yield 1.6 g (100%) of 4,6-dimethyl-5-hydroxy-1,3-benzoxathiol-2-one, mp 145–146° (lit.[2] mp 147–147.5°). The nmr spectrum ($CDCl_3$) showed three singlets at 2.24 (CH_3, 3 H), 2.28 (CH_3, 3 H), and 6.92 ppm (aromatic, 1 H).

Anal. Calcd for $C_9H_8O_3S$: C, 55.1; H, 4.1; S, 16.4. Found: C, 55.3; H, 4.2; S, 16.2.

(4) J. Thiele, *Chem. Ber.*, **31**, 1247 (1898).

(5) H. S. Wilgus, III, and J. W. Gates, Jr., *Can. J. Chem.*, **45**, 1975 (1967).

(6) L. T. Smith, J. W. Opie, S. Wawzonek, and W. W. Prichard, *J. Org. Chem.*, **4**, 318 (1939).

4-Acetyl-5-hydroxy-7-methyl-1,3-benzoxathiol-2-one.—A solution of 6.6 g (0.04 mol) of 2-acetyl-5-methylbenzoquinone[7] in 30 ml of glacial acetic acid was added to a stirred solution of 4.6 g (0.06 mol) of thiourea in 50 ml of 2 *N* hydrochloric acid. The mixture was stirred at room temperature for 30 min, then heated on a steam bath for 60 min. After cooling, the mixture was poured into 100 ml of ice–water. The yellow precipitate was collected, washed with water, and dried; it weighed 7.4 g (82%) and had a melting point of 215–217°. Recrystallization from aqueous ethanol yielded crystalline white needles, mp 217–218°. The nmr spectrum ($CDCl_3$) showed four singlets at 2.43 (CH_3, 3 H), 2.63 (CH_3CO, 3 H), 6.83 (aromatic, 1 H), and 12.4 ppm (OH, 1 H). In addition, the hydroxylic proton peak at 12.4 ppm showed no shift upon dilution and a very slight upfield shift to 12.27 on raising the temperature from 35 to 60°. These data are consistent with the structure of 4-acetyl-5-hydroxy-7-methyl-1,3-benzoxathiol-2-one in which the hydroxyl group is intramolecularly hydrogen bonded to the *o*-acetyl group.

Anal. Calcd for $C_{10}H_8O_4S$: C, 53.6; H, 3.6; S, 14.3. Found: C, 53.6; H, 3.9; S, 14.0.

5-Hydroxy-7-octyl-1,3-benzoxathiol-2-one.—To a stirred solution of 5.7 g (0.075 mol) of thiourea in 100 ml of 2 *N* hydrochloric acid was added 11.0 g (0.05 mol) of 2-octylbenzoquinone suspended in 50 ml of glacial acetic acid. The mixture was stirred until solution was complete, then heated for 40 min. During this time the mixture became cloudy, and an oil separated. The mixture was poured into 500 ml of water, and the solid which separated was collected by filtration to give 13.9 g (99%) of dried product, mp 97–100°. Thin layer chromatographic analysis indicated only one product, which was identified by nmr spectroscopy to be the 5-hydroxy-7-octyl-1,3-benzoxathiol-2-one. Recrystallization from ethanol–water containing Norit gave 12 g of light brown prisms, mp 108–109°. Its nmr spectrum (DMSO-d_6) showed a multiplet at 0.65–0.9 (CH_3, 3 H), a broad singlet at 1.25 ($-CH_2-$, 12 H), a multiplet at 2.49–2.78 ($Ph-CH_2-$, 2 H), and two doublets of an AB quartet centered at 6.64 and 6.97 ppm (aromatic, 2 H, J_{AB} = 2.5 cps).

Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.2; H, 7.2; S, 11.4. Found: C, 64.3; H, 7.2; S, 11.4.

Preparation and Isolation of Isomeric Monosubstituted 5-Hydroxy-1,3-benzoxathiol-2-ones. General Procedure.—This procedure may be illustrated by the preparation and isolation of 5-hydroxy-7-methyl- and 5-hydroxy-6-methyl-1,3-benzoxathiol-2-ones.

A solution of 12.2 g (0.1 mol) of 2-methylbenzoquinone in 70 ml of glacial acetic acid was added, with stirring, to a solution of 11.4 g (0.15 mol) of thiourea in 100 ml of 2 *N* hydrochloric acid. After a 30-min stirring, the mixture was heated on a steam bath for 1 hr, then diluted with 100 ml of hot water. The product was allowed to crystallize at room temperature, collected, washed with water, and recrystallized from ethanol–water, giving 14.9 g (82%) of 5-hydroxy-7-methyl-1,3-benzoxathiol-2-one, mp 163–164°. The nmr spectrum (DMSO-d_6) showed a singlet at 2.28 (CH_3, 3 H), two doublets of an AB quartet centered at 6.64 and 6.91 (aromatic, 2 H, J_{AB} = 2.5 cps), and a singlet at 13.2 ppm (OH, 1 H).

Anal. Calcd for $C_8H_6O_3S$: C, 52.7; H, 3.3; S, 17.6. Found: C, 52.4; H, 3.4; S, 17.4.

The filtrate from this procedure was diluted with 1 l. of water and allowed to stand overnight in the refrigerator. The solid which separated was collected and recrystallized from ethanol–water (1:10) to give 1.4 g (7%) of small needles, mp 143–144°, identified as the 6-methyl isomer. The nmr spectrum ($CDCl_3$) showed three sharp singlets at 2.27 (CH_3, 3 H), 6.89 (aromatic 1 H), and 7.03 ppm (aromatic 1 H).

Anal. Calcd for $C_8H_6O_3S$: C, 52.7; H, 3.3; S, 17.6. Found: C, 52.4; H, 3.0; S, 17.3.

To obtain the product ratio of the two isomers in the crude mixture, the reaction was repeated as just described. At the end of the reaction, the mixture was diluted with 1 l. of water and refrigerated overnight. The solid was collected, washed with water, and dried. Analysis of the crude mixture by nmr spectroscopy and vpc gave a product ratio of 90% 7-methyl isomer and 10% 6-methyl isomer.

Similarly prepared were 5-hydroxy-7-phenyl- and 5-hydroxy-6-phenyl-1,3-benzoxathiol-2-ones from 2-phenylbenzoquinone; and 7-phenylmercapto- and 6-phenylmercapto-1,3-benzoxathiol-2-ones from 2-phenylmercaptobenzoquinone.[8] For pertinent physical and analytical data, see Table IV.

7-Chloro-, 6-Chloro-, and 4-Chloro-5-hydroxy-1,3-benzoxathiol-2-ones.—To a stirred solution of 5.7 g (0.075 mol) of thiourea in 100 ml of 2 *N* hydrochloric acid was added 7.1 g (0.05 mol) of 2-chlorobenzoquinone[9] in 25 ml of glacial acetic acid. The mixture was stirred for 30 min, then heated for 1 hr. Water was added to the cloud point; after crystallization was complete, the solid was collected, washed with water, and recrystallized from ethanol–water to give 5 g (53%) of white needles, mp 180–181°. This material was identified as the 7-chloro isomer by its nmr spectrum (DMSO-d_6) which displayed two doublets of an AB quartet centered at 6.83 and 7.11 (aromatic, 2 H, J_{AB} = 2.5 cps) and a singlet at 13.4 ppm (OH, 1 H).

Anal. Calcd for $C_7H_3ClO_3S$: C, 41.5; H, 1.5; S, 15.8. Found: C, 41.5; H, 1.6; S, 15.6.

The filtrate from the crude mixture was diluted with 500 ml more water and set aside. The solid which separated was recrystallized from benzene to give a product which has a melting point and infrared spectrum identical with those of the 7-chloro isomer. The benzene filtrate was concentrated to one-half its volume. The solid which precipitated was recrystallized from ethanol–water to give 2.5 g of white needles, mp 128–130°. Nuclear magnetic resonance analysis indicated a mixture of both the 4- and 6-chloro isomers. All attempts to separate these two isomers by fractional crystallization were unsuccessful. The nmr spectrum (DMSO-d_6) showed two sharp singlets at 7.37 (aromatic, 1 H) and 7.56 (aromatic, 1 H), and two doublets of an AB quartet centered at 6.97 and 7.30 ppm (aromatic, 2 H, J_{AB} = 9.0 cps).

Anal. Calcd for $C_7H_3ClO_3S$: C, 41.5; H, 1.5; S, 15.8. Found: C, 41.6; H, 1.7; S, 16.1.

To obtain the product ratio of the isomers, the crude mixture was analyzed by vpc and found to consist of 62% 7-chloro isomer, 20% 6-chloro isomer, and 18% 5-chloro isomer.

7-Isopropyl-5-hydroxy-4-methyl-1,3-benzoxathiol-2-one.—A solution of 8.2 g (0.05 mol) of thymoquinone in 50 ml of glacial acetic acid was mixed with a solution of 5.3 g (0.07 mol) of thiourea in 50 ml of 2 *N* hydrochloric acid. After a 30-min stirring, at room temperature, it was heated on a steam bath for 30 min. Upon cooling, a mass of large white platelets crystallized and were collected. There was obtained 10.8 g (96%) of a solid, mp 156.5–157.5° (lit.[2] mp 158.5–159°). The nmr spectrum ($CDCl_3$) showed a doublet centered at 1.25 (CH_3, 6 H), a singlet at 2.10 ($Ph-CH_3$, 3 H), a quartet centered at 3.07 (CH, 1 H), and a singlet at 6.79 ppm (aromatic, 1 H).

2,5-Di-*t*-butylhydroquinone, Durohydroquinone, and 3-Bromothymohydroquinone.—A suspension of 11.0 g (0.05 mol) of 2,5-di-*t*-butylbenzoquinone in 100 ml of glacial acetic acid was stirred for 30 min with a solution of 5.3 g (0.07 mol) of thiourea in 100 ml of 2 *N* hydrochloric acid, then heated on a steam bath until the reddish brown suspension became colorless (2 hr). The solid was collected, washed with water, and dried, giving 11 g (99%) of pure white prisms, mp 212–214°. The melting point, R_f value, and infrared spectrum were identical with those of an authentic sample of 2,5-di-*t*-butylhydroquinone.

Similarly, reaction of duroquinone or 3-bromothymoquinone[10] with thiourea resulted in nearly quantitative yields of the corresponding hydroquinones.

7-Acetyl- and 4-Acetyl-5-hydroxy-1,3-benzoxathiol-2-ones.—A solution of 7.5 g (0.05 mol) of freshly prepared 2-acetylbenzoquinone[11] in 50 ml of glacial acetic acid and a solution of 5.7 g (0.075 mol) of thiourea in 100 ml of 2 *N* hydrochloric acid were mixed and stirred at room temperature for 30 min. Thin layer chromatographic analysis indicated a mixture of two compounds, one of which fluoresced strongly under a uv lamp. After being heated for 40 min, the fluorescent compound was completely converted into a new product, but the other compound remained unchanged, as indicated by tlc. The mixture was diluted with 50 ml of water and cooled. The solid was collected, washed with water, and dried; it weighed 8.3 g (79%) and had mp 185–187°. Recrystallization from ethanol–water yielded a product, mp 187–188°, which was identified by nmr spectroscopy as the 4-acetyl-5-hydroxy-1,3-benzoxathiol-2-one. The nmr spectrum

(7) E. Kurosawa, *Bull. Chem. Soc. Jap.*, **34**, 303 (1961).

(8) J. M. Snell and A. Weissberger, *J. Amer. Chem. Soc.*, **61**, 452 (1939).

(9) J. Conant and L. F. Fieser, *ibid.*, **45**, 2201 (1923).

(10) F. Kehrmann, *Ber.*, **22**, 3264 (1889).

(11) M. C. Kloetzel, R. P. Dayton, and B. Y. Abadir, *J. Org. Chem.*, **20**, 38 (1955).

($CDCl_3$) showed a sharp singlet at 2.75 (CH_3, 3 H) and two doublets of an AB quartet centered at 6.99 and 7.28 ppm (aromatic, 2 H, J_{AB} = 9.0 cps).

Anal. Calcd for $C_9H_6O_4S$: C, 51.4; H, 2.9; S, 15.3. Found: C, 51.6; H, 2.9; S, 15.6.

The filtrate was combined with the washings and heated on a steam bath. After 1 hr of heating, no change was detected by tlc. Only upon prolonged heating (3 hr) did a reaction occur. The mixture was poured into 500 ml of water, and the precipitate was collected and recrystallized from ethanol–water to give 1.5 g (11%) of yellow needles, mp 209–210°. This material was identified by nmr spectroscopy as the 7-acetyl isomer. Its nmr spectrum (DMSO-d_6) showed a sharp singlet at 2.64 (CH_3, 3 H) and two doublets of an AB quartet centered at 7.21 and 7.42 ppm (aromatic, 2 H, J_{AB} = 2.5 cps).

Anal. Calcd for $C_9H_6O_4S$: C, 51.4; H, 2.9; S, 15.3. Found: C, 51.5; H, 2.7; S, 15.3.

The product ratio of the crude mixture was analyzed by nmr spectroscopy and vpc to be 83% 4-acetyl isomer and 17% 7-acetyl isomer.

Registry No.—4,7-Dimethyl-5-hydroxy-2-imino-1,3-benzoxathiole hydrochloride, 17630-80-7; **9**, 17631-02-6; **10**, 17631-03-7; **13**, 17631-04-8; **14**, 17631-05-9; **15**, 17630-66-9; **16**, 17630-71-6; 4,7-dichloro-5-hydroxy-2-imino-1,3-benzoxathiol-2-one, 17630-72-7.

Acknowledgment.—The authors gratefully acknowledge the assistance of Dr. T. H. Regan and Mr. R. L. Young in the preparation and interpretation of the nmr spectra.

Base-Induced Cyclization of 2-Oximinophosphonium Salts. Synthesis and Spectroscopic Properties of 1,2,5-Oxazaphosph(V)ol-2-ines

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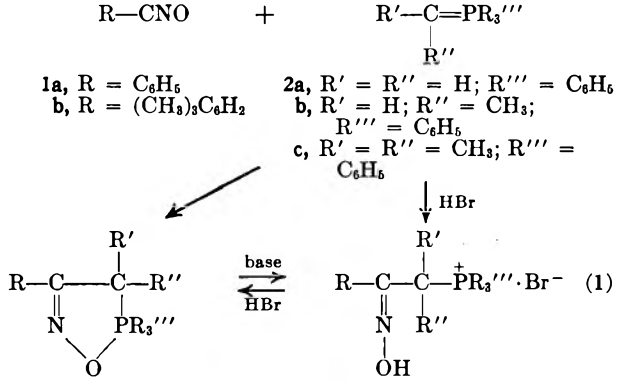
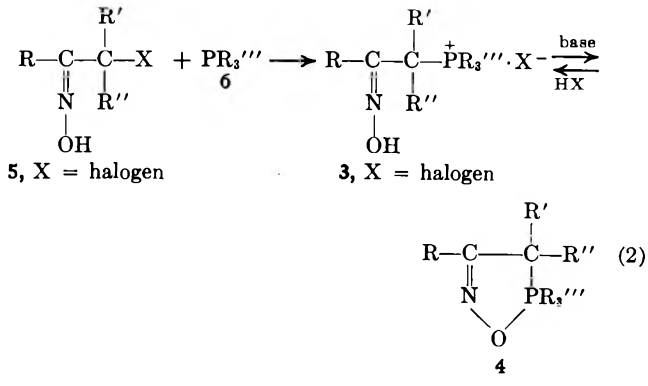
Received April 23, 1968

Several 1,2,5-oxazaphosph(V)ol-2-ines (**4**) have been prepared in high yield by basic treatment of 2-oximinophosphonium salts (**3**). These salts were easily obtained either by reaction of α halo ketoximes with triphenyl- or tri-*n*-butylphosphine, by oximation of the corresponding 2-keto phosphonium salts, or finally by reaction of nitrile oxides with phosphonium ylides in dimethyl sulfoxide. The reaction of desyl bromide with triphenylphosphine in benzene gave a mixture of the keto (**8**) and enol phosphonium (**8a**) salts. Treatment of **8** with hydroxylamine gave the corresponding ylide (**9**) instead of the expected oxime. The ring of 1,2,5-oxazaphosph(V)ol-2-ines can be opened by treatment with acids in the cold, affording the corresponding 2-oximinophosphonium salts. Thermal decomposition of 3-(4-bromophenyl)-5,5,5-triphenyl-1,2,5-oxazaphosph(V)-ol-2-ine (**4d**) gave 2H-3-(4-bromophenyl)azirine (**10**) together with triphenylphosphine oxide. The comparison of the mass spectra of 1,2,5-oxazaphosph(V)ol-2-ines with the spectra of the corresponding phosphonium salts confirmed the cyclic structure of the former. ^1H nmr spectra of the title compounds and of the corresponding salts (**3**) were measured in several solvents and discussed. From the chemical-shift and coupling-constant values it can be deduced that the P–O bond in the cycles (**4**) has high covalent character. The effect of substituents on chemical shifts and coupling constants are discussed.

In a recent paper[2] two of us reported the reaction between benzonitrile oxide (**1a**) and a few phosphonium ylides (**2**). The reaction of **1a** with triphenylphosphonium methylide (**2a**) and ethylide (**2b**) in dimethyl sulfoxide (DMSO), after the work-up in acidic medium, gave the 2-oximinophosphonium salts **3a** and **3b** (eq 1). We also reported the successful transformation of **3a** into the corresponding cyclic compound **4a** by means of base, and the reverse reaction which leads from **4a** to **3a** with hydrobromic acid. We pointed out that such a cyclization could be the final step of an easy route to 1,2,5-oxazaphosph(V)ol-2-ines (**4**), starting from α-halo oximes (**5**) and phosphines (**6**), through the phosphonium salts (**3**) (eq 2).





The only members of this class of cyclic compounds **4** so far known are **4a** and its mesityl analog **4a′** obtained by Huisgen and Wulff[3] directly from **1a** and **1b**, respec-

(1) In alphabetical order.

(2) A. Umani-Ronchi, M. Acampora, G. Gaudiano, and A. Selva, *Chim. Ind.* (Milan), **49**, 388 (1967).

(3) R. Huisgen and J. Wulff, *Tetrahedron Lett.*, 917 (1967).

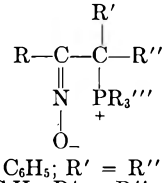
TABLE I

2-OXIMINOPHOSPHONIUM SALTS (3)

Compd no.	Formula	Method of preparation[b]	Yield,[a] %	Reaction conditions: Solvent	Temp, °C	Time, hr	Mp, °C
3a	$C_6H_5C(NOH)CH_2P^+(C_6H_5)_3\cdot Br^-$ [c,d]	A	40				231
3a′	$C_6H_5C(NOH)CH_2P^+(C_6H_5)_3\cdot Cl^-$	B	100	$CHCl_3$	Reflux	2	215
3b	$C_6H_5C(NOH)CH(CH_3)P^+(C_6H_5)_3\cdot Br^-$ [c]	A	65				157
3c	$C_6H_5C(NOH)CH(n\text{-}C_3H_7)P^+(C_6H_5)_3\cdot Br^-$	A	45				191
3d	$p\text{-}BrC_6H_4C(NOH)CH_2P^+(C_6H_5)_3\cdot Br^-$	B	51	EtOH	20	72	219
3e	$\beta\text{-}C_{10}H_7C(NOH)CH_2P^+(C_6H_5)_3\cdot Br^-$ [e]	B′	81	Aq. MeOH	Reflux	30	226
3f	$CH_3C(NOH)CH_2P^+(C_6H_5)_3\cdot Cl^-$	B	57	$CHCl_3$	20	72	223
		B′	56	Aq. EtOH	Reflux	10	
3g	$(CH_2)_4C(NOH)CHP^+(C_6H_5)_3\cdot Cl^-$	B	55	Ether	20	72	198
3h	$C_6H_5C(NOH)CH_2P^+(n\text{-}C_4H_9)_3\cdot Cl^-$	B	87	Ether	20	46	197
3i	$p\text{-}BrC_6H_4C(NOH)CH_2P^+(n\text{-}C_4H_9)_3\cdot Br^-$	B	85	Ether	20	48	168

[a] No systematic attempt was made to improve yields by modification of the reaction conditions. [b] A, from the corresponding nitril oxide[2]; B, from the α-halo oxime; B′, from the corresponding 2-oxophosphonium salt by oximation. [c] See ref 2. [d] An attempt to synthesize **3a** by method B, using the oxime obtained from ω-bromoacetophenone and hydroxylamine hydrochloride, according to H. Korten and R. Scholl [*Ber.*, **34**, 1901 (1901)], resulted in a mixture of **3a** and **3a′** (revealed by the mass spectrum). Evidently, according to the observation of Masaki,[5] the oximation of ω-bromoacetophenone by $NH_2OH\cdot HCl$ affords a mixture of the ω-bromo- and ω-chloroacetophenone oximes by halogen exchange. [e] $C_{10}H_7$ = naphthyl.

tively, and **2a** in benzene.[4] In addition, in a more recent paper, Masaki, *et al.*, reported the basic cyclization of **3a** and **3d** to **4a** and **4d**.[5] They stated that the ^1H nmr and the analytical data of the dehydrohalogenated compounds could also suggest an open betainic structure (**7a** and **7d**) analogous to that (**7c**) proposed by Bestmann and Kunstmann[6] for the product obtained from **1a** and **2c**. On the other hand Huisgen and Wulff discarded the betainic structures **7a** and **7a′** for their products on the basis of the chemical-shift value in the ^{31}P nmr spectra. In this paper we report the synthesis



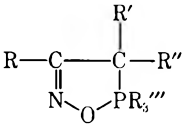
7a, R = R‴ = C_6H_5; R′ = R″ = H
a′, R = $(CH_3)_3C_6H_2$; R′ = R″ = H; R‴ = C_6H_5
c, R = R‴ = C_6H_5; R′ = R″ = CH_3
d, R = 4-$NO_2C_6H_4$; R′ = R″ = H; R‴ = C_6H_5

of several members of this new class of heterocycles (**4**) by the methods outlined in eq 1 (method A, through the phosphonium salts) and eq 2 (method B), and discuss the nmr and mass spectra of these compounds which support the cyclic covalent structures shown. We also report the synthesis and spectral data of the corresponding 2-oximinophosphonium salts (**3**), none of which was known before our earlier report.[5]

Method A.—This method (eq 1) was only used in three cases by running the reaction in DMSO. The salts obtained (see Table I) were cyclized as indicated under method B. Actually the use of nitrile oxides for the synthesis of such heterocycles, even if useful in some cases, offers a more limited route of synthesis, when compared with the reaction depicted in eq 2. This is because of the limited availability of nitrile oxides,[7] which usually are less easily obtained than α-halo oximes (**5**) and the evident difficulty of obtaining by this method cyclic phosphonium salts like **3g** (see Table I) and the corresponding 1,2,5-oxazaphosph(V)-ol-2-ines (**4g**) (see Table II). Moreover the reaction requires the use of phosphonium ylides instead of simple phosphines.

TABLE II

1,2,5-OXAZAPHOSPH(V)OL-2-INES FROM 2-OXIMINOPHOSPHONIUM SALTS

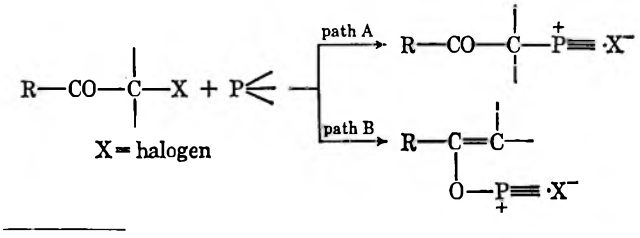


4, R′ = H

Compd no.	R	R″	R‴	Yield, %	Mp, °C
4a[a]	C_6H_5	H	C_6H_5	98[b]	129–130
4b	C_6H_5	CH_3	C_6H_5	85[b]	100
4c	C_6H_5	$n\text{-}C_3H_7$	C_6H_5	70,[b] 98[c]	96
4d	$p\text{-}BrC_6H_4$	H	C_6H_5	91,[b] 100[c]	157
4e	$\beta\text{-}C_{10}H_7$[d]	H	C_6H_5	90[b]	142
4f	CH_3	H	C_6H_5	74[c]	116
4g	$(CH_2)_4$	$(CH_2)_4$	C_6H_5	53[b]	102
4h	C_6H_5	H	$n\text{-}C_4H_9$	80[b]	[e]
4i	$p\text{-}BrC_6H_4$	H	$n\text{-}C_4H_9$	85[b]	96

[a] See ref 2 and 3. [b] By the resin method. [c] By NaOH or KOH. [d] $C_{10}H_7$ = naphthyl. [e] Liquid.

Method B.—When an α-halo carbonyl compound reacts with phosphines either a 2-oxophosphonium salt or an enol phosphonium salt (or both) can be formed,



(4) A few species of 1,2,5-oxazaphosph(V)olidines, the dihydro derivatives of the title compounds, have been recently synthesized by the same authors [J. Wulff and R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **6**, 457 (1967)].

(5) In this paper, M. Masaki, K. Fukini, and M. Ohta, *J. Org. Chem.*, **32**, 3564 (1967), the preparation of four 2-oximinophosphonium salts (**3**) is reported. The cyclization of two of these salts (**3a** and **4a**) was performed by the authors by basic treatment, as already reported by us.[2] Evidently, because of the close timing, the authors did not notice our earlier paper on this subject.

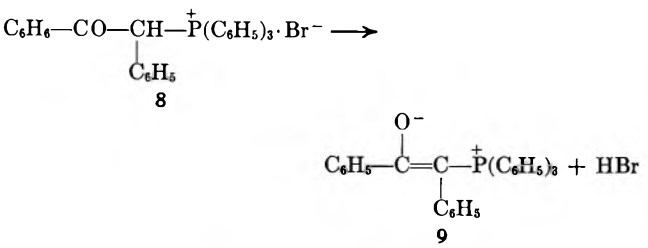
(6) H. J. Bestmann and H. Kunstmann, *Angew. Chem.*, **78**, 1059 (1966).

(7) A. Quilico in "The Chemistry of Heterocyclic Compounds," Interscience Publishers, New York, N. Y., 1962; C. Grundmann in Houben-Weyl's "Methoden der organischen Chemie," Vol. 10/3, G. Thieme Verlag, Stuttgart, 1965.

depending on the nature of the α-halo carbonyl compound, the phosphine, and the solvent.[8]

It has been found that when the reaction is run in a protic solvent the formation of the enol salt is favored. Since a similar behavior might be expected for the reaction of the α-halo oximes with phosphines, in order to obtain the quaternary C salts (path A), we choose an aprotic solvent.[9] Actually when an α-halo oxime reacts with triphenyl- or tributylphosphine in ether or chloroform in the cold or at reflux, the quaternization of the phosphine takes place smoothly, giving a good yield of 2-oximinophosphonium salt.[10]

An alternative route to the phosphonium salts (**3**) based on the oximation of the corresponding 2-oxophosphonium salts can also be used and is recommended when the α-halo oxime is not easily obtained or its reaction with phosphine gives unsatisfactory yields. The oximation of the 2-oxophosphonium salts is usually performed by using hydroxylamine in a slightly acidic medium to avoid the formation of the ylide corresponding to the salt. Under these conditions, however, the oximation requires many hours at water-bath temperature, and in some cases, does not occur at all. An attempt at oximation of the phosphonium salt (**8**)[11] by hydroxylamine hydrochloride failed even after 6 days at 80°, and attempts with free or partially free hydroxylamine resulted in the formation of the ylide (**9**).



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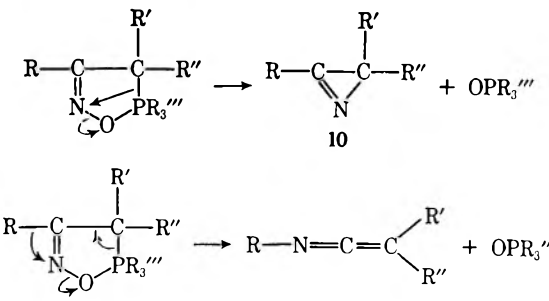
9

The phosphonium salts that we have obtained by these two methods are listed in Table I.

The cyclization of the 2-oximinophosphonium salts (**3**) to the corresponding 1,2,5-oxazaphosph(V)ol-2-ines (**4**) can be best performed by percolating an alcoholic solution of the salt through a basic ion exchange resin, whereby the cycle is obtained in high yield and purity. Alternatively, the cyclization can be accomplished by using cold aqueous NaOH or KOH. The use of cold pyridine as base is not adequate for the cyclization. In fact the nmr spectra of the salts can be measured in pyridine. The cycles obtained by basic treatment of the corresponding salts are listed in Table II.

1,2,5-Oxazaphosph(V)ol-2-ines (**4**) are in general crystalline solids with melting points rather lower than the corresponding salts. When R and R''' are aromatic they are scarcely soluble in the common organic solvents. These compounds are opened by acid treatment in the cold, affording the corresponding salts by the P–O bond fission[2,5] (eq 2). They are thermally unstable giving an azirine and/or ketenimine, by loss of OPR_3'''.[3,6] Accordingly, from **4d**, by thermal decomposition, we isolated a solid azirine (**10**, R = *p*-BrC_6H_4; R′ = R″ = H): ir (Nujol) 1730 cm^{-1}; nmr ($CDCl_3$), δ 1.80 (s).



10

Nmr Spectra.—Since few nmr data concerning pentacovalent phosphorus-containing molecules are available,[12,13] we will discuss here in some detail the ^1H nmr spectra of this class of new compounds, the 1,2,5-oxazaphosph(V)ol-2-ines (**4**), together with their corresponding oximinophosphonium salts (**3**).

Huisgen[3,4] has shown the phosphorus atom to be pentacovalent in **4a** and **4a′** and in some 1,2,5-oxazaphosph(V)olidines, because of the positive chemical shift value of ^{31}P signals. Comparing the ^1H nmr parameters of 1,2,5-oxazaphosph(V)ol-2-ines and the corresponding oximinophosphonium salts, we have found some interesting features.

First it is noteworthy that even from the ^1H chemical shifts and coupling constants it can be deduced that the P–O bond in 1,2,5-oxazaphosph(V)ol-2-ines has a high covalent character.

The two hydrogens at C_4 are magnetically equivalent in both salts and cyclic compounds; indeed the latter have a plane of symmetry identified with the plane of the heterocyclic ring, assuming rapid flipping of this ring and free rotation of the phenyl groups. The spectra are not temperature dependent over a range from +30 to −50°.[14]

Chemical Shifts.—Comparing the chemical-shift values of cyclic compounds with that of the corresponding oximinophosphonium salts,[15] a marked difference in the δ value of the protons on C_4 can be observed; the localized positive charge on the P atom in the salts produces a strong deshielding on these protons which appear at a lower field than the corresponding 1,2,5-oxazaphosph(V)ol-2-ines [$\Delta\delta = -(1.3\text{–}1.7)$[16]].

It is interesting to note that such an effect in the salts is exerted through three, four, and even five bonds. For example the CH_3 signals (three bonds away) in the **3b**–**4b** pair show $\Delta\delta = -0.14$;[16] the CH_3 signals (five bonds away) of the **3c**–**4c** pair give $\Delta\delta = -0.10$; and

(8) For a recent review on this subject, see A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., 1967, p 117; see also I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967).

(9) With the only exception of compound **3d**.

(10) The reaction of some 2-bromoacetophenone oximes with $P(C_6H_5)_3$ in acetonitrile has been recently investigated by Masaki.[5]

(11) This salt, according to the report of H. Hoffmann and H. J. Diehr [*Angew. Chem.*, **76**, 944 (1964)], based on unpublished results (Hoffmann and Beller), can be obtained in high yield from desyl bromide and triphenylphosphine in benzene. Actually in our hands the reaction afforded essentially the corresponding enol salt (**8a**), $C_6H_5C(=CHC_6H_5)OP^+(C_6H_5)_3\cdot Br^-$, together with a minor amount of the keto salt **8**. In fact the mixture of the salts obtained from desyl bromide and $P(C_6H_5)_3$, after treatment with water, gave a large amount of $PO(C_6H_5)_3$ and desoxybenzoin, both compounds being indicative of the formation of the enol salt[8] (see Experimental Section).

(12) G. Mavel in "Progress in Nmr Spectroscopy," J. W. Emsley, J. Feeney, L. H. Sutcliffe, Ed., Pergamon Press Ltd., Oxford, 1966.

(13) See, for example, F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **31**, 3159 (1966); R. Burgada, D. Houlla, and R. Wolf, *C. R. Acad. Sci., Paris, Ser. C*, **264**, 356 (1967); F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, *J. Amer. Chem. Soc.*, **90**, 751 (1968).

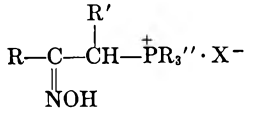
(14) This measurement was performed on **4i** in $CDCl_3$ solution.

(15) No effect of halide ion on either chemical shift or *J* was observed in the salts.

(16) $\Delta\delta = \delta_{cycle} - \delta_{salt}$; chemical shifts are compared in $CDCl_3$.

TABLE III

NMR SPECTRAL DATA FOR 2-OXIMINOPHOSPHONIUM SALTS[a]



Compd	R	R′	R″	J, cps	CDCl₃	DMSO-d_6	Pyridine-d_5	Grouping	Chemical shifts, δ, ppm: CDCl₃	DMSO-d_6	Pyridine-d_5
3a	C_6H_5	H	C_6H_5	$^2J_{P,H}$		16.8[b]	15.0[c]	CH_2P^+		5.16 (d)[b]	5.37 (d)[c]
								OH		12.16 (s)[b]	*d*
3d	*p*-BrC_6H_4	H	C_6H_5	$^2J_{P,H}$		16.5	14.7[c]	CH_2P^+		5.20 (d)	5.23 (d)[c]
								OH		12.40 (s)	*d*
3e	2-$C_{10}H_7$[e]	H	C_6H_5	$^2J_{P,H}$		16.5	15.5[c]	CH_2P^+		5.27 (d)	5.72 (d)[c]
								OH		12.33 (s)	*d*
3f	CH_3	H	C_6H_5	$^2J_{P,H}$		14.0	13.5[f]	CH_2P^+		4.99 (d)	5.76 (d)[f]
								CH_3		1.84 (s)	2.29 (s)
								OH		11.05 (s)	*d*
3h	C_6H_5	H	$(CH_2)_3CH_3$	$^2J_{P,H}$	16.7	16.9	16.8	CH_2P^+	4.20 (d)	4.04 (d)	4.80 (d)
								CH_2[g]	1.9–2.5	1.8–2.5	2.4–3.0
								CH_3[h]	0.82[i]	0.82[i]	0.82[i]
								OH	12.56 (s)	12.63 (s)	*d*
3i	*p*-BrC_6H_4	H	$(CH_2)_3CH_3$	$^2J_{P,H}$	16.7	16.8		CH_2P^+	4.21 (d)	4.04 (d)	
								CH_2[g]	1.8–2.5	1.7–2.5	
								CH_3[h]	0.85[i]	0.83[i]	
								BrC_6H_4[j]	7.44, 7.73	7.65, 7.83	
								OH	12.71 (s)	12.65 (s)	
3b	C_6H_5	CH_3	C_6H_5	$^2J_{P,H}$	13.5	13.5[b]	10.5–10.8	CHP⁺	4.91 (qd)	5.16 (qd)[b]	5.26 (qd)
				$^3J_{P,Me}$	19.0	18.5[b]	19.0	CH_3	1.80 (dd)	1.83 (dd)[b]	2.01 (dd)
				$^3J_{H,Me}$	7.0	7.0[b]	7.1	OH	*k*	12.50 (s)[b]	*d*
3c	C_6H_5	CH_2^A–CH_2^B–CH_3	C_6H_5	$^2J_{P,H}$	12.5–13.0	13.0		CHP⁺	5.01[l]	5.21[l]	5.46[f]
				$^3J_{H,H^A}$	10.5–11.0	10.5–11	*m*	CH_2^A	2.41, 1.84[n]	1.8–2.6	2.1–2.8
				$^3J_{H_AH_B}$	3.5	4.0		CH_2^B	1.53[o]	1.1–1.7	1.3–2.0
								CH_3	0.83 (t)	0.86 (t)	0.78 (t)
								OH	12.05 (s)	12.58 (s)	*d*

[a] A few data are missing because of either low solubility or scarcity of some products. [b] See ref 2. [c] Concentration 0.05 *M*. [d] Together with H_2O signal. [e] $C_{10}H_7$ = naphthyl. [f] Concentration 0.1 *M*. [g] Broad, six protons (CH_2P^+) of butyl groups. [h] Three equivalent CH_3 of butyl groups. [i] Strongest transition of the A_3B_2 pattern, part A. [j] A_2B_2 pattern, δ_A and δ_B values are given. [k] Not visible. [l] Eight-line pattern. [m] Not analyzed. [n] Centers of broad absorptions, measured by decoupling experiments. [o] Quintet, J = 7 cps.

even the aromatic protons *meta* to Br (five bonds away) in the **3i**–**4i** pair show a $\Delta\delta = -0.18$ (protons *ortho* to Br, $\Delta\delta = +0.02$).[17] A model inspection shows that the influence of the anisotropy of phenyl groups is comparable in each salt–cycle pair, so that it can not be responsible for this effect. If fact the deshielding is also observed when phenyls on P are replaced by butyls (**3i**).

As for the effect of substituents at P on the δ value of the C_4 protons, we have found the same behavior in both salts and cyclic compounds. Inspection of the data in Tables III and IV shows that, when butyl groups instead of phenyls are attached at the phosphorus, the methylene protons shift more than 1 ppm upfield. The effect of substitution at C_3, as expected, is not so strong; on going from C_6H_5 to C_6H_4Br and $C_{10}H_7$ only a very slight deshielding is observed, whereas the presence of a CH_3 causes C_4 protons to shift upfield, as expected. This effect is a little more marked in the cyclic derivatives [δ (**4a**) − δ (**4f**) = +0.4] than in the salts.

Coupling Constants. The two-bond coupling constant $^2J_{P,H}$ in oximinophosphonium salts[15] is always higher in modulus than in cyclic derivatives. The positive shift[18] on going from polar structures (P hybridization ~sp^3) to cyclic ones is in agreement with a view of a high contribution of pentacovalent character of the P atom in the latter compounds (hybridization ~sp^3d).[12] The value of $^2J_{P,H}$ is found to be independent of substituents on the phosphorus atom in both phosphonium salts, as already observed by Griffin,[19] and cyclic compounds. However this geminal coupling is sensitive, as expected, to change in substituents on C_4. It is interesting to note that, while the change of $^2J_{P,H}$ upon alkylation at C_4 in the phosphonium salts falls in the same range as reported by Mavel[12] [*e.g.*, **3a** (J = 16.8 cps) → **3b** (J = 13.5 cps)], in the cyclic compounds this change is drastic [*e.g.*, **4a** (J = 11.9 cps) → **4b** (J = 3.5 cps)].

It has not yet been possible to determine the sign of these constants.[20] From the available data[12] we could assume that the large couplings are negative, but, concerning the small ones, no assumption can be made. In any case such a variation (positive shift) is strong and cannot adequately be explained solely in terms of a change of the s character of the bonding orbitals of carbon to phosphorus due to the effect of the electronegativity of the substituent.[12] This is because of the small difference in electronegativity between hydrogen and alkyl and also because in several cases reported in the literature an opposite trend has been observed.[21]

In the salt series, but not in cyclic compounds, $^2J_{P,H}$ is also sensitive to change in the nature of the substituent on C_3; it decreases in modulus when aryl substitu-

(17) There are only two exceptions in this trend, for the CH_3 signals in the **4f**–**3f** pair ($\Delta\delta$ = +0.12 in DMSO-d_6) and for the CH_3 signals in the **4i**–**3i** pair ($\Delta\delta$ = +0.08). However, a model inspection can explain these exceptions on the basis of a shielding effect of the phenyls which can operate only in the salts, where free rotation is allowed at C_3–C_4 and C_4–P.

(18) The sign of the $^2J_{P,H}$ for the phosphonium salts is assumed negative; see ref 12 and S. L. Manatt, G. L. Juvinall, R. I. Wagner, and D. D. Elleman, *J. Amer. Chem. Soc.*, **88**, 2689 (1966). On account of their large modulus we assume the $^2J_{P,H}$ to be negative also in the cyclic compounds.

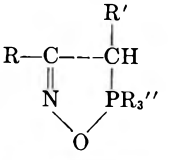
(19) C. E. Griffin and M. Gordon, *J. Organometal. Chem.*, **3**, 414 (1965).

(20) In a more recent decoupling experiment, made on **4b**, $^2J_{P,H}$ and $^3J_{P,H}$ appeared to be of opposite relative sign. Further investigations are in progress.

(21) J. B. Hendrickson, M. L. Maddox, J. J. Sims, and H. D. Kaesz, *Tetrahedron*, **20**, 449 (1964); D. W. Allen, I. T. Millar, and J. C. Tebby, *Tetrahedron Lett.*, 745 (1968).

Table IV

Nmr Spectral Data for 1,2,5-Oxazaphosph(V)ol-2-ines[a]



Compd	R	R′	R″		J, cps CCl4	CDCl3	DMSO-d6	Pyridine-d5	Grouping	Chemical shifts, δ, ppm CCl4	CDCl3	DMSO-d6	Pyridine-d5
4a	C_6H_5	H	C_6H_5	$^2J_{P,H}$		11.9[b]	11.9		CH_2P		3.40[b]	3.88	
4d	p-BrC_6H_4	H	C_6H_5	$^2J_{P,H}$			12[c]	11.8[d]	CH_2P			3.90	3.88[d]
4e	2-$C_{10}H_7$[e]	H	C_6H_5	$^2J_{P,H}$			11.8	11.8[d]	CH_2P			3.98	4.05[d]
4f	CH_3	H	C_6H_5	$^2J_{P,H}$		11.2	11.5[f]	11.5–12.0	CH_2P		3.03	3.39	3.29
				$^4J_{H,Me}$		0.7			CH_3		2.08	1.96	2.11
4h	C_6H_5	H	$(CH_2)_3CH_3$	$^2J_{P,H}$	12.0				CH_2P	2.50			
									CH_2[g]	1.3–1.7			
									CH_3[h]	0.93			
4i	p-BrC_6H_4	H	$(CH_2)_3CH_3$	$^2J_{P,H}$	11.9	12.0	12.4		CH_2P	2.40	2.51	2.73	
									CH_2[g]	1.2–1.7	1.2–1.8	1.2–1.8	
									CH_3[h]	0.93	0.93	0.88	
									BrC_6H_4[i]	7.38, 7.48	7.46, 7.55	7.54, 7.62	
4b	C_6H_5	CH_3	C_6H_5	$^2J_{P,H}$		3.5	3.6	3.5	CHP		3.34 (qd)	3.78 (qd)	3.70 (qd)
				$^3J_{P,Me}$		19.7	19.5	19.8	CH_3		1.66 (dd)	1.54 (dd)	1.67 (dd)
				$^3J_{H,Me}$		7.3	7.3	7.2					
4c	C_6H_5	CH_2^A–CH_2^B–CH_3	C_6H_5	$^2J_{P,H}$		3.5–4		4.0	CHP		3.55[j]	3.96	3.93[j]
				$^3J_{H,H}{}^A$		4.0[k]	l	4.0	CH_2^A		1.8–2.4[m]		2.0–2.6
				$^3J_{H,H}{}^{A'}$		8.0[k]		8.0	CH_2^B		1.27[n]		1.36[n]
									CH_3		0.73 (t)	0.66	0.62 (t)

[a] A few data are missing because of either low solubility or scarcity or decomposition of some products when dissolved. [b] See ref 3. [c] Very little soluble. [d] Concentration 0.1 *M*. [e] $C_{10}H_7$ = naphthyl. [f] Partially overlapped with the H_2O signal. [g] Six protons (CH_2P) of butyl groups. [h] Strongest transition, A6, of the A_3B_2 pattern, part A. [i] AA′BB′ pattern, δ_A and δ_B values are given. [j] Five-line pattern. [k] The $^3J_{H,H}{}^A$ of the not equivalent CH_2^A protons were assigned by decoupling. [l] Not analyzed. [m] Broad absorption centered at δ 2.1. [n] Slightly broadened quintet.

Table V

Mass Spectra of Compounds **3h**, **3i**, **4h**, and **4i**

Significant peaks 3h m/e	3h %	3i m/e	3i %	4h m/e	4h %	4i m/e	4i %	Fragmentation	Product
335	7	413[a]	0.5					M − HX (X = Cl or Br)	a
318	6	396[a]	3					a − OH	b
306	5	384[a]	0.3					a − C_2H_5	c
290	0.5	368[a]	0.5					b − C_2H_4	d
278	2	356[a]	1					a − C_4H_9	e
276	1	354[a]	0.5					b − C_3H_6	f
262	11	340[a]	3					b − C_4H_8	g
218	6	218	4	218	7	218	4	$PO(C_4H_9)_3$	h
189	30	189	36	189	37	189	26	h − C_2H_5	i
176	9	176	7	176	9	176	7	h − C_3H_6	j
162	19	162	17	162	24	162	18	h − C_4H_8	k
161	17	161	18	161	17	161	12	h − C_4H_9	l
147	20	147	18	147	22	147	18	i − C_3H_6	m
134	22	134	24	134	26	134	22	k − C_2H_4	n
120	35	120	30	120	40	120	38	k − C_3H_6	o
104	7	182[a]	7	104	36	182[a]	13	$YC_6H_4CH{=}CH_2$ (Y = H or Br)	p
92	100	92	100	92	100	92	100	Z[b]	q
77	73	155[a]	10	77	25	155[a]	5	YC_6H_4 (Y = H or Br)	r

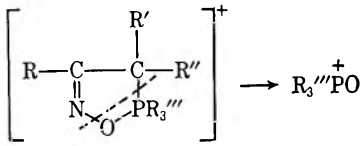
[a] Values corresponding to ions containing one ^{79}Br. [b] This fragment, whose structure has not been formulated, should contain part of the $P(C_4H_9)_3$ grouping inasmuch as it is absent in the corresponding $P(C_6H_5)_3$ derivatives.

ents (J = 16.5–16.9 cps) are replaced by methyl (J = 14.0 cps). The $^3J_{P,Me}$ in **3b** and **4b** have the normal value expected for a three-bond coupling in a saturated fragment PCCH.

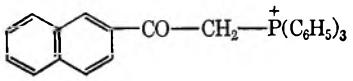
Mass Spectra.—Further support of the cyclic (**4**) against the betainic form (**7**) of the dehydrohalogenated compounds is found when the mass spectra of these substances are compared with the spectra of the corresponding salts (**3**). In fact the mass spectra of the tributylphosphine salts (**3h** and **3i**) (see Table V) exhibit the peak corresponding to the parent ion less HX, together with other peaks over *m/e* 218 [$P^+O(C_4H_9)_3$], whereas the spectra of the corresponding dehydrohalogenated compounds (**4h** and **4i**) do not show any peak above *m/e* 218. This is indicative of the formation from the salts, before or upon electron impact, of a species (M − HX) different from the dehydrohalogenated compounds (**4h** and **4i**). Moreover, the comparison of the spectra suggests an open form for this species (M − HX) and clearly indicates a cyclic structure, with a preformed P–O bond, for **4h** and **4i**.

In the case of the triphenylphosphine salts (**3a**–**3g**) the spectra are often rather similar to those of the corresponding dehydrohalogenated compounds (**4a**–**4g**), whose dominant features are given by the peaks corresponding to the $P^+O(C_6H_5)_3$ ion (the heaviest frag-

ment) and its fragmentation species. This is probably due, for the salts, to the easy formation, before or upon the electron impact, of the P–O bond, presumably in the same cyclic pentaatomic structure as in **4**, followed by the fragmentation



In fact, the mass spectrum of the phosphonium salt **11**,



11

where the formation of a P–O bond through a cyclic four-membered intermediate is much less probable, does not show any peak corresponding to $P^+O(C_6H_5)_3$. The evidence for a cyclic structure of the dehydrohalogenated compounds (**4a**–**4g**) is less straightforward than for the tributylphosphine analogous derivatives (**4h** and **4i**). However, even in this case the mass spectral data at least appear more favorable to a cyclic rather than a betainic structure.

Experimental Section

All melting points are uncorrected. Infrared spectra were determined in Nujol, unless otherwise specified, with a Perkin-Elmer Model 137 Infracord spectrophotometer. Only prominent peaks are reported. Ultraviolet spectra (95% ethanol as solvent) were recorded on a Beckman DK2 spectrophotometer. Proton nmr spectra were recorded with Varian HA-60 and HA-100 spectrometers; decoupling experiments were performed in "frequency sweep." Chemical shifts were measured in parts per million (δ) from TMS as internal standard, with a Hewlett-Packard frequency counter. No appreciable variation in chemical shift and J was found within the range of concentration used (0.15–0.25 M), unless otherwise specified. Chemical shifts are reported either in Table III and Table IV or in the Experimental Section. Mass spectra were measured on a Hitachi-Perkin-Elmer RMU6D (single focus) spectrometer with the inlet system at 250° and an electron ionizing voltage of 70 eV (80 μ A). The values of significant peaks are reported in the General or in the Experimental Section.

Starting Materials.—The α-halo oximes **6** were prepared by the methods reported in the literature, as indicated below under the corresponding phosphonium salts. Commercial samples of triphenylphosphine and tributylphosphine[22] were used in the preparation of the salts **3**; no purification was needed.

β-Naphthacyltriphenylphosphonium Bromide (11).—A mixture of β-naphthacyl bromide (5.0 g), chloroform (40 ml), and triphenylphosphine (5.2 g) was refluxed for 30 min. The filtered solution was added to 300 ml of anhydrous ether. The precipitate was collected and crystallized from ethanol, giving 8 g (78%) of **11**: mp 251°; uv max 228 (s) (ϵ 51,100), 327 (14,000); ir 2680, 1670, 1465, 1220, 1195, 1120, 995, 940, 840, 810, 753, 748, 721, 690 cm^{-1}; nmr (DMSO-d_6) CH_2P^+ δ 5.26 ($J_{P,H}$ = 16.5 cps); mass spectrum m/e (relative intensity) 430 (100), 429 (75), 401 (24), 303 (95), 277 (42), 228 (27), 202 (39) 201 (23).

Anal. Calcd for $C_{30}H_{24}BrOP$: C, 70.5; H, 4.7; Br, 15.7; P, 6.1. Found: C, 70.6; H, 4.5; Br, 15.7; P, 6.0.

2-Oximinophosphonium Salts. Method A Illustrated for the Oxime of 1-Propylphenacyltriphenylphosphonium Bromide (3c).—A solution of benzylidenetriphenylphosphorane was prepared as follows. A 50% NaH–paraffin oil mull (3.2 g) was introduced into a dry round-bottomed flask equipped with a mercury sealed stirrer, a dropping funnel, a reflux condenser, and an inlet tubing for nitrogen, to exclude oxygen during the reaction. The NaH was washed three times in the flask with hexane, and 150 ml of DMSO (distilled over CaH_2) was added. The mixture was then kept at 75–80° for 45 min. After cooling in an ice bath, 100 ml of dry tetrahydrofuran (THF) and 26 g of butyltriphenylphosphonium bromide[23] were added while stirring. In the meantime a solution of benzonitrile oxide was prepared by dissolving 10.0 g of benzohydroxamyl chloride[24] in 50 ml of dry THF at −20°, by adding 9.0 ml of triethylamine and filtering from the triethylamine hydrochloride. The solution was immediately added to the phosphorane, while stirring and cooling at 0°, during 5 min. The mixture was then kept for 2 hr at room temperature with continuous stirring and then poured into a cold (ice) dilute solution of HBr in water. After three washings with ether, the solution was left for a long time at room temperature. The salt **3c** began to separate after several hours, but the precipitation was complete only after 2 weeks. The salt (14.5 g, 45%) was collected, dissolved in ethanol–ether, and crystallized by cooling to −40°: mp 191° dec; uv max 262 mμ (s) (ϵ 9800); ir 1470, 1450, 1105, 1100, 995, 950, 750, 725, 695 cm^{-1}.

Anal. Calcd for $C_{29}H_{25}BrNOP$: C, 67.2; H, 5.6; Br, 15.4; N, 2.7; P, 6.0. Found: C, 67.1; H, 5.3; Br, 15.8; N, 2.8; P, 6.3.

2-Oximinophosphonium Salts. Method B Illustrated for the Oxime of Phenacyltriphenylphosphonium Chloride (3a′).—A mixture of ω-chloroacetophenone oxime[25] (2.0 g), triphenylphosphine (3.23 g) and chloroform (70 ml) was refluxed for 3 hr. The white precipitate (5.2 g, 100%, mp 211°) was collected and crystallized from a little ethanol. The pure salt (**3a′**) showed mp 215° dec; uv max 226 (s) (ϵ 33,300), 258 (s) (11,000); ir 1435, 1310, 1110, 960, 757, 750, 695 cm^{-1}.

Anal. Calcd for $C_{25}H_{23}ClNOP$: C, 72.3; H, 5.4; Cl, 8.2; N, 3.2; P, 7.2. Found: C, 72.0; H, 5.4; Cl, 8.5; N, 3.4; P, 7.7.

The same procedure was followed for the other salts but varying the solvent, time, and temperature, according to the data reported in Table I. Other data and modifications of the standard procedure, if any, are reported below.

The oxime of *p*-bromophenacyltriphenylphosphonium bromide (3d) was obtained from *p*-bromophenacyl bromide oxime[26] and triphenylphosphine. Owing to its solubility in the reaction medium, after elimination of most of the solvent at reduced pressure, the salt **3d** was isolated by precipitation with ether. After crystallization from a little ethanol it melted at 219° dec: uv max 225 (s) (ϵ 21,600), 263 (15,100); ir 1430, 1105, 962, 748, 690 cm^{-1}.

Anal. Calcd for $C_{26}H_{22}Br_2NOP$: C, 56.2; H, 3.9; Br, 28.8; N, 2.6; P, 5.6. Found: C, 56.8; H, 4.1; Br, 29.5; N, 2.5; P, 5.6.

2-Oximinopropyltriphenylphosphonium chloride (3f) was obtained from chloroacetone oxime[27] and triphenylphosphine: white crystals from ethanol; mp 223°; yield 57%; uv max 224 (s) (ϵ 26,100), 269 (3200), 277 (2600); ir 3500, 1110, 820, 755, 720, 690 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}ClNOP$: C, 68.2; H, 5.7; Cl, 9.6; N, 3.8; P, 8.4. Found: C, 67.9; H, 5.8; Cl, 9.6; N, 3.6; P, 8.5.

2-Oximinocyclohexyltriphenylphosphonium chloride (3g) was obtained from 2-chlorocyclohexanone oxime[28] and triphenylphosphine: mp 198° (from ethanol–ether); yield 55%; uv max 225 (s) (ϵ 20,000), 269 (3000), 277 (2400); ir 3400, 1465, 1110, 1005, 998, 750, 728, 698 cm^{-1}.

Anal. Calcd for $C_{24}H_{25}ClNOP$: Cl, 8.6; N, 3.4; P, 7.6. Found: Cl, 8.5; N, 3.5; P, 7.5.

The oxime of phenacyltri-*n*-butylphosphonium chloride (3h) was obtained from ω-chloroacetophenone oxime[25] and tri-*n*-butylphosphine: mp 197° (from ethanol); yield 87%: uv max 248 mμ (ϵ 10,500); ir 2950, 1470, 1405, 1300, 1045, 965, 802, 748, 705 cm^{-1}.

The oxime of *p*-bromophenacyltri-*n*-butylphosphonium bromide (3i) was obtained from *p*-bromophenacyl bromide oxime[26] and tri-*n*-butylphosphine: mp 168° (from ethanol); yield

(22) Fluka AG, Buchs SG, Switzerland.

(23) R. Mechoulam and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 4386 (1958).

(24) O. Piloty and H. Steinbock, *Ber.*, **35**, 3101 (1902).

(25) See Korten and Scholl, Table I, footnote *d*.

(26) A. Collet, *Bull. Soc. Chim. Fr.*, **27** [3], 539 (1902).

(27) R. Scholl and G. N. Matthaiopoulos, *Ber.*, **29**, 1550 (1896).

(28) We thank Dr. A. Nenz (Istituto G. Donegani, Novara) for the kind gift of this compound.

85%; uv max 259 mμ (ε 15,500); ir 1460, 1400, 1300, 1045, 960, 920, 845, 725 cm^{-1}.

Anal. Calcd for $C_{20}H_{34}Br_2NOP$: Br, 32.3; N, 2.8; P, 6.3. Found: Br, 32.5; N, 2.9; P, 6.5.

2-Oximinophosphonium Salts. Method C Illustrated for the Oxime of β-Naphthacyltriphenylphosphonium Bromide (3e).—To a solution of **11** (6.0 g) in methanol (60 ml) was added 10 g of $NH_2OH \cdot HCl$ dissolved in the minimum amount of water. The mixture was refluxed for 30 hr and then poured into water; The precipitate was collected and crystallized from ethanol–water, giving 5.0 g (81%) of **3e**: mp 226°; uv max 230 mμ (ε 46,000), 277 (13,000), 287 (11,600), 297 (10,400); ir 3000, 1430, 1300, 1105, 975, 925, 820, 742, 692 cm^{-1}.

Anal. Calcd for $C_{30}H_{25}BrNOP$: C, 68.4; H, 4.7; Br, 15.2; N, 2.6; P, 5.9. Found: C, 68.6; H, 4.5; Br, 14.6; N, 2.6; P, 5.9.

2-Oximinopropyltriphenylphosphonium chloride (3f) was prepared by the same procedure from 2-oxopropyltriphenylphosphonium chloride,[29] using ethanol instead of methanol; reflux time was 10 hr; yield was 56%.

1-Benzoylbenzyltriphenylphosphonium Bromide (8).[11]—Desyl bromide[30] (9.0 g, 32.7 mmol) dissolved in 100 ml of dry benzene was refluxed for 5 hr together with 8.6 g (32.7 mmol) of triphenylphosphine. After cooling, the whole mixture was shaken with water. The undissolved solid, collected and crystallized from ethanol, gave 2.9 g (5.4 mmol, 17%) of **8**: mp 237–239°; uv max 268 mμ (ε 11,000); ir 1675, 1445, 1220, 1115, 997, 760, 708 cm^{-1}.

Anal. Calcd for $C_{32}H_{26}BrOP$: P, 5.8; Br, 14.9. Found: P, 6.1; Br, 15.4.

The benzene solution, after elimination of the solvent, gave a solid residue which was triturated with ether. The undissolved portion (6.8 g, 24.5 mmol, 75%) was shown to be essentially pure $OP(C_6H_5)_3$ from its ir and tlc comparison with an authentic sample. From the ethereal solution were obtained 5.1 g (26.0 mmol, 80%) of desoxybenzoin, identified by its ir spectrum and by tlc comparison with an authentic sample. Only traces of unreacted triphenylphosphine were detected by tlc.

Attempt at Oximation of 1-Benzoylbenzyltriphenylphosphonium Bromide. 1-Benzoylbenzyltriphenylphosphonium Benzylide (9). A.—A mixture of 0.61 g of **8** and 1.0 g of $NH_2OH \cdot HCl$ in 95% ethanol was refluxed for 6 days. After dilution with water the filtered solid showed an ir spectrum identical with that of the starting material.

B. A mixture of 1.1 g (2 mmol) of **8**, 0.7 g (10 mmol) of $NH_2OH \cdot HCl$ and 0.8 g (8 mmol) of potassium acetate was refluxed in an aqueous alcoholic solution for 1.5 hr. After dilution with water the filtered solid (0.88 g, 93%) was identified as the ylide **9**, mp 188–190° (lit.[31] mp 191–192°); in fact its mass spectrum showed an intense peak at 456 *m/e* (M^+) and no peaks corresponding to Br^+ or $(HBr)^+$. The ir spectrum showed bands at 1510, 1480, 1430, 1380, 1250 1105, 970, 848, 725, 705 cm^{-1}.

1,2,5-Oxazaphosph(V)ol-2-ines (4). A. By Ion-Exchange Resin.—The appropriate 2-oximinophosphonium salt (1 mmol) was dissolved in about 30 ml of ethanol and the solution was slowly percolated through a few grams of a basic ion-exchange resin[32] previously treated with 2 *N* KOH, then with water, and finally with ethanol. The less soluble 1,2,5-oxazaphosph(V)ol-2-ines (**4**) precipitated in pure form from the eluates and could be collected by filtration. For the more soluble **4** concentration under reduced pressure in the cold was necessary. Owing to the thermal instability of these compounds, the crystallization, when necessary, was performed most effectively by dissolving the compound in the appropriate solvent at room temperature and then cooling to about −30°. This general procedure was used for the following compounds.

3,5,5,5-Tetraphenyl-4-methyl-1,2,5-oxazaphosph(V)ol-2-ine (4b) showed the following characteristics: mp 100° (from benzene–hexane); yield 85%; uv max 269 mμ (ε 11,900); ir 1460, 1080, 970, 830, 773, 760, 740, 722, 698 cm^{-1}.

Anal. Calcd for $C_{27}H_{24}NOP$: C, 78.3; H, 5.9; N, 3.4; P, 7.7. Found: C, 78.6; H, 6.0; N, 3.5; P, 8.0.

3,5,5,5-Tetraphenyl-4-*n*-propyl-1,2,5-oxazaphosph(V)ol-2-ine (4c) showed the following characteristics: mp 96° (from benzene–hexane); yield 70%; uv max 223 (s) (ε 29,000), 259 (s) (8400); ir 1455, 1430, 1080, 980, 765, 755, 743, 725, 700 cm^{-1}.

Anal. Calcd for $C_{29}H_{28}NOP$: C, 79.6; H, 6.4; N, 3.2; P, 7.1. Found: C, 79.4; H, 6.4; N, 3.3; P, 7.3.

3-*p*-Bromophenyl-5,5,5-triphenyl-1,2,5-oxazaphosph(V)ol-2-ine (4d) showed the following characteristics: mp 157° (from hot ethyl acetate); yield 91%; uv max 261 mμ (ε 12,900); ir 1475, 1425, 1080, 1040, 985, 805, 745, 692 cm^{-1}.

Anal. Calcd for $C_{26}H_{21}BrNOP$: C, 65.8; H, 4.5; Br, 16.9; N, 2.9; P, 6.5. Found: C, 66.3; H, 4.7; Br, 16.6; N, 2.7; P, 6.5.

3-β-Naphthyl-5,5,5-triphenyl-1,2,5-oxazaphosph(V)ol-2-ine (4e) showed the following characteristics: mp 142° (from warm benzene); yield 90%; uv max 229 (ε 37,700), 287 (10,300), 298 (9800); ir 1435, 1080, 1045, 985, 945, 810, 760, 742, 700 cm^{-1}.

Anal. Calcd for $C_{30}H_{24}NOP$: C, 80.9; H, 5.4; N, 3.1; P, 7.0. Found: C, 80.5; H, 5.4; N, 3.2; P, 7.2.

3,4-Tetramethylene-5,5,5-triphenyl-1,2,5-oxazaphosph(V)ol-2-ine (4g) showed the following characteristics: mp 102°; yield 53%; uv max 263 (ε 2800), 269 (2800), 276 (2100); ir 1480, 1430, 1080, 990, 952, 760, 737, 720, 696 cm^{-1}.

Anal. Calcd for $C_{24}H_{24}NOP$: C, 77.2; H, 6.5; N, 3.7; P, 8.8. Found: C, 76.8; H, 6.4; N, 3.8; P, 8.7.

3-Phenyl-5,5,5-tri-*n*-butyl-1,2,5-oxazaphosph(V)ol-2-ine (4h) showed the following characteristics: liquid; yield 80%; uv max 249 mμ (ε 9500); ir (neat) 2950, 1460, 1085, 1055, 1010, 990, 918, 760, 698 cm^{-1}.

Anal. Calcd for $C_{20}H_{34}NOP$: N, 4.2; P, 9.2. Found: N, 4.1; P, 9.0.

3-*p*-Bromophenyl-5,5,5-tri-*n*-butyl-1,2,5-oxazaphosph(V)ol-2-ine (4i) showed the following characteristics: mp 70° (from petroleum ether, bp 30–60°); yield 85%; uv max 259 mμ (ε 11,700); ir 2950, 1530, 1465, 1400, 1075, 1005, 918, 810 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}BrNOP$: C, 58.0; H, 8.0; Br, 19.3; N, 3.4; P, 7.5. Found: C, 58.1; H, 7.9; Br, 19.4; N, 3.3; P, 7.6.

B. By Treatment with Aqueous Alkali. 3,5,5,5-Tetraphenyl-4-*n*-propyl-1,2,5-oxazaphosph(V)ol-2-ine (4c).—**3c** (1.0 g) was dissolved in 10 ml of ethanol; the solution was made alkaline by dropwise addition of a few milliliters of aqueous 1 *N* KOH at 0°. The white precipitate (0.84 g, 98%), collected and crystallized from benzene–hexane, melted at 95–96°. Its ir spectrum was identical with that of **4c** prepared from **3c** by the resin method.

3-*p*-Bromophenyl-5,5,5-triphenyl-1,2,5-oxazaphosph(V)ol-2-ine (4d) was prepared by the same procedure as **4c**: yield 100%.

3-Methyl-5,5,5-triphenyl-1,2,5-oxazaphosph(V)ol-2-ine (4f).—**3f** (0.46 g) was dissolved in 50 ml of water and the solution was made slightly alkaline by the addition of the stoichiometric amount of 0.5 *M* NaOH. The solution was immediately extracted several times with ether and the extracts were dried over Na_2SO_4. After removal of the solvent under vacuum at room temperature, 0.31 g (74%) of **4f** was obtained as a white solid, mp 116° dec. The compound is very unstable expecially in solution even at room temperature, giving $PO(C_6H_5)_3$. It could not be purified by crystallization: uv max 224 (s) (ε 26,000), 268 (2800); ir 1430, 1080, 1025, 945, 747, 717, 698 cm^{-1}.

Anal. Calcd for $C_{21}H_{20}NOP$: C, 75.5; H, 6.1; N, 4.2. Found: C, 76.5; H, 6.1; N, 3.9.

Thermal Decomposition of 3-*p*-Bromophenyl-5,5,5-triphenyl-1,2,5-oxazaphosph(V)ol-2-ine (4d). 2H-3-*p*-Bromophenylazirine (10).—**4d** (20 mg) was placed in a small test tube under vacuum (0.5 torr) and the bottom of the tube was gradually heated in an oil bath up to 148–150°.[33] The azirine (**10**, 3 mg, 31%) condensed in the cold portion of the test tube as white crystals: mp 78°; uv max 257 mμ (ε 11,600); ir 1730, 1590, 1480, 1470, 1400, 1075, 1000, 832, 818 cm^{-1}; nmr ($CDCl_3$) δ 1.80 (s).

Anal. Calcd for C_8H_6BrN: C, 49.0; H, 3.1; Br, 40.8; N, 7.1. Found: C, 49.4; H, 3.3; Br, 41.0; N, 7.1.

Registry No.—**3a**, 14264-66-5; **3a′**, 14181-79-4; **3b**, 15055-54-6; **3c**, 17631-10-6; **3d**, 17631-11-7; **3e**, 17658-49-0; **3f**, 17631-12-8; **3g**, 17631-13-9; **3h**, 17631-14-0; **3i**, 17631-15-1; **4a**, 14264-70-1; **4b**, 17631-17-3; **4c**, 17631-18-4; **4d**, 17631-19-5; **4e**,

(29) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

(30) H. Limpricht and H. Schwanert, *Ann.*, **155**, 68 (1870).

(31) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 3874 (1959).

(32) Dowex 2, 8 × 50–100 mesh, supplied by Fluka AG, Buchs SG, Switzerland.

(33) When the sublimation was carried out at higher temperature a mixture of **10** and $PO(C_6H_5)_3$ was obtained.

17631-20-8; **4f**, 17631-21-9; **4g**, 17631-22-0; **4h**, 17631-23-1; **4i**, 17631-24-2; **8**, 1530-47-3; **10** (R = *p*-BrC_6H_4; R′ = R″ = H), 17631-26-4; **11**, 2689-60-3.

Acknowledgment.—We are indebted to Dr. A. Selva for the mass spectra. We wish to thank Mr. A. Arnone for his assistance in taking the nmr spectra.

Quinazolines and 1,4-Benzodiazepines. XLII.[1] Photochemistry of Some N-Oxides

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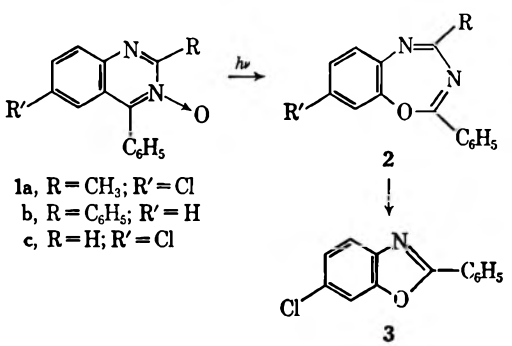
Quinazoline 3-oxides **1** are photoisomerized to benzo[*f*]-1,3,5-oxadiazepines **2**. 6-Chloro-2-methyl-4-phenylquinazoline 1-oxide (**4**) gives 1-acetyl-5-chloro-3-phenylindazole (**6**) on irradiation. 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 3-oxide (**9**) gives a mixture of 9-chloro-5-methylamino-2-phenyl-4H-benzo[*g*]-1,3,6-oxadiazocine (**11**) and 1-benzoyl-7-chloro-1,2-dihydro-3-methylaminoquinoxaline (**12a**). These transformations are believed to proceed by rearrangement of the oxaziridines formed as primary isomerization products.

Aromatic N-oxides are quite generally labile to irradiation with ultraviolet light,[2] as illustrated by the photoisomerization of quinazoline 3-oxides **1** to benzo[*f*]-1,3,5-oxadiazepines **2**.[3] We wish to report two further examples of this isomerization as well as the photochemical behavior of two related N-oxides.



1a, R = CH_3; R′ = Cl
b, R = C_6H_5; R′ = H
c, R = H; R′ = Cl

2

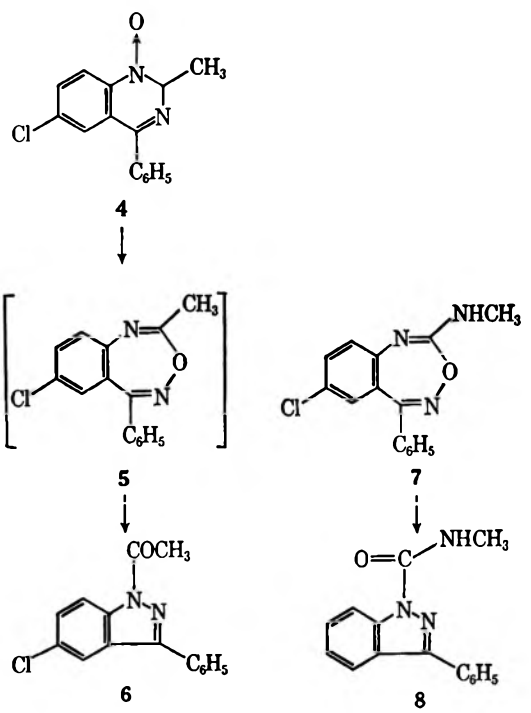
3

The irradiation products **2a** and **2b** were obtained in excellent yield; however, irradiation of **1c** gave only a low yield of **3**. Presumably **3** was formed from **2c** during work-up of the reaction mixture.[4]

In an attempt to obtain evidence for the presence of isolable intermediates in the photoisomerization of **1a**, the ultraviolet spectrum of an irradiated acetonitrile solution of **1a** was measured at intervals. These spectra showed isosbestic points at 298, 332, and 345 mμ which would indicate the absence of stable intermediates.

The quinazoline 1-oxide **4**[5] was also irradiated. By analogy with the quinazoline N-oxides the formation of **5** was expected.[2c] The product, however, displayed a prominent carbonyl band at 1720 cm^{-1} and was readily identified as **6** by comparison with a sample obtained by acetylation of 5-chloro-3-phenylindazole. Its formation *via* **5** as an intermediate is not ruled out since it has been shown that **7**, synthesized by non-photochemical means, gave **8** on exposure to light (Scheme I).[6]

SCHEME I



4

5

6

7

8

The photochemistry of the benzodiazepine 4-oxide **9**, which may be considered to be a homoquinazoline N-oxide, was reinvestigated. It has been reported that irradiation with sunlight gives the oxaziridine **10**[7] which is reconverted into **9** on heating (Scheme II). Irradiation of **10**, formed as primary product,[7] or more vigorous irradiation of **9** led to the formation of two new photoisomers **11** and **12a**. Direct crystallization of the reaction mixture gave **11** which was shown to be isomeric with the starting material by elemental analysis and mass spectrometry. Mild acid hydrolysis of **11** gave **13a** whose structure was proved by dechlorination to **13b**.[8] In addition, structure **11** was supported

(1) Paper XLI: A. Stempel, I. Douvan, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2963 (1968).

(2) (a) O. Buchardt, B. Jensen, and I. K. Larsen, *Acta. Chem. Scand.*, **21**, 1841 (1967); (b) O. Buchardt and J. Fenney, *ibid.*, **21**, 1399 (1967); (c) C. Kaneko, S. Yamada, I. Yokoe, and M. Ishikawa, *Tetrahedron Lett.*, 1873 (1967); (d) O. Buchardt, *ibid.*, 6221 (1966); (e) O. Buchardt, C. Lohse, A. M. Duffield, and C. Djerassi, *ibid.*, 2741 (1967).

(3) C. Kaneko and S. Yamada, *ibid.*, 5233 (1967).

(4) See ref 2 for a similar ring contraction.

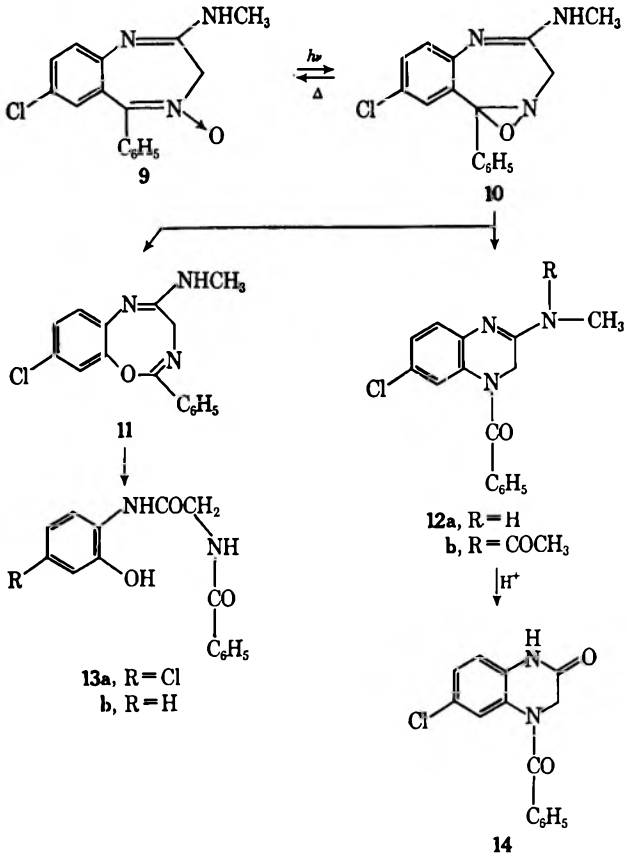
(5) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Amer. Chem. Soc.*, **82**, 475 (1960).

(6) W. Metlesics, G. Silverman, and L. H. Sternbach, *Monatsh. Chem.*, **98**, 633 (1967).

(7) L. H. Sternbach, B. A. Koechlin, and E. Reeder, *J. Org. Chem.*, **27**, 4671 (1962).

(8) J. L. Abernathy and G. L. Leonardo, *J. Chem. Educ.*, **41**, 53 (1964).

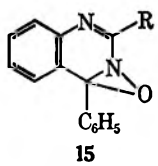
SCHEME II



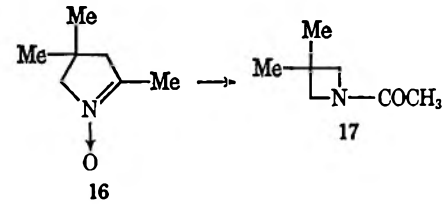
by the infrared spectrum which shows a band at 3460 cm^{-1} (consistent with an NH group but not with an OH group) and the nmr spectrum which shows a doublet at δ 2.84 (3, J = 5 Hz, $-NHCH_3$) and a singlet at 4.03 (2, $-CH_2-$).

The other photoisomerization product **12a** was isolated after mild acid hydrolysis of the whole reaction mixture. This converted **11** into **13a** which was insoluble in acid while **12a** remained in solution. The structure of **12a** was proved by acetylation to **12b** which, on mild acid hydrolysis, gave the known **14**.[9]

It has been postulated that the isomerization of quinazoline 3-oxides **1** to benzoxadiazepines **2** proceeds by way of the unisolated[2] oxaziridines **15**. Isolation of the oxaziridine **10**[7] and its photoisomerization thus support the above postulate, although **15** was not isolated owing to its apparent instability. Since **10** reverts to **9** on heating without giving **11** or **12a**, analogy suggests that the ring expansion of **15** to the benzoxadiazepines **2** is a photochemical process.



The stability of the oxaziridine **10** permits an additional possible type of photoisomerization to **12a**. This second path is analogous to the transformation of the aliphatic nitrone **16** into **17**.[10] Furthermore,



participation of the 1,2 double bond in the ring expansion of **15** to **2** is indicated since where its proximity to the nitrone function is decreased by insertion of a methylene group as in **9** a second type of product **12a** appears.

Experimental Section[11]

Irradiation of Quinazolines.—A solution of 10 g of the quinazoline **1** in 1.4 l. of benzene was irradiated with a Hanovia 200-W medium-pressure lamp in a quartz immersion well until thin layer chromatography indicated the disappearance of starting material. Times were 16–96 hr. The solution was then concentrated *in vacuo*.

6-Chloro-2-phenylbenzoxazole (**3**).—Crystallization of the residue from irradiation of **1c** from methanol gave 2.5 g of crude **3**. Three recrystallizations from ethanol gave a pure sample, mp 106–108° (lit.[12] mp 98–100°), undepressed on admixture of authentic material.

8-Chloro-4-methyl-2-phenyl-1,3,5-benzoxadiazepine (**2a**).—Crystallization of the residue from irradiation of **1a** from ether gave 8.3 g of **2a**, mp 133–138°. Recrystallization from ethanol gave yellow needles: mp 137–140°; ir 1642 cm^{-1}; uv max 323 mμ (ϵ 5500), 248 (23,000).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.37; H, 3.87; N, 10.18.

2,4-Diphenyl-1,3,5-benzoxadiazepine (**2b**).—Crystallization of the residue from irradiation of **1b** from ether gave 8.3 g of **2b**, mp 130–137°. Recrystallization from 2-propanol gave yellow needles: mp 135–137.5°; ir 1642 cm^{-1}; uv max 343 mμ (ϵ 3000), 266 (36,500); mass spectrum m/e 298, 195, 167.

Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73. Found: C, 80.70; H, 4.97.

1-Acetyl-5-chloro-3-phenylindazole (**6**). **A. From Photolysis of 6-Chloro-2-methyl-4-phenylquinazoline 1-Oxide** (**4**).—A solution of 7 g of **4** in 1.4 l. of benzene was irradiated with the Hanovia lamp for 6 days and then concentrated *in vacuo*. The residue was slurried with a mixture of hexane and ether, collected, and then washed with methanol to give 2.1 g of crude product, mp 120–135°. Recrystallization from ethyl acetate gave off-white needles: mp 157–159°; ir 1720 cm^{-1}; uv max 313 mμ (ϵ 13,500), 247 (sh) (26,000), 228 (30,400); mass spectrum m/e 270 (M^+), 228 (M − 42).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.79; H, 4.02; N, 10.26.

B. From Acetylation of 5-Chloro-3-phenylindazole.—A solution of 4.6 g of 5-chloro-3-phenylindazole[13] in 20 ml of pyridine was cooled in an ice bath and treated with 2 ml of acetyl chloride. After standing at room temperature for 2 hr the reaction mixture was diluted to 100 ml with water and the solid collected. Recrystallization from ethyl acetate gave 3.5 g of **6**, mp 155–159°, identified by mixture melting point, infrared spectrum, and thin layer chromatogram.

Irradiation of 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (**9**).—A solution of 10 g of **9** in a mixture of 400 ml of ethanol and 1 l. of benzene was irradiated for 18 hr with the Hanovia lamp. The solution was concentrated *in vacuo*, and the residue crystallized from ether to give 5 g of a mixture of two photoisomers **11** and **12a** as judged by tlc, mp 165–170°. Recrystallization of a portion of this mixture three times from

(9) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **29**, 506 (1964).
(10) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc., C*, 2295 (1966).

(11) All melting points were determined in capillaries and are corrected. The ultraviolet spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer, the nmr spectra on a Varian A-60 instrument, and the infrared spectra (in chloroform solution unless otherwise noted) on a Beckman IR-9 spectrophotometer. Thin layer chromatography was done on silica gel G plates using 5% methanol in chloroform or ethyl acetate as developer.

(12) J. T. Edward, *J. Chem. Soc.*, 222 (1956).

(13) K. Dziewonski and L. Sternbach, *Bull. Intern. Acad. Polon. Sci., Classe Med.*, **A333** (1935); *Chem. Abstr.*, **30**, 2972[1] (1936).

ethanol gave 9-chloro-5-methylamino-2-phenyl-4H-1,3,6-benzoxadiazocine (**11**) as beige needles: mp 240–243° dec with sintering at 180°; ir 3460, 1660, 1620, 1480 cm^{-1}; uv max 245 mμ (ε 23,000); mass spectrum *m/e* 299, 230, 196 ($-C_6H_5CN$), 167, 154; nmr (DMSO), δ 2.48 (d, 3, J = 5 Hz, $-NHCH_3$) and 4.03 (s, 2, $-CH_2-$) ppm.

Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.14; H, 4.79; N, 14.16.

To a solution of 5 g of the above mixture of **11** and **12a** in 125 ml of hot ethanol was added 25 ml of 1 *N* hydrochloric acid, and the mixture was heated on the steam bath for 5 min. Dilution to 375 ml with water and cooling gave 2.8 g of crude 2-benzamido-4′-chloro-2′-hydroxyacetanilide (**13a**), mp 228–234° dec. Recrystallization from methanol gave grayish prisms: mp 233–236° dec; ir (KBr) 1665, 1540 cm^{-1}; uv max 290 mμ (ε 7400), 257 (sh) (14,200) and 248 (19,000); mass spectrum *m/e* 304, 286, 268, 162 ($C_6H_5CONH-CH_2C^+O$), 143, 134, 105.

Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.20. Found: C, 59.49; H, 4.31; N, 9.20.

The aqueous mother liquors left after separation of **13a** were neutralized with concentrated ammonium hydroxide, and 2.2 g of 4-benzoyl-6-chloro-3,4-dihydro-2-methylaminoquinoxaline (**12a**), mp 216–222° dec, precipitated. Recrystallization from ethanol gave colorless needles: mp 220–230° dec; ir (KBr) 3430, 1630, 1575 cm^{-1}; uv max 320 mμ (sh) (ε 5100), 290 (sh) (13,500) and 262 (21,000); mass spectrum *m/e* 299, 194, 165, 153.

Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 63.92; H, 4.97; N, 13.84.

Thin layer chromatography (10% MeOH–$CHCl_3$ on silica gel G) showed that **11** was converted into **13c** while **12a** remained unchanged.

2-Benzamido-2′-hydroxyacetanilide (13b).—A mixture of 1.2 g (4 mmol) of 2-benzamido-4′-chloro-2′-hydroxyacetanilide (**13a**), 8 g of Raney nickel slurry, 1 ml of triethylamine, and 200 ml of ethanol was hydrogenated at room temperature and atmospheric pressure until 105 ml of hydrogen was taken up. The catalyst was filtered, and the filtrate acidified with acetic acid. This solution was concentrated *in vacuo*, and water was added to the residue to give 1 g of **13b**, mp 199–203°. Recrystallization from ethanol gave 0.6 g, mp 202–204°, undepressed on admixture with a sample prepared from hippuryl chloride[8] and *o*-aminophenol. The infrared spectra were also identical.

1-Benzoyl-7-chloro-1,2-dihydro-3-(N-methylacetamido)quinoxaline (12b).—A mixture of 24 g (80 mmol) of **12a**, 1.6 g of sodium acetate, and 200 ml of acetic anhydride was warmed on a steam bath until a clear solution was obtained and then stirred without further heating for 1 hr. The residue left on removal of the acetic anhydride *in vacuo* was crystallized from ether and then recrystallized from benzene–hexane to give 23.6 g (84%) of **12b**: mp 123–126°; ir 1690, 1660, 1615 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.71. Found: C, 63.26; H, 4.91.

4-Benzoyl-6-chloro-3,4-dihydroquinoxalin-2(1H)-one (14).[9]—A mixture of 8.54 g (25 mmol) of **12b**, 125 ml of dioxane, and 25 ml of 1 *N* hydrochloric acid was allowed to stand at room temperature for 2.5 hr, and then diluted with ice water to 500 ml. The precipitate was collected and washed with ether to give 5.4 g (80%) of **14**, mp 259–263°, identified by mixture melting point and infrared spectra.

Irradiation of 9 with Isolation of 10.—A solution of 2 g of **9** in 150 ml of ethanol was irradiated for 55 min through a Pyrex filter. The solution was concentrated *in vacuo* and the residue crystallized from ether to give 1.3 g of the crude oxaziridine **10** which was purified by filtration of a solution in ether–methylene chloride through 60 g of Florisil and elution with ether. The residue obtained on concentration of the filtrate (reduced pressure, 40°) was crystallized from ether to yield 0.9 g of **10** which showed on tlc (silica gel G–ethyl acetate) only a trace of **9**. A solution of 0.6 g of this material in 150 ml of ethanol was then irradiated as before and aliquots were removed at 5 min intervals. Examination of these aliquots by tlc in the above system showed that the trace of **9** disappeared in 10 min. This was followed by a gradual formation of **11** and **12a** until after 3 hr **11** and **12a** were the main components contaminated only by a trace of **10**.

Registry No.—**2a**, 17953-20-7; **2b**, 17953-21-8; **6**, 17953-22-9; **10**, 17953-23-0; **11**, 17953-24-1; **12a**, 17953-25-2; **12b**, 17953-26-3; **13a**, 17953-27-4; **13b**, 17953-28-5.

Acknowledgment.—We thank Mr. S. Traiman for the infrared spectra, Dr. T. Williams for the nmr spectra, Dr. V. Toome for the ultraviolet spectra, Dr. F. Vane for the mass spectra, Dr. F. Scheidl for the microanalyses, and Mr. T. Flynn for his skillful technical assistance.

Reaction of N,N-Dichlorourethan with Indole and Derivatives[1]

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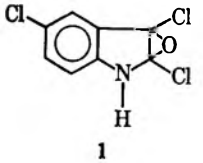
Contrary to literature reports, the major product of reaction of N,N-dichlorourethan (DCU) with indole and indole-2- or -3-carboxylic acid is 3,3,5-trichlorooxindole (**5**). Reaction of the methyl esters with DCU yields 2-carbomethoxy-2,5,7-trichloroindoxyl (**8**) and 3-carbomethoxy-3,5-dichlorooxindole (**10**), respectively. Structures have been assigned by physical and chemical methods.

The report of Chabrier[4] that reaction of N,N-dichlorourethan (DCU) with indole-2-carboxylic acid yields 2,3,5-trichloro-2,3-epoxyindole (**1**), a high melting, stable compound, aroused our interest. By neutral dehalogenation **1** might, hopefully, be converted into the corresponding oxirene, an unknown small-ring compound.

Aside from the apparent failure of **1** to undergo facile halogen migration, as 2-chloro epoxides are prone to



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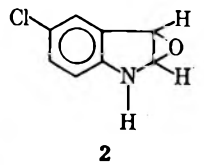

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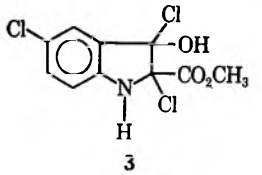

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do,[5] it was surprising that reduction was claimed to yield the dihydro product, 5-chloro-2,3-epoxyindoline

(1) Pseudohalogens. XII. Part XI: H. C. Hamann and D. Swern, *J. Amer. Chem. Soc.*, **90**, 6481 (1968).

(2) Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia, Pa. 19118.

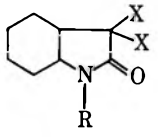
(3) To whom enquiries should be addressed. The authors acknowledge with thanks support of this investigation by U. S. Public Health Service Grants No. CA-07803 and CA-07174 from the National Cancer Institute.

(4) P. Chabrier, *Ann. Chim.*, **17**, 353 (1942).

(5) R. N. McDonald and P. A. Schwab, *J. Org. Chem.*, **29**, 2459 (1964); *J. Amer. Chem. Soc.*, **85**, 4004 (1963).

(2), cleanly and in high yield without destruction of the epoxide function. Furthermore, reaction of the methyl ester of indole-2-carboxylic acid with DCU under similar conditions was also reported to yield a product with three chlorine atoms, assigned the improbable structure 2,3,5-trichloro-2-carbomethoxy-3-hydroxyindoline (3), but only *one* chlorine atom could be removed by reduction to yield an unidentified product.

The reaction of positive halogen sources, such as the hypohalous acids, with N-alkylindoles has long been known to yield 3,3-dihalooxindoles (4).[6-8] The discrepancy between these results and those of Chabrier prompted us to reexamine the reactions of DCU with indole, indole-2- and -3-carboxylic acids, and their methyl esters.



4, R = alkyl; X = Cl, Br

Results and Discussion

Reaction of 2 mol of DCU (four atoms of positive chlorine) with 1 mol of indole (5a), indole-2-carboxylic acid (5b), or indole-3-carboxylic acid (5c) in 80:20 acetic acid–water at 25–35° gave 3,3,5-trichlorooxindole (5), mp 191–192°, as the major product (40% yield from indole; 85–90% from the carboxylic acids). Although the melting point of 5 (191–192°) agreed essentially with that reported by Chabrier (188°) and its elemental analysis was also consistent with the molecular formula of 1, $C_8H_4Cl_3NO$, the ir spectrum showed strong carbonyl absorption, thus eliminating 1 as a possible structure. Absorption at 1760 (C=O), 3480 (NH), and 1630 cm^{-1} (aromatic) permitted a tentative structural assignment of 5 as a halo-substituted oxindole,[9] confirmed by chemical evidence. Reduction of 5 with zinc–copper couple in glacial acetic acid gave the known 5-chlorooxindole (6),[10] mp 195–196°, in 75% yield. Hydrolysis of 5 in refluxing aqueous methanol yielded 5-chloroisatin (7) (85% yield), which on reduction with zinc–copper couple in glacial acetic acid also gave 6 (65% yield).[11]

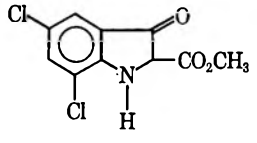
Reaction of 1 mol of methyl indole-2-carboxylate (8a) with 2 mol of DCU as described for the free acid gives 2-carbomethoxy-2,5,7-trichloroindoxyl (8), mp 203–204°, in almost 90% yield, not 3 as claimed.[4] The structure of 8 was determined by elemental analysis and spectral and chemical means. Besides ir absorption at 3450 (NH) and 1620 cm^{-1} (aromatic), two carbonyl bands were obtained at 1750 and 1720 cm^{-1} corresponding, respectively, to ester and ketone functionality. The nmr spectrum showed absorption at 7.52 (2 H, J = 3 cps), consistent with *meta* substitution of the chlorine atoms in the aromatic nucleus, 3.28 (1 H, N–H) and 3.88 ppm (TMS, 0) (3 H, OCH_3). Reduction of 8 with zinc–copper couple in glacial acetic acid removed only one chlorine atom and gave 5,7-dichloroindoxyl (9), mp 242–243°, in 80% yield. Its ir spectrum showed absorption at 3300 (NH), 1725 (C=O), and 1610 cm^{-1} (aromatic). The nmr spectrum (signal at 7.38 ppm, 2 H, J = 3 cps) indicated *meta* substitution of the chlorine atoms in the aromatic ring and, in addition, the nmr spectrum contained two weakly split singlets (2 H and 1 H, $J \leq 1$ cps) at 3.62 and 3.24 ppm, respectively. Treatment of 9 with deuterium oxide and a trace of trifluoroacetic acid caused the singlet at 3.24 (NH) to disappear and the methylene protons at 3.62 ppm to coalesce to a sharp singlet.

In contrast with the identical behavior of indole-2- and 3-carboxylic acids on reaction with DCU, methyl indole-3-carboxylate (10a) behaved differently from the 2 isomer and gave 3-carbomethoxy-3,5-dichlorooxindole (10), mp 195–196°, in about 75% yield. Its structure was confirmed by its ir spectrum and facile reduction to 5-chlorooxindole (6) in 89% yield.

The products of reaction of DCU with indole and its derivatives can be rationalized by a single assumption, namely, that DCU in aqueous acetic acid generates electropositive chlorine which is the reactive species.[12a] It is of interest that DCU in acetic acid is an excellent source of positive halogen, whereas in benzene DCU behaves as a free-radical source.[12b]

The reactions that have been described proceed extremely rapidly at about 30° and are complete usually within 30 min thus precluding the isolation of intermediates. With the exception of indole as starting material yields of products are high. Although we visualize that chlorination of the aromatic ring occurs as the last step in the chlorination process, it may be occurring concurrently. The exact time such chlorination occurs is not relevant to the major argument that Cl^+ is the sole active species required to rationalize the products obtained.

Reduction of 8 and 10 to 9 and 6, respectively, by zinc–copper couple in acetic acid, should proceed *via* the dehalogenated species, 11 and 12, respectively, which undergo acidolysis in refluxing acetic acid followed by facile decarboxylation, as expected of β-keto acids.



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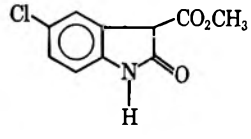

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Experimental Section

N,N-Dichlorourethan (DCU) was prepared by chlorination of urethan in buffered aqueous solution.[12b] Indole and indole-2- and indole-3-carboxylic acids were obtained from Aldrich Chemical Co. and were used as received. Ir spectra were obtained on a Perkin-Elmer Infracord 137. Nmr spectra were obtained on a Varian A-60A spectrometer using tetramethylsilane as internal standard. Microanalyses were performed by Microanalysis, Inc., Wilmington, Del.

3,3,5-Trichlorooxindole (5). A.—Indole-2-carboxylic acid (5b) (3.22 g, 0.020 mol) was suspended in acetic acid–water (80:20) (60 ml) in a 100-ml three-neck flask equipped with a stirrer, thermometer, and dropping funnel. DCU (6.32 g, 0.040

(6) E. Fischer and O. Hess, *Ber.*, **17**, 564 (1884).
(7) H. G. Coleman, *Ann.*, **248**, 116 (1888).
(8) A. Michaelis, *Ber.*, **30**, 2811 (1897).
(9) A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 3809 (1956).
(10) W. B. Wright, Jr., and K. H. Collins, *J. Amer. Chem. Soc.*, **78**, 221 (1956). The melting point given by Chabrier for the reduction product of 1 was 192°.
(11) W. C. Sumpter, *Chem. Rev.*, **34**, 393 (1944).
(12) (a) J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966); (b) T. A. Foglia and D. Swern, *ibid.*, **31**, 3625 (1966).

mol) was added dropwise to the stirred suspension maintained at 30–35° by an ice–water bath. The mixture became homogeneous when DCU addition was complete, and it was stirred for an additional 0.5 hr. The reaction solution was poured into water (300 ml), and the precipitate of **5** was filtered and dried (4.32 g, 92% yield): mp 186–190° (lit.[4] mp 188°).

Analytically pure **5**, mp 191–192°, was obtained by recrystallization from benzene: ir ($CHCl_3$) 3480 (NH), 1760 (C=O), 1630 (C=C), 1480, 1190, 1180, 970, 850, 825 cm^{-1}.

Anal. Calcd for $C_8H_4Cl_3NO$: C, 40.63; H, 1.70; Cl, 44.97; N, 5.92. Found: C, 40.49; H, 1.66; Cl, 45.10; N, 5.71.

B.—Indole-3-carboxylic acid (**5c**) (3.22 g, 0.020 mol) was treated with DCU as just described to give **5** (4.20 g, 89% yield), mp 180–185°, identical in every respect (melting point, mixture melting point, ir, nmr) with that obtained from the 2 isomer.

C.—Indole (**5a**) (2.34 g, 0.020 mol) yielded crude **5** (4.20 g), mp 150°, containing considerable colored tarry material. Recrystallization failed to yield the pure product. Chromatography on Florisil (1 g of crude **5**/40 g of adsorbent) and elution with 75% ether–pentane yielded analytically pure **5**, mp 188–191° (0.4 g, 40%), identical in every respect with that obtained from **5b** and **c**.

5-Chlorooxindole (6).—To a stirred solution of **5** (2.36 g, 0.01 mol) in hot glacial acetic acid (20 ml), zinc–copper couple[13] (7.0 g in 25 ml of acetic acid) was added, and the mixture was refluxed for 18 hr. After filtration, the filtrate was poured into water (250 ml) and the precipitated solid was filtered and dried: yield of crude **6**, 1.32 g (75%); mp 190–195°. Analytically pure **6**, mp 198–198.5° (lit. mp 192°[4] and 195–196°[10]), was obtained by two recrystallizations from ethanol: ir ($CHCl_3$) 3480 (N–H), 1740 and 1710 (C=O), 1640 (C=C), 1480, 1160, 1100, 870 cm^{-1}.

Anal. Calcd for C_8H_6ClNO: C, 57.33; H, 3.61; Cl, 21.15; N, 8.36. Found: C, 57.23; H, 3.73; Cl, 21.03; N, 8.31.

5-Chloroisatin (7).—A solution of **5** (1.18 g, 0.005 mol) in 50% aqueous methanol (50 ml) was refluxed for 6 hr, and the cooled solution was poured into water (250 ml). The precipitated red solid was filtered and dried: yield of crude **7**, 0.80 g (85%); mp 250–252°. Analytically pure **7**, mp 251–252° (lit.[14] mp 246–247°), was obtained by two recrystallizations from ethanol: ir ($CHCl_3$) 3460 (N–H), 1760 (C=O), 1620 (C=C), 1470, 1445, 1290, 1190, 1170, 965, 845 cm^{-1}.

Anal. Calcd for $C_8H_4ClNO_2$: C, 52.92; H, 2.22; Cl, 19.52; N, 7.71. Found: C, 52.46; H, 2.40; Cl, 19.60; N, 7.67.

Reduction of **7** (1.40 g, 0.008 mol) with zinc–copper couple as described for **5** also yielded **6**, mp 194–196° (0.85 g, 65%), identical in every respect (ir, melting point, mixture melting point) with an authentic sample.

Methyl Indole-2-carboxylate (8a).—This was prepared in 90% yield from **5b** by conventional esterification with methanol (sulfuric acid catalyst), mp 151–152° (lit.[15] mp 150–151.5°).

Methyl Indole-3-carboxylate (10a).—As described for the 2 isomer **5c** was converted into analytially pure **10a** in 60% yield: mp 146–147° (lit.[16] mp 147–148°).

2-Carbomethoxy-2,5,7-trichloroindoxyl (8).—**8a** (3.50 g, 0.020 mol) was treated with DCU as previously described for **5a–c** to give crude **8** (4.3 g, 90% yield), mp 191–195° (lit.[4] mp 184°). Analytically pure **8**, mp 203–204°, was obtained after two crystallizations from ethanol: ir ($CHCl_3$) 3450 (N–H), 1750 and 1720 (C=O), 1620 (C=C), 1470, 1220, 1170, 1040, 875 cm^{-1}.

Anal. Calcd for $C_{10}H_6Cl_3NO_3$: C, 40.78; H, 2.05; Cl, 36.11; N, 4.76. Found: C, 40.53; H, 2.35; Cl, 36.03; N, 5.07.

5,7-Dichloroindoxyl (9).—A solution of **8** (1.50 g, 0.005 mol) was reduced with zinc–copper couple (3.25 g) in acetic acid (35 ml) as described for the reduction of **5** to give **9** (0.8 g, 80% yield), mp 241–242°. Analytically pure **9**, mp 242–243°, was obtained by recrystallization from ethanol: ir (Nujol) 3300 (N–H), 1725 (C=O), 1610 (C=C), 1450, 1305, 1215, 1170, 945, 875, 860, 715 cm^{-1}.

Anal. Calcd for $C_8H_5Cl_2NO$: C, 47.56; H, 2.50; Cl, 35.09; N, 6.93. Found: C, 47.79; H, 2.54; Cl, 34.81; N, 6.74.

3-Carbomethoxy-3,5-dichlorooxindole (10).—**10a** (3.50 g, 0.02 mol) was treated with DCU as previously described for **5a–c** and **8a** to give **10** (3.70 g, 75% yield), mp 192–195°. Recrystallization from ethanol yielded pure **10**: mp 195–196°; ir ($CHCl_3$) 3400 (N–H), 1760 and 1740 (C=O), 1620 (C=C), 1470, 1445, 1290, 1190, 1170, 855 cm^{-1}.

Anal. Calcd for $C_{10}H_7Cl_2NO_3$: C, 46.18; H, 2.71; Cl, 27.26; N, 5.39. Found: C, 46.44; H, 2.78; Cl, 27.02; N, 5.27.

Reduction of **10** (1.30, 0.005 mol) with zinc–copper couple (3.25 g) in hot acetic acid gave 5-chloroxindole (**6** 0.75 g, 89% yield), mp 191–193°, identical with an authentic sample (melting point, mixture melting point, ir).

Registry No.—N,N-Dichlorourethan, 13698-16-3; **5**, 17630-74-9; **5a**, 120-72-9; **6**, 17630-75-0; **7**, 17630-76-1; **8**, 17630-77-2; **9**, 17630-79-4; **10**, 17630-78-3.

(13) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).
(14) N. Buu-Hoi, *Rec. Trav. Chim. Pays Bas*, **73**, 197 (1954).
(15) C. Zatti and J. Ciaician, *Ber.*, **21**, 1929 (1888).
(16) C. Zatti and A. Ferratini, *ibid.*, **23**, 2296 (1890).

Reaction of Tosyl Isocyanate with Carboxylate Salts[1]

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p-Toluenesulfonyl isocyanate reacts readily with carboxylate salts at room temperature to give N-acyl-*p*-toluenesulfonamides. Benzenediazonium-2-carboxylate, however, gives a more complex reaction leading ultimately to N-(*o*-azidobenzoyl)-*p*-toluenesulfonamide. The mechanism of this reaction is discussed.

The reaction of benzyne with phenyl isocyanate was studied by Sheehan and Daves,[2] who found only products derived from 1,4 addition, phenanthridone and 6-phenoxyphenanthridine. In view of the tendency of isocyanates (and other cumulated double-bond systems) to give 1,2 cycloadditions in some cases[3] we felt that investigation of the reaction of benzyne with isocyanates incapable of reacting by 1,4 addition would be of interest as a route to benzazetinones[4] *via* 1,2 cycloaddition.

This led us to decompose benzenediazonium-2-carboxylate (I) in solutions of aliphatic isocyanates and of tosyl isocyanate (II) in the hope of obtaining benzazetinone products *via* 1,2 cycloaddition. Although no such 1,2 cycloadditions were found, a reaction of tosyl isocyanate with I and with other carboxylate salts was found. This reaction constitutes the major portion of this paper.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord, Model 137-B, calibrated with a polystyrene film. Proton magnetic resonance spectra were obtained on a Varian A-60 spectrometer and are reported as τ values relative to tetramethylsilane as internal standard (τ 10.00). All melting points are un-

(1) Presented in part before the Division of Organic Chemistry, 154th Meeting of the American Chemical Society, Chicago, Ill, Sept 13, 1967.
(2) J. C. Sheehan and G. D. Daves, Jr., *J. Org. Chem.*, **30**, 3247 (1965).
(3) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967, pp 135–189.
(4) E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966).

corrected. Magnesium sulfate was used as drying agent throughout.

Benzenediazonium-2-carboxylate (I).[5]—A 250-ml two-necked flask fitted with dropping funnel and drying tube was charged with 6.0 ml of butyl nitrite, 30 ml of tetrahydrofuran (THF) (freshly distilled from $LiAlH_4$), and a few crystals of trichloroacetic acid. The solution was cooled in ice and stirred magnetically while a solution of 6.85 g (0.050 mol) of anthranilic acid in 30 ml of THF was slowly added from the dropping funnel. After the addition was complete (45–60 min), stirring was continued at 0° for 15–30 min. The resulting suspension was filtered rapidly; the precipitate was washed with fresh THF and carbon tetrachloride, and rapidly transferred while wet to a stirred solution of the desired reactant in methylene chloride.

Reaction of I with Butyl Isocyanate.—Benzenediazonium-2-carboxylate, I, prepared by the above procedure, was suspended in a mixture of 9.90 g (0.10 mol) of freshly distilled butyl isocyanate, $n^{25}D$ 1.4048, and 100 ml of methylene chloride. The mixture was refluxed for 1.5 hr, then allowed to stand at room temperature for 6 hr. It was cooled in ice, and 9.30 g (0.10 mol) of aniline was added dropwise to destroy excess isocyanate. After standing overnight the solvent was stripped, and ether was added to the residue, leaving a tan solid (A) and a brown solution (B). The solid A was recrystallized from ethanol, which gave 13.30 g of 1-butyl-3-phenylurea: mp 129–131° (74%) (lit.[6] mp 129–130°); infrared bands at 2.95 (N–H), 6.05 (C=O), 13.3 and 14.1 μ (C_6H_5). The mother liquors and solution B were combined and evaporated, and the residue was chromatographed on silicic acid, which yielded, in addition to small amounts of unidentified materials, some unreacted aniline and an additional 1.99 g (12%) of crude 1-butyl-3-phenylurea, mp 120–125°. A quantity of black material was not eluted from the column, even using more polar solvents.

In another run, I was decomposed in a suspension of 20.0 ml (19.80 g, 0.20 mol) of neat butyl isocyanate by warming gently for 2.5 hr. The excess butyl isocyanate was stripped off at reduced pressure. Chromatography of the residue on silica gel again failed to give usable quantities of recognizable products; the major portion of the material appeared as a brown tar eluted only with methanol. Similar results were obtained with methyl isocyanate, neat or in methylene chloride solution.

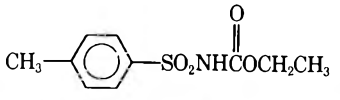
Reaction of I with Phenyl Isocyanate.—I was decomposed by refluxing in a stirred solution of 25 ml of methylene chloride and 10.00 ml (10.95 g, 92.4 mmol) of phenyl isocyanate. After 4 hr, 25 ml of water was added, and the mixture was stirred overnight. The resulting mixture was filtered, and the precipitate was washed with 50 ml of water and four 25-ml portions of ether. Drying left 7.16 g of 1,3-diphenylurea, mp 238–240° (lit.[7] mp 238–240°). The infrared spectrum was identical with an authentic spectrum.[8] The two-layer filtrate was separated, and the aqueous layer was washed with two 50-ml portions of ether. The combined ether layers were dried and evaporated, leaving a brown oily residue, which was chromatographed on Florisil. Elution with 50% benzene–hexane yielded 0.76 g of crude 6-phenoxyphenanthridine (2.8 mmol, 11%), mp 116–118° after recrystallization from ethanol (lit.[2] mp 118–119°); the ir spectrum showed bands at 6.3 (C=N), 6.85, 7.38, 13.2, 13.8, and 14.5 μ. Benzene–ether mixtures of increasing polarity yielded in turn 0.71 g of ethyl carbanilate (4.3 mmol, 4%, identified by infrared comparison with an authentic spectrum[9]) 0.25 g of 1,3,5-triphenylbiuret [mp 148–150° (lit.[2] mp 150–151°), ir bands at 3.01 (N–H), 5.85, 6.25, 8.45, 13.2, and 14.4 μ], and an additional 1.57 g of 1,3-diphenylurea (mp 230–235°, ir identical with authentic[8]), making a total yield of 8.73 g (41.2 mmol, 89%) of the urea. Elution with methanol left a black tar, sublimation of which at 160° (0.2 mm) gave 0.045 g of phenanthridone: mp 287–289° (lit.[2] 285–290°); ir identical with authentic.[10]

Reaction of I with *p*-Toluenesulfonyl Isocyanate (II).—I was added to a solution of 10.0 ml (11.9 g, 0.060 mol) of II in 25 ml of methylene chloride. Reaction began immediately, with vigorous gas evolution, which was complete within 15 min, leaving a homogeneous solution. The solvent was stripped; water was cautiously added to destroy any excess II; and more gas was evolved. Chloroform was added, and the layers were separated. The water layer was washed with chloroform and the combined chloroform layers were extracted with 10% aqueous sodium bicarbonate solution until no more material was extracted (about 200 ml). The bicarbonate layers were acidified with concentrated hydrochloric acid and extracted with four 40-ml portions of ether. Evaporation of these ether layers left material A. Extraction of the chloroform layers with 1% sodium hydroxide followed by acidification left 5.13 g of a red solid, B. The chloroform solution remaining was dried and evaporated, leaving material C. Recrystallization of B from cyclohexane, ethanol–water, and carbon tetrachloride yielded a material of mp 153.5–154.5° with gas evolution. The infrared spectrum of this material in Nujol showed bands at 3.02, 4.65, 5.92, 6.23, 7.40, 8.53, 11.15, 11.8, 12.3 and 13.3 μ. The nmr spectrum in $CDCl_3$ showed resonances at τ −0.2 (s, 1), 1.7–2.0, (m, 3), 2.4–2.9 (m, 5), and 7.58 (s, 3). Titration of the material in 50% aqueous ethanol with 0.02 *N* sodium hydroxide gave a neutralization equivalent of 306 ± 12. These data suggested that the material was N-(*o*-azidobenzoyl)-*p*-toluenesulfonamide, III.

Anal. Calcd for $C_{14}H_{12}N_4SO_3$: C, 53.2; H, 3.79; N, 17.7; S, 10.1; mol wt, 314. Found: C, 53.0; H, 3.74; N, 17.6; S, 9.8.

Hydrolysis of a 0.093-g sample by refluxing for 24 hr in 5% aqueous hydrochloric acid, followed by extraction of the solution with ether, and drying and evaporating the ether left 0.053 g of *p*-toluenesulfonamide, mp 126–131°, (100%); mixture melting point with authentic material, mp 136–138°, was 128–132°.

Chromatography of the material A on silicic acid yielded (1) 0.082 g (1%) of *p*-tolyl *p*-toluenethiolsulfonate, mp 70–72° (lit.[11] mp 75°), infrared and nmr spectra identical with authentic;[11,12] (2) an additional 0.083 g of III, mp 145–147°; (3) 0.47 g of light yellow oil whose spectra were uniquely consistent with the structure[13]



and which was hydrolyzed to *p*-toluenesulfonamide, mp 133–135° (mmp 134–136° with authentic sample), on 3 hr boiling with 5% aqueous hydrochloric acid; and (4) 2.43 g of crude *p*-toluenesulfonamide, mp 136–138° after recrystallization from benzene–heptane, mmp 135–137° with authentic material. Similar chromatography of the residue from the mother liquors from recrystallization of B yielded 0.037 g of *p*-tolyl *p*-toluenethiosulfonate, 0.167 g of III, 0.467 g of N-carbethoxy-*p*-toluenesulfonamide, and 1.85 g of *p*-toluenesulfonamide. Chromatography of the neutral material C gave no identifiable products.

The total crude yields of products are III (5.30 g, 16.8 mmol, 56%); *p*-tolyl *p*-toluenethiolsulfonate (0.94 g, 3.9 mmol, 6%); and *p*-toluenesulfonamide (4.28 g, 25.0 mmol, 41%).

Synthesis of Authentic III.—*o*-Azidobenzoic acid was prepared by the method of Bamberger.[14] The acid (0.56 g, 3.4 mmol) was dissolved in 20 ml of THF and treated with 0.0256 g (3.2 mmol) of lithium hydride. After a few minutes gas evolution ceased, and then 1.00 ml (1.19 g, 6.00 mmol) of II was added. The mixture was stirred at room temperature for 18 hr, then poured into 75 ml of 3% sodium bicarbonate. The resulting solution was extracted with ether to remove *p*-toluenesulfonamide, then acidified and reextracted with ether. Drying and evaporation of the latter ether extracts left 0.68 g of product, which was recrystallized from ethanol–water to yield 0.43 g of III, mp 146–149°, mmp 149–151° with III obtained as described above. The ir and nmr spectra were the same for both samples.

Reaction of Benzenediazonium-4-carboxylate with II.–A 250-ml three-necked flask fitted with stopper, dropping funnel, and drying tube was charged with 6.00 ml of butyl nitrite, 30 ml of THF, and a few crystals of trichloroacetic acid. The solution was ice cooled, and a solution of 6.85 g of *p*-aminobenzoic acid (0.050 mol) in 50 ml of THF was slowly added while the mixture was stirred magnetically. After addition was complete, stirring

(5) L. Friedman, *J. Amer. Chem. Soc.*, **89**, 3071 (1967). We are grateful to Professor Friedman for describing this very convenient method of preparing I to us before publication.

(6) T. L. Davis and N. D. Constan, *J. Amer. Chem. Soc.*, **58**, 1800 (1936).

(7) G. Young and E. Clark, *J. Chem. Soc.*, **73**, 361 (1898).

(8) Sadtler Standard Spectrum No. 3899, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967.

(9) Sadtler Standard Spectrum No. 23619; *cf.* ref 8.

(10) Sadtler Standard Spectrum No. 21101; *cf.* ref 8.

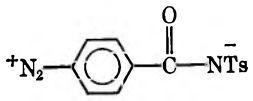
(11) H. Rottendorf and S. Sternhell, *Aust. J. Chem.*, **16**, 647 (1963).

(12) Sadtler Standard Spectrum No. 15579; *cf.* ref 8.

(13) K. Lanyi and Z. Szabo, *Acta. Chim. Acad. Sci. Hung.*, **29**, 85 (1961); *Chem. Abstr.*, **56**, 7194*f* (1963).

(14) E. Bamberger and E. Demuth, *Ber.*, **37**, 1337 (1901).

was continued an additional 75 min, then the mixture was filtered, and the yellow precipitate was washed with fresh THF and added to a solution of 10.00 ml (11.9 g, 0.060 mol) of II in 25 ml of methylene chloride. After 19 hr, the reaction mixture was filtered, and the precipitate was washed with methylene chloride, and dried under vacuum. This yielded 1.02 g of white solid, mp 148–160° with gas evolution. The infrared spectrum showed bands at 4.35, 6.25, 6.4, 7.5, 7.95, 8.5, 8.75, 12.05, 12.35, and 13.1 μ. The nmr spectrum in 5% aqueous NaOH solution showed only aromatic protons at τ 1.7–3.0 and methyl protons at 7.5 (relative areas about 3:1). Addition of a small quantity of this material to an alkaline solution of β-naphthol gave an instantaneous wine-red color. These data suggested that the material was



A sample of this solid (0.914 g, 3.04 mmol) was added in small portions to a solution of 100 ml of 50% hypophosphorous acid at 0°, containing a few crystals of cupric sulfate. Gas was evolved slowly as the solution was stirred for 4.5 hr at 0°, then allowed to warm to room temperature. The solution was diluted with 100 ml of water and extracted with four 40-ml portions of ether. The combined ether layers were extracted with four 25-ml portions of 10% aqueous sodium bicarbonate solution; the resulting solution was acidified with hydrochloric acid and reextracted with three portions of ether. Drying and evaporating the final ether extracts left 0.716 g of red solid, mp 124–135° (85% crude yield of N-benzoyl-*p*-toluenesulfonamide). Recrystallization from ethanol–water gave pink needles, mp 144–147°, mmp 144–147° with authentic material (*vide infra*).

The filtrate from which the above solid was obtained showed no evidence of azide groups in the infrared, either before or after extraction with base, nor did any of the base-soluble products. Consequently further work with these materials was abandoned.

Reaction of II with Sodium Benzoate.—Solid sodium benzoate (1.74 g, 12.1 mmol) was slowly added to a solution of 2.00 ml (2.38 g, 12.1 mmol) of II in 10 ml of methylene chloride. The mixture was magnetically stirred for 15 hr, then water was added. No gas was evolved. The material was dissolved in ether and 10% aqueous sodium bicarbonate solution, and the layers were separated. The ether layer was extracted with another portion of sodium bicarbonate, and the combined aqueous layers were acidified with hydrochloric acid. The resulting white precipitate was collected by filtration and recrystallized from ethanol–water to yield 3.02 g of white needles, mp 145–148° (91%), of N-benzoyl-*p*-toluenesulfonamide. An additional recrystallization brought the melting point to 147–148° (lit.[15] mp 147°). The infrared spectrum was identical with an authentic one.[16]

Potassium acetate reacted similarly, giving a 99% yield of N-acetyl-*p*-toluenesulfonamide, mp 136–138° (lit.[17] mp 139°).

Results

No evidence of direct reaction between phenyl isocyanate or the aliphatic isocyanates and benzenediazonium-2-carboxylate (I) was obtained. The phenyl isocyanate reacted with benzyne from decomposition of I to give 6-phenoxyphenanthridine and phenanthridone, in yields of 11 and <1%, respectively, based on I.[2] The aliphatic isocyanates did not yield characterizable products under these conditions.

In contrast, the more electrophilic *p*-toluenesulfonyl isocyanate (II) reacted immediately and vigorously with I. Addition of I to a methylene chloride solution of II resulted in immediate reaction, with evolution of gas; the reaction was complete in 15 min. Work-up yielded as the principal product a white solid, mp 153.5–154.5° with decomposition. Its spectra, its analysis, and its neutralization equivalent suggested that this material was N-(*o*-azidobenzoyl)-*p*-toluenesulfonamide (III). This was confirmed by its hydrolysis to *p*-toluenesulfonamide on boiling in 5% aqueous hydrochloric acid, and synthesis of an authentic sample by treating lithium *o*-azidobenzoate with II.

A small quantity of *p*-tolyl *p*-toluenethiolsulfonate was also obtained, presumably from disproportionation of *p*-toluenesulfinic acid.

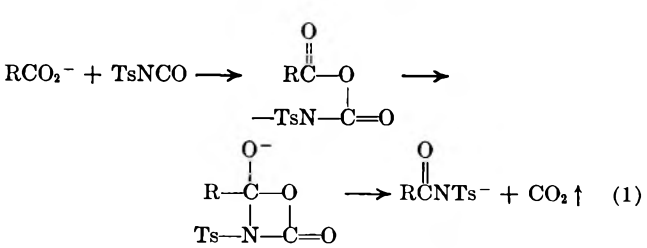
In order to ascertain whether conversion of the diazonium group into the azide group is a result of the proximity of the diazonium and carboxylate groups in I or is a general reaction of II with diazonium salts, the reaction of II with the isomeric benzenediazonium-4-carboxylate was run. This reaction produced in low yield the inner salt, benzenediazonium-4-(N-*p*-toluenesulfonyl)carboxamidate. The structure of this material was shown by its spectra, its coupling reaction with sodium β-naphthoxide, and its reduction by hypophosphorous acid[18] to N-benzoyl *p*-toluenesulfonamide. Neither the crude reaction mixture nor any fractions showed any evidence of azide groups in the infrared spectrum, before or after treatment with base.

Lastly, the reaction of II with some simple carboxylate salts was shown to produce excellent yields of N-acyl-*p*-toluenesulfonamides.[19]

Discussion

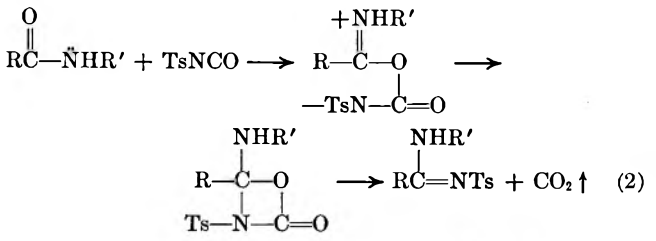
The tendency of the isocyanate group to react with nucleophiles at the central carbon atom is greatly enhanced in the sulfonyl isocyanates.[20] This is clearly illustrated by the facile reaction of tosyl isocyanate with the weakly nucleophilic carboxylate salts, even under heterogeneous conditions. The products, N-acyl-*p*-toluenesulfonamides, have frequently been prepared heretofore by reaction of II with the carboxylic acid at high temperatures.[20] The procedure presented herein of converting the acid into the salt and adding excess tosyl isocyanate at room temperature is rapid and proceeds in high yield. This therefore represents an improved method for the synthesis of N-acylsulfonamides, which can readily be isolated by extraction from the reaction mixture with aqueous sodium bicarbonate. Acidification cleanly regenerates the product.

The reaction of II with a carboxylate salt presumably proceeds by attack of the nucleophile at the central carbon of the isocyanate group, followed by loss of CO_2 (eq 1).



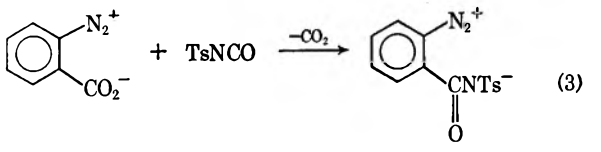
(15) A. D. Kemp and H. Steven, *J. Chem. Soc.*, 110 (1948).
(16) Sadtler Standard Spectrum No. 3643; *cf.* ref 8.
(17) E. Mundlos and R. Graf, *Ann.*, **677**, 108 (1964).
(18) N. Kornblum, *Org. Reactions*, **2**, 294 (1944).
(19) This reaction has also been observed by Dr. Henri Ulrich of the Upjohn Co., North Haven, Conn. We are grateful to Dr. Ulrich for communicating this information to us.
(20) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965).

A similar process has been found to occur with some amides[20] (eq 2).



(2)

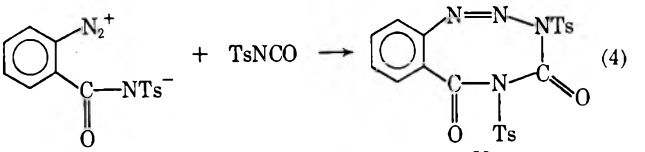
The reaction of II with benzenediazonium-2-carboxylate apparently is initiated in the same manner as the reaction with other carboxylate salts to produce the inner salt, IV (eq 3). This species may react with



(3)

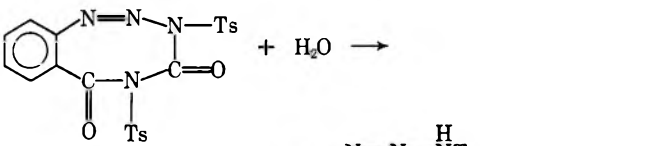
IV

another molecule of II to produce a relatively stable intermediate V,[21] hydrolysis of which on work-up produces the observed product, III (eq 4–6). The last step (eq 6), loss of *p*-toluenesulfinate ion from the sulfonyltriazene anion, is also a key step in the con-

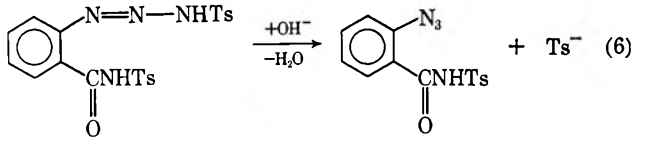


(4)

V



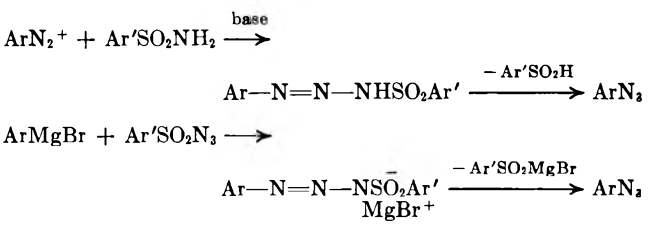
(5)



(6)

III

version of diazonium salts into azides by use of sulfonamides,[22] and reaction of sulfonyl azides with aryl Grignard reagents to give aryl azides.[23]

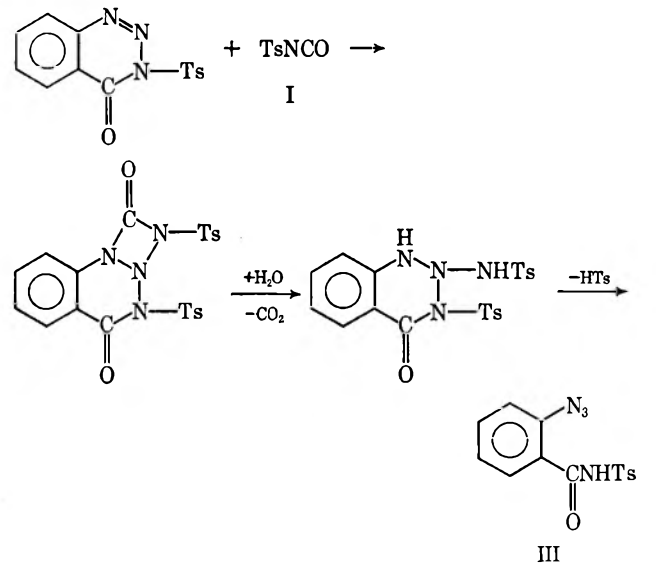


The cyclic nature of the reaction proposed herein is further supported by the fact that benzenediazonium-4-carboxylate fails to yield any products containing azide groups on reaction with II, although reaction at the carboxylate group is rapid, as evidenced by evolution of CO_2.

Registry No.—I, 1608-42-0; II, 4083-64-1; III, 17953-93-4; PhNCO, 103-71-9; benzenediazonium-4-carboxylate, 1837-05-4; BuNCO, 111-36-4; sodium benzoate, 532-32-1.

Acknowledgment.—This work was supported by grants from the Petroleum Research Fund, administered by the American Chemical Socity, and the Research Foundation of the State University of New York. We gratefully acknowledge this support.

(21) An alternative scheme for the formation of III may be formulated, involving cycloaddition of tosyl isocyanate to the ring-closed tautomer of



IV. However, work being conducted in these laboratories by Mr. Thomas Ryan has shown no evidence of cycloaddition reactions between azo compounds or triazenes and II.

(22) H. Bretschneider and H. Rager, *Monatsh.*, **81**, 970 (1950).

(23) P. A. S. Smith, L. B. Bruner, and L. O. Krbecheck, unpublished results, quoted in P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, p 248.

Nitrene. II.[1] Novel Conversion of 1-(2-Nitrobenzyl)isoquinoline Derivatives into Benz[*a*]carbazoles through Nitrene

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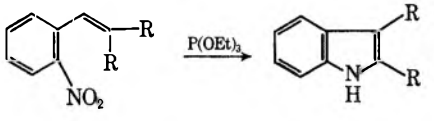
Novel conversion of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline (**3**) into benz[*a*]carbazole (**4**) by treatment with triethyl phosphite was established. Furthermore, 6′-nitrolaudanosine (**5**) was also converted into the corresponding dihydrobenz[*a*]carbazole derivative (**6**), but, in case of its methiodide (**7**) and 6′-nitropapaverine (**9**), benz[*a*]carbazole derivatives were not obtained.

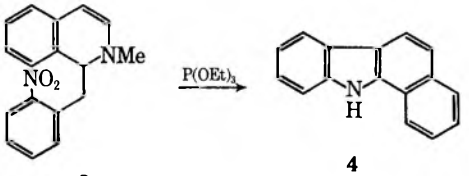
Although many investigations of the reductive cyclization of nitro compounds (**1**) to indoles (**2**) with triethyl phosphite have hitherto been carried out (eq 1),[1-8] the above-titled novel cyclization has never been investigated. We now wish to report our results which demonstrate the conversion of 1-(2-nitrobenzyl)-isoquinoline derivatives into the corresponding benz-[*a*]carbazoles by heating with an excess of triethyl phosphite under a current of nitrogen.



(1)

1 **2**

R = H; alky; acyl; aryl



(2)

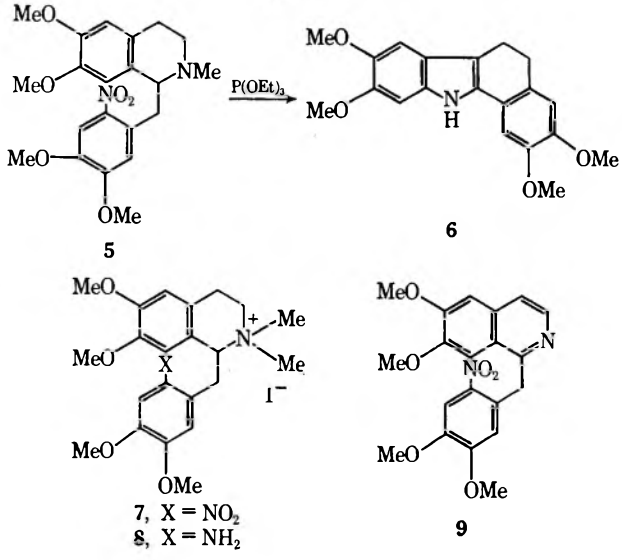
3 **4**

Treatment of the compound[9] **3** with triethyl phosphite at 160–165° gave the benz[*a*]carbazole (**4**) in 37% yield (eq 2). The product **4** was completely identical with an authentic specimen[10] from the point of the mixture melting point, ir (KBr), and nmr (in Me_2SO) spectra. Secondly, similar treatment of 6′-nitrolaudanosine (**5**)[11] with triethyl phosphite also afforded 5,6-dihydro-2,3,8,9-tetramethoxybenz[*a*]carbazole (**6**), mp 202°, in 38% yield, whose structure was elucidated from spectral data as follows; the nmr spectrum (parts per million, in $CDCl_3$) showed the C_5- and/or C_6-methylene protons at 3.08 (2 H, triplet, J = 8 cps) and 4.13 (2 H, triplet, J = 8 cps), four O-methyl protons at 3.87 (3 H), 3.90 (3 H), and 3.92 (6 H), four aromatic protons at 6.74, 6.80, 7.08, and 7.20 as singlets, respectively, and a characteristic NH proton at 6.62 as singlet, which disappeared with D_2O. Furthermore, the mass spectra of **4** and **6** showed its molecular ion peaks at m/e 217 (M^+) and 339 (M^+) as its base peak, respectively. The other strong ion peaks were not detected. This fact shows that both compounds **4** and **6** are stabilized owing to their conjugation.

On the other hand, application of this novel conversion into 6′-nitrolaudanosine methiodide (**7**) gave none of the expected benz[*a*]carbazole; reduction of the 6′-nitro group by triethyl phosphite occurred to give 6′-aminolaudanosine methiodide (**8**). The same treatment of 6′-nitropapaverine (**9**)[12] afforded no benz[*a*]carbazole, but an unknown compound of $C_{20}H_{18}O_5N_2$ (**10**) having two nitrogens was isolated in 4.5% yield.

These facts reveal that the unshared electron pair at the N_2 position participates in the formation of benz-[*a*]carbazole and it seems to be necessary that the 1,2-dihydro- and 1,2,3,4-tetrahydroisoquinolines should be used as starting materials for this novel conversion. In this reaction the nitrene intermediate, which would be assumed to be formed by treatment with triethyl phosphite, would attack the saturated carbon atom to give the indole derivatives, but the precise mechanism is under examination (Scheme I).

SCHEME I



5 **6**

7, X = NO_2
8, X = NH_2

9

(1) T. Kametani, K. Ogasawara, and T. Yamanaka, *J. Chem. Soc., C*, 1006 (1968).

(2) J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc.*, 361 (1962).

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(6) G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, **31**, 3882 (1966).

(7) R. J. Sundberg and T. Yamazaki, *ibid.*, **32**, 290 (1967).

(8) J. I. G. Cadogan and M. J. Todd, *Chem. Commun.*, 118 (1967).

(9) J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963). Their assignment of compound **3** as 1,2,3,4-tetrahydro-2-methyl-1-(2-nitrobenzal)isoquinoline was incorrect. One of the referees kindly showed that our results were closely similar to J. L Neumeyer, *J. Org. Chem.*, **33**, 2890 (1968).

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Experimental Section

The nmr spectra were determined on a Hitachi H-60 spectrometer with deuteriochloroform as solvent and tetramethylsilane as an internal reference. The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer, using an all-glass inlet system heated to 300°. The ionizing energy was maintained at 70 eV and ionizing current at 80 μA.

Benz[*a*]carbazole (4).—A mixture of 1.4 g (0.005 mol) of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline[9] (**3**) and 2.5 g (0.015 mol) of triethyl phosphite was refluxed in an oil bath at 160–165° for 20 hr. After cooling, excess triethyl phosphite was removed by distillation and the residue was purified by silica gel chromatography using benzene as an eluent. Removal of the benzene fraction and recrystallization from benzene–hexane afforded 0.4 g (37%) of the benz[*a*]carbazole (4) as colorless needles: mp 227–228° (lit.[10] mp 228°); mass (*m/e*) 217 (M^+); ν_{max} (KBr) 3430 cm^{-1}; δ (Me_2SO) 7.10–8.65 (10 H, multiplet, aromatic protons), 12.12 ppm (1 H, singlet, NH proton, disappeared with D_2O).

Anal. Calcd for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.62; H, 5.14; N, 6.36.

5,6-Dihydro-2,3,8,9-tetramethoxybenz[*a*]carbazole (6).—A mixture of 1 g (2.7 mmol) of 6′-nitrolaudanosine[11] (**5**) and 2.24 g (13.5 mmol) of triethyl phosphite was heated under reflux in an oil bath at 165–170° for 20 hr. After cooling the excess reagent was distilled off *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent. Evaporation of the benzene eluate and recrystallization from ethanol gave 0.35 g (38.5%) of the benz[*a*]carbazole derivative (**6**) as colorless scales: mp 202°; mass (*m/e*) 339 (M^+); ν_{max} (KBr) 3400 cm^{-1} (NH); δ ($CDCl_3$) 3.08 (2 H, triplet, J = 8 cps, C_5 or C_6 methylene protons), 3.87 (3 H, singlet, OCH_3), 3.90 (3 H, singlet, OCH_3), 3.92 (6 H, singlet, 2-OCH_3), 4.13 (2 H, triplet, J = 8 cps, C_5 or C_6 methylene protons), 6.62 (1 H, singlet, NH proton, disappeared with D_2O), 6.78, 6.80, 7.08, and 7.20 ppm (4 H, four singlets, aromatic protons).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24, N, 4.13. Found: C, 71.00; H, 6.32; N, 4.42.

6′-Nitrolaudanosine Methiodide (7).—A mixture of 6 g of 6′-nitrolaudanosine (**5**), 30 ml of methanol, and 10 g of methyl iodide was heated on a water bath for 10 min, crystals of **5** being thus dissolved and then those of **7** separated in turn. After an additional 10-min heating, the crystals were collected by filtration and recrystallized from ethanol–dimethylformamide to give 7.2 g (89%) of the methiodide (**7**) as colorless prisms, mp 240°.

Anal. Calcd for $C_{22}H_{29}N_2O_6I$: C, 48.54; H, 5.39; N, 5.15. Found: C, 48.72; H, 5.47; N, 5.40.

6′-Aminolaudanosine Methiodide (8).—A mixture of 5.44 g (0.01 mol) of 6′-nitrolaudanosine methiodide (**7**) and 8.3 g (0.05 mol) of triethyl phosphite was heated under reflux in an oil bath at 160–165° for 20 hr. After removal of excess reagent, the residue was crystallized from a small amount of benzene. Recrystallization from ethanol gave 4.1 g (80.1%) of the methiodide (**8**) as a yellow powder: mp 231° dec; ν_{max} (KBr) 3400 cm^{-1} (NH_2 and H_2O); δ (CF_3CO_2H) 7.85, 7.50–6.60 (4 H, multiplet, aromatic protons), 4.28 (1 H, multiplet, C_1 H), 4.05, 3.99, 3.97 (12 H, three singlets, 4-OCH_3), 3.70–3.00 ppm (6 H, multiplet, C_3 H_2, C_4 H_2, and 1-benzylic proton).

Anal. Calcd for $C_{22}H_{31}N_2O_4I \cdot 0.5H_2O$: C, 50.44; H, 5.92; N, 5.16. Found: C, 50.45; H, 6.28; N, 5.58.

Reduction of 6′-Nitropapaverine[12] (9) with Triethyl Phosphite.—A mixture of 5 g of 6′-nitropapaverine (**9**) and 11.2 g of triethyl phosphite was heated under reflux in an oil bath at 160–165° for 20 hr. After removal of the excess of the reagent, the residue was dissolved in a small amount of ethanol, whose solution was allowed to stand to separate the crystals. Recrystallization from chloroform gave 0.2 g (4.2%) of deoxygenated product (**10**) as yellow prisms: mp 277–278°; mass (*m/e*) 366 (M^+) (base peak) (no characteristic patterns were observed); ν_{max} (KBr) 1618 cm^{-1}; δ ($CDCl_3$) 4.00, 4.04, 4.15 (6 H, 3 H, 3 H, three singlets), 6.99, 7.07, 7.73 (each 1 H, singlets), 7.48, 8.37 (each 1 H, doublets, J = 7 cps), 10.35 (1 H, singlet). None of these disappeared with D_2O.

Anal.[13] Calcd for $C_{20}H_{18}O_5N_2$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.67; H, 5.00; N, 7.68.

Registry No.—**4**, 239-01-0; **6**, 17953-40-1; **7**, 17953-41-2; **8**, 17953-42-3.

Acknowledgment.—We wish to express our gratitude to Miss R. Hasebe and Miss T. Yamaki for the microanalyses and Miss Y. Tadano for the nmr determinations.

(13) The structure of compound **10** could not be determined.

Reissert Compound Studies. XVIII. Analogs Derived from Chloroformates[1,2a]

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The reaction of quinoline or isoquinoline and potassium cyanide with a variety of chloroformates has given rise to the formation of the Reissert compound analogs of the types **6** and **7**. The reactions of these analogs are compared with the reactions of Reissert compounds and other Reissert compound analogs.

In connection with our studies of Reissert compounds (**1** and **2**)[3] we have previously prepared analogs of the types **3**,[4] **4**,[5] and **5**[1] from the reaction of isoquinoline and potassium cyanide with carbamoyl chlorides, sulfonyl chlorides, and chlorophosphates, respectively. The corresponding analogs could not be isolated in the quinoline series.

We now wish to report on the use of chloroformates in this reaction. Reaction of isoquinoline, potassium cyanide, and a variety of chloroformates in methylene chloride–water gave compounds of the type **6**. These compounds are included in Table I. Under these same conditions quinoline reacted to give products of the type **7** which are also included in Table I. It is of interest to note that in contrast to Reissert compounds[3,6] and Reissert compound analogs **3**–**5**[1,4,5] several of these new analogs exhibited weak absorption in the nitrile region of the infrared at 220 cm^{-1}.

Since **1** undergoes a variety of reactions such as alkylation and/or rearrangement in the presence of base,[1,6,7] **3** was unreactive in base,[4] **4** underwent elimina-

(1) Part XVII: D. M. Spatz and F. D. Popp, *J. Heterocycl. Chem.*, **5**, 497 (1968).

(2) (a) Supported in part by a Research Grant (T-329) from the American Cancer Society. Portions of this material were presented at the 1st International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967, and the 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968. (b) National Science Foundation Undergraduate Research Participant. (c) National Institutes of Health Predoctoral Fellow.

(3) F. D. Popp, *Advan. Heterocycl. Chem.*, **9**, 1 (1968).

(4) F. D. Popp, J. M. Wefer, and A. Catala, *J. Heterocycl. Chem.*, **2**, 317 (1965).

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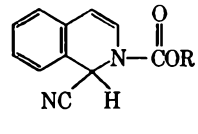
(6) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(7) F. D. Popp and J. M. Wefer, *Chem. Commun.*, 207 (1966).

TABLE I

REISSERT ANALOGS



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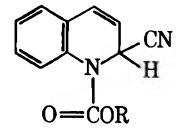
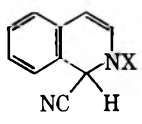


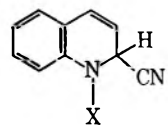
7

Type	R	Mp, °C[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6	CH_3	83–85	24	67.28	4.71	13.08	67.43	4.70	12.91
7	CH_3	72–73	56	67.28	4.71		67.30	4.74	
6	C_2H_5	84–86	57	68.41	5.30	12.28	68.43	5.32	12.39
7	C_2H_5	70–72	43	68.41	5.30	12.28	68.44	5.31	12.29
6	CH_2CCl_3	104–106[b]	82	47.09	2.74	8.45	47.11	2.85	8.41
6	$C_6H_5CH_2$	84–85	18	74.47	4.86	9.65	74.48	4.92	9.66
6	C_6H_5	156–158	99	73.90	4.38	10.14	73.91	4.36	10.14
6	p-$CH_3OC_6H_4$	182–183	99	70.58	4.61		70.62	4.71	

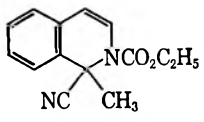
[a] Recrystallized from ethanol, unless otherwise noted. [b] Recrystallized from ethanol–water.



1, X = O=CR
3, X = O=CNR$_2$
4, X = SO_2R
5, X = P(O)(OR)$_2$ or P(S)(OR)$_2$
6, X = O=COR



2, X = O=CR
7, X = O=COR



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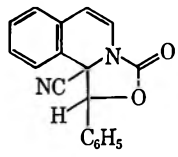

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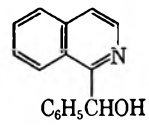

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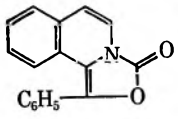

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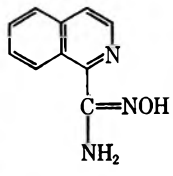

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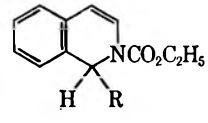
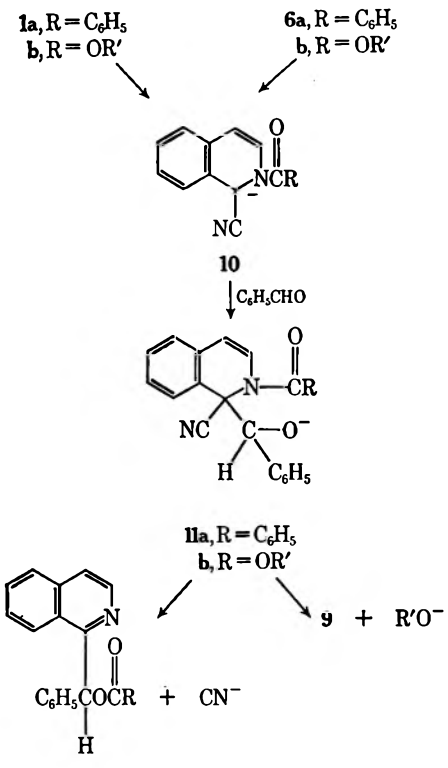


15, R = NH_2C=NOH
16, R = $CONH_2$
18, R = NH_2C=$NOCO_2C_2H_5$

SCHEME I



12

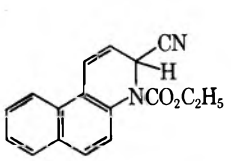
tion in base,[5] and **5** underwent alkylation or elimination in base;[1] it was thought to be of value to examine the behavior of **6** in the presence of base. Treatment of **6** (R = C_2H_5) with methyl iodide and sodium hydride in N,N-dimethylformamide[7] gave **8** in good yield. Confirmation of structure **8** was available since the compound could be readily hydrolyzed to 1-methylisoquinoline.

Treatment of **6** (R = CH_3, C_2H_5, or p-$CH_3OC_6H_4$) with benzaldehyde in the presence of n-butyllithium at −30° gave **9**. This differs, as shown in Scheme I, from the reaction of **1** with benzaldehyde. This difference is easily explained, however, when one considers that **11a** (from **1** *via* **10a**) can only reasonably lose a cyanide ion to give **12**, whereas **11b** (from **6** *via* **10b**) can also lose alkoxide and the reactions proceed through this latter route. When the reaction of **6** and benzaldehyde was carried out with sodium hydride in N,N-dimethylformamide at room temperature with no attempt to control the heat of the reaction, **13** was obtained, although in one case **14** was isolated and easily hydrolyzed by base to **13**.

Hydrolysis of **6** (R = C_2H_5) with hydrobromic acid in glacial acetic acid yielded isoquinoline which was identified as its picrate. This hydrolysis is similar to that reported for **4**[5] and **5**[1] but differs from the normal hydrolysis of a Reissert compound.[6] Treatment of **6** (R = C_2H_5) with sodium hydride gave rise to isoquinaldonitrile. This is analogous to the behavior of **4** and **5** but differs from **1** which undergoes rearrangement under these conditions.

Reaction of **6** (R = C_2H_5) with hydroxylamine by the method of Rupe and Gassman[8] yielded the amidoxime **15** together with a small amount of the amide **16**. Excess base caused the formation of **16** to be favored and none of the amidoxime was isolated. Hydrolysis of **16** with base gave isoquinaldamide. Reaction of isoquinaldonitrile with hydroxylamine

(8) H. Rupe and A. Gassman, *Helv. Chim. Acta*, **22**, 1241 (1939).



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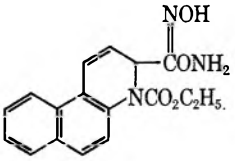

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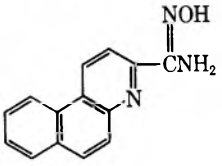

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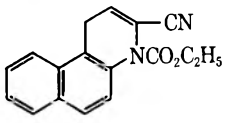

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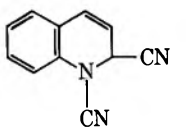

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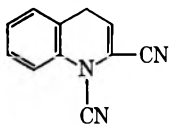

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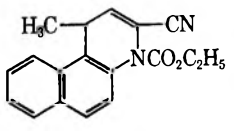

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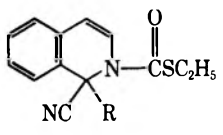

26, R = H
27, R = CH_3

yielded an amidoxime **17**. Both **15** and **17** gave a purple color with ferric chloride in ethanol, and the formation of metal complexes from these amidoximes is being studied further in this laboratory. Reaction of **15** with acetic anhydride gave the O-acetylamidoxime, but reaction of **15** with benzenesulfonyl chloride yielded a product identified as the O-carboethoxyamidoxime apparently resulting from intermolecular transethoxycarbonylation. Reaction of **15** with ethyl chloroformate yielded **18** thus confirming this structure.

As previously reported[9] benzo[*f*]quinoline reacted with potassium cyanide and ethyl chloroformate to give the benzo analog of **6** (**19**). Reaction of **19** with hydroxylamine (this reaction differs from the reaction of **6** with hydroxylamine in that N,N-dimethylformamide was added to improve solubility) gave a mixture of four products. The expected amidoxime (**20**) was obtained in 11% yield. A small amount of benzo[*f*]quinaldamide which apparently resulted from hydrolysis of starting material was isolated. A third product, obtained in 6% yield, was **21** which apparently resulted from the hydrolysis and oxidation of **20**. The structure **21** was confirmed by treating benzo[*f*]quinaldonitrile with hydroxylamine to yield a compound identical in all respects with **21**. The major product (35% yield) of the hydroxylamine reaction was identified as **22**. The nmr spectrum of **22** showed that it was indeed the 1,4-dihydro compound by its AX_2 splitting pattern. Bramley and Johnson[10] have studied a similar series of compounds, **23** and **24**, and the nmr spectrum reported by them is consistent with this series. Seeley and coworkers[11] have studied the ultraviolet spectrum of **23** and **24**, and the spectra found in this work for **19** and **22** are consistent. Methylation of either **19** or **22** with methyl iodide in the presence of sodium hydride in N,N-dimethylformamide gave rise to the same methylated product **25**. The spectra of **25** was again consistent with the 1,4-dihydro structure, and hydrolysis of **25** yielded the known benzo[*f*]lepidine.[12] It should be noted that alkylation of the quinoline Reissert compound (**2**) with methyl iodide occurs in the 4 position.[13]

Reaction of isoquinoline, potassium cyanide, and ethyl chlorothioformate gave **26** which is the sulfur analog of **6**. Treatment of **26** with methyl iodide and sodium hydride in N,N-dimethylformamide gave rise to the methylated product **27** in good yield. Acid-catalyzed hydrolysis of **26** gave isoquinoline.

Experimental Section[14]

Preparation of Reissert Analogs from Chloroformates.—To a mixture of 0.16 mol of isoquinoline (or quinoline) in 150 ml of methylene chloride and 0.48 mol of potassium cyanide in 40 ml of water was added 0.32 mol of the appropriate chloroformate over a 2-hr period. After an additional 4 hr of stirring, the solution was washed with water, dilute HCl, water, dilute NaOH, and water. Concentration of the methylene chloride and recrystallization yielded the products indicated in Table I.

Alkylation of 6 (R = C_2H_5).—To a mixture of 0.01 mol of **6** (R = C_2H_5) and 0.02 mol of methyl iodide in 40 ml of N,N-dimethylformamide was added with stirring 0.01 mol of a 30% sodium hydride in oil dispersion. Stirring was continued for 90 min, and the mixture was poured onto 500 g of crushed ice to give a 92% yield of solid, mp 69–70°. Recrystallization from ethanol gave **8**, mp 72–73°.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.41; H, 5.82; N, 11.69.

Hydrolysis of **8** with alcoholic potassium hydroxide gave 1-methylisoquinoline in 89% yield. The picrate, mp 231–233°, was identical with an authentic sample.

Condensation of 6 (R = C_2H_5) with Benzaldehyde.—To a solution of 0.005 mol of **6** (R = C_2H_5) in anhydrous ether and sufficient anhydrous dioxane to cause solution at −30° under a nitrogen atmosphere was added with stirring sufficient *n*-butyllithium solution to generate a permanent red color. To the red solution was added 3.0 ml of benzaldehyde, and the mixture was stirred at −30° for 1 hr. After stirring for an additional 13 hr at room temperature, the solution was washed with water, dilute hydrochloric acid, and water. Evaporation of the ether and recrystallization from ethanol gave a 38% yield of **9**: mp 166–167°; nmr (DMSO-d_6) τ 2.9 and 3.6 (doublets of the olefinic H's), 3.4 (singlet), 2.4 [multiplet, (9 H), of the aromatic H's].

Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.06; H, 4.25; N, 9.66.

The same product was obtained using other analogs of **6**.

Treatment of 0.01 mol of **6** (R = C_2H_5) with 0.01 mol of benzaldehyde and 0.02 mol of sodium hydride as described above for the alkylation in N,N-dimethylformamide gave a 47% yield of **13**, mp 107–109°, which was identical with an authentic sample.

Use of 0.01 mol of sodium hydride in this procedure led to the isolation of a 13% yield of **14**, mp 166–168° (hexane–ethyl acetate). The nmr spectrum lacked the singlet present in the nmr spectrum of **9**.

Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.22; H, 4.07; N, 5.39.

Hydrolysis of **14** with alcoholic potassium hydroxide gave an 88% yield of **13**.

Acid Hydrolysis of 6 (R = C_2H_5).—A mixture of 0.5 g of **6** (R = C_2H_5), 10 ml of acetic acid, and 10 ml of hydrobromic acid was heated on the steam bath for 3 hr. The solution was cooled, made basic, and extracted with ether. Concentration of the ether gave a 74% yield of isoquinoline which was identified as its picrate.

Treatment of 6 (R = C_2H_5) with Sodium Hydride.—A mixture of 0.01 mol of **6** (R = C_2H_5) and 0.01 mol of a 30% sodium hydride oil dispersion was stirred for 90 min and poured onto 500 g of ice to give 0.47 g (32%) of isoquinaldonitrile, mp 87–89°,

(9) L. E. Katz and F. D. Popp, *J. Heterocycl. Chem.*, **5**, 249 (1968).
(10) R. Bramley and M. D. Johnson, *J. Chem. Soc.*, 1372 (1965).
(11) M. G. Seeley, R. E. Yates, and C. R. Noller, *J. Amer. Chem. Soc.*, **73**, 772 (1951).
(12) K. N. Campbell and I. J. Schaffner, *ibid.*, **67**, 86 (1945).
(13) V. Boekelheide and J. Weinstock, *ibid.*, **74**, 660 (1952).
(14) All melting points are corrected and taken in capillaries. Analyses by Spang Microanalytical Laboratories, Ann Arbor, Mich.

which was identical with an authentic sample. Substitution of dimethyl sulfoxide for the N,N-dimethylformamide gave an 84% yield of the nitrile.

Reaction of 6 (R = C_2H_5) with Hydroxylamine.—To 6.35 g (0.0278 mol) of **6** (R = C_2H_5) in 140 ml of absolute methanol at −8° was added a cooled solution of 0.64 g (0.0278 g-atom) of Na and 1.22 g (0.0278 mol) of hydroxylamine hydrochloride in 40 ml of absolute methanol. The mixture was stirred at −8° for 50 min and filtered to give 2.24 g of starting material. The filtrate was evaporated, and 3.64 g of solid was obtained. Recrystallization from ethanol gave **15**: mp 153–155°; ir (KBr) 3480, 3430, 3345, 1680, 1662, 1030 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.80; H, 5.79; N, 16.10. Found: C, 59.74; H, 5.83; N, 16.16.

After the isolation of **15**, 0.02 g of **16**, mp 183–185°, was obtained from the filtrate: ir (KBr) 3420, 3300, 3220, 1715, 1670, 1030 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.66; H, 5.75; N, 11.42. Found: C, 63.61; H, 5.67; N, 11.33.

Use of 0.01 g-atom of Na to 0.0046 mol of **6** gave only **16**.

Hydrolysis of 16.—A mixture of 0.02 g of **16** and 0.10 g of potassium hydroxide in 5 ml of ethanol was refluxed for 15 min and concentrated. The residue was dissolved in water and extracted with ether. Concentration of the ether gave isoquinaldamide which was identical with an authentic sample.

Preparation of 1-Amidoxamidoisoquinoline (17).—To a solution of 0.62 g (0.0044 mol) of isoquinaldonitrile in 20 ml of methanol at −10° was added with stirring a cooled solution of 0.305 g (0.0044 mol) of hydroxylamine hydrochloride and 0.11 g (0.0044 g-atom) of Na in methanol. The mixture was stirred at −10° for 30 min and concentrated to give a solid which was washed with water. Crystallization of the solid from a minimum of ethanol and then methanol gave 0.185 g (23%) of **17**, mp 126–128°.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.20; H, 4.85. Found: C, 64.32; H, 4.95.

Reaction of 15 with Acetic Anhydride.—A mixture of 5 ml of acetic anhydride and 0.11 g (0.0004 mol) of amidoxime **15** was heated for 30 min at 100° and then concentrated to give a solid. Recrystallization from ethanol gave the O-acetylamidoxime, mp 135–136°.

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.87. Found: C, 59.45; H, 5.61; N, 13.82.

Reaction of 15 with Benzenesulfonyl Chloride.—A mixture of 0.62 g (0.0024 mol) of the amidoxime **15**, 10 ml of pyridine, and 0.65 g (0.0035 mol) of benzenesulfonyl chloride was stirred at 0° for 5 hr and then concentrated. Treatment of the residue with hexane and methylene chloride caused a solid to form, and recrystallization from toluene gave 0.055 g (7%) of a solid (**18**): mp 133–134°; ir (KBr) 3430, 3375, 1765, 1710, 1635, 1577, 1020 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.50; H, 5.75; N, 12.60. Found: C, 57.74; H, 5.76; N, 12.55.

This same product **18** was obtained in 74% yield by the reaction of **15** and ethyl chloroformate in pyridine at 0°.

Reaction of 19 with Hydroxylamine.—To a mixture of 2.75 g (0.001 mol) of **19**,[9] 50 ml of methanol, and 50 ml of N,N-dimethylformamide was added a cooled solution of 0.23 g (0.001 mol) of sodium and 0.80 g (0.001 mol) of hydroxylamine hydrochloride in 20 ml of methanol. The mixture was stirred at −8° for 80 min and concentrated *in vacuo*. When all of the methanol was removed, the solution was added to 450 g of ice, and a crude solid collected. Chromatography of this solid on alumina gave four components. Elution with benzene gave 0.98 g (35%) of a solid (**22**): mp 135–136° (ethanol); ir (KBr) 2250, 1715, 1030 cm^{-1}; uv 218 mμ (log ε 4.68), 238 (4.63) [the starting material **19** had no ir peak at 2250 cm^{-1} and had uv peaks at 207 mμ (log ε 4.34), 243 (4.63), and 319 (3.63)]; nmr (CCl_4) a quartet (2 H) and triplet (3 H) at τ 5.6 and 8.6 (ethyl), a multiplet at 2.0–2.8 (6 H, aromatic), and an AX_2 pattern at 3.6 (1 H) and 6.3 (2 H).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.45; H, 5.07; N, 10.05. Found: C, 73.28; H, 4.98; N, 10.24.

The next component further elution with benzene had mp 239° and was identical with an authentic sample of benzo[*f*]-quinaldamide.

Elution with ethanol gave 0.145 g (6%) of solid **21**, mp 211–213° from benzene. This sample was identical with the material described below.

Further elution with ethanol gave 0.33 g (11%) of solid **20**, mp 182–183° from ethanol.

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.65; H, 5.50; N, 13.50. Found: C, 65.49; H, 5.48; N, 13.70.

Preparation of 23.—To a mixture of 0.715 g (0.0035 mol) of benzo[*f*]quinaldonitrile and 20 ml of methanol was added a solution of 0.08 g (0.0035 mol) of sodium and 0.25 g (0.0035 mol) of hydroxylamine hydrochloride in 10 ml of methanol. After stirring in the cold for 30 min, 0.47 g (56%) of solid was collected and recrystallized from ethanol to give **23**, mp 211–212°, identical with that reported above.

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.97; H, 4.68; N, 17.72. Found: C, 70.97; H, 4.71; N, 17.69.

Methylation of 19 and 22.—To a solution of 0.133 g (0.0005 mol) of **22** in 5 ml of N,N-dimethylformamide at 0° was added 0.10 g (0.012 mol) of 30% sodium hydride in oil with stirring. To the purple solution was then added a few drops of methyl iodide. After disappearance of the color, the solution was poured on ice, and 0.11 g (78%) of solid **25**, mp 152–153° from ethanol, was obtained: nmr (CCl_4) τ 2.0–2.7 (multiplet, 6 H, 3.5 (doublet 1 H, H_2), 5.8 (multiplet, 3 H, H_1 and CH_2 of ethyl), 8.5 (multiplet 6 H, two CH_3).

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 74.00; H, 5.58; N, 9.58. Found: C, 74.02; H, 5.60; N, 9.60.

In a similar manner **19** gave the same product.

Hydrolysis of 25 to Benzo[*f*]lepidine.—A small amount of the methylated compound **25** was refluxed with alcoholic potassium hydroxide. Concentration gave a solid, mp 98–100° from hexane (lit.[14] mp 100–101° for benzo[*f*]lepidine).

Preparation of Sulfur Analog 26.—Use of ethyl chlorothiolformate and isoquinoline in the preparation of **6** described above gave a 44% yield of **26**, mp 107–108° from ethanol.

Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.89; H, 4.90; N, 11.41.

Alkylation of 26.—Reaction of **26** with methyl iodide as described above for the preparation of **8** from **6** gave a nearly quantitative yield of **27**, mp 79–81° from ethanol.

Anal. Calcd for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.16; H, 5.61; N, 10.71.

Acid Hydrolysis of 26.—Hydrolysis of **26** with acetic acid–hydrobromic acid as described above for the hydrolysis of **6** gave isoquinoline, isolated as its picrate.

Registry No.—**6** (R = Me), 17954-40-4; **6** (R = Et), 17954-22-2; **6** (R = CH_2CCl_3), 17954-24-4; **6** (R = CH_2Ph), 17954-25-5; **6** (R = Ph), 17954-26-6; **6** (R = *p*-$MeOC_6H_4$), 17954-27-7; **7** (R = Me), 17954-21-1; **7** (R = Et), 17954-23-3; **8**, 17954-28-8; **9**, 17954-29-9; **14**, 17954-30-2; **15**, 17954-31-3; **15** (O-acetylamidoxime, 17953-94-5; **16**, 17954-32-4; **17**, 17954-33-5; **18**, 17954-34-6; **20**, 17954-36-8; **21**, 17954-41-5; **22**, 17954-35-7; **25**, 17954-37-9; **26**, 17954-38-0; **27**, 17954-39-1.

Product Ratio Analysis of the Reaction of Methyl *cis*- and *trans*-β-(Acetylthio)acrylates with Diazomethane[1]

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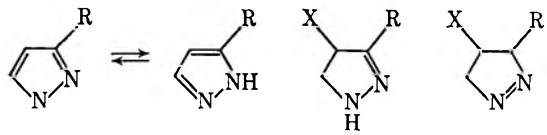
The relative yield of methyl *cis*-β-(methylmercapto)acrylate (**5**), 1-methyl-5-carbomethoxypyrazole (**6**), 3-carbomethoxypyrazole (**7**), and 1-methyl-3-carbomethoxypyrazole (**8**), when methyl *cis*- or *trans*-β-(acetylthio)-acrylate undergo reaction with excess diazomethane in ether, was determined by means of gas–liquid partition chromatography. The analysis shows product formation to be dependent upon the stereochemistry of the starting methyl β-(acetylthio)acrylate. Competing reaction pathways are proposed to account for the different yields of products.

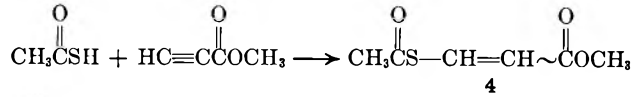
A number of syntheses have been developed for pyrazoles (**1**)[2] and pyrazolines (**2** and **3**).[3] One method involves condensation of aliphatic diazo compounds with olefins containing an activated double bond. Substituted 1- and 2-pyrazolines (R = electron-withdrawing group in **2** and **3**), for example, are



1 **2** **3**

formed from α,β-unsaturated aldehydes, ketones, and esters by concerted reaction with diazomethane.[2-4] Alternatively, pyrazoles are synthesized when one of the vinyl carbon atoms is substituted with a suitable leaving group.[2,5]

The stereochemistry of formation of 1-pyrazolines (**2**) has been elucidated.[4c] Reaction of diazomethane with β-substituted α,β-unsaturated esters affords 1-pyrazolines with the same geometry as the starting olefin. When X in **2** or **3** represents a leaving group pyrazolines may be converted into the corresponding pyrazole by elimination of HX.[2] Use of appropriately substituted pyrazolines shows elimination of HX to be most facile by a *trans* mechanism.[6] For reactions previously studied the intermediate pyrazoline was isolated and conversion into the corresponding pyrazole required either acid or base catalysis or warming depending upon the nature of X. Under reaction conditions similar to those described in this communication pyrazolines could be isolated from reaction of ethyl β-bromoacrylate with diazomethane. On standing the isolated pyrazoline lost HBr, affording the pyrazole, but the reaction was not studied stereochemically.[7] Availability of both methyl *cis*- and *trans*-β-(acetylthio)acrylates (**4**) prompted study of their reaction with diazomethane in ether to determine the mechanism of formation of pyrazoles and the dependence of their formation upon the configuration of the starting olefin.



4

Results and Discussion

A mixture of *cis*- and *trans*-β-(acetylthio)acrylates is obtained by free-radical addition of thiolacetic acid to methyl propiolate.[8] Whereas geometrical isomers of **4** are reportedly separable by spinning-band distillation, in our laboratories pure samples could only be obtained by column chromatography (chloroform on silicic acid). Pure *cis* **4** elutes first, followed by a mixture of *cis* and *trans*, and pure *trans* last. Analysis of the nmr spectra in the vinyl proton region agreed with the reported values of chemical shifts and coupling constants for *cis* and *trans* **4**.[9]

Reaction of *cis* **4** with excess distilled diazomethane in ether at −5 to 0° for 8 hr, followed by standing at room temperature for 3.5 days, affords, by gas–liquid partition chromatography, methyl *cis*-β-(methylmercapto)acrylate (**5**), 1-methyl-5-carbomethoxypyrazole (**6**), 3-carbomethoxypyrazole (**7**), and 1-methyl-3-carbomethoxypyrazole (**8**) in a ratio of 3.3:1.8:1.7:1.2, respectively (Figure 1).[10] No detectable quantity of methyl *cis*-β-(methylmercapto)acrylate (**5**) or the corresponding *trans* isomer was obtained during the reaction of *trans* **4** under identical conditions. The major product, 1-methyl-5-carbomethoxypyrazole (**6**), formed in nearly 50% yield, is found along with **7** and **8** in a ratio of 4.8:0.8:1.9, respectively (Figure 2).[10] Methyl thiolacetate was found gas chromatographically. A number of uncharacterized minor products (peaks labeled B in chromatograms, Figures 1 and 2) are obtained during the reaction of both *cis* and *trans* **4** with distilled diazomethane. The unidentified components

(1) Presented at the 1st Central Regional Meetings of the American Chemical Society, Akron, Ohio, May 1968.

(2) A. N. Kost and I. I. Grandberg, *Advan. Heterocycl. Chem.*, **6**, 347 (1966).

(3) (a) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955); (b) R. Locquin and R. Heilmann, *C. R. Acad. Sci., Paris*, **181**, 120 (1925); (c) I. A. D'yakonov, "Aliphatic Diazocompounds," Goshimisday, Leningrad, 1958.

(4) (a) T. L. Jacobs in "Heterocyclic Compounds," Vol. 5, R. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 45 ff; (b) K. D. Gundermann and R. Thomas, *Ber.*, **93**, 883 (1960); (c) T. V. vanAuken and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962); (d) W. R. Brown and J. P. Mason, *J. Chem. Eng. Data*, **11**, 265 (1966).

(5) (a) W. E. Parham and J. L. Bleasdale, *J. Amer. Chem. Soc.*, **72**, 3843 (1950); **73**, 4664 (1951); (b) K. von Auwers and O. Ungemach, *Ber.*, **66**, 1198 (1933); (c) A. N. Nesmeyanov and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR*, **77**, 65 (1951); (d) N. K. Kochetkov, I. Ambrush, and A. I. Usov, *Zh. Obshch. Khim.*, **29**, 2578 (1959).

(6) (a) I. L. Finar and K. E. Godfrey, *J. Chem. Soc.*, 2293 (1954); (b) H. Jörlander, *Ber.*, **49**, 2782 (1916); (c) N. H. Cromwell and G. Mercer, *J. Amer. Chem. Soc.*, **79**, 3815, 3819 (1957); (d) N. H. Cromwell and R. Mohrbacher, *ibid.*, **75**, 6252 (1953); (e) N. H. Cromwell, N. Barker, R. Wankel, P. Vanderhorst, E. Olson, and J. Hill, *ibid.*, **73**, 1044 (1951).

(7) (a) E. Buchner, *Ann.*, **273**, 214 (1893); (b) E. Buchner and M. Fritsche, *Ber.*, **26**, 256 (1893); (c) G. P. Rice, *J. Amer. Chem. Soc.*, **52**, 2094 (1930); (d) A. N. Nesmeyanov and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 686 (1951).

(8) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3109 (1949).

(9) W. H. Mueller, *J. Org. Chem.*, **31**, 3075 (1966).

(10) The reactions studied were run for 3.5 days to ensure completion. However, gas–liquid partition chromatographic analysis showed the same ratio of products to be formed after 6 hr at −5 to 0° and all reactant to be consumed.

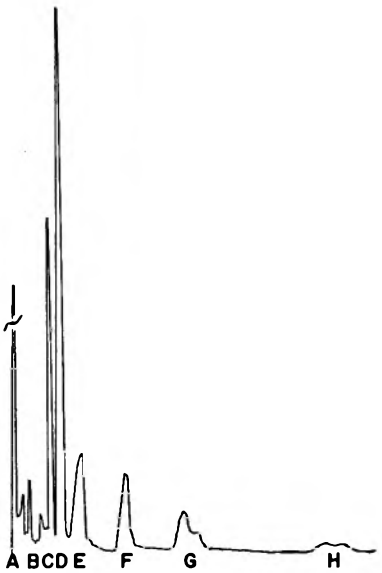
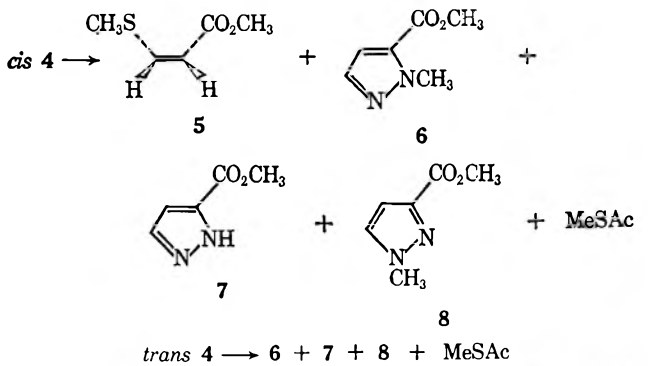


Figure 1.—Gas chromatograph of the reaction products of methyl *cis*-β-(acetylthio)acrylate in distilled diazomethane in ether: A, solvent ether plus methyl thiolacetate; B, uncharacterized minor products; C, 1-methyl-5-carbomethoxypyrazole (**6**); D, methyl *cis*-β-(methylmercapto)acrylate (**5**); E, 3-carbomethoxypyrazole (**7**); F, 1-methyl-3-carbomethoxypyrazole (**8**); G, uncharacterized; H, uncharacterized.

(G in Figures 1 and 2) are by-products of the reaction of 3-carbomethoxypyrazole (**7**) and diazomethane under the same conditions (Figure 3).[10]



If the diazomethane in ether was not distilled, both *cis* and *trans* **4** afforded methyl *cis*-β-(methylmercapto)-acrylate (**5**) in 20% isolated yield. Gas–liquid partition chromatography of the reaction mixture showed that neither the *cis* nor *trans* isomer of **4** affords any detectable quantity of methyl *trans*-β-(methylmercapto)acrylate. Pure **5** was obtained by column chromatography of the reaction products using chloroform on silicic acid. Its *cis* configuration was confirmed by partial isomerization to the thermodynamically more stable *trans* isomer during distillation. Coupling constants were in agreement with the configurational assignment; J_{AX} for the vinyl protons of the *cis* isomer is 10.3 ± 0.5 cps and J_{AX} for the vinyl protons of the *trans* isomer is 15.0 ± 0.5 cps.[9]

When undistilled diazomethane in ether is used **9** is a most likely intermediate since *cis* **5**, free of *trans* isomer, is formed from both *cis* and *trans* **4**. The undistilled diazomethane in ether is decanted from KOH pellets. Base-catalyzed hydrolysis of the thiolacetate group of either *cis* or *trans* **4** would yield the thioenolate ions which rapidly isomerize and abstract a proton from

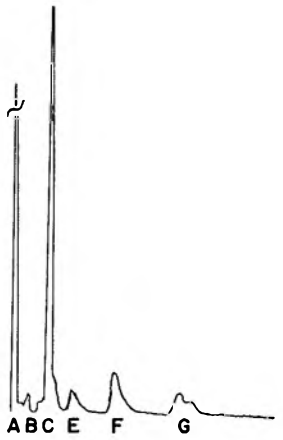
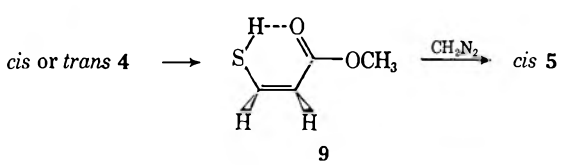


Figure 2.—Gas chromatograph of the reaction products of methyl *trans*-β-(acetylthio)acrylate in distilled diazomethane in ether: A, solvent ether plus methyl thiolacetate; B, uncharacterized minor products; C, 1-methyl-5-carbomethoxypyrazole (**6**); E, 3-carbomethoxypyrazole (**7**); F, 1-methyl-3-carbomethoxypyrazole (**8**); G, uncharacterized.

the medium. The result would be intermediate **9** whose stability is enhanced by intramolecular hydrogen bonding. Similar structures for β diketones have been shown to exist 95% in the intramolecularly hydrogen bonded *cis*-enol form in ether.[11] Reaction of **9** with



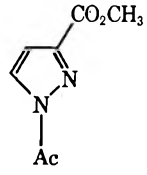
diazomethane by insertion between the S and H atoms of the thiol group would afford *cis* **5**. Support for the interpretation of these data was provided by gas–liquid partition chromatographic analysis of the reaction mixture containing *trans* **4** and distilled diazomethane in ether to which 10 mg of KOH powder was added.[10] Methyl *cis*-(β-methylmercapto)acrylate (**5**) was produced. Further work is needed, however, before the differences in reaction of *cis* and *trans* **4** in distilled diazomethane in ether can be interpreted and the nature of the intermediates (*cis* **4** → *cis* **5**) proposed.

In the reaction of *trans* **4** with distilled diazomethane in ether approximately 75% of the total reaction product are pyrazoles **6**, **7**, and **8**. With *cis* **4** they account for only 47% of the reaction products. Competing formation of methyl *cis*-β-(methylmercapto)-acrylate (**5**) satisfactorily explains the lower yield of pyrazoles when *cis* **4** is the reactant. Gas chromatographic analysis of the reaction of *trans* **4** in distilled diazomethane in ether to which 10 mg of KOH powder was added showed the same product ratio of pyrazoles formed as in the reactions containing distilled diazomethane in ether free of KOH. Therefore, concurrent formation of methyl *cis*-(β-methylmercapto)acrylate (**5**) has little or no influence on the ratio of pyrazoles formed.

On one occasion, when the reaction was run at room temperature, without previous cooling, a small yield (<1.0%) of 1-acetyl-3-carbomethoxypyrazole (**10**) was obtained. When diazomethane entrained in a stream

(11) B. Eistert, F. Arndt, L. Loewe, and E. Ayca, *Ber.*, **84**, 156 (1951).

of nitrogen was added to a stirred mixture of *cis* and *trans* **4** at 85°, 1-acetyl-3-carbomethoxypyrazole (**10**) was isolated in 21% yield. This compound results from acetylation of 3-carbomethoxypyrazole (**7**) by either *cis* or *trans* **4**. Heating 3-carbomethoxypyrazole (**7**) with **4** affords **10** in quantitative yields.



10

Pyrazoles **6**, **7**, **8**, and **10** were synthesized by an alternate method and characterized by means of their nmr spectra. Reaction of methyl propiolate with diazomethane in ether by a modified method of Reimlinger[12] yields 3-carbomethoxypyrazole (**7**). Acetylation of **7** in refluxing acetic anhydride yields **10**.[13] Reaction of **7** with excess diazomethane in ether[14] at −5 to 0° affords **6**, **7**, and **8** in a ratio of 5.9:1.2:1.2 (Figure 3).[10]

Assignment of the substituent position for pyrazoles **6**, **8**, and **10** was determined by nmr.[13,15] The chemical shift for the H_4 proton in 1,3,5-trisubstituted or 3,5-disubstituted pyrazoles may be calculated[15a] according to eq 1, where δ_4 (S) is the chemical shift for the H_4

$$\delta_4 = \delta_4\,(S) + \alpha_1 + \alpha_3 + \alpha_5 \qquad (1)$$

proton of 1,3,5-trimethylpyrazole in solvent S, and α_1, α_3, and α_5 are empirical constants representing the effect of replacing a methyl group by another substituent at position 1, 3, and 5, respectively. The calculated and experimental results (Table I) are in excellent agreement. Coupling constants are also in accord with those reported in the literature for N-methyl-substituted pyrazoles.[15a,c]

TABLE I[a]

Compd	δ_4, calcd	δ_4, found	δ_3	δ_5	δ_{N-CH_3}	$J_{4,5}$, cps	$J_{3,4}$, cps
10	6.94	6.92		8.32		3.0	
6	6.66	6.68	7.42		3.72		1.9
8	6.62	6.64		7.42	3.82	2.2	

[a] Coupling constants and chemical shifts were taken in deuteriochloroform at 10% concentrations utilizing trimethylsilane as an internal standard.

More data are necessary before all of the possibilities concerning intermediates in pyrazole formation from *cis* and *trans* **4** may be sorted out and the differences in pyrazole product ratio explained. However, by considering these results in conjunction with similar reactions, some tentative proposals can be made. Concerted addition of diazomethane to *cis* and *trans* **4** is expected to yield intermediate 1-pyrazolines **11** and **12**, respectively.[4c] Since *cis* and *trans* **4** yield different product ratios of N-methylpyrazoles, the results cannot be accounted for on the basis of a single reaction

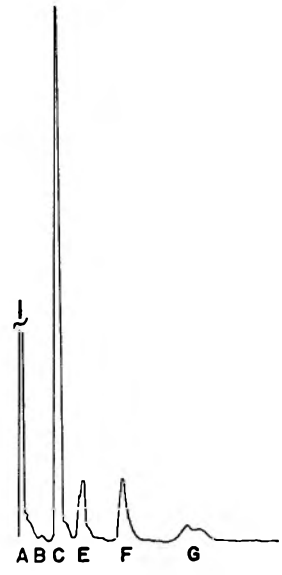
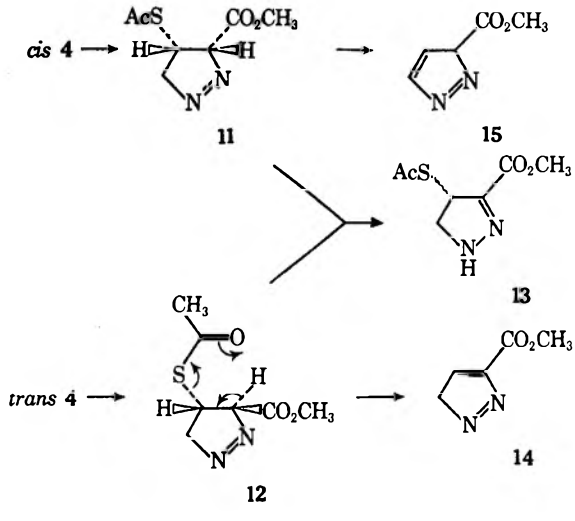


Figure 3.—Gas chromatograph of the reaction products of 3-carbomethoxypyrazole in distilled diazomethane in ether: A, solvent ether; B, uncharacterized minor products; C, 1-methyl-5-carbomethoxypyrazole (**6**); E, 3-carbomethoxypyrazole (**7**); F, 1-methyl-3-carbomethoxypyrazole (**8**); G, uncharacterized.

pathway and/or a common intermediate such as the 2-pyrazoline **13** which could result from isomerization of either **11** or **12** (Scheme I).[16]

SCHEME I



When either *trans* **4** or 3-carbomethoxypyrazole (**7**) serves as the reactant, the same ratio of pyrazoles is obtained. This is evidence that **6** is an intermediate in the reaction of *trans* **4** with diazomethane. Subsequent methylation of **7** by excess diazomethane would afford **6** and **8**. Apparently, *cis* **4** undergoes a competing reaction pathway since N-methylpyrazoles **6** and **8** are formed in nearly equal amounts and in a different ratio than when *trans* **4** serves as starting material.

One explanation for the exclusive formation of intermediate **7** from *trans* **4** and not *cis* **4** is that the 1-pyrazoline **12** undergoes a relatively faster *cis* elimina-

(12) H. K. Reimlinger, *Ber.*, **93**, 1857 (1960).

(13) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).

(14) (a) K. von Auwers and H. Hollmann, *Ber.*, **59**, 1282 (1926); (b) K. von Auwers and T. Breyhan, *J. Prakt. Chem.*, [2] **143**, 259 (1935).

(15) (a) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966); (b) J. D. Albright and L. Goldman, *ibid.*, **31**, 273 (1966); (c) C. L. Habraken and J. A. Moore, *ibid.*, **30**, 1892 (1965).

(16) 1-Pyrazolines were isolated even when the 2-pyrazolines contained conjugated systems. Rearrangement to 2-pyrazolines occurs on recrystallization or brief heating with halogen acid. See (a) L. I. Smith and W. Pings, *J. Org. Chem.*, **2**, 23 (1937); (b) L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.*, **65**, 159, 165 (1943).

tion (12 → 14) of thiolacetic acid (detected gas chromatographically as methyl thioacetate) than does the 1-pyrazoline 11 (*i.e.*, 11 → 15) since the proton α to the carbomethoxy group in the former case is more acidic. Apparently, *cis* elimination (12 → 14) also is faster than isomerization (11 or 12 → 13) under these reaction conditions.[16] Intermediate 14 could gain aromatic stabilization by rapidly tautomerizing to 7.[17] Although small quantities of impure compounds having physical properties expected for 13 were obtained by chromatography of the *cis* 4 reaction mixture, failure to identify these substances and study their reaction with diazomethane precludes further speculation on the product ratio differences.

Experimental Section[18]

Methyl β-(acetylthio)acrylate (4) was prepared by a modification of the method of Owen and Sultanbawa.[8] A mixture of 64 g (0.81 mol) of methyl propiolate and 138 g (1.81 mol) of thiolacetic acid was allowed to stand for 1 week at room temperature and then heated on a steam bath for 2 hr. Removal of excess thiolacetic acid along with unreacted methyl propiolate under reduced pressure followed by fractional distillation of the residue gave 35.7 g (28%) of methyl β-(acetylthio)acrylate. Repetition of this procedure utilizing recovered methyl propiolate and thiolacetic acid in two consecutive runs increased the over-all yield to 75%. Column chromatography on silicic acid 40% chloroform in Skellysolve C afforded the respective *cis* and *trans* isomers. Recrystallization from methanol yielded the *cis* compound, mp 58–59° (lit.[8] mp 58–58.5°), and the *trans* compound, mp 82–83.5° (lit.[8] mp 84.5°). The nmr spectra indicated each isomer to be free of the other and the parameters were in agreement with those reported in the literature.[9] Infrared absorption spectra showed characteristic bands at 1362, 997, 810, and 785 cm^{-1} for the *cis* isomer and at 1312, 1010, 978, 850, and 825 cm^{-1} for the *trans* compound.

Reaction of Methyl *cis*-β-(Acetylthio)acrylate (4) in Undistilled Diazomethane in Ether.—To undistilled diazomethane in ether,[19] decanted from KOH pellets, was added 1.0 g (6.3×10^{-3} mol) of methyl *cis*-β-(acetylthio)acrylate. The temperature was maintained at −5 to 0° for approximately 8 hr and then allowed to warm to room temperature. After standing for 3.5 days[10] the solvent ether[20] was removed under reduced pressure. The residue was chromatographed on silicic acid with chloroform yielding the following compounds: methyl *cis*-β-(methylmercapto)acrylate (5), bp 43–45° (0.5 mm) [lit.[9] bp 35–38° (0.25 mm)], 208.4 mg (21%) (*Anal.* Calcd for $C_5H_8O_2S$: C, 45.45; H, 6.06; S, 24.24. Found: C, 45.63; H, 6.17; S, 24.19.); 1-methyl-5-carbomethoxypyrazole (6), bp 49–51° (0.5 mm) [lit.[21] bp 103–104° (7 mm)], 185.6 mg (19%) (*Anal.* Calcd for $C_6H_8N_2O_2$: C, 51.35; H, 5.75; N, 19.99. Found: C, 50.87; H, 5.76; N, 19.54.); 1-methyl-3-carbomethoxypyrazole (8), bp 126–127° (1.4 mm), 34 mg (3.5%)[22] (*Anal.* Calcd for $C_6H_8N_2O_2$: C, 51.35; H, 5.75; N, 19.99. Found: C, 50.81; H, 5.71; N, 19.81.).

Similar yields were obtained for 5, 6, and 8 when methyl *trans*-β-acetylthioacrylate (4) was employed in the above reaction.

Reaction of Methyl *cis*-β-(Acetylthio)acrylate (4) in Distilled Diazomethane in Ether.—A procedure analogous to the above reaction was utilized.[20] The reaction mixture was analyzed gas chromatographically on silicone gum rubber (UC-W98)[23] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature of 125°, detector temperature of 210°, injection port temperature of 275°, inlet pressure of 35 psi, and carrier gas (He) flow rate of 50 ml/min gave a retention time of 0.9 min for 1-methyl-5-carbomethoxypyrazole (6), 1.12 min for methyl β-(methylmercapto)acrylate (5), 1.5 min for carbomethoxypyrazole (7), 2.3 min for 1-methyl-3-carbomethoxypyrazole (8), and 3.5 and 6.2 min for other uncharacterized compounds (Figure 1).

Reaction of Methyl *trans*-β-(Acetylthio)acrylate (4) in Distilled Diazomethane in Ether.—The same reaction and gas chromatography conditions were used as in the reaction with 4 above.[20] The retention times observed were 0.9 min for 6, 1.5 min for 7, 2.3 min for 8, and 3.5 min for an uncharacterized product (Figure 2).

Reaction of Methyl *cis*-β-(Acetylthio)acrylate (4) with Diazomethane at 85°.—Methyl *cis*-β-(acetylthio)acrylate (1 g, 6.3×10^{-3} mol) was heated to 85°. To this liquid was bubbled diazomethane entrained in N_2[24] for approximately 3 hr. The reaction mixture was further heated for 6 hr at 85°. The residual oil was chromatographed on silicic acid with chloroform yielding methyl *cis*-β-(methylmercapto)acrylate (5), 200 mg (20%), and 1-acetyl-3-carbomethoxypyrazole (10), mp 77–78° (ether–chloroform), 203 mg (21%) (*Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.65. Found: C, 49.70; H, 4.77; N, 16.92.).

3-Carbomethoxypyrazole (7) was prepared by a modification of the method of Reimlinger.[12] Methyl propiolate (8.4 g, 0.1 mol) was treated with dry ethereal diazomethane solution at −5 to 0°. The reaction product immediately precipitated from the ether solution. Concentration under reduced pressure followed by recrystallization from ether afforded 11.3 g (90%) 3-carbomethoxypyrazole, mp 136–138° [lit.[25] mp 138° (140°)].[12] *Anal.* Calcd for $C_5H_5N_2O_2$: C, 47.63; H, 4.80; N, 22.21. Found: C, 48.06; H, 4.82; N, 21.84.

1-Acetyl-3-carbomethoxypyrazole (10) from 3-Carbomethoxypyrazole (7) and Acetic Anhydride.—3-Carbomethoxypyrazole (7, 1 g, 7.2×10^{-3} mol) was refluxed with 2 ml of acetic anhydride for 48 hr. The excess acetic anhydride and acetic acid were removed under reduced pressure. The residue was recrystallized from methanol yielding 1.2 g (90%) of 1-acetyl-3-carbomethoxypyrazole (10).

1-Acetyl-3-carbomethoxypyrazole (10) from 3-Carbomethoxypyrazole (7) and Methyl *cis*- or *trans*-β-(Acetylthio)acrylate.—Methyl *cis*- or *trans*-β-(acetylthio)acrylate (0.48 g, 3×10^{-3} mol) and 3-carbomethoxypyrazole (0.41 g, 3×10^{-3} mol) were heated for 24 hr at 85°. The crude product was recrystallized from methanol affording 0.4 g (90%) of 1-acetyl-3-carbomethoxypyrazole (10).

1-Methyl-3(5)-carbomethoxypyrazole (6 and 8).—3-Carbomethoxypyrazole (1 g, 7.2×10^{-3} mol) was treated with excess distilled diazomethane in ether at −5 to 0° for 8 hr. The mixture was allowed to warm to room temperature and after standing for 3.5 days the solution was filtered and the solvent removed under reduced pressure. The residual oil was chromatographed on silicic acid with chloroform affording 328 mg (32%) of 1-methyl-5-carbomethoxypyrazole (6). A small amount of 1-methyl-3-carbomethoxypyrazole (8) was detected gas chromatographically.

In another reaction the mixture was analyzed by gas–liquid partition chromatography under the same conditions employed for analysis of the reactions involving *cis* and *trans* 4. The retention times observed were 0.9 min for 6, 1.5 min for 7, 2.3 min for 8, and 3.5 min for an uncharacterized product (Figure 3).

Registry No.—Diazomethane, 334-88-3; 4 (*cis*), 17830-98-7; 4 (*trans*), 17830-99-8; 6, 17827-60-0; 8, 17827-61-1; 10, 17827-62-2.

Acknowledgment.—We are grateful to the National Center for Radiological Health, National Institutes of Health, Rockville, Md., for support of this work through Grant No. RH-00529.

(17) The well-established tautomerization of pyrazoles is assumed during this discussion. See ref 2 and 15c.

(18) Nmr spectra were recorded utilizing a Varian A-60A spectrometer. Infrared spectra were recorded utilizing a Beckman IR-5a and IR-10. Gas chromatographs were taken using an F & M Model 402 gas chromatograph equipped with flame ionization detector and glass columns. Melting points are corrected and were taken with a Thomas–Hoover melting point apparatus. Analyses were run by Clark Microanalytical Laboratory, Urbana, Ill.

(19) H. A. Blatt, Ed., "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1955, p 165.

(20) A small amount (<1%) of white polymeric material separated from the ether solution during the reaction.

(21) V. F. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.*, **32**, 2888 (1962).

(22) Gas chromatographic analysis shows 1-methyl-3-carbomethoxypyrazole is formed in 7% yield.

(23) Hewlett-Packard, Moseley Division, Pasadena, Calif.

(24) F. W. Breitbeil, J. J. McDonnell, T. A. Marolewski, and D. T. Dennerlein, *Tetrahedron Lett.*, 4627 (1965).

(25) H. von Pechmann and E. Burkard, *Ber.*, **33**, 3594 (1900).

Synthesis of Sugar Analogs with Phosphorus as the Ring Heteroatom

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Reaction of 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose or 5-*O*-*p*-tolylsulfonyl-3-*O*-methyl-α-D-xylofuranose with triethyl phosphite yields the corresponding diethyl phosphonate. Reduction of the phosphonate with lithium aluminum hydride gives, presumably, 5-deoxy-5-phosphine-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose, which upon treatment with acid followed by air oxidation produces a mixture of stable crystalline 5-deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose and 5-deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose. The former is converted into the latter by oxidation with bromine.

As a part of a program to examine the behavior of carbon-bonded phosphorus in sugar derivatives,[1] our interest has been directed toward the preparation of sugar analogs wherein phosphorus replaces the oxygen heteroatom in the D-xylopyranose ring. D-Xylose has served previously as a satisfactory starting material for the introduction of sulfur into the pyranose ring.[2] Phosphorus is introduced at position C-5 through application of the Michaelis–Arbuzov reaction. The ester obtained is reduced with lithium aluminum hydride to the phosphine[3] which reacts intramolecularly with the aldehydic function to form a phosphorus hemiacetal[4] with phosphorus in the sugar ring.

The starting compound for the Michaelis–Arbuzov reaction requires a reactive leaving group, such as halogen or tosylate,[5] at C-5. The hydroxyl group at C-3 is blocked with a methyl group to prevent its participation in the displacement reaction. As can be anticipated, substantially higher yields of desired product are obtained when the C-3 hydroxyl is blocked with a methyl than with an acetyl group.

Methylation of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose with methyl iodide and silver oxide in *N*,*N*-dimethylformamide affords 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (I). This compound is converted into 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (II) by nucleophilic displacement of the tosyloxy group using tetraethylammonium bromide in N,N-dimethylformamide. 5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (III) is obtained in nearly quantitative yield by treating II with a large excess of triethyl phosphite. The same phosphonate ester is obtained in lower yield when the corresponding tolylsulfonyl ester, I, is treated with an excess of triethyl phosphite. Hydrolysis of the phosphonate ester with aqueous acetic acid yields 5-deoxy-5-(diethyl phosphonate)-3-*O*-methyl-D-xylofuranose (VIII), which is characterized as the osazone.

Reduction of III with lithium aluminum hydride in ether furnishes, presumably, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-phosphine-α-D-xylofuranose (IV), which rapidly produces acidic materials during isolation, but is relatively stable in ether after washing with essentially oxygen-free water. Only one component is initially present in the ether solution as shown by thin layer chromatography.

On acid treatment, the furanose ring in IV shifts to a cyclic six-membered ring containing a secondary phosphine group. This compound, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-phosphine-D-xylopyranose (V), reacts readily with oxygen. It is converted immediately by air oxidation into the stable crystalline secondary phosphine oxide, IV, and phosphinic acid, VII (Scheme I).

Secondary phosphine oxides and phosphinic acids are readily obtainable by air oxidation of secondary phosphines.[6,7] Rauhut and Currier,[6] on oxidizing secondary phosphines with air, produced phosphine oxides, but found no phosphinic acids among the products. Other workers,[8] on the other hand, have oxidized certain secondary phosphines in air directly to phosphinic acids without obtaining secondary phosphine oxides.

5-Deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose (VI) and 5-deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose (VII) are obtained in an over-all yield of 15 and 3.5%, respectively, from the phosphonate ester. The phosphinic acid is obtained also from the oxide by bromine oxidation[9] at 25°.

The ^{1}H nmr spectra of compound VI in deuterium oxide is shown in Figure 1. The spectrum determined at 40° shows a triplet centered at τ 5.40, which represents only half of the H-1 proton resonance. The signal of another half-proton is only partially observable because of interference by the HOD signals. The latter signal is shifted upfield[10] in the spectrum measured at 80° and the triplets appeared at τ 5.15 and 5.30.

The splitting pattern of the signals suggests that compound VI has phosphorus in the ring. H-1 is split by phosphorus into two peaks, each of which is further split into two peaks by the phosphorus-bonded deuterium. Each of these four peaks are again split by H-2 to give eight peaks. Only six (two triplets) of the theoretical eight peaks (two quartets) are observed. The wide coupling (8.5 Hz) is assigned to the phosphorus and H-1 interaction on the basis that it was not affected when decoupling was attempted at −220 to −440 Hz and at +47 to +160 Hz. Because of complex second-order effects from long-range coupling,

(1) For example, see R. L. Whistler, C. C. Wang, and S. Inokawa, *J. Org. Chem.*, **33**, 2495 (1968).

(2) (a) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Amer. Chem. Soc.*, **84**, 122 (1962); (b) T. J. Adley and L. N. Owen, *Proc. Chem. Soc.*, 418 (1961); (c) J. C. P. Schwarz and K. C. Yule, *ibid.*, 417 (1961); (d) J. K. N. Jones and W. A. Szarek, *Can. J. Chem.*, **41**, 636 (1963).

(3) F. Pass and H. Schindbauer, *Monatsh. Chem.*, **90**, 148 (1959).

(4) (a) H. Hellman and O. Schumacher, *Angew. Chem.*, **72**, 211 (1960); (b) S. A. Buckler and M. Epstein, *J. Org. Chem.*, **27**, 1090 (1962); (c) S. A. Buckler and M. Epstein, *Tetrahedron*, **18**, 1231 (1962).

(5) L. Horner, H. Hoffmann, and P. Beck, *Ber.*, **91**, 1583 (1958).

(6) M. M. Rauhut and H. A. Currier, *J. Org. Chem.*, **26**, 4626 (1961).

(7) K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960).

(8) (a) C. Dorken, *Ber.*, **21**, 1505 (1888). (b) A. W. Hoffmann, *ibid.*, **4**, 605 (1871); **6**, 292 (1873). (c) S. A. Buckler and V. P. Wystrach, *J. Amer. Chem. Soc.*, **83**, 168 (1961).

(9) P. Nylen, *Z. Anorg. Allg. Chem.*, **235**, 161 (1938).

(10) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).

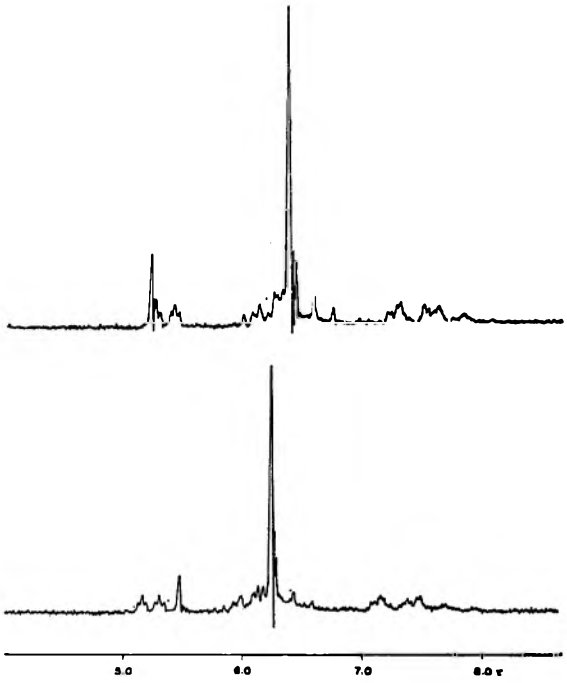


Figure 1.—^{1}H nmr spectra of 5-deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose in deuterium oxide at 40° (upper) and 80° (lower).

the line-spacing values for $J_{1,2}$ (2.5 Hz) and $J_{1,D}$ (2.0 Hz) are only rough estimates. Two one-proton multiplets at τ 7.24 and 7.54 might be assigned to the 5 hydrogens.

The signals for the phosphorus-bonded hydrogen[11] appear when the spectrum is determined in water. They are observed as two half-proton multiplets centered at τ −1.42 and 6.88, which shows a coupling constant of 498 Hz for the interaction between phosphorus and its proton.[12]

Although the two half-proton triplets at τ 5.15 and 5.30 and the absence of mutarotation indicate that compound VI constitutes only one anomer both in the crystalline form and in solution, it is not possible to assign the configuration of the anomeric carbon. On the assumption that the ring adopts a *C1* conformation, the sugar would have, most likely, an α-D configuration, since the coupling constant $J_{1,2}$ is relatively small. On the other hand, if a *1C* conformation should predominate, the small coupling constant could account for both α-D and β-D configurations, since H-2 bisects the hydrogen and hydroxyl on C-1 producing about the same dihedral angle for both α-D and β-D forms.

The infrared spectra of compound VI in a Nujol mull shows a P–H stretching vibration[13] at 2430 cm^{-1} which disappears on deuteration. A strong absorption at 1237 cm^{-1} is attributed to the phosphoryl group.

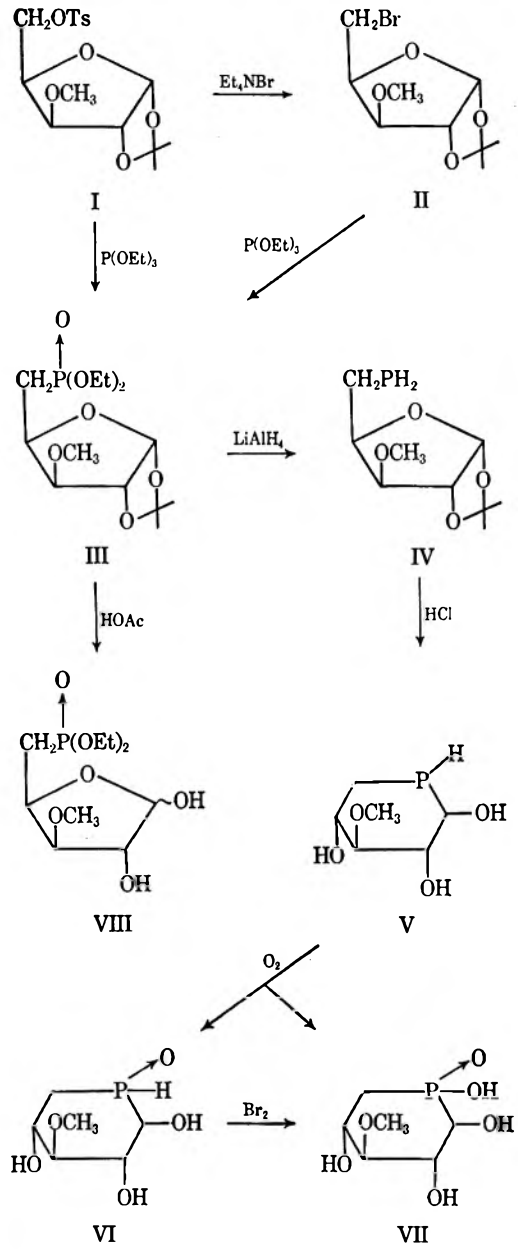
The secondary phosphine oxide structure of VI is supported also by its neutrality and relative stability toward air oxidation.[8] On exposing to a dry atmosphere at 25° for several weeks, compound VI does not show a change in melting point.

(11) D. D. Magnelli, G. Tesi, T. U. Lowe, Jr., and W. E. McQuistion, *Inorg. Chem.*, **5**, 457 (1966).

(12) J. R. Dyer, Applications of Absorption Spectroscopy of Organic Compounds, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 96.

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 320.

SCHEME I



Although the nmr spectral results obtained with the phosphinic acid, VII, are difficult to interpret because of their complexity, a spectrum in methyl sulfoxide-d_6 shows that, while other signals remain at about the same regions as those of VI, the signals of both C-1 and C-5 protons become evident because they occur farther upfield. C-1 proton signals appear at τ 7.07 and 7.20 (5.70 and 5.85 for VI) and C-5 protons appear at 7.85–8.14 and 8.17–8.50 (7.55–7.76 and 7.80–8.10 for VI). These observations are consistent with the structures assigned since the protons on C-1 and C-5 would be those most affected by the substitution of P–OH (VII) for P–H (VI).

The infrared spectra of this acid shows a broad shallow absorption at 2260 cm^{-1} which is clearly to be associated with the phosphinic acid group as it disappears on salt formation.[14] The phosphoryl group was observed at 1224 cm^{-1}. Such characteristic phosphoryl group and phosphinic acid group vibration

(14) Reference 13, p 319.

positions indicate an enhanced hydrogen-bonding effect.[14]

When compounds VI and VII are subjected to sodium metaperiodate oxidation at room temperature, the former consumes 3 mol of oxidant with the liberation of 0.79 mol of formic acid, and the latter consumes 2 mol of oxidant with the production of 0.77 mol of formic acid. The yield of formic acid agrees reasonably with the theoretical value of 1 mol. These results indicate that α-hydroxy phosphinic acids are susceptible to periodate cleavage. Since VI can be readily converted into VII by oxidation, the extra mole of periodate consumed by VI can be accounted for by the oxidation of the P–H bond. These results greatly substantiate the assigned structures.

The titration curve and neutralization equivalent of VII are consistent with a monobasic acid. Its pK_a is calculated from apparent dissociation constants, uncorrected for activities, to be 1.61. This indicates that it is a stronger acid than orthophosphoric acid which has a pK_1 of 2.1.[15] The increase in acidity can be rationalized in terms of internal hydrogen bonding of the phosphinic acid group with an adjacent hydroxyl group in a manner analogous to the sugar phosphates.[16]

Although a phosphorus atom cannot be proven to be in the ring in compound V, the isolation and characterization of VI and VII indicate that V has the structure shown.

Experimental Section

Melting points were determined by a Fisher-Johns apparatus. Infrared spectra were measured on a Perkin-Elmer 521 grating spectrophotometer. Nuclear magnetic resonance spectra were recorded at 40° unless otherwise stated on a Varian A-60A spectrometer, with tetramethylsilane as an external or internal reference; the samples were saturated solutions. The first-order coupling constants recorded are the measured peak spacings and are considered accurate to ±0.5 Hz. Deuteration of the samples was performed by double evaporation in deuterium oxide. Evaporation was performed in a water bath at 40° unless otherwise stated. Thin layer chromatograms were run on silica gel in (a) ethyl acetate–Skellysolve B (1:1 v/v), (b) isopropyl alcohol–ethyl acetate–water (7:1:2 v/v), and (c) ethanol–ammonium hydroxide–water (5:3:1 v/v). Compounds on the chromatograms were detected by spraying with 5% sulfuric acid in ethanol and heating.

1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (I).—1,2-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose[17] (2.0 g) was dissolved in 20 ml of dry *N*,*N*-dimethylformamide[18] and to this was added 3.0 g of silver oxide and 2 ml of iodomethane. The mixture was shaken in the dark at 25° for 20 hr. It was then filtered and the residue extracted several times with chloroform. The combined chloroform extracts were filtered to remove a white precipitate and were concentrated to a thick syrup which crystallized readily from ethanol–Skellysolve B. The yield was 95%, mp 113–114°, $[\alpha]^{25}D$ −27.0° (*c* 1.87, chloroform). The following constants for this compound, prepared by another procedure,[19] have been recorded: mp 114°, $[\alpha]D$ −27.2° (*c* 2.173, chloroform).

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (II).—1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (5.0 g) was dissolved in 100 ml of *N*,*N*-dimethylformamide and to this was added 10 g of tetraethylammonium bromide. The solution was heated at 100° in an oil bath for 15 hr. Water (200 ml) was added after cooling and it was extracted four times with 60-ml portions of chloroform. The chloroform extracts were combined and washed with water, dried over sodium sulfate, filtered and the last trace of *N*,*N*-dimethylformamide was removed by evaporation at 90° (6 mm). The remaining residue was then distilled at 100° (bath temperature) (0.2 mm) to give a pure product, yield 3.5 g (90%), $[\alpha]^{25}D$ −94.8° (*c* 1.80, ethanol).

Anal. Calcd for $C_9H_{15}O_4Br$: C, 40.48; H, 5.66; Br, 29.92. Found: C, 40.68; H, 5.80; Br, 29.87.

5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (III).—A mixture of 4 g of 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose and 12 ml of freshly distilled triethyl phosphite was refluxed gently under nitrogen for 7 hr at 165°. Excess phosphite was distilled at 70° (0.3 mm) and the desired phosphonate ester was obtained as a colorless oil in nearly quantitative yield which was sufficiently pure for subsequent conversion. An analytical sample was obtained by distillation at 140° (5×10^{-3} mm): $[\alpha]^{25}D$ −36.3° (*c* 1.63, methanol).

Anal. Calcd for $C_{13}H_{25}O_7P$: C, 48.09; H, 7.72; P, 9.56. Found: C, 47.64; H, 7.71; P, 9.08.

The phosphonate ester was also obtained in 30% yield by substituting 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose for the bromoxylose derivative above. ^1H nmr data (chloroform-*d*) were as follows: τ 4.16 (one-proton doublet, $J_{1,2}$ = 3.5 Hz, H-1), 5.41 [one-proton doublet, partially overlaps with $P(OCH_2-)$ signals, H-3], 5.86 [four-proton multiplet, J_{P,H^α} = 7.5 Hz, J_{H^α,H^β} = 7.0 Hz, $P(OCH_2-)$], 6.56 (three-proton singlet, OCH_3), 7.61, 7.93 (two-proton multiplets, $J_{5,P}$ = 18 Hz, H-5,5′), 8.53, 8.68 (three-proton singlets, CMe_2), 8.55, 8.68, 8.79 [six-proton triplets, $J_{P,4}$ = 0 Hz, $P(OCH_3)_2$].

5-Deoxy-5-(diethyl phosphonate)-3-*O*-methyl-D-xylofuranose (VIII).—5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-D-xylofuranose (1 g) was dissolved in 50 ml of 20% acetic acid. After heating for 6 hr at 80°, the solvent was evaporated to a syrupy residue. Examination by thin layer chromatography showed a single component, R_f 0.1 in solvent a. The product was dissolved in 20 ml of 50% ethanol and, by addition of 2 g of phenylhydrazine hydrochloride and 3 g of sodium acetate, was converted into the yellow osazone which was recrystallized from methanol: mp 86–88°.

Anal. Calcd for $C_{22}H_{31}O_5N_4P$: N, 12.11. Found: N, 11.94.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-phosphino-α-D-xylofuranose (IV).—5-Deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (1.0 g) was dissolved in 10 ml of ether and the solution was cooled to 0° in an ice bath. A suspension of 0.4 g of lithium aluminum hydride in 10 ml of ether was added and the reaction mixture was stirred at 0° for 15 min in a nitrogen atmosphere. The ice bath was removed and reaction was continued for an additional 15 min. At this point, tlc revealed one product at an approximate R_f of 0.82 in solvent a but no starting material was detected. Excess lithium aluminum hydride was cautiously destroyed with dilute sulfuric acid while maintaining the reaction mixture at 0°. The ether layer was washed with nitrogen-saturated water (10 ml) three times and then dried over anhydrous sodium sulfate. It was used immediately for the following conversion.

5-Deoxy-3-*O*-methyl-5-phosphino-D-xylopyranose (V).—The ether solution obtained above was filtered in a nitrogen atmosphere into a flask equipped with a gas inlet tube which extended to near the bottom of the flask and 25 ml of 2.4 *N* hydrochloric acid, previously saturated with nitrogen, was added. The flask was kept at 40° in a water bath for 3–7 hr, while a stream of nitrogen was passed through the solution. The water level in the bath was maintained at about or below the same height as that inside the reaction flask. Compound IV gradually went into the aqueous layer as ether was carried away by the nitrogen stream. At the end of the reaction tlc showed one spot at the base line in solvent a but with an R_f of 0.8 in solvent b. This compound could not be isolated without contaminating oxidized products. Since the latter compounds were more stable and easier to handle, procedures were developed to isolate the oxidized products as described below. No special effort was made to characterize the unoxidized product.

5-Deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose (VI). Method A.—The solution obtained above was cooled, diluted with 200 ml of water, and neutralized by passing through a column containing 100 ml of Amberlite IR-45. The column was then washed with 800 ml of water and the effluent was evaporated

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(18) M. L. Wolfrom, Y-L. Hung, P. Chakravarty, G. U. Yuen, and D. Horton, *J. Org. Chem.*, **31**, 2227 (1966).

(19) G. T. Robertson and D. Gall, *J. Chem. Soc.*, 1600 (1937).

to dryness under reduced pressure in a rotatory evaporator at 40–50°. The yellow residue was taken up in 20 ml of methanol. Examination by thin layer chromatography in solvent b showed the presence of one major spot at R_f 0.8, one minor spot at R_f 0.6, corresponding to the phosphine oxide VI, a very light streak centered around R_f 0.2, corresponding to the phosphinic acid VII, and a trace spot at the base line. The methanolic solution was filtered and made cloudy by adding ether. Traces of peroxides contained in the ether solution were sufficient to catalyze the oxidation. It was then kept at −5° for 2 days. Crystalline material was collected and washed with cold methanol. A second crop was obtained from the mother liquor by similar treatment. The products were combined (0.1 g) and recrystallized from hot methanol: mp 208–210°, $[\alpha]^{25}D$ +35.0° (*c* 1.10, water, no mutarotation in 48 hr).

Anal. Calcd for $C_6H_{13}O_5P$: C, 36.73; H, 6.68; P, 15.79. Found: C, 36.50; H, 6.71; P, 15.50.

Method B.—The solution was cooled, diluted, neutralized, and washed in the same way as described above. The effluent was evaporated in a glass circulating evaporator[20] under reduced pressure (6 mm) to about 50 ml. The solution was removed and further concentrated under reduced pressure in a rotatory evaporator at 40° to produce a brown residue. The residue was dissolved in 10 ml of methanol and the compound was crystallized at 5°, yield 0.095 g. Melting point and infrared and nmr spectra proved that compounds obtained by methods A and B were identical.

Method B was convenient for larger scale preparations in which solvent could be removed readily. VI had an approximate R_f value of 0.6 in solvent b and 0.73 in c on thin layer chromatograms. It had an approximate R_{xyl} value of 0.90 by descending chromatography on Whatman No. 1 in pyridine–ethyl acetate–acetic acid–water (5:5:1:3 v/v);[21] ammoniacal silver nitrate was used as the indicator.[22] On periodate oxidation[23] it consumed 3.0 mol of periodate and liberated 0.79 mol of formic acid/mol of compound in 12 hr.

^{1}H nmr data of VI in solvent a, deuterium oxide at 80°, follow, τ 5.15, 5.30 (half-proton triplets, $J_{1,2}$ = 2.5 Hz, $J_{1,D}$ = 2.0 Hz, H-1), 6.72 (three-proton singlet, OCH_3), 5.84–6.66 (three-proton multiplet, H-2, -3, -4), 7.24, 7.54 (one-proton multiplets, H-5, -5′); in b, water, −1.42, 6.88 (half-proton multiplets, P–H, $J_{P,H}$ = 498 Hz); in c, methyl sulfoxide, −0.60 (half-proton multiplet, P–H); in d, methyl sulfoxide-d_6, 5.09 (three-proton broad singlet, disappears on deuteration and shifts with change in concentration, OH-1, -2, -4), 5.70, 5.85 (half-proton singlets, H-1), 6.51 (three-proton singlet, OCH_3), 7.55–7.76, 7.80–8.10 (one-proton multiplets, H-5, -5′).

5-Deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose (VII).—The mother liquor obtained above from either method A or method B could be used. As a typical example, the mother liquor obtained from method B, [starting from 5 g of 5-deoxy-5-(diethyl phosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose] was evaporated to a syrup which was taken up in 20 ml of water and passed through a column containing 20 ml of Amberlite IR-45 ion-exchange resin. The column was washed successively with 50 ml of water, 25 ml of 5% NH_3 and finally water to neutrality. The effluent was evaporated to a brown residue. Water (10 ml) and cyclohexylamine (1 ml) was added. A white amorphous solid resulted upon evaporation. The solid was dissolved in methanol and precipitated by adding acetone and cooling. The fluffy precipitate was centrifuged, washed with methanol–acetone, redissolved in water, and passed through Amberlite IR-120 (5 ml). The column was washed with water to neutrality. The effluent was evaporated to a syrup which crystallized upon scratching. It was recrystallized from methanol–ether: yield 0.12 g, mp 192° dec, $[\alpha]^{28}D$ −25.8° (c 1.02, water, no mutarotation in 48 hr).

Anal. Calcd for $C_6H_{13}O_6P$: C, 33.97; H, 6.18; P, 14.60; neut equiv, 212. Found: C, 34.35; H, 6.33; P, 14.17; neut equiv, 210.

The same phosphinic acid was obtained also from 5-deoxy-3-*O*-methyl-5-(phosphine oxide)-D-xylopyranose (VI) by bromine oxidation. VI (100 mg) was dissolved in 10 ml of water, to which was added 3 drops of bromine and 100 mg of barium carbonate. The mixture was shaken until a clear yellow solution resulted and was stored at 25° in the dark for 2–5 days. Excess bromine was removed by aeration. The solution was neutralized with silver carbonate, filtered, and passed through a column containing 10 ml of Amberlite IR-120. The effluent was evaporated to a colorless syrup which crystallized upon scratching. The compound was recrystallized from methanol–ether: yield 93 mg (90%). It had the same decomposition point and infrared spectrum as the compounds indicated above.

On periodate oxidation[23] the compound consumed 2.0 mol of periodate and produced 0.77 mol of formic acid/mol of sugar in 11.5 hr.

^{1}H nmr data of VII in solvent a, deuterium oxide, follows, τ 5.50–7.00 (seven-proton multiplets, H-1, -2, -3, -4, $-OCH_3$), 7.18–8.30 (two-proton multiplets, H-5, -5′); b, methyl sulfoxide-d_6, 3.49 (four-proton singlet, disappears on deuteration and shifts with change in concentration, OH-1, -2, -4, P–OH). 6.48 (three-proton singlet, OCH_3), 7.07, 7.20 (broad half-proton singlets, H-1), 7.85–8.14, 8.17–8.50 (one-proton multiplets, H-5, -5′).

Acid Strength of 5-Deoxy-3-*O*-methyl-5-(phosphinic acid)-D-xylopyranose.—Titration was made at 25°. Several points near the middle of the curve were used and the variation of the pK_a values gave an estimate of their accuracy. The over-all error was perhaps greater than the differences indicated. Results are presented in Table I.

TABLE I

Molality × 10^{-3}	$[N^+]$ × 10^{-3}	pH	pK_a	Average pK_a
1.47	0.19	2.30	1.63	
0.84	0.40	2.50	1.57	1.61
0.55	0.47	2.70	1.61	
0.27	0.54	3.00	1.63	

Registry No.—I, 17954-92-6; II, 17954-93-7; III 17968-56-8; VI, 17954-42-6; VII, 17953-91-2; VIII 17953-63-8.

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Rotatory Dispersion of Sugar Derivatives. III.[1] Aldose Benzylphenylhydrazones

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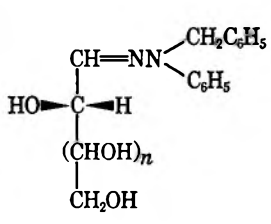
Optical rotatory dispersion and nmr spectroscopy have been used to examine the structure and conformation of two pentose and four hexose benzylphenylhydrazones. The compounds exist in solution as imines rather than *N*-glycosides. Compounds with *R* configuration at C-2 are dextrorotatory at long wavelength and have positive Cotton effects at about 300 nm. Acetylation removes intramolecular hydrogen bonding and shifts the conformational equilibria toward conformations of opposite rotatory sign. Acetates with *R* configuration at C-2 are levorotatory at long wavelength, and all but penta-*O*-acetyl-D-mannose benzylphenylhydrazone have strong negative Cotton effects at 300 nm. The same relationships apply to three other aldose arylhydrazones which have been shown previously to have the imine rather than the *N*-glycoside structure.

Despite availability of a large number of optically active phenylhydrazones from sugars, no systematic work has been done on the relationship of their optical rotatory dispersion to structure and conformation. The detailed structure of sugar phenylhydrazones involves *cis–trans* isomerism about the imine bond in acyclic cases and α and β stereochemistry at the anomeric center as well as pyranose *vs.* furanose ring size in cyclic cases. Observed mutarotation of sugar hydrazones indicates existence of more than one isomer in solution. Some aldose phenylhydrazone mutarotation curves indicate the presence of at least three isomers in the approach to equilibrium.[2] Chemical methods[3,4] have been used to distinguish cyclic from acyclic forms in favorable cases. Nmr spectroscopy has been used to examine solution structure of a few aldose phenylhydrazones[5] and X-ray crystallographic structures or partial structures are available for several aldose *p*-bromophenylhydrazones.[6] Crystalline arylhydrazones with acyclic structure are known for mannose,[7] galactose,[3,5] rhamnose,[4] and ribose.[8] Arabinose *p*-bromophenylhydrazone is cyclic.[9] Both cyclic and acyclic forms of glucose phenylhydrazone are known.[5,10] Information is available on the equilibrium concentrations of cyclic and acyclic forms in solution in only a few cases.[4,5] Little is known of the structure of the other common aldose arylhydrazones.



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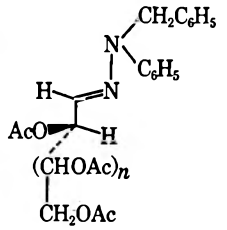

2

Hudson proposed an empirical correlation between absolute stereochemistry and long wavelength optical rotation for sugar benzylphenylhydrazones, based on the observation that 11 sugar benzylphenylhydrazones are dextrorotatory at the sodium D line if C-2 has *R* chirality (1), or levorotatory if C-2 has *S* chirality.[11] The six sugar benzylphenylhydrazones prepared subsequently have been found to have long wavelength rotations of the expected sign.[12] The validity of Hudson's correlation suggests that aldose benzylphenylhydrazones do not exhibit the isomeric complexity of aldose phenylhydrazones. Consequently the series of benzylphenylhydrazones is a logical starting point for investigation of the relationship between stereochemistry, conformation, and rotatory properties of aldose hydrazones by ORD and nmr.

The optical rotatory dispersions of sugar benzylphenylhydrazones in methanol show plain curves in the region 350–600 nm, conforming throughout that region to the Hudson correlation (Table 1). The shape of the curve is controlled by an electronic transition in the vicinity of 300 nm (Figure 1). The Cotton effect of this transition has the same sign as the long wavelength rotation. The rotatory dispersions were generally not measured so far as the first extremum because of the unfavorable rotation to absorption ratio. Qualitative differences appear when the dispersions are measured in pyridine. The magnitude of rotation was found in general to be appreciably greater in pyridine than in methanol. Acetylation in pyridine inverted the sign relationship and further enhanced the magnitude of the rotation. The long wavelength rotation of mannose benzylphenylhydrazone changes sign on acetylation, but the shift is not so marked as for the other examples. The rotatory dispersions of acetylated fucose, galactose, and arabinose benzylphenylhydrazones in methanol are qualitatively similar to dispersions measured in pyridine. Several aldose arylhydrazones of known acyclic structure are initially dextrorotatory at long wavelength and have positive first Cotton effects if C-2 has *R* chirality (Table II). Their acetates are levorotatory at the sodium D line.

There is no obvious pattern in the long wavelength optical rotation of most sugar hydrazones for which data are available. Only benzylphenylhydrazones

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TABLE I

ROTATORY DISPERSIONS OF ALDOSE BENZYLPHENYLHYDRAZONES

Benzylphenylhydrazone of	Solvent[a]	Molar rotation at wavelength 589 nm	550 nm	500 nm	450 nm	400 nm	350 nm
D-Ribose	M	−93.5	−115	−158	−233	−398	
	P	−176	−217	−300	−451	−793	
D-Arabinose	M	37.9	47.4	61.7	89.0	149	
	P	44.7	60.3	80.3	129	246	
D-Glucose	M	−61.8	−73.5	−103	−157	−276	−650
	P	−180	−215	−295	−430	−730	−1730
D-Mannose	M	70.5	87.4	123	186	314	
	P	152	188	264	404	692	
L-Fucose	M	43.7	53.4	72.0	104	182	
	P	37.5	48.0	64.0	103	202	
Lactose	M	−87.2	−106	−145	−208	−336	−723
	P	−184	−215	−271	−375	−577	
Tetra-*O*-acetyl-D-ribose	P	550	653	845	1060	1640	2880
Tetra-*O*-acetyl-D-arabinose	P	−362	−444	−581	−821	−1300	−2710
Penta-*O*-acetyl-D-glucose	P	522	618	800	1085	1580	2760
Penta-*O*-acetyl-D-mannose	P	−34.3	−38.4	−44.0	−48.1[b]	−27.4	196
Tetra-*O*-acetyl-L-fucose	P	−361	−438	−577	−801	−1260	
	M	−353	−423	−555	−783	−1230	−2730
Penta-*O*-acetyl-D-galactose	P	511	613	812	1140	1750	3580
	M	450	545	708	980	1510	3050

[a] Solvent: P = pyridine, M = methanol. [b] Trough, $[\phi]^{22}_{467}$ −48.5°.

TABLE II

ROTATORY DISPERSIONS OF SOME ALDOSE HYDRAZONES IN PYRIDINE

Compound	Molar rotation at wavelength 589 nm	550 nm	500 nm	450 nm	400 nm	350 nm
D-Galactose methylphenylhydrazone	−10.1	−10.2	−15.9	−26.0	−54.0	−173
Tetra-*O*-acetyl-D-galactose methylphenylhydrazone	148	181	222	260	288[a]	97
D-Mannose *p*-bromophenylhydrazone	102		204	310	546	1790
D-Ribose *p*-bromophenylhydrazone	−71.3	−94.7	−138	−216	−429	−1470

[a] Peak, $[\phi]^{22}_{390}$ 290°.

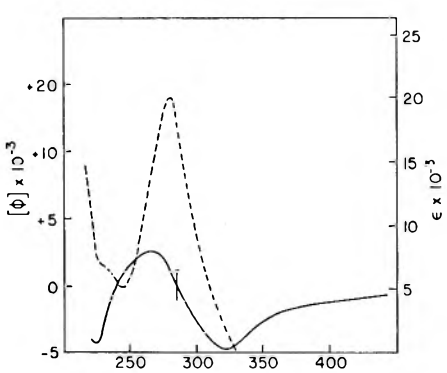

Figure 1.—Uv (– – –) and ORD (——) spectra of tetra-*O*-acetyl-L-fucose benzylphenylhydrazone in methanol.

and substituted benzylphenylhydrazones show a readily discernible relationship.[13] This indicates that for benzylphenylhydrazones, unlike most aldose hydrazones, the acyclic isomer predominates independent of stereochemistry. Cyclic and acyclic acetylated aldose phenylhydrazones are readily distinguished by nmr. In the acyclic compounds the C-1 aldimine proton resonance occurs in the region τ 0.5–3.8 while in the cyclic isomer the C-1 anomeric proton resonance occurs at τ 5.6.[5] The shielding resulting from the conversion of the imine into a glycosylamine is also detectable to a lesser extent in the shift of resonances of methine hydrogens at C-2 from τ 4.4 to *ca.* 5.0 and at C-3 from τ 4.5 to *ca.* 5.0. The chemical shift of the terminal methylene hydrogen is unaffected by cyclization. The lack of methine proton resonances above τ 5.0 and the presence of the H-1 doublet at τ 3.5 in the nmr spectra of acetylated aldose benzylphenylhydrazones (Table III) is consistent with acyclic structure 2. The acyclic structure of penta-*O*-acetyl-D-galactose benzylphenylhydrazone has already been established by unambiguous synthesis from *aldehydo*-D-galactose pentaacetate.[3]

TABLE III

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF ACETYLATED ALDOSE BENZYLPHENYLHYDRAZONES IN CHLOROFORM

Derivative	H-1, τ	H-2, τ	H-3, τ	$J_{1,2}$, Hz	$J_{2,3}$, Hz
Ribose	3.51	4.37	4.57	5.5	5
Arabinose	3.59	4.34	*Ca.* 4.6	4.8	5
Galactose	3.58	4.36	*Ca.* 4.6	4.8	1
Fucose	3.57	4.34	4.64	4.5	2
Mannose	3.47[a]	*Ca.* 4.5	*Ca.* 4.5	*a*	
Glucose	3.49	*Ca.* 4.4	*Ca.* 4.6	4.5	

[a] Unresolved, broak peak.

Structures of *cis* and *trans* isomers about the imine bond of hydrazones can be assigned on the basis of the deshielding of the aldimine hydrogen by about 30–40 Hz when the β nitrogen is *cis* to H-1.[14] However, the chemical shift of the aldimine hydrogen is strongly dependent on the nature of substituents on the β nitrogen and the solvent. A range of 3.3 ppm has been observed for monosubstituted arylhydrazones. To

(13) E. Votoček, F. Valentin, and O. Leminger, *Collect. Czech. Chem. Commun.*, **3**, 250 (1931); E. Votoček and Z. Allan, *ibid.*, **8**, 313 (1936); E. Votoček and O. Wichterle, *ibid.*, **8**, 322 (1936).

(14) G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Amer. Chem. Soc.*, **86**, 3351 (1964).

make assignment of *cis* and *trans* structures on the basis of chemical-shift difference it is necessary to have both isomers. *cis* or *trans* structures cannot be assigned to the aldose benzylphenylhydrazones on this basis because only one isomer is obtained from each aldose. Since no mutarotation was detected by ORD or by nmr, the set of isomers obtained are probably the sterically more stable isomers with H-1 and β-N *cis* (2). The conformation about the bond between C-1 and C-2 is unknown; however, the coupling constant, $J_{1,2} = 5$ Hz, is comparable with the coupling constant between H-1 and H-2 of acetaldehyde phenylhydrazone[15] consistent with a time average of appreciable contribution from several conformations.

As found for other acyclic imine derivatives of sugars,[1,5,16] deshielding of the proton resonance decreases systematically with the number of bonds intervening between the proton and imine group, reaching a limiting value of *ca.* τ 5.0 for methine hydrogen. Consequently nonfirst-order effects are more marked in hexoses than in pentoses. The terminal methylene signal for the ribose, arabinose, mannose, and glucose derivatives occurs at *ca.* τ 5.9 and is a typical ABX pattern with $J_{AB} = 12$ Hz and $J_{AB}/\delta_{AB} = 1$; for the galactose derivative $J_{AB}/\delta_{AB} = 2$. Chemical shifts between H-2 and H-3 for the mannose and glucose derivatives are insufficient at 60 MHz to permit determination of $J_{2,3}$. Virtual coupling of the aldimine hydrogen of the mannose derivative to three other hydrogens is responsible for filling in of the expected doublet. Each acetate methyl resonance of proper area could be distinguished at *ca.* τ 8.0 for many of the compounds. This is further evidence of the presence of only one geometrical isomer in the equilibrated chloroform solution. The wide variation in $J_{2,3}$ and $J_{3,4}$ indicates considerable conformational homogeneity for at least some stereochemistries of the polyacetoxyalkyl chain.

The unacetylated aldose benzylphenylhydrazones are also acyclic since acetylation of equilibrated pyridine solutions at room temperature gives acyclic products. The fact that configuration at C-2 has the dominant effect on the optical rotation of both acetylated and unacetylated aldose benzylphenylhydrazones means that it is the closest asymmetric center to the chromophore. This excludes a cyclic structure in which the new center of asymmetry at C-1, being closer to the chromophore, would have the dominant effect on the optical rotation. The ORD fits a Drude equation between 350 and 600 nm with $\lambda_0 = 300 \pm 20$ nm for both acetylated and unacetylated aldose benzylphenylhydrazones with the exception of penta-*O*-acetyl-D-mannose benzylphenylhydrazone. An optically active electronic transition at about 300 mμ is consistent with an acyclic hydrazone structure. The absorption band for a pyranosylhydrazone would be expected at shorter wavelength. Neither the rotation data nor the acetylation evidence precludes the presence of some cyclic isomer in equilibrium with acyclic hydrazone.

Penta-*O*-acetyl-D-mannose benzylphenylhydrazone has a rotatory dispersion which appears to be a composite of two close-lying Cotton effects of opposite sign. A very shallow trough occurs displaced to 450 nm and a maximum, not observable in pyridine, occurs below 335 nm. The dominance of negative rotation at wavelengths above 450 nm suggests that a positive Cotton effect is superimposed on a stronger negative one centered at somewhat shorter wavelength. Presumably both Cotton effects contribute to the long wavelength rotation of the other benzylphenylhydrazones examined as well, but the shorter wavelength effect is the dominant of the two. Failure to take the weaker effect into account in a one term Drude equation may explain the range in values found for λ_0 (300 ± 20 nm).

(15) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 2327 (1963).

(16) H. S. El Khadem, D. Horton, and T. F. Page, Jr., *J. Org. Chem.*, **33**, 734 (1968).

Experimental Section

Rotations were determined on a Cary Model 60 spectropolarimeter at temperatures between 21 and 24° using a 10-cm path length above 400 nm and 10- and 1-cm path lengths below 400 nm. Concentrations between 0.1 and 0.2% were used for all measurements above 350 nm. Solutions of benzylphenylhydrazones were allowed to stand 24 hr before rotations were measured. No mutarotation was observed after this period. Nmr spectra of acetylated benzylphenylhydrazones were measured on a Varian Model A-60 spectrometer at 10% concentration in chloroform with tetramethylsilane as internal standard.

Acetylation of Aldose Benzylphenylhydrazones.—Aldose benzylphenylhydrazones were acetylated at room temperature by adding 1 ml of acetic anhydride to 50 ml of 0.1% aldose benzylphenylhydrazone in pyridine. Progress of acetylation was followed polarimetrically. The rotation became constant after 12 hr. Rotatory dispersions were measured 24 hr after addition of acetic anhydride. The ORD remained constant over a period of at least 48 hr. Acetylated aldose benzylphenylhydrazones were recovered by removal of pyridine under vacuum and freed of traces of pyridine by repeated solution in chloroform and removal of chloroform under vacuum. Penta-*O*-acetyl-D-glucose benzylphenylhydrazone, $[\alpha]^{24}D$ 92° (*c* 0.2, pyridine), and penta-*O*-acetyl-D-galactose benzylphenylhydrazone, mp 128–130°, $[\alpha]^{24}D$ 79° (methanol), $[\alpha]^{23}D$ 90° (pyridine), had properties similar to those previously reported.[17]

Tetra-*O*-actyl-L-fucose benzylphenylhydrazone was crystallized from ethanol: mp 135–136°; $[\alpha]^{23}D$ −69.0° (*c* 0.2 methanol), $[\alpha]^{23}D$ −71° (*c* 0.2, pyridine).

Anal. Calcd for $C_{27}H_{32}N_2O_8$: C, 63.72; H, 6.29; N, 5.47. Found: C, 63.19; H, 6.31; N, 5.35.

Penta-*O*-acetyl-D-mannose benzylphenylhydrazone was obtained as an oil, $[\alpha]^{22}D$ −6° (*c* 0.2, pyridine).

Anal. Calcd for $C_{29}H_{34}N_2O_{10}$: mol wt, 570.2214. Found: mol wt, 570.2237 (mass spectral).

Tetra-*O*-acetyl-D-arabinose benzylphenylhydrazone was obtained as an oil which crystallized after a few days: mp 85–88°; $[\alpha]^{22}D$ −73° (*c* 0.1, pyridine).

Anal. Calcd for $C_{26}H_{30}N_2O_8$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.34; H, 5.94; N, 6.02.

Tetra-*O*-acetyl-D-ribose benzylphenylhydrazone was obtained as an oil, $[\alpha]^{22}D$ 110° (*c* 0.1, pyridine).

Anal. Calcd for $C_{26}H_{30}N_2O_8$: mol wt, 498.2002. Found: mol wt, 498.2006 (mass spectral).

Registry No.—Penta-*O*-acetyl-D-glucose benzylphenylhydrazone, 17693-40-2; penta-*O*-acetyl-D-galactose, benzylphenylhydrazone, 17693-41-3; tetra-*O*-acetyl-L-fucose benzylphenylhydrazone, 17693-41-4; penta-*O*-acetyl-D-mannose benzylphenylhydrazone, 17693-43-5; tetra-*O*-acetyl-D-arabinose benzylphenylhydrazone, 17693-44-6; tetra-*O*-acetyl-D-ribose benzylphenylhydrazone, 17693-45-7.

Acknowledgment.—The Cary Model 60 spectropolarimeter was purchased with funds from Public Health Service Grant GM-11966 of the National Institute of Medical Sciences and from National Science Foundation Grant GP-2125.

(17) A. Hofmann, *Ann. Chem.*, **366**, 277 (1909).

Hydroxylation of Some Dehydroabietanes with *Corticium sasakii*

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Incubation of methyl dehydroabietate (**1**) with *C. sasakii* gives methyl 3β-hydroxydehydroabietate (**2**) and methyl 3β,7β-dihydroxydehydroabietate (**3**). Incubation of **2** or methyl 7β-hydroxydehydroabietate (**4**) also gives diol **3**. Incubation of methyl 7-oxodehydroabietate (**12**) gives methyl 3β-hydroxy-7-oxodehydroabietate (**10**) as an intermediate to methyl 3β,6β-dihydroxy-7-oxodehydroabietate (**15**). Similarly, incubation of methyl 7,18-dioxodehydroabietate gives methyl 3β,6β-dihydroxy-7,18-dioxodehydroabietate. Hydroxylation appears to occur first in the C-3β position, then in the C-6β or C-7β position of the dehydroabietanes. Oxygenation of dehydroabietanes at C-3, C-6, or C-7 by this fungal oxidase(s) is analogous to the positions of oxygenation of dehydroabietanes obtained from *Juniperus* trees.

Hydroxylation and oxidation of steroids and alkaloids with fungi is well known; however, diterpenes have not received similar attention[2] even though numerous highly oxygenated diterpenoids, *i.e.*, the gibberellins, are produced by fungi. The abietanes are one of the most abundant diterpenoid families found in higher plants.

Incubation[3] of methyl dehydroabietate (**1**) with *C. sasakii* (Lilly C-616) for 96 hr gives alcohol **2** and diol **3** (Scheme I). The assignment of the hydroxyl in **2** to C-3 is based upon the following argument. The nmr spectrum of **2** shows the proton attached to the carbon bearing the hydroxyl as a multiplet at 4.03 ppm indicative of an axial proton next to a methylene. The spectrum of **2** also shows the narrow envelope of the A-ring methylene protons in **1** split into a complex multiplet overlapping the 5α and C-6 methylene multiplet. The C-17 methyl signal in the nmr of alcohol **2** is not shifted, and in **5**, the corresponding acetate, it is shifted only 0.06 ppm from the position of the C-17 methyl signal in the nmr spectrum of methyl dehydroabietate. See Table I for nmr data. Oxidation of **2** gives ketone **6** whose infrared spectrum shows a nonconjugated carbonyl. The position of the C-17 methyl group in the nmr spectrum of **6** is 0.24 ppm downfield from that of methyl dehydroabietate. Based upon steroid models,[4,5] such a downfield shift of the C-17 methyl group could only be explained if the carbonyl is located at C-1 or C-3. This conclusion is supported, as deuteration[6] of ketone **6** gives compound **7** whose mass spectrum and nmr spectrum indicate the gain of only two deuteriums. The ketone is assigned to C-3 because of the near identity of the nmr spectrum[7] of **6** with the nmr spectrum of synthetic methyl norisopropyl-3-oxodehydroabietate. If keto ester **6** possess a carbonyl at C-3, then the corresponding keto acid should readily decarboxylate to give ketone **8**. Treatment of **6** with base and then with strong acid gave a compound to which we assign structure **8** on the basis of its nmr and mass spectral data. The nmr spectrum of **8** shows a doublet for the C-4α methyl at δ 1.26 (J = 7 cps).

Assignment of a β configuration to the C-3 hydroxyl in **2** is based upon chemical and nmr evidence. Reduction of ketone **6** with sodium trimethoxyborohydride gives only alcohol **2**. Even less bulky hydrides have been used[8] to reduce triterpenoid 3-oxo-4-*gem*-dimethyl systems to give the corresponding 3β-hydroxy compound. It will be shown below that the C-3 hydroxyl group in compound **19** is identical with the hydroxyl group in **2**. Analysis of the nmr spectrum of compound **19** gives A-ring proton coupling constants which would be expected only if the C-3 hydroxyl were in the equatorial position. The accuracy of these spectral assignments was verified by their use in a computer calculation of a theoretical signal for the 3α proton of compound **19**. Using the chemical shifts and coupling constants shown below, the FREQINT IV[9] program gives a spectrum of 210 lines. The contour of the plotted spectrum closely matches the signals of the A-ring protons in the observed spectrum of **19**, especially in the width and multiplicity of the C-3α proton (Table II). The downfield shift of 0.29 ppm for the C-15 methyl in the nmr spectrum of **2** obtained in pyridine is also indicative of the β configuration[10] of the hydroxyl in **2**. The C-15 methyl shifts downfield only 0.05 ppm in the pyridine nmr spectrum of **1**.

The nmr spectra of diol **3** and of the corresponding diacetate **9** both show two protons attached to carbons bearing hydroxyl (or acetoxyl) groups. The chemical shift and appearance of the lower field proton in both spectra are identical with the C-7α proton of methyl 7β-hydroxydehydroabietate and methyl 7β-acetoxydehydroabietate, respectively. The assignment of this hydroxyl of **3** to the C-7β position is supported by the identical shifts of the aromatic protons in the nmr spectrum of **3** and methyl 7β-hydroxydehydroabietate, relative to the aromatic proton signals of methyl dehydroabietate. The higher field signal of a proton attached to a carbon bearing a hydroxyl (or acetoxyl)

(1) Mycology Section, U. S. Army Natick Laboratories, Natick, Mass.

(2) Biellmann, *et al.* [*Chem. Commun.*, 168 (1968)], have recently reported the isolation of the bacterium *Flavobacterium resinovorum* from the soil of a *Pinus maritima* forest which is able to use the nonvolatile portion of eleoresin from pine trees as the sole carbon source for its growth. Incubation of dehydroabietic acid with this organism gave them ketone **8**. They propose that **8** arises *via* enzymatic hydroxylation of dehydroabietic acid at C-3 and oxidation of the resulting alcohol to a ketone, which then undergoes decarboxylation.

(3) A preliminary account of this work has been published: *Chem. Commun.*, 681 (1968).

(4) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 19.

(5) See E. Wenkert, *et al.*, *J. Org. Chem.*, **30**, 713 (1965), for a comprehensive study of the nmr spectra of tricyclic diterpenic substances and a discussion of the conformation of 3-oxodehydroabietates.

(6) A convenient and efficient procedure was used to deuterate ketones **6**, **10**, **11**, and **12**. Approximately 20 mg of the ketone has dissolved in $CDCl_3$ in an nmr tube and 100 mg of 38% DCl in D_2O added. The tube was shaken at room temperature and nmr spectra were periodically obtained until deuteration appeared complete. Shaking for 2 hr was required for the above ketones. After removal of the DCl solution, the $CDCl_3$ solution in the nmr tube was washed with H_2O, then concentrated under vacuum. Mass spectral analysis of the resulting crystalline deuterated product showed greater than 90% exchange of all enolizable protons.

(7) Kindly furnished by Professor Ernest Wenkert, Indiana University, Bloomington, Ind.

(8) W. Lawrie, J. McLean, and J. Watson, *J. Chem. Soc.*, 1776 (1967).

(9) Obtained from A. A. Bothner-By, Mellon Institute, Pittsburgh, Pa.

(10) P. V. Demarco, *et al.*, submitted for publication.

SCHEME I

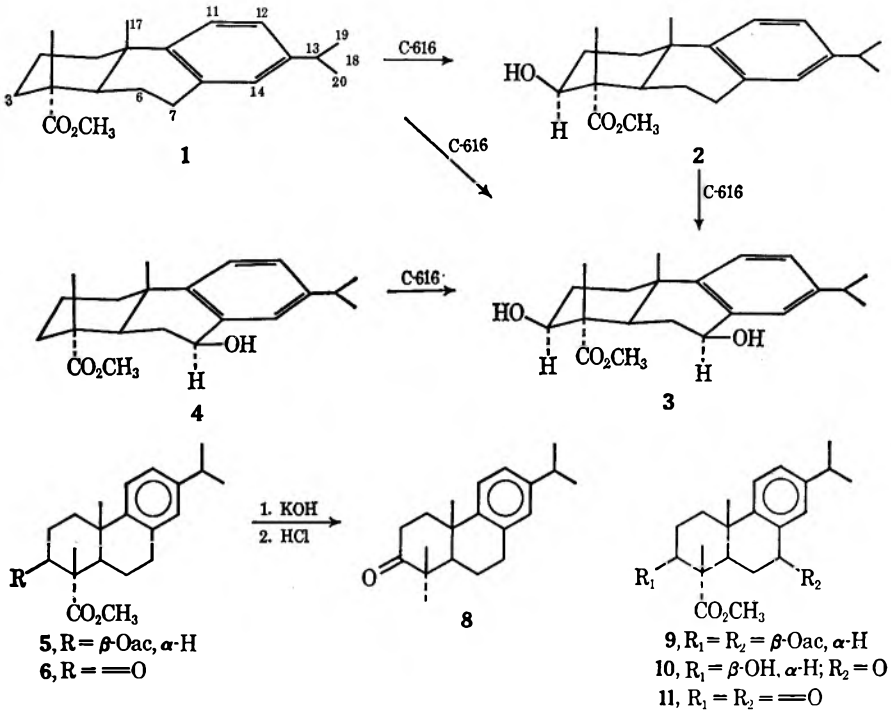


TABLE I

CHEMICAL SHIFTS[a]

Compd	C-17 Me	C-15 Me	C-3α	C-5α	C-6α	C-7α	C-11	C-12	C-14
1	1.20	1.26					7.13	7.00	6.88
1[d]	1.16	1.31							
2	1.20	1.26	m, 4.03						
2[d]	1.21	1.55							
3	1.26	1.26	m, 3.98			t, 4.80, J = 8	7.11	7.11	7.38
5	1.23	1.30	m, 5.21						
6	1.44	1.32							
8	1.26	d, 1.26, J = 7							
9	1.31	1.31	m, 5.21			t, 6.05, J = 8	(7.02, 7.16)		
10	1.26	1.31	m, 4.08						
11	1.53	1.46							
12	1.26	1.35							
13	1.30	1.38							
15	1.53	1.68	m, 4.00	d, 2.45, J = 4	d, 4.15				
16	1.55	1.55	m, 5.16	d, 2.88, J = 5	d, 5.65				
17[b]	1.65	1.65	m, 4.00	d, 2.35, J = 4	d, 4.08				
18	1.56	1.56	m, 5.16	d, 2.87, J = 5	d, 5.68				
Methyl norisopropyl-3-oxodehydro abietate	1.41[c]	1.30							
4	(1.26, 1.28)					t, 4.83, J = 8	7.11	7.11	7.40
Methyl 7β-acetoxydehydroabietate	1.28	1.28				t, 6.08, J = 8	(7.01, 7.01)		

[a] Obtained in $CDCl_3$. Expressed as parts per million from TMS. J values are in cycles per second. [b] DMSO added for solubility. [c] See ref 7. [d] Obtained in pyridine-d_5.

group in the nmr spectrum of **3** and of diacetate **9** is identical in position and appearance with the C-3α proton in the nmr spectrum of **2** and **5**, respectively. Incubation of **2** under the same conditions as incubation of methyl dehydroabietate affords diol **3**, which confirms the identity of the C-3β hydroxyl group in **3** with that of **2**. No methyl 7β-hydroxydehydroabietate is found in the crude chloroform extract of the methyl dehydroabietate conversion. However, incubation of methyl 7β-hydroxydehydroabietate with *C. sasakii* does afford diol **3**, which verifies the assignment of the C-7β hydroxyl in **3**.

Selective chromate oxidation of **3** gives hydroxy ketone **10** and dione **11**. Further chromate oxidation of **10** affords **11**. Mass and nmr spectroscopy show that compound **19**, the deuterium exchange product of hydroxy ketone **10**, contains two deuteriums, and compound **20**, the deuterium exchange product of dione **11**, contains four deuteriums. The downfield shift of the C-17 methyl group in the nmr spectrum of **11** relative to **10** is similar to the 3-keto-induced shift of the C-17 methyl of ketone **6** relative to compound **2**.

Considerable starting material is recovered from incubation of methyl dehydroabietate. However, in-

SCHEME II

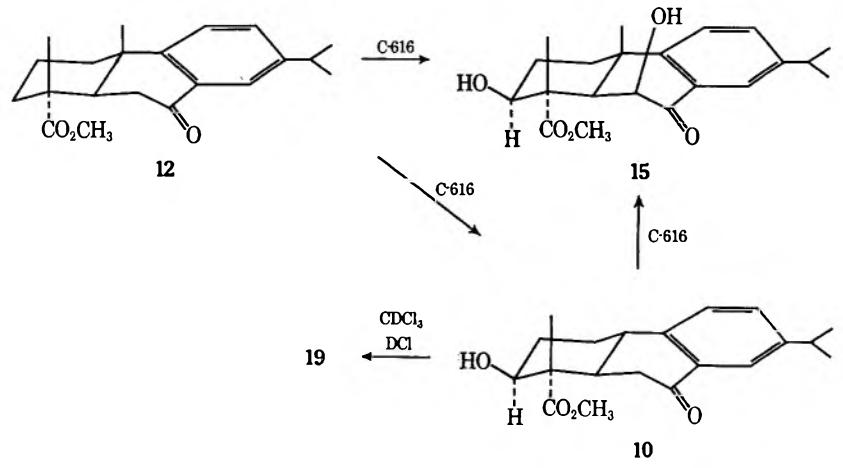
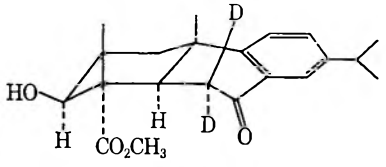


TABLE II



19

Proton	Chemical shift, δ, ppm	Coupling constants, cps
3α	4.08	$J_{3\alpha-2\alpha} = 5$
		$J_{3\alpha-2\beta} = 10$
2α	1.96	$J_{2\alpha-2\beta} = -10$
		$J_{2\alpha-1\alpha} = 5$
2β	1.78	$J_{2\alpha-1\beta} = 3$
		$J_{2\beta-1\alpha} = 10$
1α	1.92	$J_{2\beta-1\beta} = 5$
1β	2.40	$J_{1\alpha-1\beta} = -11$

creased incubation time did not result in higher yields of **2** or **3**, but did diminish the amount of starting material recovered. Some unidentified highly polar material is obtained from this conversion, indicating that **3** is further oxidized by *C. sasakii*.

Incubation of methyl 7-oxodehydroabietate (**12**) with *C. sasakii* for 48 hr gives metabolite **15** (Scheme II). The infrared spectrum of **15** also shows a conjugated carbonyl and two hydroxyl absorption. The bathochromic shift in the ultraviolet spectrum of **15** upon addition of base and the instability of **15** to alumina chromatography led us to postulate that one of the hydroxyls of diol **15** is in the C-6 position. This assignment was verified by the nmr spectrum of **15**. Analogous to the introduction of a 6β hydroxyl into a 5α steroid,[11,12] the C-17 methyl signal in the nmr spectrum of **15** is shifted downfield 0.27 ppm relative to the same methyl signal for monohydroxy ketone **10**. The nmr spectra of **15** and the corresponding diacetate **14** show both the expected doublet for the 5α proton coupled to the 6α proton and a low-field proton which is identical with the 3α proton in the nmr spectra of **2** and **5**, respectively. Incubation of **10** with *C. sasaki* gives **15**. Thus the sequence of enzymatic hydroxylation of **12** to **15** is analogous to the dihydroxylation of methyl dehydroabietate to diol **3**, *i.e.*, hydroxylation in the C-3β position followed by hydroxylation in ring B. This conversion also verifies the assignment of one of the hydroxyl groups of **15** to the C-3β position. A thin layer chromatogram developed three times shows a small amount of **10** present in the crude chloroform broth extract from incubation of **12**.

Incubation of methyl 7,18-dioxodehydroabietate (**13**) with *C. sasakii* for 48 hr gives metabolite **17**. The argument for assignment of the structure depicted in Scheme III for **17** is analogous to the proof of structure for **15**. After allowing for the different C-13 substituent and its effect on the C-17 methyl group, the nmr spectra of **17** and the corresponding diacetate **18** are similar to those of **15** and **16**, respectively.

Incubation of methyl 7-oxo-18-acetoxydehydroabietate (**14**) with *C. sasakii* results in destruction of the organism within 24 hr, whereupon starting **14** is quantitatively recovered from the fermentation broth.

Examples[13] of enzymatic hydroxylation of higher terpenoids at C-3 are rare. The origin of the C-3 oxygen in terpenoids has been explained by the requirement of a squalene cyclohydroxylase for the cyclization of squalene. However, Barton and Moss[14] have proposed that biosynthetic cyclization of terpene compounds might be initiated by H^+, the oxygen function at C-3 being introduced at a later stage by hydroxylation. This hypothesis would explain the isolation of numerous di- and triterpenoids which lack an oxygen at C-3. The hydroxylation of dehydroabietanes at C-3 by fungal oxidases is consistent with the hypothesis of cyclization followed by hydroxylation. Three *Juniperus* tree dehydroabietanes cogeneric with ferruginol—hinokiol, sugiol, and proxanthoperol—contain oxygen functions in the C-3, C-6, or C-7 positions. The fungal hydroxylation of dehydroabietanes in the same positions which bear oxygen in dehydroabietanes obtained from *Juniperus* trees provides an example of a fungus and a higher plant possessing the same oxidase selectivity.

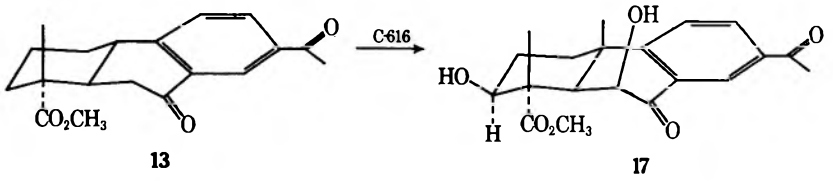
(11) D. R. Brannon, *et al.*, *J. Org. Chem.*, **32**, 1521 (1967).

(12) The similarity of the ultraviolet absorption maximum of **15** and **17** (254 mμ) to the calculated (A. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillian Co., New York, N. Y., 1964, p 109) value of an *o,m*-dialkyl-substituted acetophenone (252 mμ) implies the near coplanarity of the C-7 carbonyl with the aromatic C ring. According to Drieding models, such a conformation of the B ring makes the C-6β position of **17** analogous to a 5α steroid with respect to the A/B angular methyl.

(13) P. C. Cherry, E. R. H. Jones, G. D. Meakins, *Chem. Commun.*, 587 (1966).

(14) D. H. R. Barton and G. P. Moss, *ibid.*, 261 (1966).

SCHEME III



Experimental Section

Melting points were corrected. Analysis were performed by Mr. George Maciak and associates of these laboratories. Infrared spectra were recorded with a Beckman IR-7 spectrometer, ultraviolet spectra were determined with a Cary 14 recording spectrometer, nmr spectra were obtained with a Varian A-60 spectrometer with TMS (δ 0.00 ppm) as internal standard, and mass spectra were taken on a CEC 21-110A using 70 eV with a direct source inlet system. Thin layer chromatograms were run on Merck silica gel GF precoated plates, with detection by iodine vapor. Grace 950 silica gel was used for column chromatography.

General Methods of Incubation.—Flasks (500 ml) containing 200 ml of sterile solution consisting of 30 g of Difco malt extract, 20 g of reagent dextrose, 1 g of Bacto peptone, and 1000 ml of distilled water were inoculated with *C. sasakii* Lilly C-616 and incubated at 25° for 96 hr on a 250-rpm 2-in. rotary shaker. A solution of 100 mg of terpene dissolved in 0.8 ml of dimethylformamide was then added and incubation was continued for the number of hours indicated below. The flask contents were combined, and the mycelium was filtered off. The aqueous filtrate was extracted by stirring for 3 hr with a high-speed mechanical stirrer and with one-half of its volume of chloroform. The mycelium was extracted by the same procedure, and the extracts were combined unless otherwise indicated below.

Incubation of Methyl Dehydroabietate (1).—Methyl dehydroabietate (8 g) was incubated for 96 hr as described above. Removal of the chloroform from the crude broth extract gave 4.6 g of material. Extraction of the mycelium gave 1.2 g of chloroform soluble material. A thin layer chromatogram (ethyl acetate–benzene, 1:1) of the broth extract showed methyl dehydroabietate and **3** as major components. Compound **2** and some very polar material appeared as minor components. A thin layer chromatogram of the mycelial extract showed methyl dehydroabietate and **2** as major components compared with diol **3**. No spot corresponding to methyl 7β-hydroxydehydroabietate was detected in either chromatogram. Chromatography of the broth extract on 500 g of silica gel gave 2.4 g of methyl dehydroabietate upon ethyl acetate–benzene (1:1) elution.

Further elution with ethyl acetate–benzene (1:1) gave 220 mg of **2** which crystallized upon addition of hexane: mp 120–122°; ir (KBr) 3230, 1730, 830 cm^{-1}. The mass spectrum of **2** shows a parent ion at m/e 330 and a large P − H_2O peak at m/e 312.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.29; H, 9.25.

Further elution with ethyl acetate–benzene (1:1) gave 1.20 g of diol **3**. Recrystallization from ethyl acetate–hexane (1:3) gave mp 169–171°; ir (KBr) 3430, 1700 cm^{-1}. The mass spectrum of **3** showed a parent ion at m/e 346 and a large P − H_2O peak at m/e 328.

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.95; H, 9.00.

Elution with ethyl acetate gave 210 mg of noncrystalline material whose composition is still under investigation. Chromatography of the mycelial extract under the same conditions gave 310 mg of methyl dehydroabietate, 440 mg of **2**, and 215 mg of diol **3**, whose melting point and infrared and nmr spectra are identical with those described above.

Acetylation of Alcohol 2.—To 120 mg of **2** in 3 ml of acetic anhydride was added 3 drops of pyridine. After stirring at room temperature for 1 hr, the excess acetic anhydride was removed under vacuum, and the resulting residue was partitioned between ether and water. The ether portion, after washing with water and drying over $MgSO_4$, was concentrated to give 90 mg of crystalline **5**: mp 158–160°; ir (KBr) 1730, 1750 cm^{-1}. The mass spectrum of **5** gives a parent ion peak at m/e 372.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.15; H, 8.66; O, 17.19. Found: C, 74.08; H, 8.39; O, 17.34.

Oxidation of Alcohol 2.—To 100 mg of **2** in 10 ml of acetone was added dropwise 200 mg of CrO_3 in 5 ml of acetone. After 6 hr, a thin layer chromatogram (ethyl acetate–benzene, 1:3) showed no starting material remaining. The acetone was removed under vacuum, and the resulting residue was partitioned between ether and water. The ether portion was washed with water, dried over $MgSO_4$, and then concentrated to give 71 mg of ketone **6** which crystallized upon addition of hexane: mp 99–100°; ir (KBr) 1745 cm^{-1}. The mass spectrum of **6** shows the parent ion peak at m/e 328.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.82; H, 8.60.

To 27 mg of ketone **6** in $CDCl_3$ was added 100 μl of 38% DCl in D_2O in an nmr tube. After shaking at room temperature for 2 hr, the nmr spectrum showed greater than 90% exchange of two protons. Concentration of the chloroform portion after briefly washing with water gave a crystalline material, **7**, whose mass spectrum showed the parent ion at m/e 330. Greater than 90% of dideuterio exchange of ketone **6** occurred as calculated from the mass spectra of **6** and **7**.

Saponification and Decarboxylation of Ketone 6.—To 25 mg of **6** in 2 ml of ethylene glycol was added 22 mg of KOH in 1 ml of water. After refluxing for 6 hr, the mixture was poured into 10 ml of water and repeatedly extracted with ether. The remaining aqueous solution was concentrated to 3 ml, 1 ml of ethanol was added, and the solution was acidified with concentrated HCl solution. After stirring for 3 hr, the solution was extracted with ether. Concentration of the ether gave 15 mg of **8** which could not be crystallized, ir (film) 1700 cm^{-1}. The mass spectrum of **8** gave a parent peak at m/e 284.

Reduction of Ketone 6.—To 100 mg of ketone **6** in 10 ml of ether was added 75 mg of sodium trimethoxyborohydride. After stirring at room temperature for 2 hr, the reaction mixture was filtered and the filtrate washed repeatedly with water. The ether portion was dried over $MgSO_4$ and concentrated to give 75 mg of material. A thin layer chromatogram (ethyl acetate–benzene 1:1) showed alcohol **2** to be the only component. Addition of ethyl acetate–hexane (1:1) to the material gave crystalline **2**, which is identical in all respects with that obtained from incubation of methyl dehydroabietate as described above.

Acetylation of Diol 3.—Diol **3** (50 mg) was acetylated by the same conditions as described above for the acetylation of **2**. Addition of hexane–ether (1:1) to the reaction product gave 22 mg of crystalline **9**: mp 128–130°; ir (KBr) 1730, 1750 cm^{-1}. The mass spectrum of **9** gave a parent ion peak at m/e 430.

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; O, 22.30. Found: C, 69.70; H, 7.89; O, 22.43.

Oxidation of Diol 3.—To 200 mg of **3** in 10 ml of acetone was added dropwise 75 mg of CrO_3 dissolved in 4 ml of acetone. After stirring at room temperature for 3 hr, a thin layer chromatogram (ethyl acetate–benzene 1:1) of the reaction mixture showed starting **3** and dione **11** as minor components compared with a predominent amount of hydroxy ketone **10**. The acetone was removed under vacuum and the reaction residue partitioned between ether and water. The ether portion, after washing with water and drying over $MgSO_4$, gave 160 mg of material which was chromatographed on 50 g of silica gel. Elution with ethyl acetate–benzene (1:10) gave 30 mg of dione **11**: mp 140–142°; ir (KBr) 1680, 1720, 1745 cm^{-1}. The mass spectrum of **11** gave a parent ion peak of m/e 342.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.68; H, 7.58.

Elution with ethyl acetate–benzene (1:3) gave 140 mg of **10** which could not be crystallized, but formed a gel upon addition of hexane. Vacuum filtration of the gel gave a low-melting solid: mp 70–72°; ir (KBr) 3230, 1680 cm^{-1}. The mass spectrum of **10** gave a parent ion peak at m/e 344.

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.91; H, 7.99.

To 35 mg of hydroxy ketone **10** in $CDCl_3$ was added 100 μl of 38% DCl in D_2O in an nmr tube. After shaking for 3 hr,

the spectrum showed approximately 90% deuterio exchange of the C-6 protons. Concentration of the chloroform portion, after briefly washing with water, gave a crystalline material, **19**, whose mass spectrum showed the parent ion peak at *m/e* 346. Approximately 95% of dideuterio exchange of hydroxy ketone **10** occurred as calculated from the mass spectra of **10** and **19**.

Oxidation of Hydroxy Ketone 10.—To 50 mg of **10** in 3 ml of acetone was added dropwise 25 mg of CrO_3 in 2 ml of acetone. A thin layer chromatogram (ethyl acetate–benzene 1:1) of the reaction mixture showed complete conversion of **10** into dione **11** after stirring at room temperature for 3 hr. The usual work-up afforded 31 mg of dione **11** whose spectral and physical properties are identical with those of **11** described above. To 20 mg of dione **11** in $CDCl_3$ was added 200 μl of 38% DCl in D_2O in an nmr tube. After shaking for 2 hr, the nmr spectrum showed the loss of four protons. Concentration of the chloroform portion gave crystalline **20** whose mass spectrum showed the parent ion peak at *m/e* 346. Approximately 95% tetradeuterio exchange occurred as calculated from the mass spectrum.

Incubation of Alcohol 2.—A total of 169 mg of **2** was incubated for 48 hr as described above. Chromatography of the combined broth and mycelial chloroform extracts on 20 g of silica gel gave 21 mg of starting alcohol **2** upon elution with ethyl acetate–benzene (1:1).

Further elution gave 117 mg of crystalline **3**, mp 165–167°, whose spectral properties are identical with those described above for **3**.

Incubation of Methyl 7β-Hydroxydehydroabietate (4).—A total of 250 mg of methyl 7β-hydroxydehydroabietate was incubated for 4 days as described above. Chromatography of the combined broth and mycelial chloroform extracts on 50 g of silica gave 80 mg of starting material upon elution with ethyl acetate–benzene (1:1). Further elution with the same solvent gave 90 mg of crystalline **3**, mp 167–168°. Elution with ethyl acetate gave 30 mg of unidentified polar material.

Incubation of Ketone 12.—Ketone **12** (5 g) was incubated for 2 days as described above. Chloroform extraction of the broth gave 2.6 g of material whose thin layer chromatogram (ethyl acetate–benzene, 1:1) showed starting ketone **12**, diol **15**, and several minor components more polar than **15**. A thin layer chromatogram of the mycelial chloroform extract (980 mg) showed the same components, except ketone **12** was the most predominant component. Chromatography of the combined extracts on 250 g of silica gel gave 800 mg of starting ketone **12** upon elution with ethyl acetate–benzene (1:1).

Further elution with the same solvent gave 2.3 g of crude **15**. Two recrystallizations from ethyl acetate gave an analytical sample: mp 187–188°; ir (KBr) 3340, 3480, 1710, 1605 cm^{-1}; uv max (EtOH) 254 mμ (ε 11,400), which shifted to 375 mμ upon addition of base. The ultraviolet spectrum of **12** gave uv max (EtOH) 254 mμ (ε 10,600), which did not shift upon addition of base. The mass spectrum of **15** gave a parent ion peak at *m/e* 360.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; O, 22.20. Found: C, 69.86; H, 8.00; O, 22.22.

A thin layer chromatogram developed three times (ethyl acetate–benzene, 1:9) of the crude transformation mixture run along with **10** showed **10** present in the mixture as a minor component.

Incubation of Hydroxy Ketone 10.—Hydroxy ketone **10** (90 mg) was incubated for 48 hr as described above. A thin layer chromatogram (ethyl acetate–benzene, 1:9) developed three times showed that the mycelial extract contained **15**. The broth extract contained considerable starting material. Chromatography of the mycelial extract on 25 g of silica gel gave 35 mg of crystalline **15**, mp 182–183°, whose infrared spectrum was identical with that of **15** obtained above from incubation of **12**.

Acetylation of 15.—To 50 mg of metabolite **15** in 3 ml of acetic anhydride was added 3 drops of pyridine. After stirring for 12 hr at room temperature, the acetic anhydride was removed under vacuum and the residue was partitioned between water and ether. The ether portion gave 52 mg of material which was chromatographed on 25 g of silica gel. Elution with ethyl acetate–benzene (1:9) gave **16**. All attempts to crystallize **16** gave only amorphous material.

Incubation of Diketone 13.—Diketone **13** (5 g) was incubated for 2 days as described above. Analogous to the incubation of **12** described above, tlc showed that the mycelial extract (1.10 g) contained largely starting material, whereas the broth extract (3.2 g) contained **17** as the major component. Chromatography of the combined extracts on 250 g of silica gel gave 1.22 g of starting diketone **13** upon elution with ethyl acetate–benzene (1:1).

Further elution with the same solvent gave 2.1 g of crude metabolite **17**. Crystallization from ethyl acetate gave pure **17**: mp 193–195°, ir (KBr) 3340, 3480, 1717, 1605 cm^{-1}; uv max (EtOH) 254 mμ (ε 15,000), which shifted to 375 mμ upon addition of base. The mass spectrum of **17** gave the parent ion peak at *m/e* 360.

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; O, 26.64. Found: C, 66.57; H, 6.98; O, 26.64.

Acetylation of 17.—Diol **17** (50 mg) was acetylated under the same conditions as described above for the acetylation of **17**. Addition of ether to the crude reaction product gave crystalline **18**, mp 199–200°.

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35; O, 28.80. Found: C, 65.11; H, 6.41; O, 28.50.

Registry No.—**1**, 1235-74-1; **2**, 17751-30-3; **3**, 17751-32-5; **4**, 17751-34-7; **5**, 17831-48-0; **6**, 17831-49-1; **8**, 16898-96-7; **9**, 17831-51-5; **10**, 17751-38-1; **11**, 17831-53-7; **12**, 17751-36-9; **13**, 5335-63-7; **15**, 17810-49-0; **16**, 17831-57-1; **17**, 17831-58-2; **18**, 17831-59-3; methyl norisopropyl-3-oxodehydroabietate, 1686-52-8; methyl 7β acetoxydehydroabietate, 17901-36-9.

Acknowledgments.—We are indebted to Dr. Thomas F. Sanderson, Hercules Inc., Wilmington, Del., for numerous diterpene samples and to the Physical Chemistry Department of these laboratories for spectral measurements. We also thank Professor Ernest Wenkert, Indiana University, Bloomington, Ind., and Dr. Marvin Gorman of these laboratories for helpful discussions.

Solvent Effect in a Sterically Controlled Synthesis of Optically Active α-Amino Acids from α-Keto Acids by Hydrogenolytic Asymmetric Transamination[1]

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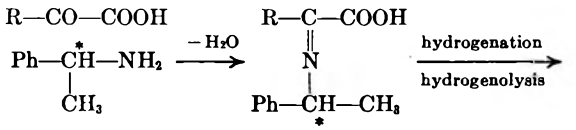
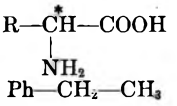
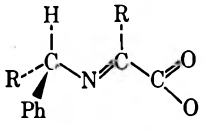
The solvent effect of the hydrogenolytic asymmetric transamination of α-keto acid with optically active α-alkylbenzylamine was studied by the use of various solvent systems. The possible steric course of the asymmetric synthesis was discussed.

Several nonenzymatic asymmetric syntheses of α-amino acids from their corresponding α-keto acids have been reported.[3-9] Hiskey and Northrop[5] reported the syntheses of optically active α-amino acids from the Schiff bases of α-keto acids with (*S*)(−)- and (*R*)(+)-α-methylbenzylamine by catalytic hydrogenation and subsequent hydrogenolysis. Harada[7] reported

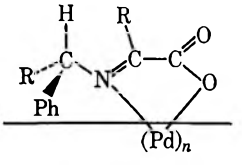




the syntheses of several optically active amino acids from α-keto acids by the use of (*S*)(+)- and (*R*)(−)-α-phenylglycine in alkaline aqueous solution. Recently, Kanai and Mitsui[8] reported the synthesis of optically active phenylglycine by the Hiskey method[4] and proposed a steric course for the asymmetric synthesis. In a recent study in this laboratory,[10] many Hiskey-type reactions were carried out in order to study the steric course using several α-keto acids and using optically active α-methyl- and α-ethylbenzylamine. From these results, it was proposed[10] that the possible conformation of the reactants could be structure I and that structure I would be a five-membered cyclic complex with the catalyst, as shown in structure II. Thus the sterically



I



II

controlled syntheses of α-amino acids from the Schiff bases of corresponding α-keto acids with optically active α-alkylbenzylamine would be explained by the formation of intermediate chelate structure II under the reaction conditions.

In the present study, in order to clarify further the steric course of the catalytic hydrogenation reaction of the Schiff bases of α-keto acids with optically active α-alkylbenzylamines, the solvent effect of the reaction was studied. The keto acids used were pyruvic acid, benzyl pyruvate, phenylglyoxylic acid, oxaloacetic acid, and α-ketoglutaric acid. Optically active amines used were (*S*)(−)- and (*R*)(+)-α-methylbenzylamine, (*S*)(−)- and (*R*)(+)-α-ethylbenzylamine, and (*R*)(+)-α-(1-naphthyl)ethylamine. Summarized results are shown in Table I.

Optically active alanine was synthesized from pyruvic acid (R′ = H) or benzyl pyruvate (R′ = $C_6H_5CH_2$) by the use of various optically active alkylamines (reactions 1–23 in Table I). Summarized results show that the optical activity of the synthesized alanine depends on the solvent used. When a less polar solvent was used, the optical activity of the resulting alanine was found to be higher (60–80%) and, when a polar solvent was used, lower optical activity (30–50%) of alanine resulted. In reactions 10–15 in Table I, higher optical activity was obtained by the use of hexane and ethyl acetate and lower optical activity resulted from the use of an aqueous dioxane solution (reaction 15). In the synthesis of glutamic acid by the use of (*S*)(−)-methylbenzylamine, when less polar solvents were used (reactions 27–29), (*S*)(+)-glutamic acid was formed as predicted by the intermediate substrate–catalyst complex. However, when polar solvents were used (reactions 30–33), (*R*)(−)-glutamic acid resulted under the same conditions. Optical activity of the resulting glutamic acid decreased dependent on the increase of polarity of the solvent used and finally the configuration of the resulting glutamic acid was reversed to the opposite structure. In other words, the configuration of glutamic acid prepared by the use of (*R*)(+)-ethylbenzylamine and (*S*)(−)-ethylbenzylamine using ethanol and a methanol–water–NaOH mixture (reactions 33 and 34, respectively) was found to be the same, *i.e.*, (*R*)(−)-glutamic acid.

Figure 1 shows the relationship between the optical activities of the amino acids and the dielectric constants of the solvents used. Because of the difficulty in estimating the dielectric constants of the mixed solvents, only a few reactions using rather simple systems are plotted in Figure 1. Generally, optical activities of the resulting amino acids decreased dependent on the increase of the dielectric constant.

The observed fact that the optical activity of the resulting amino acid decreased (alanine) or the sign of the activity inversed (glutamic acid) suggests that the

(1) Sterically controlled synthesis of optically active organic compounds VI. Part V: K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967). Contribution No. 105 of the Institute of Molecular Evolution, University of Miami.

(2) Research Laboratory, Tanabe Seiyaku Co., Ltd., Osaka, Japan.

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(5) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961).

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(9) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **87**, 1753 (1965).

(10) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

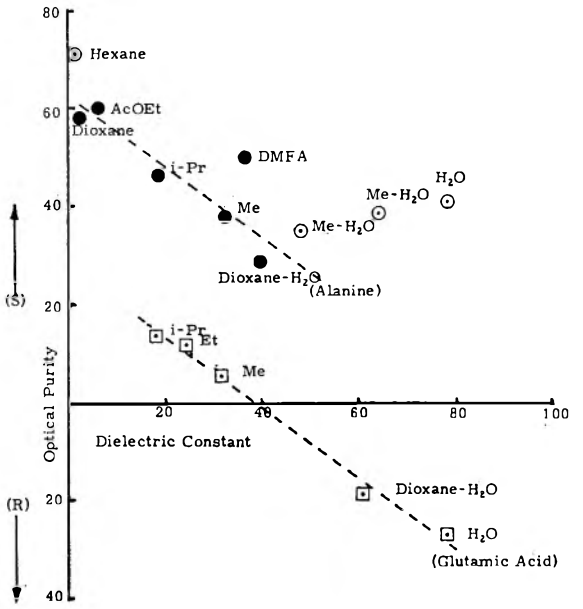

Figure 1.—Relationship between optical activities of synthesized amino acids and dielectric constants of the solvents used. Alanine was prepared from benzyl pyruvate and (*S*)(−)-α-methylabenzylamine. Glutamic acid was synthesized from α-ketoglutaric acid and (*S*)(−)-α-methylbenzylamine; ⊙ means that the reaction mixture was not homogeneous in the alanine syntheses.

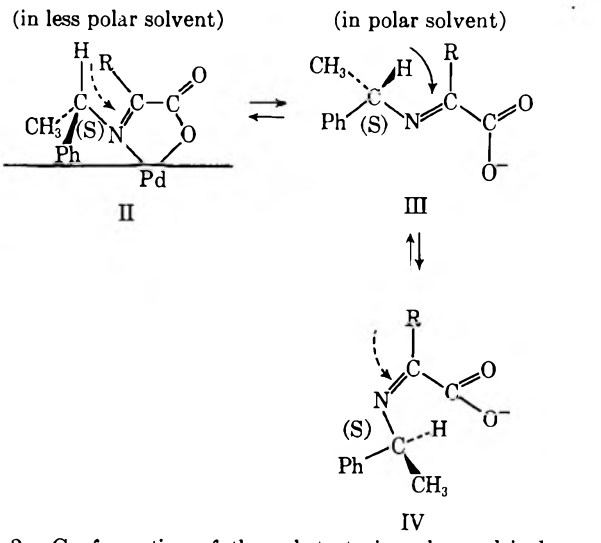

Figure 2.—Conformation of the substrate in polar and in less polar solvent.

conformation of the substrate molecule changes depending on the solvent used. As was discussed in the earlier study,[10] structure II could be the preferred conformation under conditions using a less polar solvent (hexane, ethyl acetate, alcohol). The reasons for choosing structure II are (1) electrostatic attraction between substrate and catalyst in such less polar solvents is stronger than that in polar solvents and (2) the solvation of the substrate in these less polar solvents is weak, so that the substrate could react easily with the catalyst to form the intermediate complex. On the other hand, when polar solvents were used, (1) electrostatic attraction between substrate and catalyst is weaker and (2) the strong solvation of the substrate interferes with the attraction between substrate and catalyst to form the intermediate complex. Therefore, it could be assumed that the more polar the solvent used, the greater the chance the substrate might exist in free forms in the solution. The inversion of sign of the optically active glutamic acid suggests that structure II would not be the major conformation in the polar solvent.

Figure 2 shows the postulated conformations of the substrate in polar and in less polar solvents. In the polar solvents, the proportion of nonchelate conformations III and IV could increase. When the substrate, the Schiff base of α-keto acid with optically active α-alkylamine, is hydrogenated in the polar solvent, structures III and IV could be adsorbed on the palladium catalyst at the less bulky side of the molecule without forming the intermediate complex. Therefore, when (*S*)-alkylbenzylamine was used, structures II, III, and IV resulted in the (*S*)-, (*R*)-, and (*S*)-amino acid, respectively, after catalytic hydrogenation and hydrogenolysis.

In the synthesis of alanine, structure II could be the major conformation throughout the synthesis. However, the increase of polarity of the solvent resulted in the increase of structure III so that the resulting optical activity of alanine decreased with the increasing polarity of the solvent. In the synthesis of glutamic acid, structure II could also be the major conformation in the less polar solvent. However, in the polar solvent structure III might be the major conformation. In the synthesis of aspartic acid, structures II and III might be the major conformations in the less polar and polar solvents, respectively, as in the glutamic acid synthesis. Therefore, in the polar solvent, (*R*)(−)-aspartic acid could be obtained by the use of (*S*)(−)-α-methylbenzylamine (reaction 26). However, oxaloacetic acid also resulted in (*S*)(+)-alanine. The alanine could be assumed to be synthesized from pyruvic acid which is a β-decarboxylation product of oxaloacetic acid. Accordingly, structure II could be the major conformation in the optically active alanine formation from the resulted pyruvic acid.

Free amino acids shown in Table I were isolated by ion-exchange resin. The optical activities were measured without further purification because such procedures resulted in fractionation of the optical isomers. The isolated free amino acids were converted into DNP-amino acids in the usual manner[11] and the DNP derivatives were purified by Celite column chromatography[12] without fractionation of optical isomers.[6,7,10] Therefore, the optical purity of the DNP-amino acids is more reliable than that of isolated crude free amino acids. In some experiments (in Table I), optical purity of the free amino acid is much lower than that of the corresponding DNP-amino acid, probably because of impurities.

Optical purities of amino acids prepared by the use of (+)-(1-naphthyl)ethylamine were found to be very high (78–86%). The assignment of the configurations of (−)-α-(1-naphthyl)ethylamine and (−)-α-ethylbenzylamine have been made already by the use of the optical rotary dispersion method.[13,14] Chemical evi-

(11) F. Sanger, *Biochem. J.*, **39**, 507 (1945); F. C. Green and C. M. Kay, *Anal. Chem.*, **24**, 726 (1952); K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).

(12) J. C. Perrone, *Nature*, **167**, 513 (1951); A. Court, *Biochem. J.*, **58**, 70 (1954).

(13) H. Wolf, E. Bunnenberg, and C. Djerassi, *Ber.*, **97**, 533 (1964).

(14) M. E. Warren, Jr., and H. E. Smith, *J. Amer. Chem. Soc.*, **87**, 1757 (1965).

TABLE I

OPTICALLY ACTIVE AMINO ACIDS PREPARED BY THE USE OF VARIOUS SOLVENTS

	R—CO—COOR′	Confign of amine[a]	Reaction	Solvent[b]	Yield, %	Confign of amino acid	[α]D of isolated amino acid[d] (c, 5 N HCl)	Optical purity, %, of amino acid[e]	[α]D of DNP-amino acid[f] (c, 1 N NaOH)	Optical purity,[h] %
Ala	R = Me	(S)(−)-Me	1	THF	33	(S)(+)-Ala	+9.0 (3.09)	62	+94.4 (0.22)	66
	R′ = H		2	EtOH	78	(S)(+)	+9.2 (3.55)	63	+96.9 (0.33)	67
			3	H_2O, pyridine	78	(S)(+)	+4.1 (3.17)	28	+56.9 (0.36)	40
			4	H_2O, NaOH	69	(S)(+)	+3.8 (3.14)	26	+47.3 (0.53)	33
		(S)(−)-Et	5	EtOH	76	(S)(+)	+7.5 (3.46)	52	+72.8 (0.57)	52
			6	EtOH, H_2O, NaOH	65	(S)(+)	+4.1 (3.51)	28	+53.5 (0.40)	37
			7	MeOH:H_2O (1:4), NaOH	75	(S)(+)	+2.2 (3.47)	9	+28.4 (0.49)	31
		(R)(+)-Naph	8	EtOH	76	(R)(−)	−11.6 (3.75)	80	−120 (0.40)	83
			9	EtOH, H_2O, NaOH	65	(R)(−)	−10.7 (3.13)	74	−105 (0.47)	73
	R = Me	(S)(−)-Me	10	Hexane[c]	75	(S)(+)	+7.9 (3.48)	55	+10.3 (0.45)	72
	R′ = Benzyl		11	AcOEt	49	(S)(+)	+6.4 (2.92)	44	+87.0 (0.55)	60
			12	*i*-PrOH	56	(S)(+)	+5.0 (4.63)	34	+65.7 (0.47)	46
			13	DMFA	47	(S)(+)			+72.1 (0.52)	50
			14	MeOH	61	(S)(+)	+1.4 (5.58)	10	+55.0 (0.52)	38
			15	Dioxane:H_2O (45:55)	71	(S)(+)			+41.2 (0.49)	29
			16	MeOH:H_2O (2:1)[c]	75	(S)(+)			+50.1 (0.46)	35
			17	MeOH:H_2O (1:2)[c]	63	(S)(+)			+55.8 (0.48)	39
			18	MeOH:H_2O (1:4)	76	(S)(+)	+3.4 (3.16)	14	+27.0 (0.51)	29
			19	H_2O[c]	45	(S)(+)	+3.0 (3.40)	21	+59.6 (0.45)	41
		(R)(+)-Me	20	Dioxane	72	(R)(−)	+4.2 (1.95)	29	−83.3 (0.56)	58
		(R)(+)-Et	21	Hexane[c]	66	(R)(−)	−5.7 (2.83)	39	−107 (0.49)	74
		(R)(+)-Naph	22	Hexane[c]	31	(R)(−)	−8.9 (2.22)	61	−124 (0.47)	86
			23	AcOEt	31	(R)(−)	−6.8 (1.73)	47	−112 (0.52)	78
Ph-gly	R = Ph	(S)(−)-Me	24	EtOH	73	(S)(+)-Ph-gly	+47.6 (2.51)	28	−36.0 (0.89)[g]	30
	R′ = H		25	H_2O, NaOH	60	(S)(+)	+38.6 (2.10)	23	−28.3 (0.90)[g]	24
Asp	R = CH_2COOH	(S)(−)-Me	26	EtOH, H_2O, NaOH	38	(S)(+)-Ala	+7.56 (2.99)	50	+84.0 (0.38)	58
	R′ = H				11	(R)(−)-Asp	−11.1 (2.84)	44	−41.0 (0.39)	45
Glu	R = $(CH_2)_2$-COOH	(S)(−)-Me	27	*i*-PrOH, $(C_2H_5)_3N$	82	(S)(+)-Glu	+3.7 (3.57)	12	−11.5 (0.85)[g]	14
	R′ = H		28	EtOH	74	(S)(+)	+4.2 (3.55)	13	−9.6 (0.68)[g]	12
			29	MeOH, tri Et amine	78	(S)(+)	+1.9 (2.68)	6	−4.1 (1.27)[g]	5
			30	Dioxane:H_2O (2:8), tri Et amine	60	(R)(−)	−5.9 (3.46)	19	+14.8 (0.75)[g]	19
			31	MeOH:H_2O (1:2), NaOH	68	(R)(−)	−8.3 (2.75)	26	+21.9 (0.67)[g]	27
			32	H_2O, pyridine	55	(R)(−)	−8.6 (2.27)	27	+21.9 (0.57)[g]	27
		(R)(+)-Et	33	EtOH	75	(R)(−)	−0.47 (2.82)	2	+5.17 (0.72)[g]	6
		(S)(−)-Et	34	H_2O:MeOH (2:1), NaOH	56	(R)(−)	−7.7 (3.04)	25	+24.1 (0.65)[g]	30

[a] (S)(−)-Me, (S)(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3°, benzene); (R)(+)-Me, (R)(+)-α-methylbenzylamine ($[\alpha]^{25}D$ +41.5°, benzene); (S)(−)-Et, (S)(−)-α-ethylbenzylamine ($[\alpha]^{25}D$ −21.0°, benzene); (R)(+)-Et, (R)(+)-α-ethylbenzylamine, ($[\alpha]^{25}D$ +21.7° benzene); (R)(+)-Naph, (R)(+)-α-(1-naphthyl)ethylamine ($[\alpha]^{25}D$ +88.0°, benzene). [b] THF, tetrahydrofuran; DMFA, dimethylformamide. When free α-keto acids (1 mol) were used, 2 mol of optically active amine were added. Pyridine, sodium hydroxide, and triethylamine were also used to neutralize the keto acids. [c] The reaction mixtures were not homogeneous solutions. [d] Optical rotations of amino acids which were isolated by the use of ion exchange resins were listed. [e] Defined as ([α]D obsd/[α]D lit. × 100. (S)-Ala, $[\alpha]^{25}D$ +14.6° (5 N HCl); (S)-Ph-gly, $[\alpha]^{25}D$ +168° (5 N HCl); (S)-Asp, $[\alpha]^{25}D$ +25.4° (5 N HCl); (S)-Glu, $[\alpha]^{25}D$ +31.8° (5 N HCl): J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1961 (alanine, p 1819; phenylglycine, p 2694; aspartic acid, p 1856; glutamic acid, p 1929). [f] Dinitrophenylamino acids were isolated by column chromatography. [g] Optical rotations were measured in glacial acetic acid. [h] Defined as [α]D obsd/[α]D lit. × 100. DNP-(S)-Ala, $[\alpha]^{25}D$ +143.9° (1 N NaOH); DNP-(S)-Asp, $[\alpha]^{25}D$ +91.9° (1 N NaOH); DNP-(S)-Glu, $[\alpha]^{25}D$ +80.8° (AcOH): K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954); DNP-(R)-Phe-gly, $[\alpha]^{25}D$ +119.2° (AcOH).

dence obtained in this study also supports the fact that the configuration of (+)-(1-naphthyl)-ethylamine and (−)-α-ethylbenzylamine could be *R* and *S*, respectively. It was found in this study that the α-(1-naphthyl)ethylamine is also hydrogenolyzed to α-ethylnaphthalene and ammonia as α-alkylbenzylamine[5,10] and phenylglycine[7] by the use of palladium hydroxide on charcoal.

Experimental Section[15]

Optically active amines are as follows: (S)(−)-α-methylbenzylamine,[16,17] $[\alpha]^{25}D$ −42.3° (benzene); (R)(+)-α-methylbenzylamine,[16,17] $[\alpha]^{25}D$ +41.5° (benzene); (S)(−)-α-ethylbenzylamine,[14,18] $[\alpha]^{25}D$ −21.0° (benzene); (R)(+)-α-ethylbenzylamine,[14,18] $[\alpha]^{25}D$ +21.7° (benzene); (R)(+)-α-(1-naphthyl)-ethylamine, $[\alpha]^{25}D$ +88.0° (benzene).

(15) All optical rotation measurements were carried out by the use of the Rudolph Model 80 polarimeter with PEC-101 photometer. All hydrogenations and hydrogenolyses were carried out by the use of Parr 3910 shaker-type hydrogenation apparatus.

(16) W. Theilacker and H. Hinkler, *Chem. Ber.*, **87**, 690 (1954).

(17) W. Leithe, *Ber.*, **64**, 2831 (1931).

(R)(−)-**Alanine.**—A solution of pyruvic acid, 0.88 g (0.01 mol) in 30 ml of ethanol, was mixed with a solution of (R)(−)-α-(naphthyl)ethylamine, 3.42 g (0.02 mol) in 40 ml of ethanol, and the solution was kept standing for 30 min at room temperature. To this was added 1.0 g of 10% palladium on charcoal, and the solution was hydrogenated for 10 hr at room temperature (initial pressure, 40 psi). The catalyst was removed by filtration and washed with 3 *N* hydrochloric acid to remove N-substituted alanine. The combined solution was evaporated to dryness under reduced pressure. Water was added and the solution evaporated to dryness to minimize free hydrochloric acid. The residue was dissolved in 60 ml of water and the pH was adjusted to about 4.5 by the use of sodium hydrogen carbonate. Palladium hydroxide on charcoal,[5] 3.0 g, was added to the solution and hydrogenolysis was carried out for 24 hr. After hydrogenolysis was completed, the catalyst was removed by filtration. The solution was then acidified by hydrochloric acid and evaporated to dryness and the residue was extracted with absolute alcohol. The alcoholic solution was evaporated to dryness under reduced pressure and the residue was dissolved in 10 ml of water. The solution was applied to a Dowex 50-X2 column (hydrogen form) and alanine was eluted with 1 *N* ammonia. Fractions which contained alanine were combined and evaporated to dryness *in vacuo*.

(18) A. J. Little, J. McLean, and F. J. Wilson, *J. Chem. Soc.*, 337 (1940).

Alanine (680 mg, 76%) was obtained, $[\alpha]^{25}D$ −11.6° (*c* 3.75, 5 *N* HCl), 80% optically pure. The alanine was converted into DNP-alanine in the conventional manner,[11] and the resulting DNP derivative was purified by the use of a Celite column treated with pH 7.0 citrate buffer.[12] The DNP-alanine was extracted and crystallized: mp 170–173°; $[\alpha]^{25}D$ −120° (*c* 0.40, 1 *N* NaOH), 83% optically pure.

Optically active aspartic acids were prepared in the same way as above from oxaloacetic acid (reaction 26). The resulting aspartic acid and alanine were separated by the use of a Dowex 2-X8 column (formate form) by eluting with water. The aspartic acid combined with the resin was eluted with 1 *N* formic acid.

Other experimental procedures used in this study were similar to those which were reported already.[10]

Registry No.—(*S*)(+)-ala, 56-41-7; (*R*)(−)-ala, 338-69-2; (*S*)(+)-ala benzyl ester, 17831-01-5; (*R*)(−)-ala benzyl ester, 17831-02-6; (*S*)(+)-ph-gly, (*S*)(+)-asp, 56-84-8; (*R*)(−)-asp, 1783-96-6; (*S*)(+)-glu, 56-86-0; (*R*)(−)-glu, 6893-26-1.

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Novel 1-Thiovinyl Phosphates and Related Materials

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Phosphites react with aryl and aralkyl chlorothiolacetates to give principally 1-thiovinyl phosphates; simple alkyl chlorothiolacetates give mixtures containing appreciable amounts of the isomeric phosphonates. Di- and trichlorothiolacetates give almost exclusively phosphates. Several of the phosphates were oxidized to the corresponding 1-sulfinyl and 1-sulfonylvinyl analogs. Proof of structure and mechanisms are given.

The literature on the reaction of halothiolacetates and trialkyl phosphites has been confusing. As early as 1951, S-ethyl,[1,2] S-carbethoxymethyl, S-phenyl, and other S-aryl trichlorothiolacetates[2] with triethyl phosphite were claimed to give phosphonates. Mel'nikov, *et al.*,[3,4] claimed the phosphonate structure for the products from ethyl, *p*-chlorophenyl, and 2,4,5-trichlorophenyl chlorothiolacetates similar to the products obtained from alkyl and aryl chloroacetates.[5] Patent literature[6−8] available after most of the work reported herein had been completed has disclosed 1-thiovinyl phosphates and the corresponding 1-sulfinylvinyl phosphates having only —C=CHCl and —C=C-Cl_2 groups. The —C=CCl_2 compounds might be expected since the structure of the reaction products obtained from trialkyl phosphites and trichloroacetates has been shown[9−11] to be that of the vinyl phosphate; however, the corresponding phosphonate structure from the trichloroacetates has also been indicated in some earlier literature.[12,13] More recently, Gololobov[14] reported a series of 1-thiovinyl phosphates obtained from S-ethyl mono-, di-, and trichlorothiolacetates and phosphites. Gololobov reported obtaining mixtures with the monochloro ester and only vinyl phosphates with the di- and trichloro esters.

1-Thiovinyl Phosphates.—Our work independently showed that alkyl esters of monochlorothiolacetates gave mixtures while the corresponding aryl esters gave predominantly the 1-thiovinyl phosphates. All of the di- and trichloro esters used in this work gave the vinyl phosphates as the only detectable product.

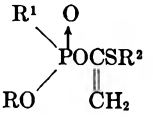
The S-substituted 1-thiovinyl phosphates,[15] yields, analyses, and properties are shown in Tables IA and IB. Yields in general were high. The phosphates generally are high-boiling liquids, not well purified by distillation. In one case where the thiovinyl phosphate (**1**) and the isomeric phosphonate were separated by distillation, the phosphonate was the higher boiling. Elemental analysis does not distinguish the 1-thiovinyl phosphates from the isomeric phosphonate; however, infrared spectra clearly established the 1-thiovinyl phosphate structure and were also used to detect the presence of phosphonate. Calibrated infrared spectra were not obtained, and a minimum of 5–10% of the phosphonate could probably be detected.

Proof of Structure.—It was noted early in this work that the infrared spectra did not confirm the phosphonate structure, primarily owing to the absence of a carbonyl band in the 5.5–6.0-μ region. The phosphate structure was assigned on the basis of the presence of a C=C band in the 6–6.2-μ region and a split P→O band characteristic of phosphates.[16]

The spectrum of **1**, like those of all of the 1-thiovinyl phosphates, had no C=O absorption at 5.89 μ which was present in the spectra of the phosphonates of this type. A moderately strong C=C absorption at 6.21 μ was present in **1** but absent in the phosphonates. Also, **1** had a split P→O absorption at 7.7 and 7.8 μ which is characteristic of a phosphate group, while the phosphonates had a single P→O absorption at 7.95 μ characteristic of a phosphonate grouping.[17]

(1) Ciba A.-G., Switzerland Patent 310,409 (1955).
(2) Farbenfabriken Bayer A.-G., German Patent Application F10,391 (120 23/03) (1955).
(3) N. N. Mel'nikov, *et al.*, USSR Patent 116,879 (1958).
(4) N. N. Mel'nikov, Ya. A. Mandel'baum, and V. I. Lomakina, *J. Gen. Chem. USSR* (Engl. Transl.), **29**, 3252 (1959).
(5) Ciba A.-G., Switzerland Patent 310,410 (1955).
(6) Sumitomo Chemical Industries Co., Ltd., Japan Patent Publication No. 4998 (1960).
(7) Sumitomo Chemical Industries Co., Ltd., Japan Patent Publication No. 13148 (1960); see also 17015 (1960).
(8) Sumitomo Chemical Industries Co., Ltd., Japan Patent Publication No. 16438 (1960).
(9) P. Mueller (to J. R. Giegy A.-G.), Switzerland Patent 326,948 (1958).
(10) Sumitomo Chemical Industries Co., Ltd., Japan Patent Publication No. 13147 (1960).
(11) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).
(12) R. Sallmann (to Ciba Ltd.), U. S. Patent 2,830,927 (1958).
(13) R. Sallmann (to Ciba Ltd.), U. S. Patent 2,861,914 (1958).
(14) Yu. G. Gololobov, *J. Gen. Chem. USSR* (Engl. Transl.), **35**, 1246 (1965).
(15) L. F. Ward, Jr., and D. D. Phillips (to Shell Chemical Co.), U. S. Patent 3,069,313 (1962).
(16) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956.
(17) F. S. Mortimer, *Spectrochim. Acta*, **9**, 270 (1957).

Table IA
Structure and Properties of 1-Thiovinyl Phosphates Unsubstituted in 2 Position

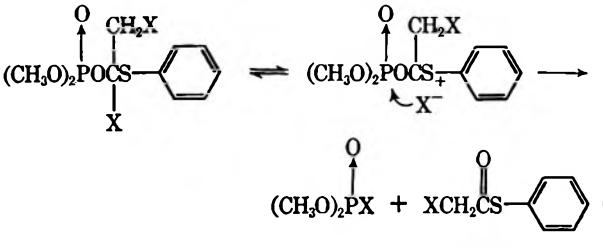


Compd	R	R¹	R²	Yield, %	Bp, °C (mm)	$n^{25}D$	d (25°)		Anal., % Found	Anal., % Calcd	Hydrolysis, 38°, half-life, hr: pH 1.1[a]	Hydrolysis, 38°, half-life, hr: pH 9.1[b]
1	CH_3	CH_3O	CH_3	34	67–68 (<0.02)	1.4695	1.2	P	15.7	15.7	7	60
								S	16.4	16.2		
								Cl	<0.1	0.0		
2	CH_3	CH_3O	C_6H_5	68	95–98 (0.018)	1.5320	1.2	P	11.8	11.9	<7	170
								S	11.7	12.3		
								Cl	0.2	0.0		
3	CH_3	CH_3O	2-$C_{10}H_7$	75	145–150 (0.001)	1.6000	1.3	P	9.5	10.0	7	70
								S	10.7	10.3		
								Cl	0.46	0.0		
4	C_2H_5	C_6H_5	C_6H_5	72	145–150 (0.001)	1.5684	1.0	P	9.8	9.7	7	10
								S	10.1	10.0		
								Cl	0.26	0.0		
5	C_2H_5	C_2H_5O	C_6H_5	81	110–120 (0.001)	1.5182	1.1	P	10.8	10.8	<5	>100
								S	11.0	11.1		
								Cl	<0.1	0.0		
6	*i*-C_3H_7	*i*-C_3H_7O	C_6H_5	72	90 (0.001)	1.5032	1.1	P	9.6	9.8	9	120
								S	10.3	10.1		
								Cl	0.39	0.0		
7	C_4H_9	C_4H_9O	C_6H_5	80	125 (0.001)	1.5028	1.1	P	9.0	9.0	9	120
								S	9.0	9.3		
								Cl	0.35	0.0		
8	CH_3	CH_3O	*p*-ClC_6H_4	78	100–105 (0.001)	1.5442	1.3	P	10.6	10.5	<7	110
								Cl	12.3	12.1		
9	C_2H_5	C_2H_5O	*p*-ClC_6H_4	76	115 (0.001)	1.5302	1.2	P	9.1	9.6	<7	>300
								S	9.9	10.5		
10	CH_3	CH_3O	$Cl_3C_6H_2$	90	Crude	1.5610	1.5	P	8.5	8.5	24	35
								S	8.3	8.8		
								Cl	28.8	29.3		
11	C_2H_5	C_2H_5O	$Cl_3C_6H_2$	85	Crude	1.5568	1.4	P	7.1	7.9	14	115
								S	7.7	8.2		
								Cl	27.7	27.2		
12	CH_3	CH_3O	*p*-$NO_2C_6H_4$	76	Mp 70–71	...	...	P	10.3	10.2	24	75
								S	11.0	10.5		
								Cl	0.25	0.0		
13	CH_3	CH_3O	*p*-$CH_3C_6H_4$	71	118–122 (0.001)	1.5328	1.2	P	11.3	11.3	11	58
								S	11.8	11.6		
								Cl	0.4	0.0		
14	CH_3	CH_3O	$C_6H_5CH_2$	67	135–140 (0.001)	1.5295	1.2	P	11.8	11.3	12	35
								S	11.5	11.7		
								Cl	0.64	0.0		
15	C_2H_5	C_2H_5O	$C_6H_5CH_2$	68	125 (0.001)	1.5197	1.2	P	10.5	10.3	13	36
								S	10.8	10.6		
								Cl	0.27	0.0		

[a] 0.2–2.0 ppm in aqueous HCl. [b] 0.2–2.0 ppm in aqueous $K_2B_4O_7$.

With these exceptions and a band at 10.0–10.2 μ in the spectra of **1**, tentatively assigned to the C=CH_2 group, the spectra were otherwise very similar. The nmr spectra were also obtained for four 1-thiovinyl phosphates, and the nmr parameters are shown in Table II. These confirmed the presence of olefinic protons and absence of a saturated methylene group. In the case of **16** and **17** the presence of two doublets near 3.6 and 6.5 ppm indicated the presence of isomers around the double bond.

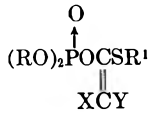
Halogenation of **2** and **5** afforded additional evidence of structure. Addition of 1 mol of chlorine (from sulfuryl chloride) to each of these materials gave the dichloroethyl phosphates. The infrared spectra of these two products no longer contained the C=C band at 6.2 μ. In addition, a band at about 10.2 μ present in all of the 1-thiovinyl phosphates containing either a C=CH_2 or C=CCl_2 grouping had been eliminated. Bromination of **2** also appeared to give the similar dibromoethyl phosphate. Both the chlorinated and brominated products decomposed to two immiscible materials shown by infrared spectra to be dimethyl halophosphate and S-phenyl halothiolacetate, presumably as shown in eq 1. Even though the halo-



(1)

TABLE IB

STRUCTURE AND PROPERTIES OF 1-THIOVINYL PHOSPHATES SUBSTITUTED IN 2 POSITION

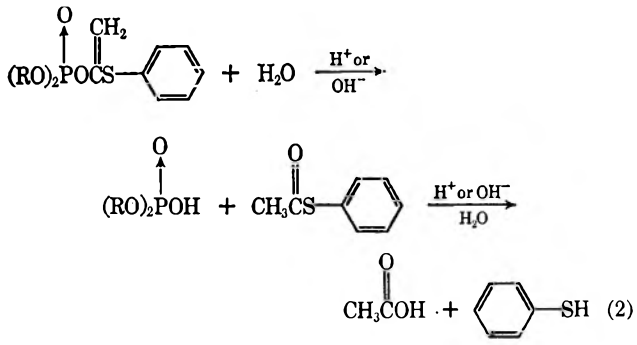


Compd	R	R¹	X	Y	Yield, %	Bp, °C (mm)	$n^{25}D$	d (25°)		Anal., % Found	Anal., % Calcd	Hydrolysis, 38°, half-life, hr pH 1.1[a]	Hydrolysis, 38°, half-life, hr pH 9.1[b]
16	CH_3	CH_3	H	Cl	90	80–81 (0.02)	1.4892	1.4	P	13.6	13.3	45	35
									S	13.9	13.8		
									Cl	15.4	15.3		
17	CH_3	C_6H_5	H	Cl	84	110 (0.001)	1.5468	1.3	P	10.6	10.5	120	28
									S	11.0	10.9		
									Cl	11.7	12.0		
18	C_2H_5	$C_6H_5CH_2$	H	Cl	65	125 (0.001)	1.5269	1.2	P	9.2	9.2		
									S	9.8	9.5		
									Cl	10.0	10.5		
19	C_2H_5	C_6H_5	Cl	Cl	77	110 (0.001)	1.5402	1.4	P	8.6	8.7	140	70
									S	8.7	9.0		
									Cl	20.1	19.9		
20	CH_3	C_6H_5	Cl	Cl	75	95 (0.001)	1.5565	1.4	P	9.3	9.4	77	14
									S	9.7	9.7		
									Cl	21.4	21.6		
21	CH_3	CH_3	Cl	Cl	87	94 (0.02)	1.5030	1.4	P	11.5	11.6	93	17
									S	12.0	12.0		
									Cl	26.5	26.6		
22	CH_3	C_6H_5	F	F	75	75–82 (0.001)	1.5023	1.3	P	10.9	10.5	170	13
									S	11.1	10.8		
									Cl	<0.1	0.0		

[a] 0.2–2.0 ppm in aqueous HCl. [b] 0.2–2.0 ppm in aqueous $K_2B_4O_7$.

genation was not a simple process, the intermediate and final products nevertheless substantiate the vinyl phosphate structure assigned.

Hydrolysis, described in more detail later, also afforded additional evidence of structure. In both acidic and basic solutions, the simple thiovinyl phosphates **2** and **5** hydrolyzed first at the POC bond followed by hydrolysis of the resultant thiolacetate (eq 2). This was demonstrated both by infrared spectra



and by glpc during the first 10–20% of hydrolysis in which essentially all of the material was present either as the 1-thiovinyl phosphate or as the thiolacetate. The thiolacetate was converted into benzenethiol during the later stages of hydrolysis.

Selectivity of Reaction.—Many variations were made both in substituents of the S-ester group as well as in the groups attached to phosphorus. The various changes affected the rate of reaction as followed by infrared spectroscopy. Conditions required for complete reaction varied from 1 hr at 60° to 14 hr at 110–130°. From the reaction times and temperatures, the following general conclusions concerning reactivity

TABLE II

NMR PARAMETERS

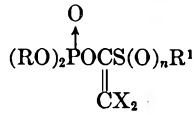
Compd	Group	Chemical shift δ, ppm	Coupling constant, Hz	Multiplicity	No. of protons
2	$-OCH_3$	3.6	$J = 11$	Doublet	6
	$=CH_2$	5.0	$J = 2$	Triplet	1
		5.32	$J = 2$	Triplet	1
	Aromatic	7.37			5
1	$-SCH_3$	2.31			3
	$-OCH_3$	3.82	$J = 11$	Doublet	6
	$=CH_2$	4.76	$J = 2$	Quartet	1
		5.10	$J = 2$	Quartet	1
16	$-SCH_3$	2.4			3
	$-OCH_3$	3.86, 3.87	$J = 11$	Two doublets	6
	$=CH-$	6.11	$J = 1$	Doublet	0.4
		6.38	$J = 3$	Doublet	0.6
17	$-OCH_3$	3.60, 3.67	$J = 11$	Two doublets	6
	$=CH-$	6.38	$J = 1.5$	Doublet	0.3
		6.6	$J = 3.0$	Doublet	0.7
	Aromatic	7.36			5

were drawn for the S-esters and phosphites reacted: (1) with S-phenyl chlorothiolacetate and different phosphites $C_6H_5P(OCH_3)_2 > (CH_3O)_3P > (C_2H_5O)_3P \cong (CH_3O)_2PN(CH_3)_2 > (i\text{-}C_3H_7O)_3P \cong (n\text{-}C_4H_9O)_3P \gg (CH_3O)_2POC_6H_5$: (2) with trimethyl phosphite and with variation in the R group of $ClCH_2C{=}OSR$ (a) $p\text{-}NO_2C_6H_4 > C_6H_5 \cong p\text{-}ClC_6H_4 \cong 2,4,5\text{-}Cl_3C_6H_2 > p\text{-}t\text{-}C_4H_9C_6H_4 > p\text{-}CH_3C_6H_4 \gg o\text{-}CH_3C_6H_4$, (b) $C_6H_5 > 2\text{-}C_{10}H_7 > C_6H_5CH_2 \gg C_6H_5CHCH_3$, (c) $C_6H_5CH_2 \gg CH_3OC{=}OCH_2 \gg CH_3$.

S-Aryl Analogs.—S-Aryl monochloro-, dichloro-, and trichlorothiolacetates were all found to yield only the corresponding S-substituted 1-thiovinyl phosphates as detected by infrared spectroscopy. This is in direct contrast to the product obtained from

Table III

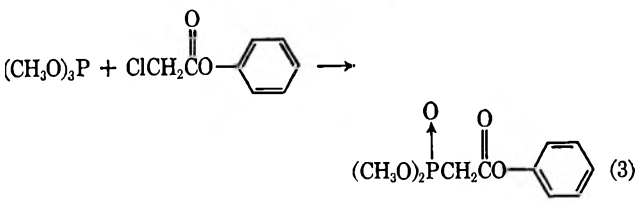
Structure and Properties of 1-Sulfinylvinyl and 1-Sulfonylvinyl Phosphates



Compd	R	R¹	X	n	Precursor (1-thiovinyl phosphate)	Yield, %	Bp, °C (mm)	$n^{25}D$	d (25°)		Anal., % Found	Anal., % Calcd	Hydrolysis, 38°, half-life, hr pH 1.1[c]	Hydrolysis, 38°, half-life, hr pH 9.1[d]
23	C_2H_5	C_6H_5	H	1	5[a]	69	115–120 (0.008)	1.5173	1.25	P	10.5	10.2	100	14
										S	10.5	10.5		
24	CH_3	p-ClC_6H_4	H	1	8[a]	44	120 (0.001)	1.5431	1.4	P	10.0	10.0	29	9
										S	10.8	10.3		
25	C_2H_5	$C_6H_5CH_2$	H	1	15[a]	66	125 (0.001)	1.5205	1.22	P	9.9	9.8	170	12
										S	10.2	10.1		
26	CH_3	CH_3	H	1	1[a]	51	75–80 (0.001)	1.4709	1.28	P	14.6	14.5	26	<7
										S	15.4	15.0		
27	C_2H_5	C_6H_5	H	2	5[b]	66	130–135 (0.009)	1.5045	1.25	P	9.8	9.7	40	8
										S	10.6	10.0		
28	CH_3	p-ClC_6H_4	H	2	8[b]	53	128 (0.001)	1.5321	1.4	P	9.2	9.5	17	<7
										S	10.3	9.8		
29	C_2H_5	p-ClC_6H_4	H	2	9[a]	68	125–130 (0.008)	1.5140	1.3	P	9.0	8.7	13	<7
										S	9.3	9.0		
30	CH_3	$Cl_3C_6H_2$	H	2	10[b]	79	Crude	1.5560	...	P	7.8	7.9	30	<8
										S	7.8	8.1		
31	C_2H_5	$C_6H_5CH_2$	H	2	15[a]	61	120–125 (0.001)	1.5082	1.24	P	9.3	9.3	46	<7
										S	9.9	9.6		
32	CH_3	CH_3	H	2	1[a]	80	Crude	1.4545	...	P	13.6	13.5	13	<7
										S	13.7	13.9		
33	C_2H_5	C_6H_5	Cl	2	19[b]	92	Crude	1.5322	...	P	7.8	8.0	...	...
										S	7.9	8.2		

[a] Peracetic acid used as oxidizing agent. [b] Monoperphthalic acid used as oxidizing agent. [c] 0.2–2.0 ppm in aqueous HCl. [d] 0.2–2.0 ppm in aqueous $K_2B_4O_7$.

phenyl chloroacetate (eq 3) which was only the phosphonate shown by the absence of any bands in the C=C region of the infrared spectra.



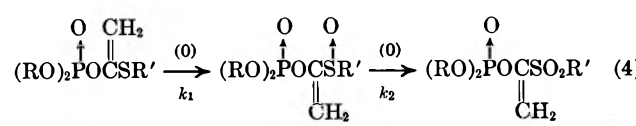
(3)

S-Aralkyl Analogs.—Aralkyl esters, *i.e.*, S-benzyl chlorothiolacetate, like the aryl analogs, also normally gave thiovinyl phosphates. These thiolacetates were in general less reactive than the S-phenyl materials, but gave the same high yields. However, the S-*p*-methylbenzyl and S-α-methylbenzyl chlorothiolacetates reacted with trimethyl phosphite very slowly, and both products contained some inseparable isomeric phosphonate. These exceptions might indicate that more of the 1-thiovinyl phosphates contain small amounts of the isomeric phosphonates, not detected with the methods used.

S-Alkyl Analogs.—All of the simple S-alkyl chlorothiolacetates gave mixtures of phosphates and phosphonates. The S-methyl ester gave about a 1:1 ratio of the 1-thiovinyl phosphate 1 (Table IA) and phosphonate. These two materials were separated by distillation, with the phosphate being the lower boiling component. Infrared spectrum of the mixture from the S-butyl ester indicated a predominance of phosphate. In contrast, although infrared spectroscopy indicated the presence of phosphate during the reaction, the S-allyl ester gave the phosphonate as the only isolable material. The methoxycarbonyl group when substituted on the methyl group of methyl chlorothiolacetate acted much like the phenyl portion of the benzyl group, discussed above, in that the vinyl phosphate was obtained in high yield. A consequence of this observation is discussed in the section devoted to the mechanism of the reaction.

The dichloro- and trichlorothiolacetates with S-alkyl ester groups reacted similarly to the corresponding S-aryl and S-aralkyl esters; *e.g.*, only 1-thiovinyl phosphates were detected or isolated. The S-alkyl dichloro- and trichlorothiolacetates had about the same reactivity requiring about 1 hr at 100°, whereas the corresponding monochloro derivatives were much less reactive requiring 13–14 hr at 100° for complete reaction.

Other Chemistry of 1-Thiovinyl Phosphates. Oxidation.—Several of the 1-thiovinyl phosphates were oxidized to the corresponding sulfoxides and sulfones.[18] These compounds and their properties are shown in Table III. The reaction with 2 equiv of oxidant apparently went stepwise *via* the sulfoxide. This was evidenced by the absence of the sulfone (SO_2) bands (7.4, 8.7 μ) in the infrared spectra of products obtained when exactly 1 equiv of oxidant was used. Thus, k_1 must be many times faster than k_2 (eq 4).



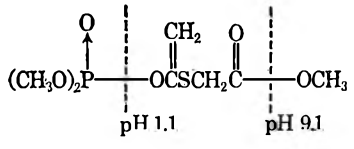
(4)

(18) D. D. Phillips and L. F. Ward, Jr. (to Shell Chemical Co.), U. S. Patent 3,151,147 (1964).

Hydrolysis.—The hydrolysis studies of the vinyl phosphates and related materials were carried out on aqueous solutions containing 0.2–2.0 ppm of the phosphate, using HCl for pH 1.1 and potassium tetraborate buffer for pH 9.1. In general, diethyl phosphates were more stable than the corresponding dimethyl compounds. Under strongly acidic conditions, hydrolysis was extremely rapid, especially with phosphates containing the C=CH_2 grouping, and very little difference in stability of ethyl–methyl pairs was noted.

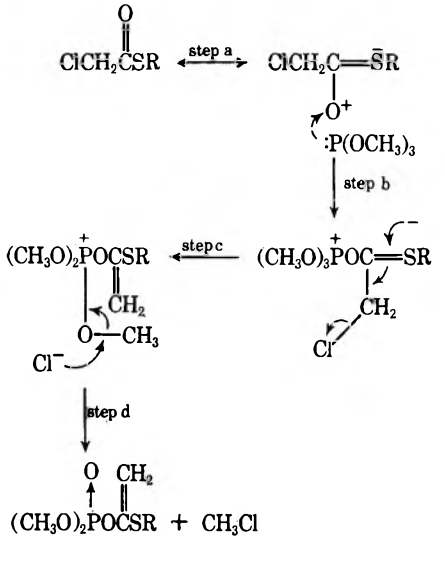
Except for the 1-thiovinyl phenylphosphonate (**4**) and the methoxycarbonylmethyl compound shown below, all of the phosphates containing an unoxidized sulfur (CSR′) and an unsubstituted α-methylene group (C=CH_2) were much less stable at pH 1.1 than at 9.1. This could be expected in view of their resemblance to acetals. However, when one of the α-methylene hydrogens was replaced by a methyl group, the stability at the two pH's was about the same. When one or both hydrogens were replaced by chlorine, the stability picture was reversed, and these halogenated derivatives were more stable at pH 1.1 than at pH 9.1. In general, the dichloro compounds were less stable than the corresponding monochloro analogs. Oxidation of the sulfur either to sulfoxide or sulfone also resulted in greater stability in acid solution, with the sulfoxide being the most stable. These results were expected owing to an inductive effect caused by the electron-withdrawing power of halogens and sulfoxide or sulfone groups which would tend to make the displaced anion and subsequent alcohol more stable as noted by Vernon.[19] There was no obvious reason for the instability of **4** in base, but the electron-attracting character of the benzene ring might make the P—O—C=C bond more susceptible to attack by bases.

In the case of the methoxycarbonylmethyl compound, an additional site is provided for hydrolysis. Carboxylic esters are rapidly hydrolyzed in base.[16] Consequently, under basic conditions, the hydrolysis of the O=$COCH_3$ group was probably the rate-determining step, whereas in acid the hydrolysis of the POC=C bond determined the rate as shown. Hydrolysis of one or both of the methyl ester groups on phosphorus was also possible. However, as discussed earlier, only starting phosphate and thiolacetate were detected in the early stages of hydrolysis.



Mechanism of Reaction.—The mechanism of the reaction of trialkyl phosphites with α-halocarbonyl compounds to give vinyl phosphates has not been established. Attack of the carbonyl carbon by phosphorus followed by intramolecular rearrangement has been proposed to be the most likely mechanism with attack at the carbonyl oxygen less likely.[11,20,21] With halothiolacetates, however, attack on the carbonyl oxygen is most likely.

This mechanism involves the ability of the sulfur atom to expand its outer valence shell to ten electrons by use of the d orbitals, thus making the carbonyl oxygen somewhat positive (eq 5, step a). The electron-withdrawing character of the SR group is demonstrated by the infrared studies of Baker and Harris[22] who show that in thiolacetates, $O^+=C=\bar{S}R$ is present. This electron-withdrawing character of the SR groups is also evidenced by the contrasting reactions of ethynyl ethers and thio ethers with nucleophilic reagents.[23] It will be noted that reaction of the unpaired electrons of trimethyl phosphite with the positive oxygen (step b) can give the phosphate bond directly; then the normal bond shifts (steps c and d) produce the 1-thiovinyl phosphate. The type of resonance depicted in step a becomes especially attractive when there is attached to sulfur a group which acts as an electron sink such as phenyl and substituted phenyl groups. This allows the negative charge to be delocalized to a greater extent and thus stabilizes the resonance hybrid.



(5)

The chemistry discussed earlier lends support to this mechanism. Attack on carbonyl oxygen can account for the formation of the vinyl phosphate from S-alkyl chlorothiolacetates. Simple alkyl groups are not electron sinks; in fact, they are somewhat electron donating.[24] However, the electron-withdrawing capacity of the sulfur apparently is still strong enough to produce some positive charge on the carbonyl oxygen. Thus, the reaction proceeds partly by this path when R is methyl and almost completely by step a when R is aryl.

The structural effect on reactivity of the aryl and aralkyl chlorothiolacetates mentioned earlier also lends support for attack on oxygen. Thus, substitution in the *para* position with a very strong electron-withdrawing group such as nitro increases the reactivity whereas substitution with electron-donating groups such as methyl or *t*-butyl decreases the reactivity.

In addition to the electron-attracting properties of the sulfur, one must consider the inductive effect of the

(19) C. A. Vernon, "Phosphoric Esters and Related Compounds," Special Publication No. 8, The Chemical Society, London, 1957, p 31.

(20) E. L. Gefter, "Organophosphorus Monomers and Polymers," Associated Technical Services Inc., Glen Ridge, N. J., 1962, pp 31–36.

(21) B. Miller, "Topics in Phosphorus Chemistry," Vol. 2, Interscience Publishers, New York, N. Y., 1965.

(22) A. W. Baker and G. H. Harris, *J. Amer. Chem. Soc.*, **82**, 1923 (1960).

(23) B. A. Raphael, E. C. Taylor, and H. Wynberg, *Advan. Org. Chem.*, **2**, 151 (1960).

(24) A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1947, p 149.

halogens. Additional chlorines as in di- and trichlorothiolacetates cause the carbonyl oxygen to become even more positive and account for the increased rates of reaction noted. Even when R is methyl, only two chlorines are required to shift product formation entirely over to the vinyl phosphate **16**.

Thus, based on the chemistry above and the work reported on thio esters,[22,23] attack on oxygen appears to be the most reasonable mechanism for thiolacetates.

Experimental Section

Instruments.—The infrared spectra were obtained on a Beckman IR-4 spectrophotometer, using carbon disulfide or methylene chloride as solvent and a 0.1-mm sodium chloride cell. Certain spectra were obtained with a Beckman IR-5 spectrophotometer. The nmr spectra were obtained in a Varian A-60 instrument with tetramethylsilane as internal reference standard. Chemical shifts are reported in parts per million (δ) from tetramethylsilane and coupling constants are reported in cycles per second (cps).

Preparation of Chlorothiolacetates.—All of the chlorothiolacetates used in the preparation of the thiovinyl phosphates and related materials were made from the appropriate thiols and haloacetyl chlorides following the procedure described by Dalgleish and Mann.[25] Yields generally were in excess of 70%.

Preparation of 1-Thiovinyl Phosphates and Isomeric Materials.—Two examples are given: (1) a preparation which gave vinyl phosphate cleanly, and (2) a preparation from which both 1-thiovinyl phosphate and the isomeric phosphonate were isolated.

Diethyl 1-(Phenylthio)vinyl Phosphate (5).—To S-phenyl chlorothiolacetate (259 g, 1.39 mol) at 90–100° was added triethyl phosphite (266 g, 1.60 mol), heated for a total of 4.5 hr at 110–120° and stripped to 125° (0.05 mm) (kettle temperature) to remove lower boiling materials. Molecular distillation of the residue gave an 81% yield of **5** as a pale yellow liquid: boiling range 110–120° (0.001 mm); n^{25}D 1.5182; ir 3.23 (=CH), 6.2 (C=C), 7.62, 7.7 (P→O) (phosphate), 10.1 μ (C=CH_2).

Anal. Calcd for $PSO_4C_{12}H_{17}$: P, 10.8; S, 11.1; Cl, 0.0. Found: P, 10.8; S, 11.0; Cl, <0.1.

Dimethyl 1-(Methylthio)vinyl Phosphate (1) and S-Methyl (Dimethoxyphosphinyl)thioacetate.—Trimethyl phosphite (97% pure) (119 g, 0.92 mol of 100% purity) was added over 1 hr to the chloro ester (100 g, 0.80 mol) at 90–95°. The mixture was then heated for 13.5 hr at 90–115°, checking by infrared spectroscopy periodically to determine the extent of reaction. The mixture was then Claisen distilled to give two main fractions: (1) 58 g; bp 76–78° (0.02 mm); infrared, strong C=C, weak C=O, (2) 31 g; bp 95–105° (0.02 mm); infrared, very weak C=C, very strong C=O. Redistillation of fraction 1 through an 8-in. Bantam-ware unpacked column gave 41 g (26% yield) of **1** as a yellow liquid: bp 73° (0.02 mm); n^{25}D 1.4710. Fraction 2, above, gave 31 g (20% yield) of the isomeric phosphonate, a yellow liquid, which was not further purified: bp 95–105° (0.02 mm); n^{25}D 1.4770. Infrared analysis indicated that little if any phosphonate was present in **1**.

Anal. Calcd for $PSO_4C_5H_{11}$: P, 15.7; S, 16.2; Cl, 0.0. Found for **1**: P, 16.0; S, 15.5; Cl, 0.2. Found for crude phosphonate: P, 16.6; S, 13.6; Cl, 0.5.

Phenyl (Dimethoxyphosphinyl)acetate.—Trimethyl phosphite (27.5 g, 0.22 mol) was added to phenyl chloroacetate (34 g, 0.20 mol) at 35°. The resultant mixture was heated over 1.25 hr to a kettle temperature of 140°. Heating was continued for an additional 7 hr at 115–140°. The crude product was stripped at 95° (0.001 mm) and molecularly distilled at 105–110° (0.001 mm) to give 28 g (58% yield) of the phosphonate: n^{25}D 1.5011; ir 3.50 (O—CH_3), 5.65 (C=O), 7.82 (P→O) (phosphonate), 9.6 μ (P—O—C). The infrared spectra of samples taken during the reaction and also prior to stripping showed no vinyl phosphate formation as evidenced by the absence of bands in the 6.0–6.2-μ region.

Anal. Calcd for $PO_5C_{10}H_{13}$: P, 12.7; Cl, 0.0. Found: P, 12.6; Cl, 0.5.

Diethyl 1-(Phenylsulfinyl)vinyl Phosphate (23).—To the 1-thiovinyl phosphate **5** (57.6 g, 0.20 mol) in 150 ml of chloroform was added 136 ml of a solution of peracetic acid in chloroform (15.9 g, 0.21 mol) over a 2.25-hr period at 20–30° with ice-bath cooling as needed. The mixture was stirred for an additional 1 hr at 25–30° when titration indicated only the excess (0.7 g) of peracetic acid remained. The solution was washed with cold aqueous 10% sodium bicarbonate solution until the washings were slightly basic to pH paper, separated, dried with magnesium sulfate, and stripped to remove solvent. The residual liquid was stripped and molecular distillation gave 42 g (69% yield) of **23** as a yellow liquid: bp 115–120° (0.008 mm); n^{25}D 1.5173; infrared spectrum, similar to **5** except bands at 8.4, 9.15, and 9.45 μ, new or stronger; S→O near normal with smaller band near 8.5 μ.

Anal. Calcd for $PSO_5C_{12}H_{17}$: P, 10.2; S, 10.5. Found: P, 10.5; S, 10.5.

Dimethyl 1-(Methylsulfonyl)vinyl Phosphate (32). Method 1. Monoperphathalic Acid.—To the phosphate **1** (4.95 g, 0.025 mol) in 30 ml of ether was added 156 ml of an ethereal solution of monoperphthalic acid (9.55 g, 0.053 mol). The temperature rose spontaneously to 35°. The mixture was refluxed for 1 hr when titration showed 0.08 g of per acid remaining. The solution was filtered and washed with a 5% aqueous sodium bicarbonate solution until washings were basic to pH paper. The washings were saturated with sodium chloride and extracted five times with 50 ml of methylene chloride each. The ether and methylene chloride solutions were combined, and the total was dried with magnesium sulfate. The solvent was removed, and the residual liquid was stripped to a final temperature of 50° (0.2 mm) to give 4.5 g (80% yield) of **32** as a yellow liquid: n^{25}D 1.4545; infrared spectrum, some changes from **1**, with the most prominent being the SO_2 bands at 7.5 and 8.8 μ.

Anal. Calcd for $PSO_6C_5H_{11}$: P, 13.5; S, 13.9. Found: P, 13.6; S, 13.7.

Method 2. Peracetic Acid.—To **1** (45.5 g, 0.23 mol) in 20 ml of chloroform was added 385 ml of a solution of peracetic acid (41 g, 0.54 mol) in chloroform, and the temperature was maintained at 25–35° by ice-bath cooling as needed. The mixture was stirred for an additional 1.5 hr at 25–30° when titration showed only the excess (6.2 g) per acid remained. Work-up similar to method 1 and molecular distillation gave 32 g (60% yield) of **32** as a very pale yellow liquid: bp 85° (0.002 mm); n^{25}D 1.4552; infrared spectrum, similar to that in method 1 above, 7.49 and 8.78 μ for SO_2 bands.

Anal. Calcd for $PSO_6C_5H_{11}$: P, 13.5; S, 13.9. Found: P, 13.8; S, 14.1.

1,3-Dichloro-2-(phenylthio)ethyl Diethyl Phosphate.—To the phosphate **5** (10.3 g, 0.036 mol) in 25 ml of methylene chloride cooled to 5° was added sulfuryl chloride (4.7 g, 0.035 mol) in 10 ml of methylene chloride. The temperature was maintained at 5–10° by use of a Dry Ice–acetone bath as needed. The resultant solution was warmed to ambient temperature over a period of 30 min and then stripped at 25° (1.0 mm) for 2 hr to give 12.6 g (99% yield) of 1,2-dichloro-2-(phenylthio)ethyl diethyl phosphate as a yellow oil: n^{25}D 1.5196.

Anal. Calcd for $PSO_4Cl_2C_{12}H_{17}$: P, 8.6; S, 8.9; Cl, 19.8. Found: P, 8.5; S, 9.1; Cl, 19.8.

Registry No.—**1,** 17604-41-0; **2,** 17604-42-1; **3,** 17604-43-2; **4,** 3661-33-4; **5,** 2274-95-5; **6,** 17604-46-5; **7,** 3661-28-7; **8,** 2595-53-1; **9,** 3842-84-0; **12,** 17604-50-1; **13,** 17604-51-2; **14,** 17604-52-3; **15,** 2595-51-9; **16,** 17604-16-9; **17,** 17604-17-0; **18,** 17604-18-1; **19,** 17604-54-5; **20,** 17604-55-6; **21,** 17604-56-7; **22,** 17604-57-8; **23,** 17659-02-8; **24,** 17604-58-9; **25,** 17604-59-0; **26,** 17604-60-3; **27,** 17604-61-4; **28,** 17604-62-5; **29,** 17604-63-6; **31,** 17604-64-7; **32,** 17604-65-8; **33,** 17604-66-9; phenyl (dimethoxyphosphinyl)acetate, 17604-67-0; 1,3-dichloro-2-(phenylthio)ethyl diethyl phosphate, 17604-68-1.

(25) C. E. Dalgliesh and F. C. Mann, *J. Chem. Soc.*, 559 (1947); *Chem. Abstr.*, **41**, 5445 (1947).

Peptide Synthesis *via* Oxidation of N-Acyl-α-amino Acid Phenylhydrazides. III. Dialanyl-Insulin and Diphenylalanyl-Insulin[1]

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t-Butyloxycarbonylamino acid phenylhydrazides were prepared by a papain-catalyzed reaction between the *t*-butyloxycarbonylamino acids and phenylhydrazine. These phenylhydrazides were oxidized with N-bromosuccinimide to give *t*-butyloxycarbonylamino acid phenyldiimides which were used in peptide syntheses. *t*-Butyloxycarbonyl-L-phenylalanine phenyldiimide reacted with glycine phenylhydrazide to give *t*-butyloxycarbonyl-L-phenylalanylglycine phenylhydrazide. *t*-Butyloxycarbonyl-L-alanine phenyldiimide and *t*-butyloxycarbonyl-L-phenylalanine phenyldiimide reacted with insulin in N,N-dimethylformamide and imidazole to give di-*t*-butyloxycarbonyl-L-alanyl- and di-*t*-butyloxycarbonyl-L-phenylalanyl-insulin. Upon treatment of the insulin derivatives with anhydrous trifluoroacetic acid, the *t*-butyloxycarbonyl groups were removed to yield diaminoacylinsulins. These diaminoacyl-insulins were treated with 2,4-dinitrofluorobenzene. Amino acid analysis of the resulting product indicated that the two aminoacyl groups were on the N terminals of the A and B chain and not on the ε-amino group of lysine 29 of the B chain. These diaminoacyl-insulins showed about the same biological activity which amounted to about 50% of that of bovine insulin in the mouse convulsion assay.

Previous communications have demonstrated that the oxidation of acylamino acid phenylhydrazides to yield phenyldiimides may be used as a procedure for carboxyl activation in peptide synthesis.[2] In the earlier studies the benzyloxycarbonyl group was used to protect the amino function. In view of recent developments in peptide chemistry involving extensive use of the *t*-butyloxycarbonyl (*t*-BOC)[3-5] group for amino protection, it was of interest to determine whether this protective group could be used successfully in the phenyldiimide activation.

There have been several procedures reported for the addition of amino acid residues to the amino groups of insulin. Fraenkel-Conrat[6] and Virupaksha and Tarver[7] treated aqueous solutions of insulin with carbamino anhydrides of amino acids (Leuchs' anhydrides). Although the anhydrides reacted to some extent with both of the α-amino groups at the N-terminus of the insulin chains as well as with the ε-amino groups of lysine, in no case did all of the amino groups react completely. Levy and Carpenter have recently reported a procedure by which new amino acid residues can be attached to all of the amino groups in insulin in such a fashion as to put only one amino acid residue on each amino group.[8] The procedure involved the reaction of *t*-butyloxycarbonyl- (*t*-BOC-) amino acid *p*-nitrophenyl esters with insulin in dimethylformamide, followed by removal of the *t*-BOC groups in anhydrous trifluoroacetic acid.

It was of interest to see if N-acyl-α-amino acid phenyldiimides could also be used as reagents for adding amino acid residues to insulin. We now wish to report a procedure by which new amino acid residues can be attached to the two α-amino groups of insulin leaving the ε-amino groups largely unsubstitued. The procedure involves the reaction of *t*-butyloxycarbonyl-amino acid phenyldiimides with insulin in dimethylformamide using imidazole as the base. The *t*-BOC groups are then removed in anhydrous trifluoroacetic acid.

Experimental Section[9,10]

Materials.—Bovine zinc insulin was obtained from Eli Lilly and Co. (lot no. 0LV000). *t*-BOC-amino acids were obtained from Calbiochem, Los Angeles, Calif. Dimethylformamide was purified by refluxing for 2 hr over calcium hydride followed by distillation under vacuum.

***t*-Butyloxycarbonylamino Acid Phenylhydrazides.**—The *t*-butyloxycarbonylamino acid phenylhydrazides were prepared by a papain-catalyzed method similar to that previously reported for other acylamino acids.[11] The *t*-butyloxycarbonylamino acid (5 mmol) and 35 mmol of sodium acerate were dissolved in a minimum volume (20–200 ml) of pH 4.7, 2 mol/l. acetate buffer. To this solution was added 20 mmol of phenylhydrazine hydrochloride, 10 mmol of cysteine hydrochloride, and 0.2 g of papain. The solution was flushed with nitrogen and incubated for 12–24 hr at 40°. At the end of this time the product was filtered, dried, and recrystallized from ethanol–water or ethyl acetate–petroleum ether (bp 30–60°). The yields, melting points, and elemental analyses are shown in Table I.

***t*-Butyloxycarbonylamino Acid Phenyldiimides.**—To a solution of *t*-butyloxycarbonylamino acid phenylhydrazide (0.01 mol) and pyridine (0.011 mol) in 100 ml of dichloromethane was added 0.01 mol of N-bromosuccinimide. The mixture was stirred for 15 min. The resulting red solution was washed with 100 ml of water, 100 ml of 1% citric acid, 100 ml of 5% sodium bicarbonate, and 100 ml of water. The dichloromethane solution was dried over magnesium sulfate; then the solvent was removed under vacuum to give a red oil. This material was used directly in further reactions without purification.

Reaction of *t*-Butyloxycarbonyl-L-alanine Phenyldiimide with (−)-2-Amino-4-methylpentane.—*t*-Butyloxycarbonyl-L-alanine phenyldiimide, prepared from 0.0279 g (0.1 mmol) of *t*-BOC-L-

(1) Supported in part by U. S. Public Health Service Research Grants AM 00608 and GM 11835 from the National Institutes of Health. For I and II of this series, see ref 2.

(2) (a) H. B. Milne and W. D. Kilday, *J. Org. Chem.*, **30**, 64 (1965); (b) H. B. Milne and Clark Most, Jr., *ibid.*, **33**, 169 (1968).

(3) L. A. Carpino, *J. Amer. Chem. Soc.*, **81**, 955 (1959).

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(5) R. Schwyzer and H. Kappeles, *Helv. Chim. Acta*, **44**, 1991 (1961).

(6) H. Fraenkel-Conrat, *Biochim. Biophys. Acta*, **10**, 180 (1953).

(7) T. K. Virupaksha and H. Tarver, *Biochemistry*, **3**, 1507 (1964).

(8) D. Levy and F. H. Carpenter, *J. Amer. Chem. Soc.*, **88**, 3676 (1966); *Biochemistry*, **6**, 3559 (1967).

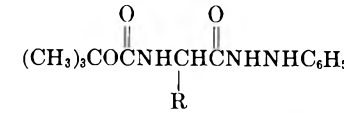
(9) The melting points are corrected. The microanalytical work was done by the Chemistry Department, University of California at Berkeley, Berkeley, Calif. The infrared spectra were determined with a Beckman IR-8 spectrophotometer. Visible and ultraviolet spectra were determined with a Cary Model 15 recording spectrophotometer. Biological assays by the mouse convulsion test and immuno assays were performed at Eli Lilly and Co. Amino acid analyses were performed on a Beckman-Spinco Model 120B automatic amino acid analyzer.[10] All hydrolyses were carried out in 6 *N* HCl in sealed evacuated tubes for 6 hr at 120°. Analysis for N-ε-DNP-lysine was performed on the short column using a pyridine (0.21 *M*) containing buffer at pH 5.28 according to an unpublished procedure of B. Africa.

(10) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(11) E. L. Bennett and C. Niemann, *J. Amer. Chem. Soc.*, **70**, 2610 (1948); H. B. Milne and C. M. Stevens, *ibid.*, **72**, 1742 (1950); H. B. Milne and C. H. Peng, *ibid.*, **79**, 645 (1957).

TABLE I

t-BUTYLOXYCARBONYLAMINO ACID PHENYLHYDRAZIDES



t-BOC amino acid phenylhydrazide	Registry no.	Yield,[a] %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
L-Ala	17790-84-0	74[b]	151–152	$C_{14}H_{21}N_3O_3$	60.17	7.58	15.04	60.25	7.53	15.34
Asp-β-benzyl ester	17790-85-1	57[b]	109–110	$C_{22}H_{27}N_3O_5$	63.89	6.58	10.16	63.98	6.59	9.95
Gly	17790-86-2	56[c]	122–123	$C_{13}H_{19}N_3O_3$	58.83	7.22	15.84	58.52	6.89	16.09
L-Leu	17790-87-3	74[c]	134–135	$C_{17}H_{27}N_3O_3$	63.53	8.47	13.07	63.39	8.33	12.99
L-Phe	17790-88-4	68[b]	134–135	$C_{20}H_{25}N_3O_3$	67.59	7.09	11.82	67.87	6.87	12.03
L-Trp	17790-89-5	66[b]	168–169	$C_{22}H_{26}N_4O_3$	66.94	6.65	14.20	66.82	6.68	14.42
L-Phe-Gly	17790-90-8	48[c]	145.5–146.5	$C_{22}H_{28}N_4O_4$	64.06	6.84	13.58	63.99	6.77	13.82

[a] After one recrystallization. [b] Recrystallized from ethanol–water. [c] Recrystallized from petroleum ether–ethyl acetate.

alanine phenylhydrazide in the usual manner, was mixed with a solution of 0.05 g (0.2 mmol) of (−)-2-amino-4-methylpentane tartrate and 0.04 ml of triethylamine in 10 ml of dichloromethane. After 15 hr the light yellow solution was diluted to 20 ml with dichloromethane. This solution was washed with 30 ml of water, 30 ml of 1% citric acid, 30 ml of 5% sodium bicarbonate, and 30 ml of water. The solution was then dried with anhydrous magnesium sulfate. The dichloromethane was removed under vacuum and the residue was redissolved in 5 ml of dichloromethane. This solution was analyzed by the glpc method of Halpern, *et al.*[12] The chromatogram indicated the presence of a large amount of *t*-BOC-L-alanine (−)-4-methyl-2-pentylamide and showed no evidence for *t*-BOC-D-alanine (−)-4-methyl-2-pentylamide.

Reaction of *t*-Butyloxycarbonyl-L-leucine Phenyldiimide with (−)-2-Amino-4-methylpentane.—*t*-Butyloxycarbonyl-L-leucine phenyldiimide, prepared from 0.0323 g (0.1 mmol) of *t*-BOC-L-leucine phenylhydrazide in the usual manner, was mixed with a solution of 0.05 g (0.2 mmol) of (−)-2-amino-4-methylpentane tartrate and 0.04 ml of triethylamine in 10 ml of dichloromethane. After 15 hr the yellow solution was diluted to 20 ml with dichloromethane and washed with 30 ml of water, 30 ml of 1% citric acid, 30 ml of 5% sodium bicarbonate, and 30 ml of water. The solution was dried over anhydrous magnesium sulfate, and the dichloromethane was removed under vacuum. The residue was dissolved in 5 ml of dichloromethane, and the resulting solution was analyzed by Halpern's glpc method. The resulting chromatogram showed the presence of *t*-BOC-L-leucine (−)-4-methyl-2-pentylamide but showed no evidence of *t*-BOC-D-leucine (−)-4-methyl-2-pentylamide.

***t*-Butyloxycarbonyl-L-phenylalanylglycine Phenylhydrazide.**—To a solution of 3.55 g (0.01 mol) of *t*-butyloxycarbonyl-L-phenylalanine phenylhydrazide and 0.81 ml of pyridine in 100 ml of dichloromethane was added 1.78 g (0.01 mol) of N-bromosuccinimide. The mixture was shaken for 15 min. The resulting red solution was washed with 100 ml of water, 100 ml of 1% citric acid, 100 ml of 5% sodium bicarbonate, and 100 ml of water. The solution was dried over magnesium sulfate; then the solvent was removed under vacuum to give a red oil. This oil was added to a solution of 2.70 g (0.0165 mol) of glycine phenylhydrazide[2b] in 75 ml purified dioxane. After 15 min the color had turned from red to yellow. At this time the solution was evaporated to dryness. The residue was dissolved in 100 ml of dichloromethane and washed with 100 ml of water, two 100-ml portions of 1% citric acid, and 100 ml of water. The dichloromethane solution was dried over magnesium sulfate, 250 ml of petroleum ether (bp 30–60°) was added, and the solution was stored overnight in a refrigerator. The mixture was filtered, yielding 1.53 g of white crystals, mp 144–145°. The filtrate was evaporated to dryness and the residue was dissolved in 30 ml of dichloromethane. About 200 ml of petroleum ether was added and the solution was stored in a refrigerator. An additional crop of crystals was obtained (0.48 g), total yield 2.01 g (50.2%). The *t*-butyloxycarbonyl-L-phenylalanylglycine phenylhydrazide was recrystallized from dichloromethane–petroleum ether to give a product: mp 144–145°; λ 280 mμ (ε 1480), 235 (10,700).

Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.99; H, 6.77; N, 13.82.

Insulin Derivatives.—*t*-Butyloxycarbonyl-L-alanine phenylhydrazide (0.1–1.2 mmol), 1 equiv of pyridine, and 1 equiv of purified N-bromosuccinimide were mixed in 100 ml of dichloromethane. After the reaction was complete (10–20 min) the solution was washed with 100 ml of water, 100 ml of 1% citric acid, 100 ml of 5% sodium bicarbonate, and 100 ml of water. The solution was then dried over magnesium sulfate. The solvent was removed under vacuum to give a red crystalline solid. This solid was added to a solution of 60 mg of insulin hydrochloride[13] and 0.01 ml of triethylamine or 50 mg of imidazole in 5 ml of purified dimethylformamide. The mixture was allowed to react at room temperature for the time indicated in Table II. At this time the insulin was precipitated and washed with ether. The resulting product was dried over phosphorus pentoxide under vacuum and then dissolved in 2.0 ml of anhydrous trifluoroacetic acid. The solution was kept for 2 hr at room temperature; then the insulin derivative was precipitated and washed with ether and dried. The residue was dissolved in 7 ml of 0.5 mol/l. acetic acid (containing 1 mg of zinc acetate/ml) and precipitated by adjusting the pH to 5.0 with ammonium hydroxide. The final precipitate was collected by centrifugation, washed with 10 ml of water, 25 ml of acetone, and 25 ml of ether, and dried over phosphorus pentoxide under vacuum.

Acid hydrolysis and amino acid analysis revealed the incorporation of 2.0 to 3.0 alanine residues and the disappearance of 0 to 1 histidine residues as indicated in Table II.

TABLE II

INSULIN ALANYL DERIVATIVES

Sample no.	Diimide, g (μmol)	Reaction time, hr	Triethylamine, ml (imidazole, g)	Amino acid analysis Alanine	Amino acid analysis Histidine
1	0.10 (300)	18.5	0.01	5.25	1.62
7	0.40 (1200)	60	0.01	5.5	1.00
14	0.279 (1000)	4.0	(0.10)	4.90	1.97
12	0.20 (600)	4.5	(0.05)	5.00	1.85
11	0.20 (600)	8.5	(0.05)	5.53	1.93
10	0.20 (600)	20	(0.25)	5.7	2.12

Dinitrophenyl-insulins.—Insulin hydrochloride or the insulin derivative (1 mg each) along with 10 mg of sodium bicarbonate in 1 ml of water was added to drawn out combustion tubes. Dinitrofluorobenzene in ethanol (2 ml of 5% w/v) was added to each tube. The tubes were shaken at room temperature for 21 hr. At this time 0.1 ml of concentrated hydrochloric acid was added to each tube. Each solution was extracted with two 7-ml portions of ether. The remaining ether was removed from the aqueous solution with an aspirator. Concentrated hydrochloric acid (1 ml) was added to each tube and the contents were frozen and degassed. The tubes were sealed under vacuum. The hydrolysis proceeded for 6 hr at 120°. The results of the amino acid analysis are shown in Table III.

(12) B. Halpern, L. F. Chew, and J. W. Westley, *Anal. Chem.*, **39**, 399 (1967).

(13) F. H. Carpenter, *Arch. Biochem. Biophys.*, **78**, 539 (1958).

TABLE III

AMINO ACID ANALYSES OF INSULIN DERIVATIVES

Amino acid	Insulin	Control insulin	Di-Ala-insulin	Di-Phe-insulin	DNP-insulin	DNP-di-Ala-insulin
Asp	3	3.12	3.09	2.96	3.08	2.91
Thr	1	1.06	0.94	0.92	1.10	0.95
Ser	3	2.85	2.90	2.93	2.55	2.69
Glu	7	7.15	6.85	6.97	6.91	7.00
Pro	1	1.06	0.78	0.87	0.79	0.81
Gly	4	4.05	4.18	4.15	**3.08**	**3.98**
Ala	3	3.01	**5.01**	3.06	2.78	2.86
Cys	6	5.50	5.60	5.53	4.60	4.55
Val	5	4.75	4.77	4.81	4.75	4.80
Ile	1	0.75	0.80	0.91	0.69	0.68
Leu	6	6.03	5.85	5.80	6.07	6.05
Tyr	4	4.17	3.90	4.02		
Phe	3	3.00	2.93	**4.85**	**1.93**	**2.82**
Lys	1	1.04	1.06	1.09	**0.09**	**0.20**
His	2	1.90	2.01	1.99		
Arg	1	1.06	0.94	.93	0.73	1.04
N-ε-DNP-Lys					**1.01**	**0.85**

Discussion

t-Butyloxycarbonylamino Acid Derivatives.—t-Butyloxycarbonylamino acid phenylhydrazides were used in these studies because Levy and Carpenter[8] had demonstrated that the t-butyloxycarbonyl group may be coupled to insulin and then removed by treating the insulin derivative with anhydrous trifluoroacetic acid with very little reduction in the activity of the regenerated insulin.

The t-BOC-amino acid phenylhydrazides were prepared by a papain-catalyzed reaction[12] between the t-BOC-amino acids and phenylhydrazine. The t-BOC-amino acids proved to be effective substrates for this reaction. In each case the reactions were rapid, the yields were high, and the resulting t-BOC-amino acid phenylhydrazides were easily purified.

The t-BOC-amino acid phenylhydrazides were oxidized with N-bromosuccinimide in dichloromethane to give t-BOC-amino acid phenyldiimides which were used directly in the coupling reactions without purification.

Absence of Racemization.—The recently developed gas chromatographic technique developed by Halpern, Chew, and Westley[12] was used to determine the extent of racemization when t-BOC-amino acid phenyldiimides were used in peptide synthesis. t-BOC-L-alanine phenyldiimide and t-BOC-L-leucine phenyldiimide were allowed to react with (−)-2-amino-4-methylpentane in dichloromethane and the reaction mixtures were used in the glpc analyses. The analysis indicated that the resulting t-BOC-L-alanine (−)-4-methyl-2-pentylamide and the t-BOC-L-leucine (−)-4-methyl-2-pentylamide were uncontaminated with any of the D-(−) diastereoisomers. Halpern, *et al.*, have shown that in this method 2% of the D-(−) diastereoisomers could be detected.

In order to demonstrate the usefulness of the t-BOC-amino acid phenyldiimides in peptide synthesis, t-BOC-phenylalanine phenyldiimide was allowed to react with glycine phenylhydrazide to give t-BOC-L-phenylalanylglycine phenylhydrazide in 50% yield.

$$t\text{-BOC-L-Phe-N=N-C}_6\text{H}_5 + \text{H}_2\text{N-Gly-NHNHC}_6\text{H}_5 \longrightarrow t\text{-BOC-L-Phe-Gly-NHNHC}_6\text{H}_5 + \text{C}_6\text{H}_6 + \text{N}_2$$

Insulin Derivatives.—The t-BOC-L-alanine phenyldiimide was used for the initial reaction with insulin. A large excess of t-BOC-L-alanine phenyldiimide was allowed to react with insulin hydrochloride in dimethylformamide using triethylamine as the base. After an appropriate time the coupled product was separated from the reaction mixture by precipitation with ether. Amino acid analysis of these products indicated that when the time of reaction was long (60 hr) there was a loss of histidine equivalent to one residue (Table II). This product was light brown. The t-BOC group was removed in TFA and the derivative was precipitated at pH 4.9. Amino acid analysis of the resulting insulin showed a total of 5.5 residues of alanine and 1 residue of histidine which indicated the addition of 2.5 residues of alanine and the loss of 1 residue of histidine. This material assayed at 3.6 ± 0.7 units/mg in the mouse convulsion assay (Table IV).

Because it seemed probable that the loss of histidine in this reaction was either due to a reaction between the acylamino acid phenyldiimide or some active species formed in the reaction with the imidazole ring of histidine, the reaction between t-BOC-L-alanine phenyldiimide and imidazole was studied. The ultraviolet spectrum of a mixture of t-BOC-alanine phenyldiimide and imidazole in dimethylformamide was unchanged after 24 hr indicating that any reaction between t-BOC-L-alanine phenyldiimide and imidazole was too slow to interfere with the reaction with insulin and that imidazole could be used as a base in these reactions. It was hoped that, if there were an active species formed in the reaction, it would react with the imidazole and not the histidine in the insulin. This proved to be the case. When imidazole was used as a base there was no loss of histidine in the amino acid analysis of the resulting insulin derivatives.

However, the use of imidazole as a base in these reactions should be used with caution. Benzyloxycarbonylglycine phenyldiimide reacted with imidazole in dioxane to give a 1:1 addition product rather than the expected N-benzyloxycarbonylglycylimidazole. The nature of this reaction is being investigated further.

The reaction between t-BOC-alanine phenyldiimide and insulin was followed by precipitating the insulin from samples of the reaction mixture with ether and testing the resulting insulin with ninhydrin. The results indicated that two amino groups of the insulin were covered within 4.5 hr and that further reaction was much slower. The t-BOC group was removed with anhydrous TFA from the insulin which had reacted for 4.5 hr with the t-BOC-L-alanine phenyldiimide. After an isoelectric precipitation the amino acid analysis of the product indicated the addition of two alanines with no loss of histidine (Table II).

In order to obtain evidence for the location of the two new alanines in the dialanyl-insulin, the derivative was treated with 2,4-dinitrofluorobenzene. Amino acid analysis of the resulting product indicated 3.98 Gly, 2.82 Phe, 0.20 Lys, and 0.85 N-ε-DNP-Lys. If there were a random distribution of two alanines on the three amino groups of insulin, the values expected would be 3.66 Gly, 2.66 Phe, 0.66 Lys, and 0.33 N-ε-DNP-Lys. On the other hand, if the analines were exclusively on the α-amino groups, the expected values would be 4 Gly, 3 Phe, 0 Lys, and 1 N-ε-DNP-Lys.

TABLE IV
BIOLOGICAL ASSAYS

Amino acid added	Reaction conditions	Amino acid residues added	Histidine residues in product	Mouse assay, units/mg	Immuno assay, units/mg
Control		0	1.83	21.4 ± 4.3	23.8
Alanine	60 hr (triethylamine)	2.5	1.02	3.6 ± 0.7	10.38
Alanine	4 hr (imidazole)	2.2	2.06	11.8 ± 2.1	15.6
Phenylalanine	5 hr (imidazole)	1.8	2.00	10.2 ± 1.7	15.4

The above results indicate that about 90 ± 5% of the two added alanines are on the α-amino groups of the insulin and about 10 ± 5% on the ε-amino group of the insulin. Also little or no substitution took place on tyrosine or histidine which were lost on dniitrophenylation. If they had been substituted with alanine, they would have been recovered upon hydrolysis of the DNP derivative.

The biological activity of the dialanyl-insulin was 11.8 ± 2.1 units/mg by the mouse convulsion assay. This value may be compared with 10 ± 0.8 units/mg reported by Levy and Carpenter for the trialanyl-insulin.[8]

In the trialanyl-insulin, amino acid residues were added to the ε-amino group as well as to the N-terminal α-amino groups. It was impossible to ascertain whether the decreased biological activity exhibited by this derivative was due to covering the N-terminal groups or of the ε-amino group of lysine at position 29 or perhaps to a combination of both. The fact that the dialanyl derivatives prepared here, which involves primarily the substitution of the N-terminal amino groups with very little reaction on the ε-amino group, have approximately the same biological activity as the trialanyl-insulin indicates that the N-terminal groups are relatively more important for biological activity than the ε-amino group. However, as the dialanyl-insulin was prepared by the phenyldiimide method and the trialanyl-insulin was prepared *via* *p*-nitrophenyl ester, one or the other reaction could have caused a change in the insulin which would be reflected in the assay but not in the amino acid analyses. Diphenylalanyl-insulin prepared by the same method assayed 10.2 ± 1.7 units/mg.

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Aromatic Boronic Acids. Synthesis of o-Boronophenylalanine[1]

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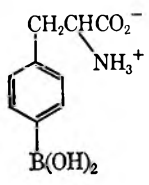
Syntheses of N-acetyl-*o*-boronophenylalanine, α-amino-*o*-boronobenzylmalonic anhydride, and *o*-boronophenylalanine anhydride are described. Alkylation of diethyl acetamidomalonate with *o*-(bromomethyl)benzeneboronic anhydride yields *o*-(2-carbethoxy-2-acetamidoethyl)benzeneboronic acid rather than the expected *o*-(2,2-dicarbethoxy-2-acetamidoethyl)benzeneboronic acid. It is postulated that decarbethoxylation occurs through participation of the boronic acid function in ester hydrolysis. Decarboxylation of α-amino-*o*-boronobenzylmalonic anhydride requires an unusually high temperature; this observation is interpreted in terms of a bridged, polycyclic structure. The decarboxylation product, the boronic anhydride related to *o*-boronophenylalanine, gives no indication of the zwitterionic structure, presumably because of interaction between the nitrogen and boron atoms.

The synthesis of *p*-boronophenylalanine (IV) has been reported.[2] *p*-(Bromomethyl)benzeneboronic acid



IV

(I) was condensed with sodio diethyl acetamidomalonate, and the product (II) was saponified and decarboxylated to give the acetyl derivative (III) which was hydrolyzed. The general method was that of Snyder, Shekleton, and Lewis.[3] The infrared spectrum of IV indicated the zwitterionic structure common to amino acids.

The above procedure has now been applied in an attempt to prepare *o*-boronophenylalanine. Condensation of *o*-(bromomethyl)benzeneboronic anhydride with sodio diethyl acetamidomalonate does not yield the expected *o*-(2,2-dicarbethoxy-2-acetamidoethyl)-benzeneboronic acid, but rather *o*-(2-carbethoxy-2-acetamidoethyl)benzeneboronic acid (IX). Evolution of carbon dioxide occurs when the alkylation mixture is acidified and warmed to 50°. Decarbethoxylation, with concomitant formation of diethyl carbonate, is known to occur sometimes as a side reaction in the alkylation of malonic esters;[4] however, decarbethoxylation *via* diethyl carbonate formation is considered unlikely, since alkylation of the *p*-bromomethyl analog proceeded normally, and also since, under the

(1) This work was supported in part by a grant from the Atomic Energy Commission, Report No. COO-314-11.

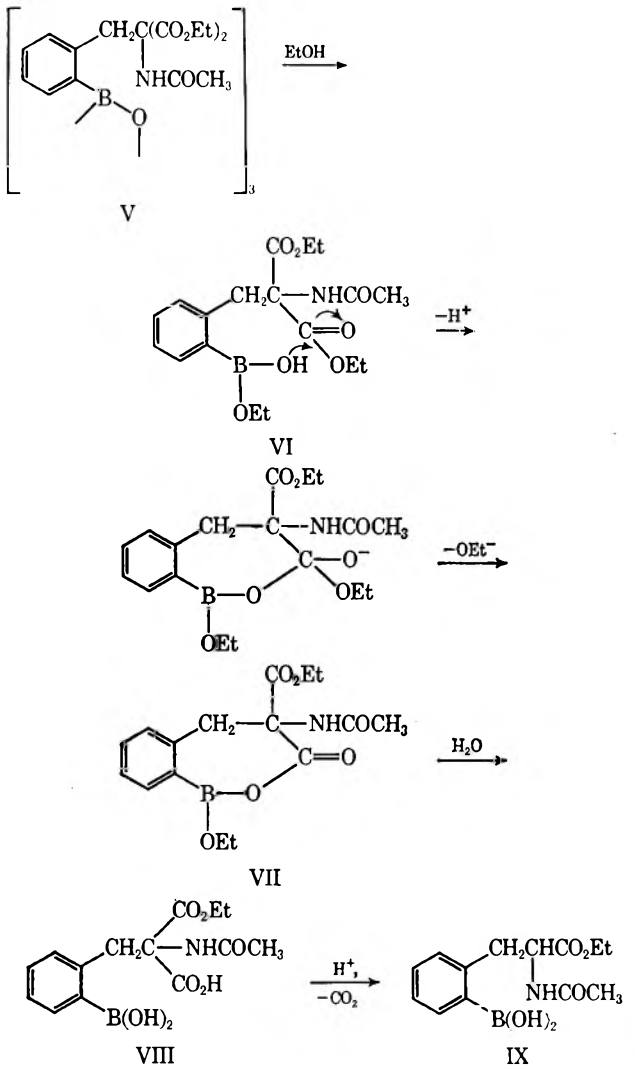
(2) H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Amer. Chem. Soc.*, **80**, 835 (1958).

(3) H. R. Snyder, J. F. Shekleton, and C. D. Lewis, *ibid.*, **67**, 310 (1945).

(4) A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 107 (1957).

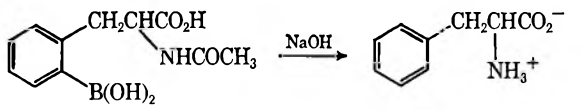
conditions employed, diethyl carbonate has been shown not to give rise to rapid generation of carbon dioxide. An alternative explanation is based on participation of the boronic acid group in the ester hydrolysis reaction. In ethanol, the initially formed boronic anhydride V could give the half-acid ester VI, which, after cyclization to the boronic carboxylic acid anhydride VII, followed by hydrolysis and decarboxylation, would yield the observed product IX (Scheme I). Boronic

SCHEME I



half-acid esters analogous to VI have not been isolated, but it is probable that they are intermediates in the preparation of boronic esters by the alcoholysis of boronic anhydrides.[5] Acyl borates are known to hydrolyze readily,[5] and it might be expected that an acyl boronate such as VII would exhibit similar properties. A comparable example of intramolecular participation in ester hydrolysis is the facile hydrolysis of acylsalicylic acids due to participation of the *ortho* carboxyl group.[6]

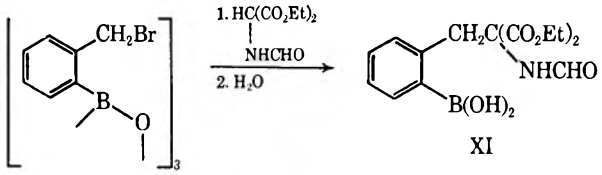
The carbethoxy group in IX was saponified to give the carboxylic acid X. The N-acetyl group in X proved unexpectedly resistant to alkaline hydrolysis. When refluxed for 11 hr with approximately 1 *N* sodium



X

hydroxide, X was recovered in 30% yield; the only other product isolated was phenylalanine. These results indicate that the rate of hydrolytic deboronation is comparable to the rate of amide hydrolysis.

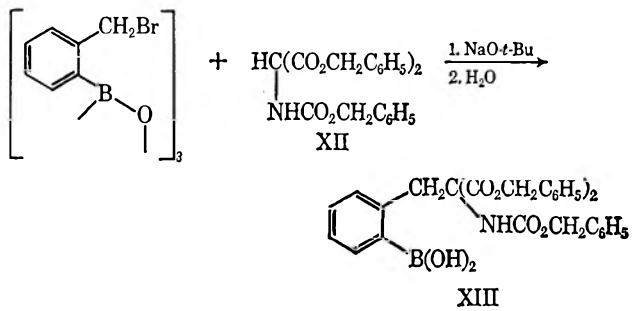
Alkylation of diethyl formamidomalonate with *o*-(bromomethyl)benzeneboronic anhydride, with a smaller excess of base than had been employed in the alkylation of diethyl acetamidomalonate, proceeded in normal fashion to give the dicarbethoxy compound



XI

XI. It was hoped that the N-formyl derivative could be hydrolyzed readily; Hellman[7] accomplished the one-step hydrolysis and decarboxylation of the analogous tryptophan derivative under mild conditions. When XI was treated under the same conditions, a boron-containing mixture was obtained which gave a positive ninhydrin test; however, this mixture resisted all attempts at purification.

An alternative route to *o*-boronophenylalanine which would not require hydrolysis steps is one based on hydrogenolysis and decarboxylation of an appropriate benzyl ester. Kissman and Witkop[8] synthesized tryptophan by condensation of dibenzyl carbobenzyloxyaminomalonate (XII) with a substituted Mannich base, followed by hydrogenolysis and decarboxylation. When *o*-(bromomethyl)benzeneboronic anhydride was treated with XII in the presence of sodium *t*-butoxide, the benzyl ester XIII was produced. Hydrogenolysis



XII

XIII

of XIII in the presence of palladium–charcoal catalyst proceeded with evolution of 1 mol of carbon dioxide; recrystallization of the product by addition of tetrahydrofuran (THF) to a concentrated aqueous solution gave a material whose analysis corresponded to that calculated for a 1:1 complex of THF with a dehydrated form of the aminomalonic acid. Infrared and nmr spectra further indicated the presence of THF. Struc-

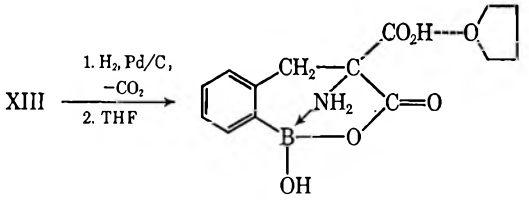
(5) M. F. Lappert, *Chem. Rev.*, **56**, 959 (1956).

(6) F. Kagan and R. D. Birkenmeyer, *J. Amer. Chem. Soc.*, **81**, 1986 (1959).

(7) H. Hellman, *Z. Physiol. Chem.*, **284**, 163 (1949).

(8) H. M. Kissman and B. Witkop, *J. Amer. Chem. Soc.*, **75**, 1967 (1953).

ture XIV is favored for this complex, because of the similarity of its infrared spectrum with that of the non-complexed anhydride XV, whose preparation and structure determination are described below.



XIV

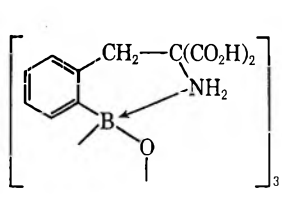
When *t*-butyl alcohol was used in the recrystallization of the hydrogenolysis product, a similar complex formed. However, upon drying overnight *in vacuo*, some of the *t*-butyl alcohol was lost from this complex, as indicated by the slightly low percentage of carbon in the sample. The nmr spectrum of this complex possessed a strong signal at τ 8.78, providing further evidence for the presence of *t*-butyl alcohol.

The THF proved unexpectedly difficult to remove from the complex XIV. After the complex had been heated *in vacuo* overnight at 100°, the elemental analysis indicated that some THF was still present. Heating at 180° for 30 min *in vacuo* proved sufficient to remove the THF; surprisingly, no decarboxylation took place during this treatment.

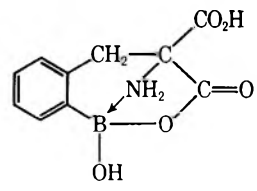
For larger scale syntheses, the hydrogenolysis product could be recrystallized from a minimum amount of water. After drying at 100°, the product was the same aminomalonic anhydride XV that had been obtained by heating the THF complex to 180°.

Several possible structures were considered for this anhydride. The nuclear magnetic resonance spectrum of XV, obtained in deuterated dimethyl sulfoxide, was of value in ruling out most of the proposed structures. Multiplets at τ 2.95 (relative area 3) and at τ 2.45 (relative area 1) were assigned to the aromatic protons. A singlet at τ 6.75 (relative area 2) was attributed to the aliphatic $-CH_2-$ group. Only two other peaks were present in the spectrum, each having a relative area of 2, the first at τ 1.30 (broad) and the second at τ 6.18 (broad). One of these two peaks represents protons of XV which are either of the carboxylic acid or hydroxyl variety (or both, since the hydrogen atoms of carboxylic acids and hydroxyl compounds are known to undergo rapid exchange[9]). The other peak must, therefore, represent the two protons of the NH_2 group. Amines do not undergo rapid exchange unless a base is present to promote it. The broadness of the two peaks at τ 1.30 and 6.18 may be ascribed to slow exchange between the amine hydrogen atoms and the carboxylic–hydroxylic hydrogen atoms.

Since two hydrogen atoms are present on the nitrogen atom, only structures XVa and XVb need be considered for the aminomalonic anhydride. A molecular weight measurement in 95% ethanol was in agreement with that calculated for a monomeric species; however, the boroxine XVa cannot be ruled out on this basis, since in 95% ethanol a boroxine could be converted into a boronate ester, which process would furnish as many



XVa



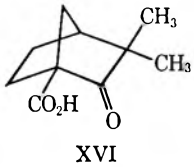
XVb

particles as a monomer and hence the apparent molecular weight would correspond to a monomeric anhydride.

The infrared spectrum of XV had absorption peaks at 654 (medium, broadened), 734 (strong, sharp) and 764 cm^{-1} (medium, sharp). Snyder, Konecky, and Lennarz[10] found that boroxines possess a characteristic peak, invariably strong and sharp, in the region 680–705 cm^{-1}. Hawkins[11] found this band as low as 672 cm^{-1} for two *o*-dialkylaminomethylbenzeneboronic anhydrides. Serafinowa and Makosza[12] have suggested that the region of absorption characteristic of boroxines be extended to 736–688 cm^{-1}. The strong, sharp peak at 734 cm^{-1} in XV might be ascribed to a boroxine, but it is more likely due to *ortho* disubstitution of the aromatic ring.[13]

The carbonyl stretching frequencies at 1730 and 1685 cm^{-1} are consistent with structures XVa and XVb; un-ionized carboxylic acids absorb in the range 1725–1700 cm^{-1},[13] and acyloxy boron compounds at 1786–1700 cm^{-1}.[14]

The difficulty of decarboxylation of XV provides a basis for favoring structure XVb over XVa. Generally, malonic acids lose carbon dioxide fairly readily; the *para*-substituted acetamidomalonic ester II, for instance, after saponification with dilute base, was decarboxylated by refluxing in dilute acid for 1 hr. Decarboxylation of XV, on the other hand, took place at 180–220°. An explanation for this extraordinary difficulty of decarboxylation can be derived from structure XVb. The polycyclic skeleton present in XVb is extremely rigid, and the carboxyl group may be considered as attached to a "bridgehead" carbon atom. Bridgehead carboxylic acids such as XVI[15] may be decarboxylated only with extreme difficulty. On the basis of chemical and spectral characteristics, XVb is therefore considered the most likely structure for the aminomalonic anhydride.



XVI

On standing for a few days in an atmosphere saturated with water vapor, the anhydride XV absorbed 2 mol of water. The infrared spectrum of the resulting acid did not differ greatly from that of its anhydride in the regions attributed to boroxine absorption and carbonyl absorption.

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959.

(10) H. R. Snyder, M. S. Konecky, and W. J. Lennarz, *J. Amer. Chem. Soc.*, **80**, 3611 (1958).

(11) R. T. Hawkins and H. R. Snyder, *ibid.*, **82**, 3863 (1960).

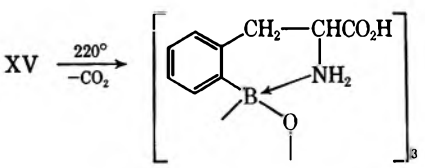
(12) B. Serafinowa and M. Makosza, *Rocz. Chem.*, **35**, 937 (1961).

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1959.

(14) L. A. Duncanson, W. Gerrard, M. F. Lappert, H. Pyszora, and R. Shafferman, *J. Chem. Soc.*, 3652 (1958).

(15) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

The product of decarboxylation of XV was the amino acid anhydride. The boroxine structure XVII is suggested by the strong infrared absorption at 660



XVII

cm^{-1}; other structures are conceivable. A strong, broad band at 1710 cm^{-1}, characteristic of an unionized carboxylic acid, was present in the infrared spectrum. The *para* isomer of XVII, *p*-boronophenylalanine,[2] existed as the normal zwitterionic form, IV. The boron atom in close proximity to the nitrogen atom of XVII probably reduces the basicity of the amine function sufficiently to prevent protonation by carboxylic acid. Boronic acids are much weaker acids than carboxylic acids, and it is surprising that the boronic anhydride function of XVII can compete effectively with the carboxylic group for the basic center, the nitrogen atom. Evidently, the favorable steric orientation of the boron and nitrogen atoms in XVII more than compensates for the normal difference in acidity.

In contrast to the aminomalonic anhydride XV, the amino acid anhydride XVII did not absorb water readily when allowed to stand in an atmosphere saturated with water vapor. Some water was taken up very slowly; it is possible that on prolonged standing a hydrated species would form.

The amino acid derivatives IX, XV, and XVII are of interest in connection with a proposed cancer therapy based on nuclear disintegration of the B^{10} atom upon capture of a neutron.[16] Soloway[17] has found that compounds which possess a high water to benzene partition coefficient show the greatest tendency to localize selectively in mouse brain tumors. Organoboron compounds such as IX, XV, and XVII, which contain polar functional groups, may offer possibilities for meeting some of the requirements of the proposed therapy.

Experimental Section[18]

***o*-(2-Carbethoxy-2-acetamidoethyl)benzeneboronic Acid.**—To a solution of sodium ethoxide prepared from 0.92 g (0.040 g-atom) of sodium and 75 ml of absolute ethanol was added 12.96 g (0.045 mol) of diethyl acetamidomalonate. After the malonate had dissolved, 5.92 g (0.010 mol) of *o*-(bromomethyl)benzeneboronic anhydride[19] was added. A white precipitate began to form almost immediately. The mixture was stirred and heated to reflux for 6 hr, cooled to *ca.* 50°, and acidified with 4 ml of 3 *N* hydrochloric acid. The solution was then maintained at 50–60° for 30 min, during which time carbon dioxide evolution was followed by bubbling the evolved gases into calcium hydroxide solution. At the end of this period, gas evolution was very slow. The pH was adjusted to *ca.* 4–5 with 10% sodium hydroxide and the solution was concentrated *in vacuo*. The resulting semisolid residue was recrystallized from 95 ml of boiling water. The crystals (4.31 g) melted at 135–145°.

Concentration of the mother liquors afforded a second crop (4.26 g, mp 65–175°), which was combined with the first crop and used without further purification in the preparation of *o*-(2-carboxy-2-acetamidoethyl)benzeneboronic acid.

From a small sample of the first crop of crystals an analytical sample, mp 147–150°, was prepared by twofold recrystallization from water and subsequent drying *in vacuo* over calcium chloride for 10 hr.

Anal. Calcd for $C_{13}H_{18}BNO_5$: C, 55.94; H, 6.50; N, 5.01. Found: C, 56.20; H, 6.47; N, 5.28.

***o*-(2-Carboxy-2-acetamidoethyl)benzeneboronic Acid.**—A solution prepared from 8.39 g (0.03 mol) of crude *o*-(2-carbethoxy-2-acetamidoethyl)benzeneboronic acid and 70 ml of 5% sodium hydroxide was refluxed for 4 hr and then concentrated *in vacuo* to *ca.* 50 ml and the solution acidified with 25 ml of 4 *N* hydrochloric acid. A white precipitate formed. The mixture was stirred and heated to *ca.* 50–70° for 30 min, during which time no carbon dioxide evolution was observed. The mixture was cooled, then partially neutralized by the addition of 8 ml of 10% sodium hydroxide, and chilled for several hours to give 3.00 g (43% yield) of product, mp 192–193°.

Recrystallization from 350 ml of 50% ethanol afforded 1.95 g of crystals which melted at 196–197°.

An analytical sample was prepared by twofold recrystallization from 50% ethanol and drying *in vacuo* over calcium chloride (mp 203–204°).

Anal. Calcd for $C_{11}H_{14}BNO_5$: C, 52.60; H, 5.62; N, 5.59. Found: C, 53.06; H, 5.50; N, 5.54.

Attempted Hydrolysis of *o*-(2-Carboxy-2-acetamidoethyl)-benzeneboronic Acid.—A solution prepared from 500 mg (0.0020 mol) of *o*-(2-carboxy-2-acetamidoethyl)benzeneboronic acid and 560 mg (0.0136 mol) of sodium hydroxide in 11 ml of water was refluxed for 11 hr and then cooled and acidified to pH 2–3 by dropwise addition of concentrated hydrochloric acid. The resultant white precipitate (*ca.* 150 mg) was identified as impure *o*-(2-carboxy-2-acetamidoethyl)benzeneboronic acid from its infrared spectrum.

The pH of the filtrate from the acidified mixture described above was adjusted to 6.8–7.0 with dilute ammonium hydroxide. A small amount of white, flocculent precipitate formed. The mixture was concentrated *in vacuo* to *ca.* one-half the original volume. The flask was cooled in an ice bath and the precipitate collected and dried. This material (*ca.* 70 mg) reacted with ninhydrin and was identified as phenylalanine from its infrared spectrum. Another 30–40 mg of phenylalanine was obtained by further concentration of the filtrate.

o-(2,2-Dicarbethoxy-2-formamidoethyl)benzeneboronic Acid. A solution of sodium ethoxide was prepared from 0.41 g (0.0180 g-atom) of sodium and 40 ml of absolute ethanol. Next, 3.78 g (0.0186 mol) of diethyl formamidomalonate was added. After the malonate dissolved, 2.96 g (0.0050 mol) of *o*-(bromomethyl)-benzeneboronic anhydride[19] was added. A white precipitate began to form almost immediately. The mixture was stirred and heated to reflux for 5 hr, then cooled to *ca.* 40°, and acidified with 2 ml of 4 *N* hydrochloric acid. After 20 min, the inorganic salt was removed by filtration and the filtrate concentrated *in vacuo*. Recrystallization of the residue from 70 ml of boiling water afforded 1.68 g (33.4%) of crystals, mp 115–124° dec.

An analytical sample prepared by twofold recrystallization from water melted at 125–131° dec.

Anal. Calcd for $C_{15}H_{20}BNO_7$: C, 53.43; H, 5.96; N, 4.16; B, 3.22. Found: C, 53.47; H, 6.02; N, 4.31; B, 2.93.

Attempts were made to improve the yield in the synthesis of *o*-(2,2-dicarbethoxy-2-formamidoethyl)benzeneboronic acid; however, condensations carried out in benzene with sodium hydride, in benzene–ethanol mixture with sodium ethoxide and in dimethylformamide with sodium hydride led only to oily or gummy materials which resisted attempts at purification.

Preparation of *o*-(2,2-Dicarbobenzyloxy-2-carbobenzyloxyaminoethyl)benzeneboronic Acid.—A solution of sodium *t*-butoxide in *t*-butyl alcohol was prepared by dissolving 4.06 g (0.176 mol) of sodium in 310 ml of dry *t*-butyl alcohol. The solution was stirred under nitrogen and heated nearly to boiling; then 78.00 g (0.180 mol) of dibenzyl carbobenzyloxyaminomalonate was added. To the clear, yellow solution was added 37.20 g (0.063 mol) of *o*-bromomethylbenzeneboronic anhydride (prepared according to the method of Kurz[19]). After refluxing for 1 hr, the reaction mixture was no longer alkaline. The mixture was cooled and poured onto 300 ml of a mixture of ice and water; the resulting slurry was extracted with one 500-ml and three 100-ml portions of chloroform. The combined chloroform extracts were washed with water, dried, and evaporated *in vacuo* to give 108.4 g of

(16) P. G. Kruger, *Proc. Natl. Acad. Sci. U. S.*, **26**, 181 (1940).

(17) A. H. Soloway, *Science*, **128**, 1572 (1958).

(18) Microanalyses and molecular weight determinations were performed by Mr. Josef Nemeth and associates.

(19) R. K. Kurz, Ph.D. Thesis, University of Illinois, 1961.

white crystals. These were taken up in a mixture of benzene and petroleum ether (bp 60–70°), applied to a column of 2 lb of alumina, and chromatographed. Elution with benzene gave 25 g of impure dibenzyl carbobenzyloxyaminomalonate. Further elution with ether and absolute ethanol gave 47.2 g (47%) of *o*-(2,2-dicarbobenzyloxy-2-carbobenzyloxyaminoethyl)benzeneboronic acid as an oil, which was crystallized from aqueous *t*-butyl alcohol. An analytical sample was prepared by threefold recrystallization from 1,2-dichloroethane–petroleum ether, mp 110–111°.

Anal. Calcd for $C_{32}H_{30}BNO_8$: C, 67.73; H, 5.33; N, 2.47; B, 1.92. Found: C, 67.89; H, 5.33; N, 2.59; B, 1.83.

Preparation of α-Amino-*o*-boronobenzylmalonic Anhydride.—The 30% palladium-on-charcoal catalyst used in this experiment was washed with distilled water and absolute ethanol and dried *in vacuo*. Thus treated, the catalyst was highly pyrophoric. To a solution of 15.00 g (0.026 mol) of *o*-2,2-dicarbobenzyloxy-2-carbobenzyloxyaminoethyl)benzeneboronic acid in 200 ml of ethyl acetate under nitrogen, 3 g of 30% palladium-on-charcoal catalyst was added. The mixture was stirred while hydrogen was passed through rapidly for 7.5 hr. During this time, a precipitate of barium carbonate formed in a barium hydroxide trap connected to the apparatus; after being washed and dried *in vacuo*, this precipitate weighed 5.22 g (0.026 mol).

The hydrogenolysis mixture was filtered and washed with 100 ml of ethyl acetate. The residue remaining on the filter was extracted with 250 ml of water; the resultant aqueous solution was freed of a small amount of insoluble material by filtration through a fine sintered-glass funnel and evaporated *in vacuo*, giving 6.668 g (99.7%) of white crystals which could be recrystallized from water, mp 249–262°.

Anal. Calcd for $C_{10}H_{10}BNO_5$: C, 51.11; H, 4.29; N, 5.96; B, 4.60. Found: C, 51.09; H, 4.49; N, 5.94; B, 4.27.

Preparation of α-Amino-*o*-boronobenzylmalonic Anhydride Complex with Tetrahydrofuran.—A concentrated aqueous solution of α-amino-*o*-boronobenzylmalonic acid was treated with one-fourth its volume of tetrahydrofuran; the crystals which separated were dried overnight at room temperature *in vacuo*, mp 248–264°.

Anal. Calcd for $C_{14}H_{18}BNO_6$: C, 54.75; H, 5.91; N, 4.56. Found: C, 54.89; H, 5.96; N, 4.63.

Preparation of α-Amino-*o*-boronobenzylmalonic Anhydride Complex with *t*-Butyl Alcohol.—A concentrated aqueous solution of α-amino-*o*-boronobenzylmalonic acid was treated with ten times its volume of *t*-butyl alcohol and allowed to stand at 5° for 3 days; the crystals which separated were dried at room temperature *in vacuo* overnight, mp 250–253° dec, with gas evolution at 170–180°.

Anal. Calcd for $C_{14}H_{20}BNO_6$: C, 54.39; H, 6.52; N, 4.53. Found: C, 53.91; H, 6.48; N, 4.42.

Preparation of α-Amino-*o*-boronobenzylmalonic Acid Hydrate.—α-Amino-*o*-boronobenzylmalonic anhydride (0.2588 g, 0.0011 mol) was allowed to stand for 7 days in a desiccator saturated with water vapor. At the end of this time, the sample weighed 0.2997 g. The calculated value for the addition of 2 mol of water was 0.2992 g.

Anal. Calcd for $C_{10}H_{14}BNO_7$: C, 44.32; H, 5.21; N, 5.17. Found: C, 44.28; H, 5.16; N, 5.09.

Preparation of *o*-Boronophenylalanine Anhydride.—α-Amino-*o*-boronobenzylmalonic acid hydrate (2.271 g, 0.008 mol) was heated at 220° (0.1 mm) for 3.75 hr. The yellow powder was extracted with 125 ml of hot water and the insoluble residue removed by filtration. The filtrate was treated with Darco and evaporated *in vacuo* to give 1.178 g (73.5%) of white crystals. An analytical sample was prepared by twofold recrystallization from a minimum amount of water, followed by drying at 100° *in vacuo* overnight, mp 252–262°.

Anal. Calcd for $C_9H_{10}BNO_3$: C, 56.59; H, 5.28; N, 7.33. Found: C, 56.49; H, 5.22; N, 7.44.

Registry No.—IX, 17604-89-6; X, 5115-46-8; XI, 17604-90-9; XIII, 17604-91-0; XIV, 17659-05-1; XVb, 17604-92-1; α-amino-*o*-boronobenzylmalonic anhydride complex with *t*-butyl alcohol, 17604-93-2; α-amino-*o*-boronobenzylmalonic acid, 77604-94-3; *o*-boronophenylalanine anhydride, 17604-95-4.

Arylboronic Acids. Imino Derivatives from *o*-Formylbenzeneboronic Acid[1]

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Received May 27, 1968

o-Formylbenzeneboronic anhydride reacts with aniline, *p*-toluidine, benzylamine, and *n*-propylamine to give Schiff bases which are isolated as the trimeric boronic anhydrides. These substances react with catechol to give the catechol derivatives of the boronic acids, in which the boron atom interacts with the neighboring nitrogen atom and becomes tetracovalent. When the free acid, *o*-formylbenzeneboronic acid, reacts with methoxyamine, the expected oxime ether is formed. Attempts to convert the product, N-*o*-boronobenzalmethoxyamine, into the boronic anhydride are complicated by the occurrence of a transformation of the Beckmann type, by which oximino ether groups are converted into nitrile groups, some of which are hydrolyzed to amide groups, with the result that a complex mixture of simple and mixed trimeric boronic anhydrides is formed. The previously known heterocyclic substance, 4-hydroxy-4,3-boroxaroisoquinoline, formed from the formylboronic acid and hydroxylamine, likewise undergoes a Beckmann transformation on heating and yields a mixture of trimeric simple and mixed anhydrides containing nitrile and amide groups.

Because of the ease of formation and the stability of the lactone ring in boronophthalide, I, one might expect *o*-formylbenzeneboronic acid, or its anhydride II, to react with primary amines to form substituted aminoboronophthalides rather than simple Schiff bases. The lactone ring of I forms so readily that the hydroxyboronic acid is unknown,[3,4] and the carbon–boron bond of I is stable to strong acids or strong bases[4] under conditions which effect the deboronation of most boronic acids.[5,6] It is surprising to find that the trimeric anhydride of II reacts with primary aromatic and aliphatic amines, such as aniline, *p*-toluidine, benzylamine, and *n*-propylamine, to give Schiff bases, readily obtained as the trimeric boronic anhydrides, III. The structures IIIa–d are indicated by the analyses, by the occurrence of –C=N– absorption in the region of 1622–1648 cm^{-1}, and by the occurrence of the boronic anhydride[7] B—O absorption in the 1315–1390-cm^{-1} region, as well as by the absence of absorption due to OH or NH

(1) This work was supported in part by a grant from the Atomic Energy Commission, Report No. C00-314-12.

(2) Phillips Petroleum Fellow, 1962–1963.

(3) K. Torssell, *Arkiv Kemi*, **10**, 509 (1957).

(4) H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Amer. Chem. Soc.*, **80**, 835 (1958).

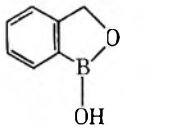
(5) M. F. Lappert, *Chem. Rev.*, **56**, 994 (1956).

(6) A. D. Ainley and F. Challenger, *J. Chem. Soc.*, 2171 (1930).

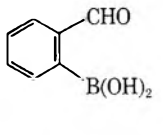
(7) See R. L. Letsinger, Advances in Chemistry Series, No. 42, American Chemical Society, Washington, D. C., p 3.

groups or to the boronophthalide ring system.[8] All of the compounds react readily with catechol to give the catechol esters IV. The catechol derivatives exhibit a broad absorption band centered at 1220 cm^{-1}, sometimes a resolved doublet, which may be due to B–N stretching, and which does not occur in the spectra of IIIa–d. It appears that the interaction of nitrogen and boron is a more prominent feature of the structures of the catechol esters IV than of the boronic anhydrides III (Chart I).

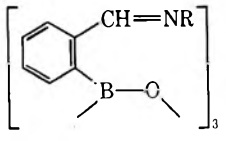
CHART I



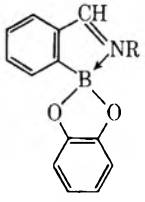
I



II



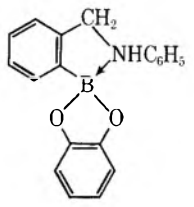
IIIa, R = C_6H_5
b, R = p-$CH_3C_6H_4$
c, R = $C_6H_5CH_2$
d, R = $CH_3CH_2CH_2$



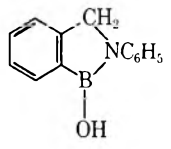
IVa, R = C_6H_5
b, R = p-$CH_3C_6H_4$
c, R = $C_6H_5CH_2$
d, R = $CH_3CH_2CH_2$

Part of the interest in the Schiff bases lies in their possible utility as intermediates for aminoboronic acids, to which they should be convertible by chemical or catalytic reduction. Since Hawkins and Blackham[9] have recently studied the more direct synthesis of such amino compounds by alkylation of aliphatic and aromatic amines with o-bromomethylbenzeneboronic anhydride, this possible utilization of the Schiff bases has been tested only in connection with the aniline compound (IIIa). The fact that pyridine and arylboronic anhydrides form 1:1 adducts which are nicely crystalline compounds of low solubility[10] suggested that the benzylamine derivative obtainable by reduction of IIIa might be an easily isolable solid, possibly polymeric since the interaction between the nitrogen atom and the boroxole ring could be intermolecular rather than intramolecular. In a hydrogenation over 30% palladium-on-charcoal catalyst, conducted in THF, o-boronobenzalaniline anhydride (IIIa) consumed almost the theoretical amount of hydrogen. The product, however, proved to be an oil, characterized as the nicely crystalline catechol derivative V.

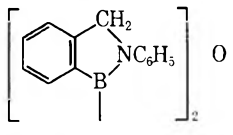
From a reduction of IIIa with lithium aluminum hydride in ether and THF, followed by treatment with water and eventual precipitation from ether with dry hydrogen chloride, the hydrochloride of o-boronobenzylaniline (mp 167° dec, lit.[9] mp 169–171° dec) was obtained. From a reduction with lithium aluminum hydride in THF, there was obtained a solid the composition of which indicated it to be largely N-phenylboronophthalimidine (VI) contaminated with a little o-boronobenzylaniline. Further dehydration of this solid by heating in cyclohexane gave a mixture of N-phenylboronophthalimidine and its dimeric anhydride (VII). Hawkins and Blackham[9] have noted the difficulty of isolating compounds of type VI and have suggested that they are to be formulated as shown rather than with an additional dative bond between the nitrogen and boron atoms (borazaindene structure). The rapid dehydration of VI in boiling cyclohexane would not have been predicted from the behavior of the oxygen analog (boronophthalide), since the latter is converted into its anhydride (VIII) only under more severe conditions.[11]



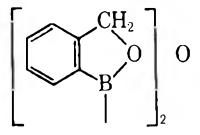
V



VI



VII



VIII

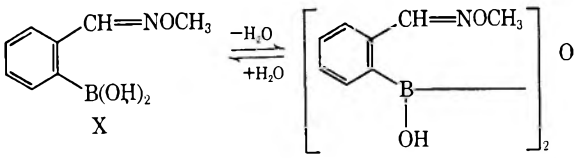
Reedy[4] obtained a cyclic product, 4-hydroxy-4,3-boroxaroisoquinoline (IX), by reaction of hydroxylamine hydrochloride with o-formylbenzeneboronic acid. He observed the substance to melt at 150–155°. Dewar and Dougherty[12] reported that on slow heating IX was observed to melt much higher (264–265°), with a change in crystalline form at 164°. In some of our experiments with slow heating, melting was observed at 148–150°, followed by decomposition (bubbling) at about 158°, with resolidification occurring at about 164°. It would appear possible, therefore, to prepare the dimeric anhydride of IX by simply heating at temperatures near 160°. However, a number of attempts, performed under a variety of conditions, gave products which were obviously mixtures and which, according to the infrared spectra, contained nitrile groups and usually also amide groups. Evidently the formation of the dimeric anhydride is accompanied or followed by a transformation of the Beckmann type, introducing cyano groups, some of which are converted into amide groups by water liberated as trimeric boronic anhydrides are formed.

If the Beckmann transformation in the decomposition of IX or its dimeric anhydride depends on the existence of the boron–oxygen–nitrogen bonds in the molecule, the thermal behavior of o-boronobenzalmethoxyamine (X) might be entirely different. The oxime ether (X) was easily prepared in excellent yield, and analysis of the first crop from recrystallization from chloroform was in excellent agreement with that expected. However, all attempts to convert the oxime ether (X) into the trimeric boronic anhydride with the oximino ether groups intact failed. As in the dehydration of IX, complex mixtures containing cyano, amide, and probably oximino ether groups were formed and

(8) R. R. Haynes, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1963.
(9) R. T. Hawkins and A. U. Blackham, *J. Org. Chem.*, **32**, 597 (1967).
(10) H. R. Snyder, M. S. Konecky, and W. J. Lennarz, *J. Amer. Chem. Soc.*, **80**, 3611 (1958).
(11) R. R. Haynes and H. R. Snyder, *J. Org. Chem.*, **29**, 3229 (1964).
(12) M. J. S. Dewar and R. C. Dougherty, *J. Amer. Chem. Soc.*, **86**, 433 (1964).

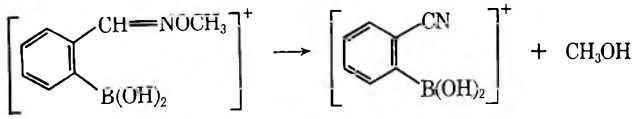
the mixtures resisted attempted separation (there can be ten different simple and mixed trimeric anhydrides with three different substituents on the benzene ring). Evidently the Beckmann transformation can result from the coordination of the ether oxygen atom of X with the boron atom.

Evidence for an unstable dimeric semianhydride of X was obtained from the nmr spectral examination of crystals from a second crop in the chloroform recrystallization. The nmr spectrum of the first crop showed peaks at τ 1.71, 2.55, and 6.00, with relative areas of 4:3:3. When the sample was shaken with deuterium oxide, the relative areas reduced to 2:3:3. The spectrum of a sample from the second crop had peaks centered at τ 1.75, 2.55, and 6.00, with relative areas of 2:4:3. When the sample was shaken with water, the spectrum became identical with that of the first-crop sample, and the spectrum after exposure to deuterium oxide was indistinguishable from that of first-crop material treated with deuterium oxide. These results can be explained on the assumptions that the second-crop material is the dimeric semianhydride (XI), and that the resonances near 1.71 are due to boronic acid protons, the proton on the carbon atom adjacent to the aromatic ring, and one of the aromatic protons, the resonances at 2.55 are due to the remaining aromatic protons, and those at 6.00 are due to the methyl protons.



X XI

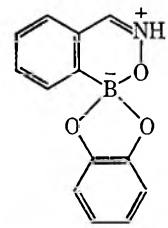
The mass spectrum of X obtained with no heating of the sample exhibits the parent mass at 179 along with a mass peak at 147 and a metastable peak at 121.[13] The appearance of these peaks suggests this ionic reaction.



As the sample of X is heated, the mass peak at 179 disappears and peaks corresponding to molecular ions of trimers appear, but there is no indication of the simple trimeric anhydride (mass 483) of X; only mass peaks corresponding to trimers which have lost one, two, or three molecules of methanol are observed (mass peaks at 451, 419, and 387). As expected, there is no indication in the mass spectra of the very unstable semianhydride XI. The mass spectrum of 4-hydroxy-4,3-boroxaroisoquinoline IX, obtained at low ionizing voltage, on the other hand, does contain a peak (mass 276) corresponding to a dimeric anhydride as well as one (mass 147) corresponding to the monomer. Even the catechol derivative of X undergoes loss of methanol in the mass spectrometer, the spectrum showing the parent mass at 253, a mass peak at 221 (loss of methanol), and a metastable peak at 193. The fragmentation pattern evidently is the same as the first stage of that of X.

(13) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw Hill Book Co., Inc., New York, N. Y., 1962, pp 154–156.

It would not be surprising if 4-hydroxy-4,3-boroxaroisoquinoline (IX) were unreactive toward catechol under the conditions employed in the preparation of the other catechol derivatives reported here, because of the greater aromaticity of the system and the resulting loss of Lewis acidity at the boron atom.[12] Nevertheless, the substance (IX) did react rapidly to give a derivative of the expected composition in good yield. The infrared spectrum of the derivative reveals no strong band in the 1315–1390-cm^{-1} region; there is strong absorption at 1200 cm^{-1}, and also a broad band at 2680 cm^{-1}. The spectrum seems best accommodated by structure XII, with the proton located either on the nitrogen atom as shown or, less probably, on any of the three oxygen atoms.



XII

Experimental Section[14]

Preparation of Schiff Bases. o-Boronobenzalaniline Anhydride.—A mixture of 4.50 g of *o*-formylbenzeneboronic acid[15] and 100 ml of benzene was refluxed for 2 hr in a flask fitted with a Dean–Stark water separator, during which time the theoretical amount of water was removed. To the remaining solution was added 2.79 g of freshly distilled aniline. The mixture was again refluxed and the theoretical amount of water codistilled. A white solid separated and the reaction mixture was allowed to cool to room temperature. The product weighed 4.64 g (74.7% yield, mp 223–225° dec). An analytical sample (mp 229.5–230.5°) was prepared by recrystallizing the product twice from chloroform–cyclohexane and drying (0.1 mm over phosphorus pentoxide) at 52.6° for 20 hr.

Anal. Calcd for $(C_{13}H_{10}BNO)_3$: C, 75.43; H, 4.87; N, 6.77. Found: C, 75.36; H, 4.97; N, 6.87.

***o*-Boronobenzal-*p*-toluidine anhydride**, mp 232–235°, was prepared similarly but in much more dilute solution. An analytical sample was prepared by recrystallizing twice from nitromethane, with heating for 10 hr at 0.1 mm to remove residual nitromethane.

Anal. Calcd for $(C_{14}H_{12}BNO)_3$: C, 76.06; H, 5.47; N, 6.36. Found: C, 75.65; H, 5.48; N, 6.36.

***o*-Boronobenzalbenzylamine anhydride**, mp 181–185°, was prepared similarly and recrystallized from toluene for analysis.

Anal. Calcd for $(C_{14}H_{12}BNO)_3$: C, 76.08; H, 5.47; N, 6.34; mol wt, 663. Found: C, 76.28; H, 5.63; N, 6.26; mol wt (mass spectrum), 663.

***o*-Boronobenzalpropylamine anhydride**, mp 168–178°, was prepared similarly and recrystallized from toluene for analysis.

Anal. Calcd for $(C_{10}H_{12}BNO)_3$: C, 69.42; H, 6.99; N, 8.10. Found: C, 69.37; H, 6.93; N, 8.12.

Reactions with Catechol. Catechol Derivative of *o*-Boronobenzalaniline.—A mixture of 3.00 g of *o*-boronobenzalaniline anhydride, 1.59 g of catechol, and 15 ml of absolute ethanol immediately turned orange. It was heated to reflux for 1 min, filtered, and chilled. A red-orange crystalline product (3.36 g) was obtained (yield 77.5%). After recrystallization from absolute ethanol and drying (0.1 mm) over calcium chloride at 56° for 3 hr, brilliant orange crystals (mp 156–159°) were obtained.

(14) Microanalysis was performed by Mr. Josef Nemeth and his associates. All melting points are uncorrected. Infrared spectra were determined by the staff of the Spectroscopy Laboratory of the Department of Chemistry and Chemical Engineering using a Perkin-Elmer Model 21 infrared spectrophotometer (with sodium chloride optics). The mass spectra were determined by Mr. Joseph Wrona on an Atlas CH4 spectrometer.

(15) P. Tschampel and H. R. Snyder, *J. Org. Chem.*, **29**, 2168 (1964).

Anal. Calcd for $C_{19}H_{14}BNO_2$: C, 76.29; H, 4.72; N, 4.68. Found: C, 76.13; H, 4.69; N, 4.75.

The catechol derivative of *o*-boronobenzal-*p*-toluidine, yellow-orange crystals, mp 161–163°, was prepared similarly.

Anal. Calcd for $C_{20}H_{16}BNO_2$: C, 76.69; H, 5.15. Found: C, 76.84; H, 5.18.

The catechol derivative of *o*-boronobenzalbenzylamine, yellow crystals, mp 164–166°, was prepared similarly.

Anal. Calcd for $C_{20}H_{16}BNO_2$: C, 76.69; H, 5.15; N, 4.62. Found: C, 76.72; H, 5.16; N, 4.40.

The catechol derivative of *o*-boronobenzalpropylamine, pure light yellow crystals, mp 154–155°, was prepared similarly.

Anal. Calcd for $C_{16}N_{16}BNO_2$: C, 72.48; H, 6.09; N, 5.29. Found: C, 72.51; H, 6.19; N, 4.99.

Catalytic Reduction of *o*-Boronobenzalaniline Anhydride.—From 4.00 g (6.44 mmol) of *o*-boronobenzalaniline anhydride, 150 ml of tetrahydrofuran, and 0.4 g of 30% palladium on carbon (Engelhard Lot C03051), shaken in a Parr apparatus (initial pressure 21.4 psi at 27°) for 33 min, there was obtained a gold oil indicated to be a mixture of *o*-boronobenzylaniline anhydride and tetrahydrofuran by its nmr spectrum in carbon tetrachloride; hydrogen consumption was 94%. The product was characterized as the catechol derivative (mp 197–200°).

Preparation of *o*-Boronobenzylaniline Hydrochloride by Lithium Aluminum Hydride Reduction of *o*-Boronobenzalaniline Anhydride.—To 20 ml of dry ether and 0.038 g (1 mmol) of lithium aluminum hydride was added a slurry of 0.500 g (0.805 mmol) of *o*-boronobenzalaniline anhydride in 20 ml of ether, and the mixture was refluxed for 2 hr. Since it appeared that no reaction had taken place, 12 ml of dry tetrahydrofuran was added and the mixture was refluxed for 2 hr and cooled. After treatment with water and 50 ml of a 20% solution of sodium potassium tartrate, the mixture was separated and the aqueous layer extracted with three 100-ml portions of ether. The solvent was removed *in vacuo* from the dried extract to give a yellow oily emulsion which could not be induced to crystallize. To the oily emulsion was added 10 ml of ether. Dry hydrogen chloride was bubbled through the solution and 0.53 g of a white precipitate formed (mp 167° dec, lit.[9] mp 169–171° dec). The nmr spectrum in deuterium oxide indicated that reduction had taken place and that the product was the hydrochloride of *o*-boronobenzylaniline.

Preparation of the Catechol Derivative of *o*-Boronobenzylaniline.—To 0.200 g (0.318 mmol) of *o*-boronobenzylaniline anhydride which contained a small amount of tetrahydrofuran were added 2 drops of water, 5 ml of absolute ethanol, and 0.105 g (0.954 mmol) of catechol. The reaction mixture was heated 1 min, then cooled and chilled. The clear quartzlike crystals which formed weighed 0.025 g. On cooling 48 hr, the mother liquor deposited a second crop (0.039 g, total yield 22%).

The analytical sample was obtained by drying the first crop (0.1 mm) over phosphorus pentoxide at 56.2° for 1 hr (mp 197–200°).

Anal. Calcd for $C_{19}H_{16}BNO_2$: C, 75.78; H, 5.36; N, 4.65. Found: C, 75.76; H, 5.38; N, 4.39.

The infrared spectrum (KBr) showed no absorption at 1620 cm^{-1}, confirming the absence of the CH=N group. The N—H stretch appeared at 3155 cm^{-1}, substantially lower than the range 3300–3500 characteristic of most secondary amines.[16]

N-(Phenyl)boronophthalimidine and Its Anhydride by Reduction of *o*-Boronobenzalaniline Anhydride.—A THF solution of 1.04 g of *o*-boronobenzalaniline anhydride was added slowly to a stirred slurry of 0.38 g of $LiAlH_4$ in THF. Upon completion of the addition, the reaction mixture was heated at reflux for 1 hr; the excess $LiAlH_4$ was decomposed (water); and the mixture obtained was filtered. The residue was washed with THF. The filtrate and the wash solution were combined and evaporated. The solid thus obtained was extracted with three 50-ml portions of ether which upon evaporation gave 0.59 g of product. Recrystallization from benzene–hexane gave a compound whose analysis (C, 73.47; H, 5.91) indicated it to be a mixture of *o*-boronobenzylaniline (C, 68.78; H, 6.22) and N-(phenyl)-boronophthalimidine (C, 74.70; H, 5.79). Azeotropic distillation of cyclohexane–water gave a mixture of the N-(phenyl)-boronophthalimidine and its anhydride (*Anal.* Calcd for $C_{26}H_{22}B_2N_2O$: C, 78.07; H, 5.54. Found: C, 76.72; H, 5.61.). The mass spectrum indicated a molecular weight of 400 which is that calculated for the anhydride of N-(phenyl)boronophthalimidine.

Preparation of the Catechol Derivative of 4-Hydroxy-4,3-boroxaroisoquinoline.—A solution prepared from 0.147 g of 4-hydroxy-4,3-boroxaroisoquinoline, 0.11 g of catechol, and 2 ml of absolute ethanol turned yellow as it was heated to reflux. The hot solution was filtered, then cooled to give yellow crystals (0.145 g, yield 60.6%), mp 207–211° dec. The analytical sample was recrystallized twice from absolute ethanol and dried at 0.1 mm at 56° for 2 hr, then at 100° for 1 hr.

Anal. Calcd for $C_{13}H_{10}BNO_3$: C, 65.33; H, 4.22; N, 5.86. Found: C, 65.15; H, 4.32; N, 5.66.

Preparation of N-(*o*-Boronobenzal)methoxyamine.—The pH of a solution prepared from 3.95 g of *o*-formylbenzeneboronic acid, 3.00 g of methoxyamine hydrochloride, and 100 ml of water was adjusted to 7 by adding approximately 10 ml of 10% sodium hydroxide solution. This mixture was refluxed for 15 min, cooled to room temperature, stoppered, and placed in the refrigerator overnight. The beautiful long transparent needles weighed 4.38 g (yield 93%). An analytically pure sample was obtained by recrystallization from chloroform (mp 87–87.5°).

Anal. Calcd for $C_8H_{10}BNO_3$: C, 53.68; H, 5.63; N, 7.83; mol wt, 179. Found: C, 53.55; H, 5.61; N, 7.72; mol wt (mass spectrum) 179.

Preparation of the Catechol Derivative of N-(*o*-Boronobenzal-methoxyamine.—In an apparatus equipped with a Dean–Stark water separator, water and benzene were codistilled from a solution of 2.56 g of N-(*o*-boronobenzal)methoxyamine in 100 ml of benzene. The reaction mixture was allowed to cool to 70° and 1.57 g of catechol was added. Codistillation was continued for 1.25 hr. The remaining solvent was removed *in vacuo*, and 2.7 g (yield 75%) of crude product was obtained. It was dissolved in toluene, treated with Darco, filtered, and caused to crystallize by the addition of low petroleum ether (bp 30–60°). The white needles obtained melted at 98–99°.

An analytical sample was obtained by recrystallizing the white needles twice from toluene and drying at 0.1 mm at 56° over calcium chloride for 8 hr (mp 102–103°).

Anal. Calcd for $C_{14}H_{12}BNO_3$: C, 66.43; H, 4.78; N, 5.54. Found: C, 66.76; H, 4.82; N, 5.30.

Registry No.—IIIa, 17604-35-2; IIIb, 17604-69-2; IIIc, 17743-98-5; IIId, 17659-03-9; IVa, 17604-19-2; IVb, 17604-20-5; IVc, 17604-21-6; IVd, 17604-22-7; V, 17692-14-7; X, 17604-70-5; XII, 17668-52-9; catechol deivative of N-(*o*-boronobenzal)methoxyamine, 17604-34-1.

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 249.

Arylation by Aromatic Nitro Compounds at High Temperatures. V. Reactions of Nitrotoluenes

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At 600°, *m*- and *p*-nitrotoluenes arylate benzene and chlorobenzene to give methylbiphenyls and methylchlorobiphenyls, respectively; *o*-nitrotoluene shows a markedly different behavior. It interchanges its oxygen and methyl hydrogen atoms to form anthranilic acid. With methanol, it gives methyl anthranilate; in benzene, it decarboxylates to aniline. Methyl anthranilates and anilines containing *meta* substituents are produced by reaction at high temperature of substituted *o*-nitrotoluenes with methanol and benzene, respectively. With benzene-d_6, *o*-nitrotoluene gives an appreciable amount of aniline-d_5, indicating transfer of the nitro group in a complex where the nitro oxygens and toluene hydrogens react. 2,4-Dinitrotoluene with mixtures of methanol and arenes give aryl-substituted methyl anthranilates.

In the first three papers of this series we described the formation of free radicals from aromatic nitro compounds at high temperatures,[1a] and the reactions of radicals from nitrobenzene with benzene[1b] and fluorinated arenes.[1c]

The fourth paper was concerned with the products of the reaction of nitrobenene with toluene and toluene-α-d_3, as well as of nitrobenzene-d_5 with toluene at 600°.[1d] The results were compared with those obtained in the pyrolyses of toluene and toluene-α-d_3 alone; the comparison gave strong evidence that, in the absence of added free radicals, toluene pyrolyzed largely by a nonradical mechanism.

This paper describes the reactions of the nitro derivatives of toluene at 400–600° with benzene, benzene-d_6, chlorobenzene, and methanol. A marked difference showed for the *ortho* as against the *meta* and *para* isomers; this has led to a one-step synthesis of methyl anthranilates and anilines containing *meta* substituents from substituted *o*-nitrotoluenes.

Experimental Section

Procedure.—Chemicals were reagent grade. Arylations were run in a Vycor tube filled with Vycor beads in an electric furnace maintained at 600 ± 1° under pure dry nitrogen with contact times indicated in the tables. Solutions of reactants were fed to the Vycor tube by a syringe whose needle fitted through a rubber septum in a glass adapter connected with the Vycor tube by a 24/40 joint; the syringe was pumped by a diffusion pump (Harvard Apparatus Co., Dover, Mass., compact diffusion pump Model 975) at a rate to give the required contact time. Rates were reproducible to 1% or better. The vapors were condensed in a bulb at −60°, the condensate was distilled to recover unreacted material, and the residue was analyzed. Some typical experiments are described.

A. *o*-Nitrotoluene with Benzene.—A solution of 6.14 ml (0.05 mol) of *o*-nitrotoluene in 44.44 ml (0.5 mol) of benzene was passed through a Vycor tube filled with Vycor chips, at 600° under nitrogen flowing at 20 cc/min. Contact time was 20 sec. The vapors were condensed in a bulb at −60°; the condensate was distilled to recover 37 ml of benzene and leave a residue boiling above 165° of 5.3 g, which was analyzed both by mass spectrometry and gas chromatography.

Analyses were performed with a Consolidated Model 21-103c mass spectrometer with the inlet system at 250 or 325°; with a directly coupled gas chromatograph–mass spectrometer combination[2] also employing a Model 21-103c instrument with an electron multiplier in place of the Faraday cup detector; and by gas chromatography, usually on a column of polyethylene glycol sebacate on Chromosorb W. Other types of columns were used in special analyses. Mass spectra were measured at the conventional 70 ionizing V and at low voltage—7.5 V, uncorrected. For the low-voltage measurements, the repellers were maintained at an average potential of 3 V, the exact values being selected to give maximum sensitivity.

Relative intensities in the low-voltage (7.5 V, uncorrected) mass spectra of product mixtures were taken as a first approximation to relative concentrations. Sensitivity, *i.e.*, the proportionality factor between parent-peak intensity and concentration, differs from one compound to another. However, closely related compounds have roughly equal sensitivities at the ionizing voltage employed in our work.[3] For example, in the same sample analyzed by both low-voltage mass spectrometry and gas chromatography, the ratios of peak intensities and areas, respectively, of a series of compounds were those given in Table I. In any case, the use of relative intensities is perfectly valid for intercomparison of concentration ratios of identical components in separate samples,[4] within the limits of reproducibility of the low-voltage data.

TABLE I

Compounds	Ratios— Low-voltage mass spectrometry	Gas chromatograpy
Biphenyl:fluorene	6.0	6.16
$C_{14}H_{14}$ isomers:biphenyl	2.39	2.89
Toluene:$C_{14}H_{14}$ isomers	1.37	1.30

Analysis by the two methods of the products from the reaction of *o*-nitrotoluene with benzene are shown in Table II.

B. *o*-Nitrotoluene with Methanol.—A solution of 3.68 ml (0.03 mol) of *o*-nitrotoluene in 12.1 ml (0.3 mol) of methanol was passed through the Vycor tube at 600° with a contact time of 16 sec. The condensate was distilled to recover 8.7 ml of methanol, and the residue boiling above 130° (3.8 g) was analyzed with the results shown in Table III. Considerable care should be taken in the reactions of 2,4-dinitrotoluene and 2,4,6-trinitrotoluene; although no difficulties were encountered in the vapor phase reactions, some explosions occurred during work-up of the liquid products.

Results and Discussion

Nitrotoluene Isomers.—The products of reaction of the three nitrotoluenes with benzene and chlorobenzene are shown in Table IV. At the temperature and con-

(1) (a) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 724 (1967); (b) *ibid.*, **89**, 3224 (1967); (c) *J. Org. Chem.*, **32**, 3114 (1967); (d) *ibid.*, **33**, 2815 (1968).

(2) R. S. Gohlke, *Anal. Chem.*, **31**, 535 (1959); L. P. Lindemann and J. L. Annis, *ibid.*, **32**, 1742 (1960); J. T. Watson and K. Bremann, *ibid.*, **36**, 1135 (1964).

(3) G. F. Crable, G. L. Kearns, and M. S. Norris, *Anal. Chem.*, **32**, 13 (1960).

(4) S. Meyerson and E. K. Fields, *Chem. Commun.*, 275 (1966).

TABLE II

Product	Estimated by mass spectrometry Ion %	Analysis by gas chromatography Area %	Yield,[b] mol %
Toluene	2.8	3.4	3.9
Aniline	56.4	37.8	43.1
Phenol	5.6	6.2	7.0
o-Cresol	7.9	9.9	9.7
Biphenyl	18.9	19.7	13.6
Fluorene	1.1	1.7	1.1
2-Methylbiphenyl	3.4	4.0[a]	2.5
Stilbene	1.1	1.8	1.1
Bibenzyl and isomers	2.8	3.2[a]	1.9

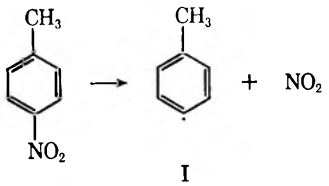
[a] Overlapping peaks, as described in ref 1d. There were additionally eight unknowns of higher boiling point than bibenzyl. [b] Calculated on the basis of 0.05 mol of *o*-nitrotoluene giving 0.05 mol of product if the yield were quantitative.

TABLE III

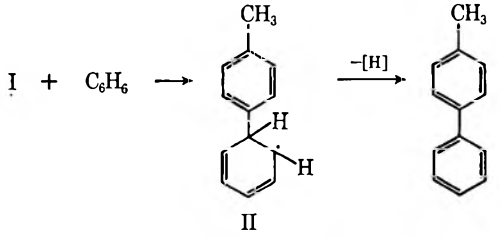
Product	Estimated by mass spectrometry Ion %	Analyzed by gas chromatography Area %	Yield,[a] mol %
o-Toluidine	10.5	7.4	5.3
Aniline	40.3	26.4	19.4
o-Cresol	7	8.9	7.6
N-Methyl-*o*-toluidine	3.3	1.9	1.8
Methyl anthranilate	38.7	45.2	37.8
Bibenzyl and isomers	0.3	0.6	0.9

[a] Calculated on the *o*-nitrotoluene.

tact times used in this work, no nitrotoluene survived. The products from *m*- and *p*-nitrotoluenes are generally similar, although the relative amounts differ somewhat. Other then biphenyl, which also formed from benzene alone, methylbiphenyl is the major product and this results from arylation of benzene by the tolyl radical



I



II

(I). The tolylcyclohexadienyl radical II is presumably restored to aromaticity by NO_2, itself a free radical, which goes to HNO_2 and its decomposition products, ultimately water, N_2, and NO.[1b]

Toluene results from hydrogen abstraction by I; the cresols, from the nitro–nitrite rearrangement observed in the high-temperature reactions of nitrobenzene.[1b]

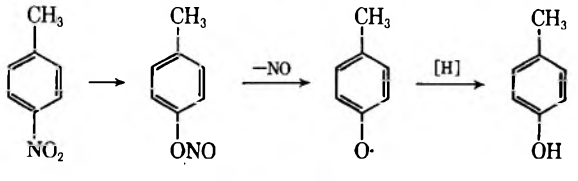


TABLE IV

REACTION PRODUCTS OF NITROTOLUENES WITH BENZENE AND CHLOROBENZENE[a]

Nitrotoluene isomer	None[c]	*ortho*	*meta*	*para*
Total weight of products, g	0.06	5.3	8.0	6.3
	Rel concn[c] with benzene			
Products				
Toluene		15	11	15
Aniline		300		
Phenol		30	12	8
Cresol		42	15	7
Biphenyl	100	100	100	100
Fluorene		6		
Methylbiphenyl		18	49	67
Stilbene		6	2	2
Bibenzyl and isomers		15	6	5
Nitrotoluene isomer	None[d]	*ortho*	*meta*	*para*
Total weight of products, g	0.75	4.25	4.1	6.5
	Rel concn[c] with chlorobenzene			
Products				
Aniline		9		
Cresol		4	28	8
Chlorophenol		28		
Carbazole		22		
Methylbiphenyl		8	31	18
Chlorobiphenyl	23	33	120	64
Methylchlorobiphenyl		20	51	104
Chlorocarbazole		53		
Dichlorobiphenyl	100	100	100	100

[a] Conditions: 600°, 20-sec contact time, nitrogen at 20 cc/min, moles of nitrotoluene:benzene or chlorobenzene 0.05:0.25. [b] Benzene alone (0.25 mol). [c] Relative intensities in the low-voltage (7.5 V nominal) mass spectrum normalized to biphenyl = 100 for the reaction products from benzene, and dichlorobiphenyl = 100 for the reaction products from chlorobenzene. [d] Chlorobenzene alone (0.25 mol).

The products of mass 182 from the three nitrotoluenes, bibenzyl and isomers, may include bitolyls from dimerization of tolyl radicals; however, as shown in the earlier papers of this series,[1] dimerization of aryl radicals at high temperatures, as well as in the liquid phase,[1d,5] is a minor reaction compared with addition to aromatic compounds. The formation of stilbene from all three nitrotoluenes in about the same concentration ratio to "bibenzyl and isomers" may be taken as evidence that bibenzyl is formed in all cases. The other dehydrodimers of toluene are probably also present, as in the reaction of nitrobenzene with toluene.[1d]

o-Nitrotoluene behaved markedly differently from the other two isomers. With benzene it gave only small amounts of *o*-methylbiphenyl and its dehydrogenation product, fluorene. Aniline was the major product, evidently as result of reduction of the nitro and loss of the methyl groups.

To clarify this reaction, we pyrolyzed solutions of the nitrotoluenes in methanol with the results shown in Table V. Methyl anthranilate was formed from the *ortho* isomer in yield about equal to that of aniline. At high temperatures, *o*-nitrotoluene apparently undergoes intramolecular oxidation and reduction to give anthranilic acid; in the absence of methanol to esterify and stabilize it, the carboxyl group is lost to yield

(5) J. K. Hambling, D. H. Hey, S. Orman, and G. H. Williams, *J. Chem. Soc.*, 3108 (1961); J. D. Burr, J. M. Scarborough, J. D. Strong, R. I. Akawie, and R. A. Meyer, *Nuclear Sci. Eng.*, **11**, 218 (1961); G. W. Taylor, *Can. J. Chem.*, **35**, 739 (1957); J. E. Bennett, B. Mile, and A. Thomas, *Chem. Commun.*, 265 (1965).

TABLE V

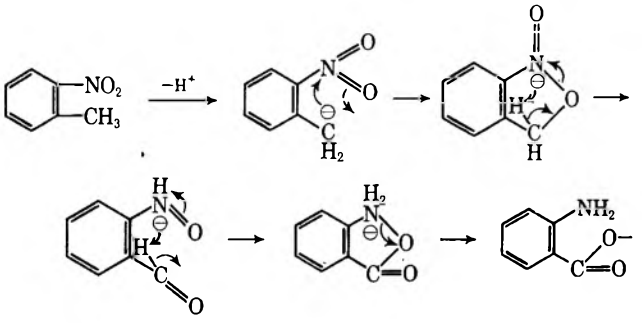
REACTION PRODUCTS OF NITROTOLUENES WITH METHANOL[a]

Nitrotoluene isomer	*ortho*	*meta*	*para*
Total weight of products, g	3.8	1.65	1.7
	Relative concn[b]		
Products			
Toluidine	100	100	100
Aniline	385	6	4
Cresol	67	62	38
N-Methyltoluidine	31	29	17
Methyl aminobenzoate	369		
Bibenzyl and isomers	3	73	17

[a] Conditions: 600°, 16-sec contact time, nitrogen at 20 cc/min, moles of nitrotoluene:methanol 0.03:0.3. [b] Relative intensities in the low-voltage (7.5 V nominal) mass spectrum normalized to toluidine = 100.

aniline.[6] No methyl aminobenzoate was formed from *m*- or *p*-nitrotoluenes.

A complex mixture of products containing *inter alia* anthranil and anthranilic acid has resulted from treatment of *o*-nitrotoluene with concentrated alkali.[7] The mechanism at the high temperature may thus involve formation of a carbanion species followed by a series of hydrogen and oxygen shifts.[8,9] In our work,



the proton and carbon or nitrogen anions are presumably never separated to any extent, as the reaction occurs in the gas phase. Evidence has been reported for interchange of hydrogen and oxygen atoms in the sequential loss of OH, CO, and HCN from *o*-nitrotoluene under electron impact in the mass spectrometer;[9] the two processes thus resemble each other closely. Numerous examples of parallel behavior in pyrolysis and under electron impact have been found in other contexts.[4,10a] The high-temperature formation of anthranilic acid also resembles to some extent the thermal elimination of sulfur dioxide from *o*-methyldiarylsulfones to give diarylmethanes.[10b]

(6) W. Lob [*Z. Elektrochem.*, **8**, 715 (1902)] found that *o*-nitrotoluene exploded when passed through a metal tube heated until it glowed light red. By diluting the nitrotoluene with steam, he obtained 8% crude and an unspecified yield of pure anthranilic acid.

(7) I. I. Kukhtenko, *Dokl. Akad. Nauk SSSR*, **132**, 609 (1960); G. A. Russell and E. G. Jansen, *J. Amer. Chem. Soc.*, **89**, 300 (1967), and earlier references cited therein.

(8) When a formally charged species is written in a gas phase reaction, it should be understood, of course, that the counterion is assumed to remain in close association with the charged species. As noted by a referee, a similar mechanism can be written to explain the interchange of O and H atoms *via* a free-radical process, by initial abstraction of H atom and half-arrows to denote 1-electron shifts. The carbanion scheme proposed formally parallels that apparently occurring under electron impact.[9]

(9) S. Meyerson, I. Puskas, and E. K. Fields, *J. Amer. Chem. Soc.*, **88**, 4974 (1966).

(10) (a) For example, E. K. Fields and S. Meyerson, *Chem. Commun.*, 474 (1966); E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 2836 (1966). (b) H. Drews, E. K. Fields, and S. Meyerson, *Chem. Ind.* (London), 1403 (1961).

Substituted methyl anthranilates result under the same conditions from *o*-nitrotoluenes containing nuclear substituents, as shown in Table VI.[11] The yields, although not high, are sufficient to be of interest for synthetic use, especially as they were obtained in one-step reactions.

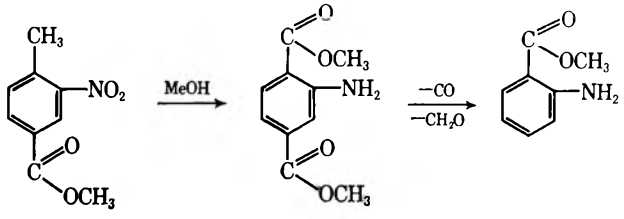
TABLE VI

METHYL ANTHRANILATES FROM *o*-METHYLNITROARENES AND METHANOL[a]

o-Methylnitroarene	Product	Yield, mol %
o-Nitrotoluene	Methyl anthranilate	38[b]
4-Chloro-2-nitrotoluene	Methyl 4-chloroanthranilate	36[b]
4-Fluoro-2-nitrotoluene	Methyl 4-fluoroanthranilate	21[c]
Nitro-*p*-xylene	Methyl 4-methylanthranilate	25[c]
5-Nitropseudocumene	Methyl 3,4-dimethylanthranilate	20[c]
Methyl 3-nitro-4-methylbenzoate	Dimethyl 2-aminoterephthalate	6[c]
	Methyl anthranilate	37[c]
2-Methyl-1-nitronaphthalene	Methyl 1-amino-2-naphthoate	11[c]

[a] Conditions: 600°, 16-sec contact time, mole ratio of *o*-methylnitroarene:methanol 1:10. [b] By gas chromatography. [c] Estimated by low-voltage mass spectrometry.

Methyl 3-nitro-4-methylbenzoate gave only a small amount of dimethyl 2-aminoterephthalate; the major product evidently results by loss of the original CO_2-Me group, possibly as CO and CH_2O.



In an attempt to increase the yield of methyl anthranilate, we passed *o*-nitrotoluene with methanol 1:10 at 525° over activated alumina. Only 0.5% methyl anthranilate formed; the major products were N-methylaniline (13%), N,N-dimethylaniline (14%), and N,N-dimethyl-*o*-toluidine (6%). Evidently the alumina promoted decarboxylation of anthranilic acid and catalyzed methylation of the resulting aniline.

Formation of aniline from *o*-nitrotoluene in the absence of methanol suggested that this reaction might be utilized to prepare substituted anilines. *o*-Nitrotoluene was heated at 600°, 11-sec contact time, alone and at a 1:3 mole ratio with various hydrocarbons to determine a set of conditions to be used with substituted *o*-nitrotoluenes. The yields of aniline are given in Table VII. As benzene gave the highest yield of aniline, it was used for the preparation of substituted anilines, with the results shown in Table VIII.

TABLE VII

Hydrocarbon	Yield,[a] mol %
None	33
Cyclohexane	35
Toluene	36
Benzene	57

[a] By gas chromatography.

(11) E. K. Fields and S. Meyerson, *Tetrahedron Lett.*, 1201 (1968).

TABLE VIII

AROMATIC AMINES FROM *o*-METHYL NITRO AROMATICS[a]

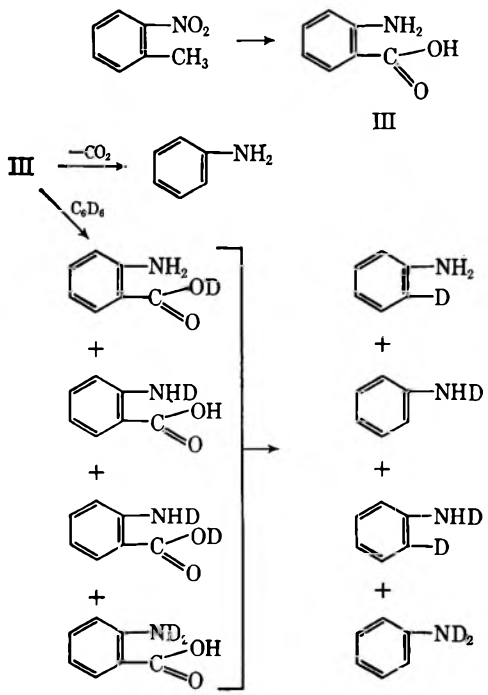
o-Methyl nitro aromatics	Amine	Yield, mol %
o-Nitrotoluene	Aniline	57[b]
Nitro-*p*-xylene	*m*-Toluidine	59[b]
4-Chloro-2-nitrotoluene	*m*-Chloroaniline	15[b]
4-Fluoro-2-nitrotoluene	*m*-Fluoraniline	27[c]
5-Nitropseudocumene	4-Amino-*o*-xylene	19[c]
Methyl 3-nitro-4-methylbenzoate	Methyl 3-aminobenzoate	32[c]
2-Methyl-1-nitronaphthalene	1-Naphthylamine	70[b]

[a] Conditions: 600°, 20-sec contact time, mole ratio of nitro compound:benzene 1:4. [b] By gas chromatography. [c] Estimated by low-voltage mass spectrometry.

No attempt was made to find optimum conditions; the large variation in yields suggests that these probably differ considerably among the nitro compounds. Our novel preparation gives amines in one step, in most cases with a *meta* substituent. These are usually the most difficult to synthesize by other methods.

To determine the mode of formation of the products with benzene shown in Table IV, nitrotoluene isomers were allowed to react separately with benzene-d_6 at 600°. The products and their isotopic compositions are listed in Table IX.

The major aniline species from *o*-nitrotoluene were d_0, d_1, and d_2. Aniline-d_1 and -d_2 may arise by a rapid exchange of the reactive carboxyl and amino hydrogens with benzene-d_6. The high reactivity of



amino and carboxyl hydrogens in solution presumably carries over to the gas phase provided that the pressure is high enough to permit solvation. The exchange may be by way of the anthranilic acid zwitterion before it loses carbon dioxide.

Aniline-d_3 could be similarly rationalized, but the d_4, d_5, and d_6 species, which almost certainly came from benzene-d_6, are not so easily explained. The formation of these aniline species parallels the formation of chlorocarbazole from *o*-nitrotoluene and chlorobenzene shown in Table IV. Likewise, aniline formed

TABLE IX

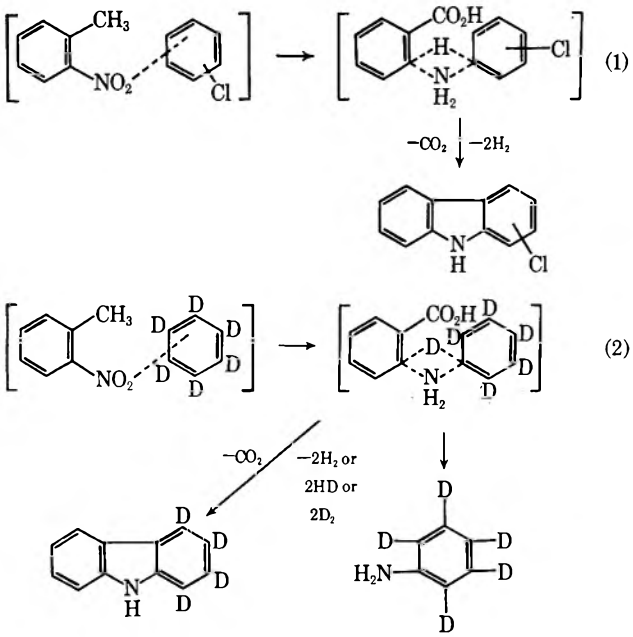
REACTION PRODUCTS OF NITROTOLUENES WITH BENZENE-d_6[a]

	Relative concn[b] — Nitrotoluene isomer			
Products	*ortho*	*meta*	*para*	*e*
Benzene-d_4	1.2		1.8	
-d_5	15.5	15.2	18.5	
-d_6	83.3	84.8	79.7	
Aniline-d_0	100			
-d_1	90			
-d_2	40			
-d_3	13			
-d_4	6			
-d_5	9			
-d_6	16			
Phenol-d_0	*c*	10	10	
-d_1	*c*	10	8	
-d_2	*c*	4	4	
-d_3	*c*	2	3	
-d_4	*c*	5	6	
-d_5	*c*	18	7	
Cresol-d_0	*d*	30	14	
-d_1	*d*	19	7	
-d_2	*d*	17	3	
Biphenyl-d_0	0.4	1	1	490
-d_1	0.4	2	3	50
-d_2	0.4	2	4	25
-d_3	0.4	2	4	75
-d_4	3	7	11	450
-d_5	13	34	48	850
-d_6	10	35	48	50
-d_7	3	15	27	25
-d_8	5	10	14	125
-d_9	33	37	47	278
-d_{10}	100	100	100	100
Methylbiphenyl-d_0	5	3	6	
-d_1	7	6	10	
-d_2	14[f]	7	10	
-d_3	29[f]	6	9	
-d_4	19[f]	16	24	
-d_5	19[f]	75	92	
-d_6	24[f]	50	57	
-d_7	15[f]	20	21	
Bibenzyl + isomers	5	6	5	
Terphenyl-d_4			1	
-d_5			4	
-d_6	0.7		4	
-d_7	1		4	
-d_8	9		3	
-d_9	9	6	9	
-d_{10}	6	11	17	
-d_{11}	1	6	10	
-d_{12}	0.8		4	
-d_{13}	0.8		3	
-d_{14}	4		5	

[a] Conditions: 600°, 8.5-sec contact time, mole ratio of nitrotoluene:benzene-d_6 1:5; isotopic composition of initial benzene, 96.4% d_6, 3.6% d_5. [b] Relative intensities in the low-voltage (7.5 V, uncorrected) mass spectra normalized to biphenyl-d_{10} = 100. [c] Overlapping peaks with aniline. [d] Overlapping peaks with *o*-toluidine. [e] From nitrobenzene-d_5 with toluene.[1d] [f] Mainly deuterated carbazole and diphenylamine (see text).

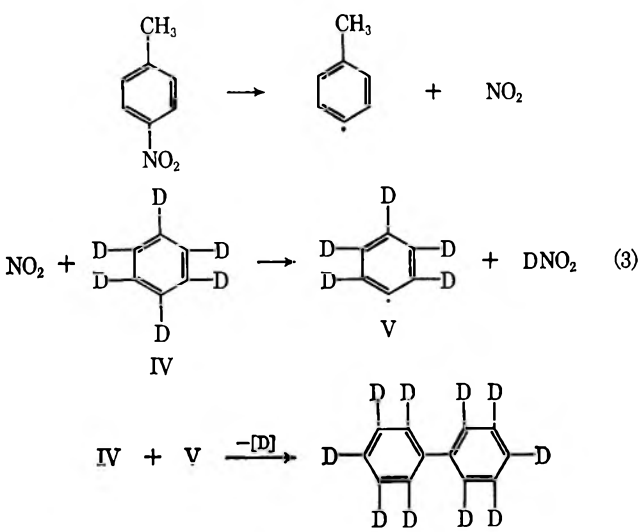
in only trace amounts in the reaction of nitrobenzene and nitrobenzene-d_5 with toluene, as well as that of nitrobenzene with toluene-α-d_3.[1d] Transfer of the nitro group from *o*-nitrotoluene to chlorobenzene or benzene-d_6 seems thus to occur in a complex involving a concerted reaction with the methyl group (eq 1 and 2). The 167–169 mass region of the products from *o*-nitrotoluene with unlabeled benzene shows relative

intensities of 19, 5, and 13 for carbazole, methylbiphenyl, and diphenylamine, respectively. Therefore, the region of masses 168–175, shown in Table IX under the methylbiphenyl species, probably involves for *o*-nitrotoluene mainly deuterated species of carbazole and diphenylamine, with only a minor contribution from *o*-methylbiphenyl. Thus the major isotopic species of carbazole is d_4 and that of diphenylamine is d_5, which fit neatly into the proposed scheme (eq 1 and 2).

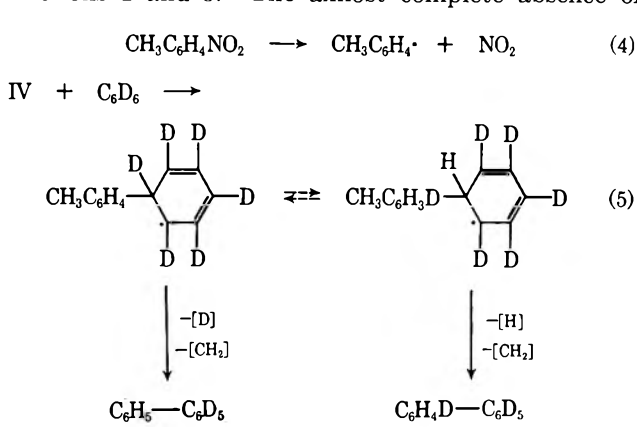


The analysis of reaction products from *o*-nitrotoluene with benzene-d_6, because of overlapping peaks in the 167–177 region, is not perhaps so clear-cut as one would like; however, taken together with analysis of the same reaction with unlabeled benzene and chlorobenzene, it enables us to derive a fairly coherent reaction pattern.

The biphenyl region is free from overlapping species of other products and is therefore relatively uncomplicated. Almost no biphenyl arises from two benzene rings derived solely from nitrotoluenes. The main component, biphenyl-d_{10}, comes from benzene-d_6, presumably by abstraction of a deuterium by NO_2 (eq 3).



From total weights of products and relative proportions of biphenyl shown in Table IV, appreciably more biphenyl is formed in the reaction with benzene from the *m*- and *p*-nitrotoluenes than from the *ortho* isomer, as would be expected. The nitro group in the *ortho* isomer is involved in the intramolecular reaction with the methyl group rather than in cleavage of the aryl–nitro bond. Much biphenyl is formed from a benzene ring derived from both benzene-d_6 and nitrotoluene; the nearly equal amounts of d_5 and d_6 species indicate reactions 4 and 5. The almost complete absence of



biphenyl-d_0 and -d_1 in this work contrasts with the considerable amount from the reaction of nitrobenzene-d_5 with toluene,[1d] shown under column *e* in Table IX. This indicates that loss of a methyl or CH_2 group from toluene or its derivatives probably occurs from the intermediates of radical addition or abstraction, rather than as a primary process in pyrolysis as postulated by previous workers (see ref 12 and references cited therein). Similarly, we have reported evidence

$$C_6H_5—CH_3 \longrightarrow C_6H_5\cdot + \cdot CH_3$$

for different dominant mechanisms in thermal decomposition of toluene alone and in the presence of free radicals.[1d]

Some of the products in Table IV and Table IX may be derived by transfer of a nitro group from nitrotoluene to benzene (reaction 6). At first glance the widely

$$CH_3C_6H_4NO_2 + C_6D_6 \longrightarrow CH_3C_6H_4D + C_6D_5NO_2 \quad (6)$$

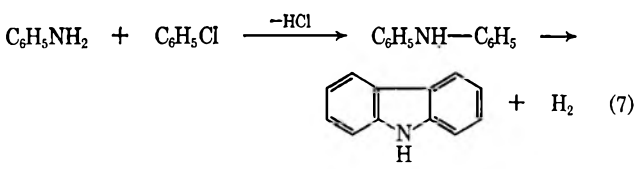
differing concentrations of biphenyl species in Table IX under column *e* and the other columns would seem to render this reaction unlikely. However, reactant ratios were considerably different in the two studies; furthermore, phenol-d_4 and -d_5 shown in Table IX appear to demand a nitro–nitrite rearrangement of nitrobenzene-d_5 from reaction 6.

The main terphenyl species are d_9 and d_{10}, with as much d_8 as d_9 in the *o*-nitrotoluene reaction. These evidently arise from the combination of biphenyl-d_8, -d_9, and -d_{10} with a molecule of nitrotoluene as shown in the scheme for biphenyl formation. Terphenyl-d_{11} may be the result of deuterium–protium scrambling, although somewhat more formed from *m*- and *p*-nitrotoluenes than might be anticipated from the complete absence of other species in the *m*- and much lower amounts in the *p*-nitrotoluene reactions. Some or most terphenyl-d_{11} might be the result of nitrobenzene-

(12) G. B. Badger and T. M. Spotswood, *J. Chem. Soc.*, 4420 (1960).

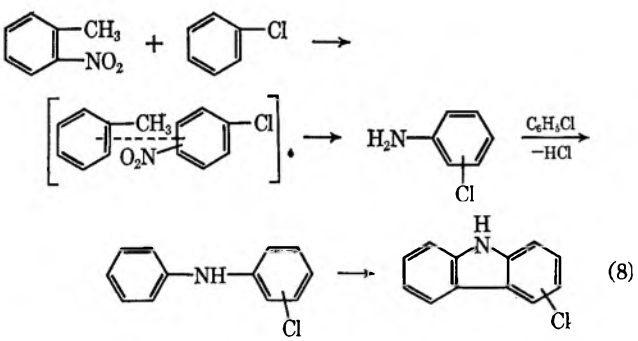
d_5 attack on methylbiphenyl-d_6 with subsequent or concerted loss of the methyl group.

Carbazole shown in Table IV probably arises by reaction of aniline from *o*-nitrotoluene with chlorobenzene (reaction 7). Carbazole results both from



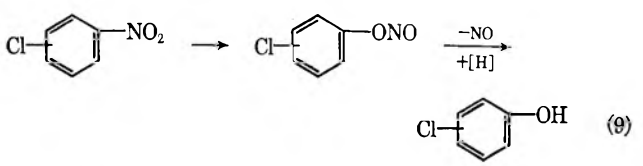
(7)

diphenylamine[13] and 2-aminobiphenyl[14] at high temperatures. Chlorocarbazole, however, indicates transfer of a nitro group from *o*-nitrotoluene to chlorobenzene reduction to chloroaniline, and reaction with another molecule of chlorobenzene (reaction 8). Additional



(8)

evidence for formation of nitrochlorobenzene is chlorophenol, about half as much as chlorocarbazole, most readily accounted for by a nitro–nitrite rearrangement (reaction 9). With benzene, *o*-nitrotoluene gave an appreciable amount of phenol, presumably also by transfer of its nitro group to benzene.



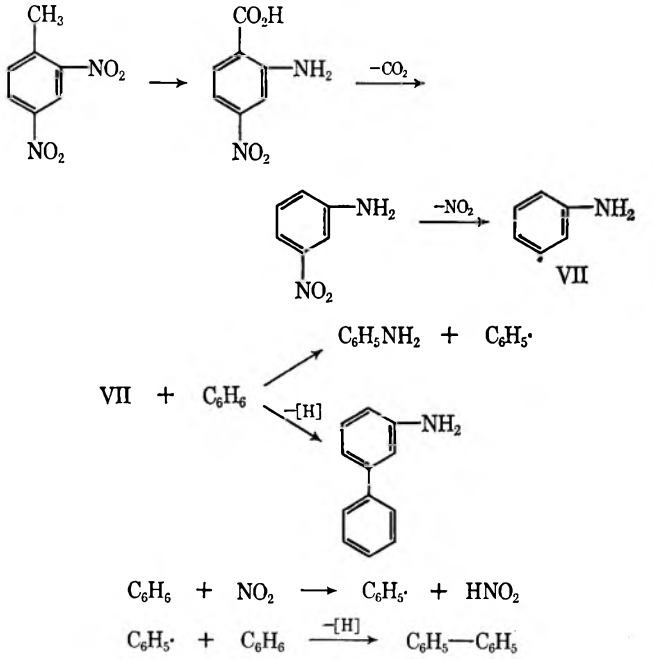
(9)

2,4-Dinitrotoluene with benzene both at 500 and 550° gave mainly biphenyl, and about one-fourth as much each of aniline and aminobiphenyl. The *m*-aminophenyl radical (VII) evidently abstracts hydrogen almost as readily as it adds to aromatic systems (Scheme I).

The reaction products of 2,4-dinitrotoluene with methanol alone, with methanol plus benzene, and with methanol plus fluorobenzene are shown in Table X. Methyl anthranilate and aniline were major products from the anthranilic acid rearrangement followed by esterification or loss of carbon dioxide. The aryl radical formed by cleavage of the second nitro group evidently abstracts hydrogen more readily than it adds to benzene or fluorobenzene, at least at 600°. The ratio of methyl anthranilate to aniline from the methanol reaction is much higher than in the same reaction of *o*-nitrotoluene; apparently, 4-nitroanthranilic acid esterifies faster than anthranilic acid. The ratio of

(13) C. Graebe, *Ber.*, **5**, 377 (1872); *Ann.*, **167**, 128 (1873); **174**, 180 (1874).
(14) A. Blank, *Ber.*, **24**, 306 (1891).

SCHEME I



abstraction to addition products might change appreciably at lower temperatures to give more arylated methyl anthranilates.

TABLE X

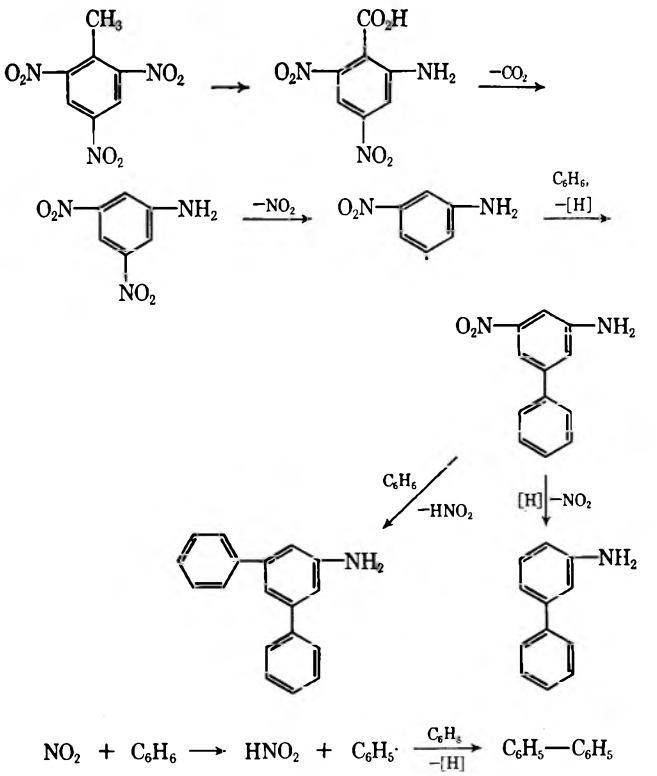
REACTIONS OF 2,4-DINITROTOLUENE[a]

Reactant, mol	Methanol, 1.2	Methanol, 0.625; benzene, 0.5	Methanol, 0.625; fluorobenzene, 0.5
Total weight of products, g	2.75	5.25	2.5
		Relative concn[b]	
Products			
Aniline	20	93	45
Biphenyl		185	
Difluorobiphenyl			4
Methylbiphenyl		133	
Fluoromethylbiphenyl			15
Methyl anthranilate	100	100	100
Methyl phenylanthranilate		25	
Methyl fluorophenylanthranilate			8

[a] Conditions: 600°, 10-sec contact time, N_2 at 20 cc/min, moles of dinitrotoluene 0.05. [b] Relative intensities in the low-voltage (7.5 V, uncorrected) mass spectrum normalized to methyl anthranilate = 100.

2,4,6-Trinitrotoluene.—The products from the reaction of 2,4,6-trinitrotoluene (TNT) with benzene at various temperatures are listed in Table XI. The predominant product in all cases was biphenyl. Benzene alone under these conditions gives only a trace of biphenyl; therefore, the relatively large amounts from the TNT reactions probably arise from phenyl radicals by way of hydrogen abstraction. The products in the table indicate the series of reactions in Scheme II. Interchange of oxygen and hydrogen atoms probably occurs before or at the same time as loss of nitro groups; were it to take place appreciably more slowly, we would anticipate finding some products that retain the methyl group (or at least the corresponding fluorene by dehydrogenation), which is not the case.

SCHEME II



$$NO_2 + C_6H_6 \longrightarrow HNO_2 + C_6H_5\cdot \xrightarrow[-[H]]{C_6H_5} C_6H_5{-}C_6H_5$$

Aminobiphenyl is present in appreciably greater amount than aniline. This may be because the radical from dinitroaniline must participate in two hydrogen abstractions rather than one as in the case of the aminobiphenyl radical.

With increasing temperature the products still containing nitro groups, dinitroaniline and nitroaminobiphenyl, decreased, as would be anticipated. Even at the lowest temperature, 400°, no trinitrotoluene apparently survived; it is therefore considerably less stable than *o*-nitrotoluene, 50% of which was recovered after 20 sec at 500°.

TABLE XI

PRODUCTS FROM 2,4,6-TRINITROTOLUENE WITH BENZENE AT VARIOUS TEMPERATURES[a]

Total weight of products, g	2.75	3.7	3.92	4.0
Temperature, °C	400°	450°	500°	550°
	Relative concn[b]			
Products				
Aniline	5	7	20	19
Biphenyl	100	100	100	100
Aminobiphenyl	13	29	29	27
Dinitroaniline	8	3	1	1
Nitroaminobiphenyl	2	3	0.4	0.3
Aminoterphenyl		3	5	6

[a] Conditions: 20-sec contact time, N_2 at 20 cc/min, moles of TNT:benzene 0.05:0.5. [b] Relative intensities in the low-voltage (7.5 V, uncorrected) mass spectrum normalized to biphenyl = 100.

The present work has shown a striking difference in the reactions of *o*-nitrotoluene and substituted *o*-nitrotoluenes from those of the *meta* and *para* isomers. We are pursuing this study further by examining the behavior of labeled and unlabeled *o*-nitroethylbenzene, *o*-nitrocumene, and *o*-nitro-*t*-butylbenzene at 600°.

Registry No.—Benzene, 71-43-2; benzene-d_6, 1076-43-3; chlorobenzene, 108-90-7; methanol, 67-56-1; *o*-nitrotoluene, 88-72-2; *m*-nitrotoluene, 99-08-1; *p*-nitrotoluene, 99-99-0; 2,4-dinitrotoluene, 121-14-2; 2,4,6-trinitrotoluene, 118-96-7.

Acid-Catalyzed Cleavage of 1-Methylnortricyclene[1]

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The preparation of 1-methylnortricyclene (**7**) was accomplished in good yield from 1-methyl-2-norbornanone *p*-toluenesulfonylhydrazone (**6**). The kinetic product from reaction of **7** with acetic acid was 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**), which was slowly converted into 1-methyl-2-*exo*-norbornyl acetate (**3**), and 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**) under the reaction conditions. Cleavage with acetic acid-O-*d* gave a mixture of **3**, **9**, and **10** containing up to five deuteriums per molecule. Treatment of the acetates with alumina, ozonolysis, and washing with aqueous alkali gave monodeuterated 2-norbornanone (**1**). The infrared spectrum of this material showed that the deuterium was 62 ± 3% 6-*endo* and 38 ± 3% 6-*exo*, demonstrating that cleavage of the cyclopropyl C–C bond by the electrophile, D^+, occurs with predominating retention of configuration. The results are accounted for in terms of a carbonium ion intermediate which can react by any of five paths; qualitative conclusions are presented on the way in which the intermediate partitions among these paths.

Studies of cleavage of the cyclopropane ring in tricyclo[2.2.1.$0^{2,6}$]heptanes with acetic acid have been concerned for the most part with the question of product distribution. In the case of unsymmetrically substituted tricyclo[2.2.1.$0^{2,6}$]heptanes, any one of three bonds may cleave, and each can add an unsymmetrical reagent like acetic acid with either of two modes of orientation. Thus, as many as six different products can be formed, neglecting stereochemistry. Compounds such as apocyclene[2] (3,3-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane) and epicyclene[3] (3,3,4-trimethyltricyclo[2.2.1.$0^{2,6}$]heptane), which have hydrogens on all three cyclopropyl carbons, give mixtures of isomeric acetates on reaction with acetic acid. In contrast, derivatives of 1-methylnortricyclene (**7**) have been reported to be converted cleanly into substituted 1-methyl-2-norbornyl acetates;[4] 1-methylnortricy-

(1) This research was supported in part by a National Science Foundation Undergraduate Research Participation grant to the Department of Chemistry, Swarthmore College.

(2) S. S. Nametkin and Z. Alexandrova, *J. Russ. Phys. Chem. Soc.*, **57**, 395 (1926); S. S. Nametkin and Z. Alexandrova, *Ann.*, **467**, 191 (1928).

(3) S. S. Nametkin and L. Bryusova, *J. Russ. Phys. Chem. Soc.*, **62**, 333 (1930).

(4) S. Moycho and F. Zienkowski, *Ann.*, **340**, 17 (1905).

clene itself is a typical example, giving only 1-methyl-2-*exo*-norbornyl acetate (**3**).[5] However, 2-*endo*-methyl-2-*exo*-norbornyl acetates are now known to rearrange to 1-methyl-2-*exo*-norbornyl acetates under conditions considerably less vigorous than those employed for cyclopropyl ring cleavage.[6,7] The secondary acetates obtained may have been kinetic products; alternatively, tertiary acetates may have formed first and subsequently rearranged to the secondary isomers. No evidence has previously been presented on this point.

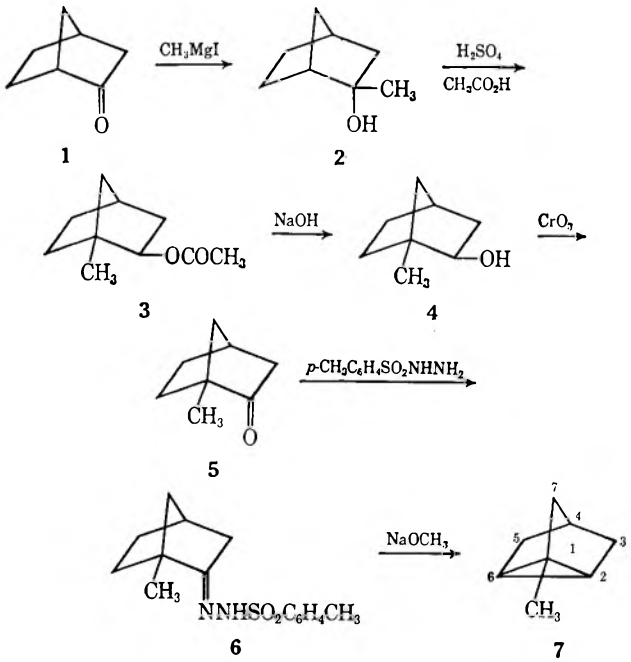
A second point of interest is the stereochemistry of addition of acetic acid to nortricyclene derivatives. Cleavage of nortricyclene by acetic acid-O-*d* occurs with complete lack of stereospecificity for the deuteration and complete *exo* specificity for the acetate, implying that the reaction proceeds through a carbon-bridged norbornyl cation (or the equivalent with respect to these experiments, an equilibrating pair of classical cations).[8] If there is a preferred stereochemistry for deuteration, in the unsubstituted norbornyl system it is unobservable because of the symmetry of the bridged ion. Introduction of a group other than hydrogen at the 1 position would destroy this symmetry and allow determination of the stereochemistry of deuteration.

Our investigation of acetic acid cleavage of 1-methylnortricyclene was undertaken to shed light on these two questions: (1) identification of the kinetic product of cleavage, and (2) determination of the preferred stereochemical course for the deuteration step.

Discussion and Results

Synthesis of 1-Methylnortricyclene.—2-Norbornanone (**1**) was converted into 1-methyl-2-norbornanone (**5**) by a series of known reactions (Scheme I).[9] Treatment of **1** with methylmagnesium iodide gave 2-*exo*-methyl-2-*endo*-norbornanol (**2**). Simultaneous rearrangement and acetylation of **2** with sulfuric acid in acetic acid yielded 1-methyl-2-*exo*-norbornyl acetate (**3**), which was saponified to the corresponding alcohol (**4**). Chromium trioxide oxidation of **4** gave 1-methyl-2-norbornanone (**5**). The *p*-toluenesulfonylhydrazone of **5** reacted with sodium methoxide in refluxing diglyme to give an 88% yield of 1-methylnortricyclene (**7**). Analysis by gas chromatography showed **7** to be 99% pure, and the infrared spectrum showed cyclopropyl C–H stretching absorption at 3055 cm^{-1} and characteristic 1-substituted nortricyclene absorption[10] at 849 and 785 cm^{-1}.

SCHEME I



Ring Cleavage in Acetic Acid.—Addition of acetic acid to 1-methylnortricyclene (**7**) could lead to any of eight possible products (Scheme II). Cleavage of the C-2–C-6 bond would give 1-methyl-2-*exo*-norbornyl acetate (**3**) or its 2-*endo*-acetoxy epimer (**8**). Cleavage of the C-1–C-2 bond could occur by either of two orientation modes. Markovnikov addition would yield 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) or its 2-*exo*-methyl-2-*endo*-acetoxy epimer (**10**). Anti-Markovnikov cleavage of this bond could give any of four 6-methyl-2-norbornyl acetates: 6-*exo*-methyl-2-*exo* acetate (**11**), 6-*exo*-methyl-2-*endo* acetate (**12**) 6-*endo*-methyl-2-*exo* acetate (**13**), or 6-*endo*-methyl-2-*endo* acetate (**14**).

The ring-cleavage experiments were carried out at 24.5 ± 0.1° in the presence of 0.005 *M* sulfuric acid. After 2 hr 1-methylnortricyclene (**7**) was 15 ± 5% converted into acetate. The product was isolated by pentane–water extraction and vacuum distillation. Comparison of the infrared (ir) spectrum of this material with spectra of acetates **3**, **8**, **9**, and **10** established that the cleavage product was 2-*endo*-methyl-2-*exo* norbornyl acetate (**9**) containing no detectable **3**, **8**, or **10**. Examination of spectra of artificial mixtures of **9** with **3**, with **8**, and with **10**, showed that as little as 2.5% of any one of these three isomers could have been detected with certainty. Thus, the kinetic product of acetic acid addition to **7** is pure or nearly pure tertiary *exo*-acetate (**9**), the product of C-1–C-2 cleavage and Markovnikov addition. The fact that only *exo* acetate is formed suggests that the reaction proceeds through a 2-norbornyl cation; these ions are well known to react with acetate from the *exo* side under conditions of kinetic control. Two other reactions which proceed by way of the same cation, acetolysis of 1-methyl-2-*exo*-norbornyl *p*-toluenesulfonate[11a] and nitrosative deamination of 2-*endo*-methyl-2-*exo*-norbornylamine in acetic acid,[11b] were reported to give **9** as the kinetic product.

When the cleavage reaction was continued for 42 hr, conversion of **7** into acetates was nearly complete. The ir spectrum of the product mixture revealed the presence of three acetates, 1-methyl-2-*exo*-norbornyl acetate (**3**), 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**), and 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**), and comparison of this spectrum with spectra of artificial mixtures of the three isomers indicated that the product consisted of 55 ± 5% the kinetic product,

(5) J. Paasivirta, *Suomen Kemistilehti*, **B33** (2), 57 (1960).

(6) H. Meerwein and K. van Emster, *Ber.*, **53**, 1815 (1920); **55**, 2500 (1922).

(7) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2590 (1967).

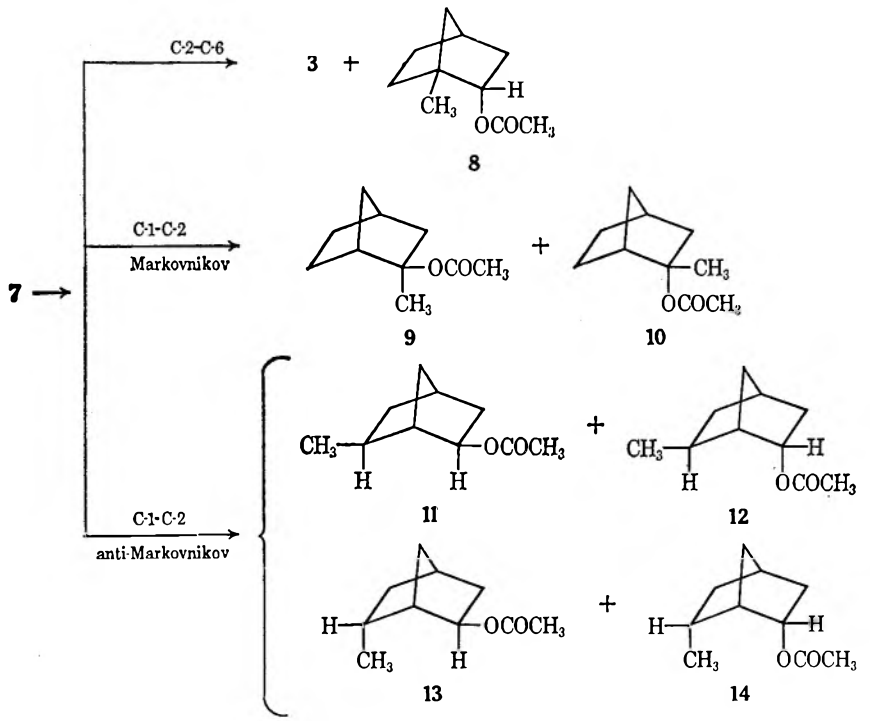
(8) A. Nickon and J. H. Hammons, *ibid.*, **86**, 3322 (1964).

(9) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

(10) H. Hart and R. A. Martin, *J. Org. Chem.*, **24**, 1267 (1959).

(11) (a) J. A. Berson, A. W. McRowe, and R. G. Bergman, *J. Amer. Chem. Soc.*, **89**, 2573 (1967); (b) S. Beckmann, R. Schaber, and R. Bamberger, *Ber.*, **87**, 997 (1954).

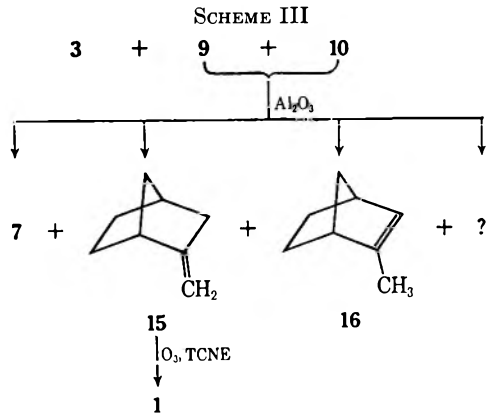
SCHEME II



9, 28 ± 5% **3**, and **17** ± 5% **10**;[12a] none of the secondary *endo* acetate **8** appeared to be present. The four 6-methyl-2-norbornyl acetates, **11**, **12**, **13**, and **14**, were not prepared and therefore could not be demonstrated with certainty to be absent from the reaction mixture. However, the superimposability of the infrared spectrum of the product on that of an artificial mixture of **3**, **9**, and **10** argues against the formation of any of these isomers, and this argument is supported by the gas chromatograph of the acetate mixture which showed that no substance of retention time longer than that for **9** was present.[12b]

Degradation of 2-*endo*-Methyl-2-*exo*-norbornyl Acetate to 2-Norbornanone.—The second purpose of our investigation was to determine the stereochemistry of the deuteration step in reaction of 1-methylnortricyclene (**7**) with acetic acid-O-*d*. No direct method was available for analysis of the stereochemistry of the deuterium at C-6 of 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**). A possible indirect method involved degradation of 6-deuterated **9** to 6-deuterated 2-norbornanone (**1**) and analysis of the stereochemistry of the deuterium by comparison of the ir spectrum of this compound with spectra of the known 6-*exo*-*d*- and 6-*endo*-*d*-2-norbornanone.[13] Our plan of attack was to separate **9** from **3** and **10** by chromatography and to convert **9** into 2-methylenenorbornane (**15**), which would be readily oxidized to **1** (see Scheme III). Chromatography of pure **3** on alumina of activity grade I let to recovery of unchanged **3**. In contrast, **9** was cleanly converted into a mixture of four lower boiling compounds. The major component, which constituted

SCHEME III



56% of the mixture, was identified both by its ir spectrum and by vpc retention time as the desired alkene, **15**. Two of the minor components had retention times identical with those of **7** and 2-methyl-2-norbornene (**16**); the remaining product was not identified. Chromatography of **10** gave some unchanged **10**, together with the same four low-boiling compounds previously obtained from acetate **9**; **15** constituted 49% of the more volatile fraction obtained from the *endo* acetate.

Ozonolysis of **15** in the usual way gave primarily oxidation products other than **1**, but ozonolysis in the presence of an equimolar amount of tetracyanoethylene[14] resulted in successful conversion of **15** into **1**; **1** was readily purified by sublimation.

In view of the fact that an adequate yield could be obtained from the ring cleavage only with reaction times long enough to produce substantial amounts of the thermodynamic products **3** and **10**, it was necessary to decide in the later experiments with deuterated acetates whether to separate the acetate mixture before treatment with alumina or to chromatograph the mixture directly. Our decision was to subject the mixture

(12) (a) Analysis of this mixture by vapor phase chromatography was not satisfactory for two reasons. First, partial pyrolysis of **9** lowered the accuracy considerably; second, **3** and **10** were not resolved on any of our columns. (b) Acetates **3**, **9**, and **10** are known to have markedly shorter retention times on a triscyanoethoxypropane column than any of 13 isomeric methyl-2-norbornyl acetates, including **11** and **13**; see ref 11a.

(13) A. Nickon, J. H. Hammons, J. L. Lambert, and R. O. Williams, *J. Amer. Chem. Soc.*, **85**, 3713 (1963).

(14) This method was reported for ozonolysis of camphene by R. Criegee and P. Günther, *Ber.*, **96**, 1564 (1963).

itself to chromatography. This choice was made for the following reasons. First, no anomalous results would be observed as a consequence of the presence of **3**, as this acetate was shown not to be converted into alkenes on alumina. Second, although **10** is partially converted into alkenes on alumina, there are sound reasons for thinking that the stereochemistry of the deuterium at C-6 in **10** would not be significantly different from that in the *exo* epimer **9**. As the arguments in the concluding section of the Discussion indicate, the stereochemistry of the deuterium at C-6 is determined when D^+ adds to **7** to form carbonium ion **17**, and it is unchanged by subsequent events. Acetate **10** is formed by *endo* attack of acetic acid on deuterated ion **17** after the deuteration step is complete. The possibility that *endo* acetate is formed from **7** by a completely different path involving different stereochemistry for the C-6 deuterium is ruled out by the facts that the protonation step is irreversible and that the amount of *endo* acetate in the kinetic product is too small to be detected.

The conversion of deuterated alkene **15** into 2-norbornanone (**1**) was also accomplished by direct ozonolysis of the four-component mixture produced by chromatography and not by isolation of pure **15** followed by ozonolysis. This approach is justified on the ground that none of the three minor components of the mixture would give **1** on ozonolysis.

Cleavage in Deuterated Acetic Acid. Deuterium Incorporation.—The acetic acid-O-*d* used in these experiments was prepared from distilled acetic anhydride and a slight excess of D_2O (99.77% D) and contained 0.5% water by Karl Fischer analysis. The ring cleavage mixture, consisting of 0.12 *M* 1-methylnortricyclene (**7**) and 0.0061 *M* sulfuric acid-d_2 in acetic acid-O-*d*, was maintained at 24.5 ± 0.1° for 39 hr. Work-up of the reaction mixture and fractional distillation of the recovered materials gave a small amount of a low-boiling fraction, shown by gas chromatography to contain 96% starting material and 4% 2-methylenebornane (**15**), and a large higher boiling fraction which consisted of 58 ± 5% 2-*endo*-methyl-2-*exo*-norbornyl acetate and 42 ± 5% isomeric acetates **3** and **10**.

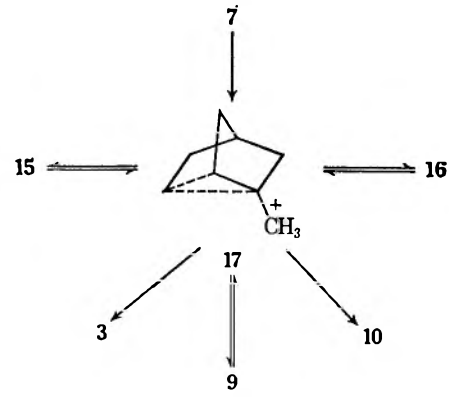
When a portion of the acetate fraction was converted into alcohols and analyzed by mass spectrometry, the alcohols were found to contain not just the one deuterium to be expected on the basis of simple addition of one molecule of acetic acid-O-*d* to **7**, but instead up to five deuterium atoms per molecule. Thus, the original objective of determination of the stereochemistry of the 6-deuterium could be accomplished only if the extra four deuterium atoms could be located and removed. Examination of the fragmentation patterns for the deuterated alcohols and for undeuterated 2-*endo*-methyl-2-*exo*-norbornanol (**18**) yielded useful information. A major fragmentation peak for **18** occurred at mass 111 (M − 15), corresponding to loss of the methyl group. For the deuterated sample the major peaks appeared at mass 112 and 113 (mono- and dideuterated ions), and the peaks at mass 114, 115, and 116 were barely greater than that calculated for natural isotopic abundance. Clearly three of the deuterated positions were in the methyl group.

This conclusion was confirmed by the results of degradation of the mixture of deuterated acetates to 2-norbornanone (**1**). Chromatography on alumina of activity grade I gave a mixture of four components (**7**, **15**, **16**, and the unidentified one) containing up to four deuterium atoms per molecule, and ozonolysis of the alkene mixture in the presence of tetracyanoethylene yielded 2-norbornanone (**1**) which was 96% composed of un-, mono-, and dideuterated molecules. Degradative removal of the methyl group of acetate **9**, then, was accompanied by loss of three deuterium atoms.

The fragmentation patterns of **1** and dideuterated **1** gave a clue as to the location of the remaining extra deuterium. The base peak for **1** appeared at mass 67. By analogy to the fragmentation of camphor, which loses ketene and a methyl radical to give a base peak at mass 95, attributed to an allylic dimethylcyclopentenyl cation,[15] we attribute the base peak of 2-norbornanone to an allylic cyclopentenyl cation formed by loss of ketene and a hydrogen atom from C-7. In our deuterated **1** the base peak appeared at mass 68. This result was consistent with the presence of one deuterium at C-6 and a second at C-3. Treatment of dideuterated **1** with methanolic aqueous alkali to remove enolizable deuterium gave a sample of **1** which was 83% mono- and 17% undeuterated, thus demonstrating that the last of the extra deuterium atoms had been incorporated in the 3 position of **9**.

These deuterium incorporation results are readily explained in terms of a bridged methylnorbornyl cation (**17**) or a pair of classical cations interconvertible by Wagner–Meerwein rearrangement (Scheme IV).

SCHEME IV



Deuteration of 1-methylnortricyclene (**7**) gives a cation (**17**) which is labeled at C-6. Loss of a proton from a carbon α to the charged site yields an alkene, which can add D^+ and regenerate the carbonium ion. Repeated loss of a proton from the methyl to form 2-methylenenorbornane (**15**), followed by addition of D^+ to the methylene carbon, results in introduction of three deuterium atoms into the methyl of the carbonium ion (**17**). Loss of a proton from C-3 yields 2-methyl-2-norbornene (**16**), which can regenerate the carbonium ion by addition of D^+ to C-3. As the 2-norbornanone from ozonolysis contained up to two deuterium atoms per molecule and as only one deuterium could be removed by treatment with alkali, evidently only one deuterium atom in acetate **9** was located at C-3. Therefore, proton loss and deuteration at C-3 are ap-

(15) D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, **31**, 115 (1966); D. R. Dimmel and J. Wolinsky, *ibid.*, **32**, 410 (1967).

parently highly stereoselective. Similar stereoselectivity has recently been reported in base-catalyzed deuteration of 2-norbornanone, camphor, and isofenchone,[16a] and in addition of deuterium chloride to norbornene in methylene chloride;[16b] nmr data indicated that *exo* deuteration was the preferred path in each case.

Rationalization of the incorporation of three extra deuterium atoms per molecule in terms of the intermediate formation of 2-methylenenorbornane (**15**) requires that **15** should react substantially faster than 1-methylnortricyclene (**7**) does under the cleavage conditions, and that it should give the same product distribution as **7**, namely, clean conversion into 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**).[17] In fact **15** reacted with a half-life approximately $^1/_{30}$ that of **7**, and, when the addition reaction was interrupted after about one half-life, the product was pure **9**. Further confirmation of the role of this alkene as an intermediate was obtained by actual isolation of a trace of it from a large-scale cleavage of 1-methylnortricyclene (**7**) in acetic acid-O-*d*. Fractional distillation of the product mixture permitted separation of the low-boiling alkene and starting material from acetates, and preparative gas chromatography yielded a small amount of pure alkene (**15**). The compound contained up to four deuterium atoms per molecule. The amount of material was too small to permit location of these deuteriums by degradation, but the ir spectrum provided evidence that up to two deuterium atoms per molecule were on the methylene carbon. The significant peaks were the following: 3055 (vinyl H stretch), 2305 and 2255 (vinyl D stretch), 2170 (alkyl D stretch), 1660, 1645, and 1630 (assigned to C=CH_2, C=CHD, and C=CD_2 stretch, respectively), 870 (vinyl H out-of-plane bend), and 800 cm^{-1} (possibly due to vinyl D out-of-plane bend). These results are all readily accounted for on the basis of reversible formation of 2-methylenenorbornane.

Examination of the stability of 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) under the cleavage conditions gave the following results. After 40 hr **9** was more than 50% rearranged to 1-methyl-2-*exo*-norbornyl acetate (**3**) and 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**). When **9** was subjected to the cleavage conditions in acetic acid-O-*d* and the mixture of deuterated **9**, **3**, and **10** was converted into alcohols with lithium aluminum hydride, the alcohols contained up to four deuterium atoms per molecule. Clearly conversion of **9** into 2-methyl-2-norbornyl cation (**17**) does occur, and the cation can revert to **9**, incorporate deuterium by way of alkenes **15** and **16**, or undergo conversion into either of the two isomeric acetates, **3** and **10**. In contrast to the behavior of **9**, neither 1-methyl-2-*exo*-norbornyl acetate (**3**) nor 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**) was detectably rearranged after 170 hr, and **3** was shown to have incorporated no deuterium after 40 hr with acetic acid-O-*d*.[18] Apparently neither of these acetates reverts to cation **17** under these conditions.

The 2-methyl-2-norbornyl cation (**17**) can be converted into either of two alkenes and to any one of three acetates. The above observations, together with several additional experimental results, provide much information on the way in which the cation partitions among the five paths. Acetic acid-O-*d* treatment of 2-methylenenorbornane (**15**) converted it into acetate **9**, which gave 2-*endo*-methyl-2-*exo*-norbornanol (**18**) on reaction with lithium aluminum hydride; mass spectrometric analysis of the alcohol showed that it was 6.7% d_0, 84.4% d_1, and 8.9% d_2. As reversible formation of either alkene would lead to multiply deuterated acetate, the fact that **18** was only 8.9% multiply deuterated implies that carbonium ion **17** is converted into 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) roughly ten times faster than it is to either of the alkenes. The rate ratio may in fact be much larger than ten, as the acetate **9** may be rapidly reconverted into the carbonium ion under these conditions; deuterium incorporation and rearrangement of **9** to the isomeric acetates **3** and **10** provide ways to measure a minimum rate for the reconversion, but no way to prove that the actual rate of reconversion is not very much faster than this minimum.[19]

Qualitative conclusions can also be drawn about the partition of cation **17** between alkene formation and combination with acetic acid to yield 1-methyl-2-*exo*-norbornyl acetate (**3**) and 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**). The extent of alkene formation can be estimated from deuteriumin corporation, and, because of the stability of acetates **3** and **10** in the reaction medium, the product distribution gives the total amount of conversion of the carbonium ion (**17**) into these acetates directly. In the acetate mixture from acetic acid-O-*d* cleavage of 1-methylnortricyclene (**7**) or from acetic acid-O-*d* treatment of 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**), the deuterium content of the deuterated positions approached a value corresponding to equilibrium with the solvent pool. Thus, conversion of the cation **17** into alkenes **15** and **16** must be fast compared with irreversible formation of acetates **3** and **10**.

Although conversion of 2-methyl-2-norbornyl carbonium ion (**17**) into 2-methylenenorbornane (**15**) and 2-methyl-2-norbornene (**16**) is clearly slow relative to formation of the tertiary *exo* acetate (**9**) and fast with respect to formation of the secondary *exo* or tertiary *endo* acetate (**3** or **10**), our results give no information as to whether the cation loses a proton more rapidly from the methyl, giving **15**, or from C-3, giving **16**. Unlike these alkenes, acetates **3** and **10** *are* stable in the reaction medium, and the way in which cation **17** partitions between the two paths can be readily evaluated from the product distribution. Isomerization of 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) to 28 ± 5% 1-methyl-2-*exo*-norbornyl acetate (**3**) and 17 ± 5% 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**) indicates

(16) (a) A. F. Thomas and B. Willhalm, *Tetrahedron Lett.*, 1309 (1965); see also J. M. Jerkunica, S. Borcic, and D. E. Sunko, *ibid.*, 4465 (1965); (b) H. C. Brown and K. T. Liu, *J. Amer. Chem. Soc.*, **89**, 3900 (1967).

(17) The same conditions hold for 2-methyl-2-norbornene (**16**) if it is to be proposed as an intermediate. Preliminary experiments have shown that **16** [prepared as described by K. Alder and H. J. Ache, *Ber.*, **95**, 503 (1962)] is converted into pure **9** in acetic acid containing 0.005 *M* H_2SO_4 at 24.5 ± 0.1°; the reaction is approximately 100 times more rapid than cleavage of **7**.

(18) Deuterium incorporation in 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**) was not examined.

(19) Only observable changes can be used to measure the rate of conversion of 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) into the carbonium ion, and there is no way to prove that the rate of the fastest observable process is the same as the actual rate of this conversion. Acetate **9** might be interconverted with the cation many times without any observable change. In this context, it would be interesting to study the rate of loss of ^{18}O from **9** labeled in the etherlike oxygen.

that acetate attacks **17** on the *exo* side of the secondary carbon 1.1–2.8 times faster than it attacks the *endo* side of the methyl-bearing carbon. The low accuracy of our ir analytical method does not permit more precise determination of the rate ratio. A sixth and final reaction of carbonium ion **17** which must be considered is loss of a proton from C-6 to regenerate 1-methylnortricyclene (**7**).[20] Two deuterium incorporation results show that this path does not compete successfully with the five observed reactions of the cation. First, the 2-norbornanone from acetic acid-O-*d* cleavage of **7** was cleanly monodeuterated at C-6. Second, 1-methylnortricyclene recovered from incomplete cleavage contained less than 0.2% monodeuterated molecules in excess of the natural abundance. Therefore, protonation of **7** is apparently irreversible under these conditions.

The Stereochemistry of Deuteration at C-6.—The monodeuterated 2-norbornanone (**1**) obtained from ring cleavage, degradation, and treatment with alkali, was used to investigate the stereochemistry of attack of D^+ on 1-methylnortricyclene (**7**). The ir spectrum of this sample, consisting of 17% 1-d_0 and 83% 1-d_1, was compared with spectra of known mixtures of 6-*exo*-*d*- and 6-*endo*-*d*-2-norbornanone.[21] It proved to be superimposable in all significant regions on a spectrum of a mixture of 12% **1**-d_0 and 88% **1**-d_1, the monodeuterated portion of which was 62.2% 6-*endo*-*d* and 37.8% 6-*exo*-*d*; the only detectable differences were in regions of strong absorption by undeuterated **1**. Mixtures composed of 6-*endo*-*d*- and 6-*exo*-*d*-2-norbornanone in the ratios 57.6:42.4 or 66.8:33.2 gave spectra which differed appreciably from that of the ketone derived from ring cleavage. The deuterium at C-6 in this ketone, therefore, is 62 ± 3% *endo* and 38 ± 3% *exo*.

We believe that these percentages accurately reflect the stereoselectivity of attack by D^+ on 1-methylnortricyclene (**7**). One way in which the apparent stereoselectivity could be lowered would be through repeated conversion of the carbonium ion back into **7**. Occurrence of this process is ruled out by the absence of deuterium in the recovered starting material; further confirmation comes from the fact that none of the **1** derived from acetic acid-O-*d* cleavage is doubly deuterated at C-6.

The second process which could lower the apparent stereoselectivity is 6,1- or 6,2-hydride shift. This step could occur in the cation during the cleavage reaction; the same cation may be formed in alumina in the chromatographic conversion of 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) into alkenes **15** and **16**, and hydride shift may occur at this point. Examination of the consequences of each possible mode of 6,2 shift makes it possible to establish that the stereochemistry of the 6 deuterium in our compounds is not changed by rearrangements of this type. The unlikely process of 6,2 shift, which in this system converts a tertiary cation into a secondary one, would lead to 6-methyl-2-norbornyl acetates, none of which was found. A 6,1 shift of hydrogen would not reverse the stereochemistry of the 6 deuterium, but would give a 1-*d*-2-norbornanone after degradation. With respect to 6,1 shifts of deuterium, four types are conceivable: *exo,exo*, *endo,endo*, *exo,endo*, and *endo,exo*. Berson and Grubb recently presented evidence that the preferred path for 6,2 shift is the *endo,endo* one,[22] and the results of Benjamin and Collins provide support for this conclusion.[23] The direct conversion of optically active 2-*exo*-methyl-2-*endo*-norbornanol (**2**) into 1-methyl-2-*exo*-norbornyl acetate (**3**), which proceeds through the 2-methyl-2-norbornyl cation (**17**), is accompanied by substantial, though not complete, racemization;[9] presumably the racemization results from *endo,endo* 6,2-hydride shift in the cation. As our cleavage of 1-methylnortricyclene was run in the same medium and led to the same cationic intermediate, a significant amount of *endo,endo* 6,2 shift may have occurred in our experiments as well. Neither this process nor the corresponding *exo,exo* shift produces a stereochemical change, however. Only the stereochemically unfavorable process of *exo,endo* (or *endo,exo*) shift of deuterium would reverse the orientation of the 6 deuterium. If this process were a major one for the cation, 6,1 shift of hydrogen would also become a major process; the reaction product would be partially deuterated at C-1 and should lead to 2-norbornanone with deuterium at C-1. The spectrum of our 2-norbornanone from cleavage appeared to be the spectrum of a mixture of **1**-d_0, 6-*endo*-*d*-**1**, and 6-*exo*-*d*-**1**. There was no indication of the presence of a fourth component. For this reason we feel that no more than a minor amount of 6,1 shift of the *endo,exo* or *exo,endo* type could have occurred. The stereochemical purity of the 6 deuterium in our 2-norbornanone (**1**) is an accurate measure of the stereoselectivity of D^+ attack on 1-methylnortricyclene (**7**).

It is now evident that the stereochemical course of electrophilic substitution at saturated carbon can range from complete retention to complete inversion of configuration. In a number of cases of substitution with retention, it has been suggested that the initial step is formation of a bond between the attacking electrophile and the leaving group, and that the electrophilic substitution is a cyclic, internal process. Winstein and Traylor hypothesized that cleavage of di-4-camphylmercury by acetic acid, a reaction which cannot occur with inversion, occurs by formation of a bond from mercury to an oxygen of acetic acid, followed by intramolecular conversion into camphane and 4-camphylmercuric acetate.[24] Nickon, *et al.*, found that 1-hydroxynortricyclene and 1-acetoxynortricyclene undergo cleavage of the cyclopropyl ring in acetic acid-O-*d* to yield 6-*d*-2-norbornanone in which the deuterium is at least 90% *endo*.[13] Cram suggested that the high degree of retention at the electrophilic substitution site can be rationalized in terms of protonation of the hydroxyl oxygen, providing an internal electrophile for attack on the 6 carbon from the more accessible *endo* side.[25] The same argument can be used to account for the retention of configuration which has been observed in

(20) There are several other paths which the carbonium ion might take. Of these, loss of a proton to give 1-methyl-2-norbornene can be ruled out on the basis of the deuterium incorporation results. Various 3,2- and 6,2-hydride shifts either are ruled out by the evidence or are not required to explain the results.

(21) We are most grateful to Professor A. Nickon for supplying samples of 6-*endo*-*d*- and 6-*exo*-*d*-2-norbornanone; see ref 13.

(22) J. A. Berson and P. W. Grubb, *J. Amer. Chem. Soc.*, **87**, 4016 (1965).

(23) B. M. Benjamin and C. J. Collins, *ibid.*, **88**, 1556 (1966).

(24) S. Winstein and T. G. Traylor, *ibid.*, **78**, 2597 (1956).

(25) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 115.

other acid-catalyzed cleavage reactions of cyclopropanols.[26,27] If this reasoning is correct, one might expect cyclopropane cleavage to take quite a different stereochemical course when no heteroatom substituents are present on the ring, and in fact LaLonde recently reported that sulfuric acid-d_2 in acetic acid-O-d cleaves the C-2–C-4 bond of *exo*-tricyclo[3.2.1.$0^{2,4}$]octane with essentially complete inversion for the deuteration step.[28] However, this hydrocarbon is not a typical case, as the authors point out, in that protonation with retention is subject to severe steric hindrance.

Interpretation of our stereochemical result is not complicated by the presence of a heteroatom substituent on the three-membered ring, but steric effects may well play a part. The methyl at C-1 hinders attack of a proton on C-6 from the C-1 side, whereas the hydrogen at C-2 is less of an obstacle to attack from the C-2 side; steric effects would favor electrophilic attack with inversion. Although the degree of stereoselectivity is low, the dominating path is the sterically unfavorable one of retention. Apparently the stereoelectronic preference for front-side attack is large enough to override the opposing steric hindrance by a small margin.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Band positions are expressed in cm^{-1}. Gas chromatograms were done on an Aerograph Model A-90-P instrument, and the column used was 0.125 in. in diameter with tris-β-cyanoethoxypropane as the liquid phase, unless otherwise indicated. Mass spectra were run at the Chemistry Department of the University of Pennsylvania by Mr. Robert Graff on a Consolidated Electrodynamics Corp. Model 21-130 spectrometer, with an ionizing potential of 76 eV.

2-*exo*-Methyl-2-*endo*-norbornanol (2).—The alcohol **2** was prepared from 2-norbornanone (**1**, 490 g; Aldrich Chemical Co.) and methylmagnesium iodide by the procedure of Toivonen, *et al.*,[29] to yield 395 g (70%), bp 166–172°.

1-Methyl-2-*exo*-norbornyl Acetate (3).—Alcohol **2** (370 g) was rearranged and acetylated with sulfuric acid and acetic acid by the method of Toivonen, *et al.*,[29] to yield crude acetate **3**, 451 g (91%).

1-Methyl-2-*exo*-norbornanol (4).—This alcohol (**4**) was prepared by saponification of the corresponding acetate (**3**). A mixture of 207 g of **3**, 375 g of sodium hydroxide, 500 ml of water, and 2 l. of ethanol was refluxed for 16 hr on a steam bath. The solution was cooled and extracted with two 1-l. portions of pentane. The pentane layers were combined, washed with four 2-l. portions of water, and dried over magnesium sulfate and charcoal. Evaporation of the pentane through a Vigreux column left 118 g (76%) of crude **4**.

1-Methyl-2-norbornanone (5).—Oxidation of 236 g of alcohol **4** with chromium trioxide and sulfuric acid in acetone, by the method of Berson, *et al.*,[9] gave 120 g (52%) of ketone **5**, bp 168–175°.

1-Methyl-2-norbornanone *p*-Toluenesulfonylhydrazone (6).—A mixture of 109 g of ketone **5**, 170 g of *p*-toluenesulfonylhydrazine, 9 ml of acetic acid, and 900 ml of ethanol was refluxed for 90 min on a steam bath. The mixture was cooled at 0° overnight and filtered. The filter cake was washed with 300 ml of cold ethanol and dried to yield 205 g of **6**, mp 146.5–148.0°. Concentration of the mother liquor to 100 ml yielded an additional 28.5 g, mp 146.0–148.5° (total yield, 91%).

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.61; H, 6.89. Found: C, 61.61; H, 6.88.

1-Methylnortricyclene (7).—A mixture of 54 g of **6**, 115 g of freshly prepared sodium methoxide, and 500 ml of dry diglyme was stirred and refluxed for 3 hr. The mixture was distilled to remove the low-boiling **7** and methanol, plus 25 ml of diglyme. An additional 58 g of **6** and 200 ml of diglyme were added to the reaction mixture, which was again refluxed for 3 hr. The product **7**, together with methanol and diglyme, was removed by distillation as before, and the two distillates were combined and extracted with pentane and water. The dried ($MgSO_4$) pentane extract was concentrated and fractionally distilled to give 36.5 g (88%) of **7**: bp 110–112°; $n^{20}D$ 1.4516 (lit.[30] bp 114–114.5°; $n^{20}D$ 1.4555); 99% homogeneous by vpc; ir (neat) 3055 (cyclopropyl H stretch) and 840, 785 cm^{-1} (lit.[10] 850, 785 cm^{-1}).

2-*endo*-Methyl-2-*exo*-norbornanol (18).—Reaction of alcohol **2** with HCl and treatment of the crude chloride with NaOH according to the procedure of Toivonen[29] gave alcohol **18**: mp 82.5–84.0° (lit.[29] mp 86°).

2-*endo*-Methyl-2-*exo*-norbornyl Acetate (9).—Alcohol **18** was acetylated with acetyl chloride and dimethylaniline in ether:[31] bp 95–98° (29 mm); $n^{20}D$ 1.4606 [lit.[29] bp 93.4° (22 mm); $n^{20}D$ 1.4610].

2-*exo*-Methyl-2-*endo*-norbornyl Acetate (10).—Acetylation[31] of alcohol **2** gave **10**: bp 106.0–106.5° (50 mm); $n^{25}D$ 1.4575 [lit.[29] bp 88.5–89.0° (22 mm); $n^{20}D$ 1.4587].

1-Methyl-2-*endo*-norbornyl Acetate (8).—Ketone **5** was reduced to 1-methyl-2-*endo*-norbornanol with lithium aluminum hydride as reported.[32] The alcohol was acetylated with acetic anhydride in pyridine: bp 91–93 (21 mm); $n^{20}D$ 1.4554.

2-Norbornanemethanol.—Reaction of lithium aluminum hydride with methyl 2-norbornanecarboxylate (Aldrich Chemical Co.) in the usual way gave the alcohol in 91% yield: bp 106–108° (25 mm); $n^{20}D$ 1.4884.

2-Methylenenorbornane (15).—2-Norbornanemethanol was converted into the methyl xanthate, which was pyrolyzed to give alkene **15**:[33] bp 120–121° (lit. bp 123°); ir (neat) 3065 (vinyl H stretch), 1665 (C=C stretch), and 874 cm^{-1} (*gem*-disubstituted alkene); 100% homogeneous by vpc.

Cleavage of 1-Methylnortricyclene (7) in Acetic Acid.—A solution of 2.0 g of **7** (99% pure) and 0.0052 M sulfuric acid in 20 ml of glacial acetic acid was kept at 24.5 ± 0.1° for 122 min. The solution was poured into 100 ml of pentane, and the pentane extract was washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The relative absorptions of the pentane solution in the ir spectrum at 1745 (C=O) and 850 cm^{-1} (due to **7** only) indicated that the cleavage was 15 ± 5% complete. Bulb-to-bulb distillation gave 0.44 g (14%) of acetate, bp ~97–103° (22 mm). The ir spectrum of this product was superimposable in all regions with that of pure 2-*endo*-methyl-2-*exo*-norbornyl acetate (**9**) and differed markedly from the spectra of acetates **3**, **8**, and **10** in the fingerprint region. Solutions of the four acetates (200 mg of acetate in 10 ml of CS_2) were used to prepare artificial mixtures, and comparison of the ir spectra of these mixtures with that of the cleavage product **9** showed that the latter contained less than 2.5% **3**, **8**, or **10**.

A second cleavage run, with 0.5 g of **7** and 0.0052 M H_2SO_4 in 5 ml of glacial acetic acid, was continued at 24.5 ± 0.1° for 42 hr. Bulb-to-bulb distillation gave 0.45 g (59%) of acetate product, bp 100–104° (22 mm). The ir spectrum (CS_2) of this product was superimposable on that of a mixture of 55% acetate **9**, 28% 1-methyl-2-*exo*-norbornyl acetate (**3**), and 17% 2-*exo*-methyl-2-*endo*-norbornyl acetate (**10**).

Stability of Acetates 3 and 10 in H_2SO_4–HOAc.—A solution of 0.5 g of 1-methyl-2-*exo*-norbornyl acetate (**3**) and 0.0052 M H_2SO_4 in 5 ml of glacial acetic acid was kept at 24.5 ± 0.1° for 194 hr. The acetate was recovered and purified by the same method used for the cleavage experiments. The ir spectrum (CS_2) of the product was superimposable on that of pure **3**, and comparison with spectra of artificial mixtures of **3** with **10** showed that less than 5% **10** had been formed. 2-*exo*-Methyl-2-*endo*-norbornyl acetate (**10**) was treated with H_2SO_4 in acetic acid in the identical manner. The spectrum (CS_2) of the recovered acetate was superimposable on that of pure **10**, and the amount of **3** present was shown to be less than 5%.

Conversion of Acetates 9 and 10 into Alkene 15 on Alumina.—Chromatography of acetate **9** on Woelm basic alumina of activity

(26) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **31**, 2480 (1966).
(27) C. H. DePuy and F. W. Breitbeil, *J. Amer. Chem. Soc.*, **85**, 2176 (1963).
(28) R. T. LaLonde, J. Ding, and M. A. Tobias, *ibid.*, **89**, 6651 (1967).
(29) N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae Ser. A II*, **64** (1955).
(30) M. Blanchard and J. E. Germain, *Compt. Rend.*, **254**, 3351 (1962).
(31) C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. S. Shivers, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 142.
(32) S. Beckmann and R. Mezger, *Ber.*, **89**, 2738 (1956).
(33) O. Diels and K. Alder, *Ann.*, **470**, 62 (1929).

grade I gave a product which was eluted readily with 5% ether–95% pentane and which decolorized bromine. Vpc analysis on the Ucon column showed that the product mixture consisted of four components. The first three of these, constituting 2, 27, and 56% of the mixture, had retention times identical with those of 1-methylnortricyclene (**7**), 2-methyl-2-norbornene (**16**), and 2-methylenenorbornane (**15**), respectively; the fourth component (15%) was not identified. Chromatography of acetate **10** in the same manner led to recovery of the same four products in the proportions 9, 14, 49, and 28%, together with some unreacted **10**. Chromatography of acetate **3** gave no alkene; elution with 100% ether yielded unchanged **3** nearly quantitatively.

Ozonolysis of 2-Methylenenorbornane (15).—Alkene **15** was ozonolyzed in ethyl acetate in the presence of an equimolar amount of tetracyanoethylene, according to the procedure of Criegee and Gunther.[14] Fractional distillation up to 77° and vacuum distillation of the residue gave a brown semisolid, which was chromatographed on alumina. Concentration of the 20% ether–80% pentane fraction and sublimation of the residue gave pure 2-norbornanone (**1**): 100% homogeneous by vpc; ir (CS_2) identical with that of authentic **1**.

Acetic Acid-O-*d* from Acetic Anhydride.—Distilled acetic anhydride (953 ml, 10.1 mol, bp 138.5–140.0°) and deuterium oxide (210.6 g, 10.5 mol, 99.75% deuterium; E. Merck, Darmstadt) were stirred at room temperature for 163 hr, and the solution was dried over Na_2SO_4. Titration with Karl Fischer reagent[34] indicated the presence of 0.5% water.

Cleavage of 1-Methylnortricyclene (7) in Acetic Acid-*O-d*.—A solution of 26.4 g of **7** (99% pure) and 0.307 g of D_2SO_4 (0.00614 *M*) in 500 ml of acetic acid-O-*d* was kept at 24.5 ± 0.1° for 39 hr. The reaction mixture was poured into 1 l. of pentane, and the pentane extract was washed with 1 l. of water and 1 l. of aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. Molecular distillation on a vacuum line gave a highly volatile fraction of 6.5 g, shown by vpc to consist of pentane, starting material (**7**), and a trace of **15**, plus a less volatile fraction of 27.5 g. The major fraction was distilled (12 mm) to give 21.75 g (53%) of deuterated acetates; vpc indicated that the mixture contained 58 ± 5% **9** and 42 ± 5% **3** and **10**. A portion of the mixture was converted into alcohols with $LiAlH_4$; the mass spectrum showed that the alcohols (mol wt 126) contained up to five deuteriums per molecule: 126 (15), 127 (40), 128 (65), 129 (90), 130 (100), 131 (60), and 132 (5).

Fractional distillation of the volatile 6.5-g fraction, followed by preparative vpc on a Ucon column of 0.25-in. diameter, gave unreacted starting material (**7**) plus 55 mg of a substance with retention time identical with that of alkene **15**. Each substance was 100% homogeneous by vpc. The mass spectrum of the recovered **7** showed that it had incorporated no deuterium: 105 (100) and 109 (9.0). Mass spectrometric analysis of the second component showed that it contained up to four deuteriums per molecule: 108 (100), 109 (40), 110 (46), 111 (53), 112 (36), and 113 (3.4).

Conversion of Deuterated Acetate Mixture into Alkenes.—Chromatography of 13.0 g of the deuterated acetate mixture from ring cleavage on 360 g of Woelm basic alumina of activity I and concentration of the pentane eluate through a fractionating column left a residue of 4.6 g. Distillation of this residue gave 2.7 g of product, bp 113–125°. The alkene mixture contained up to four deuteriums per molecule by mass spectrometric analysis: 108 (15), 109 (76), 110 (100), 111 (75), 112 (13), and 113 (2).

Ozonolysis of Deuterated Alkene Mixture.—The mixture (2.46 g) of deuterated **7**, **15**, **16**, and the unidentified component was ozonolyzed in the presence of tetracyanoethylene,[14] as described for undeuterated **15**. Concentration of the solution by fractional distillation gave a residue of 6 ml. Chromatography on 150 g of Woelm neutral alumina (activity I) with 2700 ml of 20% ether–80% pentane, concentration of the eluate by fractional distillation, and sublimation of the residue gave 2-norbornanone (**1**). Mass spectrometric analysis showed the product contained up to two deuteriums per molecule: 110 (34), 111 (100), 112 (81), 113 (14), and 114 (2.6).

A 500-mg portion of this sample was mixed with 11.0 ml of methanol, 1.1 g of KOH, and 5.0 ml of water, and the resulting solution was stirred for 100 hr at room temperature. The mixture was poured into 100 ml of pentane, and the pentane layer was washed twice with water, dried ($MgSO_4$), and concentrated. The residual **1** was purified by sublimation; mass spectrometric analysis showed it to be 17% undeuterated and 83% monodeuterated: 110 (29), 111 (100), and 112 (8.9).

Analysis of the Stereochemistry of the 6-Deuterium.—Samples of 6-*exo*-*d*-**1** and 6-*endo*-*d*-**1** were generously supplied by Professor A. Nickon.[35] The 6-*exo*-*d*-**1** was 89.7% monodeuterated and 10.3% undeuterated, and the deuterium was at least 90% *exo;* the 6-*endo*-*d*-**1** was 86.6% monodeuterated and 13.4% undeuterated, and the deuterium was at least 94.5% *endo*. Two standard solutions were prepared; one contained 198.8 mg of 6-*endo*-*d*-**1** in 10.0 ml of Spectrograde CS_2, and the other contained 205.1 mg of 6-*exo*-*d*-**1** in 10.0 ml. Artificial mixtures were prepared from these standard solutions with a 100-μl syringe, and their ir spectra were recorded in matched 0.5-mm KBr cells with CS_2 as a reference. Monodeuterated **1** (94 mg), from ozonolysis and alkaline removal of enolizable deuterium, was dissolved in 4.58 ml of CS_2, and the ir spectrum of the solution was recorded in the same way. This spectrum was superimposable in all significant regions on that of a mixture containing 6-*endo*-*d*-**1** and 6-*exo*-*d*-**1** in ratio 62.2:37.8; the only differences were in regions of strong absorption by undeuterated **1**, and could readily be accounted for on the basis of the slightly larger amount of undeuterated **1** in our product. Mixtures of 6-*endo*-*d*-**1** and 6-*exo*-*d*-**1** in the ratios 57.6:42.4 or 66.8:33.2 gave spectra which differed appreciably from that of our product.

Incorporation of Deuterium in Acetates 3 and 9.—A solution of 1.61 g of acetate **3** in 20 ml of acetic acid-O-*d* (99.7% deuterium) containing 0.0065 *M* H_2SO_4 was kept at 24.5 ± 0.1° for 40 hr. The reaction mixture was poured into pentane, and the pentane was washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The acetate was purified by bulb-to-bulb distillation under vacuum. Conversion of the acetate into alcohol with $LiAlH_4$ and analysis by mass spectrometry showed that less than 2% monodeuterated **3** had been formed: 126 (100) and 127 (11.9).

Identical treatment of 1.07 g of acetate **9** in 13 ml of H_2SO_4–DOAc and treatment of the recovered acetates with $LiAlH_4$ gave a mixture of alcohols containing up to four deuteriums per molecule: mass spectrum 126 (25), 127 (35), 128 (70), 129 (100), 130 (70), and 131 (7).

Addition of Acetic Acid to 2-Methylenenorbornane (15).—A solution of 1.01 g of **15** in 10 ml of acetic acid containing 0.0052 *M* H_2SO_4 was kept at 24.5 ± 0.1°. Aliquots were withdrawn and poured into pentane, and the pentane was washed with water and aqueous $NaHCO_3$ and dried ($MgSO_4$). The progress of the reaction was followed by the disappearance of the ir peak (pentane) at 1665 cm^{-1} (C=C stretch) and the appearance of the 1745-cm^{-1} peak (C=O stretch) of the acetate. Reaction was virtually complete after 50 min, and the spectrum of the purified product was superimposable on that of acetate **9** and distinctly different from spectra of acetates **3**, **8**, and **10**.

Addition of Acetic Acid-O-*d* to 15.—A solution of 0.81 g of **15** in 10 ml of acetic acid-O-*d* containing 0.0065 *M* H_2SO_4 was kept at 24.5 ± 0.1° for 50 min. The usual work-up gave acetate which was converted into alcohol with $LiAlH_4$. Mass spectrometric analysis showed that the alcohol was mostly monodeuterated: 126 (20), 127 (100), 128 (21), 129 (2.1).

Registry No.—**2**, 3212-16-6; **3**, 17410-98-9; **5**, 10218-04-9; **6**, 13533-72-7; **7**, 4601-85-8; **8**, 17410-99-0; **9**, 17411-09-5; **10**, 17411-10-8; **15**, 497-35-8; 2-norbornanemethanol, 5240-72-2.

(34) J. Mitchell, Jr., and D. M. Smith, "Aquametry: Application of the Karl Fischer Reagent to Quantitative Analyses Involving Water," Interscience Publishers, Inc., New York, N. Y., 1948, pp 19–38, 71–82.

(35) A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **88**, 3354 (1966).

Thermal Rearrangements of Benzonorcaradiene, Benzonorbornadiene, and 1,2-Benzotropilidene

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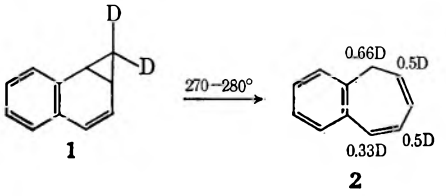
The thermal rearrangement reactions of 7,7-dideuteriobenzonorcaradiene (**1**), 5,6-dideuterio-2,3-benzonorbornadiene (**7**), and 3,5,7,7-tetradeuterio-1,2-benzotropilidene (**11**) have been studied. Pyrolysis of **1** produced 1,2-benzotropilidene with 0.33, 0.5, 0.5, and 0.66 deuteron in positions 3, 4, 6, and 7, respectively, presumably *via* either a 1,2- or a 1,5-hydrogen shift mechanism. Pyrolysis of **7** gave 1,2-benzotropilidene with, initially, 0.5, 1, and 0.5 deuteron in positions 4, 5, and 6, respectively, ruling out 6,7-benzobicyclo[3.2.0]hept-2,6-diene as a possible intermediate. Further thermal rearrangement of **7** or **11** showed that positions 3, 4, 6, and 7 completely equilibrated their hydrogens. Three mechanisms are postulated for this rearrangement; 1,2- and/or 1,5-hydrogen shift or methylene group rearrangement. In all of these thermal reorganizations 1,5-hydrogen shift, between positions 3 and 7, occurs very rapidly, even below 250°.

During the course of our study of the photochemical rearrangements of 1,2-benzotropilidene and 3,4-benzotropilidene,[1] we required a specifically deuterated 1,2-benzotropilidene to rule out a possible mechanistic pathway. We therefore looked at the known thermal rearrangements of benzonorcaradiene[2] and benzonorbornadiene[3] to 1,2-benzotropilidene.

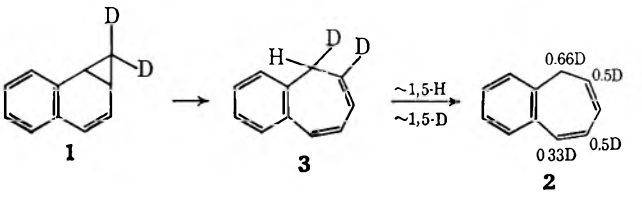
7,7-Dideuteriobenzonorcaradiene (**1**)[4] was prepared by Doering's method of the photolysis of dideuteriodiazomethane[5] in the presence of naphthalene.[6] Upon heating **1** at 270–280° (gas phase) for 1 hr, 1,2-benzotropilidene was formed with deuterium labeling as shown in structure **2**. In addition, partial rearrangement at 260° gave **2** with the same deuterium labeling,



1 **2**

while recovered **1** showed no scrambling. Therefore **2** is the first observable product. The location of deuterium in the product (**2**) was accomplished by nmr spectroscopy after assigning the various absorptions in 1,2-benzotropilidene. The doublet (J = 6 Hz) at τ 7.05 ppm was assigned to the methylene hydrogens, at the 7 position. Spin decoupling of the methylene hydrogens indicated that the hydrogen at the 6 position (to which the methylene hydrogens were coupled) was at τ 4.3 ppm. The aromatic hydrogens appeared at τ 2.9 ppm and partially obscured the peaks at τ 3.05 ppm. This latter absorption was shown, by spin decoupling, to be coupled only to the hydrogen at τ 3.55 ppm. Therefore, the peak at τ 3.05 ppm must be due to the hydrogen at position 3 and the one at τ 3.55 ppm is due to the hydrogen at position 4. The additional hydrogen, at the 5 position, appears at τ 3.9 ppm. This result is completely consistent with the nmr spectrum of what was proven previously to be 3,5,7,7-tetradeuterio-1,2-benzotropilidene.[1]

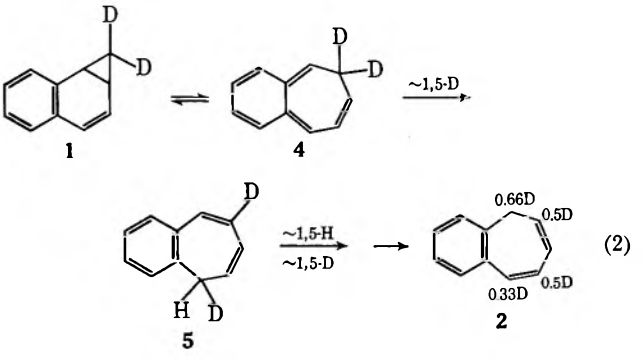
Two possible mechanisms can be formulated to account for the observed labeling pattern. First is a cyclopropane to propylene, 1,2-hydrogen migration to produce **3** (eq 1) followed by a series of rapid 1,5-hydrogen shifts (between positions 3 and 7). Such



1 **3** **2** (1)

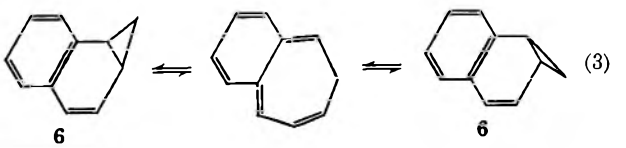
1,5-hydrogen shifts are known to be quite rapid at these temperatures. With tropilidene itself the activation energy for this shift is 31 kcal/mol and with 7-phenyltropilidene it is 27 kcal/mol; the reaction therefore occurs very fast at temperatures below 150°.[7]

The alternative mechanism is valence tautomerization of **1** to produce **4**, followed by 1,5-hydrogen shift to give **5**. This in turn would undergo the rapid 1,5-hydrogen shifts already discussed with the production of the observed product, **2** (eq 2).



1 **4** **5** **2** (2)

The intermediate **4** (without the deuterium atoms) has been previously implicated in the "ring-flipping" of benzonorcaradiene (eq 3) by Vogel. This reaction



6 **6** (3)

(1) M. Pomerantz and G. W. Gruber, *J. Amer. Chem. Soc.*, **89**, 6798, 6799 1967).

(2) E. Müller, H. Fricke, and H. Kessler, *Tetrahedron Lett.*, 1525 (1964).

(3) R. K. Hill and R. M. Carlson, *J. Org. Chem.*, **30**, 2414 (1965); S. J. Cristol and R. Caple, *ibid.*, **31**, 585 (1966).

(4) The deuterons here shown to be in the 7 position by nmr spectroscopy.

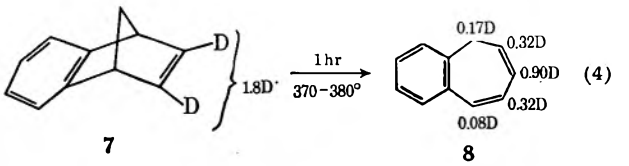
(5) W. von E. Doering and P. P. Gaspar, *J. Amer. Chem. Soc.*, **85**, 3043 (1963).

(6) W. von E. Doering and M. J. Goldstein, *Tetrahedron*, **5**, 53 (1959).

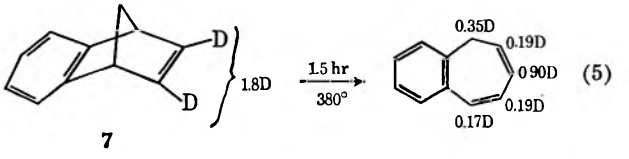
(7) A. P. ter Borg, H. Kloosterziel, and N. Van Meurs, *Proc. Chem. Soc.*, 359 (1962).

occurs quite readily at low temperatures with an activation energy of 19.4 kcal/mol.[8] It should also be pointed out that phenylcyclopropane, a compound analogous to benzonorcaradiene, undergoes thermal ring opening very much more slowly than **6** and apparently not by a cyclopropane to propylene rearrangement. The major products here were shown to be *n*-propylbenzene and 2-phenyl-1-propene and were postulated to arise by a free-radical pathway.[9] It is therefore tempting to speculate that the second mechanism (eq 2) is more reasonable, but a clear-cut choice cannot at present be made.

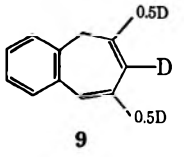
As a second approach to a suitable deuterated 1,2-benzotropilidene we examined the thermal rearrangement of 5,6-dideuterio-2,3-benzonorbornadiene (**7**). The starting deuterated compound (**7**) was prepared by a series of metalations of benzonorbornadiene with *n*-butylsodium followed by quenching of the vinyl carbanion with D_2O.[10] Six such reactions gave **7** with 1.8 deuterons in the vinyl positions and 0.2 deuteron in the benzene ring. Pyrolysis of this compound at 370–380° for ~1 hr resulted in 85% conversion into **8** with the labeling as indicated (eq 4). In addition,



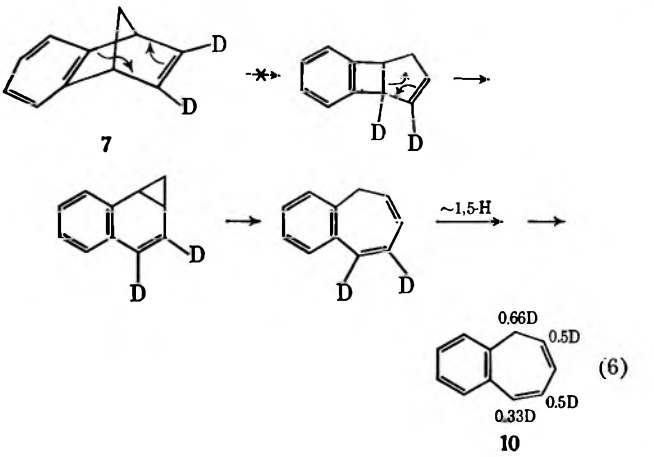
the recovered starting material (**7**) had not scrambled any deuterium. When the reaction was allowed to proceed for 1.5 hr at 380° there was essentially total scrambling among positions 3, 4, 6, and 7 as indicated



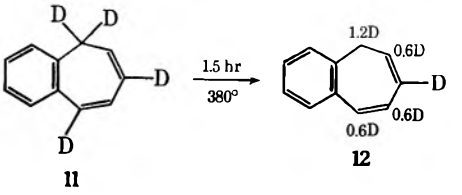
(eq 5). Therefore compound **9** is the first-formed product and this subsequently goes on to scramble



deuterium. While the results of these labeling experiments are not unique for one particular mechanism, they do serve to rule out 6,7-benzobicyclo[3.2.0]hepta-2,6-diene as an intermediate.[11] As shown in eq 6, the anticipated product from such a pathway would have been **10** and not **9**.

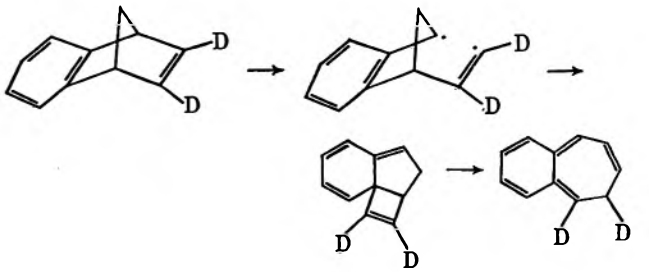


The apparent 1,2 shift of hydrogen in compound **9** (and **8**) is rather interesting. Exactly the same phenomenon was observed in the pyrolysis of 3,5,7,7-tetradeuterio-1,2-benzotropilidene (**11**).[1] Heating **11** at 380° for 1.5 hr resulted in the scrambling of deuterium among positions 3, 4, 6, and 7 to give **12**.



Three mechanisms can be postulated for these hydrogen rearrangements. First is a simple propylene to cyclopropane ring closure with 1,2-hydrogen migration followed by rapid rearrangement by the known benzonorcaradiene to 1,2-benzotropilidene reaction (*vida supra*) to give a partially scrambled 1,2-benzotropilidene (**13**). This would then undergo a series of rapid 1,5-hydrogen shifts and additional propylene to cyclopropane ring closures and reversals to give, finally, the

(11) A referee has pointed out that these results also rule out the following possible mechanism.



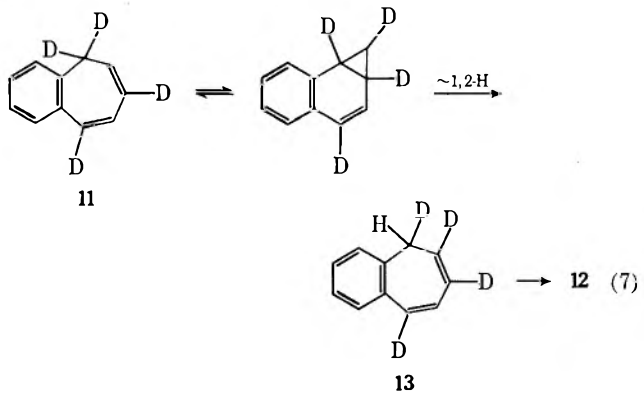
However, at least two additional mechanisms are allowed by our data: cleavage of the 1,7 bond followed by reclosure at either position 3 or position 5 to produce i or ii, respectively. These processes might be diradical or con-

certed, but in either case these intermediates would lead to the 1,2-benzotropilidene with the deuterium labeling that we have observed. Experiments to distinguish between these possibilities are in progress.

(8) E. Vogel, D. Wendisch, and W. R. Roth, *Angew. Chem. Intern. Ed. Engl.*, **3**, 442 (1964).

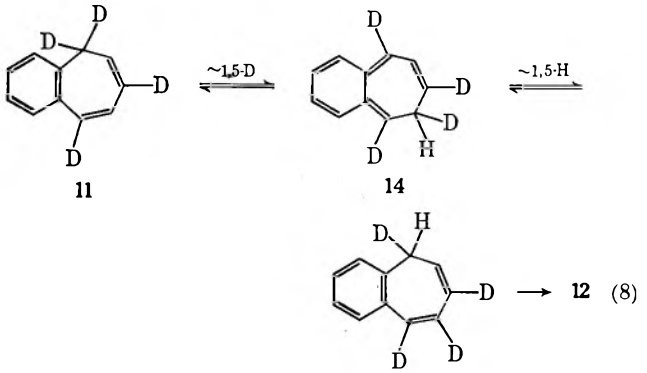
(9) P. A. Leermakers and M. E. Ross, *J. Org. Chem.*, **31**, 301 (1966).

(10) T. Goto, A. Tatematsu, Y. Hata, R. Muneyuki, H. Tanida, and K. Tori, *Tetrahedron*, **22**, 2213 (1966).



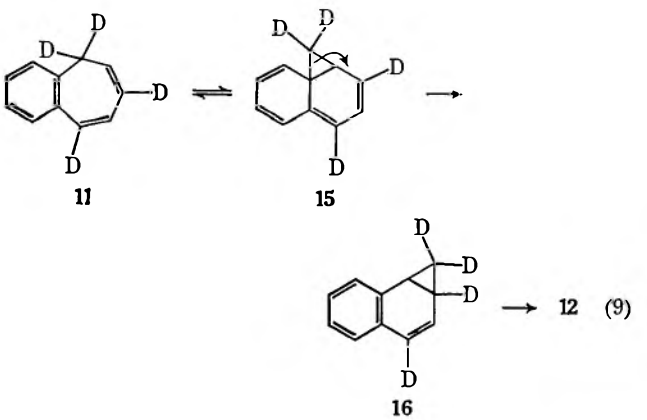
observed product (12 in the case of 11, eq 7). It should be pointed out that the deuterium distribution in 13 might be different depending upon the exact mechanism of the benzonorcaradiene to 1,2-benzotropilidene rearrangement; the end product, however, would still be the same (12). Also, rather than, or in addition to, structures such as benzonorcaradiene it is possible that their valence tautomers are the intermediates.

The second mechanism involves 1,5-hydrogen shifts as indicated in eq 8. Once again, norcaradiene or



tropilidene valence tautomers might be the intermediates. In addition, the benzonorcaradiene valence tautomer of 14 might rearrange by a 1,2-hydrogen shift to give a different intermediate but ultimately the same product (12).

The third alternative involves the valence tautomer of 11 (15) rearranging, in a reaction similar to that discovered by Berson and Willcott[12] to 16 which, by pathways previously discussed, would yield the observed product (eq 9). The reverse reaction, 16 →



(12) J. A. Berson and M. R. Willcott, III, *Rec. Chem. Progr.*, **27**, 139 (1966); *J. Amer. Chem. Soc.*, **88**, 2494 (1966); J. A. Berson, *Accounts Chem. Research*, **1**, 152 (1968).

11, has already been ruled out. A similar mechanism has been proposed for the thermal rearrangement of 1,6-methano[10]annulene to 1,2-benzotropilidene.[13] A choice between these three alternatives cannot be made at present.

It should also be pointed out that the three thermal reorganization reactions discussed were run with and without powdered Pyrex present. In all cases the extent of reaction for a particular rearrangement and for a given reaction time was the same with and without the glass. The reactions, therefore, are not surface catalyzed.

Experimental Section

7,7-Dideuteriobenzonorcaradiene (1).[5,6]—To a mixture of 95 g of naphthalene in 300 ml of benzene and 45 ml of 40% KOH solution, in an erlenmeyer flask cooled in ice, was added slowly, with magnetic stirring, 15 g of N-methyl-N-nitrosourea. The diazomethane solution was decanted onto KOH pellets and the aqueous layer extracted with an additional 50 ml of benzene. After the combined organic solution was dried over solid KOH (ice bath, 20 min), it was treated with 85 ml of 20% KOD in D_2O, while stirring (ice bath) for 7 hr. This solution was then irradiated (100-W GE Hg lamp; Pyrex filter) for 4.5 hr and filtered and the benzene distilled through a 30-cm Heli-pak column until *ca.* 150 ml remained. Crystallization afforded a solid which was filtered and washed with cold pentane. The combined mother liquor and pentane solution was distilled through a 30-cm Heli-pak column until *ca.* 40 ml remained. Crystallization afforded additional solid which was filtered and washed with cold pentane. The mother liquor and the pentane solution were combined and the concentration–crystallization procedure was repeated four additional times. At this point the mother liquor (*ca.* 2 ml) contained about 40–50% of 7,7-dideuteriobenzonorcaradiene. Further purification was by vlpc (2 m × 0.25 in., 15% triisodecyl trimellitate on 60–80 mesh Chromosorb P column). Nmr analysis indicated 82% deuteration of the cyclopropylmethylene hydrogens.

5,6-Dideuterio-2,3-benzonorbornadiene (7).[10]—In a 500-ml three-necked flask equipped with a mechanical stirrer, reflux condenser, nitrogen inlet and a dropping funnel was placed 6 g (0.26 g-atom) of dispersed sodium and 300 ml of pentane. To this was added 12 g (0.13 mol) of *n*-butyl chloride at 0° with rapid stirring, followed by 9 g (0.063 mol) of benzonorbornadiene.[14] The resulting slurry was refluxed for 8 hr, cooled, cautiously quenched with 25 ml of deuterium oxide, refluxed for 30 min, and further diluted with 100 ml of water. After separation, the aqueous layer was extracted five times with 100-ml portions of ether. The combined organic material was dried ($MgSO_4$) and concentrated to *ca.* 40 ml. This was then allowed to react, as above, with butylsodium and the procedure repeated an additional five times. The resulting solution was fractionally distilled through a 6-in. Vigreux column, pure 7 (3.5 g, 39%) being collected at 30–31° (0.2 mm). Nmr analysis indicated 90% two vinyl deuterons and 5% four aromatic deuterons.

3,5,7,7-Tetradeuterio-1,2-benzotropilidene (11).—In a 15-ml test tube was placed 1 ml of *t*-butyl alcohol-O-*d* and enough potassium to make a saturated solution of potassium *t*-butoxide. To this was added 800 μl of DMSO-d_6 and *ca.* 250 μl of 1,2- (or 3,4-) benzotropilidene.[3,15] The resulting solution was allowed to stand at room temperature for 8 hr before being quenched with 2 ml of water and extracted three times with 3-ml portions of pentane. The combined pentane solution was dried ($MgSO_4$) and concentrated to *ca.* 500 μl under a stream of nitrogen. Pure 11 was obtained by preparative vlpc.[16]

In addition to four aromatic hydrogens (τ 2.9 ppm) the nmr spectrum showed two broad singlets (τ 3.55 ppm, 1 H, and τ 4.3 ppm, 1 H) as well as a trace (*ca.* 3% 2 H) absorption at τ

(13) V. Rautenstrauch, H. J. Scholl, and E. Vogel, *Angew. Chem. Intern. Ed. Engl.*, **7**, 288 (1968).

(14) We wish to thank Professor L. Friedman and Mr. D. Smith for a generous gift of benzonorbornadiene.

(15) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958).

(16) An 8 ft × 0.25 in. 20% Carbowax 20M on 45/60 mesh Chromosorb P column at 160° was employed.

7.05 ppm confirming the presence of a dideuteriomethylene moiety.

Pyrolysis of 7,7-Dideuteriobenzonorcaradiene (1).—In a partial rearrangement reaction 100 μl of **1** was sealed in an evacuated 50-ml Pyrex vessel, heated at 260–270° for 2 hr (40% rearrangement), and cooled; it was then opened. Preparative vlpc[16] afforded a pure sample of **2**. Nmr analysis provided this ratio for the hydrogens at positions 3–7, respectively: 0.73:0.59:1.0:0.59:1.46. In the same reaction, recovery of unreacted **1** allowed an nmr demonstration that no deuterium scrambling occurred in the starting material.

Pyrolysis of 5,6-Dideuterio-2,3-benzonorbornadiene (7).—In typical reactions to completion, 100–200 mg of **7** was sealed in an evacuated 50-ml glass vessel and heated at 370–390° for 50–70 min. Nmr data were in some cases obtained directly from the crude reaction mixture. Alternatively, purification was achieved by preparative vlpc.[16] In either case, nmr analysis showed that the ratio of hydrogens at positions 3–7, respectively, was 0.83:0.81:0.10:0.81:1.65.

A partial completion reaction (375°, 30 min, 70% rearrangement) showed that deuterium scrambling into positions 3 and 7 lagged considerably behind rearrangement. The ratio of hydrogens at positions 3–7, respectively, was 0.94:0.65:0.10:0.64:1.87.

Starting material recovered from this reaction was shown by nmr analysis to have undergone no deuterium scrambling.

Pyrolysis of 3,5,7,7-Tetradeuterio-1,2-benzotropilidene (11).—In a typical run, 30 μl of **11** was sealed in an evacuated 50-ml glass vessel and heated at 380–400° for 80 min. The vessel was then cooled and opened. Pure 1,2-benzotropilidene-d_4 was then obtained by preparative vlpc.[16] An nmr spectrum (CCl_4 solution) afforded the following protium ratio for positions 3–7, respectively: 0.40:0.40:0.03:0.40:0.80.

Surface Catalysis Experiments.—Samples of **1**, **7**, and **11** were partially pyrolyzed in the presence of powdered glass, simultaneously with samples without added glass. Gas chromatography revealed that the ratio of reactant to product in the pyrolysis of **1** and **7** was the same with and without the powdered glass. Preparative vlpc[16] afforded pure samples in each case, which by nmr analysis were shown to have scrambled, within experimental error, the same amount of deuterium (Table I).

TABLE I

Compound	Temp, °C	Time, min	Extent of reaction, %	1,2-Benzotropilidene nmr ratios by position 3	4	5	6	7
1[a]	400	5	80	0.69	0.65	1.0	0.65	1.38
1 + powdered glass[a]	400	5	80	0.68	0.66	1.0	0.68	1.36
7	400	14	89	0.87	0.75	0.1	0.75	1.74
7 + powdered glass	400	14	87	0.87	0.75	0.1	0.75	1.74
11	380–400	20		0.10	0.85	0.0	0.85	0.20
11 + powdered glass	380–400	20		0.11	0.83	0.0	0.83	0.22

[a] Since these reactions were run at 400° partial equilibration of positions 4 and 6 with 3 and 7 occurred by the same mechanism which accounts for deuterium scrambling observed in **7** and **11**.

Registry Nos.—**1**, 17790-63-5; **7**, 17818-07-4; **11**, 17790-64-6; benzonorcaradiene, 3463-79-4; benzonorbornadiene, 4453-90-1; 1,2-benzotropilidene, 264-08-4.

Retro Diels–Alder Reactions. IV.[1] Kinetics of the Thermal Decomposition of Bornylene and the Thermal Rearrangement of 1,5,5-Trimethylcyclopentadiene[2]

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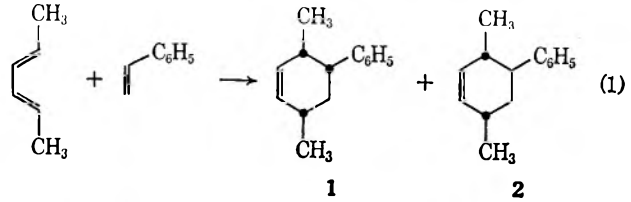
The temperature dependence of the gas phase rate of decomposition of bornylene to produce 1,5,5-trimethylcyclopentadiene and ethylene has been determined. The rate equation for this homogeneous first-order reaction is $\log k = 14.1 - (46{,}000/2.3RT)$. Comparisons are made with other retro Diels–Alder reactions, and the results are considered to support a concerted cycloaddition mechanism. The thermal rearrangement of 1,5,5-trimethylcyclopentadiene is interpreted as involving a rate-determining 1,5-sigmatropic methyl shift. This reaction is also first order and homogeneous; the rate equation is $\log k = 13.7 - (45{,}100/2.3RT)$.

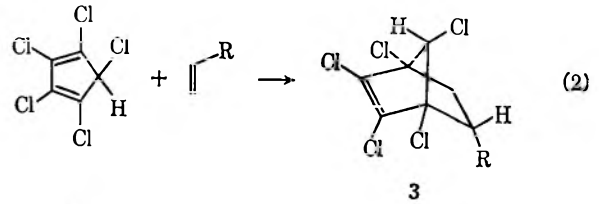
Over 30 years have elapsed since the classic paper by Alder and Stein on the mechanism of the Diels–Alder reaction.[5] Hundreds of Diels–Alder reactions have been carried out in the laboratory since that time; yet the precise details of the mechanism are still obscure, and the lack of detail still continues to beguile the organic chemist.

One of the perplexing features is the effect of substituent groups on the course of the reaction. The specific problem that we refer to is evident in two recently reported investigations. Korver, *et al.*,[6] found that the reaction of styrene with *trans,trans*-2,4-hexadiene (eq 1) gave the all-*cis* adduct **1** and the *trans* adduct **2** in an 8:5 ratio, respectively, and Williamson, *et al.*,[7] reported that pentachlorocyclopentadiene undergoes reactions with various dienophiles (eq 2), in most cases



(1)

1 **2**



(2)

3

(1) Previous papers: (a) W. C. Herndon and L. L. Lowry, *J. Amer. Chem. Soc.*, **86**, 1922 (1964); (b) W. C. Herndon, W. B. Cooper, and M. J. Chambers, *J. Phys. Chem.*, **68**, 2016 (1964); (c) W. C. Herndon, C. R. Grayson, and J. M. Manion, *J. Org. Chem.*, **32**, 526 (1967).

(2) Taken in part from a dissertation by J. M. Manion submitted to the faculty of the University of Mississippi in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Author to whom inquiries should be addressed at Texas Technological College.

(4) National Defense Education Act Fellow, 1962–1965.

(5) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

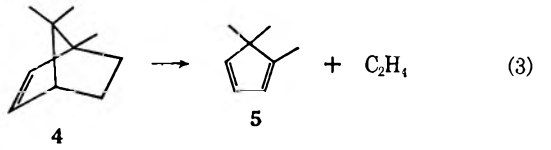
(6) O. Korver, T. L. Kwa, and C. Boelhouwer, *Tetrahedron*, **24**, 1025 (1968).

(7) K. L. Williamson, Y.-F. Hsu, and R. E. Lacko, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, P-45.

to yield a preponderance of the *anti*-7-chloro adduct **3**. In both cases the predominant product is that which would be formed *via* the more sterically crowded transition complex. These kinds of results are general; both Titov[8] and Sauer[9] cite numerous examples in their respective review articles.

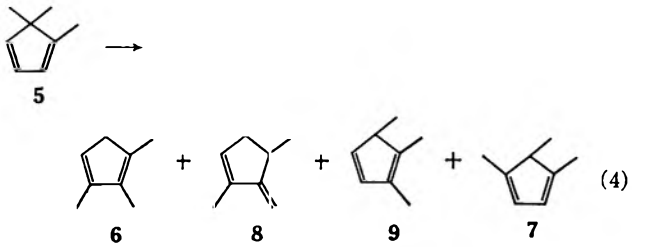
We are interested in obtaining quantitative measures of substituent effects like those described above. Accordingly, we will now describe a kinetic study of the gas phase retro Diels–Alder reaction of bornylene (1,7,7-trimethylbicyclo[2.2.1]heptene-2), and the results will be compared with our previous study[1b] of the thermal decomposition of the unsubstituted norbornylene (bicyclo[2.2.1]heptene). In principle, studies of retro Diels–Alder reactions can reveal information about the forward reactions. In the present case, kinetic investigation of the forward reaction was not even feasible, since the cyclopentadiene moiety undergoes self-condensation much more easily than it undergoes reaction with dienophilic ethylene.

Anticipating the results, we found that bornylene undergoes a clean decomposition in the gas phase to yield ethylene and 1,5,5-trimethylcyclopentadiene (eq 3). The trimethylcyclopentadiene which is produced then undergoes further reactions (eq 4), and the kinetics of this secondary process were also investigated.



(3)

4 5



5

6 8 9 7

(4)

Experimental Section

Kinetic Experiments.—Bornylene, prepared from borneol by a Chugaeff reaction,[10] was allowed to flow in a stream of nitrogen through a gas phase, stirred flow reactor which has been described in detail previously.[1a,11] A Pyrex flow reactor with a volume of 60.06 ml was used in this work. At least four flow rates and two partial pressures of reactant were studied at each temperature. Flow rates varied from 0.1 ml/sec at lower temperatures to a maximum flow rate of 3.4 ml/sec at the highest temperature investigated. The reactions are investigated under the conditions (relatively slow flow rate, high temperature) where the contents of the reactor are well mixed and time invariant concentrations result. The reactor was immersed in a molten lead bath constructed from a stainless steel beaker. The major part of the heat required for the reaction temperature was provided by a heating mantle and variable transformer. Fine temperature control was maintained by a proportional temperature controller (Bailey Model 104) and a cartridge heater. The temperature of the reactor was constant to within ±0.05° as determined with a Bureau of Standards calibrated Chromel–Alumel thermocouple inserted in the reactor.

Quantitative product analyses were carried out by gas chromatography. An Aerograph Hy-Fi gas chromatograph with hydrogen flame detector, fitted with a 1-m column packed with 5% SF-96 silicon oil on Chromosorb W support was used. The detector was calibrated with known samples synthesized by independent methods. Peak areas were integrated with a Disc integrator.

Product Isolation and Identifications.—The primary products of the pyrolysis of bornylene were isolated by running the reaction at low conversion and separating the products by gas chromatography (Aerograph Autoprep) using a 25-ft column of 25% butanediol succinate on Chromosorb maintained at 95°. One of the primary products was identified as 1,5,5-trimethylcyclopentadiene from its uv, ir, and nmr spectra. The other primary product was confirmed as ethylene by comparing the retention times of the product and an authentic sample of ethylene.

The rearrangement products of 1,5,5-trimethylcyclopentadiene were obtained by carrying out the pyrolysis of bornylene to very high extents of conversion and trapping the products in liquid nitrogen. The product mixture was then separated into three fractions by preparative gas chromatography using a 12-ft silicon oil (SF-96) column at room temperature. The two major products were identified as 1,2,3-trimethylcyclopentadiene and 3-methylene-2,4-dimethylcyclopentene by comparing their respective ir and uv spectra with those of authentic samples, synthesized in the manner described by Mironov, *et al.*[12] The small third fraction had a uv spectrum consistent with a tentative identification as a mixture of 1,2,5-trimethylcyclopentadiene and 1,4,5-trimethylcyclopentadiene. A sufficient quantity for positive identification was not obtained.

It should be noted that during the kinetic analysis it was necessary to analyze gas samples taken directly from the hot reactor in order to obtain consistent and precise results.

Results

The thermal decomposition of bornylene and the subsequent rearrangement of 1,5,5-trimethylcyclopentadiene were investigated over the temperature range 328.7–429.1°. Preliminary experiments indicated that at least two consecutive unimolecular reactions were taking place as indicated in eq 5. In our stirred flow

$$4 \xrightarrow{k_1} \text{ethylene} + 5 \qquad (5)$$
$$5 \xrightarrow{k_2} 6 - 9$$

reactor system the kinetic equations are simple algebraic expressions which can be derived from material balance equations;[13] for the present system a material balance equation for product **5** leads to the kinetic expression (eq 6) where k_1 and k_2 are first-order rate con-

$$k_1[(4)/(5)] - k_2 = \frac{u}{v} \qquad (6)$$

stants, and u and v are the flow rate of the gas and the volume of the reactor, respectively. An excellent adherence of the rate data at each temperature to this kinetic expression confirmed the postulated reaction scheme. The rate constant for the first reaction (bornylene decomposition) could also be calculated by determining the fraction of bornylene which underwent reaction at a particular flow rate and reactor volume. In the same manner, a determination of the mole ratio of all rearrangement products to 1,5,5-trimethylcyclopentadiene can yield the rate constant for the second reaction. Rate constants determined in this way are in satisfactory agreement with those determined by using eq 6.

(8) Yu. A. Titov, *Russ. Chem. Rev.*, **31**, 267 (1962).
(9) J. Sauer, *Angew. Chem. Intern. Ed. Eng.*, **6**, 16 (1967).
(10) H. R. Nace, *Org. Reactions*, **12**, 87 (1962).
(11) W. C. Herndon, M. B. Henley, and J. M. Sullivan, *J. Phys. Chem.*, **67**, 2843 (1963).
(12) V. A. Mironov, E. V. Sobolev, A. N. Elizaro, *Tetrahedron*, **19**, 1939 (1963).
(13) W. C. Herndon, *J. Chem. Educ.*, **41**, 425 (1964).

More than one series of experiments was carried out, some ascending in temperature, some descending in temperature, and in two experiments the reactor was packed with Pyrex tubing in order to ascertain the effect of a different surface to volume ratio. The first-order rate constants, from eq 6, are given in Table I. In a few earlier experiments only one of the two consecutive reasons was quantitatively analyzed.

TABLE I
RATE CONSTANTS FOR GAS PHASE THERMAL DECOMPOSITION OF BORNYLENE (k_1) AND THERMAL REARRANGEMENT OF 1,5,5-TRIMETHYLCYCLOPENTADIENE (k_2)

Temp, °K	$k_1 \times 10^2$, sec^{-1}	$k_2 \times 10^2$, sec^{-1}
608.2	0.378	0.314
611.3	0.361	0.372
614.6	0.482	
617.7	0.578	0.709
623.5		0.906
626.0	1.16	1.11
632.0	1.17	1.00
634.3	1.93	1.50
640.1	2.01	2.41
640.4[a]	2.83	2.29
641.1	2.28	2.34
647.0	4.23	3.10
651.3	3.56	3.37
653.7		4.90
655.7	4.90	3.96
664.0	8.44	5.92
669.0	11.7	
670.3[a]	12.0	9.57
670.4	10.8	13.4
679.8	17.7	
680.2	24.4	17.0
681.6	18.3	23.0
692.8	31.3	30.7
693.2	37.2	
702.1	56.9	

[a] Reactor packed with glass tubing.

Imprecise and erratic results were obtained at temperatures higher than those listed in Table I. Above about 710°K a surface catalysis of both reactions was evident; so we have not included such results. In the temperature range of Table I, the reported reactions were not affected to a significant degree (over 10% variation) by seasoning of the reaction vessels or by a tenfold change in the partial pressure of introduced reactant bornylene. However, the precision of the data, especially the variation with temperature of the ratio of k_1 to k_2, is not so good as those results which we have reported in earlier papers.[1] Even so, by carrying out the large number of experiments summarized in Table I, we were then able to obtain activation parameters with reasonably small error limits. In Table II the activation parameters are listed. The error limits are standard deviations from a least-squares regression line.

TABLE II
ACTIVATION PARAMETERS FOR THERMAL DECOMPOSITION OF BORNYLENE (k_1) AND REARRANGEMENT OF 1,5,5-TRIMETHYLCYCLOPENTADIENE (k_2)

	k_1	k_2
Preexponential factor	$10^{14.1 \pm 0.3}$	$10^{13.7 \pm 0.4}$
Energy of activation	46.0 ± 0.9 kcal/mol	45.1 ± 1.2 kcal/mol
Entropy of activation	2.3 ± 1.3 eu	0.7 ± 1.9 eu
Enthalpy of activation	44.7 ± 0.9 kcal/mol	43.8 ± 1.2 kcal/mol

One other experimental result is of interest. The relative ratios of the rearrangement products of 1,5,5-trimethylcyclopentadiene were found to be flow rate independent at each temperature, and also to be temperature independent. The approximate yields are **6**, 83%; **7**, 13%; and **8** and **9**, 4%.

Discussion

The two reactions which we are reporting on in this paper are separate and distinct even though they are studied simultaneously in the same system. We will therefore discuss each reaction in a separate section. The kinetic parameters for the thermal decomposition of bornylene also raise a question about the so-called "quasi-heterolytic" gas phase pyrolyses[14] of bornyl and isobornyl halides and esters. This question is discussed briefly in a separate paper.[15]

Retro Diels–Alder Reaction of Bornylene.—Bornylene undergoes the retro Diels–Alder reaction at a slower rate than does norbornylene. Rate constants at 350° are, for bornylene, 8.51×10^{-3} and, for norbornylene, 66.1×10^{-3} sec^{-1}.[1b] The order of magnitude difference in rate is primarily due to a 3-kcal/mol difference in energy of activation, the Arrhenius equation for norbornylene being $\log k = 13.78 - (42{,}750/2.3RT)$.[1b]

Straightforwardly we might assign this 3-kcal/mol difference to a steric factor which increases the activation energy in the methyl substituted bornylene. We take as our model for the transition state the model which was described by Herndon and Hall,[16] which has recently received some additional support.[17] The electronic nature of the transition state corresponds to that of the separated diene and dienophile but the two molecules are oriented in a state closely resembling the gross skeleton of the adduct. The rationale for this picture of the activated complex is described in the earlier paper.[16]

Now, as the bornylene molecule begins to dissociate, flattening of the cyclopentadiene and ethylene moiety must occur. The *anti*-methyl group at C-7 would then be much closer to the departing ethylene molecule than it is in the ground state. Assuming bond distances and bond angles for the bicycloheptane system reported by Wilcox[18] and Kitaygordsky,[19] the distance from the center of the methyl group to the center of the double bond is approximately 3 Å. Assuming a transition state in which the diene portion is planar and breaking bonds have been extended 10% (longer extensions are not likely since entropies of activation for retro Diels–Alder reactions are close to zero), the methyl group–double-bond distance is shortened to 2 Å. The calculation is very crude, but it does indicate an increase of steric interference of the methyl group as progress is made along the reaction coordinate.

Our original expectation was that the methyl group might have an accelerating effect upon the retro Diels–Alder reaction, analogous to that found by Williamson,

(14) For the most recent review, see A. Maccoll and P. J. Thomas, "Progress in Reaction Kinetics," Vol. 4, C. Porter, Ed., Pergamon Press, Oxford, 1967, p 119.
(15) W. C. Herndon and J. M. Manion, *Tetrahedron Lett.*, in press.
(16) W. C. Herndon and L. H. Hall, *ibid.*, 3095 (1967).
(17) D. C. F. Law and S. W. Tobey, *J. Amer. Chem. Soc.*, **90**, 2376 (1968).
(18) C. F. Wilcox, Jr., *ibid.*, **82**, 414 (1960).
(19) A. I. Kitaygordsky, *Tetrahedron*, **14**, 230 (1961).

et al.,[7] for the chlorine atom at position 5, in the reaction of pentachlorocyclopentadiene with ethylenic dienophiles (eq 2). The effect in that case is ascribed to stabilizing dispersion interactions between the closely held partners in the transition state. However, the effect of the methyl group is destabilizing rather than stabilizing. One possible explanation is related to the relative van der Waals sizes of the substituent chlorine atom and methyl group (1.8 and 2.0 Å, respectively).[20] It is possible that, in the transition state, the methyl group position may be close enough to the dienophilic ethylene moiety to be in the repulsive part of the van der Waals potential. The chlorine atom, being smaller, could still be in the attractive part of the potential. If the role of dispersion forces is a major one in stabilizing the transition complex, the distance from the C-7 substituent to ethylenic moiety might be delineated within 0.2 Å. More experimental measurements with substituents in various positions will be useful in this regard.

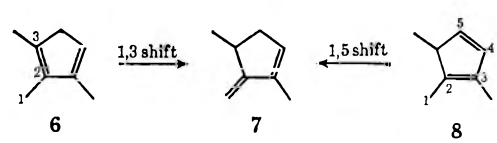
The discussion till now has assumed a concerted cycloaddition mechanism for the Diels–Alder reaction and its inverse. We believe that our results support the concerted cycloaddition mechanism. If only one carbon–carbon single bond were severed in the rate-determining step, and if a diradical intermediate were formed, such a diradical could become free of steric interaction with substituents at C-7 by rotation around carbon–carbon single bonds. A substituent at the 7 position might even be expected to accelerate the reaction if such a mechanism is functioning. The observation of the steric effect seems more consistent with a transition state in which both dienophile–diene bonds are partially broken.

In summary, *anti*-methyl substituents at C-7 in the bicyclo[2.2.1]heptane series destabilize the transition state for the Diels–Alder reaction. *anti*-7-Chloro substituent seems to stabilize the transition state.[7] Both of these effects are probably steric in origin, and concerted cycloaddition mechanisms are thereby supported.

Rearrangement of 1,5,5-Trimethylcyclopentadiene (5).—The thermal lability of **5** was noted by Alder and Muders in 1958,[21] and they reported rearrangement to **6** at 400°. De Haan and Kloosterziel[22] later reported a kinetic study of the thermal isomerization with results differing from ours in some respects. They do not report the obtention of **7**, and their activation parameters, $\Delta H^{\ddagger} = 40.3$ kcal/mol, $\Delta S^{\ddagger} = -4$ eu, are much different from those which we find, $\Delta H^{\ddagger} = 43.8$ kcal/mol and $\Delta S^{\ddagger} = 0.7$ eu. However we do note that these two different sets of activation parameters give very similar rate constants over a large range of temperature. The more positive enthalpy of activation in our results is compensated for by the more positive entropy for activation. De Haan and Kloosterziel did not publish the details of their kinetic work;[22] so it is difficult to resolve the discrepancy. They also studied the thermal rearrangements of 2,5,5-trimethylcyclopentadiene,[22] reactions very similar to the reactions of **5**. In this case they found activation enthalpies of 44.4 and 44.2 kcal/mol (for methyl shift in the two different possible directions). These figures could be construed as supporting our results.

The rearrangement reactions of **5** can be formulated as a rate-determining allowed suprafacial 1,5-sigmatropic methyl shift[23,24] to produce 1,2,5-trimethylcyclopentadiene. At the elevated temperatures required for the rate-determining step, further allowed 1,5-sigmatropic shifts of hydrogen atoms would occur immediately to produce the other cyclopentadiene molecules which are observed. 1,5-Sigmatropic hydrogen shifts have been studied extensively,[12,25] and activation energies are on the order of 20 kcal/mol. The magnitude of the activation energy for rearrangement of **5** seems quite reasonable, and is comparable with the increased activation energy found for carbon shifts *vs.* hydrogen shifts in the tropilidene series.[24]

The formation of the exocyclic isomer **7** is more difficult to explain. Superficially, **7** can arise from either **6** or **8** (eq 7). However, the 1,3 shift is not a supra-



6 7 8 (7)

facially allowed reaction, and is inconceivable in an antarafacial manner. The allowed 1,5-shift **8** → **7** also does not seem to be sterically possible. Compound **7** is normally produced during acid- or base-catalyzed dehydration of 2,3,4-trimethylcyclopent-2-en-1-ol, along with the major product, compound **6**.[12] Because of this fact, we believe that **7** may be formed through a heterogeneous mechanism, perhaps catalyzed by the walls of the flow reactor. At this time we have no information on this point.

We conclude that the gross nature of the rearrangement of **5** is well explained as an intramolecular 1,5 shift of a methyl group in general agreement with previous workers.

Registry No.—**4**, 464-17-5; **5**, 4249-09-6.

Acknowledgment.—The support of the National Science Foundation (Grant No. GP-247) is gratefully acknowledged.

(20) L. Pauling, "Nature of the Chemical Bond," 2nd ed, Cornell University Press, Ithaca, N. Y., 1948, p 189.

(21) K. Alder and R. Muders, *Ber.*, **91**, 1083 (1958).

(22) J. W. De Haan and H. Kloosterziel, *Rec. Trav. Chim. Pays Bas*, **84**, 1594 (1965).

(23) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(24) J. A. Berson, *ibid.*, **1**, 152 (1968).

(25) D. S. Glass, J. Zirner, and S. Winstein, *Proc. Chem. Soc.*, 277 (1963); S. McLean and P. Haynes, *Tetrahedron Lett.*, 2385 (1964); S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965); W. R. Roth, *Tetrahedron Lett.*, (1964).

The Reaction of 2-Methoxybutadiene with Enols and Phenols, a Novel Claisen Rearrangement[1a]

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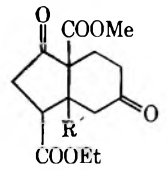
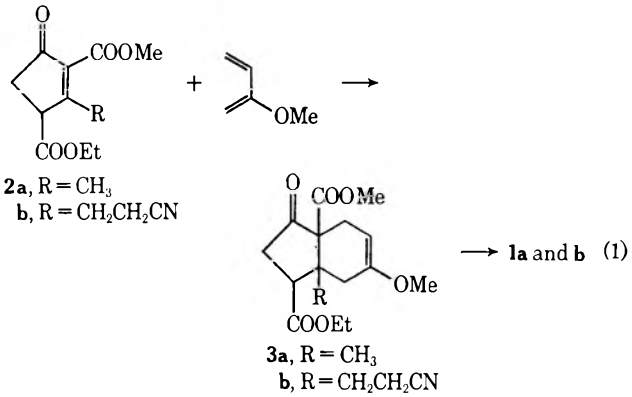
The reaction of 2-methoxybutadiene with highly enolic compounds such as the cyclopentenone **2b** and dimedone gives products **10** and **14**, respectively, in which a four-carbon side chain bearing an enol ether function has been introduced. It is thought that the enolic hydroxyl adds to the diene to produce an allylic enol ether (*e.g.*, **13**). Claisen rearrangement then gives the observed product. Phenols also react with 2-methoxybutadiene to yield rearranged products. However, the products are methoxy chromanes which are formed by closure of the initially formed allyl phenols. These reactions proceed in high yields with the formation of monosubstitution products.

For the preparation of certain multiply substituted perhydroindandiones (*e.g.*, **1a** and **1b**) it was attractive



1a, R = CH_3
b, R = CH_2CH_2CN

to examine the reaction of the highly activated dienophiles **2a** and **2b** with 2-methoxybutadiene. Diels–Alder reaction would be expected to yield the enol ethers **3a** and **3b**,[2] which would give the desired ketones upon hydrolysis (eq 1).

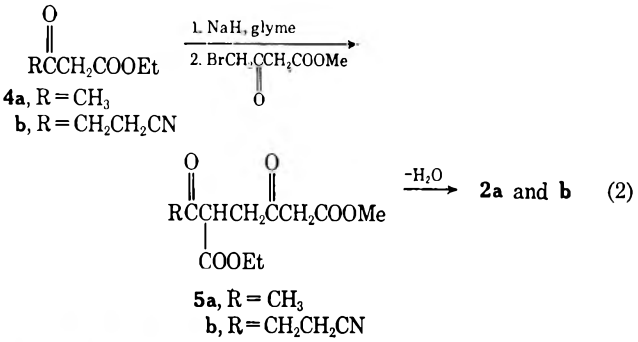


2a, R = CH_3
b, R = CH_2CH_2CN

3a, R = CH_3
b, R = CH_2CH_2CN

→ **1a** and **b** (1)

The required cyclopentenones were prepared in high yields by condensation of the sodium enolates of the β-keto esters **4a** and **4b** with methyl 4-bromoacetoacetate in 1,2-dimethoxyethane (eq 2). The initial reaction is undoubtably formation of the linear diketo diesters **5a** and **5b**, followed by cyclization. The latter step is favored by formation of the sodium enolate of the highly acidic product, and a twofold excess of starting keto ester and sodium hydride was commonly employed. The cyclopentenones prepared in this way are soluble in dilute bicarbonate solution, and they may be conveniently separated from less acidic impurities by extractive work-up. Material obtained by acidification of the bicarbonate extracts is a mixture of



4a, R = CH_3
b, R = CH_2CH_2CN

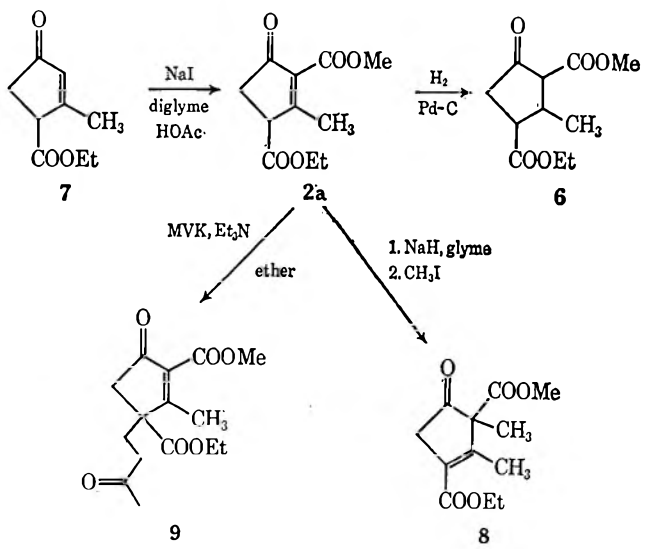
5a, R = CH_3
b, R = CH_2CH_2CN

2a and **b** (2)

keto and enol forms which may be separated by fractional crystallization. The spectral properties (ir and nmr) of the tautomeric forms differ; however, the nmr spectrum in pyridine of keto and enol **2a** as obtained from the extract showed a simple pattern (as opposed to that in $CDCl_3$).

The following transformations (Scheme I) were carried out on **2a**. Catalytic reduction gave the cyclopentanone **6**, clearly showing normal five-membered-

SCHEME I



7 **2a** **6** **9** **8**

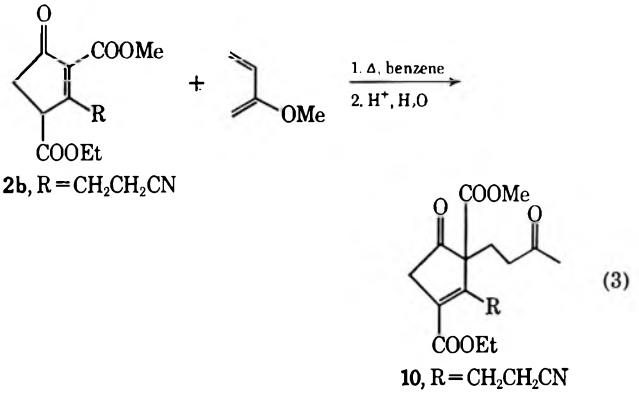
ring carbonyl absorption (1765 cm^{-1}) in its ir spectrum. Decarbomethoxylation of **2a** was conveniently carried out by sodium iodide in boiling diglyme–acetic acid to give **7** whose ir (1730, 1720, 1630 cm^{-1}) and nmr spectra (δ 5.92 ppm, 1 H) indicate preservation of the Δ^2-cyclopentenone system. Formation of the anion of **2a** in 1,2-dimethoxyethane followed by treatment with methyl iodide gave **8** in which the position of

(1) (a) The authors gratefully acknowledge financial support from the National Science Foundation (Grant 1266 GP3822) and a Public Health Service Career Program Award (1-K3-NB-28, 105) from the National Institute of Neurological Diseases and Blindness. (b) Alfred P. Sloan Research Fellow. (c) National Institutes of Health Postdoctoral Fellow (Fellowship 1-F2-GM-39, 115-01). (d) NDEA Predoctoral Fellow, 1966–present.

(2) In analogy, the reaction of 2-methoxybutadiene with acrolein gives a single product having the proper orientation [H. L. Holmes, *Org. Reactions*, 4, 64 (1948)].

methylation is shown by the ir spectrum (1755 cm^{-1}, unconjugated five-membered-ring carbonyl). Confirming evidence for the position of unsaturation is provided by the nmr spectrum, which indicates homoallylic coupling between the methyl group attached to C-3 and the two protons of C-5 (J = 2 cps). Reaction of **2a** with methyl vinyl ketone gave **9** which bears the newly introduced side chain at position 4 as shown by ir and nmr (Experimental Section).

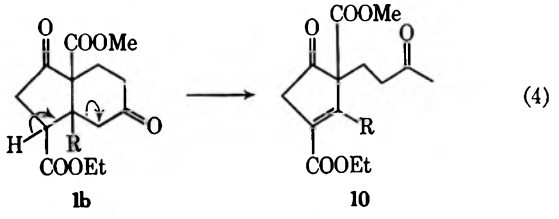
The reaction of cyclopentenones of this type with 2-methoxybutadiene does not lead to the desired perhydroindanones as postulated in eq 1. Treatment of **2b** with 2-methoxybutadiene in refluxing benzene, followed by hydrolysis with dilute hydrochloric acid, gave a substance shown to be **10** (eq 3). The high-



2b, R = CH_2CH_2CN **10**, R = CH_2CH_2CN (3)

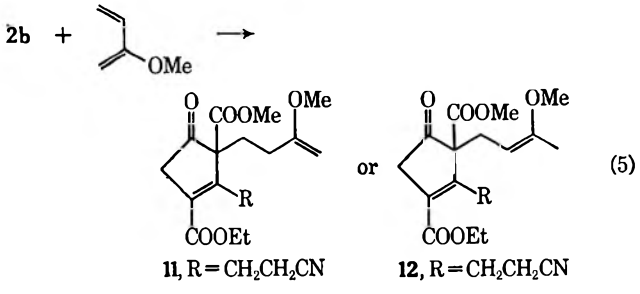
frequency (1770 cm^{-1}) carbonyl absorption of **10** in the ir spectrum points to an unconjugated five-membered-ring carbonyl group, and the nmr spectrum shows the presence of a methyl group adjacent to a carbonyl (δ 2.12 ppm).

Although the formation of **10** might be considered to proceed *via* **1b** in a reverse Michael reaction (eq 4),



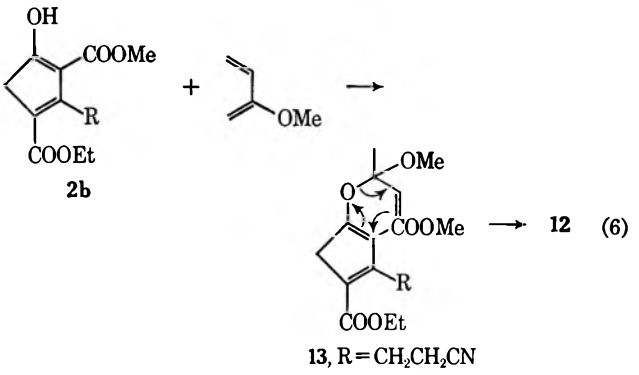
1b **10** (4)

such a reversal is not precedented for the mild acidic conditions employed during hydrolysis.[3] It appeared far more likely that one of the two possible enol ethers **11** or **12** was formed directly by reaction of **2b** with 2-methoxybutadiene (eq 5), and that subsequent hydrol-



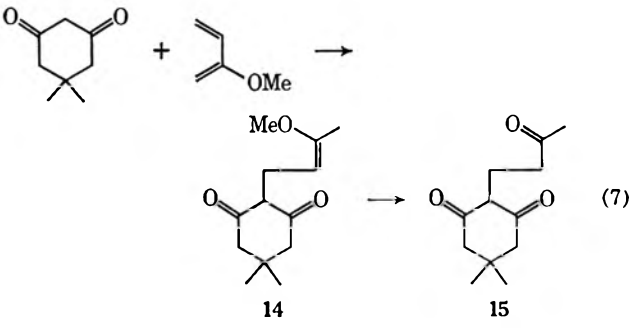
11, R = CH_2CH_2CN **12**, R = CH_2CH_2CN (5)

ysis gave **10**. Since it is difficult to explain addition of **2b** to the diene at position 4 (addition of ROH, *e.g.*, takes place at position 2[4]), the possibility was considered that the enol form of **2b** adds normally *at the enol oxygen* to give **13**, and that subsequent Claisen rearrangement leads to **12** (eq 6).



13, R = CH_2CH_2CN (6)

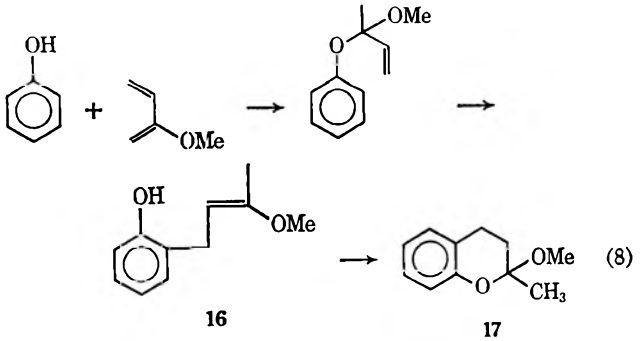
A test of this suggestion lies in the reaction of 2-methoxybutadiene with other highly enolic substances. To this end, dimedone was permitted to react with the diene in refluxing benzene to give an excellent yield of the enol ether **14** (eq 7) which was identified by ir and



14 **15** (7)

nmr spectra and by hydrolysis to the triketone **15**. The reaction of dimedone with methyl vinyl ketone gives **15** along with disubstituted material;[5] however, the diene pathway leads to the formation of essentially pure monoadduct.

Phenols also react with 2-methoxybutadiene to yield rearranged products. In the case of phenol it was found that polymerization of the diene took place in the absence of base. However, the addition of a trace of triethylamine inhibited polymerization; and the desired reaction was effected at a temperature of 150° to give the chromane **17**. This material is presumably formed by closure of the initial rearrangement product, **16** (eq 8). The reaction of *o*-cresol with 2-



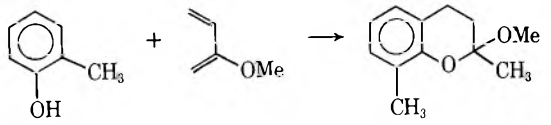
16 **17** (8)

(3) E. D. Bergman, D. Ginsberg, and R. Pappo, *Org. Reactions*, **10**, 187 (1959).

(4) R. O. Norris, J. J. Verbanc, and G. F. Hennion, *J. Amer. Chem. Soc.*, **60**, 1159 (1938).

(5) I. N. Nazarov and S. I. Zav'yalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); *Chem. Abstr.*, **48**, 13667 (1954).

methoxybutadiene takes place less readily. Addition of triethylamine to this reaction mixture is not necessary or desirable as the base exerts a very pronounced inhibitory effect. In the absence of base at 160° chromane **18** is formed in good yield after 21 hr (eq 9).



(9)

18

In conclusion it may be pointed out that these reactions of 2-methoxybutadiene provide a method for introduction of the elements of methyl vinyl ketone to enols and phenols that differ greatly in reactivity and specificity from the reactions of the unsaturated ketone. The formation of monoadduct **14** in the dimedone reaction is especially attractive in that monomethyl vinyl ketone condensation products are less easily obtained in good yields.

Experimental Section

Methyl 4-Bromoacetoacetate.—Bromination of methyl acetoacetate in carbon tetrachloride solution in a manner analogous to that of Burger and Ullyot[6] gave methyl 4-bromoacetoacetate in 64% yield: bp 78–86° (2 mm); ir $\nu_{max}^{CCl_4}$ 1740, 1720 cm^{-1}; nmr (CCl_4) δ 3.67 (s, 2 H), 3.74 (s, 3 H), 4.05 (s, 2 H).

4-Carbethoxy-2-carbomethoxy-3-methyl-Δ^2-cyclopentenone (2a).—In a 1-l. flask equipped with reflux condenser, addition funnel, and magnetic stirrer were placed 700 ml of 1,2-dimethoxyethane and 23.0 g (1.00 g-atom) of sodium metal. The flask was cooled to 0°, and 130 g (1.00 mol) of ethyl acetoacetate was added with stirring over 0.5 hr. The mixture was then permitted to come to about 50° as the last of the sodium dissolved. The cooling bath was replaced, and 98.0 g (0.500 mol) of methyl 4-bromoacetate was added in one portion. After stirring for 2.5 hr, the reaction mixture was concentrated by removal of most of the solvent under reduced pressure. Water, *ca.* 1.5 l., was then added until a homogeneous mixture was obtained, and the material was then washed with three 300-ml portions of ether. Acidification of the aqueous solution followed by extraction with two 300-ml portions of ether afforded 66.4 g of crude substance after drying over magnesium sulfate and removal of solvent. Distillation gave 54.5 g (0.241 mol, 48%) of product as a semi-solid mixture of keto and enol forms: bp 140–150° (0.5 mm).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.36; H, 6.34.

Pure enol form of **2a** was obtained by crystallization of the distillate from ether: melting point variable and ill defined; ir $\nu_{max}^{CHCl_3}$ 3200 (very broad), 1720, 1680, 1600, 1550 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (t, J = 7 cps, 3 H), 2.15 (t, J = 2.5 cps, 3 H), 3.40 (q, J = 2.5 cps, 2 H), 3.87 (s, 3 H), 4.23 (q, J = 7 cps, 2 H), 11.34 (broad singlet, 1 H); uv λ_{max}^{EtOH} 350, 300, 226 mμ (ϵ_{max} 1650, 2200, 9330); $\lambda_{max}^{EtOH\text{-}NaOH}$ 353, 298 mμ (ϵ_{max} 11,700, 13,300).

Nearly pure keto form of **2a** was obtained as an oil by distillation of the residues left from crystallization of the enol: ir $\nu_{max}^{CHCl_3}$ 1720 (broad), 1640 cm^{-1}; nmr (CCl_4) δ 1.28 (t, J = 7 cps, 3 H), 2.33 (s, 3 H), 2.58 (d, J = 5 cps, 2 H), 3.77 (s, 3 H) on top of *ca.* 3.74 (poorly defined triplet, 1 H), 4.17 (q, J = 7 cps, 2 H).

A mixture of keto and enol forms showing sets of overlapping bands in the nmr spectrum (in $CDCl_3$) was dissolved in pyridine. The nmr spectrum in this basic solvent became greatly simplified corresponding to one form: in C_5H_5N δ 1.20 (t, J = 7 cps, 3 H), 2.41 (s, 3 H), *ca.* 2.8 (multiplet, 2 H), 3.80 (s, 3 H) and 4.20 (q, J = 7 cps, 2 H) superimposed on multiplet (1 H) centered at *ca.* 3.9 ppm.

4-Carbethoxy-2-carbomethoxy-3-methylcyclopentanone (6).—In 50 ml of ethyl acetate was dissolved 2.26 g (10.0 mmol) of **2a**, and 0.1 g of 10% Pd–C was added. Hydrogenation was carried out at atmospheric pressure until gas uptake ceased. Filtration of the resulting mixture followed by removal of solvent and evaporative distillation at 70° (0.005 mm) gave 1.81 g (7.9 mmol, 79%) of reduction product: ir $\nu_{max}^{CCl_4}$ 1765, 1730 cm^{-1}; nmr (CCl_4) δ 1.17 and 1.34 (t and d superimposed, J = 7 cps, 6 H), 2.3–3.4 (complex, 5 H), 3.72 (s, 3 H), 4.16 (q, J = 7 cps, 2 H).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.80; H, 7.29.

4-Carbethoxy-3-methyl-Δ^2-cyclopentenone (7).—In a 250-ml flask equipped with stirrer and reflux condenser were placed 100 ml of diglyme, 10 ml of acetic acid, 60 g (400 mmol) of sodium iodide, and 25.5 g (113 mmol) of **2a**. The mixture was refluxed until gas evolution ceased (*ca.* 15 min) and then was cooled to room temperature. The mixture was added to 250 ml of water and was extracted with one 200-ml and two 100-ml portions of ether. The combined ethereal extracts were washed with one 100-ml portion of water followed by two 100-ml portions of 5% sodium bicarbonate solution. After drying over magnesium sulfate the solution of product was concentrated under reduced pressure and distilled under vacuum to give 8.81 g (52.5 mmol, 46.5%) of substance: bp 70–75° (*ca.* 0.5 mm); ir $\nu_{max}^{CCl_4}$ 1730, 1720, 1630 cm^{-1}; nmr (CCl_4) δ 1.28 (t, J = 7 cps, 3 H), 2.13 (s, 3 H), 2.51 (d, J = 5 cps, 2 H), *ca.* 3.7 (complex, 1 H), 4.23 (q, J = 7 cps, 2 H), 5.92 (complex, 1 H); uv λ_{max}^{EtOH} 272, 221 mμ (ϵ_{max} 561, 8740).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.17.

The 2,4-dinitrophenylhydrazone was prepared in the usual way: mp 135–137° (EtOAc).

4-Carbethoxy-2-carbomethoxy-2,3-dimethyl-Δ^3-cyclopentenone (8).—In a 50-ml flask equipped with a stirrer, addition funnel, and drying tube were placed 48 mg (2.0 mmol) of oil-free sodium hydride and 20 ml of 1,2-dimethoxyethane. To the resulting suspension was added with stirring 452 mg (2.00 mmol) of **2a** in 5 ml of 1,2-dimethoxyethane. When hydrogen evolution had ceased methyl iodide (1.0 g, 6.8 mmol) was added, and the mixture was allowed to stir 23 hr at room temperature. The solvent was removed, and the residue was taken up in 40 ml of ether. Extraction with two 15-ml portions of 2% sodium hydroxide solution removed unchanged starting material, and the ethereal solution was then dried over magnesium sulfate. Evaporation of solvent gave 230 mg (0.96 mmol, 48%) of product: ir $\nu_{max}^{CCl_4}$ 1755, 1730, 1710, 1640 cm^{-1}; nmr (CCl_4) δ 1.1–1.5 (s and t, J = 7 cps, 6 H), 2.12 (t, J = 2.0 cps, 3 H), 3.18 (q, J = 2.0 cps, 2 H), 3.70 (s, 3 H), 4.22 (q, J = 7 cps, 2 H); uv λ_{max}^{EtOH} 226, 212 (sh) mμ (ϵ_{max} 8860, 8150).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.29; H, 6.67.

4-Carbethoxy-2-carbomethoxy-4-(3-ketobutyl)-3-methyl-Δ^2-cyclopentenone (9).—To a solution of 4.52 g (20.0 mmol) of **2a** in 50 ml of ether was added 1.60 g (23 mmol) of methyl vinyl ketone and 0.2 ml of triethylamine. After standing at room temperature for 5 min the reaction mixture was extracted with two 50-ml portions of 5% sodium bicarbonate solution to remove unreacted starting cyclopentenone. The ethereal solution was dried over magnesium sulfate and concentrated under reduced pressure. The residue was evaporatively distilled at 120° (5 μ) to give 4.71 g (15.9 mmol, 80%) of product: ir $\nu_{max}^{CCl_4}$ 1730 (broad), 1630 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (t, J = 7 cps, 3 H), 4.20 (q, J = 7 cps, 2 H), singlets at 2.17, 2.30 and 3.83 (3 H each), and a complex pattern between 2.2 and 3.2 (6 H); uv λ_{max}^{EtOH} 294, 236, 225 mμ (ϵ_{max} 662, 8680, 8290).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.70; H, 6.62.

β-Cyanopropionyl Chloride.—To a solution of thionyl chloride (143 ml, 2.0 mol) in 500 ml of ether maintained below 20° was added 121 g (1.00 mol) of anhydrous sodium β-cyanopropionate[7] over about 15 min. The mixture was then allowed to stir at about 30° for an additional 0.5 hr. Celite, 10 g, was added, and the suspension of solids was removed by filtration through a 7-cm sintered funnel (coarse grade) upon which had been prepared a bed of Celite, 20 g. The filtrate was concentrated to 200 ml by rotary evaporator, and the residual thionyl chloride was then removed at oil-pump pressure. Distillation of the residue gave 100.0 g (0.85 mol, 85%) of light yellow oil: bp 78–80° (0.5 mm); ir $\nu_{max}^{CCl_4}$ 2260, 1795 cm^{-1}; nmr (CCl_4) δ *ca.* 2.6 and 3.2, complex multiplets of equal intensity (A_2B_2).

(6) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 346 (1947).

(7) T. L. Gresham, *J. Amer. Chem. Soc.*, **74**, 1323 (1952). Anhydrous material was obtained by drying the monohydrate under vacuum at 100°.

The product decomposed slowly upon standing even at −10° and was used without further treatment.

Ethyl δ-Cyano-β-ketovalerate (4b).—In a 1000-ml flask equipped with stirrer, addition funnel, and drying tube were placed 400 ml of 1,2-dimethoxyethane and 26.2 g (1.09 mol) of oil-free sodium hydride. The suspension was cooled to about −20°, and 102.2 g (0.544 mol) of ethyl *t*-butyl malonate[8] was added over 15 min. To the stirred, cooled solution was then added over 30 min 70.5 g (0.600 mol) of β-cyanopropionyl chloride. Precipitation of a solid was noticeable after a few minutes. After 1 hr the cooling bath was removed, and the mixture was allowed to stir and additional 16 hr. An ice-cold solution of 50 ml of concentrated HCl in 250 ml of water was added to the reaction mixture with stirring. The resulting material was transferred to a separatory funnel, and two layers separated upon standing. The bottom layer was removed and discarded, whereas the upper was concentrated under reduced pressure. This residue was taken up in 250 ml of ether which was then washed with three 300-ml portions of 5% sodium bicarbonate solution and dried over magnesium sulfate. After removal of solvent the crude substance was pyrolyzed under aspirator pressure (150–170°) to give a distillate consisting mainly of ethyl *t*-butyl malonate and the desired product. Fractionation of the material through a 70-cm Podbielniak spiral column gave 45.7 g (0.270 mol, 49.6%) of ethyl δ-cyano-β-ketovalerate: bp 128–138° (*ca.* 1 mm); ir $\nu_{max}^{CCl_4}$ 3300 (very broad), 2250, 1740, 1725, 1650 cm^{-1}; nmr (CCl_4) δ 1.28 (t, J = 7 cps, 3 H), *ca.* 2.6 and 2.8 (A_2B_2, 4 H), 3.48 (s, 2 H), 4.17 (q, J = 7 cps. 2 H).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 57.06; H, 6.60; N, 7.82.

4-Carbethoxy-2-carbomethoxy-3-(2-cyanoethyl)-Δ²-cyclopentenone (2b).—In a 1000-ml flask equipped with stirrer, addition funnel, and drying tube were placed 6.48 g (240 mmol) of oil-free sodium hydride and 500 ml of 1,2-dimethoxyethane. The suspension was cooled to −10°, and 45.6 g (270 mmol) of ethyl δ-cyano-β-ketovalerate was added with stirring over 15 min. To the resulting light brown solution was added 26.3 g (135 mmol) of methyl 4-bromoacetoacetate over about 5 min. The cooling bath was removed, and the mixture was allowed to come to room temperature during which time precipitation of solid took place. After 2 hr, the solvent was removed by rotary evaporator, and the residue was taken up in 500 ml of water. The aqueous mixture was washed with three 150-ml portions of methylene chloride, then acidified to pH 2, and extracted three times with 150-ml volumes of methylene chloride. After drying over magnesium sulfate and removal of solvent, the residual semisolid substance was crystallized from ether to give 24.23 g (93 mmol, 68%) of the enol form of **2b**: ir $\nu_{max}^{CCl_4}$ 3200 (very broad), 2250, 1730, 1700, 1665, 1550; nmr ($CDCl_3$) δ 1.32 (t, J = 7 cps, 3 H), 2.62 (broadened triplet, J = 7 cps, 2 H), a broad singlet at 3.48 partly superimposed on a broadened triplet (J = 7 cps) centered at 3.40 (4 H over-all), 3.92 (s, 3 H), 4.24 (q, J = 7 cps, 2 H), 11.25 (broad singlet, 1 H); uv λ_{max}^{EtOH} 353 (broad sh), 302, 268 mμ (ϵ_{max} 15,000, 15,300).

No satisfactory elemental analysis for this compound could be obtained; however, the mass spectrum exhibited a parent peak at *m/e* 265 with the base peak at 233 (corresponding to loss of MeOH) having respective relative intensities of 51:100.

4-Carbethoxy-2-carbomethoxy-3-(2-cyanoethyl)-2-(3-ketobutyl)-Δ³-cyclopentenone (10).—In a 100-ml flask equipped with reflux condenser and provision for nitrogen atmosphere were placed 6.88 g (25.9 mmol) of **2b**, 3.63 g (43.2 mmol) of 2-methoxybutadiene, 50 ml of dry benzene, and 75 mg of 2,6-di-*t*-butylhydroquinone. Air was excluded from the flask, and the mixture was refluxed for 19 hr. The benzene solution was cooled and extracted with 30 ml of 5% sodium bicarbonate solution to remove unreacted starting material and then dried over magnesium sulfate. Evaporation of solvent under reduced pressure gave 9.49 g of crude enol ether which was dissolved in 50 ml of dioxane. Concentrated hydrochloric acid, 1 ml, was added, and the mixture was warmed to *ca.* 80° for 5 min. The dioxane solution was concentrated on the rotary evaporator, and the residue was taken up in 100 ml of ether. The ethereal solution was washed with 50 ml of 5% sodium bicarbonate solution and then dried over magnesium sulfate. Evaporation yielded a viscous oil which was evaporatively distilled at 130° (5 μ) to give 6.12 g of product (18.3 mmol, 71%) which solidified upon standing: mp 98–100° (benzene–isooctane); ir $\nu_{max}^{CHCl_3}$ 2250, 1770, 1730 (sh), 1715, 1630 cm^{-1}; nmr ($CDCl_3$) δ 1.37 (t, J = 7 cps, 3 H), 2.12 (s, 3 H), 2.25–3.45 (complex, 10 H), 3.75 (s, 3 H), 4.33 (q, J = 7 cps, 2 H); uv λ_{max}^{EtOH} 285, 225 mμ (ϵ_{max} 625, 7800).

Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.91; H, 6.13; N, 4.23.

5,5-Dimethyl-2-(3-methoxy-2-butenyl)cyclohexane-1,3-dione (14).—In a 50-ml flask equipped with stirrer and condenser were placed 25 ml of benzene, 7.00 g (50 mmol) of 5,5-dimethylcyclohexane-1,3-dione, and 4.62 g (55.0 mmol) of 2-methoxybutadiene. The mixture was refluxed for 16.5 hr, and the solvent was then removed under reduced pressure. Evaporative distillation of the crude substance through a short-path apparatus at 80° (5 μ) gave 10.23 g (45.7 mmol, 91.5%) of pure product which solidified upon standing: mp 55–58° (hexane); ir $\nu_{max}^{CCl_4}$ 3010, 2990, 2920, 2850, 1630 (broad), 1380, 1082, 1060 cm^{-1}; nmr (CCl_4) δ 1.05 (s, 6 H), 1.45 (s, 3 H), 1.7–2.3 (complex, 8 H), 3.26 (s, 3 H).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.23; H, 9.13.

A small amount of **14** was hydrolyzed by shaking a dilute ethereal solution with 3 *N* HCl to give 5,5-dimethyl-2-(3-ketobutyl)cyclohexane-1,3-dione: mp 101–102° (lit.[5] mp 100–101°).

2-Methoxy-2-methylchromane (17).—In a 20 × 600 mm thick-walled Pyrex tube were placed 9.40 g (100 mmol) of phenol, 50 ml of dry benzene, 0.1 g of 2,5-di-*t*-butylhydroquinone, and 0.15 ml of triethylamine followed by 9.24 g (110 mmol) of 2-methoxybutadiene. The contents of the tube were degassed in the usual way, and the tube was sealed under vacuum. After heating at 150° for 11.5 hr, the tube was opened, and most of the benzene was removed on the rotary evaporator. The crude product was taken up in 150 ml of ether and washed with two 50-ml portions of 5% sodium hydroxide solution. The organic phase was dried over potassium carbonate and evaporated to give a light yellow oil which was distilled through a 70-cm Podbielniak spiral column under reduced pressure to yield 14.62 g (82 mmol, 82%) of 2-methoxy-2-methylchromane: bp 108–112° (14 mm); ir (CCl_4) shows no hydroxyl or carbonyl absorptions; nmr (CCl_4) δ 1.47 (s, 3 H), 1.6–3.1 (complex, 4 H), 3.20 (s, 3 H), 6.4–7.2 (complex, 4 H).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.01; H, 8.17.

2,8-Dimethyl-2-methoxychromane (18).—In a 20 × 250 mm thick-walled Pyrex tube were placed 2.70 g (25.0 mmol) of *o*-cresol, 2.31 g (27.5 mmol) of 2-methoxybutadiene, and 10 ml of dry benzene. The contents of the tube were degassed in the usual way, and the tube was sealed under vacuum. After heating at 160° for 21 hr, the tube was opened, and its contents were taken up in 60 ml of ether. This solution was washed with two 30-ml portions of 5% sodium hydroxide solution. The combined aqueous basic solutions were washed once with 30 ml of ether and then acidified to give upon extraction 0.54 g (5 mmol, 20%) of crude recovered *o*-cresol. Removal of solvent from the dried neutral fraction followed by distillation under reduced pressure gave 3.64 g (19.0 mmol, 76%) of 2,8-dimethyl-2-methoxychromane: bp 78–85° (*ca.* 1 mm); ir (CCl_4) shows no hydroxyl or carbonyl absorptions; nmr (CCl_4) δ 1.47 (s, 3 H), 1.6–2.1 (complex, 2 H), 2.16 (s, 3 H), 2.2–3.1 (complex, 2 H), 3.18 (s, 3 H), 6.5–7.0 (complex, 3 H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.66; H, 8.34.

Registry No.—2-Methoxybutadiene, 3588-30-5; keto **2a**, 17790-69-1; enol **2a**, 17790-70-4; enol **2b**, 17790-71-5; **4b**, 17790-72-6; **6**, 17790,-73-7; **7**, 17790-74-8; **7** 2,4-dinitrophenylhydrazone, 17790-75-9; **8**, 17790-83-9; **9**, 17790-76-0; **10**, 17790-77-1; **14**, 17790-78-2; **17**, 17790-79-3; **18**, 17790-80-6; methyl 4-bromoacetoacetate, 17790-81-7; β-cyanopropionyl chloride, 17790-82-8.

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Carboxylation by Alkali Salts and Carbon Monoxide. II.[1] A Selective Preparation of *p*-Hydroxybenzoic Acid

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The reaction of potassium phenoxide with carbon monoxide and potassium carbonate was studied in detail. The effects of reaction variables on the yield and the selectivity were investigated. The reaction proceeds very smoothly at a temperature above the melting point of potassium formate (167°) even under low pressure of carbon monoxide to afford dipotassium *p*-hydroxybenzoate and potassium formate in very high yield. The carboxylation occurs mainly at the *para* position to the hydroxyl group. When the molar ratio of potassium carbonate to potassium phenoxide is larger than unity, tripotassium 4-hydroxyisophthalate is also formed by the subsequent but rather slow carboxylation.

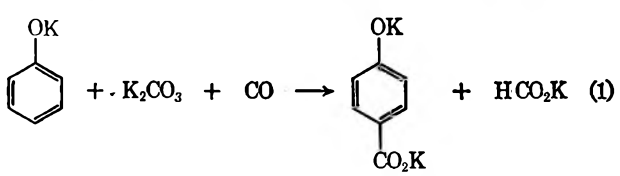
p-Hydroxybenzoic acid (or its potassium salt) has been prepared by various procedures. One of the most practical is the Kolbe–Schmitt reaction.[2,3]

On the other hand, the carboxylation of potassium benzoate by carbon monoxide and potassium carbonate to give dipotassium terephthalate was reported by Murase, *et al.*[4] Although the mechanism of the reaction is not clear, the reaction probably proceeds through the following steps: potassium carbonate reacts first with carbon monoxide to form potassium oxalate[5] as an intermediate, and then the potassium oxalate converts potassium benzoate into dipotassium terephthalate.[6]

The carboxylation reaction of potassium phenoxide with carbon monoxide and potassium carbonate was reported in the previous paper.[1] The reaction is investigated in detail in this paper.

Results and Discussion

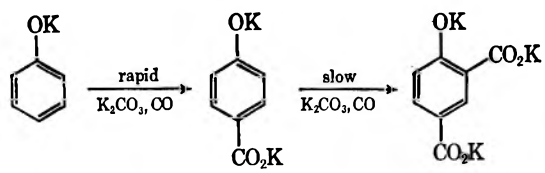
Effects of the Reaction Variables.—The equimolar mixture of potassium phenoxide and potassium carbonate was heated under fairly high pressure of carbon monoxide at an appointed temperature for 5 hr (Figure 1). Even at 125°, the carboxylated products, though the conversions were very low, were detected. The yield and the selectivity of *p*-hydroxybenzoic acid increased slowly with temperatures up 170°. At above 170°, near the melting point of potassium formate (167°), an abrupt increase of the yield was observed. At temperatures above 210°, the yield of *p*-hydroxybenzoic acid was almost quantitative. The almost stoichiometrical absorption of carbon monoxide and the almost quantitative formation of formic acid show the reaction to be formulated as



One of the reasons of the low reaction rate at a temperature below 167° is presumably that there is no liquid phase in the reaction mixture. At temperatures above 210°, the change of carbon monoxide pressure indicated that the reaction rate depends considerably on the temperature (Figure 2).

The effect of the carbon monoxide initial pressure on the yield of *p*-hydroxybenzoic acid was examined at 240° (Figure 3). When the reaction was carried out in the absence of carbon monoxide, no carboxylated product was obtained. When carbon monoxide was present enough for the amount of potassium phenoxide (0.050 mol of carbon monoxide corresponds to a pressure of about 15 atm, at room temperature in our system), the yield of *p*-hydroxybenzoic acid was nearly quantitative irrespective of the carbon monoxide initial pressure. This shows that the reaction proceeds even under low pressure. Figure 4 indicates clearly that the reaction rate is affected by the initial pressure.

The effect of the molar ratio of potassium carbonate to potassium phenoxide was studied at 240° (Figure 5). The yield of *p*-hydroxybenzoic acid corresponded to the proportion of potassium carbonate up to the ratio of unity. When 1.5 or 2.0 times as much potassium carbonate was used, a small amount of 4-hydroxyisophthalic acid was obtained. The formation of it is by the subsequent carboxylation of dipotassium *p*-hydroxybenzoate, but the reaction rate was so slow that usually *p*-hydroxybenzoic acid can be obtained preferentially (Table I).



(2)

TABLE I

CARBOXYLATION OF DIPOTASSIUM *p*-HYDROXYBENZOATE[a]

Solvent, H·CO2K, mol	Initial CO, atm	Time, hr	Yield of product,[b] % 4-HIPA	HTMA	*p*-HBA
0	50	5.0	0	0	97
0.050	50	5.0	14	0	84
0.050	50	24.0	43	4	50
0.050	10	5.0	0	0	97
0.050	10	24.0	3	0	95

[a] A mixture of 0.050 mol of dipotassium *p*-hydroxybenzoate and 0.050 mol of potassium carbonate was heated at 240°. [b] 4-HIPA, 4-hydroxyisophthalic acid; HTMA, hydroxytrimesic acid; *p*-HBA, *p*-hydroxybenzoic acid.

(1) Y. Yasuhara and T. Nogi, *Chem. Ind.* (London), 229 (1967), may be considered as part I in this series.
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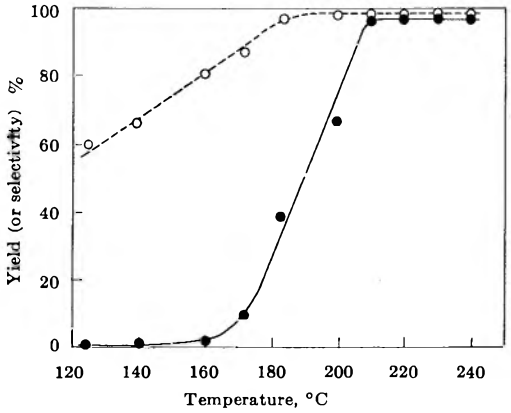

Figure 1.—Over-all yield of hydroxybenzoic acids (—●—) and selectivity of the *para* isomer (- -○- -) as a function of temperature. A mixture of 0.050 mol of PhOK and 0.050 mol of K_2CO_3 was heated under the initial pressure (80 atm) of CO at an appointed temperature for 5 hr.

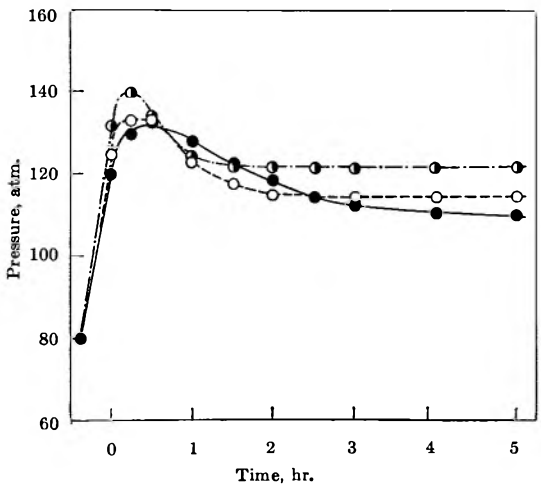

Figure 2.—Reaction velocity expressed by change of CO pressure as a function of temperature (—●—, 210°; - -○- -, 220°; - ·-◑-·-, 240°). For the reaction conditions, see Figure 1.

The fact that 4-hydroxyisophthalic acid was not detected in the reaction of dipotassium *p*-hydroxybenzoate with carbon monoxide in the absence of potassium formate may be understood in terms of the absence of liquid phase in the reaction mixture.

Mechanism of the Carboxylation Reaction.—To elucidate the course of reaction 1, the behavior of dipotassium salicylate under the present reaction conditions was examined (Table II).

TABLE II

CARBOXYLATION OF DIPOTASSIUM SALICYLATE[a]

Solvent, HCO_2K, mol	Temp, °C	Time, hr	Yield of product,[d] % SA	*p*-HBA	4-HIPA
0[b]	175	5.0	95	0	3
	240	0.4	4	90	2
	240	5.0	0	93	5[e]
0.025[c]	170	5.0	86	5	7
	170	20.0	57	25	16
	240	0.4	0	93	2
	240	5.0	0	92	4

[a] The reagents were 0.050 mol of dipotassium salicylate and 0.050 mol of potassium carbonate. [b] The initial pressure of CO was 80 atm. [c] The initial pressure of CO was 60 atm. [d] SA, salicylic acid; *p*-HBA, *p*-hydroxybenzoic acid; 4-HIPA, 4-hydroxyisophthalic acid. [e] Mainly hydroxytrimesic acid.

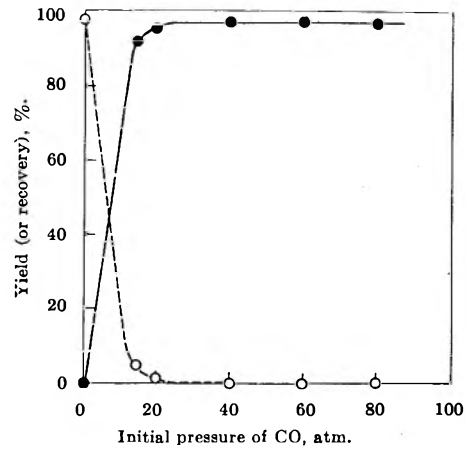

Figure 3.—Yield of *p*-hydroxybenzoic acid (—●—) and recovery of PhOH (- -○- -) as a function of initial pressure of CO. A mixture of 0.050 mol of PhOK and 0.050 mol of K_2CO_3 was heated under an appointed initial pressure of CO at 240° for 3 hr.

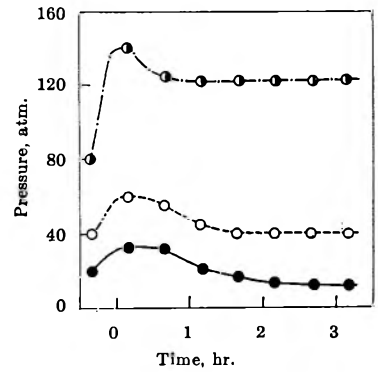

Figure 4.—Reaction velocity expressed by change of CO pressure as a function of the initial CO pressure (—●—, 20 atm; - -○- -, 40 atm; - ·-◑-·-, 80 atm). For the reaction conditions, see Figure 3.

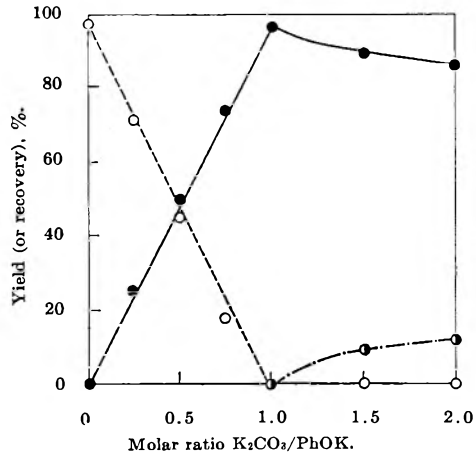

Figure 5.—Yield of *p*-hydroxybenzoic acid (—●—) and 4-hydroxyisophthalic acid (- -○- -) and recovery of PhOH (- ·-◑-·-) as a function of molar ratio of K_2CO_3 to PhOK. A mixture of 0.040 mol of PhOK and an appointed amount of K_2CO_3 was heated under the initial pressure (50 atm) of CO at 240° for 5 hr.

At temperatures below 175°, the yield of *p*-hydroxybenzoic acid obtained by the rearrangement of dipotassium salicylate was much lower than that by the carboxylation of potassium phenoxide, irrespective of the presence of potassium formate. These results lead to the conclusion that most of *p*-hydroxybenzoic acid was formed by the direct *para* carboxylation, at least at temperature below 175°.

At 240°, where dipotassium salicylate rearranges rapidly to the *para* isomer in the Kolbe–Schmitt reaction,[7-9] the rapid rearrangement was also observed accompanied with small extent of the polycarboxylation. Since the rearrangement is inhibited at the same temperature in the presence of 1 mol of potassium hydroxide[10,11] (or methoxide[8,10]) in the Kolbe–Schmitt reaction, the carboxylation was examined also in the presence of potassium hydroxide. The potassium hydroxide, however, reacted smoothly with carbon monoxide to give potassium formate.[12,13] Therefore, at 240° a possibility of the initial *ortho* carboxylation was not thoroughly avoided.

The assumption that potassium oxalate is an intermediate carboxylating agent of potassium phenoxide should be abandoned, because both were recovered on heating them together at 250° for 6 hr.

Experimental Section[14]

Reagents.—Potassium phenoxide, dipotassium *p*-hydroxybenzoate, and potassium formate were prepared by neutralization of aqueous *n*-propyl alcohol or aqueous *n*-butyl alcohol solutions, followed by distillation of solvents to yield crystals, and drying the crystals at 130° *in vacuo* (N_2, 20 mm). Dipotassium salicylate was difficult to crystallize, and so was prepared by drying an aqueous methanol solution at 150° *in vacuo*. The absence of *p*-hydroxybenzoic acid which may be formed by the thermal rearrangement on drying was confirmed by extraction of the regenerated acid with chloroform.[15] High purities (97–98%) were proved by potentiometric titration (and gravimetry of the regenerated acid) in all cases. Potassium oxalate was used after drying the commercial monohydrate at 160° *in vacuo*. Potassium carbonate and carbon monoxide (Matheson Co.) were used without further purification.

Procedure.—The pulverized reagents (usually 0.050 mol of potassium phenoxide and 0.050 mol of potassium carbonate) were mixed well, and then put into a glass vessel having a coiled capillary vent together with a steel ball. The vessel, after evacuation (N_2, 2–20 mm) at 150° for 5 hr, was placed in an autoclave (*ca.* 100 ml). The autoclave was filled with carbon monoxide to an appointed pressure at room temperature. Then the autoclave was settled in an aluminum block heater regulated within ±2° and agitated vigorously. About 20 min were required to bring the temperature of the autoclave constant.

After heating for an appointed time, the autoclave was withdrawn and the gas pressure was recorded. The pressure drop reflecting usually the extent of the carboxylation. The gas was submitted to gas chromatography [column of activated charcoal (2 m, 90°), carrier gas, He (50 ml/min)] and proved usually to consist of carbon monoxide with only a trace amount of carbon dioxide.

The glass vessel was weighed and the increase of the weight was generally equal to the amount of absorbed carbon monoxide. The crude product under the typical reaction conditions (0.050 mol of PhOK, 0.050 mol of K_2CO_3, 50 atm of CO, 240°, 5 hr) showed practically the same ir spectra and also the same titration curve as an equimolar mixture of dipotassium *p*-hydroxybenzoate and potassium formate.

Isolation and Analysis of Product.—The reaction mixture was dissolved in 50 ml of water and neutralized to pH 9.0 with 6 *N* sulfuric acid, and the regenerated phenol was extracted with ether. The solid phenol (identified by the ir spectra), obtained after evaporation of the solvent and drying, was weighed.

After acidification with 12 *N* sulfuric acid to pH 1.0, the aqueous solution was extracted again with ether. The crude *p*-hydroxybenzoic acid, obtained from the ether extract, was weighed, and its melting point and ir spectra were determined. The crude acid usually melted at 208–212°, and showed the practically identical ir spectra with that of the pure acid. After recrystallization of the crude acid from water and drying *in vacuo* (N_2, 10 mm) at 130° for 8 hr, *p*-hydroxybenzoic acid melted at 213–214° (lit.[16] mp 213–214°).

Anal. Calcd for $C_7H_6O_3$: C, 60.86; H, 4.38. Found: C, 60.92; H, 4.45.

Separation of the other acid from the crude *p*-hydroxybenzoic acid, if necessary, was carried out as follows. Salicylic acid was extracted with 160 ml of chloroform[15] from 50 ml of an aqueous suspension of the crude acid, and 4-hydroxyisophthalic acid was separated from the aqueous solution of *p*-hydroxybenzoic acid by fractional recrystallization.[17,18] Salicylic acid and 4-hydroxyisophthalic acid thus obtained were identified by the mixture melting points with authentic samples and by the ir spectra. In certain cases (for example, dipotassium *p*-hydroxybenzoate, 0.050 mol; K_2CO_3, 0.050 mol; HCO_2K, 0.050 mol; CO, 50 atm, 240°, 24 hr), hydroxytrimesic acid, mp 304–306° (crystallized from water, lit.[16] mp 306°), was isolated together with 4-hydroxyisophthalic acid.

Anal. Calcd for $C_9H_6O_7$: C, 47.80; H, 2.67. Found: C, 48.23; H, 2.81.

In some cases, formic acid was titrated potentiometrically in the following manner. The aqueous solution of the reaction product, after removal of the regenerated phenol, was acidified to pH 1.0 and extracted exhaustively with ether. The extract was titrated with 0.5 N sodium hydroxide in aqueous ethanol. The yield of formic acid was calculated from the difference between the total amount of formic acid and *p*-hydroxybenzoic acid which was determined from the end point of the titration, and the amount of *p*-hydroxybenzoic acid weighed by the above procedure. Generally the yield of formic acid was equal to that of *p*-hydroxybenzoic acid. Formic acid (bp 100–101°) was isolated from the aqueous solution, from which *p*-hydroxybenzoic acid had been removed, by exhaustive extraction with ether and fractional distillation; the ir spectra was consistent with that of an authentic sample; the anilide[19] had mp 46–48° (lit.[20] mp 50°).

Anal. Calcd for C_7H_7NO: C, 69.40; H, 5.83; N, 11.57. Found: C, 69.25; H, 5.89; N, 11.62.

Registry No.—Carbon monoxide, 630-08-0; potassium carbonate, 584-08-7; potassium phenoxide, 100-67-4; *p*-hydroxybenzoic acid, 99-96-7.

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Side-Chain Amination of Aryldialkylmethines with Trichloramine–Aluminum Chloride–*t*-Butyl Bromide[1]

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Received May 1, 1968

Various aryldialkylmethines were aminated on the alkyl side chain to form *t*-benzylamines in the system trichloramine–aluminum chloride–*t*-butyl bromide. *p*-Alkyl- and *p*-halocumenes gave the corresponding *para*-substituted cumylamines in yields of 61–80% based on trichloramine. With *p*-cyclohexyltoluene, 1-(*p*-tolyl)cyclohexylamine was produced. Amination of 3-(*p*-tolyl)pentane took place with rearrangement forming 2-(*p*-tolyl)-2-pentylamine, the same product as was obtained from 2-(*p*-tolyl)pentane. More highly alkylated benzenes produced poor results attributable to unfavorable steric influences, isomerization, and disproportionation. It was demonstrated in some cases that amination followed a single pathway even when isomeric mixtures comprised the starting material. Relative rate studies provided evidence for involvement of intermediate *t*-benzyl cations. The reaction possesses synthetic utility. Dealkylation of certain *p*-alkyl-*t*-benzylamines was effected smoothly.

In prior investigations we have shown that the combination of trichloramine and aluminum chloride is capable of aminating various types of organic compounds. The orientation of the entering group and varied nature of the organic substrates are of particular interest. For example, alkylbenzenes were found to be *meta* directing;[4] *t*-alkanes yielded *t*-carbinamines;[5] and *t*-alkyl halides were transformed into *t*-alkylamines.[6] Recently, the conversion of *p*-cymene into 8-amino-*p*-cymene was reported to proceed smoothly on exposure to trichloramine–aluminum chloride–*t*-butyl bromide.[7]

The purpose of the present study was to investigate the scope and theoretical aspects of the amination reaction with aryldialkylmethines as substrates. Our principal attention was devoted to the mechanistic features in relation to substituent effects and relative rates, as well as the synthetic utility.

Results

Since only a few of the requisite aryldialkylmethines are commercially available, literature procedures were generally followed for their preparation. Several of the hydrocarbons, namely, *p*-*t*-butylcumene, isopropylmesitylene, and 5-isopropyl-*m*-xylene, were readily obtained by Friedel–Crafts alkylation. However, in many instances this method proved unsuitable because of the formation of isomeric mixtures which were difficult to separate into the component parts. Multistep procedures were then employed, involving addition of a Grignard reagent to the appropriate ketone, dehydration of the resulting alcohol, and finally reduction of the olefin. Several miscellaneous procedures are also described.

The aminations were carried out by adding a solution of trichloramine to a mixture of the methine, aluminum chloride, and *t*-butyl bromide at 0–10°. Those experiments which met with success are summarized in Table I. The basic products were characterized by elemental analyses, ir and nmr (Table II) spectra, and amide derivatives (Table III). The *p*-alkylcumenes responded nicely producing the corresponding cumylamines in yields of 61–80% based on trichloramine. Similar findings were realized with the *p*-halocumenes. We observed essentially the same outcome (high yields of the *para*-substituted product) even when 20% of the *o*-bromo or *o*-chloro isomer was present in the aromatic starting material. Also, it was necessary to operate near room temperature with *p*-chloro- and *p*-fluorocumene to achieve optimum results. Of the two routes possible with 2-chloro-1,4-diisopropylbenzene, the one leading to 3-chloro-4-isopropylcumylamine was followed almost exclusively. In contrast, *p*-isopropylanisole resisted amination, and a number of other cumene derivatives (4-chloro-4′-isopropylbiphenyl, isopropylxylenes, 2,5-diisopropyl-*p*-xylene, 1,3,5-triisopropylbenzene, and isopropylmesitylene) gave low yields of basic material containing two to nine components.

Methine side chains, other than isopropyl, are also capable of undergoing amination. For example, 1-(*p*-tolyl)cyclohexylamine was formed in 57% yield from *p*-cyclohexyltoluene. A more complex picture with interesting ramifications emerged from our investigations with the 2- and 3-(*p*-tolyl)pentanes. In the case of the 2 isomer, reaction apparently proceeded in a straightforward manner to provide 2-amino-2-(*p*-tolyl)pentane. Quite unexpectedly, the same amine was formed as the major product from the 3 isomer.

p-Ethyltoluene gave a gross mixture of basic products in low yield.

Cumylamine, and presumably its *meta* derivatives, cannot be synthesized directly according to the general procedure since the aromatic substrate preferentially undergoes disproportionation and nuclear amination,[8] with the side chain being less susceptible to attack. Thus, cumene gave rise to a complex mixture including *m*-cumidine, cumylamine, and *p*-isopropylcumylamine.

(1) Paper XI: Chemistry of N-Halamines.

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(3) Supported by the National Science Foundation Research Participation for College Teachers Program, and the Research Corporation (Frederick Gardner Cottrell grant), 1966–1967.

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TABLE I

AMINATION OF ARYLDIALKYLMETHINES WITH TRICHLORAMINE–ALUMINUM CHLORIDE–*t*-BUTYL BROMIDE[a]

Substrate	Amine product	Yield, %	Bp, °C (mm)	Formula	Calcd, %				Found, %			
					C	H	N	X[b]	C	H	N	X[b]
p-Cymene	8-Amino-*p*-cymene[c]	80	76–77 (5.2)									
p-Ethylcumene	*p*-Ethylcumylamine	62[d]	100–108 (7.7)	$C_{11}H_{17}N$	80.94	10.47	8.58		80.73	10.65	8.41	
p-Diisopropylbenzene	*p*-Isopropylcumylamine	61	95–97 (4.5)	$C_{12}H_{19}N$	81.30	10.80	7.90		81.35	10.80	7.80	
p-*t*-Butylcumene[e]	*p*-*t*-Butylcumylamine	66	78–79.5[f]	$C_{13}H_{21}N$	81.61	11.07	7.32		81.78	11.02	7.43	
p-Fluorocumene[e]	*p*-Fluorocumylamine	72[g]	77–80 (7.3–7.5)	$C_9H_{12}FN$	70.55	7.90	9.14	12.40	70.46	7.92	9.20	12.43
p-Chlorocumene[e,h]	*p*-Chlorocumylamine	69[g]	91 (4)	$C_9H_{12}ClN$	63.71	7.13	8.26	20.90	63.81	7.31	8.13	20.75
p-Bromocumene[e,h]	*p*-Bromocumylamine	74	122–124 (8.3)	$C_9H_{12}BrN$	50.47	5.61	6.54	37.38	50.45	5.75	6.60	37.20
2-Chloro-1,4-diisopropylbenzene	3-Chloro-4-isopropylcumylamine	40[i]	133–137 (8.3–8.5)	$C_{12}H_{18}ClN$	68.06	8.56	6.61	16.74	68.34	8.50	6.57	16.72
p-Cyclohexyltoluene	1-(*p*-Tolyl)cyclohexylamine	57[j]	125–127 (1.5–1.7)	$C_{13}H_{19}N$	82.48	10.12	7.40		82.35	10.20	7.23	
3-(*p*-Tolyl)pentane	2-(*p*-Tolyl)-2-pentylamine	52[k]	108–115 (6.8–7.5)									
2-(*p*-Tolyl)pentane	2-(*p*-Tolyl)-2-pentylamine	28[l]	107–109 (7.1–7.5)	$C_{12}H_{19}N$	81.30	10.80	7.90		81.27	10.76	7.81	

[a] See the general procedure. [b] X = halogen. [c] See ref 7. [d] About 88% pure; also contains *p*-isopropylcumylamine (8%), cumylamine (1%), and unidentified material (3%). [e] Aromatic: *t*-BuBr:$AlCl_3$:NCl_3 = 10:2:2:1 molar ratio. [f] Melting point. [g] Modified general procedure; see Experimental Section. [h] Contains about 20% *ortho* isomer. [i] Contains about 6% 2-chloro-4-isopropylcumylamine. [j] Contains about 4% unidentified material. [k] About 84% pure. The remainder consists of four unidentified materials. We were unable to detect the presence of 3-(*p*-tolyl)-3-pentylamine. [l] Contains 3% unidentified component.

However, these types can conveniently be brought to hand since certain of the substituted *t*-benzylamines serve as suitable precursors. For example, on exposure to aluminum chloride–hydrogen chloride, *p*-isopropyl- and *p*-*t*-butylcumylamine were converted into cumylamine in good yield by dealkylation in the presence of toluene. In an analogous manner, *m*-chlorocumylamine was formed almost quantitatively from 3-chloro-4-isopropylcumylamine.

Several attempts were made to reduce the amount of aromatic substrate without adversely affecting yield. Since some of the aromatic reactant is being consumed through nuclear chlorination, part of the excess *p*-cymene was replaced by several candidates, namely *p*-xylene and mesitylene, which hopefully would suffer halogenation and, at the same time, participate to little or no extent in amination.[8] The experiments did not prove fruitful.

In the initial studies[9] evidence was obtained for the presence of N-chlorinated 8-amino-*p*-cymene under certain conditions in the amination of *p*-cymene. Subsequent work-up resulted in conversion into *ar*-chloro-8-amino-*p*-cymene of unknown orientation. We have now characterized the product as the 2 isomer. Identification was based upon reductive deamination of the *ar*-chloro-8-amino-*p*-cymene to a mixture of 2-chloro-*p*-cymene and, presumably, 3-chloro-4-methyl-α-methylstyrene. The results point to an intermolecular pathway for the nuclear halogenation.[10]

Discussion

The mechanistic scheme[7] for rationalization of side-chain amination is illustrated with *p*-cymene (eq 1 and 2). Alkyl groups *para* to the methine functionality

$$Cl_3N + AlCl_3 \rightleftharpoons Cl^{\delta+}(Cl_2NAlCl_3)^{\delta-} \quad (1)$$

(2)

would be expected to afford resonance stabilization[11] of the intermediate *t*-benzylic cation. Halogen atoms, although capable of effecting delocalization,[12] also possess an unfavorable inductive influence which apparently accounts for the increased temperatures required for optimum results with the more electronegative members.

In a number of cases (4-isopropyl-*m*-xylene, 2-isopropyl-*p*-xylene, 2,5-diisopropyl-*p*-xylene, isopropylmesitylene, and *o*-chlorocumene) the decreased susceptibility to amination can be interpreted by steric inhibition[11,12] of resonance including the participation of less favorable *o*-quinoid structures. This hypothesis nicely accounts for the preferential formation of 3-chloro-4-isopropylcumylamine from 2-chloro-*p*-diisopropylbenzene. The importance of resonance stabilization of the carbonium ion is further pointed up by the poor results obtained when the *para* position is un-

(9) P. Kovacic and R. J. Hopper, *Tetrahedron*, **23**, 3965 (1967).
(10) L. O. Brown and F. G. Soper, *J. Chem. Soc.*, 3576 (1953).
(11) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, **79**, 1897 (1957).
(12) H. C. Brown, Y. Okamoto, and G. Ham, *ibid.*, **79**, 1906 (1957).

TABLE II

PROTON MAGNETIC RESONANCE DATA[a,b]

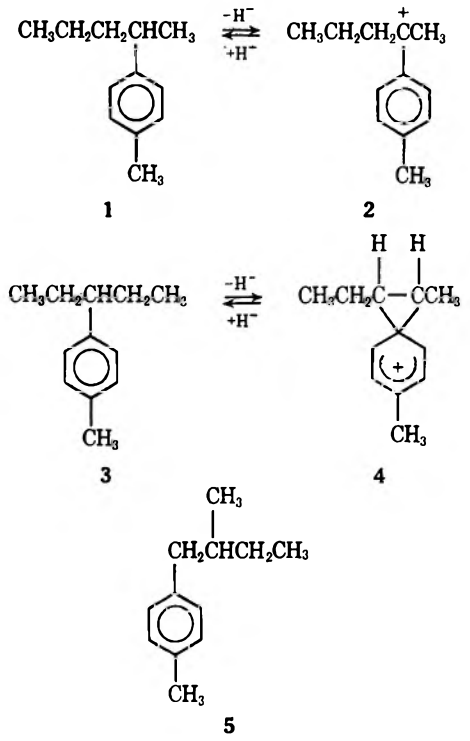
Compound	Registry no.	Chemical shifts, δ (ppm) ArH	ArCH	RCH	NCCH	NH	Rel intensities
p-Ethylcumylamine	17797-07-8	6.61 (dd)	2.29 (q)	1.01 (t)	1.17 (s)		3.9:2:11[c]
p-Isopropylcumylamine	17797-08-9	7.28 (dd)	2.82 (h)	1.17 (d)	1.33 (s)	1.36 (s)	4:0.9:14[c]
p-*t*-Butylcumylamine	17797-09-0	7.05 (d)		1.15 (s)	1.26 (s)		3.9:9:7.9[d]
p-Fluorocumylamine	17797-10-3	6.42–7.25 (c)			0.98 (s)	1.08 (s)	1:2[d]
p-Chlorocumylamine	17797-11-4	7.02 (dd)			1.04 (s)	1.17 (s)	1:1.9[d]
p-Bromocumylamine	17797-12-5	7.32 (bs)			1.32 (bs)		1:2[d]
3-Chloro-4-isopropylcumylamine	17797-13-6	6.81–7.32 (c)	3.11 (h)	0.92 (d)	1.02 (s)		3.5:0.9:14[c]
1-(*p*-Tolyl)cyclohexylamine	17797-15-8	6.94 (dd)	2.00 (s)	1.33 (c)		0.89 (s)	3.9:2.7:10[e]:1.8
2-(*p*-Tolyl)-2-pentylamine	17797-14-7	6.93 (dd)	1.93 (s)			*f*	
m-Chlorocumylamine	17790-50-0	6.77–7.39 (c)			1.01 (s)		1.1:2[d]

[a] Tetramethylsilane as external reference. [b] s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; dd, two doublets; c, complex; b, broad. [c] RCH, NCCH, NH combined. [d] NCCH, NH combined. [e] RCH, NCCH combined. [f] A complex pattern from 0.56 to 1.48 with overlapping singlets at 1.06 (3H) (CH_3C) and 0.91 (2H) (NH_2). The remainder of the pattern, assigned to the *n*-propyl group, is similar to that obtained from 2-hydroxy-2-(*p*-tolyl)pentane (see the Experimental Section). The spectrum is consistent with that predicted for 2-(*p*-tolyl)-2-pentylamine. If the amino group is attached at some other position, the peak at 1.06 would be a doublet. If an isopropyl group, instead of *n*-propyl, were present, a doublet at about 0.9 and a heptet near 2.0 would be expected.

substituted (no steric inhibition of resonance since *ortho* positions are open) (cumene, 5-isopropyl-*m*-xylene, and 1,3,5-triisopropylbenzene). Lack of amination in the case of *p*-isopropylanisole is apparently due to inactivation of the catalyst by coordination with the ether oxygen.

Data resulting from variation in the nature of the side chain proved to be informative. The satisfactory response from *p*-cyclohexyltoluene is in accord with prior studies with related systems. Thus, solvolysis at a tertiary position which is part of the cyclohexane structure proceeds at about the same rate as for the acyclic analog.[13] Previous investigations[14] on isomerization of the analogous pentylbenzenes serve as a useful basis for discussion of our findings with the *p*-tolylpentanes. 2-Phenylpentane (A), 3-phenylpentane (B), and 1-phenyl-2-methylbutane (C) exist in mobile equilibrium in contact with aluminum chloride at 80°. After 24 hr, the composition was 50% A, 35% C, and 15% B, with C being much more stable toward rearrangement. A and B were interconverted rapidly, whereas production of C from either of these isomers was slower. The mechanistic features, which apparently include a phenonium ion intermediate, have been treated in some detail by Roberts and Fonken.[14]

With 2-(*p*-tolyl)pentane (**1**) abstraction of hydride to form the *t*-benzyl cation (**2**) would be followed by combination with the nitrogenous nucleophile. The rather low yield (28%) can be rationalized by steric interfence involving the β-alkyl group. In the case of the 3 isomer (**3**), we believe that abstraction of the tertiary hydrogen, which is hindered by two substituents β to the reaction center, is less likely than removal of a secondary hydrogen with formation of **4**, since steric blocking is diminished through anchimeric assistance by the aryl group.[14] Subsequently, **4** is converted into **2**. The better yield (52%) of 2-(*p*-tolyl)-2-aminopentane from 3-(*p*-tolyl)pentane indicates that **2** is more readily obtained from **3** than from **1**. Support for these conclusions is derived from an examination of the neutral products. In the amination of **1** no other isomers were detected in the neutral fraction, whereas with **3** the isomers, **3**, **1**, and **5**, were present in the ratio 81:17:2. The presence of rearranged products points to the formation of carbonium ion intermediates which would be susceptible to capture by an appropriate nucleophile. Control experiments, in which trichloramine was omitted, also demonstrated that **3** is more prone to rearrange than **1**. Starting with **3** we obtained **3**, **1**, and **5** in the ratio 58:40:2; under the same conditions **1** is altered only to a slight extent, **1**:**3** = 95:5. These findings are in accord with earlier observations with related systems.[14]



The unsatisfactory behavior of *p*-ethyltoluene, in contrast to *p*-cymene, probably reflects the greater difficulty in forming a *sec*-benzylic carbonium ion on hydride abstraction.

Additional evidence for participation of positively charged intermediates in the amination sequence was

(13) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York, N. Y., 1962, p 96.

(14) R. M. Roberts and G. J. Fonken in "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1963, pp 839–843.

TABLE III

AMIDE DERIVATIVES OF *t*-BENZYLAMINES

Compound	Registry no.	Derivative	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % X[a]	Found, % C	Found, % H	Found, % N	Found, % X[a]
p-Ethylcumylamine	17790-51-1	Benzamide	155–156	$C_{18}H_{21}NO$	80.85	7.92	5.24		80.81	7.94	5.41	
p-Isopropylcumylamine	17790-52-2	Benzamide	162–164	$C_{19}H_{23}NO$	81.10	8.24	5.00		81.08	8.20	5.15	
p-*t*-Butylcumylamine	17790-53-3	Benzamide	199–201	$C_{20}H_{25}NO$	81.31	8.53	4.74		81.05	8.52	4.80	
p-Fluorocumylamine	17790-54-4	Acetamide	132.5–133.5	$C_{11}H_{14}FNO$	67.67	7.21	7.17	9.74	67.52	6.99	7.20	9.91
p-Chlorocumylamine	17790-55-5	Acetamide	173–174	$C_{11}H_{14}ClNO$	62.41	6.67	6.62	16.76	62.18	6.49	6.60	16.56
p-Bromocumylamine	17818-09-6	Acetamide	175.5–176	$C_{11}H_{14}BrNO$	51.60	5.47	5.47	31.21	51.63	5.57	5.60	31.07
3-Chloro-4-isopropylcumylamine	17790-56-6	Benzamide	178–179.5	$C_{19}H_{22}ClNO$	72.25	7.02	4.43	11.22	72.21	7.01	4.59	11.01
1-(*p*-Tolyl)cyclohexylamine	17790-57-7	Benzamide	151–152.5	$C_{20}H_{23}NO$	81.87	7.90	4.77		81.91	7.85	4.60	
2-(*p*-Tolyl)-2-pentylamine	17790-58-8	Benzamide	193–194	$C_{19}H_{23}NO$	81.10	8.24	5.00		80.93	8.27	4.96	
m-Chlorocumylamine	17790-59-9	Benzamide	192.5–194	$C_{18}H_{16}ClNO$	70.19	5.89	5.11	12.94	70.04	5.97	5.07	13.06

[a] X = halogen.

TABLE IV

RELATIVE RATES OF SIDE-CHAIN AMINATION

AH = *p*-YC_6H_4-$CH(CH_3)_2$	BH = *p*-ZC_6H_4-$CH(CH_3)_2$	Molar ratio	$[ANH_2]$:$[BNH_2]$	$k_{AH}:k_{BH}$
CH_3	Cl	1:8	0.766	6.13
Cl	$CH(CH_3)_2$	8:1	1.54	0.385[a]
CH_3	$CH(CH_3)_2$	1:2	0.395	1.58[a]
CH_3	$CH(CH_3)_2$	1:1	0.845	1.69[a]
CH_3	$CH(CH_3)_2$	1:1	0.620	1.24[a]
CH_3	$CH(CH_3)_2$	2:1	1.34	1.34[a–c]

[a] Per isopropyl group in the case of *p*-diisopropylbenzene. [b] $k_{CH_3}:k_{CH(CH_3)_2}$ = 1.46 (av); average deviation, 12%. [c] $k_{CH_3}:k_{CH(CH_3)_2}$ = 2.36, calculated from $(k_{CH_3}:k_{Cl}) \times (k_{Cl}:k_{CH(CH_3)_2})$.

provided by a study of relative rates (Table IV). The fairly large average deviation (12%) in the data can be explained in part by the limited occurrence of disproportionation reactions under the Lewis acid conditions. Our findings with *p*-$ZC_6H_4CH(CH_3)_2$, CH_3:$CH(CH_3)_2$:Cl = 1.46–2.36:1:0.38, fall in the same order as for solvolysis[11,12] of *para*-substituted cumyl chlorides in aqueous acetone at 0°, CH_3:$CH(CH_3)_2$:Cl = 1.48:1:0.012. Lack of precise agreement is not surprising since the media differ quite appreciably. In comparison, decomposition of *para*-substituted azocumenes, which exhibits the characteristic earmarks[15] of free-radical transformations, provided the indicated order,[16] Cl:CH_3:$CH(CH_3)_2$ = 2.72:1.46:1.

Finally, a summary of the synthetic aspects is appropriate. When the aromatic substrate is readily available by halogenation or Friedel–Crafts alkylation, *e.g.*, *p*-isopropyl-, *p*-*t*-butyl-, and *p*-halocumenes, the present technique comprises the most convenient route to the corresponding *t*-benzylamine. An additional advantage, as demonstrated with the halocumenes, is that the starting material need not be isomerically pure. Conceivably, the Ritter reaction might be the method of choice in certain cases from the standpoint of over-all yield based on the aromatic substrate. For example, Christol and coworkers[17] prepared α-methyl-α-isopropylbenzylamine in 60% yield from the requisite *t*-benzyl alcohol. However, α,α-dimethyl- and α,α-diethylbenzylamine were produced in low yield (5–10%) by the prior procedure. Conversion of alkylamines into various derivatives *via* the diazonium salt is discussed in review articles.[18]

Experimental Section[19]

Materials.—Most reagents were high purity commercial materials which were used as received. Purchased *p*-chlorocumene (Eastman, practical) and *p*-bromocumene (Columbia, practical) contained about 20% *ortho* isomer. Other required substrates, prepared as described, were checked for purity by glpc, and for the expected substitution pattern in the ir spectrum. 1,2-Dichloroethane was distilled from calcium hydride.

Analytical Procedures.—Infrared spectra of the starting materials and products were obtained with a Beckman 1R-5A or 1R-8 spectrophotometer on neat samples, or dilute solutions in

(15) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968).

(16) P. Kovacic, R. R. Flynn, J. F. Gormish, A. H. Kappelman, and J. R. Shelton, unpublished data.

(17) H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 2319 (1961).

(18) R. J. Baumgarten, *J. Chem. Educ.*, **43**, 398 (1966); S. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1967).

(19) Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected.

carbon disulfide or carbon tetrachloride. The amine products gave the expected pattern in the aromatic and amine regions. Nuclear magnetic resonance spectra (Table II) were obtained with a Varian A-60 instrument and on the same solutions as in the ir study. When necessary, samples were purified by glpc. Gas chromatographic work was carried out with a Matronic instrument on the indicated columns: (A) 8 ft by 0.25 in., Carbowax 20M (20%) on Chromosorb W (30–60 mesh) (5% KOH); (B) same as column A except 2 ft in length; (C) 6 ft by 0.25 in., Apiezon L (14%) on Chromosorb P (40–60 mesh) (5% NaOH); (D) 6 ft by 0.25 in., SF-96 (20%) on acid-washed Chromosorb P (30–60 mesh).

Preparation of Trichloramine Solutions.—A published procedure[20] (method B) was used with 1,2-dichloroethane as solvent. Analysis for positive halogen was performed by an iodometric method in acetic acid.[20] Caution: exercise the necessary precautions when working with N-halamines. Excess trichloramine can be destroyed by slow addition with stirring into a cold solution of sodium metabisulfite.

Amination with Trichloramine–Aluminum Chloride–*t*-Butyl Bromide.—A published procedure (B2)[7] was used except for *p*-fluoro- and *p*-chlorocumene, in which cases the temperature was increased to 25° after trichloramine addition was complete. The results are listed in Table I. Microanalyses were performed on samples collected by glpc.

Some of the substrates produced a mixture of bases in low yield [substrate (% crude yield, number of basic components)]: 4-isopropyl-*m*-xylene (32, 7); 5-isopropyl-*m*-xylene (18, 6); 2-isopropyl-*p*-xylene (20, 5); 2,5-diisopropyl-*p*-xylene (20, 4); isopropylmesitylene (24, 9); *p*-ethyltoluene (11, 10); 1,3,5-triisopropylbenzene (3, 3); *p*-isopropylanisole (0); 4-chloro-4′-isopropylbiphenyl (26, 2; crystallization of the crude product from heptane resulted in a 50% recovery of material, mp 152–185°, containing two components by glpc analysis); cumene[21] (39, 4; *p*-isopropylcumylamine, 66%; cumylamine, 14%; *m*-cumidine, 12%; unidentified, 8%).

The neutral layer from amination of *p*-cymene contained chlorination products in the ratio, *ar*-chloro-*p*-cymene/*p*-cymene = 0.41 (theory, 0.48). Analysis was carried out by comparison with an authentic mixture of *ar*-chloro-*p*-cymene (80% 2 isomer, 20% 3 isomer; glpc column D).

The experiments in which part of the excess *p*-cymene was replaced by *p*-xylene or mesitylene are described in Table V.

TABLE V

EFFECT OF AROMATIC ADDITIVES ON *p*-CYMENE AMINATION

p-Cymene, mol	Additive	Mol	8-Amino-*p*-cymene— Yield, %	Purity, %
0.5	*p*-Xylene	0.5	61	94[a]
0.3	*p*-Xylene	0.7	58	94[a]
0.2	*p*-Xylene	0.8	60	95[a]
0.1	*p*-Xylene	0.9	34	86[a]
0.5	Mesitylene	0.5	40	78[b]

[a] The remainder was mainly 2,5-dimethylanilme along with small amounts of unidentified material. [b] The remainder was unknown material.

Glpc determinations of the *p*-tolylpentanes were made with column C at 150°.

Competitive Aminations.—A mixture of the two substrates (0.2 mol total) in 100 ml of 1,2-dichloroethane was cooled to 0°, and aluminum chloride (5.32 g, 0.04 mol) was added in one portion followed immediately by *t*-butyl bromide (6.7 ml, 0.06 mol). At this point, the reaction mixture became homogeneous except for a very small amount of solid, presumably undissolved aluminum chloride. Then, while a nitrogen purge was maintained, trichloramine solution (40 ml, 0.02 mol) was added dropwise during 10 min at 0 to 5°. After an additional 5 min, the reaction mixture was poured over ice–hydrochloric acid and worked up. The amine products were analyzed by glpc (column A, 190°) with calibration by standard mixtures of pure materials (Table IV).

Examination of the neutral layer after reaction revealed the presence of about 3% disproportionation products (based on the aromatic substrate): cumene from *p*-diisopropylbenzene and toluene from *p*-cymene. No isomerization products were found.

Dealkylation of Alkylcumylamines.—Dry hydrogen chloride was bubbled through a mixture of *p*-isopropylcumylamine (4.9 g, 0.027 mol), toluene (58 ml) and anhydrous aluminum chloride (18.5 g, 0.138 mol) during 0.5 hr. After 25 hr of stirring at room temperature addition to ice–hydrochloric acid and subsequent work-up gave cumylamine (75% yield), bp 62–64° (5mm). The ir spectrum was identical with that of material prepared by a literature method.[22] The same procedure was used with *p*-t-butylcumylamine to give cumylamine (70% yield), and with 3-chloro-4-isopropylcumylamine to form *m*-chlorocumylamine (96% yield), bp 101–102° (7.5–7.8 mm). The ir spectrum showed characteristic absorption at 785 and 695 cm^{-1} in the *meta* region.

Anal. Calcd for $C_9H_{12}ClN$: C, 63.71; H, 7.13; N, 8.26; Cl, 20.89. Found: C, 63.56; H, 7.33; N, 8.38; Cl, 21.16.

Amide Derivatives.[23]—Benzamides were prepared by treating the amine in pyridine with benzoyl chloride. Acetamides were formed with acetic anhydride (Table III).

***p*-*t*-Butylcumene.**[24]—Cumene was alkylated with *t*-butyl alcohol and 85% sulfuric acid according to a literature procedure.[25]

Isopropylmesitylene.—To a cold (5–10°) mixture of isopropyl alcohol (47 ml, 0.615 mol) and mesitylene (416 ml, 3 mol) was added a cooled mixture of concentrated sulfuric acid (500 ml) and water (110 ml) during 3 hr. After being stirred at 24° for 19 hr, the mixture was worked up yielding 79 g (79%) of a fraction boiling at 82–84° (5.4–5.6 mm) [lit. bp 82.5–83.5° (5.5 mm),[26] 220° [27]]. The ir spectrum was identical with that of authentic material prepared by an alternate route.[27,28]

***p*-Ethylcumene.**—Attempts to prepare this compound by alkylation[29] gave a product which contained substantial amounts of other isomers. Better quality material was obtained by the indicated procedure. Cumene was acylated by an established technique[30] to give *p*-isopropylacetophenone from which *p*-ethylcumene was synthesized in 77% yield by a modified Wolff-Kishner reduction:[31] bp 194–196° (742 mm) [lit.[29] bp 193° (744 mm)].

Isopropyl-*p*-xylene.—To a mixture of *p*-xylene (375 ml) and isopropyl alcohol (50 ml) at 15° was added cold 85% sulfuric acid (250 ml) during 2 hr. After 20 hr at 23–25°, work-up provided a 56% yield of product, bp 196–199° (745 mm) [lit. bp 111.9–113.4° (60 mm),[26] 195–196° [27]].

5-Isopropyl-*m*-xylene.—This preparation is described by Nightingale and Carton.[32]

4-Isopropyl-*m*-xylene.—Since an attempt to prepare this material by a literature route[32] gave a mixture of products, an alternate multistep procedure was used. Acylation of *m*-xylene in the conventional manner[30] yielded 2,4-dimethylacetophenone,[33] bp 97–99° (8.5 mm) (88% yield). The ketone together with an equimolar amount of methylmagnesium iodide produced 2,4-dimethylcumyl alcohol. Dehydration was effected by the method of Hibbert.[34] A crystal of iodine was added to the crude alcohol and distillation at atmospheric pressure was continued until the calculated amount of water was collected. The residue was combined with the distillate; the organic phase was separated, washed with a dilute solution of sodium thiosulfate, and further worked up to give 2,4-dimethyl-α-methylstyrene, bp 71–75° (7.4–8 mm) (71% yield based on the ketone). Subsequently,

(20) P. Kovacic, C. T. Goralski, J. J. Hiller, Jr., J. A. Levisky, and R. M. Lange, *J. Amer. Chem. Soc.*, **87**, 1262 (1965).

(21) In the absence of *t*-butyl bromide, a 27% yield of *m*-cumidine (85% pure) was obtained in contrast to the 53% yield previously reported (see ref 8).

(22) A. C. Cope, T. T. Foster, and P. H. Towle, *ibid.*, **71**, 3929 (1949).

(23) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 226.

(24) We wish to thank Mr. J. T. Uchic for carrying out this preparation.

(25) G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **17**, 1102 (1952).

(26) B. V. Ioffe and T. H. Yang, *Zh. Obshch. Khim.*, **33**, 2196 (1963).

(27) R. M. Roberts and D. Shiengthong, *J. Amer. Chem. Soc.*, **86**, 2851 (1964).

(28) We wish to thank Professor R. M. Roberts for kindly supplying the spectrum of isopropylmesitylene.

(29) C. E. Welsh and G. F. Hennion, *ibid.*, **63**, 2603 (1941).

(30) C. F. H. Allen in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 3.

(31) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

(32) D. Nightingale and B. Carton, Jr., *ibid.*, **62**, 280 (1940).

(33) G. Marino and H. C. Brown, *ibid.*, **81**, 5929 (1959).

(34) H. Hibbert, *ibid.*, **37**, 1748 (1915).

it was found that addition of about 1 g of hydroquinone to the crude alcohol and washing the dehydrated product with dilute sodium hydroxide improved the yield somewhat, while decreasing the amount of high-boiling residue. The olefin (124 g) was hydrogenated on a Parr low-pressure apparatus with 10% palladium on charcoal (0.5 g) to yield 4-isopropyl-*m*-xylene, bp 72–75° (7–7.4 mm) (81% yield).

p-Cyclohexyltoluene.—A modification of a published procedure was used[35] (dehydration was accomplished with iodine as described in the preceding section).

p-Chlorocumene.—Synthesis from *p*-chloroacetophenone was accomplished by an adaptation of the method of Benkeser and coworkers[36] (dehydration was performed with iodine; see 4-isopropyl-*m*-xylene).

3-(*p*-Tolyl)pentane.—The sequence involved reaction of 3-pentanone with the Grignard reagent from *p*-bromotoluene, dehydration of the carbinol with iodine (see 4-isopropyl-*m*-xylene), and subsequent hydrogenation of the olefin. The product boiled at 83–85° (8.5 mm) (lit.[37] bp 205°).

2-(*p*-Tolyl)pentane.—The method was identical with that for 3-(*p*-tolyl)pentane, except that 2-pentanone was used. The intermediate alcohol was collected by glpc.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.92; H, 10.08.

Examination of the nmr spectrum revealed the indicated signals: ArH, δ 6.9–7.35 (two doublets); ArCH, 2.29 (singlet); OH, 2.03 (broad singlet); C–CH, 1.43 (singlet superimposed on a complex pattern at 0.78–1.67). The end product was obtained in 60% over-all yield, bp 80–83° (7.5–7.8 mm) [lit.[38] bp 70.5–72° (4 mm)].

1-(*p*-Tolyl)-2-methylbutane.—The synthesis was accomplished from α-chloro-*p*-xylene and 2-butanone by means of a slightly modified published procedure.[39] Dehydration of the intermediate 1-(*p*-tolyl)-2-methyl-2-butanol with boric acid was incomplete after 17 hr at reflux. The olefin was isolated by distillation, bp 94–96° (7.5 mm) [lit.[39] bp 102–104° (13 mm)], and then hydrogenated with palladium catalyst to give the desired material, bp 90–91° (7.8 mm) [lit.[39] bp 92.5° (12.5 mm)].

This material was used for characterization (glpc retention time) of the corresponding substance present in the neutral layer from amination of 3-(*p*-tolyl)pentane.

2-Chloro-1,4-diisopropylbenzene.—Chlorine was passed into a solution of *p*-diisopropylbenzene in carbon tetrachloride at 10–15° in the presence of a small amount of powdered iron catalyst. The reaction was terminated when about 90% of the hydrocarbon was consumed (glpc analysis). Work-up, according to a published procedure[40] for bromination of triethylbenzene, afforded the desired compound in 51% yield, bp 100–104° (6.9 mm) [lit.[41] (impure material) bp 131–135° (35 mm)]. Our product contained about 5% impurity.

4-Chloro-4′-isopropylbiphenyl.—Methylmagnesium iodide was prepared from magnesium (8.75 g, 0.36 mol) and methyl iodide (22.42 ml, 0.36 mol) in 400 ml of anhydrous ether. Then a solution of 4-chloro-4′-acetylbiphenyl[42] (81 g, 0.351 mol) in 250 ml of warm benzene was added during 1 hr. After 0.5 hr at reflux, the mixture was poured over dilute hydrochloric acid with stirring. The solid which separated together with that obtained by evaporation of the organic liquid phase was recrystallized from 95% ethanol to give 70.3 g (81% yield) of the carbinol, mp 130–133° (not further purified).

The alcohol was dissolved in benzene, and gaseous hydrogen chloride was passed into the solution for 0.5 hr. After work-up and removal of the solvent, the crude product was dissolved in ligroin. Filtration and solvent evaporation gave the chloride, mp 98–100° dec (not further purified). A mixture of the chloride with excess pyridine was refluxed for 10 min. The hot solution was poured into water, and the resulting solid was collected by filtration. Purification, including repeated recrystallization from heptane, afforded 4-chloro-4′-isopropenylbiphenyl, mp 147–148°.

Anal. Calcd for $C_{15}H_{13}Cl$: 78.77; H, 5.73; Cl, 15.50. Found: C, 78.60; H, 5.75; Cl, 15.36.

Hydrogenation was accomplished on small portions of the olefin (10–15 g) in benzene (350 ml) with 10% palladium on charcoal (0.1 g). Work-up gave 4-chloro-4′-isopropylbiphenyl (88% yield from the chloride), mp 135–137° from ethanol.

Anal. Calcd for $C_{15}H_{15}Cl$: C, 78.08; H, 6.55; Cl, 15.36. Found: C, 77.85; H, 6.40; Cl, 15.36.

p-Isopropylanisole.—Alkylation of *p*-isopropylphenol,[43] with methyl sulfate was carried out according to a literature procedure.[44]

N,N-Dichloro-8-amino-*p*-cymene.—To a stirred suspension of "HTH" (70% calcium hypochlorite, 6.21 g, 0.03 mol) in methylene chloride (30 ml) and water (20 ml) cooled to −5° was added over a period of 15 min a solution of 8-amino-*p*-cymene (4 g, 0.027 mol) in water (100 ml) and concentrated hydrochloric acid (33 ml, 0.04 mol). The mixture was stirred at −10° for 15 min; the organic layer was separated, washed three times with water, and then dried. Iodometric titration indicated a 50% yield. No N–H band[45] was present in the ir spectrum.

2-Chloro-8-amino-*p*-cymene. Preparation.—A published procedure was followed.[9]

Reductive Deamination.—The method[46] of Nickon and Hill yielded a mixture. One component (20%) was 2-chloro-*p*-cymene which was identified by glpc comparison with authentic material[9] prepared by iodine-catalyzed chlorination of *p*-cymene. The major product (80%), apparently 3-chloro-4-methyl-α-methylstyrene, gave a positive test with bromine.

Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.11; H, 6.60; Cl, 21.29. Found: C, 72.01; H, 6.40; Cl, 21.42.

The nmr spectrum possessed the indicated characteristics: ArH, δ 6.53–6.81 (multiplet); C=CH, 4.48 and 4.76 (singlets); ArCH, 1.92 (singlet); C=C—CH, 1.66 (singlet).

Registry No.—Trichloramine, 10025-85-1; aluminum chloride, 7446-70-0; *t*-butyl bromide, 507-19-7; 4-chloro-4′-isopropenylbiphenyl, 17790-60-2; 4-chloro-4′-isopropylbiphenyl, 17790-61-3; 3-chloro-4-methyl-α-methylstyrene, 17790-62-4.

Acknowledgment.—We are grateful to the National Institutes of Health, Public Health Service, and the Petroleum Research Fund, administered by the American Chemical Society, for principal support of this work.

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The 4-(Methylthio)phenyl and 4-(Methylsulfonyl)phenyl Esters in the Preparation of Peptides and Polypeptides.[1] Synthesis of the Protected Heptapeptide (A_{82}–A_{88}) of Bovine Chymotrypsinogen A

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The syntheses of some N-*t*-butyloxycarbonyl-L-amino acid pentachlorophenyl esters, prepared for facile peptide synthesis, are described. Their use is illustrated by the synthesis of the protected tripeptide N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester which corresponds to the sequence (A_{82}–A_{84}) of bovine chymotrypsinogen A. Oxidation of this tripeptide derivative yielded the protected tripeptide 4-(methylsulfonyl)phenyl activated ester without rupture of the protecting groups or peptide bonds. By a similar method the protected tetrapeptide L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)-phenyl ester hydrochloride, sequence A_{85}–A_{88} of the same material, was prepared. The protected heptapeptide sequence (A_{82}–A_{88}) of bovine chymotrypsinogen A, N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester, was obtained by coupling the protected tripeptide (A_{82}–A_{84}) with the tetrapeptide derivative (A_{85}–A_{88}) through the 4-(methylsulfonyl)-phenyl activated ester.

The use of a protective ester which can be converted into an ester activated toward aminolysis should be of great utility in peptide and polypeptide synthesis. For this purpose we have suggested[1] the use of the 4-(methylthio)phenyl ester (MTP) as a carboxyl protecting group which can be easily converted into the 4-(methylsulfonyl)phenyl activated ester (MSO_2P). The MTP esters have the following important properties: they can be easily prepared by the N,N′-dicyclohexylcarbodiimide (DCC) method;[3] the N-carbobenzoxy and N-t-butyloxycarbonyl protecting groups can be easily removed in their presence; and mild oxidation, even in the presence of the N-carbobenzoxy and *t*-butyl ester protecting groups, yields the activated MSO_2P esters.

To extend the utility of this method for peptide synthesis, it was necessary to see if the conversion of the protective MTP ester into the MSO_2P activated ester could be achieved on a larger peptide, and also to utilize this activated ester to couple blocks of peptides together. To this end the synthesis of the protected heptapeptide N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester (**1**),

Z-Lys-Leu-Lys-Ile-Ala-Lys-Val-OMTP
Z Z Z

1

corresponding to the sequence A_{82}–A_{88} of bovine chymotrypsinogen A,[4] is described.

The approach used was to prepare the protected tripeptide (A_{82}–A_{84}), N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylsulfonyl)-phenyl ester (**2**) and couple it to the tetrapeptide derivative (A_{85}–A_{88}), L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester hydrochloride (**3**). For the facile synthesis of both, the protected tripeptide and tetrapeptide blocks of N-*t*-butyloxycarbonyl-L-amino acid pentachlorophenyl esters were used.[5] They are easily prepared from the N-*t*-butyloxycarbonyl-L-amino acid and pentachlorophenol by the use of N,N′-dicyclohexylcarbodiimide.[3] The resulting esters are far more stable than the corresponding N-hydroxysuccinimide esters and are of higher melting point than the *p*-nitrophenyl esters, both of which have been used for rapid peptide synthesis.[6,7] The physical constants of a number of N-*t*-butyloxycarbonyl-L-amino acid pentachlorophenyl esters are given in the Experimental Section.

N-*t*-Butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester (**4**) was prepared in good yield from N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine and 4-(methylthio)phenol by condensation with N,N′-dicyclohexylcarbodiimide. Treatment of **4** with 1 *N* hydrogen chloride in glacial acetic acid afforded ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester hydrochloride (**5**). N-*t*-Butyloxycarbonyl-L-leucine pentachlorophenyl ester was coupled to **5** in methylene chloride to yield the protected dipeptide N-*t*-butyloxycarbonyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester (**6**). The N-*t*-butyloxycarbonyl protecting group was removed from **6** by treatment with 1 *N* HCl–acetic acid to give L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester hydrochloride (**7**). N,N′-Dicarbobenzoxy-L-lysine pentachlorophenyl ester[5] was coupled to **7** to yield the blocked tripeptide N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester (**8**). Oxidation of **8** using 30% hydrogen peroxide in glacial acetic acid for a period of 12 hr gave, without appreciable decomposition, the protected tripeptide activated ester N,N′-dicarbobenzoxy-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylsulfonyl)phenyl ester (**2**) in good yield. For the synthesis of the protected tetrapeptide, 4-(methylthio)-phenyl ester hydrochloride **3**, N-*t*-butyloxycarbonyl-L-valine MTP ester (**9**) was prepared by the DCC condensation of N-*t*-butyloxycarbonyl-L-valine and 4-(methylthio)phenol. The blocking N-*t*-butyloxycarbonyl group was removed by treatment with 1 *N*

(1) This is the second article in this series. See B. J. Johnson and P. M. Jacobs, *Chem. Commun.*, 73 (1968), for previous paper.

(2) To whom any correspondence should be sent.

(3) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).

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(7) M. Bodanszky, M. A. Ondetti, S. D. Levine, and N. J. Williams, *ibid.*, **89**, 6753 (1967).

hydrogen chloride in glacial acetic acid to give L-valine MTP ester hydrochloride (**10**) in good yield. The hydrochloride **10** was coupled to N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine pentachlorophenyl ester to give the blocked dipeptide N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysyl-L-valine MTP ester (**11**). Treatment of **11** with 1 *N* HCl–acetic acid gave ε-N-carbobenzoxy-L-lysyl-L-valine MTP ester hydrochloride (**12**). The protected dipeptide was lengthened by treating it first with N-*t*-butyloxycarbonyl-L-alanine pentachlorophenyl ester to give N-*t*-butyloxycarbonyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine MTP ester (**13**) and then 1 *N* HCl–glacial acetic acid to produce L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine MTP ester hydrochloride (**14**). Further reaction of **14** with N-*t*-butyloxycarbonyl-L-isoleucine pentachlorophenyl ester produced the blocked tetrapeptide N-*t*-butyloxycarbonyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine MTP ester (**15**). Finally, reaction of **15** with 1 *N* HCl–glacial acetic acid gave the protected tetrapeptide hydrochloride, L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester hydrochloride (**3**), in good yield.

To prepare the protected heptapeptide corresponding to the sequence A_{82}–A_{88} of bovine chymotrypsinogen A, N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine MTP ester (**1**), it was necessary to couple the blocked tetrapeptide hydrochloride **3** to the protected tripeptide N,N′-dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine MSO_2P ester (**2**). With other methods of preparing peptides, the presence of salts of tertiary amines has been shown to increase the degree of racemization of the amino acid residue carrying the activated moiety.[8] Thus to minimize this possibility of racemization occurring the free amine of **3** was added to the protected tripeptide **2** to give the fully protected heptapeptide **1**. The optical purity of the protected heptapeptide was calculated to be 97.1 ± 5% by determining the optical activity of the acid hydrolysate and comparing it with that of a control.

It would appear from this work that the N-*t*-butyloxycarbonyl derivatives of amino acid pentachlorophenyl esters are useful intermediates for the facile synthesis of peptide blocks. It has also been shown that the protective 4-(methylthio)phenyl ester can be converted into the activated 4-(methylsulfonyl)phenyl ester without decomposition of the fully protected tripeptide to which it was attached. Also, the 4-(methylsulfonyl)phenyl ester is of use for the coupling of blocks of peptides together without appreciable racemization occurring under the coupling conditions used. It is anticipated that this method of activation will be of little use for peptides which include the amino acid residues, methionine, cysteine, cystine, and possibly tryptophan.

Experimental Section[9]

General Procedure for the Preparation of N-*t*-Butyloxycarbonyl-L-amino Acid Pentachlorophenyl Esters.—The general procedure of preparation of these esters is illustrated by the preparation of **N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine pentachlorophenyl ester**. To a solution of N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine[10] (11.5 g, 30.3 mmol) and pentachlorophenol (8.06 g, 30.3 mmol) in methylene chloride (100 ml) was added dicyclohexylcarbodiimide (6.86 g, 33.3 mmol). The mixture was stirred at room temperature overnight. The solid N,N′-dicyclohexylurea was filtered off, and the filtrate was concentrated under reduced pressure. The solid product was dissolved in ethyl acetate (300 ml), and the insoluble urea was filtered off. The filtrate was washed with 10% citric acid solution (100 ml), water (100 ml), 1 *N* sodium hydrogen carbonate solution (100 ml), and water (two 100-ml portions). The solution was dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the solid pentachlorophenyl ester. It was crystallized from methanol (yield 14.0 g, 73.5%), mp 140–141°. Further recrystallization from ethyl acetate–hexane increased the sharpness of the melting point to 141°, $[\alpha]^{29}D$ −15.0° (*c* 4.99, chloroform).

Anal. Calcd for $C_{25}H_{27}Cl_5N_2O_6$: C, 47.8; H, 4.3; N, 4.5. Found: C, 47.7; H, 4.5; N, 4.7.

The following compounds were also prepared by the same method: *t*-butyloxycarbonyl-L-alanine pentachlorophenyl ester [mp 166°, $[\alpha]^{25}D$ −22.2° (*c* 5.12, chloroform) (*Anal.* Calcd for $C_{14}H_{14}Cl_5NO_4$: C, 38.45; H, 3.2; Cl, 4.05. Found: C, 38.7; H, 3.4; Cl, 40.3)]; *t*-butyloxycarbonylglycine pentachlorophenyl ester [mp 142° (*Anal.* Calcd for $C_{13}H_{12}Cl_5NO_4$: C, 36.8; H, 3.0; Cl, 41.8. Found: C, 37.0; H, 2.9; Cl, 42.0)]; *t*-butyloxycarbonyl-L-isoleucine pentachlorophenyl ester [mp 119°, $[\alpha]^{29}D$ −28.0° (*c* 5.18, ethyl acetate) (*Anal.* Calcd for $C_{17}H_{20}Cl_5NO_4$: C, 42.6; H, 4.2; Cl, 36.95. Found: C, 42.6; H, 4.25; Cl, 37.05)]; *t*-butyloxycarbonyl-L-leucine pentachlorophenyl ester[11] [mp 111°, $[\alpha]^{29}D$ −35.3° (c 4.95, ethyl acetate) (*Anal.* Calcd for $C_{17}H_{20}Cl_5NO_4$: C, 42.6; H, 4.2; Cl, 36.95. Found: C, 42.6; H, 4.25; Cl, 37.05)]; *t*-butyloxycarbonyl-L-phenylalanine pentachlorophenyl ester[11] [mp 148°, $[\alpha]^{29}D$ −47.1° (*c* 4.82, ethyl acetate) (*Anal.* Calcd for $C_{20}H_{18}Cl_5NO_4$: C, 46.8; H, 3.5; Cl, 34.5. Found: C, 46.8; H, 3.4; Cl, 34.5)]; *t*-butyloxycarbonyl-O-benzyl-L-tyrosine pentachlorophenyl ester [mp 142°, $[\alpha]^{29}D$ −26.8° (*c* 4.98, chloroform) (*Anal.* Calcd for $C_{27}H_{24}Cl_5NO_5$: C, 52.3; H, 3.9; Cl, 28.6. Found: C, 52.25; H, 3.5; Cl, 28.65)]; *t*-butyloxycarbonyl-L-valine[11] pentachlorophenyl ester [mp 126°, $[\alpha]^{29}D$ −38.1° (*c* 5.00, ethyl acetate) (*Anal.* Calcd for $C_{16}H_{18}Cl_5NO_4$: C, 41.3; H, 3.9; Cl, 38.1. Found: C, 41.5; H, 4.0; Cl, 38.4)]; N,N′-di-*t*-butyloxycarbonyl-L-lysine pentachlorophenyl ester [mp 148°, $[\alpha]^{25}D$ −20.6° (*c* 4.6, dimethylformamide) (*Anal.* Calcd for $C_{22}H_{29}Cl_5N_2O_6$: C, 44.4; H, 4.9; Cl, 29.8. Found: C, 44.7; H, 4.9; Cl, 29.8)].

N-*t*-Butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine 4-(Methylthio)phenyl Ester (4).—To a solution of N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine (9.0 g, 0.0237 mol) in methylene chloride (150 ml) was added 6.12 g of DCC; after stirring for 5 min at room temperature 3.32 g of 4-(methylthio)phenol was added. The reaction mixture was stirred overnight. The precipitated urea was filtered off, and the solvent was evaporated to give an oil. The oil was dissolved in ethyl acetate and washed with sodium bicarbonate solution (100 ml) and water (two 150-ml portions), dried (Na_2SO_4), and evaporated under reduced pressure to give a solid. This was recrystallized from ethyl acetate–hexane to yield the 4-(methylthio)phenyl ester (10.1 g, 85%): mp 96–97°; $[\alpha]^{25}D$ −21.6° (*c* 2.4, dimethylformamide).

Anal. Calcd for $C_{26}H_{34}N_2O_6S$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.2; H, 6.9; N, 5.5.

ε-N-Carbobenzoxy-L-lysine 4-(Methylthio)phenyl Ester Hydrochloride (5).—N-*t*-Butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester (9.5 g, 0.0189 mol) was added to 57 ml of 1 *N* hydrogen chloride in glacial acetic acid and left at room temperature for 30 min. The hydrochloride was precipitated by the addition of anhydrous ether and filtered off. It was recrystallized from methanol–ether to yield 7.9 g (95%): mp 147°; $[\alpha]^{25}D$ +18.0° (c 4.8, methanol).

Anal. Calcd for $C_{21}H_{27}ClN_2O_4S$: C, 57.4; H, 6.2; N, 6.4. Found: C, 57.1; H, 6.3; N, 6.1.

N-*t*-Butyloxycarbonyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(Methylthio)phenyl Ester (6).—ε-N-Carbobenzoxy-L-lysine 4-(methylthio)-phenyl ester hydrochloride (3.65 g, 0.008 mol) was added to a solution of N-*t*-butyloxycarbonyl-L-leucine pentachlo-

(8) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964).

(9) All melting points are uncorrected. Analyses were carried out by either Dr. S. N. Nagy of Massachusetts Institute of Technology, Cambridge, Mass., or the Galbraith Laboratories, Inc., Knoxville, Tenn. Optical rotations were taken on a Carl Zeiss precision polarimeter. Thin layer chromatography employed Silicar TLC-7G as support, methanol–chloroform (1:9) as solvent, and iodine for detection purposes.

(10) R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959).

(11) A. J. Corcoran, this laboratory.

rophenyl ester (4.0 g, 0.008 mol) in methylene chloride (50 ml) containing 0.85 g of triethylamine. The solution was stirred at room temperature overnight and then evaporated under reduced pressure to give a solid. This solid was suspended in ethyl acetate and washed with 10% citric acid solution (50 ml) and water (three 200-ml portions), dried (Na_2SO_4), and evaporated to yield a solid. Recrystallization of this crude material from ethyl acetate–hexane yielded the dipeptide 4-(methylthio)-phenyl ester (3.9 g, 77%): mp 87°; $[\alpha]^{24}D$ −21.3° (*c* 6.7, dimethylformamide).

Anal. Calcd for $C_{32}H_{45}N_3O_7S$: C, 62.4; H, 7.4; N, 6.8. Found: C, 62.3; H, 7.55; N, 6.6.

L-Leucyl-ε-N-Carbobenzoxy-L-lysine 4-(Methylthio)phenyl Ester Hydrochloride (7).—N-*t*-Butyloxycarbonyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester (3.5 g, 0.00568 mol) was added to 17 ml of 1 *N* hydrogen chloride in glacial acetic acid and left at room temperature for 35 min. Addition of anhydrous ether to the reaction mixture precipitated the hydrochloride (2.9 g, 92%): mp 185°; $[\alpha]^{24}D$ −7.7° (*c* 5, methanol).

Anal. Calcd for $C_{27}H_{38}ClN_3O_5S$: C, 58.7; H, 6.9; N, 7.6. Found: C, 58.9; H, 7.1; N, 7.6.

N,N′-Dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(Methylthio)phenyl Ester (8).—To a solution of N,N′-dicarbobenzoxy-L-lysine pentachlorophenyl ester[5] (3.03 g 0.00457 mol) in dimethylformamide (20 ml) containing 0.5 g of triethylamine was added 2.5 g (0.00453 mol) of L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthio)phenyl ester hydrochloride. The mixture was stirred overnight at room temperature and then poured into 300 ml of water. The precipitated material was filtered off, dried, and crystallized from ethyl acetate–ether to yield the protected tripeptide (2.9 g, 70%): mp 153°; $[\alpha]^{25}D$ −34.5° (*c* 5.8, dimethylformamide).

Anal. Calcd for $C_{49}H_{61}N_5O_{10}S$: C, 64.5; H, 6.7; N, 7.7. Found: C, 64.5; H, 6.8; N, 7.5.

N,N′-Dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(Methylsulfonyl)phenyl Ester (2).—To N,N′-Dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylthiophenyl ester (2.5 g, 0.00274 mol) dissolved in 100 ml of glacial acetic acid was added 10 ml of 30% hydrogen peroxide solution. The mixture was left at room temperature for 12 hr and then evaporated under reduced pressure to a small volume. Addition of water afforded a white precipitate, which was filtered off, dried, and chromatographed on a column of silicic acid (pH 7) using chloroform as eluent. The major fraction was crystallized from ethyl acetate–ether to give the protected tripeptide active ester (2.0 g, 77%): mp 179°; $[\alpha]^{24}D$ −33.0° (*c* 3.8, dimethylformamide); R_f 0.69.

Anal. Calcd for $C_{49}H_{61}N_5O_{12}S$: C, 62.3; H, 6.5; N, 7.4. Found: C, 62.2; H, 6.8; N, 7.4.

N-*t*-Butyloxycarbonyl-L-valine 4-(Methylthio)phenyl Ester (9).—To a solution of N-*t*-butyloxycarbonyl-L-valine (8.7 g, 0.04 mol) in 100 ml of methylene chloride was added 8.3 g of DCC; solution was stirred at room temperature for 10 min. 4-(Methylthio)phenol (5.6 g) was added to the solution, and stirring was continued overnight. The precipitated urea was filtered off, and the filtrate evaporated to give an oil. The oil was dissolved in ethyl acetate, washed with sodium bicarbonate solution and water, and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave an oil. This oil was chromatographed on a column of Silicar CC-7 (pH 7) using chloroform as the eluent. The major fraction was collected and evaporated to give the 4-(methylthio)phenyl ester as an oil (8.5 g, 62.5%): $[\alpha]^{25}D$ −6.1° (*c* 8.2, in dimethylformamide); ν_{max}^{Nujol} 1755 cm^{-1} (C=O ester).

Anal. Calcd for $C_{17}H_{25}NO_4S$: C, 60.2; H, 7.4. Found: C, 60.35; H, 7.7.

L-Valine 4-(Methylthio)phenyl Ester Hydrochloride (10).—To N-*t*-butyloxycarbonyl-L-valine 4-(methylthio)phenyl ester (8.6 g, 0.0254 mol) was added 76 ml of 1 *N* hydrogen chloride in glacial acetic acid. The solution was left at room temperature for 30 min and then poured into anhydrous ether. The precipitated hydrochloride was collected and crystallized from methanol–ether to give 5.5 g (79%): mp 220° dec; $[\alpha]^{28}D$ +18.9° (*c* 1.3, methanol).

Anal. Calcd for $C_{12}H_{18}ClNO_2S$: C, 52.3; H, 6.6; S, 11.6. Found: C, 52.3; H, 6.75; S, 11.8.

N-*t*-Butyloxycarbonyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)phenyl Ester (11).—To a solution of 6.29 g (0.01 mol) of N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine pentachlorophenyl ester and 2.76 g (0.01 mol) of L-valine 4-(methylthio)phenyl ester hydrochloride in 50 ml of methylene chloride was added 1 g of triethylamine. The solution was stirred overnight at room temperature. The solvent was evaporated, and the residue was suspended in ethyl acetate and washed with 10% citric acid and then water. The organic extracts were dried (Na_2SO_4) and then evaporated to give a solid. This material was crystallized from ethyl acetate–hexane to give 5.1 g (85%) of the protected dipeptide: mp 93°; $[\alpha]^{25}D$ −5.3° (*c* 1.1, methanol); R_f 0.78.

Anal. Calcd for $C_{31}H_{43}N_3O_7S$: C, 61.85; H, 7.2; N, 7.0. Found: C, 62.1; H, 7.3; N, 6.9.

ε-N-Carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)phenyl Ester Hydrochloride (12).—To 3.0 g (0.005 mol) of N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)-phenyl ester was added 14 ml of 1 *N* hydrogen chloride in glacial acetic acid, and the solution was left at room temperature for 30 min. Addition of dry ether precipitated the hydrochloride which was recrystallized from methanol–ether to yield 2.5 g (93%) of pure product: mp 145°; $[\alpha]^{26}D$ −8.6° (*c* 4.1, methanol).

Anal. Calcd for $C_{26}H_{36}ClN_3O_5S$: C, 58.0; H, 6.7; N, 7.8. Found: C, 57.8; H, 7.0; N, 7.75.

N-*t*-Butyloxycarbonyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)phenyl Ester (13).—To N-*t*-butyloxycarbonyl-L-alanine pentachlorophenyl ester (1.63 g, 0.00305 mol) dissolved in 50 ml of methylene chloride was added 2.0 g (0.00373 mol) of ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester hydrochloride and 0.4 g of triethylamine. The solution was stirred overnight at room temperature. The solvent was removed *in vacuo*, and the residue was suspended in ethyl acetate. This was washed with 10% citric acid solution and then water, dried (Na_2SO_4), and evaporated under reduced pressure to give a solid. This material was run through a short column of Silicar CC-7 using chloroform as eluent to yield 2.1 g (84%) of the protected tripeptide: mp 151°; $[\alpha]^{26}D$ −35.0° (*c* 7, dimethylformamide); R_f 0.71.

Anal. Calcd for $C_{34}H_{48}N_4O_8S$: C, 60.7; H, 7.2; N, 8.3. Found: C, 60.8; H, 7.5; N, 8.2.

L-Alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)-phenyl Ester Hydrochloride (14).—N-*t*-Butyloxycarbonyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester (2.0 g, 0.00297 mol) was added to 9 ml of 1 *N* hydrogen chloride in glacial acetic acid. The solution was left at room temperature for 35 min. Addition of dry ether precipitated 1.5 g (83%) of the hydrochloride: mp 193°; $[\alpha]^{27}D$ −33.1° (*c* 4.9, methanol).

Anal. Calcd for $C_{29}H_{41}ClN_4O_6S$: C, 57.2; H, 6.8; N, 9.2. Found: C, 57.2; H, 6.9; N, 9.0.

N-*t*-Butyloxycarbonyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)phenyl Ester (15).—N-*t*-Butyloxycarbonyl-L-isoleucine pentachlorophenyl ester (0.8 g, 0.00166 mol) was dissolved in 50 ml of methylene chloride and 1.0 g (0.00165 mol) of L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester hydrochloride was added. To this mixture 0.17 g of triethylamine was introduced, and the solution was stirred overnight. The solvent was removed, and the residue was dissolved in ethyl acetate and washed with 10% citric acid and then water, dried (Na_2SO_4), and evaporated to give a solid. This material was crystallized from ethyl acetate–hexane to give 0.9 g (76%) of the protected tetrapeptide: mp 188–189°; $[\alpha]^{24}D$ −28.9° (*c* 2.6, dimethylformamide); R_f 0.65.

Anal. Calcd for $C_{40}H_{59}N_5O_9S$: C, 61.1; H, 7.6; N, 8.9. Found: C, 61.2; H, 7.7; N, 9.1.

L-Isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-Methylthio)phenyl Ester Hydrochloride (3).—To 2 ml of 1 *N* hydrogen chloride in glacial acetic acid was added 0.5 g (0.00064 mol) of N-*t*-butyloxycarbonyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester, and the resulting mixture was left at room temperature for 50 min. Addition of dry ether precipitated 0.41 g (89%) of the hydrochloride: mp 230° dec; $[\alpha]^{25}D$ −38.6° (*c* 5.8, methanol).

Anal. Calcd for $C_{35}H_{52}ClN_5O_7S$: C, 58.2; H, 7.3; N, 9.7. Found: C, 58.1; H, 7.4; N, 9.4.

N,N′-Dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)phenyl Ester (1).—L-Isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(methylthio)phenyl ester hydrochloride (0.4 g, 0.000554 mol) was suspended in 10 ml of ethyl acetate and 0.05 g of triethylamine was added. The precipitated triethylamine hydrochloride was removed by filtration. The filtrate was added to a solution of 0.55 g of N,N′-dicarbobenzoxy-L-

lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysine 4-(methylsulfonyl)-phenyl ester in 10 ml of dimethylformamide, and the resulting solution was stirred overnight. This was poured into 300 ml of water containing 50 ml of 10% citric acid solution and stirred for 2 hr. The precipitate was filtered off, dried, and crystallized from chloroform–ether to yield 0.6 g (73%) of the fully protected heptapeptide: mp 118–120°; $[\alpha]^{25}D$ −25° (*c* 1.0, dimethylformamide); R_f 0.49.

Anal. Calcd for $C_{77}H_{104}N_{10}O_{16}S$: C, 62.1; H, 7.0; N, 9.4. Found: C, 62.4; H, 7.1; N, 9.3.

Optical Purity of N,N′-Dicarbobenzoxy-L-lysyl-L-leucyl-ε-N-carbobenzoxy-L-lysyl-L-isoleucyl-L-alanyl-ε-N-carbobenzoxy-L-lysyl-L-valine 4-(Methylthio)phenyl Ester (1).—The protected heptapeptide **1** (0.078 g, 5.237×10^{-5} mol) was dissolved in 10 ml of 6 *N* hydrochloric acid–glacial acetic acid (1:1) and heated under reflux at 100–105° for 24 hr. The solution was evaporated to dryness, and the residue was dissolved in 6 *N* hydrochloric acid–glacial acetic acid (4:1) so that the final volume was 2 ml: $[\alpha]^{30}D$ +28.69° (calculated on the basis of the expected amounts of lysine, leucine, isoleucine, alanine, and valine).

A control of 0.0073 g of 4-(methylthio)phenol, 0.0287 g of lysine hydrochloride, 0.0069 g of L-leucine, 0.0069 g of L-isoleucine, 0.0046 g of L-alanine, 0.0061 g of L-valine, 0.0056 g of benzyl alcohol, and 10 ml of 6 *N* hydrochloric acid–glacial acetic acid (1:1) was heated simultaneously with and under the same conditions as those used for the protected heptapeptide **1**. After 24 hr the solution was evaporated to dryness and made up to 2 ml with 6 *N* hydrochloric acid–glacial acetic acid (4:1), $[\alpha]^{30}D$ +29.54°, to give an optical purity of 97.1 ± 5%.

Registry No.—**1**, 17693-03-7; **2**, 17693-04-8; **3**, 17693-05-9; **4**, 17693-06-0; **5**, 17693-07-1; **6**, 17693-08-2; **7**, 17743-96-3; **8**, 17693-09-3; **9**, 17693-10-6; **10**, 17693-11-7; **11**, 17693-12-8; **12**, 17693-13-9; **13**, 17743-97-4; **14**, 17693-14-0; **15**, 17693-15-1; N-*t*-butyloxycarbonyl-ε-N-carbobenzoxy-L-lysine pentachlorophenyl ester, 17693-16-2; *t*-butyloxycarbonyl-L-alanine pentachlorophenyl ester, 17693-17-3; *t*-butyloxycarbonylglycine pentachlorophenyl ester, 17693-18-4; *t*-butyloxycarbonyl-L-isoleucine pentachlorophenyl ester, 17693-19-5; *t*-butyloxycarbonyl-L-leucine pentachlorophenyl ester, 17693-20-8; *t*-butyloxycarbonyl-L-phenylalanine pentachlorophenyl ester, 17693-21-9; *t*-butyloxycarbonyl-O-benzyl-L-tyrosine pentachlorophenyl ester, 17693-22-0; *t*-butyloxycarbonyl-L-valine pentachlorophenyl ester, 17693-23-1; N,N′-di-*t*-butyl oxycarbonyl-L-lysine pentachlorophenyl ester 17693-24-2.

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Notes

The 4-(Methylsulfonyl)phenyl Activated Ester. Susceptibility to Racemization[1]

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In a previous communication[3] it was shown that N-protected amino acid or peptide 4-(methylthio)phenyl esters could be converted by oxidation into 4-(methylsulfonyl)phenyl esters, which were sufficiently activated to be used in peptide synthesis. However, to evaluate the utility of this method, it was necessary to investigate the susceptibility of the activated ester to racemization. Since the most common mechanism is thought to be racemization through the oxazolone, Young's model[4] was chosen for study, because it is especially susceptible to racemization in this manner.

N-*t*-Butyloxycarbonyl-L-leucine 4-(methylthio)phenyl ester (**1**), was prepared from N-*t*-butyloxycarbonyl-L-leucine and 4-(methylthio)phenol using DCC. Treatment of **1** with hydrogen chloride in glacial acetic acid yielded L-leucine 4-(methylthio)phenyl ester hydrochloride (**2**), which was benzoylated to give N-benzoyl-L-leucine 4-(methylthio)phenyl ester (**3**). Oxidation of **3** with excess hydrogen peroxide in glacial acetic acid for 12 hr gave N-benzoyl-L-leucine 4-(methylsulfonyl)phenyl ester (**4**). Under these oxidative conditions the 4-(methylthio)phenyl ester is converted completely[3] into the 4-(methylsulfonyl)-phenyl ester as shown by infrared data. The presence of the optically active 4-(methylsulfinyl)phenyl ester was inferred to be absent. Thus it was considered that a comparison of the optical activity of the total acid hydrolysate of compounds **3** and **4** would indicate the amount of optical retention during this conversion. To this end N-benzoyl-L-leucine 4-(methylthio)phenyl ester (**3**) and N-benzoyl-L-leucine 4-(methylsulfonyl)-phenyl ester (**4**) were hydrolyzed using 6 *N* hydrochloric acid–glacial acetic acid (1:1) mixture, under identical conditions. Comparison of the the specific rotations of the hydrolysates of **3** and **4** showed that nearly 100% optical purity had been maintained.

In order to study the susceptibility of the 4-(methylsulfonyl)phenyl-activated ester to racemization in the presence of base, solutions of the ester **4** and tertiary amine (in 1:2 molar ratio) were mixed together in a 1-dm polarimeter tube; changes in optical rotation were observed on a Carl Zeiss polarimeter.

The general mechanism proposed[5,6] for racemization through the formation of an oxazolone provides the rate expression

$$\frac{-d[L]}{dt} = k_1[B]([L] - [D])$$

(1) This is the third article in this series. For the previous paper see B. J. Johnson and E. G. Trask, *J. Org. Chem.*, **33**, 4521 (1968).

(2) To whom any correspondence should be sent.

(3) B. J. Johnson and P. M. Jacobs, *Chem. Commun.*, 73 (1968).

(4) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).

(5) M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86**, 2918 (1964). M. Goodman and W. J. McGahren, *ibid.*, **87**, 3028 (1965).

(6) M. W. Williams and G. T. Young, *J. Chem. Soc.* 3701 (1964).

Since the base concentration was in a large excess it can be considered as a constant, thus integration yields

$$\ln \frac{[L_0]}{[L] - [D]} = k_1[B]t$$

where $k_1[B]$ is the pseudo-first-order rate constant k_I and k_1 is the second-order rate constant k_{II}. Thus a plot of ln ([L] − [D]) or ln α_{obsd} will give a straight line of slope $-k_{II}[B]$.

The half-time of the pseudo-first-order reaction is then given by

$$t_{1/2} = \ln 2/k_I = \ln 2/k_{II}[B]$$

Experimentally, plots of ln α_{obsd} *vs.* time gave straight-line curves; thus pseudo-first-order kinetics are followed at a ratio of the activated ester to the base of 1:2. The results are shown in Table I. As expected,[7] the reaction was found to be faster in dioxane–water than in chloroform.

TABLE I

RACEMIZATION OF N-BENZOYL-L-LEUCINE 4-(METHYLSULFONYL)PHENYL ESTER IN THE PRESENCE OF TERTIARY AMINE

Amine[a]	Solvent	T, °C	$k_I \times 10^3$, sec^{-1}[b]	$k_{II} \times 10^3$, sec^{-1}[c]	$t_{1/2}$, min[d]
TEA	Chloroform[e]	24.0	0.63 ± 0.09	1.26 ± 0.17	18.3
	Chloroform	33.7	1.1 ± 0.15	2.2 ± 0.29	10.4
	80% dioxane–water	32.1	6.82 ± 0.10	13.64 ± 1.99	1.7
TBA	Chloroform	33.0	No reaction after 24 hr		

[a] TEA = triethylamine; TBA = tribenzylamine. Amine concentration 0.5 *M*, ester concentration 0.25 *M*. [b] Pseudo-first-order rate constant. [c] Second-order rate constant = $k_I/[B]$. [d] Time for optical rotation to drop by one-half. [e] Contains 0.75% ethanol.

Bodanszky,[8] studying the *p*-nitrophenyl ester, used the same ratio of ester to base, but at lower concentration. Since the pseudo-first-order half-life is inversely proportional to the base concentration, it was necessary to convert the half-times of racemization into the same base concentration in order to compare the 4-(methylsulfonyl)phenyl ester to the *p*-nitrophenyl ester. Bodanszky[8] reported a half-time of 30 min at 24° for the racemization of the *p*-nitrophenyl ester in chloroform in the presence of 0.1 *M* triethylamine; at this base concentration, the 4-(methylsulfonyl)phenyl ester would have a half-life of approximately 90 min.

The high stability of the N-benzoyl-L-leucine *p*-nitrophenyl ester in the presence of tribenzylamine has also been reported.[8] We therefore investigated the effect of tribenzylamine on the racemization of N-benzoyl-L-leucine 4-(methylsulfonyl)phenyl ester. At 33°, a solution of the two showed no change in optical rotation after 24 hr. This can be ascribed to the weaker basicity and steric hindrance of the amine. From these results it has been concluded that the conversion of the 4-(methylthio)phenyl ester into the activated 4-(methylsulfonyl)phenyl ester is not accompanied by racemization. However, the resulting activated ester, like other commonly used activated esters, are subject to racemization in the presence of excess strong base.

(7) M. Goodman and W. J. McGahren, *J. Amer. Chem. Soc.*, **88**, 3887 (1966).

(8) M. Bodanszky and A. Bodanszky, *Chem. Commun.*, 591 (1967).

Experimental Section[9]

N-*t*-Butyloxycarbonyl-L-leucine 4-(methylthio)phenyl Ester (1).—N,N′-Dicyclohexylcarbodiimide (8.7 g, 0.0042 mol) was added to a solution of N-*t*-butyloxycarbonyl-L-leucine (9.3 g, 0.004 mol) and 5.6 g of 4-(methylthio)phenol in methylene chloride (150 ml). After stirring or 12 hr at room temperature, the solvent was removed under reduced pressure to give a solid. This was dissolved in ethyl acetate, filtered, washed successively with 10% citric acid and water, and dried (Na_2SO_4). Evaporation of this solution afforded a solid which was crystallized from hexane to yield 7.7 g (54.5%) of the 4-(methylthio)phenyl ester: mp 68–69°; $[\alpha]^{31}D$ −49.6° (*c* 1.19 in methanol).

Anal. Calcd for $C_{18}H_{27}NO_4S$: C, 61.2; H, 7.65; S, 9.1. Found: C, 61.4; H, 7.6; S, 8.8.

L-Leucine 4-(Methylthio)phenyl Ester Hydrochloride (2).—To 40 ml of 1 *N* hydrogen chloride in glacial acetic acid was added 4.5 g of N-*t*-butyloxycarbonyl-L-leucine-4-(methylthio)-phenyl ester. The solution was left at room temperature for 20 min and then evaporated under reduced pressure to give an oil. The oil was triturated with anhydrous ether to give 3.4 g (93%) of the hydrochloride, mp 197° dec. Recrystallization from methanol–ether raised the melting point to 201° dec; $[\alpha]^{31}D$ +20.4° (c 0.24 in methanol).

Anal. Calcd for $C_{13}H_{20}ClNO_2S$: C, 53.9; H, 6.9; Cl, 12.2. Found: C, 54.0; H, 7.05; Cl, 12.0.

N-Benzoyl-L-leucine 4-(Methylthio)phenyl Ester (3).—L-Leucine 4-(methylthio)phenyl ester hydrochloride (2) (2.1 g, 0.0112 mol) was suspended in 50 ml of ethyl acetate containing 1.6 g (0.0112 mol) of benzoyl chloride. A solution of 3.6 g (0.0336 mol) of sodium carbonate in 25 ml of water was added, and the two-phase mixture was stirred vigorously for 30 min. The aqueous layer was extracted with 100 ml of ethyl acetate; the combined organic phases were washed with 0.5 *N* hydrochloric acid, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil; upon addition of hexane, 3.9 g (95%) of the ester was obtained, mp 135–136°. Recrystallization from ethyl acetate–hexane gave 3.2 g (78%) of pure product: mp 134–136°; $[\alpha]^{30}D$ −34.6° (*c* 0.68 in acetic acid).

Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.2; H, 6.4; S, 9.0. Found: C, 67.4; H, 6.4; S, 9.0.

N-Benzoyl-L-leucine 4-(Methylsulfonyl)phenyl Ester (4).—N-Benzoyl-L-leucine 4-(methylthio)phenyl ester (4.9 g, 0.0137 mol) was dissolved in 50 ml of glacial acetic acid, and 15 ml of 30% hydrogen peroxide was added. The solution was left at room temperature for 12 hr and then poured into 600 ml of water. The precipitated 4-(methylsulfonyl)phenyl ester was collected and dried (5.1 g, 98%): mp 134–138°; ν_{max}^{Nujol} 1310, 1150 cm^{-1} (sulfone[10]); there was no absorption at 1050 cm^{-1} attributable to the sulfoxide.[10] It was recrystallized from methylene chloride–hexane which raised the melting point to 146°, $[\alpha]^{31}D$ −30.0° (*c* 0.65 in acetic acid).

Anal. Calcd for $C_{20}H_{23}NO_5S$: C, 61.7; H, 5.9; N, 3.6. Found: C, 61.6; H, 5.9; N, 3.7.

Optical Purity of N-Benzoyl-L-leucine 4-(Methylthio)phenyl Ester (3) and N-Benzoyl-L-leucine 4-(Methylsulfonyl)phenyl Ester (4).—N-Benzoyl-L-leucine 4-(methylthio)phenyl ester (3) (0.5 g, 0.00136 mol) was dissolved in 4 ml of glacial acetic acid–6 *N* hydrochloric acid (1:1) and heated to 100–105° for 24 hr. The solution was evaporated to dryness, and the residue was dissolved in glacial acetic acid so that the final volume was 5 ml: $[\alpha]^{25}D$ +11.90°. N-Benzoyl-L-leucine 4-(methylsulfonyl)-phenyl ester (4) (0.5 g, 0.00129 mol, mp 146°) was hydrolyzed concurrently with and under exactly the same conditions as those used for the ester 3. After 24 hr, the solution was evaporated to dryness and made up to 5 ml with glacial acetic acid, $[\alpha]^{25}D$ +12.18°, to give an amount of optical purity retained of 98 ± 3%.

Kinetic Studies on Racemization.—To 3 ml of a 0.5 *M* solution of N-benzoyl-L-leucine 4-(methylsulfonyl)phenyl ester in a 1-dm polarimeter tube was added 3 ml of a 1.0 *M* solution of a purified tertiary amine. It was considered to be zero time when the last of the amine solution had been added; a stopwatch was used for timing. Readings on the polarimeter were begun after suffi-

(9) Microanalyses were carried out by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Melting points were taken with a Mel-Temp apparatus. Optical rotations were taken with a Carl Zeiss precision polarimeter.

(10) L. J. Bellamy, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 48.

cient mixing to ensure homogeneity. The half-shade angle on the instrument was set at 5°, which normally gives an error of ±0.02° in α_{obsd}; since the readings had to be made rapidly, an error of ±0.04° was assigned. Error in the pseudo-first-order rate constant was evaluated by the method of limiting slopes. Results are summarized in Table I.

A. Triethylamine in Chloroform.—Runs were made at two temperatures: 33.7° ± 0.3 and 24.0° ± 0.1.

B. Triethylamine in 80% Dioxane–Water.—In this case the ester was dissolved in pure dioxane and the amine in 60% dioxane–water; the temperature was 32.1° ± 0.2.

C. Tribenzylamine in Chloroform.—There was no change in optical rotation after 24 hr at 33°.

D. Tribenzylamine Hydrochloride in 20% Methanol–Chloroform.—There was no change in optical rotation after 24 hr at 33°.

Registry No.—**1**, 17659-10-8; **2**, 17659-11-9; **3**, 17659-18-6; **4**, 17730-92-6.

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Synthesis of Optically Active Alanine from Oxaloacetic Acid by Hydrogenolytic Asymmetric Transamination[1]

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Hiskey and Northrop published a method for synthesizing optically active α-amino acids from the corresponding α-keto acids. They employed optically active α-methylbenzylamine and subsequent catalytic hydrogenation and hydrogenolysis.[2] In the previous study from this laboratory, the possible steric courses of the asymmetric synthesis have been studied.[3,4] Also, the formation of optically active amino acids from α-keto acids and optically active α-phenylglycine in alkaline aqueous solution by catalytic hydrogenation and subsequent hydrogenolysis has been studied.[5]

In this investigation, reactions of oxaloacetic acid with (*S*)(−)-α-methylbenzylamine and with (*S*)(−)-α-ethylbenzylamine in alcoholic solution were used to obtain optically active aspartic acid. However, the resulting amino acid was found to be only optically active α-alanine (optical purity 69 and 52%, respectively). No aspartic acid was identified in the reaction product. Therefore, very fast decarboxylation of oxaloacetic acid during the reaction is inferred.

To clarify the decarboxylation during the asymmetric synthesis, several amines and solvent systems were used. Benzylamine resulted in racemic alanine in an alcoholic solution, the same as the optically active α-methyl- and α-ethylbenzylamine did. When optically active (*S*)(+)-or (*R*)(−)-α-phenylglycine was used in the reaction with oxaloacetic acid in aqueous solution, the products were found to be a mixture of (*S*)(+)-alanine–(*S*)(+)-aspartic acid or (*R*)(−)-alanine–(*R*)(−)-aspartic acid. The decarboxylation rate in this reaction is relatively slow compared with that in the reaction with α-alkylbenzylamine in alcoholic solution. The observed results are shown in Figure 1, in which the ratios of the resulting alanine and aspartic acid, depending on time in the reaction, are presented. The summarized results of yield and optical purity are presented in Table I.

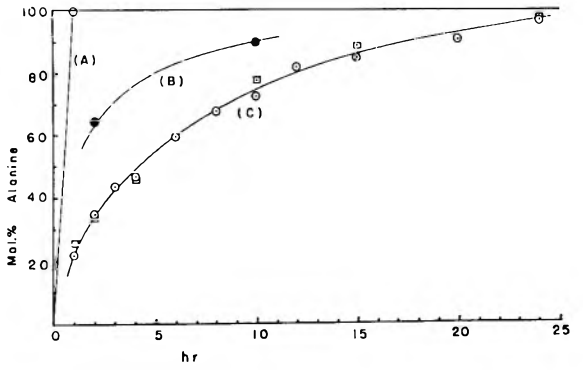
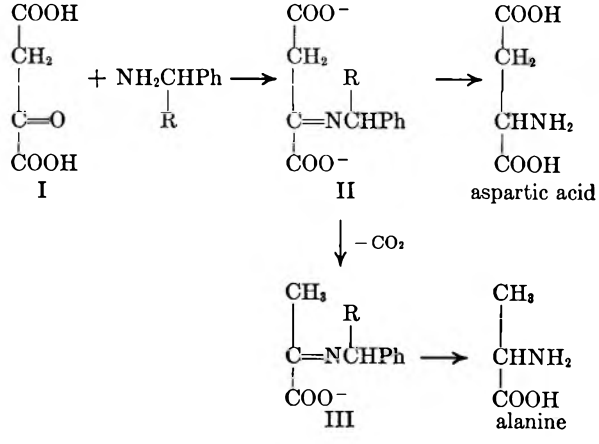


Figure 1.—Decarboxylation during the reductive amination of oxaloacetic acid. (A) oxaloacetic acid (1.32 g, 0.01 mol) + (*S*)(−)-α-methylbenzylamine (3.63 g, 0.03 mol). (B) Oxaloacetic acid (0.66 g, 0.05 mol) + pyridoxamine dihydrochloride (1.2 g, 0.005 mol). (C) Oxaloacetic acid (1.32 g, 0.01 mol) + (*R*)(−)-phenylglycine (1.51 g, 0.01 mol). ⊙, determined by amino acid analyzer; ⊡, determined by DNP method.

The inferred route of this reaction is shown in Scheme I. Oxaloacetic acid reacts with benzylamines to form

SCHEME I



the Schiff base (II). The structure II might lose its β-carboxyl group easily to convert it into the Schiff base of pyruvic acid (structure III).[6] In the reaction with benzylamine, α-alkylbenzylamine, or α-(1-naphthyl)-ethylamine, the decarboxylation rate seems to be very fast in alcoholic solution. When an aqueous solvent was used, decarboxylation was not so fast that the re-

(1) Sterically controlled synthesis of optically active organic compounds VII. Part VI: K. Harada and K. Matsumoto, *J. Org. Chem.*, **33**, 4467 (1968). Contribution No. 079 from the Institute of Molecular Evolution, University of Miami.

(2) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961).

(3) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

(4) Part VI.[1]

(5) K. Harada, *Nature*, **212**, 1571 (1966); K. Harada, *J. Org. Chem.*, **32**, 1790 (1967).

(6) The decarboxylation reaction mechanism could be similar to those of enzymatic β-decarboxylation proposed by A. Meister, J. S. Nishimura, and A. Novogradsky, "Chemical and Biological Aspects of Pyridoxal Catalysis," E. E. Snell, P. M. Fasella, A. Braunstein, and A. Rossi Fanelli, Ed., The Macmillan Co., New York, N. Y., 1963, p 229.

TABLE I

FORMATION OF OPTICALLY ACTIVE ALANINE FROM OXALOACETIC ACID

Reaction	Confign of amine[a]	Solvent	Yield,[b] %	Confign of amino acid	Isolated amino acid, $[\alpha]^{25}D$, deg (c, 5 N HCl)[c]	Optical purity,[d] %	DNP-amino acid, $[\alpha]^{25}D$, deg (c, 1 N NaOH)[e]	Optical purity,[f] %
1	(S)(−)-Me	EtOH	78 (30 min)	(S)-Ala	+10.8 (3.30)	74	+98.6 (0.44)	69
2	(S)(−)-Me	H_2O, EtOH (1:1), NaOH	60 (30 min)	(S)-Ala	+7.4 (2.99)	50	+73.8 (0.40)	51
				(R)-Asp	−11.1 (2.84)	44	−41.0 (0.39)	45
3	(S)(−)-Et	EtOH	75 (30 min)	(S)-Ala	+6.2 (3.47)	42	+74.6 (0.45)	52
4	(S)(−)-Et	H_2O, EtOH (1:1), NaOH	56 (30 min)	(S)-Ala	+5.5 (2.80)	38	+52.9 (0.31)	37
				(R)-Asp	−6.8 (2.50)	27	−23.0 (0.37)	25
5	(R)(+)-Naph	EtOH	75	(R)-Ala	−11.1 (4.10)	76	−120 (0.35)	83
6	(R)(+)-Naph	H_3O, EtOH (1:1), NaOH	65 (30 min)	(R)-Ala	−10.9 (3.13)	74	−105 (0.45)	73
7	(S)(+)-Ph-gly	H_2O, NaOH	40	(S)-Ala	+8.2 (3.00)	56	+85.3 (0.39)	60
				(S)-Asp	+12.3 (2.51)	48	+48.9 (0.60)	53
8	(R)(−)-Ph-gly	H_2O, NaOH	38	(R)-Ala	−7.9 (3.91)	54	−89.5 (0.57)	62
				(R)-Asp	−12.8 (3.14)	53	−49.1 (0.56)	53
9	Benzylamine	EtOH	78	(±)-Ala				
10	Pyridoxamine	H_2O, NaOH	20	(±)-Ala, -asp				

[a] (S)(−)-Me, (S)(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3° benzene); (S)(−)-Et, (S)(−)-α-ethylbenzylamine ($[\alpha]^{25}D$ −21.0° benzene); (S)(+)-Ph-gly, $[\alpha]^{25}D$ +164.2° (5 N HCl); (R)(−)-Ph-gly, $[\alpha]^{25}D$ −168° (5 N HCl); (R)(+)-naph, (R)(+)-α-(1-naphthyl)ethylamine, ($[\alpha]^{25}D$ +88.0° benzene). [b] Reaction time, 2 hr except reactions mentioned. [c] Optical rotations of first isolated amino acids were listed. [d] Defined as ($[\alpha]$p obsd/$[\alpha]$D lit.) × 100. (S)-Ala, $[\alpha]^{25}D$ +14.6° (5 N HCl); (S)-asp, $[\alpha]^{24}D$ +25.39° (5 N HCl). J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1961: alanine, p 1819; aspartic acid, p 1856. [e] DNP-amino acids were isolated by column chromatography. Specific rotations were measured without further purification. [f] Defined as ($[\alpha]$D obsd/$[\alpha]$D lit.) × 100. DNP-(S)-ala, $[\alpha]$D +143.9° (1 N NaOH); DNP-(S)-asp, $[\alpha]^{25}D$ +91.9° (1 N NaOH). K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).

sulting ketimine could be a mixture of II and III which would give a mixture of aspartic acid and alanine. The decarboxylation reaction also took place in the reaction of oxaloacetic acid with pyridoxamine in aqueous solution. The rate of decarboxylation was found to be lower than that from the use of α-alkylbenzylamine in alcohol, but faster than with phenylglycine in aqueous solution. It was found also that structure II combined with pyridoxamine could be hydrogenated and hydrogenolyzed by the use of palladium hydroxide on charcoal, as could N-benzyl, N-α-alkylbenzyl,[2-4] or N-α-carboxybenzyl[5] groups. After hydrogenolysis, structure II, combined with pyridoxamine, gave a mixture of alanine and aspartic acid in a ratio of 63:37.

N-Benzylideneaspartic acid was prepared to check whether the compound was decarboxylated. The N-benzylidene compound did not evolve any carbon dioxide under the same conditions employed in this study. This fact suggests that this type of compound is not a suitable structure for the decarboxylation reaction and also that the N-benzylidene compound does not convert into a structure II by migration of the double bond.

It is known that optically active phenylglycine is one of the most easily racemizable amino acids, and it is also known that in general amino acids racemize more easily when they combine with a carbonyl compound. Therefore, it was necessary to examine the racemization of optically active phenylglycine during the decarboxylation reaction. After allowing the reaction mixtures of oxaloacetic acid and (R)(−)-phenylglycine to stand for 2, 12, and 24 hr, hydrogenation and hydrogenolysis were carried out. Specific rotations of resulting DNP-alanine were −89.5, −88.9, and −89.5°, respectively (in 1 N NaOH). These results suggest that the racemization of phenylglycine during the reaction is very small or none. Free (R)(−)-phenylglycine, $[\alpha]^{25}D$ −166.8° (c 1.10, 5 N HCl), was also isolated from the reaction mixture in 97.3% yield after standing at room temperature for 24 hr. The optical purity is almost the same as that of the original (R)(−)-phenylglycine, $[\alpha]^{25}D$ −168.0° (c 1.11, 5 N HCl).

Experimental Section[7]

(S)(+)-Alanine from Oxaloacetic Acid and (S)(−)-α-Methylbenzylamine.—Oxaloacetic acid (1.32 g, 0.01 mol) in ethanol (40 ml) was added to a solution of (−)-α-methylbenzylamine[8,9] (3.63 g, 0.03 mol, $[\alpha]^{25}D$ −42.3° benzene) in ethanol (30 ml). The mixture was allowed to stand for 30 min at room temperature. Hydrogenation using 10% palladium on charcoal (1.5 g) was carried out for 6 hr at room temperature. The catalyst was removed by filtration and then washed with hot water. The filtrate was concentrated to 30 ml *in vacuo*. Ethanol was added to the concentrate until the suspended material was dissolved completely. Palladium hydroxide on charcoal (2.0 g) was added to the mixture, and hydrogenolysis was carried out at room temperature for 10 hr. The catalyst was filtered and washed with water, The combined solution was evaporated to 10 ml. The concentrate was applied to a Dowex 50 × 2 column (hydrogen form, 100–200 mesh, 1.5 × 18 cm). Acidic nonamino acid components were eluted with water; then alanine was eluted with 1 N aqueous ammonia. Fractions containing the amino acid were evaporated to dryness. (S)(+)-Alanine was obtained [0.70 g (78%); $[\alpha]^{25}D$ +10.8° (c 3.30, 5 N HCl)]. The expected aspartic acid was not found by paper chromatography in the butanol–water–acetic acid system nor by the automatic amino acid analyzer (Phoenix Model K-5000). A part of the product (0.10 g) was treated with 1-fluoro-2,4-dinitrobenzene. The resulting DNP-alanine was separated in the same way as described in previous reports:[3,10] $[\alpha]^{25}D$ +98.6° (c 0.44, 1 N NaOH); mp 172–175° dec.

Isolation of N-(α-Methylbenzyl)alanine.—A mixture of oxaloacetic acid (1.32 g, 0.01 mol), (−)-α-methylbenzylamine (3.63 g, 0.03 mol), and ethanol (70 ml) was allowed to stand for 1 hr. Hydrogenation using 10% palladium on charcoal (1.5 g) was carried out for 6 hr. The catalyst was removed by filtration and washed with water and ethanol. The filtrate was evaporated to dryness. The residue was washed with a small amount of water. The crude crystals were purified by sublimation: mp 265° dec; $[\alpha]^{25}D$ −50.5° (c 0.455, 50% EtOH) [lit.[2] mp >275°;

(7) All optical rotation measurements were carried out by the use of the Rudolph Model 80 polarimeter with PEC-101 photometer.

(8) W. Theilacker and H. Hinkler, *Ber.*, **87**, 690 (1954).

(9) W. Leithe, *ibid.*, **64**, 2831 (1931).

(10) K. Matsumoto and K. Harada, *J. Org. Chem.*, **31**, 1956 (1966); K. Harada and K. Matsumoto, *ibid.*, **31**, 2985 (1966).

[α]^{25}D +87.5° (*c* 1.02, 50% EtOH) from (+)-α-methylbenzylamine].

Anal. Calcd for $C_{11}H_{15}NO_2$: N, 7.27; Found: N, 7.23.

(*R*)(−)-Alanine and (*R*)(−)-Aspartic Acid from Oxaloacetic Acid and (*R*)(−)-Phenylglycine.[5]—A mixture of oxaloacetic acid (1.32 g, 0.01 mol), (−)-phenylglycine [1.51 g, 0.01 mol; [α]^{25}D −168° (5 *N* HCl)], and water (5 ml) was dissolved in 2 *N* sodium hydroxide (15.5 ml). The mixture was allowed to stand for 2 hr at room temperature. To the mixture, 10% palladium on charcoal (2.5 g) was added, and hydrogenation and hydrogenolysis were carried out at room temperature for 24 hr. The catalyst was filtered and washed with water. To the solution, 6 *N* hydrochloric acid was added to bring the pH to about 2. Ether extraction was carried out to remove the phenylacetic acid. The aqueous solution was evaporated to dryness. Absolute alcohol (50 ml) was added to the residue to extract the amino acid hydrochloride. Sodium chloride was removed by filtration. The alcoholic solution was evaporated, and the residue was dissolved in water (15 ml). The aqueous solution was treated with a Dowex 50 × 2 column in the same way described above. A mixture of alanine and aspartic acid was obtained (0.46 g, 38%). (Yields of amino acids at various times are almost constant: 12 hr, 36%; 24 hr, 35%.) The amino acid mixtures (0.36 g) were separated into alanine and aspartic acid by the use of an AG 1 × 8 column (formate form, 100–200 mesh, 1.5 × 16 cm). Alanine was eluted with water; then aspartic acid was eluted with 1 *N* formic acid. (*R*)(−)-Alanine (0.09 g) and (*R*)(−)-aspartic acid (0.26 g) were obtained, respectively: (*R*)(−)-alanine, [α]^{25}D −7.9° (*c* 3.91, 5 *N* HCl); (*R*)(−)-aspartic acid, [α]^{25}D −12.8° (c 3.14, 5 *N* HCl); alanine:aspartic acid = 35:65.

Separation of DNP-Alanine and DNP-Aspartic Acid.—The alanine and aspartic acid mixture (0.10 g) was treated with 1-fluoro-2,4-dinitrobenzene (0.4 g) and sodium hydrogen carbonate (0.4 g) by the usual method. Crude DNP-amino acid was separated by Celite column chromatography by the method described in previous reports:[3,10] DNP-(*R*)(−)-alanine, yield 0.073 g, [α]^{25}D −89.5° (*c* 0.57, 1 *N* NaOH); DNP-(*R*)(−)-aspartic acid, yield 0.184 g, [α]^{25}D −49.1° (c 0.56, 1 *N* NaOH); DNP-alanine:DNP-aspartic acid = 33:67.

Alanine from Oxaloacetic Acid and Pyridoxamine.—A mixture of oxaloacetic acid (0.66 g, 0.005 mol), pyridoxamine dihydrochloride (1.2 g, 0.005 mol), 2 *N* sodium hydroxide (10 ml), and water (10 ml) was allowed to stand for 2 hr at room temperature. To the mixture, palladium hydroxide (2.0 g) was added, and hydrogenation and hydrogenolysis were performed for 24 hr at room temperature. The reaction mixture was treated as above. Amino acid mixture was obtained (0.15 g, 20%). The ratio of alanine and aspartic acid was determined by the use of the automatic amino acid analyzer: alanine:aspartic acid = 63:37. Separation of DNP-amino acids was carried out as above: DNP-alanine:DNP-aspartic acid = 65:35.

Isolation of Barium Carbonate.—In a three-necked flask with a nitrogen gas inlet tube, outlet tube, and dropping funnel, a mixture of oxaloacetic acid (1.32 g, 0.01 mol), α-methylbenzylamine (3.63 g, 0.03 mol), and ethanol (70 ml) was placed. The carbon dioxide evolved was collected in traps containing 0.2 *M* barium hydroxide. After 30 min, 6 *N* hydrochloric acid (10 ml) was added to the mixture. Then nitrogen gas was passed through until the evolution of carbon dioxide ceased (30 min). Precipitated barium carbonate was collected by filtration and washed with water repeatedly. After the residue was dried, barium carbonate (1.90 g, 96.4%) was obtained.

Examination of Racemization of Phenylglycine.—A mixture of oxaloacetic acid (0.66 g, 0.005 mol), (*R*)(−)-phenylglycine [0.75 g, 0.005 mol; [α]^{25}D −168°, (5 *N* HCl)], water (2.5 ml), and 2 *N* sodium hydroxide (7.8 ml) was allowed to stand at room temperature. After 2 hr of standing, 6 *N* hydrochloric acid was added to the mixture to decompose the Schiff base. The mixture was evaporated to dryness *in vacuo*. The dried residue was extracted with absolute ethanol (50 ml). The ethanolic solution was kept in a freezer overnight, and the precipitated inorganic salt was removed by filtration. To the filtrate pyridine was added to precipitate phenylglycine. The precipitating solution was allowed to stand in a freezer overnight. The crystals were filtered to yield 0.73 g (97.3%): [α]^{25}D −166.8° (*c* 1.10, 5 *N* HCl).

Registry No.—(*S*)(+)-alanine, 10333-82-1; (*R*)(−)-alanine, 10353-30-7; oxaloacetic acid, 328-42-7; N-(α-methylbenzyl)alanine, 17791-40-1; (*R*)(−)-aspartic acid, 10333-84-3; (*S*)(+)-aspartic acid, 10353-31-8.

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A New Thiadiazepine Ring System

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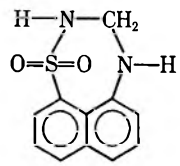
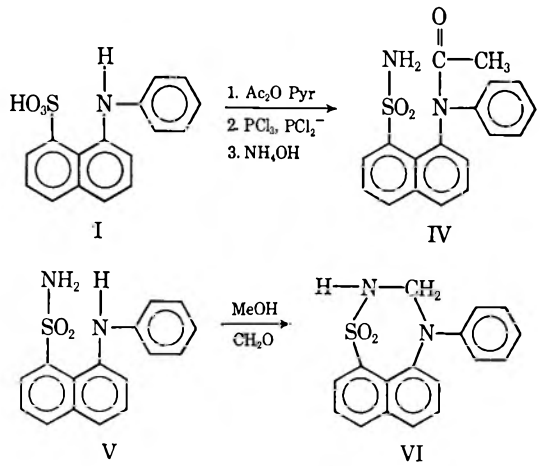
In connection with investigations dealing with the preparation of compounds for diuretic activity, we wish to report the synthesis of a new thiadiazepine ring system by two different methods, A and B. In method



A (Scheme I) the N-acetyl (II) compound was prepared from N-phenyl *peri* acid (I) by refluxing with acetic anhydride in pyridine solution, and II was converted into the corresponding sulfonyl chloride III by refluxing with PCl_5 in PCl_3. Ammoniation of III, using 10% ammonia solution, gave amide IV, and the acetyl group

SCHEME I



was then hydrolyzed by methanolic sodium hydroxide to give V. The ring closure to VI[2] was effected by condensing V with equal molar quantities of 55% Methyl Formcel in methanol.

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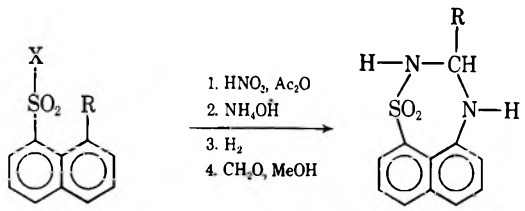
(2) The Harshaw Chemical Co.

In method B (Scheme II) the intermediate VIII was obtained (as reported by Joy and Bogert[3]) and ammoniated to compound IX which was then reduced with

SCHEME II



VII, X = Cl; R = H
VIII, X = Cl; R = NO_2
IX, X = NH_2; R = NO_2
X, X = NH_2; R = NH_2

XIa, R = H
b, R = $C_6H_5CH_2$

hydrogen in the presence of Raney nickel catalyst. Compound IX was identical with that reported by Heller.[4] The ring closure was performed as described in method A.

Experimental Section

Pyridinium 3-(N-Acetylanilino)-1-naphthalenesulfonate (II).—8-Anilino-1-naphthalenesulfonic acid (I) (100 g, 0.31 mol) was suspended in 200 ml of pyridine and refluxed in 400 ml of acetic anhydride for 2 hr. The crystals were filtered and washed with acetone: mp 217–219°; yield 87 g (63%).

Anal. Calcd for $C_{23}H_{20}N_2O_4S$: C, 67.29; H, 4.91; N, 6.82. Found: C, 67.32; H, 4.88; N, 6.89.

8-(N-Acetylanilino)-1-naphthalenesulfonyl Chloride (III).—Pyridinium 8-(N-acetylanilino)-1-naphthalenesulfonate (II) (42 g, 0.09 mol) and 21 g (0.1 mol) of PCl_5 wih 50 ml of PCl_3 were mixed and refluxed for 5 min. The syrupy mass was poured into ice with good stirring, and the formed crystals, after recrystallizing from benzene, had mp 140–141°; yield 23.0 g (71%).

Anal. Calcd for $C_{18}H_{14}NO_3SCl$: C, 60.08; H, 3.92; N, 3.90; S, 8.92; Cl, 9.86. Found: 59.92; H, 3.87; N, 3.92; S, 8.81; Cl, 9.92.

8-N-Acetylanilino-1-naphthalenesulfonamide (IV).—8-(N-acetylanilino)-1-naphthalenesulfonyl chloride (III) (23 g, 0.064 mol) was boiled with a mixture of 300 ml of 10% ammonia solution and 200 ml of methanol for 2 hr and allowed to stand for 2 hr at room temperature. The fine crystals were then filtered off and washed with 150 ml of water and twice with 50 ml of methanol. After recrystallizing from 50% methanol, the product had mp 212–214°; yield 21.0 g (96%).

Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.49; H, 4.74; N, 8.24 S, 9.24. Found: C, 63.25; H, 4.80; N, 8.23; S, 8.70.

8-Anilino-1-naphthalenesulfonamide (V).—8-(N-Acetylanilino)-1-naphthalenesulfonamide (IV) (21 g, 0.062 mol) was hydrolyzed with 350 ml of 5% NaOH solution for 17 hr. The mixture was filtered, and to the filtrate 75 ml of 50% NH_4Cl solution was added. The formed crystals were collected, washed twice with 25 ml of water, and recrystallized from MeOH with the aid of a charcoal decolorizing agent. The yield was 13 g (67%).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.63; H, 4.41; N, 9.42; S, 10.78. Found: C, 64.43; H, 4.43; N, 9.28; S, 11.00.

Naphthalene[1,8-*e*,*f*]-2,3-dihydro-4H-4-phenyl-[1.2.4]thiadiazepine 1,1-Dioxide (VI).—A solution of 5 g (0.0155 mol) of 8-anilino-1-naphthalenesulfonamide (V) 70 ml of absolute MeOH and 2 ml of 55% Methyl Formcel was refluxed for 8 min. The mixture was cooled and allowed to stand at room temperature overnight. The formed crystals yielded 2.5 g (48%); the product had mp 178°.

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.54; N, 9.02; S, 10.33. Found: C, 65.51; H, 4.27; N, 8.47; S, 10.15.

(3) H. V. Joy and M. T. Bogert, *J. Org. Chem.*, **1**, 236 (1936).
(4) J. Heller, *J. Prakt. Chem.*, **2**, 121, (1940).

8-Nitro-1-naphthalenesulfonyl chloride (VIII).—This compound was prepared by the method of Joy and Bogert:[3] yield 17%; mp 153–156° (lit.[3] mp 161–162°).

8-Nitro-1-naphthalenesulfonamide (IX).—This was prepared from compound VIII by boiling the latter in methanolic ammonia: yield 95%; mp 188–190° (lit.[5] mp 190.5–1.5°).

8-Amino-1-naphthalenesulfonamide (X).—The compound IX (1.5 g, 0.0060 mol) was reduced catalytically over Raney nickel in ethanol. The solvent was removed, giving a crystalline product which was then recrystallized from 3 ml of benzene–methanol–petroleum ether (bp 40–60°): yield 1.0 g (75%); mp 189–191°.

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.45; H, 4.53; N, 12.60; S, 14.42. Found: C, 54.41; H, 4.56; N, 12.62; S, 14.38.

Naphthalene-[1,8-*e*,*f*]-2,3-dihydro-4-H-[1,2,4]-thiadiazepine 1,1-Dioxide (XIa).—A solution of 958 mg (0.0044 mol) of 8-amino-1-naphthalenesulfonamide (X) in 450 ml of MeOH was refluxed with 15 drops of Methyl Formcel[2] (55%) for 10 min. The reaction mixture was then reduced to a 70-ml volume, and, on cooling, crystals formed which were collected and recrystallized from 4 ml of benzene: yield 750 mg (75%); mp 214–216°.

Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.95; S, 13.68. Found: C, 56.23; H, 4.46; N, 11.83; S, 13.75.

3-Benzylnaphthalene-[1,8-*e*,*f*]-2,3-dihydro-4-H-[1,2,4]-thiadiazepine 1,1-Dioxide (XIb).—To a solution of 2.0 g (0.0090 mol) of 8-amino-1-naphthalenesulfonamide (X) in 50 ml of ethanol was added 4 ml of phenylacetaldehyde in ethanol (50%). The mixture was refluxed for 1.5 hr. This mixture was concentrated to one-half volume, and, on cooling, crystals formed which were collected, washed twice with 1 ml of methanol and petroleum ether, and finally recrystallized from 130 ml of methanol: yield 1.5 g (71%); mp 176–176.5°.

Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.63; S, 9.88. Found: C, 66.25; H, 5.06; N, 8.83; S, 10.15.

Registry No.—II, 16888-87-2; III, 16888-81-6; IV, 16888-82-7; V, 16888-83-8; VI, 16932-58-4; X, 16888-84-9; XIa, 16888-85-0; XIb, 16888-86-1.

Acknowledgment.—Thanks are due to G. Robertson, Jr., Florham Park, N. J., for the microanalyses.

(5) R. E. Steiger, *Helv. Chim. Acta*, **17**, 701 (1934).

The Isolation and Structural Elucidation of 4-Demethylhasubanonine, a New Alkaloid from *Stephania hernandifolia*

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Stephania hernandifolia Walp. is a menispermaceous slender twining shrub found in India on the west and east coasts, in Cachar, Sikkim, East Bengal, and Assam.[2] The roots are reported to have use in the treatment of fever, diarrhea, dyspepsia, and urinary diseases.[3]

(1) (a) University of Wisconsin. The investigation at the University of Wisconsin was supported by Public Health Service Grant No. HE-02952 from the National Heart Institute. M. I. S. was an National Institutes of Health Predoctoral Fellow, 1966–1968. (b) University of Sussex.

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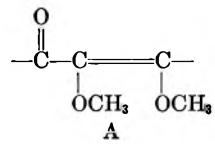
An examination of *S. hernandifolia* from the eastern coast of Australia revealed the presence of *l*-quercitol and a mixture of alkaloids.[4] In 1959,[5] Tomita and Ueda reported on the alkaloids of *S. hernandifolia* purchased as crude drug on the Bombay market. They isolated the alkaloid isotrilobine, a new tertiary phenolic base, and β-sitosterol. Moza, *et al.*, have reported that the plant contained alkaloids, steroids, and fats,[6a] and have partially characterized three alkaloids.[6b] A recent communication has described the partial characterization of an alkaloid of empirical formula $C_{20}H_{25}NO_5$.[7]

In an earlier report from this laboratory, the isolation from *S. hernandifolia* from India of the alkaloids *dl*-tetrandrine, fangchinoline, *d*-tetrandrine, and *d*-isochondrodendrine was reported.[8] Subsequent biological studies demonstrated that all four alkaloids showed significant cytotoxicity against human carcinoma of the nasopharynx carried in tissue culture (KB),[9] and that *dl*-tetrandrine and *d*-tetrandrine showed significant inhibitory activity *in vivo* against the Walker 256 intramuscular carcinosarcoma in the rat.

The present communication concerns an investigation of a new sample of roots of *S. hernandifolia*, collected in India in Jan 1965.[10] Careful examination of the alkaloid mixture revealed that this plant sample contained none of the alkaloids found earlier. We report herein the isolation and structural elucidation of 4-demethylhasubanonine (Ia), a new phenolic alkaloid of the hasubanan series.[11]

A concentrated methanolic extract of the defatted roots of *S. hernandifolia* Walp. was triturated with 6% hydrochloric acid, and the acid solution was basified with ammonium hydroxide and extracted with chloroform to yield the crude nonquaternary alkaloids.[12] The crude alkaloids were fractionated by continuous ether extraction. The ether-soluble alkaloids were chromatographed on silica to yield a fraction rich in the new alkaloid. Treatment with oxalic acid in methanol and repeated recrystallizations from methanol–ether yielded 4-demethylhasubanonine (Ia) oxalate salt, $C_{20}H_{25}NO_5 \cdot C_2H_2O_4$: mp 198–199°; $[\alpha]^{32}D$ −123°; *m/e* 359;[13] λ_{max}^{EtOH} 266 mμ (ε 8400). The infrared spectrum (KBr) showed absorption at 5.95 μ, indicative of α,β-unsaturated ketone. The alkaloid was also characterized as the perchlorate salt (mp 229–230°; $[\alpha]^{32}D$ −145°) and the brosylate ester (Ib) (mp 209–211°; $[\alpha]^{29}D$ −149°, M^+ *m/e* 576). The amorphous free base showed nmr signals at τ 3.32 and 3.45 (2 H, q, J = 9 cps, 2 aromatic H), 3.88 (1 H, OH), 5.92, 6.18, and 6.32 (9 H, 3 OCH_3), 7.48 (3 H, NCH_3). The infrared and nmr spectra indicated the presence of the partial structure A. Characterization of the



A

hydroxyl group as a phenolic hydroxyl group with an unsubstituted *para* position was supported by the positive reaction toward Gibbs reagent.

Methylation of the alkaloid with diazomethane gave hasubanonine (Ic), characterized by comparison of the physical constants of the alkaloid and its methiodide derivative with those reported in the literature.[14,15] The foregoing data established the demethylhasubanonine nature of the new alkaloid.

A comparison of the nmr signals for the methoxyl groups of the new alkaloid with those of hasubanonine (Ic), cepharamine (Id), homostephanoline (IIa), and O-ethylhomostephanoline (IIb)[16,17] (see Table I) limited alternative assignments of the free hydroxyl group to C-3 or C-4. Since the alkaloid was different from the C-3 phenolic isomer, homostephanoline (IIa), the 4-demethylhasubanonine structure (Ia) appeared most plausible. Structure Ia was supported also by the fact that the alkaloid reacted positively toward Gibbs reagent.

TABLE I

NMR METHOXYL RESONANCES IN THE HASUBANAN SERIES[a]

Compound	C-3	C-4	C-7	C-8
Ia	6.18		6.32	5.92
Ic	6.19	6.09	6.36	5.92
Id	6.15		6.35	
IIa		6.14	6.40	5.92
IIb		6.05	6.35	5.93

[a] All values are in τ for $CDCl_3$ solutions.

Unequivocal proof of structure Ia was achieved by X-ray crystallographic analysis of the brosylate Ib. The brosylate crystallized in the orthorhombic system, space group $P2_12_12_1$, with four molecules of $C_{26}H_{28}NO_7SBr$ in a cell of dimensions a = 8.52 Å, b = 24.23 Å, c = 12.60 Å. The X-ray diffraction data were recorded on equiinclination Weissenberg photographs, and visual estimation of the intensities gave a total of 1878 independent $|F_0|$ values.

Preliminary coordinates of the bromine and sulfur atoms were obtained from a Patterson synthesis, and the carbon, nitrogen, and oxygen atoms were then located in three-dimensional electron density distributions calculated with weighted Fourier coefficients.[18] Two Fourier syntheses completed the elucidation of the

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(10) The authors acknowledge with thanks the receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the U. S. Department of Agriculture by the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health.

(11) 4-Demethylhasubanonine is the sixth hasubanan alkaloid; *cf.* T. Ibuka and M. Kitano, *Chem. Pharm. Bull.* (Tokyo), **15**, 1944 (1967).

(12) We thank Riker Laboratories for the large-scale preparation of the alkaloidal extract, and the Cancer Chemotherapy National Service Center for arranging for the extraction, under Contract SA-43-PH-3764.

(13) We thank Dr. R. D. Brown and Dr. F. W. McLafferty of the Purdue Mass Spectrometry Center, supported under U. S. Public Health Service Grant FR-00354, for the mass spectral data.

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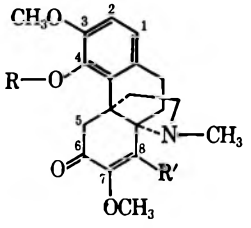
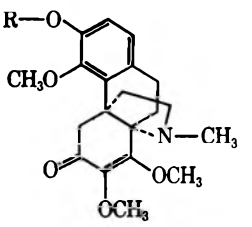
molecular structure as Ib, and an additional synthesis gave improved atomic coordinates. At this stage we included anomalous dispersion corrections in the structure factor calculations, and with coordinates appropriate to the absolute configuration shown in Ib the value of R was 19.1% whereas when the opposite configuration was tested R was 19.3%. These results are consistent with the assigned absolute configuration of hasubanonine.[19]



Ia, R = H; R′ = OCH_3
b, R = $SO_2C_6H_4Br$; R′ = OCH_3
c, R = CH_3; R′ = OCH_3
d, R = R′ = H



IIa, R = H
b, R = C_2H_5

Experimental Section

Melting points were determined with a Thomas–Hoover Unimelt apparatus and are corrected. Ir spectra were determined on Beckman double-beam recording spectrophotometers, Models IR-5A and IR-9. Uv spectra were determined in 95% ethanol on a Beckman recording spectrophotometer, Model DK2A. Optical rotations were measured with a Zeiss–Winkel polarimeter and are approximated to the nearest degree. Nmr spectra were determined on a Varian Associates spectrometer, Model A-60A. Skellysolve B is that fraction of petroleum ether boiling from 60 to 68°.

Extraction and Preliminary Fractionation.[12]—The dried root (41.4 kg) of *S. hernandifolia* was extracted twice with hexane (4 l./kg) and the hexane extracts were discarded. The defatted root was then extracted three times with methanol (3 l./kg) and twice with 70% methanol (3 l./kg) and the methanolic extracts were combined and concentrated *in vacuo* to a volume of 8 l. This material was triturated five times with 6% HCl (total of 200 l.) to give an acid solution and 1.3 kg of residual gums. The acid solution was extracted with ether (58 l.) to give 16.5 g of ether-extractable solids. The remaining acid layer was basified to pH 9.1 with NH_4OH and extracted twice with 80 l. of chloroform. The chloroform-soluble material yielded on evaporation the nonquaternary alkaloids (486 g). The aqueous solution was acidified to pH 1.8 with HCl and treated with ammonium Reineckate to precipitate the quaternary alkaloids (658 g, as Reineckates) and the remaining aqueous solution was then discarded. Continuous ether extraction of a portion of the nonquaternary alkaloids (172 g) for 21 days gave 96 g of ether-soluble alkaloids and left a residue of 75.5 g of ether-insoluble alkaloids.

4-Demethylhasubanonine (Ia).—The ether-soluble alkaloids (96 g) were chromatographed over 3.4 kg of SilicAR CC-7 (100–200 mesh, Mallinckrodt) in chloroform. After elution with chloroform (7 l.), the solvent was changed to 1% methanol–chloroform and after eluting with 4 l. of this solvent (*ca.* one retention volume) the crude 4-demethylhasubanonine was eluted with the next 9 l. of solvent. Fractions containing this material were combined to give 18.96 g of crude material which was dissolved in methanol (30 ml) and treated with 6.7 g of oxalic acid dihydrate in 30 ml of methanol. The resulting solution was heated to boiling on the steam bath, anhydrous ether was added to turbidity, and the mixture was allowed to crystallize. Two subsequent recrystallizations from methanol–ether gave pure 4-demethylhasubanonine (Ia) oxalate (12.32 g): mp 198–199°; $[\alpha]^{32}D$ −123° (*c* 3.46, methanol); λ_{max}^{EtOH} 266 mμ (ε 8400); λ_{max}^{KBr} 2.90, 3.39, 4.02, 5.85, 5.96 μ; *m/e* 359, 344, 328, 301, 300, 245.

Anal. Calcd for $C_{20}H_{25}NO_5 \cdot C_2H_2O_4$: C, 58.79; H, 6.06; N, 3.12. Found: C, 58.91; H, 6.02; N, 3.58.

4-Demethylhasubanonine Perchlorate.—4-Demethylhasubanonine oxalate (60 mg) was treated with excess 5% aqueous K_2CO_3 and extracted three times with chloroform (30 ml). The chloroform extracts were combined, dried (Na_2SO_4), and evaporated *in vacuo* to yield 48 mg of 4-demethylhasubanonine. A dilute methanolic solution of perchloric acid was added until the resulting solution was distinctly acid to litmus. The resulting solution was evaporated and the residue crystallized on addition of water. The crystalline material was filtered and recrystallized twice from chloroform–ether to give colorless needles (37 mg): mp 229–230°; $[\alpha]^{32}D$ −145° (*c* 0.51, methanol); λ_{max}^{EtOH} 262 mμ (ε 8360); λ_{max}^{KBr} 2.95, 3.25, 3.36, 5.95, 6.15, 6.69 μ.

4-Demethylhasubanonine Brosylate (Ib).—To *p*-bromobenzenesulfonyl chloride (2.71 g) in pyridine (dried over KOH) was added 236 mg of 4-demethylhasubanonine (liberated from oxalate salt as above) and the mixture was allowed to stand for 15 hr. The reaction mixture was taken up in 50 ml of chloroform and shaken with a saturated solution of $NaHCO_3$ to pH 8. The chloroform layer was removed and the aqueous phase extracted with three more portions of chloroform. The combined, dried (Na_2SO_4) chloroform solution was evaporated and residual pyridine was azeotroped with dry benzene to give a pale yellow oil which crystallized on trituration with Skellysolve B. Three crystallizations from acetone–Skellysolve B gave colorless needles (57 mg): mp 209–211°; $[\alpha]^{29}D$ −149° (*c* 0.42, $CHCl_3$); λ_{max}^{EtOH} 233 mμ (ε 21,750), 269 (14,650); λ_{max}^{Nujol} 3.41, 6.00, 6.21, 6.72, 7.29, 8.50 μ; *m/e* 578, 576, 358, 301, 300, 299, 158, 156.

Anal. Calcd for $C_{26}H_{28}NSO_7Br$: C, 53.97; H, 4.88; N, 2.42; Br, 13.82. Found: C, 54.06; H, 4.94; N, 2.39; Br, 13.72.

Hasubanonine (Ic).—A solution of diazomethane prepared from Diazald (4 g, Aldrich) was added to 280 mg of 4-demethylhasubanonine in methanol (5 ml). The reaction was kept in the dark at room temperature overnight. The resulting colorless solution was evaporated, dissolved in benzene, and chromatographed over 20 g of acid-washed alumina (Merck) in benzene. Elution was carried out with 25% chloroform–benzene and the fractions were monitored by tlc (5% methanol–chloroform on silica plates visualized by spraying with Dragendorff reagent) until no more product was eluted. The combined fraction from 25% chloroform–benzene gave pure hasubanonine (Ic, 162 mg). Subsequent elution with chloroform gave 125 mg of unreacted starting material. Oxalic acid dihydrate (54 mg) in methanol was added to a methanolic solution of the hasubanonine. Two recrystallizations of the product from methanol–ether gave colorless needles (93 mg): mp 192–193°; $[\alpha]^{32}D$ −134° (*c* 0.82, methanol); λ_{max}^{EtOH} 267 mμ (ε 8300); λ_{max}^{KBr} 2.90, 3.38, 4.08, 5.78, 5.94, 6.17, 6.71 μ.

Anal. Calcd for $C_{21}H_{27}NO_5 \cdot C_2H_2O_4$: C, 59.60; H, 6.31; N, 3.02. Found: C, 59.45; H, 6.51; N, 2.98.

Hasubanonine Hydrochloride.—Hasubanonine (55 mg) in chloroform (20 ml) was treated with HCl gas bubbled through the solution for 2 min. The solution was evaporated and the residue crystallized twice from chloroform–ether to give colorless needles (42 mg): mp 210–211°; $[\alpha]^{28}D$ −133° (*c* 1.14, methanol); λ_{max}^{EtOH} 268 mμ (ε 7300); λ_{max}^{Nujol} 3.41, 4.36, 5.96, 6.15, 6.72 μ; *m/e* 373, 358, 342, 315, 314, 284, 258, 245.

Anal. Calcd for $C_{21}H_{27}NO_5 \cdot HCl$: C, 61.53; H, 6.88; N, 3.42. Found: C, 61.08; H, 6.92; N, 3.58.

Hasubanonine Methiodide.—Hasubanonine (65 mg) in anhydrous benzene (2 ml) was treated with 0.5 ml of CH_3I (Aldrich) and the reaction was maintained at reflux for 2 hr. The crystalline material which was separated was recrystallized, first from methanol–ether and then methanol–water, to give colorless prisms (55 mg): mp 171–173° (lit.[20] mp 178°); $[\alpha]^{27}D$ −61° (*c* 0.28, methanol); λ_{max}^{EtOH} 264 mμ (ε 11,900); λ_{max}^{KBr} 2.84, 2.89, 3.39, 5.95, 6.18, 6.71 μ.[21]

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(21) NOTE ADDED IN PROOF.—Since submission of the manuscript, we have isolated and characterized 4-demethylnorhasubanonine, $C_{19}H_{23}NO_5$:[6b] mp 116–119° (chloroform–ether); $[\alpha]^{25}D$ −219° (*c* 1.30, methanol); λ_{max}^{MeOH} 266 mμ (ε 11,750); λ_{max}^{KBr} 3.02, 6.02 μ; M^+, *m/e* 345. Oxalate: mp 192–193° (methanol–ether); $[\alpha]^{25}D$ −159° (*c* 1.34, methanol); λ_{max}^{MeOH} 232 mμ sh (ε 11,185), 264 (9320); λ_{max}^{KBr} 2.89, 5.86, 5.98 μ. N-Methylation with methyl iodide gave Ia, characterized by ir, nmr, and tlc comparison with 4-demethylhasubanonine. The melting point of the oxalate salt was not depressed by admixture of authentic Ia oxalate.

Registry No.—Ia oxalate, 17968-59-1; Ia $HClO_4$, 18026-68-1; Ib, 17968-58-0; Ic oxalate, 18006-26-3; Ic HCl, 18006-27-4; Ic MeI, 18006-28-5.

A Small-Scale Synthesis of Mevalonolactone and Its 3-Ethyl-2-^{14}C Homolog

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Mevalonic acid (or its lactone, 3,5-dihydroxy-3-methylpentanoic acid γ-lactone, **2b**) has long been recognized as a precursor of the isoprene unit used by living systems in biosynthesis.[1] Analogs of mevalonolactone, however, have not been extensively tested in biological systems. Tamura, *et al.*,[2] and Stewart and Woolley[3] have synthesized several homologs and tested them for antimetabolic activity, but the question whether 3,5-dihydroxy-3-ethylpentanoic acid γ-lactone (**2a**, the 3-ethyl homolog of mevalonolactone) is metabolized by living systems was left unanswered. In order to obtain material for such a study,[4] we undertook the synthesis of **2a** labeled with ^{14}C in the 2 position.

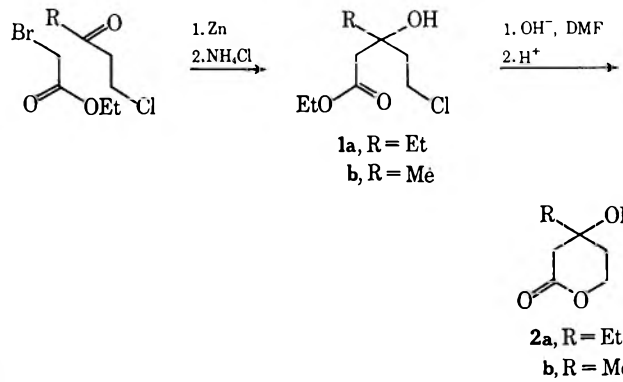
Compound **2a** has been synthesized by Tamura and Takai[5] by the method used for mevalonolactone.[6] The tetrahydropyranyl ether of the appropriate 3-keto alcohol was treated with allylmagnesium bromide; the protecting group was removed; the terminal olefin was cleaved by ozonolysis; and the lactone was obtained upon work-up, during which cyclization of the dihydroxy acid occurred.

Several other mevalonolactone syntheses have been reported. Those based on Hoffman's synthesis[7] involve a Reformatski reaction between ethyl bromoacetate and 4-acetoxy-2-butanone.[8-10] After saponification of the resulting diester, the lactone forms upon acidification. Hulcher and Hosick[11] reported an internal Reformatski reaction of 4-(bromoacetoxy)-2-butanone prepared from bromoacetyl bromide and 4-hydroxy-2-butanone. Cornforth and coworkers have reported syntheses of mevalonolactone labeled in both the 4 position and methyl group, and the 4 position alone.[12] They have also synthesized stereospecifically the (+) and (−) forms from (−)- and (+)-linalool, respectively.[13]

For the small-scale preparation of radioactively labeled **2a** or **2b**, each of the above sequences suffers from one or more of the following deficiencies: (a) three or more steps in the reaction scheme, (b) relatively low over-all conversion, (c) commerical unavailability of one of the starting materials. In addition, the final product is distilled in each of these procedures, thus making it desirable to devise another method of purification for small-scale work. We have therefore developed the procedure described below.

Compounds **2a** and **2b** have been prepared by the sequence shown in Scheme I. Where R = Et, the

SCHEME I



yield of purified product in each step is generally about 65–70%.[14] This procedure has the advantages that the sequence consists of only two steps, the starting materials are commercially available, the use of tlc in purification permits very small-scale reactions, and the product can be labeled at the 1 or 2 positions *via* the ethyl bromoacetate and at the 3 position or alkyl group *via* the acid chloride used in preparation of the chloro ketone.[15,16]

Experimental Section

Infrared spectra were determined with a Beckman Model IR-8 or a Perkin–Elmer Model 237-B spectrophotometer. The nmr spectra were determined with a Varian Model A-60 spectrometer. The chemical shifts are expressed in τ values relative to tetramethylsilane as an internal standard. Gross appearance of the peaks is reported, though some signals show higher order splitting. Mass spectra were obtained with an LKB-9000 combined gas chromatograph–mass spectrometer.[17] All spectra reported, with the exception of the ir spectrum of **2a**, are of nonradioactive materials. Preparative tlc was conducted using air-dried, unactivated[18] Mallinckrodt TLC-7GF[19] silicic acid. The 1-chloro-3-pentanone and 4-chloro-2-butanone were purchased from Aldrich and Chemical Procurement Labora-

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(14) In the single preparation of mevalonolactone (R = Me), the hydrolysis step went in lower yield (52%).
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(17) We wish to thank the National Institutes of Health for the grant with which this instrument was purchased, and Dr. C. C. Sweeley and Mr. John Naworal for the spectra.
(18) The use of freshly prepared and activated layers can cause extensive dehydration during attempted purification of the lactone.
(19) In this system, cleaner products are obtained from Mallinckrodt TLC-7GF silicic acid than from Merck silica gel G.

tories, respectively,[20] and were evaporatively distilled and stored in a freezer over type 5A molecular sieve prior to use. Gas chromatographically analyzed ethyl bromoacetate-2-^{14}C (1.5 mc; 2.09 mc/mmol) was purchased from Mallinckrodt Nuclear. Syringes were dried, when necessary, by flushing with ether which had been dried over type 4A molecular sieve. The molecular sieve was heated for at least 6 hr at 180° in a vented oven before use.

Ethyl 3-Ethyl-3-hydroxy-5-chloropentanoate-2-^{14}C (1a).—A micro stirring bar and 69.5 mg (1.06 mmol) of freshly treated zinc[21] were introduced into a 3-ml flask blown from 8-mm tubing. The flask was stoppered with a silicone rubber gas chromatographic septum and dried by flushing *via* hypodermic needles with dry nitrogen while it was heated at about 70° with a hot air blower for about 6 hr. The ethyl bromoacetate-2-^{14}C (0.718 mmol, calculated from the specific activity assuming quantitative transfer—not actually realized) was diluted with 300 μl of dry ether and transferred by syringe onto approximately 0.5 g of type 4A molecular sieve in a serum-cap-stoppered 5-ml dry pointed flask. Ether rinsings (four 300-μl portions) from its vial were similarly injected. About 82 μl (87.6 mg, 0.727 mmol) of 1-chloro-3-pentanone was injected into a flame-dried septum-stoppered pointed test tube, weighed, diluted with 100 μl of dry ether, and transferred by syringe onto the molecular sieve. One 100-μl rinsing from the test tube was also injected. The reagent mixture was allowed to dry for 3 hr[22] and was then injected into the reaction flask. The molecular sieve was rinsed with dry ether (two 250-μl portions), and the rinsings were injected into the reaction flask. The septum was sealed with a few drops of melted paraffin wax, and the reaction mixture stirred at room temperature for 18 hr. At the end of this time the solution was clear and the zinc was noticeably depleted. A further 48 hr of stirring produced no visible change. The reaction mixture was quantitatively transferred to a 5-ml flask, and hydrolyzed by magnetically stirring it for 0.5 hr with 300 μl of saturated ammonium chloride solution and 200 μl of water. The mixture was extracted 20 times by stirring with small portions of ether, the ether being withdrawn by syringe. The ether solution was dried ($MgSO_4$) and concentrated, leaving 115.4 mg of light yellow liquid. This was purified by tlc using chloroform–carbon tetrachloride (36:14) for development. The plate was scraped from just above the product front, visible as a light yellow line, to the top of the origin. The silicic acid was washed in a fine sintered funnel with several small portions of ether and the ether stripped, leaving 101.3 mg (68%) of purified product.

Analysis of the tlc-purified product by the combination vpc–mass spectrograph shows the presence of a small amount of the dehydrochlorinated compound, whose mass spectrum (70 eV) shows *m/e* 172 (molecular ion, small) and abundant fragment peaks at *m/e* 154, 143, 126, 109, 97, 81, 55, and others.

Spectra of the chlorohydroxy ester: ir (between salt plates) 3497 (OH), 1720 (C=O), 1193 (O—C), 715 (C—Cl) cm^{-1}; nmr (CCl_4) τ 5.82 (2 H, quartet, J = 7 cps, OCH_2CH_3), 6.28 (1 H, s, OH), 6.48 (2 H, t, CH_2CH_2Cl), 7.57 (2 H, s, $R_3CCH_2CO_2$), 7.9–9.3 ppm (10 H, multiplet); mass spectrum (70 eV) no molecular ion peak, chlorine-containing ion peaks in approximate 1:3 ratios at *m/e* 211, 209, 193, 191 (these high mass ions are visible only when the spectrum is off scale), 181, 179, 165, 163, 135, 133, 123, 121, abundant fragment peaks at *m/e* 145, 99, 91, 63, 57, and others.

3,5-Dihydroxy-3-ethylpentanoic Acid ζ-Lactone-2-^{14}C (2a).—A solution of 101.3 mg (0.485 mmol) **1a** in 180 μl of N,N-dimethylformamide and 40 μl water was stirred magnetically and heated at *ca.* 50° in a water bath, and 182 μl of *ca.* 5.4 *N* KOH solution (0.97 mmol) was added dropwise from a syringe. The first 90 μl was added at a rate of 1 drop/30 sec, the remainder at 1 drop/5 min. After addition of the base, the solution was stirred at 50° for 2 hr, during which a small amount of white solid formed. The mixture was cooled, and acidified to *ca.* pH 3 with 18% HCl, then acidified to *ca.* pH 2 with 5% HCl (short-range indicator paper was used). The acid solution was stirred for 10 min, transferred by means of three DMF and three ether washes into 10 ml of Spectro-Grade $CHCl_3$ which contained a large amount of magnesium sulfate, and stirred vigorously for a few minutes. The $MgSO_4$ was filtered on a fine sintered-glass funnel and washed with chloroform. On a rotary evaporator the filtrate was stripped of chloroform at 27° (*ca.* 20 mm) and then of DMF during 0.5 hr at 59–60° (0.2–0.8 mm); an ir spectrum (between salt plates) of the 66.6 mg of light yellow material remaining showed no band for DMF at 1664 cm^{-1}. After recovery of the material from the salt plates, the crude lactone was purified by tlc using ether for development. The plate was scraped from the product front, which was easily visible under a uv light or as a dampness of the layer, to the top of the origin. The silicic acid was washed with Spectro-Grade $CHCl_3$ (14 5-ml portions), and the solution was concentrated. The product consisted of 49.6 mg (71%) of light yellow liquid.

Spectra of the homomevalonolactone: ir (between salt plates) 3440 (OH), 1741–1717 (C=O), 1269 and 1236 (O—C), and nothing from the carbonyl to 1500 cm^{-1}; nmr ($CDCl_3$) 5.3–6.1 (2 H, multiplet, OCH_2CH_2), 7.18 (1 H, s, OH), 7.57 (2 H, s, $R_3CCH_2CO_2$), 8.1–8.7 (4 H, multiplet, $CH_3CH_2C(OH)(R)CH_2CH_2O$), 9.08 (3 H, t, CH_3CH_2) ± 3 ppm; mass spectrum (70 eV) molecular ion at *m/e* 144, abundant fragment peaks at 126, 115, 85, 71, 57, 53, and 43.

Radioanalysis of the Homomevalonolactone.[23]—In a liquid scintillation counter 1 μl of a 1:10 diluted solution of homomevalonolactone in $CHCl_3$ gave 3.43 × 10^5 dpm. An autoradiogram of 2 μl of this solution chromatographed on a 10% $AgNO_3$–Kieselgel G plate using chloroform–acetone (9:1) for elution showed a single spot. This system separates the hydroxy lactone from unsaturated lactone and open acid. A radiochromatogram of 1 μl of the above solution on a Packard Tri-Carb liquid scintillation spectrometer equipped with a 6-ft glass column packed with 3% OV-1 on Gas Chrom Q showed no detectable impurity except for a small amount of radioactivity which came off the column with the solvent and is attributed to decomposition in the instrument. Since the product peak on the vpc trace was a factor of 33 off scale, and we should be able to see a peak 1% of full scale, the maximum amount of impurity is estimated by vpc to be less than 0.03%.

Comments on Gas Chromatography of the Homomevalonolactone.—The presence of impurity peaks between the solvent and product peaks seems to be a function of instrumental conditions. An injection of a chloroform solution of reasonably pure homomevalonolactone onto a 10 ft × 1/8 in. steel column packed with 3% OV-1 on Gas Chrom Q (glass-lined injection port at 200°, column at 110°) showed a small impurity peak of 5% of full scale, while the product peak was off scale. Successive identical injections introduced two new impurity peaks which grew relatively larger with each injection. Upon conditioning the column for 10 min at 280°, reestablishing the operating conditions, and reinjecting the same solution, the cycle was repeated. Injection onto a freshly conditioned column followed by programming to 285° showed no spurious impurity peaks and only normal baseline rise. Another similar OV-1 column did not exhibit this behavior, but instead gave the above impurity peaks persistently; they were only slightly reduced upon reconditioning. The fully silanized glass column in the LKB-9000 combined vpc–mass spectrometer did not exhibit this anomalous behavior.

Ethyl 3-Methyl-3-hydroxy-5-chloropentanoate (1b).—Compound **1b** was prepared in 66% yield by the method given above for compound **1a** from 0.645 mmol of ethyl bromoacetate and 0.70 mmol of 4-chloro-2-butanone. Analysis of the tlc-purified product by the vpc–mass spectrograph showed relatively more dehydrochlorinated impurity than was present in its homolog **1a**. The impurity's mass spectrum (70 eV) shows *m/e* 158 (molecular ion, small) and abundant fragment peaks at *m/e* 143, 140, 131, 112, 97, 95, 88, 71, 55, and others. The mass spectrum of the chlorohydroxy ester **1b** shows no molecular ion peak, but abundant fragment peaks in approximate 1:3 ratios at *m/e* 181, 179 and 109, 107, and other fragments at *m/e* 143, 131, 113, 107, 91, 85, 71, and others.

3,5-Dihydroxy-3-methylpentanoic Acid δ-Lactone (2b).—Mevalonolactone (**2b**) was prepared by the method given above for compound **2a** from 80.7 mg of chlorohydroxy ester **1b** which contained a significant amount of dehydrochlorinated impurity. Assuming pure **1b** for purposes of calculation, the yield of the tlc-purified mevalonolactone was 52%. The ir and nmr spectra

(20) "Chem Sources," 8th ed, Directories Publishing Co., 1967, lists Frinton Laboratories, S. Vineland, N. J. 08360, as anad ditional source of 4-chloro-2-butanone.

(21) Zinc granules were washed successively with dilute HCl, water, acetone, absolute ethanol, and absolute ether. Traces of solvent were removed in a vacuum desiccator.

(22) If the ether (1800 μl) is saturated with water rather than predried, the solution is sufficiently dry at the end of 10 hr.

(23) We wish to thank Miss Sandy Baumann of Dr. C. C. Sweeley's research group for these results.

match Sadtler No. 21402[24] and Varian Associates No. 466[25] standard spectra, respectively.

Registry No.—1a (2-^{14}C), 17923-95-4; 1b, 17943-79-2; 2a (2-^{14}C), 17923-96-5; 2b, 503-48-0.

(24) Sadtler Standard Spectra, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967.
(25) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, 1963.

Participation of a Cyclopropane Ring in Extension of Conjugation

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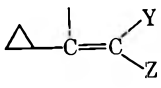
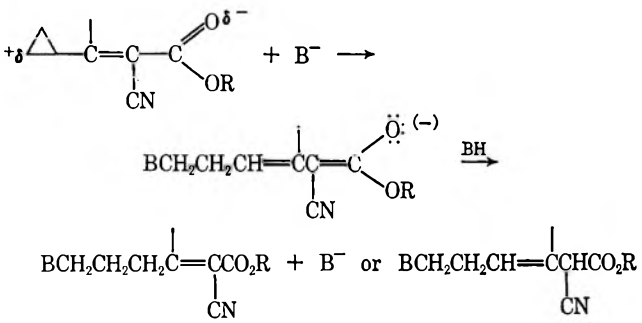
An earlier report from this laboratory[1] described ring-opening addition reactions between nucleophilic reagents and cyclopropanes which were substituted on one carbon atom of the ring by two electron-withdrawing groups.

In one simple extension of this work, the study reported here was made of the reactions of nucleophiles with structures of the type



where Y and Z represent electron-withdrawing groups such as ester and nitrile. In such reactions, extension of conjugation by participation of the cyclopropane ring would result in ring-opening 1,6 addition, whereas

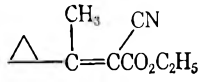


lack of participation by the ring would result in simple addition to the carbon–carbon double bond.

There are conflicting reports with respect to the ability of a cyclopropane ring to participate in conjugation (see typical ref 2–7, and references cited therein).

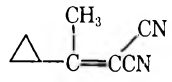
(1) J. M. Stewart and H. H. Westberg, *J. Org. Chem.*, **30**, 1951 (1965).
(2) R. C. Fuson and F. N. Baumgartner, *J. Amer. Chem. Soc.*, **70**, 3255 (1948).
(3) L. I. Smith and E. R. Rogier, *ibid.*, **73**, 3840 (1951).
(4) R. H. Eastman, *ibid.*, **76**, 4115 (1954).
(5) A. Pawda, L. Hamilton, and L. Norling *J. Org. Chem.*, **31**, 1244 (1966).
(6) W. G. Dauben and E. J. Deving, *ibid.*, **31**, 3794 (1966).
(7) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3810 (1967).

Using the method described by Cope, *et al.*,[8] for acid-catalyzed condensation of ketones with active methylene compounds, the desired starting materials, ethyl 2-cyano-3-cyclopropyl-2-butenoate (compound **1**),



1

2-cyano-3-cyclopropyl-2-butenenitrile (compound **2**),



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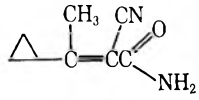
and 2-cyano-3-cyclopropyl-2-butenamide (compound **3**)



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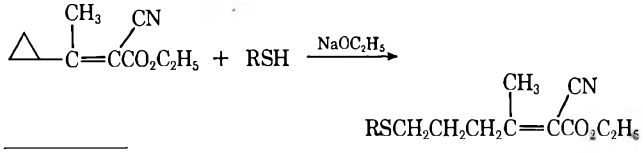
were prepared in good yield from methyl cyclopropyl ketone. Compound **1** was apparently a mixture of the geometrical isomers, a liquid and a crystalline solid, in approximately a 3:4 ratio. Both had the same infrared and near-infrared spectra and essentially the same elemental analysis. The liquid could be partially converted into the solid by heating at 140°. An equilibrium was apparently involved, for, if some of the solid was removed, more would form on further heating. The structure in which the methyl group is *cis* with respect to the nitrile group has been assigned to the solid isomer on the basis of nmr data. The methyl group singlet of the solid appears at the same point (δ 1.83) as observed in the spectrum of **2**, whereas in the liquid isomer this methyl group singlet appears at 1.73. The nitrile group thus apparently exerts a greater anisotropic deshielding effect than does the carboethoxy group.

Compound **3** also appeared to be a mixture of geometrical isomers. However, both were solids and separation was not so easily effected as in the case of **1**. The higher melting isomer was the major component of this mixture and was obtained pure by repeated recrystallizations. Attempts to prepare ethyl 2-carboethoxy-3-cyclopropyl-2-butenoate from methyl cyclopropyl ketone and diethyl malonate, using a variety of catalysts and reaction conditions, failed to give any of the desired product.

Reaction of **1** with benzenethiol and with 1-butanethiol in the presence of sodium ethoxide gave only one product in each case, resulting from exclusive 1,6 addition. The nmr spectra showed a complete absence of ethylenic protons in these products, indicating that the carbon–carbon double bond was entirely in a conjugated position. There were also no signals in the cyclopropyl hydrogen region of the spectra. (The complete nmr data are listed in the Experimental Section.)

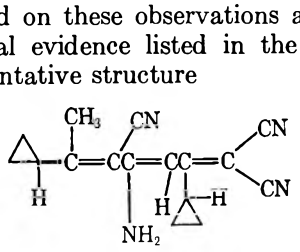


(8) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenberg, *ibid.*, **63**, 3452 (1941).

Characteristic absorption bands at 1.62–1.65 and at 2.22–2.25 μ in the near-infrared spectra have been reported by several investigators[9,10] as providing good evidence for the presence of a cyclopropane ring. In the near-infrared spectra of the addition compounds of **1** and thiols, neither of these characteristic absorption bands was present. This confirms the nmr evidence and again indicates a 1,6-addition product. In the infrared region these compounds gave a strong absorption band at 6.22 μ for the conjugated C=C group.

Reactions between various secondary amines and **1** failed to give any of the desired addition products. Short reaction times, using a solution of the reactants in ethanol in a sealed tube at 100–120°, gave mainly starting materials plus some polymer. Longer reaction times gave mainly polymers. Some of these reactions were attempted in refluxing butanol, and a new liquid compound was isolated which was the same regardless of which secondary amine was used. This compound proved to be *n*-butyl 2-cyano-3-cyclopropyl-2-butenoate, resulting from an amine-catalyzed transesterification reaction. Triethylamine failed to catalyze this exchange. Such transesterifications involving amine catalysts have been reported previously.[11]

The addition reactions of **2** were first attempted with secondary amines. Use of dimethylamine, diethylamine, and piperidine all resulted in the isolation of a single reaction product. This was a slightly yellow crystalline solid which gave the same elementary analysis as the liquid starting material. A molecular weight determination and integration of the nmr spectrum indicated that this substance was a dimer of **2**. Evidence for a possible structure for this dimer is mainly based on the ir and nmr spectra. A broad signal in the nmr spectrum at δ 5.70 with an intensity of 2 was assigned to an $-NH_2$ group, and this was confirmed by absorptions at 2.88 and 2.96 μ in the ir spectrum. A split singlet with intensity of 1 at δ 4.52 and 4.55 is believed to be due to a hydrogen attached to a carbon–carbon double bond, the splitting being due to *cis–trans* isomerism. This assignment is supported by an absorption band at 10.82 μ in the ir spectrum. The remaining 13 hydrogens all gave signals appearing as a complex multiplet between the limits of δ 0.2 and 1.66 plus one sharp singlet imposed on this multiplet at 1.23 (intensity 3). This indicates only one remaining methyl group. The compound's light yellow color and its very intense absorption in the uv spectrum centered at 323 mμ indicate a very highly conjugated system. Based on these observations and other confirming spectral evidence listed in the Experimental Section, the tentative structure



is proposed. The primary enamine grouping would be stabilized by the highly conjugated system. It is anticipated that further work will be done in an effort to elucidate further the structure of this dimer by means of chemical degradation.

Reactions of **2** with benzenethiol or 1-butanethiol in the presence of sodium ethoxide apparently gave only polymeric material.

Reactions of **3** with secondary amines failed to yield any simple addition products, and attempts to carry out base-catalyzed additions of thiols resulted only in polymers.

(9) W. H. Washburn and M. J. Mahoney, *J. Amer. Chem. Soc.*, **80**, 504 (1958).

(10) P. G. Gassman, *Chem. Ind.* (London), 740 (1962).

(11) D. W. Woodward, U. S. Patent 2,970,986 (1961); *Chem. Abstr.*, **55**, 12921 (1961).

Experimental Section

Elemental analyses were performed by Galbraith Laboratories Knoxville, Tenn. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer and on a Varian HA-60 spectrometer, using tetramethylsilane as the internal standard. Near-infrared spectra were obtained with a Hitachi Perkin–Elmer Model EPS-3T spectrophotometer, and the infrared spectra were obtained with a Beckman Model IR-5.

Condensation of Methyl Cyclopropyl Ketone[12] with Active Methylene Compounds. Preparation of 1, 2, and 3.—The condensation procedure followed the method described by Cope,[8] in which a mixture of the reactants in benzene was heated at reflux temperature in the presence of acetic acid and ammonium acetate and with a water separator.

A. Ethyl 2-Cyano-3-cyclopropyl-2-butenoate (1). Condensation with Ethyl Cyanoacetate.—After the initial reflux period of 24 hr, the solution was cooled; an equal volume of ether was added; and the solution was washed twice with water. It was then dried ($CaCl_2$) and concentrated on a steam cone, and the residue was recrystallized (70% ethanol), giving a 48% yield of the solid geometrical isomer of **1**. After six recrystallizations, this isomer melted at 81–82°: nmr ($CHCl_3$) δ 4.13 (q, 2, OCH_2CH_3), 2.22 (m, 1, cyclopropyl methine), 1.83 (s, 3, CH_3—C=C), 1.2 (t, 3, OCH_2CH_3), and 0.93 ppm (m, 4, cyclopropyl methylenes).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.33. Found: C, 66.68; H, 7.21.

The mother liquor from the first alcohol crystallization was diluted with water; the solution was saturated with sodium chloride and was extracted twice with ether. The ethereal extract was dried ($MgSO_4$), concentrated under reduced pressure, and distilled, giving a 35% yield of the liquid isomer of **1**: bp 98–99° (0.1 mm); $n^{25}D$ 1.5117; nmr signals were identical with those of the solid isomer except for a CH_3—C=C peak at 1.73 ppm.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.33; N, 7.81. Found: C, 66.84; H, 7.37; N, 7.91.

The infrared spectra of the isomers were identical in most details and included $\lambda_{max}^{CCl_4}$ 4.50 (w, C≡N), 5.80 (vs, ester C=O), and 6.32 (s, conjd C=C) μ. The near-infrared spectra showed the definitive cyclopropane C–H absorptions: $\lambda_{max}^{CCl_4}$ 1.635 (w) and 2.220 (s) μ.

B. 2-Cyano-3-cyclopropyl-2-butenenitrile (2). Condensation with Malononitrile.—Following the reflux period, the initial crude product was isolated as described for **1** above. Recrystallization (70% ethanol) gave an 88% yield of **2**, after three recrystallizations: mp 65.0–66°; $\lambda_{max}^{CCl_4}$ 4.46 (s, C≡N), 6.36 (s, conjd C=C) μ; near-ir (CCl_4) 1.627 (m) and 2.222 μ (s, cyclopropyl); nmr ($CHCl_3$) δ 2.25 (m, 1, cyclopropyl methine), 1.83 (s, 3, CH_3—C=C), and 1.15 ppm (m, 4, cyclopropyl methylenes).

Anal. Calcd for $C_8H_8N_2$: C, 72.69; H, 6.11. Found: C, 72.76; H, 6.36.

C. 2-Cyano-3-cyclopropyl-2-butenamide (3). Condensation with Cyanoacetamide.—Following the heating period of 8 hr at 115°, the mixture was chilled, diluted with an equal volume of ligroin, and filtered to give slightly yellow crystals (73%), mp 125–155°, as a mixture of geometric isomers. Two recrystallizations from benzene, followed by one from 95% ethanol, afforded the higher melting isomer as colorless long needles: mp 167–168°; ir λ_{max}^{KBr} 2.97 (s, NH_2), 3.15 (s, NH_2), 4.52 (m, C≡N), 6.08 (s, amide C=O), 6.34 (s, conjd C=C) μ; near-ir $\lambda_{max}^{acetone}$ 1.625 (m, cyclopropyl), and 2.2+ μ (absorption obscured by solvent).

(12) G. W. Cannon, R. C. Ellis, and J. R. Leal, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 597.

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.97; H, 6.72; N, 18.66. Found: C, 64.12; H, 6.71; N, 18.80.

Reaction of 1 with Benzenethiol.—To a solution of 0.05 g (0.0022 g-atom) of sodium in 20 ml of absolute ethanol was added 3.3 g (0.03 mol) of benzenethiol and then 4.5 g (0.025 mol) of 1, and the mixture was heated at reflux for 7 hr under argon. The ethanol was distilled under reduced pressure, and an ether solution of the residue was washed three times with water and once with saturated sodium chloride solution and dried ($CaCl_2$). Concentration under reduced pressure left 4.5 g of crude product which was distilled to give 3.5 g (48%) of colorless liquid (ethyl 2-cyano-3-methyl-6-phenylthio-2-hexenoate): bp 167–168° (0.2 mm); $n^{25}D$ 1.5558; near-ir $\lambda_{max}^{CCl_4}$ 1.72 (s), 1.79 (m), 2.18 (s), 2.29 (s), 2.33 (s), 2.38 (m), 2.44 (m), 2.50 (s) μ; ir $\lambda_{max}^{CCl_4}$ 4.5 (m, C≡N), 5.76 (s, ester C=O), 6.21 (s, C=C), 13.6 and 14.5 (s, C_6H_5) μ; nmr ($CDCl_3$) δ 7.25 (m, 5, C_6H_5), 4.22 (q, 2, OCH_2CH_3), 2.78 (m, 4, $SCH_2CH_2CH_2C$=C), 2.17 and 2.27 (each a singlet, *cis*- and *trans*-CH_3—C=C—), 1.86 (m, 2, $SCH_2CH_2CH_2C$=C), and 1.28 ppm (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{16}N_{19}NSO_2$: C, 66.39; H, 6.63; N, 4.84. round: C, 66.28; H, 6.71; N, 4.88.

Reaction of 1 with 1-Butanethiol.—The reaction was carried out as described for thiophenol, using 2.75 g of 1-butanethiol. Final distillation gave 2.2 g of colorless liquid ethyl 2-cyano-3-methyl-6-butylthio-2-hexenoate: bp 142–143° (0.2 mm); $n^{25}D$ 1.4992.

Anal. Calcd for $C_{14}H_{23}NO_2S$: C, 63.36; H, 8.73. Found: C, 63.19; H, 8.50.

Both infrared and near-infrared spectra showed absorptions similar to the thiophenol product except for the absence of peaks due to the aromatic ring.

Reaction of 2 with Secondary Amines. Formation of Dimer.—A secondary amine (0.022 mol) was added at a fast rate dropwise to a solution of 2 g (0.015 mol) of 2 in 10–15 ml of absolute ethanol. Dimethylamine, diethylamine, or piperidine were used. A reaction occurred immediately, and after 1 hr, concentration under reduced pressure left a thick red oil which crystallized to a large extent after standing in the refrigerator for several days. Recrystallization (50% ethanol) gave yields of 0.5–1.3 g of light yellow crystals, mp 115–116°. A final recrystallization for an analytical sample was best accomplished from heptane: mol wt, calcd 264, found (benzene) 278; ir $\lambda_{max}^{CHCl_3}$ 2.88 (w, NH_2), 2.96 (m, NH_2), 4.55 (m, conjd C≡N), 6.1–6.16 (s), 6.34 (m, conjd C=C), 9.75 (m, broad, cyclopropyl), and 10.82 μ (w, broad, —C=C—H); nmr ($CHCl_3$) δ 5.71 (s, broad, 2, $-NH_2$), 4.62 and 4.65 [two singlets due to geometric isomers, 1, $-(NH_2)CH$=C], 1.23 (s, 3, CH_3—C=C), and 0.2–1.66 ppm (m, 10, two cyclopropyl).

Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.69; H, 6.11; N, 21.20. Found: C, 72.91; H, 6.02; N, 21.37.

Transesterification of 1 with 1-Butanol in the Presence of Amines.—Diethylamine, piperidine, and morpholine all catalyzed this reaction to give the same single product in yields ranging from 32% for morpholine to 59% for the other two. The amine (0.048 mol) was dissolved in 20 ml of 1-butanol and added dropwise to a refluxing solution of 7.1 g (0.04 mol) of 1 in 30 ml of 1-butanol. The mixture was heated at reflux for an additional 2 hr and concentrated under reduced pressure, and the residue was distilled to give a colorless oil, *n*-butyl 2-cyano-3-cyclopropyl-2-butenoate: bp 109–110° (0.1 mm); $n^{25}D$ 1.5022.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.52; H, 8.28; N, 6.76. Found: C, 69.34; H, 8.41; N, 6.90.

The same transesterification could be effected by use of Triton B (ratio, 17 mol of compound 1/1 mole Triton B) in 22% yield.

Registry No.—1 (solid), 17407-28-2; 1 (liquid), 17407-29-3; 2, 17407-30-6; dimer of 2, 17407-31-7; 3, 17407-32-8; $C_{16}H_{19}NSO_2$ (*cis*), 17407-33-9; $C_{16}H_{19}NSO_2$ (*trans*), 17407-34-0; $C_{14}H_{23}NO_2S$, 17407-35-1; $C_{12}H_{17}NO_2$, 17407-36-2.

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is made to the donors of this fund. We are also grateful to Dr. Graeme Baker of Montana State University, Bozeman, Mont., for some of the nmr spectra.

Isomerization of Terpenes. The Isomerization of (−)-Perillaldehyde to *p*-Mentha-1,3-dien-7-al with Aqueous Sulfuric Acid

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Isomerization of some terpenoid compounds with aqueous acid or alkali has been observed by several workers. (−)-Perillaldehyde (1), however, has not yet been included in these investigations.

In the present paper, a monoterpene $\alpha\beta,\gamma\delta$-dienal, *p*-mentha-1,3-dien-7-al (2), was obtained from 1 on treatment with aqueous sulfuric acid. The same dienal structure as 2 has been assigned by Goryaev[1] to an oxidation product of sabinene with selenic acid and also by Matsuura[2] to one of the oxidation products of α-terpinene with *t*-butyl chromate, independently.

The apparent discrepancies in physical properties,[1,2] however, were found between the present authors' data and those by Matsuura and Goryaev. Based on the evidence to be presented below, it may be concluded that acid-catalyzed isomerization product of (−)-perillaldehyde is a monoterpene aldehyde, *p*-mentha-1,3-dien-7-al, different from the products described by Matsuura and Goryaev.

The isomerization of 1 was conducted in 10% aqueous sulfuric acid at 120–130° for 3 hr and afforded 2 in a 90% yield.

The absorption bands at 1666, 2700, and 2800 cm^{-1} in the ir spectrum of 2 are attributable to $\alpha\beta,\gamma\delta$-unsaturated aldehyde.[3-5]

In general, as the number of double bonds in conjugation increases, the C=C vibration tends to shift progressively toward lower frequencies and enhance the intensity,[6] so that the strong absorption at 1570 cm^{-1} is reasonably attributed to $\alpha\beta,\gamma\delta$ double bond conjugated with carbonyl group. Matsuura, however, has reported no absorption band in this region.

In addition to the ir data, the spectral assignment of these chromophores is demonstrated by the maximum absorption at 315 mμ (ϵ 15,600) which is comparable with the accepted absorption maximum at 320 mμ for the conjugated dienone system according to the Fieser rule. The absorption maximum and intensity at 305 mμ (ϵ 4500) of the compound reported by Matsuura are not only inconsistent with the authors', but also lower than the values to be expected from the structure 2.

Further evidence to support the structure of 2 was

(1) M. I. Goryaev and G. A. Tolstikov [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 72 (1962)] reported that the physical constants of the product were 2,4-DNPH mp 181–182° and semicarbazone mp 201–202°.

(2) T. Matsuura and T. Suga [*J. Org. Chem.*, **30**, 518 (1965)] reported that the physical constants of the product were ν_{max} 2750, 1670, 1375, 1357 cm^{-1}; λ_{max}^{MeOH} 305 mμ (ϵ 4500); 2,4-DNPH mp 230–231°, λ_{max}^{MeOH} 405 mμ (ϵ 28,000).

(3) A. Pozefsky and N. D. Coggeshall, *Anal. Chem.*, **23**, 1611 (1951).

(4) A. Ashdown and T. A. Kletz, *J. Chem. Soc.*, 1454 (1948).

(5) R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.*, **73**, 1403 (1951).

(6) R. N. Jones, P. Humphries, E. Packard, and K. Dobriner, *ibid.*, **72**, 86 (1950).

provided by the nmr spectrum (CCl_4). The methyl protons of the isopropyl group afford doublets at δ 0.99 and 1.10 ppm,[7] and the sharp band at δ 9.40 ppm unequivocally shows the presence of a CHO group carrying no α hydrogen. The line at δ 2.25 ppm consisting of four protons is assigned to CH_2 group in the ring. The signal at δ 5.92 and 6.68 ppm (each doublet J = 6 cps) can be assigned to vinyl protons of β and γ positions, respectively.

Compound 2 may be of synthetic interest from the viewpoint of its possessing the possibility of further transformations and it is fascinating that the compound can be obtained quantitatively by a simple procedure.

Experimental Section[8]

Acid Treatment on (−)-Perillaldehyde.—A mixture of (−)-perillaldehyde (10 g) and 10% aqueous sulfuric acid (150 ml) was refluxed for 3 hr at 120–130°; then the resulting solution was extracted with ether. The ether solution was neutralized, washed with water, dried over anhydrous sodium sulfate, and distilled *in vacuo* to give 9 g of 2, bp 81–82° (6 mm), in a 90% yield: d^{20}_4 0.9795; $n^{20}D$ 1.5283, MD 47.18° (calcd 45.06°); ν_{max} 2700, 2800, 1666 (CHO), 1570 ($\alpha\beta,\gamma\delta$-conjugated diene), 1360, 1380 (isopropyl), 780, 840 cm^{-1} (double bond); λ^{MeOH}_{max} 315 mμ (ϵ 15,600); δ 0.99, 1.10 (d, 6 H), 9.40 (s, 1 H), 2.25 (s, 4 H), 5.92, 6.68 ppm (each doublet J = 6 cps, 2 H); semicarbazone mp 193–194°.

Anal. Calcd for $C_{11}H_{17}ON_3$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.95; H, 8.49; N, 20.21.

Registry No.—1, 18031-40-8; 2, 1197-15-5; semicarbazone of 2, 18039-53-7; sulfuric acid, 7664-93-9.

Acknowledgments.—The authors are indebted to Dr. Yuzo Inouye, Institute for Chemical Research, Kyoto University, for his kind advice and suggestions. They also wish to express their thanks to Japan Electron Optic Laboratory Co., Ltd., for nmr analysis.

(7) S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron*, **18**, 1509 (1962).

(8) All melting and boiling points are uncorrected. Microanalysis was performed on a Yanagimoto CHN-corder. Ir spectrum was obtained with a Hitachi EPI-2 spectrophotometer using sodium chloride liquid film cell. Uv spectrum was obtained with a Hitachi EPS-3 recording spectrophotometer in methanol solution. The nmr spectrum has obtained with Japan nuclear magnetic resonance spectrum spectrophotometer JNM-4 H-100 in carbon tetrachloride contained tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in δ values (parts per million) from TMS.

Reaction of *gem*-Dibromocyclopropanes with Morpholine

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Received March 22, 1968

The reaction of *gem*-dihalocyclopropanes with electrophilic or nucleophilic reagents is a useful method of extending the carbon chain of olefins and leads to several otherwise difficultly accessible molecules.[2] In a previous paper[2] it was shown that a variety of electrophilic reagents readily react with *gem*-dihalocyclopropanes to yield allyl derivatives or dienes. Since no data exists in the literature on the reaction of basic nitrogen compounds with *gem*-dibromocyclopropanes to give N-substitution products, it was of interest to investigate the reaction of morpholine in the above reaction.

The results of this investigation indicate that refluxing a morpholine solution of substituted *gem*-dibromocyclopropane for 1–154 hr yields β-bromoallylmorpholines or the 3-bromo-1,3-diene as described in Tables I and II. The thermal ring opening of the neat *gem*-dibromocyclopropanes yielded in some cases isolable β-bromoallyl bromides or the 3-bromo-1,3-diene.

This ring-opening reaction takes place readily with the more highly alkylated *gem*-dibromocyclopropanes and follows the same order of reactivity observed with electrophilic reagents.[2] In the case of 1,1-dibromo-2,2,3,3-tetramethylcyclopropane (VII), 3-bromo-2,4-dimethyl-1,3-pentadiene (VIII) is obtained in 82% yield even in the absence of any solvent by heating to 160–162° for 2.5 hr. The reaction of 1,1-dibromo-2,2-dimethylcyclopropane (I) with morpholine yielded 3-bromo-2-methyl-4-morpholino-2-butene (II), whereas in the absence of morpholine 1,2-dibromo-3-methyl-2-butene (III) was obtained. The thermal ring opening of other neat *gem*-dibromocyclopropanes does not always lead to the isolation of clearly defined products.

Attempts to thermally rearrange the *cis*- and *trans*-butene-2-dibromocarbene adducts in the absence of solvent yielded tars. However, carrying out the same reaction in refluxing morpholine gave an immediate precipitation of morpholine hydrobromide from the *cis* adduct. The *trans* adduct gave a similar precipitation after a longer period of refluxing. Both *cis*- and *trans*-butene-2-dibromocarbene adducts yielded the same isomeric product (V) as shown by analysis using gas–liquid partition chromatography (glpc) and infrared (ir) and nuclear magnetic resonance (nmr) spectroscopy.

Recently[2] it was reported that these same *cis*- and *trans*-dibromocarbene adducts also yield one isomeric product upon reaction with aqueous silver nitrate or silver acetate–acetic acid.

In the case of *cis*- and *trans*-1,1-dibromo-2,3-dimethylcyclopropane the transition states obtained by the favored disrotatory process[3–5] can be formulated as shown in Scheme I, p 4539.

In agreement with the above predictions it is found that *cis*-dimethyl isomer reacts faster than the *trans* isomer. This has also been reported to be true for the *cis* and *trans* isomers of 1,1-dichloro-2-methyl-3-ethoxycyclopropane.[6] In the latter case the *cis* and *trans* isomers also undergo a ring-opening reaction in

(1) (a) The Borden Chemical Co., Central Research Laboratory, Philadelphia, Pa. 19124. (b) This research was described in part in the Ph.D. Thesis of S. R. S., The Pennsylvania State University, University Park, Pa. 1960.

(2) S. R. Sandler, *J. Org. Chem.*, **32**, 3876 (1967), and references cited therein.

(3) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965).

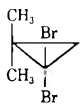
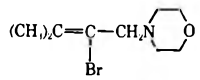
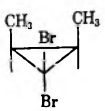
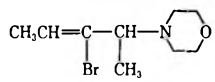
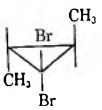
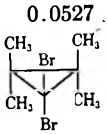
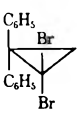
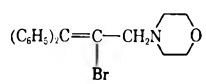
(4) C. H. DePuy, L. G. Schnack, J. W. Hauser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965).

(5) P. von R. Schleyer G. W. Van Dine, U. Schollkopf, and J. Paust, *ibid.*, **88**, 2868 (1966).

(6) L. Skattebøl, *J. Org. Chem.*, **31**, 1554 (1966).

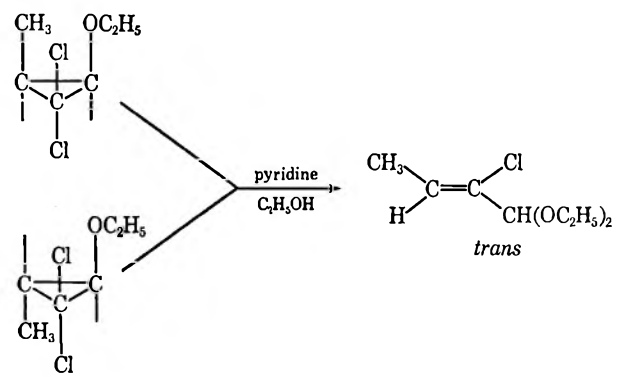
TABLE I

THE THERMAL RING-OPENING REACTION OF SUBSTITUTED *gem*-DIBROMOCYCLOPROPANES IN THE PRESENCE AND ABSENCE OF MORPHOLINE

gem-Dibromocyclopropane, mol	Morpholine, mol	Temp, °C	Time, hr	Product[a]	Yield, %	Bp, °C (mm)	n_D (°C)
 I 0.0527	0.207	128	72	 II	84	110 (5)	1.5121 (23)
I 0.0615	0	195–210	3	$(CH_3)_2C{=}C(Br){-}CH_2Br$ III	60	62–63 (3.5)	1.5471 (21)
 IV 0.0527	0.207	128	24	 V	55	103 (4.0)	1.5113 (20)
IV 0.0527	0	150	3	Tar			
 VI 0.0527	0.207	128	24	V	88	108–110 (5.0)	1.5080 (23)
VI 0.0527	0	150–170	3	Tar			
 VII 0.0277	0.207	128	1	$(CH_3)_2C{=}C(Br)(CH_3){-}C{=}CH_2$ VIII	36	46–47 (13.0)	1.4921 (20)
VII 0.100	0	160–162	2.5	VIII	82	47–48 (15.0)	1.4938 (19)
 IX 0.0284	0.207	128	154	 X	78	Mp 90–91	
IX 0.0284	0	150–170	24	Tar			

[a] The glpc analyses of the products were obtained on a 3- and 6-ft column packed with 25% silicone DC200 on Celite at concentration (P) obtained from The Burrell Corp., Pittsburgh, Pa.

the presence of pyridine and ethanol to give the same *trans* product as shown below.



The vinyl proton for *trans*-2-chloro-1,1-diethoxy-2-butene absorbs at δ 6.1 (=CH) which is similar to that observed in compound V (δ 5.78); hence by analogy we assign a *trans* configuration to the methyl group and the carbon bearing the morpholinyl group. The fact that none of the *cis* isomer is produced may be due to either isomerization of the *cis* product during this reaction or to a preferred attack by a nucleophile (morpholine) on carbonium ion (B) to give only the *trans* product. The direction of ring opening using morpholine is identical with that observed with electrophilic reagents[2] and with pyridine–ethanol.[6] Skattebøl found that 1,1-dichloro-2-ethoxy-3,3-dimethylcyclopropane gives a product similar to II on reaction with pyridine–ethanol which has the structure $(CH_3)_2C{=}CCl{-}CH(OC_2H_5)_2$. This compound shows a doublet in the nmr at δ 1.87 [$(CH_3)_2C{=}$] similar to that found for II at 1.83.

The mechanism given above is shown only to illustrate the Woodward–Hoffmann rules[3] and is not

TABLE II

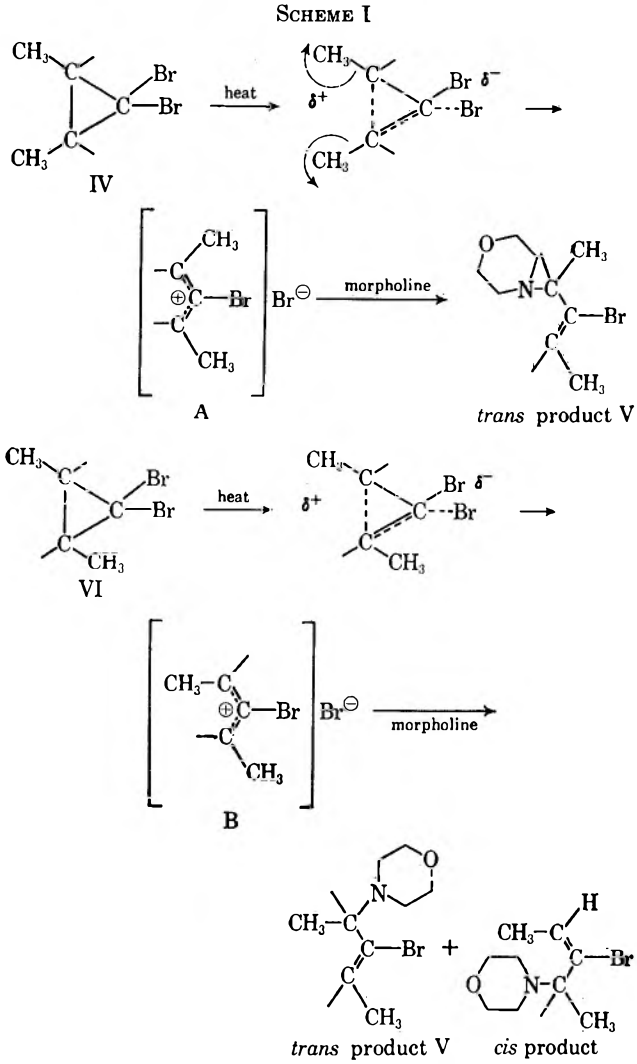
ELEMENTAL AND SPECTRAL ANALYSIS OF PRODUCTS FROM THE THERMAL AND MORPHOLINE INDUCED RING OPENING OF SUBSTITUTED *gem*-DIBROMOCYCLOPROPANES

Compd	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Spectral data[a]
II	46.20	6.85	46.03	6.90	Ir (neat) 6.05 (C=C), 9.0 μ (morpholino group); nmr doublet at δ 1.83 (CH_3C=C), singlet at 3.25 [CH_2—C(Br)=], and the characteristic absorption for the morpholine hydrogens
III	26.45	3.51	26.69	3.54	Ir (neat) 6.07 μ (C=C); nmr doublet at δ 1.83 (CH_3C=C) and a singlet at 4.32 (—CH_2Br)
V[b]	46.20	6.85	46.47	6.96	Ir (neat) 6.03, 11.59 (C=C), 8.98 μ (morpholino group); nmr doublet at δ 1.13 (CH_3CH—N—), doublet at 1.69 (CH_3CH=), quartet at 2.72 (N—CH—CH_3), quartet at 5.98 (CH_2—CH=), and characteristic absorption for the morpholine hydrogen
V[c]	46.20	6.85	46.37	6.99	Same as for compound V
VIII[d]	48.00	6.28	48.02	6.33	Ir (neat) 6.05, 6.12, 11.07, 11.35, 11.75 (C=C), 7.26 μ (CH_2); nmr singlet at δ 1.76 (CH_3C=C), singlet at 1.84 (CH_3C=C), singlet at 4.80 (—CH=C), and singlet at 4.91 (—CH=C)
VIII[e]	48.00	6.28	48.39	6.26	Same as for compound VIII
X	63.80	5.59	63.96	5.73	Ir (KBr) 3.30, 6.26 (C_6H_5), 3.45, 3.50, 3.57 (CH), 6.18, 11.48 (C=C), and 9.0 μ (morpholino group); λ_{max} (CH_3OH) 235 mμ (ϵ_{max} 12,400); nmr singlet at δ 3.25 [=(Br)C—CH_2N] singlet at 7.18 [C_6H_5—C=C(Br)—], and characteristic absorption for the morpholine hydrogens

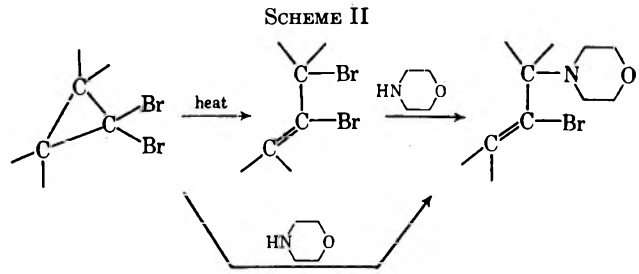
[a] The integrated spectra were consistent with the assigned structures. [b] Compound V obtained from compound IV. [c] Compound V obtained from compound VI. [d] Compound VIII obtained from VII in the presence of morpholine. [e] Compound VIII obtained from VII in the absence of morpholine.

meant to rule out the possibility of product formation through the thermally formed β-bromoallyl bromides. The results shown in Table I with compound I indicates that such a possibility might exist (Scheme II). In addition, it has been reported[7] that the solvolysis in 80% ethanol of 6,6-dibromobicyclo[3.1.0]hexane proceeds simultaneously by its direct reaction with solvent and with the thermally produced 2,3-dibromocyclohexene.

SCHEME I



SCHEME II



Experimental Section[8]

The dibromocarbene adducts were generally prepared by a procedure similar to those described earlier.[9-11] The results of these preparations are presented in a previous paper.[2]

General Procedure for the Thermal Ring-Opening Reaction of Substituted *gem*-Dibromocyclopropanes in the Presence and Absence of Morpholine.—To a single-neck round-bottom flask was added the particular *gem*-dibromocyclopropane with or without morpholine, and the contents were heated under a nitrogen blanket for the specified time. Samples were removed periodically and analyzed by glpc to determine the extent of reaction. Where morpholine was used, the samples were acidified and extracted with ether, dried, concentrated, and distilled under reduced pressure to obtain the product. The experimental conditions and products are described in more detail in Tables I and II.

Registry No.—Morpholine, 110-91-8; II, 17853-41-7; III, 17853-42-8; V, 17853-43-9; VIII, 4773-87-9; X, 17853-44-0.

Acknowledgment.—The author wishes to express his appreciation to Professor P. S. Skell of The Pennsylvania State University for his generous help throughout this investigation; to Mr. O. Lauver of the Pennsylvania State University and to Professor D. Swern of Temple University for obtaining the nmr spectra.

(7) L. Gatlin, R. E. Glick, and P. S. Skell, *Tetrahedron*, **21**, 1315 (1965).

(8) (a) The elemental analyses were obtained by Dr. Stephen M. Nagy, Belmont, Mass. (b) Melting and boiling points are uncorrected. The nmr spectra (in CCl_4) were recorded on a Varian Associates A-60-A spectrometer and the δ values are in parts per million from tetramethylsilane. The ultraviolet spectra were obtained on a Beckman DK-1 recording spectrophotometer.

(9) W. von E. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(10) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 3409 (1956).

(11) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

Preparation of 3,3,6,6-d_4-Cyclohexa-1,4-diene

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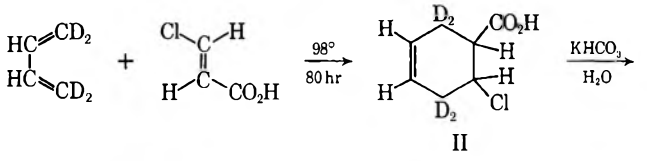
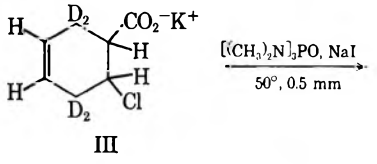
Received June 28, 1968

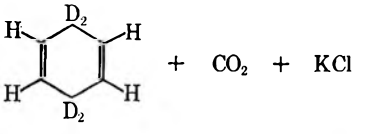
3,3,6,6-d_4-Cyclohexa-1,4-diene (I) was required in connection with some hydrocarbon pyrolysis studies. The well-known methods of preparing 1,4-cyclohexadiene by reduction of benzene[1] were not applicable in this case nor were the methods[2] used for the preparation of some other deuterated 1,4-cyclohexadienes. Therefore, a new 1,4-cyclohexadiene synthesis was devised. Its generality has not been investigated, but by proper choice of substituents on the butadiene or the β-chloroacrylic acid the preparation of a variety of substituted



II



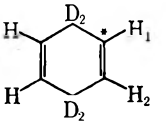
III



1,4-cyclohexadienes should be possible. One reason that this synthetic route was chosen is because 1,1,4,4-d_4-buta-1,3-diene is readily available,[3] and the reaction conditions are sufficiently mild so that hydrogen scrambling is unlikely.

Optimum reaction conditions were first established using unlabeled butadiene. The progress of the first step (Diels–Alder reaction) was followed with nmr. In the last step of the reaction it was found, by using a high-boiling polar solvent, that the reaction occurred at a reasonable temperature and that the 1,4-cyclohexadiene could be removed under reduced pressure as fast as it was generated, practically eliminating any disproportionation and oxidation. Sodium iodide was added because the reaction in the last step proceeds only to about 25% completion without it. This may mean that III is a mixture of *cis* and *trans* isomers (with respect to Cl and CO_2H) and since the *trans* isomer is the one that undergoes elimination[4] then the *cis* isomer remains unreacted. Iodide would displace chloride of the *cis* isomer giving a *trans* isomer which would then eliminate iodide and carbon dioxide. This problem was not pursued further since the addition of iodide effectively solved the problem of production of 1,4-cyclohexadiene.

The over-all yield of I based on 1,1,4,4-d_4-buta-1,3-diene (neglecting recovered starting material) was 45%. The product after one trap-to-trap distillation was about 98% I as judged from nmr and vpc data. There was about 0.1% of d_2-benzene (probably 1,4-d_2-benzene), and the remainder of the impurities were higher boiling materials including some hexamethylphosphoramide. There was no 1,3-cyclohexadiene detected by vpc or nmr. Purification by vpc eliminated the impurities within the detection limits of the vpc. The nmr spectrum of I shows a single vinylic proton peak at τ 4.36 and a very small peak (about 1% of the vinylic proton peak) at 7.40, the position of the peak for methylene protons of 1,4-cyclohexadiene. This is equivalent to the isotropic purity of the 1,1,4,4-d_4-buta-1,3-diene starting material. Hence, no hydrogen exchange at the methylene positions occurred. The vinyl



* = ^{13}C (natural abundance)

proton–^{13}C interaction gives $J_{H^{13}C}$ = 158 Hz and, for the *cis* vinyl protons, $J_{1,2}$ = 10 Hz. The mass spectrum of I shows a strong parent ion peak at *m/e* 84.

Experimental Section

2-Chlorocyclohex-4-ene-1-carboxylic Acid.—A mixture of 11.7 g (0.11 mol) of *trans*-β-chloroacrylic acid and 5.4 g (0.10 mol) of 1,3-butadiene was degassed and sealed in a glass ampoule on a vacuum line. The ampoule was heated in a bomb (partially filled with liquid trichlorofluoromethane to act as a heat-transfer medium and to pressurize the outside of the ampoule) to 98° ± 2° for 80 hr.[5] The ampoule was opened on the vacuum line and 0.014 mol of gaseous material was evolved, at least 75% of which was butadiene (by nmr analysis). The other volatile constituents were not identified. There was 15.8 g of solid remaining in the ampoule. The solid was added to 50 ml of H_2O containing 11 g of $KHCO_3$, filtered to remove small amount of polymer, and extracted with two 50-ml portions of ether. The aqueous phase was acidified with 6 *N* HCl; the crystalline solid was filtered off, washed with 20 ml cold water, and dried on the filter by drawing air through the filter for 1 hr. This gave 11 g (68% yield) of acid, mp 104–108°. Two recrystallizations from *n*-hexane gave 6.5 g of 2-chlorocyclohex-4-ene-1-carboxylic acid, mp 110–112°.

Anal. Calcd for $C_7H_9ClO_2$: C, 52.35; H, 5.65; Cl, 22.08. Found: C, 52.16; H, 5.64; Cl, 22.02.

1,4-Cyclohexadiene.—2-Chlorocyclohex-4-ene-1-carboxylic acid (5.2 g, 0.032 mol), mp 104–108°, was combined with 2.7 g of $NaHCO_3$[6] in 2.5 ml of water. After the acid was neutralized, the water was removed under reduced pressure keeping the temperature below 25°. The dry salt along with 4.9 g (0.032 mol) of NaI was added to 50 ml of vacuum-distilled $[(CH_3)_2N]_3PO$ in a 250-ml round-bottomed flask and heated to 70° at 1 mm pressure for 4 hr and then to 75° for 1 hr while stirring with a magnetic stirrer. The flask was connected to the vacuum pump through a trap cooled with Dry Ice and acetone. Two trap-to-trap distillations under vacuum gave 1.8 g (70% yield) of 1,4-cyclohexadiene of about 98% purity. The impurities, benzene and higher boiling materials, were removed by vpc using a $^3/_8$-in.

(1) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963), and references therein.

(2) 1,4-d_2-, 1,3,3,4,6,6-d_6-, and 1,2,3,3,4,5,6,6-d_8-cyclohexa-1,4-dienes were prepared by dehydration of the appropriately deuterated 1,4-cyclohexandiols: M. I. Gorfinkel and V. A. Koptyug, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 109 (1967).

(3) Available from Isotopic Products, Merck, Sharp & Dohme of Canada Ltd.

(4) S. J. Cristol and W. P. Norris, *J. Amer. Chem. Soc.*, **75**, 632 (1953).

(5) The optimum conditions for the reaction were determined by sealing equimolar amounts of the reactants into 5-mm standard walled-glass tubing and observing the change of the nmr spectrum with respect to time and temperature. The temperature was kept as low as practicable to minimize scrambling of hydrogens of the reactants or the product.

(6) Either the sodium or the potassium salt may be used.

by 20-ft aluminum column packed with 20% Apiezon L on Chromosorb W. Helium was used as the carrier gas. The infrared absorption spectrum of the gaseous product shows bands in μ at 3.2 (>CH—), 3.4 and 3.45 ($>CH_2$), 6.1 (>C=C<), and 6.9 ($>CH_2$) with two broad and complex bands centered at 10.2 and 11.2. The nmr spectrum shows a triplet due to vinyl protons at τ 4.36 and a triplet due to methylene protons at 7.26 with J = 1 Hz. The mass spectrum gives a strong parent ion peak at m/e 80. An authentic sample of 1,4-cyclohexadiene gives the same values as above.

Preparation of 3,3,6,6-d_4-Cyclohexa-1,4-diene (I).—1,1,4,4-d_4-Buta-1,3-diene (0.10 mol) and *trans*-β-chloroacrylic acid (0.11 mol) were reacted, and the product was worked up in the same manner as with the unlabeled material, except that the product was not recrystallized from hexane. 3,3,6,6-d_4-2-Chlorohex-4-ene-1-carboxylic acid (11.7 g, 0.071 mol) was neutralized with 7.1 g of $KHCO_3$ dissolved in 50 ml of water. The water was removed under reduced pressure, and the dried salt along with 11 g of NaI was added to 100 ml of vacuum-distilled hexamethylphosphoramide. The system was evacuated through a Dry Ice–acetone trap to 0.5-mm pressure and heated to 50° for 4 hr. One trap-to-trap distillation under vacuum of the volatile material gave 3.8 g (45% based on butadiene) of I of about 98% purity as shown by vpc and nmr analysis. There was about 0.1% d_2-benzene (presumably 1,4-d_2-benzene), and the remainder of the impurities were higher boiling materials. Final purification was effected with preparative vpc using the column and the conditions used for the purification of unlabeled I in the previous experiment. The infrared absorption spectrum of I (gas phase) shows bands in μ at 3.25 (>CH—), 4.62 and 4.76 ($>CD_2$), 6.1 (>C=C<), and a poorly resolved triplet centered at 9.3 ($>CD_2$), with two broad bands centered at 10.4 and 11.3. There is no detectable methylene ($>CH_2$) absorption at 3.4 or 6.9 μ as there is in the unlabeled compound. The nmr spectrum shows a singlet at τ 4.36 due to the vinyl protons and at 7.25, the methylene proton region, there is a peak of about 1% the area of the vinyl proton peak.[7] Hence there is no detectable exchange of hydrogen at the 3,3,6,6-positions during the synthesis. The mass spectrum shows a molecular ion peak, which is the base peak, at m/e 84.

Registry No.—I, 17791-27-4; 2-chlorocyclohex-4-ene-1-carboxylic acid, 17791-28-5; 1,4-cyclohexadiene, 628-41-1.

(7) The manufacturer (ref 3) claimed at least 98% isotopic purity, and a check by nmr indicated that the 1,1,4,4 positions of the labeled butadiene had about 1% ^1H.

The Selective Oxidation of Large-Ring Organoboranes with Chromic Acid. The Synthesis of Macrocyclic Musk Compounds

LAWSON G. WIDEMAN

Contribution No. 408 from The Goodyear Tire and Rubber Company, Research Division, Akron, Ohio 44316

Received June 4, 1968

The C_{16} musk compound, 8-cyclohexadecen-1-one (**5**),[1] was obtained in very low yield (*ca.* 5%) by pyrolytic cyclization of the yttrium salt of the corresponding C_{17} diacid.[2] The saturated ketone, cyclohexadecanone (**9**), was obtained in a slightly higher yield (*ca.* 16%) by cyclization (twofold condensation) of the dichloride of azelaic acid, followed by reduction of one of the carbonyl groups.[3] Both ketones were recently[4] formed by an acyloin cyclization of aleuritic acid in about 5% yield. The odors of both ketones were reported as musklike.

The disadvantages of ring-closure methods to give unsaturated ketones have been realized for some time. Recently, the synthesis of a large-ring, unsaturated compound has been demonstrated by the olefin metathesis reaction[5] of cyclo olefins, which suggests the present approach, in which a large ring is used as the starting material. The macrocyclization of cyclooctene provides a mixture of large-ring compounds.[6] Under suitable conditions[7] the reaction can be directed to appreciable (*ca.* 20%) amounts of the dimer, 1,9-cyclohexadecadiene (**1**), which occurs as a mixture of the *cis,cis* (35%), *cis,trans* (53%), and *trans,trans* (12%) isomers.

The conversion of the large-ring diene by hydroboration into the C_{16} musk compound seemed especially attractive, if a reasonable amount of monohydroboration would occur. The addition of 1 equiv of diborane ($^1/_6B_2H_6$) was expected to give approximately 50% mono- and 25% dihydroborated compounds if the reaction went to completion. The cyclic diene (**1**) was treated with diborane (Scheme I) generated *in situ* by the addition of boron trifluoride etherate to sodium borohydride in diglyme.[8] The distribution of alkylboranes varied with the proportions of diborane. The unsaturated intermediate **2**, may be formed by addition of boron to either end of the double bond. The dihydroborated intermediates, **3** and **4**, may form in equal amounts if not affected by conformational preferences. The possibly of boron-bridged intermediates (from **3** and **4**) is presently under investigation.

Oxidation of organoboranes to the corresponding ketones with aqueous chromic acid added to ethyl ether has been reported.[9,10] This type of chromic acid oxidation, which is known to be selective for secondary alcohols in the presence of carbon–carbon double bonds[11] was found in this work to be selective as well for the alkylborane group in the presence of a carbon–carbon double bond, as is shown by the desired unsaturated ketone **5** (Scheme I). Oxidation also gives the diketones **8** and **10**, from the dihydroborated compounds, but in much lower yield (Table I) than initially predicted for addition of 1 equiv of diborane to the diene. This may be attributed to the insolubility of the dialkylborane which precipitates and resists further alkylation.

Gas chromatographic and ir analyses of recovered starting materials showed that when the diene was treated with 2 or 3 equiv of diborane the *cis,cis* isomer had always reacted to a greater extent than the *trans*,-

(1) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. II, part A, Elsevier Publishing Co., New York, N. Y., 1953, p 277.

(2) L. Ruzicka, M. Stoll, W. Scherrer, H. Schinz, and C. F. Seidel, *Helv. Chim. Acta*, **15**, 1459 (1932); L. Ruzicka, M. Stoll, and H. Schinz, *ibid.*, **9**, 249 (1926).

(3) A. T. Blomquist, J. Prager, and J. Wolinsky, *J. Amer. Chem. Soc.*, **77**, 1804 (1955); A. T. Blomquist and J. Wolinsky, *ibid.*, **77**, 5423 (1955).

(4) H. H. Mathur and S. C. Bhattacharyya, *Tetrahedron*, **21**, 1537 (1955).

(5) K. W. Scott, N. Calderon, E. A. Ofstead, W. A. Judy, and J. F. Ward, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. L54; Advances in Chemistry Series, in press.

(6) N. Calderon, E. A. Ofstead, and W. A. Judy, *J. Polymer Sci.*, **5**, 2209 (1967).

(7) N. Calderon and E. A. Ofstead, unpublished data.

(8) H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.*, **80**, 1552 (1958).

(9) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2951 (1961).

(10) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951).

SCHEME I

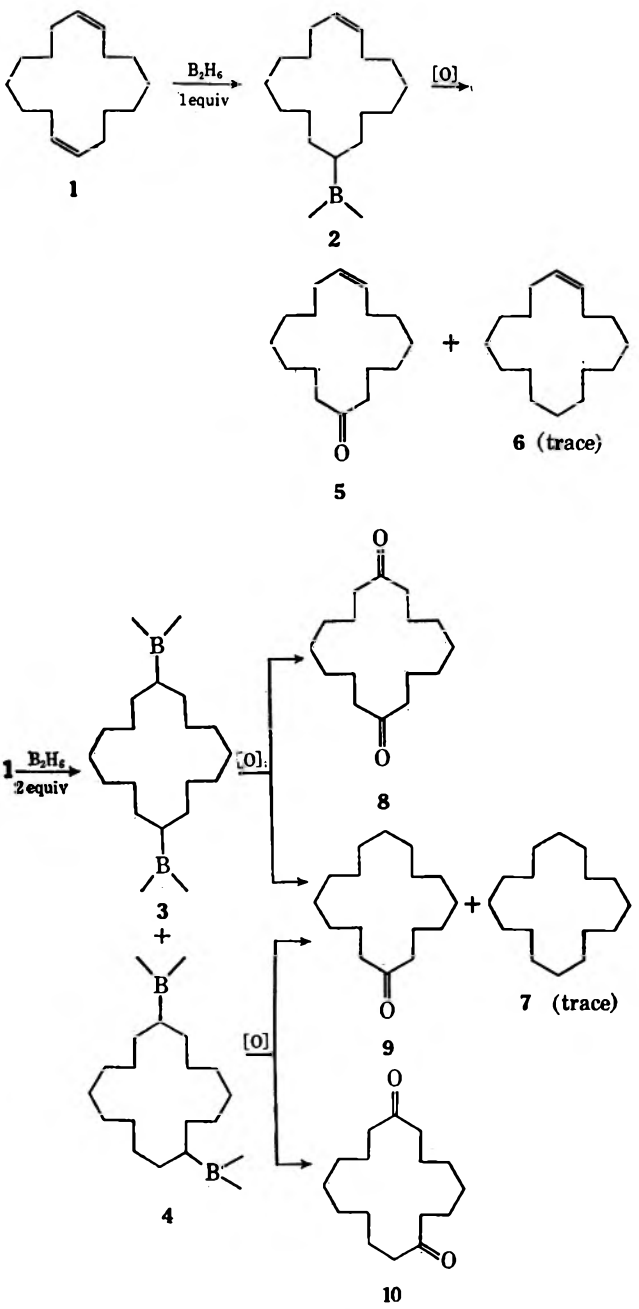


TABLE I

PRODUCT DISTRIBUTION FROM VARIED AMOUNTS OF DIBORANE[a]

Diborane diene, equiv	% 5	% 9	% (8 and 10)[b]
1	44	1	4
2	26	19	44
3	20	26	45

[a] Yields are based on glpc analysis utilizing an internal standard. [b] The diketones were shown by glpc analysis to be in equal amounts.

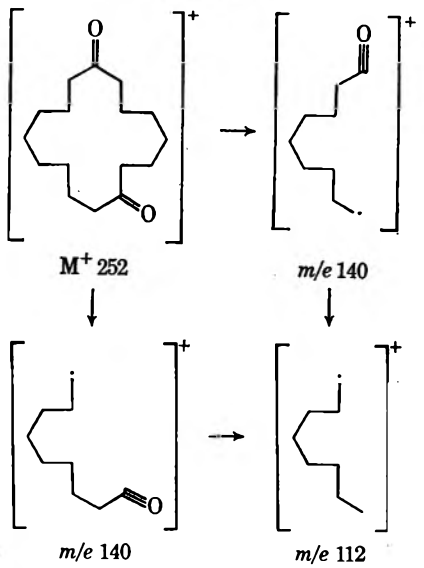
trans or *cis,trans*. However, of the six products obtained, the two that possess carbon–carbon double bonds are the cyclic alkene (**6**) and the unsaturated ketone (**5**), which are predominantly the *trans* isomers as shown by ir analysis.

The diketones possess a very mild odor similar to camphor instead of musk. The saturated monoketone has a musky odor almost identical with that of the unsaturated compound.

The presence of the saturated ketone **9** was unexpected; however, its formation is easily explained since the oxidation is carried out in the presence of mineral acid.[12] Reduction of carbon–carbon double bonds *via* hydroboration has been reported in good yield using organic acids, and in fair yield with mineral acids.[12] Protonation of one position of the dihydroborated intermediate, with oxidation at the other, would afford this saturated ketone. Traces of the saturated hydrocarbon **7** presumably arise by protonation of both hydroborated positions, while the trace of alkene **6** may arise from the monohydroborated intermediate.

The isomeric diketones have a nominal molecular weight of 252. Gas chromatographic analysis showed the presence of the two isomers with this mass, and their fragmentation patterns on the mass spectrometer can be used to distinguish between them. The proposed fragmentation pattern of the 1,8 diketone is shown in Scheme II. The fragmentation peak at *m/e*

SCHEME II



140 is not readily accessible from the symmetrical diketone as it would require cleavage β to the keto group, which does not normally occur.[13] The presence of a metastable ion at *m/e* 77.4 ($140^2/252 = 77.7$) is in agreement with this pattern. A peak at *m/e* 112 which is believed to be a secondary fragment from the *m/e* 140, as well as from the *m/e* 252, was also present. The symmetrical diketone has a base peak at *m/e* 126, which indicates symmetrical α cleavage at both carbonyls.[13,14]

The change in over-all yield (Table I) in going from 2 to 3 equiv of diborane per mole of diene is negligible. The over-all yield, however, jumps about 40% when

(12) J. R. Johnson, H. R. Synder, and M. C. Van Campen, Jr., *J. Amer. Chem. Soc.*, **60**, 115 (1938).

(13) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 17.

(14) F. W. McLafferty, "Mass Spectrometry of Organic Ions," Academic Press, Inc., New York, N. Y., 1963, pp 471–473; K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 153–157.

going from 1 to 2 equiv of diborane per mole of diene. It is apparent that when an excess of diene is available the major product after oxidation is the desired unsaturated ketone **5**.

Experimental Section

Diglyme and boron trifluoride etherate were purified according to procedures previously described.[15] The sodium borohydride (minimum 98% pure) was used as supplied by the Fisher Scientific Co.

The melting points were determined on a Fisher–Johns apparatus and are uncorrected. Elemental analyses were performed by the Analytical Section, Goodyear Tire and Rubber Co., Research Division. Infrared spectra, obtained on a Perkin-Elmer Model 137 spectrometer, are reported for liquids as films; as solids were melted on NaCl plates. The nmr spectrum was obtained on a Varian A-60 spectrometer and the mass spectra on an AEI MS-9 spectrometer. Glpc analyses were performed on a F & M instrument (Model 500), equipped with a 12 ft × 0.25 in. (o.d.) copper column containing 10% silicone rubber (SE-30) on Diatoport W. A column containing Carbowax 20M (10%) on Column Pak was used for preparative glpc.

Hydroboration.—A flask was fitted with a reflux condenser sealed with a calcium sulfate drying tube (indicator Drierite), a nitrogen inlet tube, and a dropping funnel containing 9.2 g (65 mmol) of boron trifluoride in 50 ml of diglyme. The flask contained 44.2 g (200 mmol) of 1,9-cyclohexadecadiene and 1.89 g (50 mmol) of sodium borohydride in 400 ml of diglyme. The BF_3 solution was added with stirring at a rate to maintain the temperature at 25–45° (1 hr). The reaction mixture was stirred after addition for 2 hr at room temperature.

Oxidation.—Ethyl ether (800 ml) was added for mild oxidation conditions and ease of separation. A solution of 26.6 g (266 mmol) of chromium trioxide and 39.2 g (400 mmol) of sulfuric acid in 100 ml of water (*ca.* 8 *N*) was added with stirring over a 1-hr period to maintain the temperature at 25–35°. The green chromic sulfate began to form upon addition of the oxidant. Refluxing was maintained for 3 hr after addition. Water (500 ml) was added, and the ether layer was separated. The aqueous layer was extracted twice with 200-ml portions of ether, and the extracts were combined. Excess oxidant in the ether portion was destroyed with solid sodium bisulfite, and the organic layer was then washed with a sodium carbonate solution. The organic material was dried over calcium chloride, and the solvents were removed, ethyl ether at 25 mm and diglyme by washing with water after removal of ether. The weight of the crude material was 43.0 g. The hydrocarbons were separated from the ketones by eluting them with petroleum ether (bp 37–46°) from a 1.5 × 36 in. column packed with activated alumina. The monoketones, **5** and **9**, were eluted with ethyl ether and were separated from each other by preparative glpc. The diketones, **8** and **10**, were eluted with methanol and further separated by glpc.

8-Cyclohexadecen-1-one (**5**).—A sample was prepared for analysis by vacuum distillation at 1 mm (bp 180°): mp 18–19° (lit.[2] mp 17–22°); ν_{max} 2990, 2910, 1710 (C=O), 1469, 1375, and 974 (*trans*—CH=CH—) cm^{-1}; *m/e* 236; nmr (CCl_4) δ 5.32 (broad triplet, olefinic), 2.37 (triplet, α-keto H), 1.32 (strong singlet, internal methylene H). The semicarbazone from aqueous methanol had mp 183–184° (lit.[3] mp 180–181°).

1,9-Cyclohexadecadione (**8**).—A sample was prepared for analysis by recrystallization from petroleum ether melted at 78–79° (lit.[2] mp 80–82°): ν max 2990, 2910, 1715 (C=O), 1470, 1375, 1121, 1025, and 717 cm^{-1}; *m/e* 252. The disemicarbazone from aqueous methanol had mp 228–229° (lit.[2] mp 225–227°).

Cyclohexadecanone (**9**).—A sample recrystallized twice from petroleum ether for analysis melted at 57–59° (lit.[2] mp 59.5–60.2°): ν max 2990, 2910, 1707 (C=O), 1480, and 730 cm^{-1}; *m/e* 238.

1,8-Cyclohexadecadione (**10**) was recrystallized twice from petroleum ether before analysis: mp 75–77°; ir identical with that of **8**; *m/e* 252.

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.1; H, 11.1. Found: C, 75.9; H, 11.1.

Cyclohexadecene (**6**) was separated by preparative glpc for spectral analysis: *m/e* 222; ν max 3010, 2990, 2910, 1450, 1470, 975 (strong), and 720 cm^{-1}.

Cyclohexadecane (**7**) was separated by preparative glpc for spectral analysis: *m/e* 224; ν max 2990, 2910, 1460, 1470, and 1385 cm^{-1}.

(15) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 28 (1963).

Registry No.—Chromic acid, 7738-94-5; **6**, 6568-44-1; **7**, 295-65-8; **10**, 17853-46-2.

Acknowledgment.—The author wishes to acknowledge Dr. Nissim Calderon and Dr. Eilert A. Ofstead, for providing the 1,9-cyclohexadecadiene and suggesting its potential use as a musk precursor.

Formation of 1,1-Dimethyl-3,3-diphenylindan from the Triphenylmethyl Cation and Isobutene[1]

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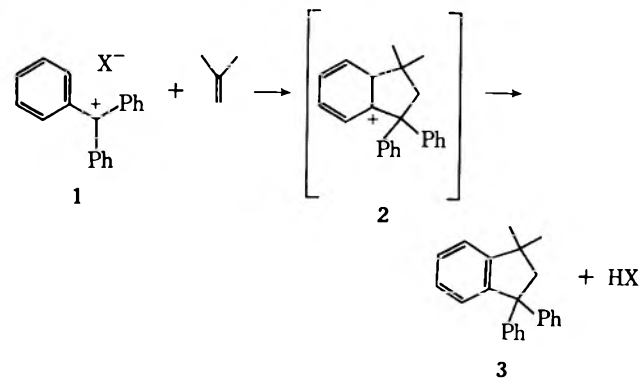
Received April 25, 1968

Addition of isobutene to solutions of salts of the triphenylmethyl cation (**1**) in organic solvents led to formation of 1,1-dimethyl-3,3-diphenylindan (**3**). This



reaction represents a direct intermolecular addition of a carbonium ion to an aliphatic alkene to form a new ring. There has previously been evidence for indan formation as a termination step in cationic polymerizations of α-methylstryene and of other aryl olefins.[4,5] In addition, indans have been observed as products of cationic dimerizations of α-methylstyrene and of other aryl olefins.[5]

Varying amounts of an oil, presumably oligomeric isobutene, also were obtained from the reactions. The amount of this material relative to the indan seemed to decrease with decreasing rate of addition of isobutene. The polymerization of isobutene was perhaps initiated

(1) Taken in part from the Ph.D. Thesis of R. K. L., The Pennsylvania State University, 1966.

(2) Alfred P. Sloan Foundation Research Fellow, 1964–1968.

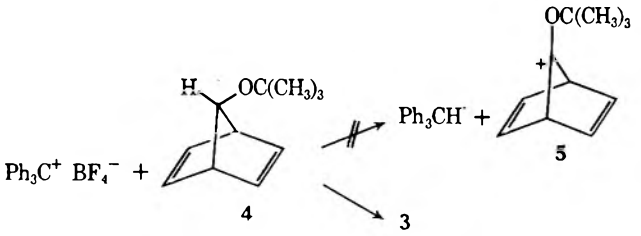
(3) National Institutes of Health Predoctoral Fellow, 1964–1966.

(4) D. C. Pepper in "Friedel–Crafts and Related Reactions," Vol. 2, part 2, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 30.

(5) S. Bywater in "The Chemistry of Cationic Polymerization," P. H. Plesch, Ed., The Macmillan Co., New York, N. Y., 1963, Chapter 7.

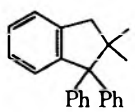
by the triphenylmethyl cation itself. Salts of this cation are thought to initiate polymerizations of reactive olefins.[4] Alternatively, the initiation may have been by the acid generated in the cyclization reaction or by catalysts generated by hydrolysis of the carbonium ion salts (**1**) due to adventitious traces of water.[6] Little oligomer was obtained from a reaction mixture which contained equimolar amounts of collidine and of **1**. Indans similar to **3** were not obtained from preliminary experiments with *cis*-2-butene or with 2,3-dimethyl-2-butene.

Indan **3** was also a product of reactions of salts of the triphenylmethyl cation with *t*-butyl ethers. In fact, **3** was first obtained from a reaction of 7-*t*-butoxynorbornadiene (**4**) and triphenylmethyl fluoroborate.



It was hoped that hydride transfer would lead to the 7-norbornadienyl cation (**5**) or products derived from its decomposition. However, triphenylmethane was not isolated as a product of this reaction. Presumably **3** was formed by reaction of the triphenylmethyl cation with isobutene that was generated from **4** (or species derived from **4**) by attack of the triphenylmethyl cation or of acids. Triphenylmethyl perchlorate and methyl *t*-butyl ether also reacted to form **3**.

The spectral properties of the hydrocarbon product of these reactions were consistent with the assignment of structure **3**, though **6** was not rigorously excluded.



6

The assignment of structure **3** was confirmed by an independent synthesis. A reaction of 4,4,4-triphenyl-2-methyl-2-butanol (**7**) in trifluoroacetic acid led to quantitative formation of **3**. Heating benzene solutions

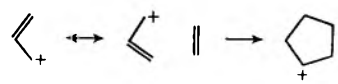
$$\underset{\mathbf{7}}{Ph_3CCH_2\overset{OH}{\overset{|}{C}}(CH_3)_2} \xrightarrow{H^+} \mathbf{3} + \underset{\mathbf{8}}{Ph_3CCH{=}C(CH_3)_2}$$

of **7** containing small amounts of *p*-toluenesulfonic acid furnished reaction mixtures which contained both **3** and olefin **8**, a dehydration product of **7**; olefin **8** was slowly converted into **3** under these reaction conditions. Formation of indans by cyclizations of alcohols or olefins such as **7** and **8** is well known.[7]

The mechanism of indan formation from isobutene and the triphenylmethyl cation probably involves two bond formation steps: addition of the triphenylmethyl cation to isobutene to form **9**, the same intermediate

$$Ph_3C^+ + CH_2{=}C(CH_3)_2 \longrightarrow \underset{\mathbf{9}}{[Ph_3CCH_2C^+(CH_3)_2]} \longrightarrow [2] \longrightarrow \mathbf{3}$$

carbonium ion presumably responsible for the cyclizations of **7** and **8**, followed by cyclization of **9** to **2**. It is also conceivable that both new C–C bonds are formed simultaneously in a concerted cycloaddition. Such a reaction would be analogous formally to the unknown concerted cycloaddition of an allyl cation to an alkene, an addition that is predicted on the basis of the orbital



symmetry arguments of Woodward and Hoffmann to be unfavorable thermally (if "*cis–cis*" in stereochemistry).[8,9]

Experimental Section[10]

Reaction of Triphenylmethyl Fluoroborate with 7-*t*-Butoxynorbornadiene (4).—Triphenylmethyl fluoroborate[11] (7.80 g, 0.024 mol) and **4** (1.50 g, 0.091 mol) were dissolved in 90 ml of acetonitrile and the solution was allowed to stand at 50° for 24 hr. Dilute sodium carbonate solution was added, and the resulting mixture was extracted with six 20-ml portions of water and three 10-ml portions of saturated sodium chloride solution. The solution was dried (Na_2SO_4), and the residue obtained after evaporation of the solvent was extracted exhaustively with petroleum ether (bp 30–60°). The petroleum ether was evaporated leaving 1.85 g of solid which was dissolved in 5 ml of warm chloroform and chromatographed on a 2.5-cm column packed with 100 g of alumina (Fisher A-540, acid washed). Elution with 500 ml of petroleum ether afforded 0.74 g (0.0025 mol, 10%) of **3**. Two recrystallizations from 95% ethanol and sublimation at 60° (5 mm) gave a sample of mp 105.5–107.5°; nmr (CCl_4) τ 2.91 (m, 15, aryl H's), 7.15 (s, 2, CH_2), and 8.85 (s, 6, CH_3) ppm; uv (95% ethanol) 272 mμ max (log ϵ 3.09), 265 max (3.12), 263 shoulder (3.09), and 259 shoulder (3.05); mass spectrum (70 eV) *m/e* (rel intensity) 298 (100), 283 (86), 221 (95), 205 (33), 143 (38), 105 (26), 91 (92), and 77 (60).

Anal. Calcd for $C_{23}H_{22}$: C, 92.57; H, 7.43; Found: C, 92.75; H, 7.43.

Further elution with 150 ml of petroleum ether gave 0.30 g of resinous material. Elution with 150 ml of benzene–petroleum ether (1:1) gave 0.20 g of material which displayed a phenyl absorption pattern between 5 and 6 μ, and elution with 200 ml of ethyl ether gave 0.30 g of triphenylcarbinol and 0.05 g of an orange oil. Triphenylmethane was not noted.

Reaction of Triphenylmethyl Perchlorate with Methyl *t*-Butyl Ether.—A solution of 2.1 g (0.024 mol) of methyl *t*-butyl ether in 6 ml of acetonitrile was added over 60 min to a solution maintained at 65° of 4.0 g (0.012 mol) of triphenylmethyl perchlorate[11] dissolved in 50 ml of acetonitrile. The reaction mixture was stirred for 16 hr at 70°. A further quantity of 0.9 g (0.010 mol) of the ether in 5 ml of acetonitrile was added in one portion and stirring was continued for another 10 hr. Water was added, and the mixture was extracted with four 20-ml portions of ether. The ether extracts were washed with water and with a saturated sodium chloride solution. Evaporation of solvent from the dried (Na_2SO_4) extracts afforded 2.85 g of material which was chromatographed on a 2.5-cm column packed with 80 g of alumina (Fisher F-20, neutral grade). Elution with pentane gave 0.71 g

(6) P. H. Plesch in "The Chemistry of Cationic Polymerization," P. H. Plesch, Ed., The Macmillan Co., New York, N. Y., 1963, Chapter 4.

(7) L. R. C. Barclay in "Friedel–Crafts and Related Reactions," Vol. 2, part 2, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 22.

(8) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965); R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(9) Apparent examples of the *cis–cis* cycloaddition of an allyl cation to a conjugated diene considered favorable[8] have recently been observed [H. M. R. Hoffmann, D. R. Joy, and K. A. Suter, *J. Chem. Soc., B*, 57 (1968)].

(10) Melting points were determined in capillary tubes with calibrated thermometers. Analyses were done by Midwest Microlab. Nmr spectra were calibrated with internal tetramethylsilane.

(11) H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).

(0.0024 mol, 20%) of crude **3**, which after recrystallization was identical with that obtained from the reaction with **4**. Elution with benzene gave 0.13 g of a yellow oil; elution with ether gave 1.37 g of triphenylcarbinol; and elution with chloroform gave 0.08 g of an oil from which N-*t*-butylacetamide sublimed on standing. Triphenylmethane was not noted.

Reaction of Triphenylmethyl Cation Salts with Isobutene.—Isobutene (40 g, 0.71 mol) was bubbled slowly over 6 hr into a solution of 4.1 g (0.012 mol) of triphenylmethyl perchlorate[11] in 45 ml of acetonitrile in a flask equipped with a gas inlet tube, a Dry Ice–acetone condenser, a magnetic stirrer, and a drying tube. The solution was maintained at 30° during the first hour and subsequently at 60°. Dilute aqueous sodium carbonate was added, and the solution was concentrated on a steam bath. The aqueous mixture was extracted with three 20-ml portions of petroleum ether and five 20-ml portions of ether. The extract was washed with two 10-ml portions of water and three 10-ml portions of saturated sodium chloride solution. The solution was dried (Na_2SO_4), and the solvent was evaporated, leaving 3.4 g of semicrystalline material which was chromatographed on a 2.5-cm column packed with 80 g of alumina (Fisher F-20, neutral grade). Elution with pentane gave 1.5 g of **3** contaminated with a small amount of a viscous liquid. Recrystallization from 95% ethanol gave 1.0 g (0.0034 mol, 28%) of **3**. Further elution with ether gave a mixture (1.2 g) of triphenylcarbinol and N-*t*-butylacetamide.

More rapid addition of the isobutene led to formation of much more of the liquid product without altering significantly the yield of **3**. The liquid material was isolated free of **3** by careful chromatography: nmr (neat) τ 8.2 (m, 1, CH_2), 9.0 (m, 3, CH_3), 5.0 (m, weak) ppm.

In another reaction, isobutene was bubbled slowly into an acetonitrile solution containing equimolar portions of triphenylmethyl perchlorate and of collidine. Little of the liquid oligomer was isolated, though **3** still was formed in about the same yield.

Slow addition of isobutene to acetonitrile and dichloromethane solutions of triphenylmethyl fluoroborate also furnished comparable yields of **3**.

Attempted Reactions of Triphenylmethyl Perchlorate with Other Olefins.—*cis*-2-Butene (15 g, 0.27 mol) was added slowly to a solution of 3.9 g (0.011 mol) of triphenylmethyl perchlorate in 50 ml of acetonitrile as described for the reaction with isobutene. The reaction mixture was worked up in the same manner, but little material was obtained by elution with pentane–benzene.

A reaction was attempted with 2,3-dimethyl-2-butene in the same manner except that the olefin was introduced through a dropping funnel and the acetonitrile solution of triphenylmethyl perchlorate contained an equimolar amount of collidine. No material was eluted with pentane–benzene.

4,4,4-Triphenyl-2-methyl-2-butanol (7).—A solution of 1.82 g (0.0058 mol) of methyl 3,3,3-triphenylpropionate[12] in 20 ml of ether and 20 ml of benzene was added to a Grignard solution prepared from 0.4 g (0.0016 mol) of magnesium and 7 g (0.0049 mol) of methyl iodide in 40 ml of ether. The mixture was stirred and warmed for 1 hr and then left overnight at room temperature. The mixture was poured onto 100 g of ice. The layers were separated, and the ether layer was washed several times with a saturated sodium chloride solution and then with water. The solution was dried (Na_2SO_4) and evaporated, leaving 1.16 g (0.037 mol, 64%) of crude product. Recrystallization from methanol gave an analytical sample of **7**: mp 122–123° (lit.[13] mp 116–119°); nmr τ 2.75 (m, 15, aryl H's), 7.12 (s, 2, CH_2), 9.08 (s, 6, CH_3), and 9.28 (broad singlet, 1, OH) ppm.

Preparation of 1,1-Dimethyl-3,3-diphenylindan (3) from 7.—A sample of **7** (50 mg) was added in small portions to 4 ml of trifluoroacetic acid, and 1 ml of dichloromethane was added. The solvent was evaporated after the reaction had stood overnight at room temperature. The nmr spectrum of the crude, solid residue was identical with that of pure **3**. Recrystallization from 95% ethanol gave **3**, mp 109.5–110.5°. The ir and nmr spectra of this solid were identical with those of the solids obtained from reactions of triphenylmethyl cation salts with isobutene and with *t*-butyl ethers.

In an alternate reaction, a solution of 0.36 g of **7** and 17 mg of *p*-toluenesulfonic acid in 5 ml of benzene was refluxed for 2.5 hr. The solution was washed with 1 ml of a sodium chloride–sodium carbonate solution. The solution was dried ($MgSO_4$), and the solvent was evaporated. The solid residue was recrystallized twice from 95% ethanol to give **8** as white plates: mp 141–144°; nmr (CCl_4) τ 2.90 (s, 15, aryl H's), 3.75 (m, 1, =CH—), 8.15 (m, 3, CH_3), and 8.95 (m, 3, CH_3) ppm. Since elemental analyses were not obtained, the physical constants may be slightly off. The ir and nmr spectra of the crude product before recrystallization also exhibited absorptions of **3**. The spectra of the crude solid obtained from a similar reaction in which the solution was refluxed for 16 hr showed it to be a mixture of **3** and **8** containing significantly more **3** than the mixture from the preceding reaction; nearly pure **3** was obtained as a second crop during recrystallization of the crude product from 95% ethanol. Refluxing a similar benzene solution of *p*-toluenesulfonic acid and **8** led to slow formation of **3**.

Registry No.—Isobutene, 115-11-7; **1**, 14699-91-3; **3**, 10271-32-6.

Acknowledgement.—We are grateful for support of this research by the National Science Foundation and by funds made available by the Alfred P. Sloan Foundation. We are pleased to acknowledge the assistance of the National Science Foundation in providing funds to aid in the purchase of the Varian A-60 nmr spectrometer and the Nuclide Analysis Associates 12-90-G1 mass spectrometer used in this research. H. R. wishes to thank the John Simon Guggenheim Memorial Foundation for a Fellowship and members of the Department of Chemistry at the University of California at Berkeley for their hospitality at the time that this Note was prepared. We thank Jean Martin and Samuel Wilson for experimental assistance.

(12) S. M. McElvain and H. F. McShane, Jr., *J. Amer. Chem. Soc.*, **74**, 2662 (1952).

(13) N. C. Deno and E. Sacher, *ibid.*, **87**, 5120 (1965).

The Formation and Reactions of Ferrocenylphenylglyoxal[1]

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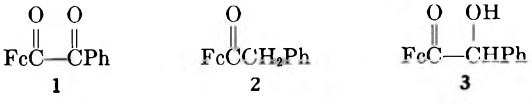
Received July 29, 1968

In this Note, we wish to report the preparation and characterization of ferrocenylphenylglyoxal (**1**) and to discuss briefly some of its chemical reactions.



The oxidation of benzyl ferrocenyl ketone (**2**) with activated manganese dioxide[2] in refluxing methylcyclohexane produced variable yields (20–50%)[3] of diketone **1**. A more satisfactory synthesis (95%) of **1** involved the oxidation of mandeloylferrocene (**3**) (from a mixed benzoin condensation of formylferrocene and benzaldehyde)[4] with activated manganese dioxide in refluxing chloroform solution. Although the oxidation of the acyloin **3** proceeded in uniformly higher

(1) Organometallic π Complexes. XV. Part XIV: M. D. Rausch and A. Siegel, *J. Organometal. Chem.*, **11**, 317 (1968).

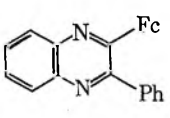
(2) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Helms, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(3) The yields of diketone **1** were dependent upon the activity of manganese dioxide used. Samples of the latter which remained exposed to air for prolonged periods resulted in diminished yields of **1**.

(4) G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, 650 (1958).

yields than the oxidation of **2**, precursor **3** is less readily available than **2**, since the latter is formed easily *via* a Friedel–Crafts reaction between ferrocene and phenacetyl chloride.[5] The infrared spectrum of **1** exhibits two carbonyl absorptions at 1660 and 1680 cm^{-1} as well as bands characteristic of ferrocenyl and phenyl substituents. Attempted oxidations of ketone **2** with freshly sublimed selenium dioxide in a variety of solvents[6] led to extensive decomposition.

Treatment of **1** with *o*-phenylenediamine in a melt phase reaction produced an 83% yield of 2-ferrocenyl-3-phenylquinoxaline (**4**). Reactions of this type are



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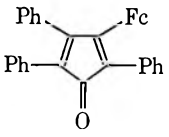

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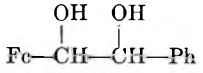
diagnostic for α diketones and acyloins, and often constitute a test for their presence.

A reaction of **1** with dibenzyl ketone in refluxing ethanolic potassium hydroxide afforded 3-ferrocenyl-2,4,5-triphenylcyclopentadienone (**5**) as a light blue amorphous solid in 81% yield. Its infrared spectrum exhibited a carbonyl band at 1710 cm^{-1}, which is characteristic of cyclopentadienone systems.

The reduction of **1** with sodium borohydride in methanol–water produced a 93% yield of 1-ferrocenyl-2-phenylethanediol (**6**). Several attempts to rearrange



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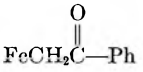

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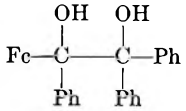
glycol **6** under acidic conditions resulted instead in conversion of **6** into phenacylferrocene (**7**). The latter was identified in each instance by its infrared and nmr spectra, and by mixture melting point determinations with an authentic sample.[7] The formation of **7** from **6**, which likely proceeds *via* dehydration and tautomeric rearrangement, might be expected to be a favored process, since the dehydration of α-ferrocenylcarbinols and the conversion of these carbinols into α-ferrocenylcarbonium ions under acidic conditions are known to be facile processes.[1,8]

It was also of interest to attempt the synthesis of pinacol **8**, in order to investigate the relative migratory



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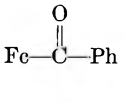

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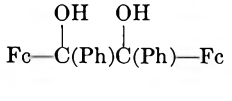

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aptitudes of the ferrocenyl and phenyl substituents under conditions of the pinacol rearrangement. Addition of an excess of phenyllithium to an ethereal solution of **1**, followed by hydrolysis, produced a yellow solution which gradually darkened on standing in air. Benzoylferrocene (**9**) and benzophenone were the only products isolated during an attempted chromatographic separation of the reaction mixture. It is of interest to note that a closely related pinacol, 1,2-diferrocenyl-1,2-diphenylethanediol (**10**), also undergoes facile oxidative cleavage to **9** when solutions of it are exposed to air.[9] Attempts to effect rearrangement of **8** or its dilithio salt under a variety of acidic conditions again led to the formation of **9** and benzophenone.

(5) N. Sugiyama, H. Suzuki, Y. Shioura, and T. Teitei, *Bull. Chem. Soc. Jap.*, **35**, 767 (1962).
(6) N. Rabjohn, *Org. Reactions*, **5**, 331 (1949).
(7) P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 2990 (1963).
(8) M. Cais, *Organometal. Chem. Rev.*, **1**, 435 (1966).

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on Beckman IR-10 and Perkin-Elmer 237 spectrophotometers, and nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Oxidation of Benzyl Ferrocenyl Ketone (2).—The ketone[6] (3.1 g, 10 mmol) and activated manganese dioxide[2] (9.0 g) were refluxed in methylcyclohexane (75 ml) for 24 hr. The mixture was cooled to room temperature and filtered. The residue was washed with two 50-ml portions of chloroform and the latter combined with the original filtrate. Concentration of the solvent followed by chromatography on alumina using hexane as eluent produced 1.5 g (47%) of **1**, which formed ruby red plates, mp 85–86°, when recrystallized from hexane: nmr spectrum ($CDCl_3$), τ 1.7–2.5 (m, 5, C_6H_5), 5.06 (t, 2, 2,5 protons), 5.30 (t, 2, 3,4 protons), 5.69 (s, 5, π C_5H_5).

Anal. Calcd for $C_{18}H_{14}FeO_2$: C, 67.96; H, 4.44. Found: C, 68.25; H, 4.57.

Hexane–benzene (1:1) was used to elute 1.1 g of **2**, mp 128–129° (lit.[5] mp 129–130°).

Oxidation of Mandeloylferrocene (3).—Mandeloylferrocene[4] (5.0 g, 16 mmol) and activated manganese dioxide (20 g) were refluxed in chloroform (100 ml) for 6 hr. The mixture was cooled to room temperature and filtered. The residue was extracted with chloroform until the extracts were colorless. The extracts and the filtrate were combined and were evaporated to dryness. Recrystallization of the residue from hexane produced 4.7 g (95%) of the diketone **1** as ruby red plates, mp 85.5–86°. The infrared and nmr spectra of this product were identical with the spectra of **2** obtained from the previous oxidation.

2-Ferrocenyl-3-phenylquinoxaline (4).—Into a 10-ml Pyrex test tube were placed 1.59 g (5.0 mmol) of ferrocenylphenylglyoxal (**1**) and 0.5 g (5 mmol) of *o*-phenylenediamine; the latter had been freshly recrystallized from water. The mixture was heated to a melt phase on a steam bath for 15 min, and then allowed to cool to room temperature. The residue was recrystallized from ethanol to give 1.62 g (83%) of deep purple plates: mp 208–209°; nmr spectrum ($CDCl_3$), τ 2.15 (m, 9, aryl protons), 5.37, (t, 2, 2,5 protons), 5.62 (t, 2, 3,4 protons), 5.90 (s, 5, π-C_5H_5).

Anal. Calcd for $C_{24}H_{18}FeN_2$: C, 73.87; H, 4.65. Found: C, 73.83; H, 4.90.

3-Ferrocenyl-2,4,5-triphenylcyclopentadienone (5).—The diketone **1** (1.59 g, 5 mmol) and dibenzyl ketone (1.0 g, 5 mmol) were heated to reflux in 20 ml of 95% ethanol. A solution of potassium hydroxide (0.2 g) in 2 ml of ethanol was added and refluxing was continued for 30 min. Upon cooling, the blue solid which separated was filtered and washed with 50 ml of cold hexane. Recrystallization of the residue from hexane afforded 2.0 g (81%) of **5** as a light blue amorphous powder: mp 217–217.5° (N_2); nmr spectrum ($CDCl_3$), τ 2.30 (m, 15, C_6H_5), 5.73 (t, 2, 3,4 protons), 6.00 (s, 5, π-C_5H_5), 6.10 (t, 2, 2,5 protons).

Anal. Calcd for $C_{33}H_{24}FeO$: C, 80.49; H, 4.91. Found: C, 80.18; H, 5.26.

1-Ferrocenyl-2-phenylethanediol (6).—To a stirred solution of diketone **1** (1.5 g, 4.7 mmol) in 20 ml of methanol was added 10 ml of a solution of sodium borohydride (1.0 g, 26 mmol) in water. After 6 hr, the deep red solution became yellow. The mixture was diluted with 50 ml of water and filtered. The residue was recrystallized from heptane to produce 1.4 g (93%) of golden yellow needles of **6**, mp 114–115° (N_2).

Anal. Calcd for $C_{18}H_{18}FeO_2$: C, 67.10; H, 5.63. Found: C, 67.30; H, 5.45.

Attempted Rearrangements of 6. A. With Hydrogen Chloride.—Glycol **6** (1.6 g, 5 mmol) was dissolved in 50 ml of dry benzene. With stirring, anhydrous hydrogen chloride was

(9) N. Weliky and E. S. Gould, *J. Amer. Chem. Soc.*, **79**, 2742 (1957

bubbled through the solution for 5 min. The solvent was removed under reduced pressure, and the oily green residue was extracted with two 50-ml portions of ethyl ether. The combined extracts were concentrated and chromatographed on alumina. Hexane eluted 1.0 g (67%) of yellow crystals of phenylacylferrocene (**7**), mp 81–82° (lit.[7] mp 80–82°). A small amount of highly polar material was not removed from the column. However, its R_f value was identical with that of glycol **6**.

B. With Aluminum Oxide.—Glycol **6** (1.6 g, 5 mmol) was intimately mixed with alumina (4.0 g) and placed in a vacuum sublimer equipped with a water-cooled probe. The system was evacuated and partially submerged in an oil bath for 8 hr at 150° (12 mm). Air was then admitted slowly and the yellow sublimate removed from the cold finger of the sublimer. The infrared and nmr spectra of this material were identical with those of phenacylferrocene (**7**) obtained in A. The total amount of **7** collected amounted to 1.0 g (67%), mp 80–81°. A tlc test of the alumina residue indicated a very small amount of **7** together with trace amounts of diketone **1**.

C. With Aqueous Sulfuric Acid.—The glycol **6** (1.61 g, 5 mmol) in 50 ml of acetone and 10 ml of 5% aqueous sulfuric acid solution was refluxed under nitrogen for 8 hr. The solution was cooled to room temperature, diluted with water, and extracted with ethyl ether. The ether portion was washed with water, 5% sodium bicarbonate solution, again with water, and was dried over anhydrous magnesium sulfate. Concentration of the solvent followed by chromatography on alumina using hexane as eluent produced 1.1 g (72%) of phenacylferrocene (**7**), mp 80–82°. No other ferrocene-containing products were detected.

Oxidation of Phenacylferrocene (7).—Phenacylferrocene (1.0 g, 3.3 mmol) and activated magnanese dioxide (5 g) were refluxed in methylcyclohexane (50 ml) for 2 hr. The mixture was cooled to room temperature and filtered. The residue was washed with two 10-ml portions of chloroform. The combined organic portions were concentrated and the residual red oil was crystallized from hexane as ruby red plates (1.0 g, 96%), mp 85–85.5°. A mixture melting point (on admixture with authentic **1**) was undepressed.

Addition of Phenyllithium to 1.—The diketone **1** (2.0 g, 6.3 mmol) was added in one portion to a stirred solution of phenyllithium (80 mmol) in 100 ml of ethyl ether under nitrogen. The mixture was allowed to stir for 3 hr, during which time the color changed from red to green and finally to gray. Water was added dropwise, and the mixture turned yellow. A tlc test (1:1 hexane–benzene) indicated a yellow band, which gradually transformed into a red band of lower R_f, and a colorless band of higher R_f. The ether portion was separated, dried over anhydrous magnesium sulfate, and evaporated to a red oil. Chromatography on alumina yielded the following products in the order cited. (1) Hexane eluted benzophenone, 1.0 g, mp 48–49°. A mixture melting point (on admixture with an authentic sample) was undepressed. (2) 1:1 Hexane–benzene eluted benzoylferrocene, 1.20 g, mp 108–109°. A mixture melting point (on admixture with an authentic sample) was undepressed.

When the gray solution was treated with methyl iodide, dry hydrogen chloride, or aqueous hydrochloric acid, benzophenone and benzoylferrocene were the only products isolated.

Registry No.—**1**, 12310-13-3; **4**, 12310-15-5; **5**, 12310-16-6; **6**, 12310-14-4.

Aziridines. XX. Isomerizations of 1-*p*-Nitrobenzoyl-2-vinylaziridine

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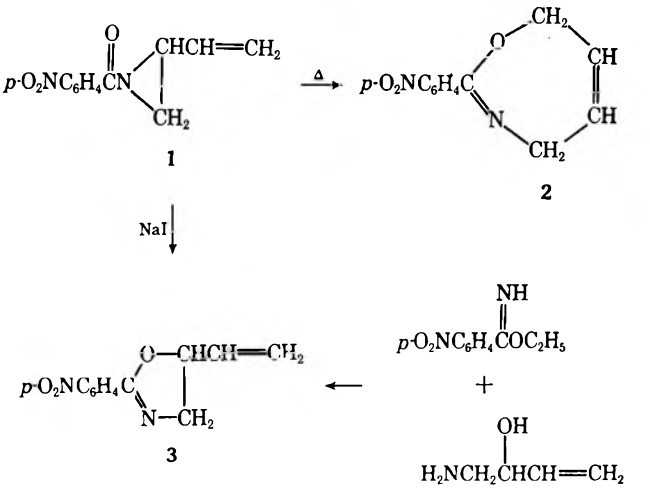
1-Aroylaziridines have been shown to undergo thermal rearrangements to 2-oxazolines, N-allylamides, and α-benzamidobenzalacetophenones. The course of the thermolysis depends in great part upon the substituents attached to the carbon of the aziridine ring. Thus 1-aroylaziridines unsubstituted on the aziridinyl carbons,[1–3] 1-aroyl-2,3-diarylaziridines,[4] and a few 1-aroylaziridines fused to another ring system[5,6] isomerize on heating to 2-oxazolines. 1-Acyl-2-alkylaziridines, on the other hand, almost always pyrolyze into N-allylamides[7] and 1,3-diaroyl-2-arylaziridines in refluxing *p*-xylene from α-benzamidobenzalacetophenones.[4]

We have now observed that 1-*p*-nitrobenzoyl-2-vinylaziridine (**1**) in refluxing toluene follows still another thermal pathway. The product of thermolysis is 2-*p*-nitrophenyl-4,7-dihydro-1,3-oxazepine (**2**). Tetrahydro- and hexahydro-1,3-oxazepines have been described, but **2** appears to be the first example of a dihydro-1,3-oxazepine. Compound **1** also reacted with iodide ion in acetone solution to give 2-*p*-nitrophenyl-5-vinyl-2-oxazoline (**3**). The iodide ion-catalyzed rearrangement of 1-aroylaziridines to 2-aryl-2-oxazolines is a well-known reaction.[4,8] The structure of **3** was confirmed by an alternate synthesis involving the reaction of 1-amino-3-buten-2-ol with ethyl *p*-nitrobenzimidate. Imido esters are known to react with amino alcohols to form 2-oxazolines.[9]

The nmr spectrum of **2** in $CDCl_3$ showed the *p*-nitrophenyl group as a quartet centered at 8.15 (4 H), the olefinic protons as a multiplet at 5.95 (2 H), and two other multiplets at 4.40 (2 H) and 4.80 ppm (2 H). The spectrum is similar to that of 4,6-dioxacycloheptene[10] which shows the olefinic protons as a multiplet at 5.74 ppm and the methylenes in the 3 and 7 positions as a multiplet at 4.32 ppm. On this basis the multiplet at 4.40 ppm in the spectrum of **2** can be assigned to the methylene next to the oxygen atom.



(1) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).
(2) A. A. Goldberg and W. Kelley, *J. Chem. Soc.*, 1919 (1948).
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(4) H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967).
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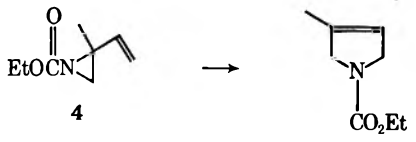
(10) High Resolution NMR Spectra Catalog, Vol. 2, Varian Associates, spectrum 437.

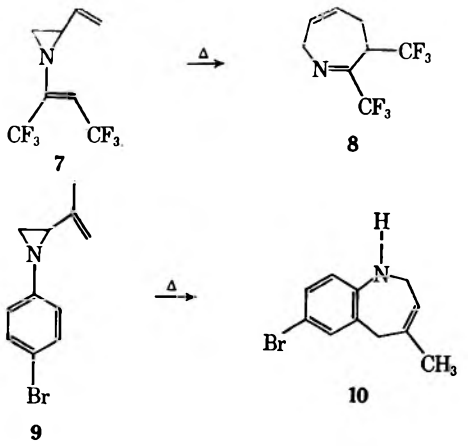
Recently it has been demonstrated that 1-carbethoxy-2-methyl-2-vinylaziridine (6) isomerizes when subjected to gas chromatography at 100° to 1-carbethoxy-3-methyl-3-pyrroline (5).[11]



4 5

Although the nmr of 2 precluded the possibility of a symmetrical 3-pyrroline being formed during the thermolysis of 1, an authentic sample of 1-*p*-nitrobenzoyl-3-pyrroline (6) was prepared. Compound 6 was different from the product of rearrangement 2 in respect to nmr spectrum, infrared spectrum, and melting point. Compound 6 was also stable under the conditions of thermolysis of 1.

The thermal isomerization of 1 to 3 resembles the thermal rearrangement of 1-[1,2-bis(trifluoromethyl)]-vinyl-2-vinylaziridine (7) to 2,3-bistrifluoromethyl-3,4-dihydro-7H-azepine (8)[12] and the rearrangement of 1-*p*-bromophenyl-2-isopropenylaziridine (9) to 7-bromo-4-methyl-2,5-dihydro-1H-1-benzazepine (10).[13]



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9 10

Experimental Section

1-*p*-Nitrobenzoyl-2-vinylaziridine (1).—A solution of 1.86 g (0.01 mol) of *p*-nitrobenzoyl chloride in 20 ml of dry ether was added to a solution of 0.691 g (0.01 mol) of 2-vinylaziridine and 1.01 g (0.01 mol) of triethylamine in 150 ml of ether. The mixture was allowed to stand at room temperature for 2 hr and was filtered. The filtrate was evaporated to give 1.76 g of crude 1. Recrystallization three times from low-boiling petroleum ether gave 1 melting at 69–70°.

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.61; N, 12.84. Found: C, 60.40; H, 4.45; N, 12.61.

The Thermal Isomerization of 1 into 2.—A solution of 125 mg of 1 in 10 ml of toluene was refluxed 4 hr. Evaporation of the solvent gave 121 mg of 2. Recrystallization of 2 from 95% ethanol formed crystals melting at 110–120°.

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.61; N, 12.84. Found: C, 60.51; H, 4.72; N, 12.78.

The Iodide Ion Catalyzed Isomerization of 1 to 3.—A mixture of 312 mg of 1, 300 mg of sodium iodide, and 15 ml of acetone was kept at room temperature for 5 hr. The solvent was evaporated, and the residue was mixed with water. The crude 3 (305 mg) was filtered and recrystallized from 95% ethanol. Pure 3 melted at 94–96°.

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.61; N, 12.84. Found: C, 60.10; H, 4.57; N, 12.85.

(11) A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.*, **33**, 481 (1968).
(12) E. L. Stogryn and S. J. Brois, *J. Amer. Chem. Soc.*, **89**, 605 (1967).
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Alternate Synthesis of 3.—A mixture of 0.108 g of ethyl *p*-nitrobenzimidate[14] and 0.044 g of 1-amino-3-buten-2-ol[15] was heated at 90–100° for 1.5 hr and then at 130–140° for 2 hr. The mixture solidified on cooling. Recrystallization from 95% ethanol gave 0.070 g of 3.

1-*p*-Nitrobenzyl-3-pyrroline (6) was prepared in an analogous manner as 1. After several recrystallizations from ethanol an analytical sample of 6 melted at 138–140°.

Anal. Calcd for $C_{11}H_{10}N_2O_3$: N, 12.84. Found: N, 12.82.

Registry No.—1, 17659-06-2; 2, 17659-07-3; 3, 17659-08-4; 6, 17659-09-5.

Acknowledgment.—We thank Dr. E. L. Stogryn for a sample of 2-vinylaziridine and the National Institutes of Health for Grant CA-10015.

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(15) M. G. Ettlinger, *ibid.*, **72**, 4792 (1950).

Pseudohalogens. XIII.[1] Preparation and Properties of N-Monochlorourethan and Its Metallic Salts

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Received May 31, 1968

Attention is being given in our laboratory to the development of new and improved methods for the generation of nitrenes, and, in this connection, we have studied nitrene production from N-monochlorourethan (MCU) and its metallic salts by α-elimination reactions. MCU was first prepared by Datta and Gupta[3] and subsequently by Traube and Goekel,[4] and by Chabrier,[5] who also prepared some metallic salts, but explicit details concerning yields, methods of isolation, purity, and physical characteristics of the products were not reported.

In this Note we describe an improved method of preparation and the properties of MCU and several of its metallic salts, such as the sodium, potassium, and silver salts, and also attempts, unfortunately unsuccessful, to generate carbethoxynitrene by thermolysis of the salts in cyclohexene solution.

Preparation and Properties of MCU and Its Metallic Salts.—MCU can be readily prepared in about 50% yield by reaction of the calculated quantity of chlorine with an aqueous solution of ethylurethan at 5–10° (eq 1). Since MCU is insoluble in water, it precipitates

$$C_2H_5OCNH_2 + Cl_2 \longrightarrow \underset{\text{MCU}}{C_2H_5OCNHCl} + HCl \quad (1)$$

as an oil, denser than water. Crude MCU is a pale yellow oil having a sharp odor; it contains a small amount of N,N-dichlorourethan (DCU). Assessment

(1) Paper XII: T. A. Foglia and D. Swern, *J. Org. Chem.*, **33**, 4440 (1968).
(2) To whom inquiries should be addressed. The authors acknowledge with thanks support of this investigation by U. S. Public Health Service Grants No. CA-07803, CA-07174, and CA-10439 of the National Cancer Institute.
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of the purity of MCU by iodometry gives a value slightly over 100% because of the DCU impurity. MCU of analytical purity, mp 9° and bp 44–45° (0.2 mm), is a colorless liquid obtained by distillation under high vacuum. High vacuum is very important in obtaining fair yields and high purity as it permits the distillation temperature to be as low as possible thus minimizing the disproportionation reaction shown in eq 2. Although separation of DCU from MCU is a facile process, ethylurethan sublimes with and contaminates the MCU.

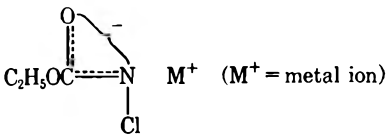
$$C_2H_5OCNHCl \longrightarrow \underset{\text{DCU}}{C_2H_5OCNCl_2} + C_2H_5OCNH_2 \qquad (2)$$

Iodometric analysis of crude and distilled MCU gives the total content of active chlorine. Composition of mixtures is readily determined by neutralization analysis as only MCU is a sufficiently strong acid to be titratable according to eq 3.

$$C_2H_5OCNHCl + NaOH \longrightarrow C_2H_5OCNCl + H_2O \qquad (3)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad Na$$

The analytically pure sodium or potassium salt of MCU can be obtained in quantitative yield by reaction of MCU with sodium or potassium hydroxide in methanol solution at 0°. Both salts are hygroscopic white crystalline solids which do not decompose on heating below 250°, contrary to literature reports.[5] When these salts are prepared from aqueous bases, anhydrous products are not obtained as water of crystallization is tightly bound. The analytically pure silver salt is obtained in quantitative yield by reaction of the sodium salt with silver nitrate in dilute aqueous solution at room temperature. When freshly prepared, it is a white crystalline solid which darkens on exposure to light and decomposes violently at or above about 127°. Attempts to isolate the lithium salt were unsuccessful.

The ir of neat MCU shows bands at 3300 (m) (N—H) and 1730 cm^{-1} (s) (C=O). In contrast, the ir of the metallic salts (KBr pellets) show no N—H absorption and the carbonyl shifts to 1600 cm^{-1} (s). The shift of the carbonyl absorption suggests that the metallic salts have the ionic structure



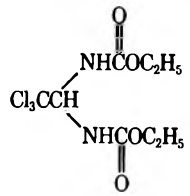
analogous to the carboxylate ion

whose carbonyl band is at lower frequencies (about 150 cm^{-1}) than that of the esters.

The uv of MCU in methanol shows weak end absorption at 206 mμ (ε 118) and 245 (186) (C=O). The sodium salt shows a single peak of medium intensity at 205 mμ (ε 267) but the potassium salt absorbs much more strongly at 211 mμ (ε 1030).

Nmr spectral data of MCU and of its sodium and potassium salts are given in the Experimental Section. Since MCU reacts violently with DMSO-d_6 and the salts are insoluble in CCl_4, we could not directly compare the chemical shifts of MCU with those of its salts in the same solvent.

Reaction of Metallic Salts of MCU with Cyclohexene.—Thermolysis of the sodium and silver salts of MCU for 48 and 24 hr, respectively, in boiling cyclohexene gives only about 50% decomposition. Many side reactions occur, as shown by glpc. Some of the reaction products are ethylurethan, 1,1,1-trichloroethylbis(carbamate) (I) and azabicyclo[4.1.0]heptane (II), the last two in very low yield. These salts react with acetone to give diacetone alcohol and ethylurethan; the nature of the oxidation product(s) is unknown.



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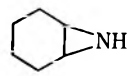

II

Experimental Section

Material and Equipment.—Ethylurethan was reagent grade obtained from Fisher Scientific Co. Chlorine gas, reagent grade, was obtained from a cylinder. Cyclohexene was distilled over metallic sodium before use. Ir spectra were obtained on a Perkin-Elmer Infracord, Model 137; uv spectra on a Perkin-Elmer ultraviolet–visible spectrometer Model 202. Nmr were obtained on a Varian A-60A spectrometer using TMS as internal standard. Refractive indices were taken on a Bausch and Lomb refractometer. Melting and boiling points are uncorrected. Microanalyses were performed by Micro-Analysis Inc., Wilmington, Del.

Iodometric Analysis.—Sufficient compound (0.1–0.2 g) was accurately weighed in an iodine flask to give a 10–15-ml titration with 0.1 *N* sodium thiosulfate. The sample was dissolved in 25 ml of water, and saturated sodium iodide solution (3 ml) was immediately added, followed by glacial acetic acid (5 ml). The solution was then titrated to a starch end point with 0.1 *N* sodium thiosulfate. A blank determination was run on the reagents.

Neutralization Analysis.—MCU (0.2–0.3 g) was accurately weighed and dissolved in 50 ml of methanol. An excess of 0.1 *N* NaOH was added, and the solution was back titrated with 0.1 *N* HCl using a pH meter. The neutralization points were determined from the usual graph.

Preparation of MCU.—An aqueous solution of ethylurethan (100 g, 1.125 mol) in water (500 ml) was placed in a 1-l. flask equipped with a stirrer, thermometer, and gas inlet tube. Chlorine gas (76 g, 1.07 mol), condensed from a cylinder, was allowed to distil slowly into the stirred solution over 4 hr at 5–10°. When chlorine addition was complete, the reaction mixture was allowed to separate into two phases and the lower organic phase was drawn off and washed successively with 20% aqueous sulfuric acid solution (two 100-ml portions) and water (two 100-ml portions). The crude MCU (69 g; 50 and 52% yield based on ethylurethan and chlorine, respectively), a pale yellow oil with a sharp odor, was then placed in a rotary vacuum evaporator to remove the last traces of water. The crude product contained a small quantity of DCU; iodometric analysis indicated a purity of 103% calculated as MCU. The oil was distilled through a Vigreux column (100 × 4 mm) under high vacuum. The main fraction (56 g) was collected at 44.0–45.0° (0.2 mm): mp 9°; $n^{25}D$ 1.4435. Iodometric and neutralization analyses indicated a purity greater than 99.4%: ir (neat) 3300 (NH), 1730 (C=O), 1440, 1380, 1330, 1240 (ester), 1070 (ester), and 765 (C—Cl)

cm^{-1}; λ_{max} (CH_3OH) 206 mμ (ε 118) and 245 (186); nmr (CCl_4) δ 1.33 (t, 3, CH_3), 4.33 (q, 2, CH_2), and 6.95 ppm (broad s, 1, NH).

Sodium Salt of MCU.—To a methanol solution of sodium hydroxide (0.8 g, 0.02 mol), MCU (2.5 g, 0.02 mol) was added dropwise with stirring at 0°. When addition was complete, the reaction mixture was evaporated to dryness in a rotary vacuum evaporator at room temperature. The crude residue was washed with ether, and the residue was again evaporated to yield the anhydrous sodium salt, a hygroscopic white solid (2.7 g, 98.7% yield). Purity by iodometric analysis exceeded 99%. The salt did not decompose on heating to 250°: ir (KBr pellet) 1600 (C=O), 1360, 1260 (ester), 1080 (ester) and 770 (C—Cl) cm^{-1}; λ_{max} (CH_3OH) 205 mμ (ε 267); nmr (DMSO-d_6) δ 1.07 (t, 3, CH_3) and 3.83 ppm (q, 2 H, CH_2).

Potassium Salt of MCU.—Prepared from equimolar quantities of MCU and potassium hydroxide, as just described for the sodium salt, except that it was purified by pouring the half evaporated methanol solution into ether. The anhydrous potassium salt, a hygroscopic white solid, was obtained as a precipitate (yield 96%; purity >96%). It did not decompose on heating to 250°: ir (KBr pellets) 1600 (C=O), 1360, 1270 (ester), 1075 (ester) and 770 cm^{-1} (C—Cl); λ_{max} (CH_3OH) 211 mμ (ε 1030); nmr (DMSO-d_6) δ 1.05 (t, 3, CH_3) and 3.78 ppm (q, 2, CH_2).

Silver Salt of MCU.—A 1% aqueous solution of silver nitrate (1.2 g, 0.007 mol) was added dropwise to a 1% aqueous solution of the sodium salt of MCU (1.0 g, 0.007 mol) with stirring at room temperature in the dark. The precipitate was filtered, washed with methanol and dried under vacuum in the dark. A white crystalline solid unstable to light was obtained (yield 100%; purity >99.0%). The anhydrous silver salt decomposed violently on heating to 127°: ir (KBr pellets) 1600 (C=O), 1360, 1270 (ester), 1075 (ester) and 768 (C—Cl) cm^{-1}.

Lithium Salt of MCU.—Attempts to prepare the lithium salt were unsuccessful. Reaction of MCU at 0° with lithium hydroxide in methanol yielded an unstable colorless liquid that decomposed at room temperature with evolution of a gas over a period of several days. The freshly prepared oil gave a precipitate on treatment with aqueous silver nitrate suggesting that some lithium salt may have formed (MCU does not react with silver nitrate). Similar results were obtained on reaction of MCU with *n*-butyllithium at −76° in tetrahydrofuran with cyclohexene present.

Reaction of Metallic Salts of MCU with Cyclohexene.—A mixture of the sodium salt of MCU (10 g, 0.069 mol) and cyclohexene (282 g, 3.45 mol) was placed in a 500-ml flask equipped with a stirrer, thermometer, condenser, and gas inlet tube. The mixture was then refluxed under nitrogen for 48 hr. The insoluble matter was filtered, washed with ether, and dried under vacuum. It was shown by analysis to be a mixture of sodium chloride and the unreacted sodium salt of MCU. (By iodometric analysis, only 60% of the sodium salt of MCU had decomposed.) After removing ether and unreacted cyclohexene from the filtrate, the liquid residue was cooled to 0° to precipitate a very small yield of colorless needles. They were recrystallized from *n*-hexane and shown to be 1,1,1-trichloroethylbis(carbamate) (I): mp 172–172.5°; ir (KBr) 3260 (NH), 2990 (CH), 1700 (C=O) and 825 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (t, 6, CH_3), 4.22 (q, 4, CH_2), 5.56 (broad, d, 2, NH), and 6.61 ppm (d, 1, CH).

Anal. Calcd for I: C, 31.24; H, 4.26; Cl, 34.58; N, 9.11; O, 20.81. Found: C, 31.42; H, 4.07; Cl, 34.85; N, 9.41; O, 20.15.

The hexane filtrate was washed with water to remove ethylurethan and then distilled under vacuum. A main fraction, azabicyclo[4.1.0]heptane, was obtained in very low yield at 31.0–32° (0.4 mm): ir (neat) 3350 (NH), 2920, 2850, 1440, 1020 and 882 cm^{-1}; nmr (CCl_4) δ 1.37 (m, ring CH_2), 1.79 (m, ring CH_2), 3.65 (broad s, ring CH), and 4.28 ppm (broad s, NH); singlet at 4.28 ppm disappears when the solution is treated with D_2O solution containing a trace of trifluoroacetic acid. The ir and nmr were identical with those of an authentic sample.

Reaction of the Sodium Salt of MCU with Acetone.—A mixture of the sodium salt (13 g, 0.089 mol) and acetone (254 g, 4.45 mol) was refluxed for 18 hr; 96% of the sodium salt decomposed. After sodium chloride was separated by filtration, the liquid product was distilled under reduced pressure; after removal of acetone a fraction was obtained as a colorless liquid (12 g) at 65.5–66.5° (13 mm), identified as diacetone alcohol by ir and nmr. The residue was dissolved in hot *n*-hexane and cooled to yield ethylurethan (4.9 g, 62% yield).

Registry No.—MCU, 16844-21-6; sodium salt of MCU, 17510-52-0; potassium salt of MCU, 17510-53-1; silver salt of MCU, 17510-54-2; I, 17528-34-6.

The Addition of Dimethylketene to Trichloroacetyl Chloride. A β-Keto Acid Halide[1]

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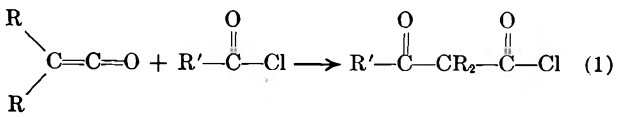
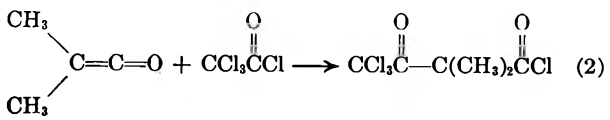
Staudinger and coworkers were the first to describe the addition of an acid chloride to a ketene to produce a β-keto acid halide[2] (eq 1). While this reaction has



(1)

been investigated, in most cases the β-keto acid halide was not isolated but converted into an ester.[3,4] Therefore, we wish to report the results of an investigation on the addition of dimethylketene to trichloroacetyl chloride and the isolation, characterization, properties, and chemical reactivity of the resultant β-keto acid halide.

Dimethylketene readily reacts with trichloroacetyl chloride at room temperature to produce 4,4,4-trichloro-2,2-dimethyl-3-ketobutanoyl chloride (I) in 61% yield (eq 2). The structure of I was proven by a combina-

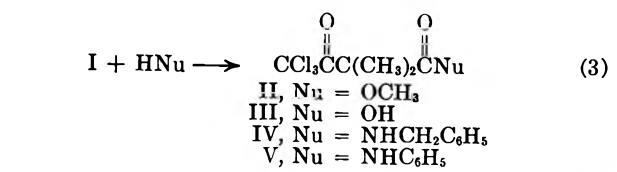


(2)

I

tion of elemental analysis and infrared (ir) and proton magnetic resonance (pmr) spectra. An ir band at 1785 revealed that the adduct was an acid halide and a band at 1740 cm^{-1} verified the presence of the β-keto group. The pmr spectrum revealed the methyl protons at 1.77 ppm.

Compound I readily undergoes the expected nucleophilic substitutions as illustrated in eq 3.



(3)

II, Nu = OCH_3
III, Nu = OH
IV, Nu = $NHCH_2C_6H_5$
V, Nu = NHC_6H_5

It is interesting to note that I reacts with an equimolar amount of benzylamine to produce the expected N-benzylamide (IV), but, when treated with an excess of amine, N,N′-dibenzyldimethylmalonamide (VI) is

(1) This work was supported by a National Science Foundation Grant GP-7386.

(2) H. Staudinger, O. Gohring, and M. Scholler, *Ber.*, **47**, 40 (1914).

(3) F. Sorm, J. Smrt, and J. Beranek, *Chem. Listy.*, **48**, 679 (1954).

(4) F. Sorm, J. Smrt, and J. Beranek, *ibid.*, **49**, 73 (1955).

produced. Also, treatment of IV with benzylamine will produce VI (eq 4). Apparently, this reaction is

$$\text{I or IV} \xrightarrow[\text{(excess)}]{\text{benzylamine}} C_6H_5CH_2NHCC(CH_3)_2CNHCH_2C_6H_5 \quad (4)$$

VI

analogous to the familiar iodoform reaction of methyl ketones.

Experimental Section

Dimethylketene was prepared by the pyrolysis of the commercially available ketene dimer, tetramethyl-1,3-cyclobutanedione, and then distilled just prior to the addition reaction.[5] All of the solvents used in this study were dried by refluxing and distilling from lithium aluminum hydride through a 30-plate Oldershaw column. The pmr spectra were recorded on a Varian A-60 instrument.

4,4,4-Trichloro-2,2-dimethyl-3-ketobutanoyl Chloride. (I).—A solution of 2.6 g of dimethylketene (0.037 mol) in 25 ml of hexane was added slowly to a stirred solution of 10 ml (0.0912 mol) of trichloroacetyl chloride in 50 ml of hexane at room temperature. After standing overnight, the solvent was removed under reduced pressure, and the residue was fractionated to yield 5.7 g (61%) of I at 68–70° (0.7 mm). The spectral data were given above.

Anal. Calcd for $C_6H_6Cl_4O_2$: C, 28.55; H, 2.20. Found: C, 28.55; H, 2.10.

Methyl 4,4,4-Trichloro-2,2-dimethyl-3-ketobutanoate. (II).—A 2-g (0.0079 mol) portion of I was added dropwise with stirring to an excess of dry methanol at room temperature. The excess methanol was evaporated, and the residue was recrystallized from ligroin to yield 1.7 g (91%) of II: mp 42–43°; ir 1755 and 1740 cm^{-1}; pmr (CCl_4) a singlet at 3.75 and 1.60 ppm. The peak areas were in the ratio of 1:2.

Anal. Calcd for $C_7H_9Cl_3O_3$: C, 33.90; H, 3.63. Found: C, 33.75; H, 3.72.

4,4,4-Trichloro-2,2-dimethyl-3-ketobutanoic Acid (III).—The dropwise addition of I to an excess of water resulted in a quantitative conversion into III which was recrystallized from ligroin: mp 115–116°; ir 1710 cm^{-1}.

Anal. Calcd for $C_6H_7Cl_3O_3$: C, 30.86; H, 3.02. Found: C, 30.95; H, 2.72.

N-Benzyl-4,4,4-trichloro-2,2-dimethyl-3-ketobutanamide (IV).—A solution of 0.75 g (0.00297 mol) of I in 25 ml of dry hexane was added dropwise to a stirred solution of 0.318 g (0.00297 mol) of benzylamine in 10 ml of dry hexane. A white precipitate formed upon addition. The reaction mixture was washed with dilute hydrochloric acid solution, followed by a water wash. Drying and evaporation of the solvent yielded 0.4 g of IV. This material was recrystallized from 70% ethanol: mp 100.5–102°; ir 1745 and 1635 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}Cl_3NO_2$: C, 48.40; H, 4.34. Found: C, 48.45; H, 4.51.

N-Phenyl-4,4,4-trichloro-2,2-dimethyl-3-ketobutanamide (V).—The anilide was prepared in the same manner as described above for the N-benzamide, except ether was used as the solvent. Recrystallization from ligroin yielded crystals with mp 146–147°; ir 1745 and 1635 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}Cl_3NO_2$: C, 46.6; H, 3.89. Found: C, 46.86; H, 3.61.

N,N'-Dibenzyldimethylmalonamide (VI).—A 3.5-g (0.0139 mol) portion of I was added dropwise with stirring to a solution of 5 g (0.0467 mol) of benzylamine in 250 ml of benzene. The reaction mixture was washed with dilute hydrochloric acid solution, followed by water. The benzene solution was dried over anhydrous magnesium sulfate, filtered, and cooled to yield 3.5 g (81%) of VI. The crude product was recrystallized from 70% ethanol to yield small white needles, mp 166–167°. A mixture melting point with an authentic sample of VI prepared from dimethylmalonyl chloride and benzylamine showed no depression.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.50; H, 7.10; mol wt, 310. Found: C, 73.50; H, 7.18; mol wt, 310 (mass spectrum).

Compound VI could also be prepared by treatment of IV with an excess of benzylamine.

(5) W. E. Hanford and J. C. Sauer, *Org. Reactions*, **3**, 136 (1946).

Registry No.—I, 17953-83-2; II, 17953-84-3; III, 17953-85-4; IV, 17953-86-5; V, 17953-87-6; VI, 17953-88-7; Me_2CCO, 598-26-5; Cl_3CCOCl, 76-02-8.

Reactions of Phenyl Isocyanate and Phenyl Isothiocyanate with Indole and Metal Derivatives of Indole

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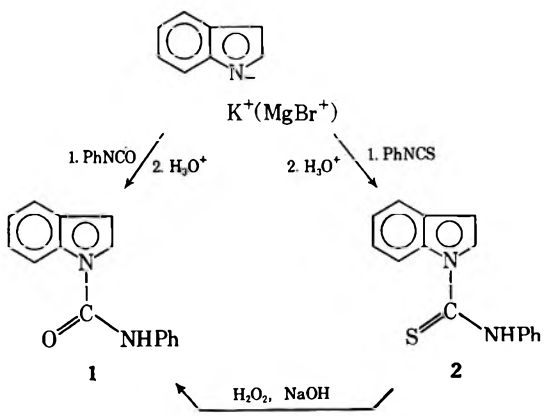
Pyrrole is known to react with phenyl isocyanate and phenyl isothiocyanate to form 2-pyrrolecarboxanilide[1] and 2-pyrrolethiocarbanilide,[2] respectively. With the same reagents, pyrrolylpotassium forms the 1-carboxanilide and 1-thiocarbanilide, whereas pyrrolylmagnesium bromide gives mixtures of the 1 and 2 derivatives.[3,4]

We wish to report now on the analogous reactions of indole, indolylpotassium, and indolylmagnesium bromide. When treated with phenyl isocyanate or phenyl isothiocyanate in tetrahydrofuran, indolylpotassium yields 1-indolecarboxanilide (1) or 1-indolethiocarbanilide (2). It is noteworthy that the same compounds are obtained from the corresponding reactions of indolylmagnesium bromide in tetrahydrofuran, despite the general tendency of this reagent to give 3-substituted indole derivatives.[5] Comparison of the infrared spectra of the crude and purified products shows that these reactions lead to the formation of 1-substituted indole derivatives only. The structure assigned to 1 is consistent with its infrared spectrum,

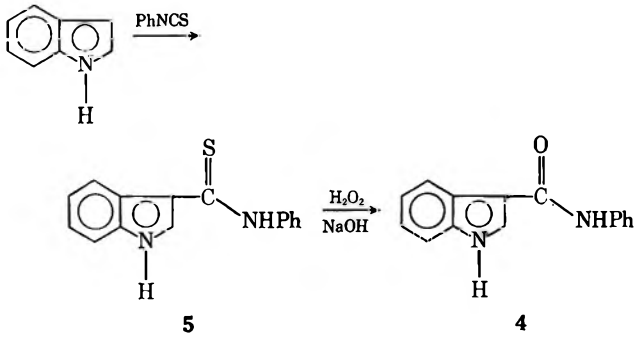


which shows a carbonyl absorption at 1710 cm^{-1}, but not the characteristic indole N–H band in the 3400–3500-cm^{-1} region.[6] Furthermore, alkaline hydrolysis of 1 yields a mixture of indole and aniline. The structure of 2 is confirmed by its smooth oxidation to 1 with alkaline hydrogen peroxide.

(1) A. Treibs and W. Ott, *Ann.*, **577**, 119 (1952).
(2) E. Bullock and R. J. Abraham, *Can. J. Chem.*, **37**, 1391 (1959).
(3) E. P. Papadopoulos and H. S. Habiby, *J. Org. Chem.*, **31**, 327 (1966).
(4) E. P. Papadopoulos, *ibid.*, **31**, 3060 (1966).
(5) M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," Edward Arnold Ltd., London, England, 1967, p 324.
(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1962.

When a mixture of equimolar amounts of indole and phenyl isocyanate is allowed to stand at room temperature for several hours, a solid mass is obtained, which, however, does not contain any of the 1-, 2-, and 3-indolecarboxanilides. So far, we have been unable to determine the nature of this product, purification of which is made difficult by its low solubility in the common solvents. The 2- (**3**), and the 3-indolecarboxanilide (**4**) have been prepared from the corresponding acids *via* the acid chlorides. The infrared spectrum of **3** has the indole N–H band at 3440 cm^{-1} and a carbonyl band at 1660 cm^{-1}; that of **4** shows corresponding absorptions at 3460 and 1655 cm^{-1}. There is good agreement between the relative positions of carbonyl absorption of N- and C-indolecarboxanilides and those of the corresponding derivatives of pyrrole[3] and imidazole.[7]

Indole reacts sluggishly with phenyl isothiocyanate to give, after prolonged heating and in low yield, a product which must be the 3-indolethiocarbanilide (**5**), as shown by its oxidation to **4** with alkaline hydrogen peroxide.

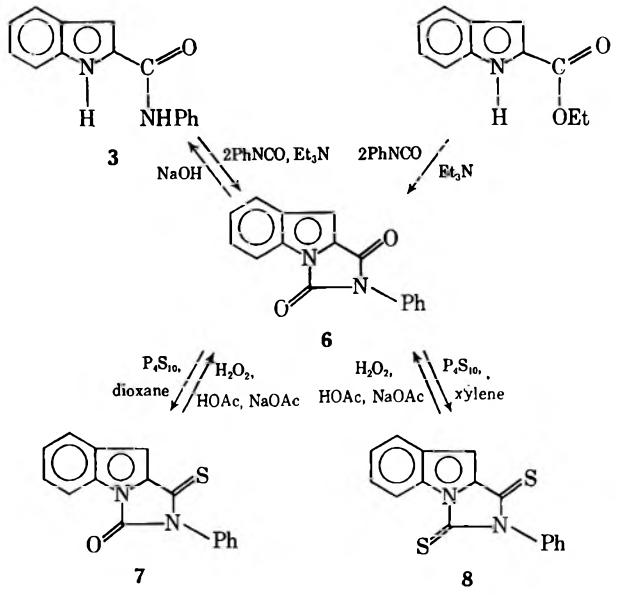


5 **4**

In complete analogy with the corresponding pyrrole derivative,[3] 2-indolecarboxanilide (**3**) reacts with phenyl isocyanate in the presence of triethylamine to form 2-phenylindolo[1,2-*c*]hydantoin (**6**) and N,N′-diphenylurea (Scheme I). The infrared spectrum of **6** shows two carbonyl bands at relatively high frequencies (1785 and 1735 cm^{-1}), consistent with the hydantoin structure[6] and in good agreement with those observed in the spectra of 2-phenylpyrrolo[1,2-*c*]hydantoin,[3] and 2,5,6-triphenylimidazo[1,2-*c*]hydantoin.[7] The structure assigned to **6** is further supported by its conversion into **3** by alkaline hydrolysis and by its formation in excellent yield from 2-ethoxycarbonylindole by the action of phenyl isocyanate and triethylamine. The two carbonyls of **6** exhibit a difference in reactivity toward phosphorus pentasulfide analogous to that observed for the corresponding pyrrole derivative.[4] Whereas refluxing with phosphorus pentasulfide in dioxane readily converts **6** into a monothiohydantoin, conversion of **6** into 2-phenylindolo[1,2-*c*]dithiohydantoin (**8**) requires prolonged refluxing of the reagents in xylene. Compared with the infrared spectrum of **6**, that of its monothio derivative retains the carbonyl absorption at higher frequency (1775 cm^{-1}), but lacks the band at lower frequency. The high frequency carbonyl absorption is consistent with the 2-phenylindolo[1,2-*c*]-1-thiohydantoin (**7**) structure, which finds its parallel in the thiohydantoin obtained in the pyrrole series by the same sequence of steps.[4] The spectrum

(7) R. Gompper, E. Hoyer, and H. Herlinger, *Ber.*, **92**, 550 (1959).

SCHEME I



of **8**, as expected, shows no absorption in the carbonyl region. Both **7** and **8** are oxidized to **6** by hydrogen peroxide, in the presence of acetic acid and sodium acetate.

Experimental Section

Melting points were determined on a calibrated Fisher-Johns melting point apparatus. Infrared spectra were run on a Perkin-Elmer Model 257 infrared spectrophotometer.

1-Indolecarboxanilide (1). A. From Indolylpotassium.—A solution of 11.7 g (0.1 mol) of indole in 100 ml of tetrahydrofuran was stirred at reflux with 3.9 g (0.1 g-atom) of potassium until all the metal had reacted. To the resulting solution of indolylpotassium, diluted with 100 ml of tetrahydrofuran and cooled to room temperature, was added dropwise over 0.5 hr 11.9 g (0.1 mol) of phenyl isocyanate dissolved in 100 ml of tetrahydrofuran. After the reaction mixture had been stirred at room temperature for an additional 15 hr, the solvent was removed by distillation under reduced pressure and the residue was cooled and treated with 200 ml of water. Acidification with dilute hydrochloric acid and filtration yielded 24.0 g of crude product, which was recrystallized from petroleum ether (bp 100–115°) to give 13.2 g (56%) of 1-indolecarboxanilide (**1**), mp 121–123°. Upon further recrystallization the melting point became 124–125°.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.38; H, 5.13; N, 11.96.

B. From Indolylmagnesium Bromide.—Indolylmagnesium bromide was prepared by dropwise addition of 11.7 g (0.1 mol) of indole dissolved in 50 ml of tetrahydrofuran to a solution of ethylmagnesium bromide made from 13.6 g (0.125 mol) of ethyl bromide and 2.4 g (0.1 g-atom) of magnesium in 100 ml of tetrahydrofuran. A solution of 10.8 g (0.09 mol) of phenyl isocyanate in 50 ml of tetrahydrofuran was introduced dropwise (0.5 hr) into the stirred reaction mixture, and the resulting solution was stirred at room temperature for 17 hr. Hydrolysis with 50 ml of water containing 10.7 g of ammonium chloride was followed by separation of the layers and extraction of the aqueous layer with ether. The combined organic solutions were treated with animal charcoal and dried over anhydrous magnesium sulfate. Evaporation of the solution under reduced pressure yielded 20.7 g of crude product, which was recrystallized from methyl alcohol to give 9.8 g of **1**, mp 122.5–124.5°, as a first crop, and 2.1 g, mp 121.5–122.5°, as a second (total yield 56%). The infrared spectra of the crude and the pure product of this reaction, respectively, were the same as those of the preceding preparation. There was no melting point depression on admixture of the two pure products.

Hydrolysis of 1-Indolecarboxanilide.—To a solution of 0.5 g of **1** in 15 ml of ethyl alcohol was added 2 g of potassium hydroxide dissolved in 5 ml of water and the mixture was refluxed for 3 hr.

Cooling of the solution was followed by ether extraction and evaporation of the extract to a small volume. Gas–liquid partition chromatography showed that the extract contained equimolar quantities of indole and aniline.

1-Indolethiocarbanilide (2). A. From Indolylpotassium.—A solution of 13.5 g (0.1 mol) of phenyl isothiocyanate in 100 ml of tetrahydrofuran was added dropwise over 0.5 hr to a stirred solution of indolylpotassium prepared as described earlier from 3.9 g (0.1 g-atom) of potassium and 11.7 g (0.1 mol) of indole in 200 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 15 hr, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in 200 ml of water. The resulting solution was washed with ether and was acidified with dilute hydrochloric acid to yield 20 g of crude 1-indolethiocarbanilide (2), mp 125–127°. Evaporation of the ether washings to dryness, treatment of the residue with petroleum ether (bp 40–80°), and recrystallization from 95% ethyl alcohol afforded a further 1.7 g of product, mp 125.5–128.5 (total yield 86%). Recrystallization from 95% ethyl alcohol gave pale yellow crystals of the pure compound melting at 128–129°.

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.41; H, 4.80; N, 11.11; S, 12.69. Found: C, 71.57; H, 4.70; N, 11.16; S, 12.73.

B. From Indolylmagnesium Bromide.—Indolylmagnesium bromide was prepared as described earlier from 11.7 g (0.1 mol) of indole, 2.4 g (0.1 g-atom) of magnesium, and 13.6 g (0.125 mol) of ethyl bromide in a total of 150 ml of tetrahydrofuran. After dropwise introduction of a solution of 10.5 g (0.09 mol) of phenyl isothiocyanate in 100 ml of tetrahydrofuran, the reaction mixture was stirred at room temperature for 21 hr. Hydrolysis with aqueous ammonium chloride and the usual work-up yielded 16.2 g of crude product, which was recrystallized from 95% ethyl alcohol to give 13.4 g (59%) of **2**, mp 125–127°. The infrared spectra of the crude and the purified product of this reaction were identical with those of the preceding one, and no melting point depression was observed upon admixture of the two pure products.

Oxidation of 1-Indolethiocarbanilide (2) to 1-Indolecarboxanilide (1).—An ice-cold solution of 1 g of **2** and six pellets of sodium hydroxide in 35 ml of ethyl alcohol and 2 ml of water was mixed with 6 ml of hydrogen peroxide (30%) and the mixture was kept at 0° for 1 hr and, subsequently, in a refrigerator overnight. Dilution with water yielded 0.8 g of a solid, mp 122–123°, the infrared spectrum of which was identical with that of **1**. One recrystallization from ethyl alcohol raised the melting point to 123.5–125°, and a mixture with authentic **1** melted at 124–125°.

2-Indolecarboxanilide (3).—A mixture of 4.0 g (0.025 mol) of 2-indolecarboxylic acid and 5.0 g (0.042 mol) of thionyl chloride was heated at 70–75° for 4 hr. After the excess of thionyl chloride had been removed by distillation under reduced pressure, the residue was treated with two 20-ml portions of petroleum ether (bp 40–80°), and each time was evaporated under reduced pressure. The final residue was treated with 300 ml of ether and the resulting solution of the acid chloride was filtered into a solution of 10 g of aniline in 100 ml of ether. The mixture was allowed to stand for 2 hr, then it was filtered, and the filtrate was washed successively with water, dilute hydrochloric acid, water, aqueous sodium bicarbonate, and water. After treatment with animal charcoal and anhydrous magnesium sulfate, the ether solution was evaporated to dryness under reduced pressure to yield 4.0 g (68%) of 2-indolecarboxanilide (**3**), mp 198–202°. Recrystallization from 95% ethyl alcohol raised the melting point to 202–203°.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.14; H, 5.04; N, 11.91.

3-Indolecarboxanilide (4).—Starting with 4.0 g of 3-indolecarboxylic acid and following the procedure described for the preparation of **3**, there was obtained 4.5 g (76%) of 3-indolecarboxanilide (**4**), mp 176.5–177.5°. After recrystallization from 50% ethyl alcohol, the pure compound melted at 178.5–179.5°.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.05; H, 5.12; N, 11.73.

3-Indolethiocarbanilide (5).—A mixture of 11.7 g (0.1 mol) of indole and 13.5 g (0.1 mol) of phenyl isothiocyanate was heated at 80–90° for 8 days. The dark, tarry product was refluxed with 100 ml of petroleum ether (bp 100–115°) and the resulting solid residue was recrystallized from 95% ethyl alcohol to yield 9.7 g (38%) of crude product, mp 180–185°. Further recrystallization from 95% ethyl alcohol gave pure 3-indolethiocarbanilide (**5**), yellow crystals, mp 188–189°.

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.41; H, 4.80; N, 11.11; S, 12.69. Found: C, 71.53; H, 4.85; N, 10.97; S, 12.83.

Oxidation of 3-indolethiocarbanilide (5) to 3-indolecarboxanilide (4) was run as described for the oxidation of **2** to **1**, except that the alcoholic solution of the product was allowed to stand at room temperature for 0.5 hr prior to its dilution with water. From 1 g of **5** there was obtained 0.8 g of **4**, mp 178–180°, raised to 178.5–180° by recrystallization from 50% ethyl alcohol. There was no melting point depression upon admixture with an authentic sample of **4**.

2-Phenylindolo[1,2-*c*]hydantoin (6). A. From 2-Indolecarboxanilide (3).—A mixture of 2.4 g (0.01 mol) of **3**, 2.4 g (0.02 mol) of phenyl isocyanate, and 3 ml of triethylamine was heated at 90° for 2 hr. The solid product was cooled, washed with petroleum ether (bp 40–80°), and mixed thoroughly with 150 ml of chloroform. Filtration of the mixture yielded 1.9 g of a solid, mp 238–240°, identified as N,N′-diphenylurea on the basis of its infrared spectrum and a mixture melting point with an authentic sample. Evaporation of the chloroform solution under reduced pressure gave 2.5 g of solid material, which was recrystallized from *n*-propyl alcohol to yield 1.9 g (72%) of 2-phenylindolo[1,2-*c*]hydantoin (**6**), mp 212–213°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.46; H, 3.78; N, 10.71.

B. From 2-Ethoxycarbonylindole.—A mixture of 2.4 g (0.0125 mol) of 2-ethoxycarbonylindole, 3.0 g (0.025 mol) of phenyl isocyanate, and 1.5 ml of triethylamine was heated at 100° for 4 hr. Cooling and washing of the solid product with four 10-ml portions of ethyl alcohol yielded 3.0 g (91%) of a solid, mp 211–213°, the infrared spectrum of which was identical with that of **6** obtained from the preceding reaction. There was no melting point depression when the products of the two reactions were mixed.

Hydrolysis of 2-Phenylindolo[1,2-*c*]hydantoin (6).—A mixture of 0.2 g of **6**, 1 ml of 10% aqueous sodium hydroxide, and 4 ml of ethyl alcohol was heated for a few moments, until the original yellowish solid had gone into solution and a colorless precipitate had started forming. Cooling and dilution with water yielded 0.1 g of a solid, mp 202–204°, identified as 2-indolecarboxanilide (**3**) on the basis of its infrared spectrum and a mixture melting point with authentic **3**.

2-Phenylindolo[1,2-*c*]-1-thiohydantoin (7).—To a solution of 1 g of **6** in 30 ml of dioxane 2 g of phosphorus pentasulfide was added and the mixture was refluxed for 4 hr. After addition of a further 2 g of phosphorus pentasulfide, refluxing was continued for an additional 4 hr. Filtration of the hot mixture and removal of the solvent by distillation under reduced pressure gave a dark residue, which was refluxed with 100 ml of petroleum ether (bp 100–115°). A new filtration of the hot mixture yielded a solution, evaporation of which gave 0.6 g of crude product, mp 168–173°. After several recrystallizations from 95% ethyl alcohol, there was obtained pure 2-phenylindolo[1,2-*c*]-1-thiohydantoin (**7**), orange-red crystals, mp 182–183°.

Anal. Calcd for $C_{16}H_{10}N_2OS$: C, 69.06; H, 3.62; N, 10.07; S, 11.50. Found: C, 69.20; H, 3.51; N, 10.08; S, 11.48.

Oxidation of 2-Phenylindolo[1,2-*c*]-1-thiohydantoin (7) to 2-Phenylindolo[1,2-*c*]hydantoin (6).—A mixture of 0.3 g of **7**, 3 ml of acetic acid, 0.3 g of sodium acetate, and 2 ml of hydrogen peroxide (30%) was stirred at room temperature for 24 hr.[8] The addition of hydrogen peroxide was repeated twice, followed each time by a 24-hr stirring period. Dilution with water gave a precipitate which was separated by filtration and washed with water to give 0.1 g of product, mp 205–209°, the infrared spectrum of which was identical with that of **6**.

2-Phenylindolo[1,2-*c*]dithiohydantoin (8).—A mixture of 0.6 g of **6**, 2.4 g of phosphorus pentasulfide, and 20 ml of xylene was refluxed for 36 hr. After filtration of the hot mixture, the solvent was removed by distillation under reduced pressure and the residue was refluxed with 50 ml of petroleum ether (bp 100–115°). Evaporation of the extract to dryness yielded 0.5 g of crude product, mp 185–188°. After several recrystallizations from 95% ethyl alcohol, the melting point of pure 2-phenylindolo[1,2-*c*]dithiohydantoin (**8**), dark purple crystals, was 195–196°.

Anal. Calcd for $C_{16}H_{10}N_2S_2$: C, 65.30; H, 3.43; N, 9.52; S, 21.75. Found: C, 65.36; H, 3.41; N, 9.35; S, 21.61.

Oxidation of 2-Phenylindolo[1,2-*c*]dithiohydantoin (8) to 2-Phenylindolo[1,2-*c*]hydantoin (6).—The reaction was run as

(8) G. Bianchetti, P. Dalla Croce, and D. Pocar, *Gazz. Chim. Ital.*, **94**, 606 (1964).

described for the conversion of **7** into **6**. From 0.2 g of **8**, 2 ml of acetic acid, 0.2 g of sodium acetate, and a total of 6 ml of hydrogen peroxide (30%) there was obtained 0.1 g of product, mp 208–210°, the infrared spectrum of which was identical with that of **6**.

Registry No.—**1**, 16036-21-8; **2**, 17954-04-0; **3**, 17954-05-1; **4**, 17954-06-2; **5**, 6954-17-2; **6**, 17954-08-4; **7**, 17954-09-5; **8**, 17954-10-8; PhNCO, 103-71-9; PhNCS, 103-72-0; indole, 102-72-9.

Acknowledgment.—This work was supported by a grant from the Arts and Sciences Research Committee of the American University of Beirut, Beirut, Lebanon. The authors are grateful to Dr. C. H. Issidorides for his constant help and encouragement.

Nitrosoazomethine Derivatives. Oxidation of Amidoximes[1]

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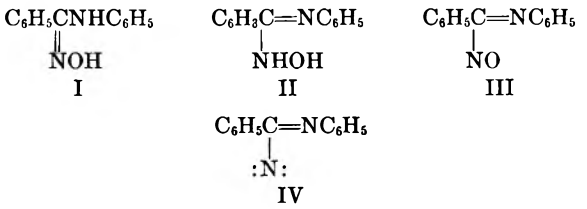
Received July 1, 1968

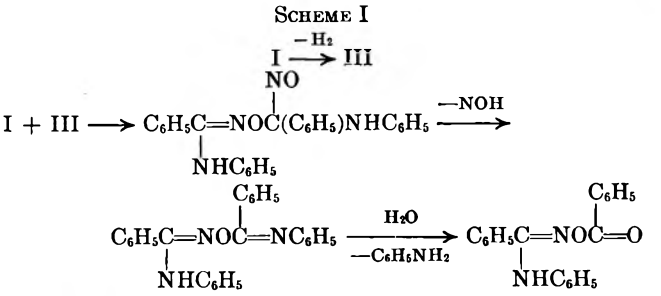
To investigate deoxygenation of nitrosoazomethine derivatives (III) as a method for the generation of azomethine nitrenes (IV), a preparation of these virtually unknown nitroso compounds[2a] by the oxidation and dehydrogenation of secondary amidoximes has been sought.



At room temperature or below, the oxime (I) of benzanilide reacts readily with lead tetraacetate, N-bromosuccinimide, or diethyl azodicarboxylate. The O-benzoyl derivative (V) of the oxime of benzanilide is produced in yields of 15.6, 13, and 57.7%, respectively. Its formation is consistent with an initial oxidation or dehydrogenation of the amidoxime into 1,2-diphenyl-2-nitrosoazomethine (III) and subsequent condensation between I and III followed by hydrolysis during the work-up (Scheme I).

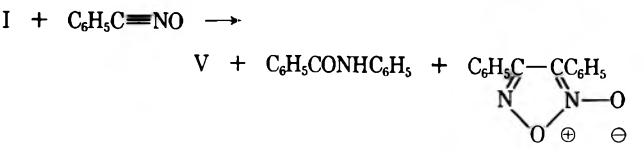
As alternative reactions leading to the formation of V, the condensation of I with either itself or benzanilide at the temperatures employed was eliminated by separate experiments which revealed no reaction in either event. A small amount of benzanilide isolated from each oxidation or dehydrogenation may be attributed to hydrolysis of anyone of the several derivatives of

SCHEME I



$C_6H_5C(NHC_6H_5)=N-$ which may be present during work-up of the reaction mixture.

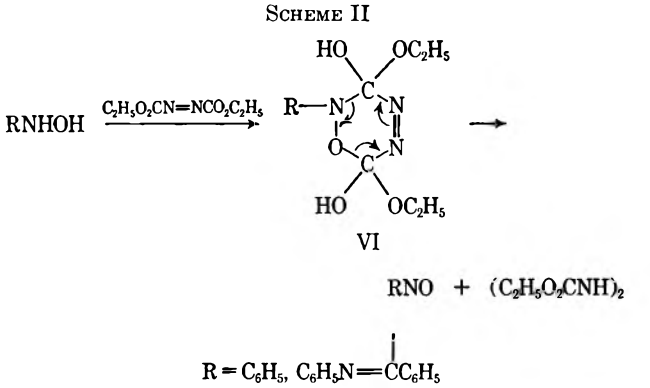
An independent synthesis of V (75.6% yield) was developed from a new reaction between benzonitrile oxide and the oxime (I). In addition to V, benzanilide



and diphenylfuroxan were formed. Although there is no direct positive evidence to support it, the possibility that benzonitrile oxide may be generated during an oxidation of I has been recognized.

Both oxidation and dehydrogenation may proceed from the tautomeric hydroxylamine (II). Facile oxidation of hydroxylamines to nitroso compounds is well established; however, dehydrogenation of the hydroxylamino function by ethyl azodicarboxylate was unknown heretofore. By this reagent phenylhydroxylamine has been dehydrogenated to nitrosobenzene in 71% yield.[2b] An explanation for the reaction is based upon a concerted or stepwise dissociation of a proposed cyclic adduct, VI (Scheme II). Ethyl hydrazocarboxylate is produced in a comparable yield of 72%. Conceivably this new preparation of a nitroso compound may be of value when carried out in the presence of other groups sensitive to oxidizing or reducing reagents. Closely related dehydrogenation of other compounds, *e.g.*, primary and secondary alcohols and primary amines and mercaptans, by diethyl azodicarboxylate has been reported.[3]

SCHEME II



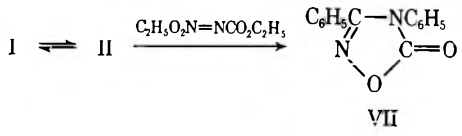
In low yield a by-product, 3,4-diphenyl-1,2,4-oxadiazolone-5 (VII), is also formed in the reaction between I ⇌ II and ethyl azodicarboxylate. It was independ-

(1) Financial assistance was received from NASA Grant No. NGR 14-012-004.

(2) (a) P. A. S. Smith ["Open-Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, Pasadena, California, 1966] discusses nitrosolic acids, RC(NO)=NOH (pp 356 and 384) and $CH_3C(=NOH)N(OH)N=C(NO)CH_3$ (p 92). J. H. Boyer in "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1959, Vol. 7, p 428] discusses $CH_3N(C_6H_5)N=C(CH_3)NO$. (b) Our work on the dehydrogenation of phenylhydroxylamine was carried out before a similar report appeared: E. C. Taylor and F. Yoneda, *Chem. Commun.*, 199 (1967).

(3) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Amer. Chem. Soc.*, **88**, 2328 (1966).

ently established that VII is not produced under comparable conditions by the interaction of ethyl hydrazocarboxylate and I ⇌ II.



VII

Experimental Section

The oxime (I) of benzanilide was prepared by refluxing an alcoholic solution of thiobenzanilide, mp 98–100°, and equivalent amounts of hydroxylamine hydrochloride and sodium carbonate for 12 hr[4] or from an ether solution of benzonitrile oxide and a large excess of aniline on standing for 12 hr.[5] Average yields of 70% of colorless solid were obtained after recrystallization from hexane–benzene (2:1), mp 136–137°.

Addition of benzoyl chloride to I afforded the **O-benzoyl derivative** (V) as a colorless solid: mp 116–117°;[4] infrared absorption in chloroform, 3450, 3010, 1755 vs, 1620, 1610, 1580, 1510, 1455, 1400, 1260–1200, 1080, 1060 and 1025 cm^{-1}; in deuteriochloroform V gave nmr for two sets of aromatic protons at δ 8.10–7.86 and 7.60–6.69.

Oxidation of the Oxime (I) of Benzanilide. A. Lead Tetraacetate.—From a closed dropping funnel, a solution of 2.12 g (0.01 mol) of the oxime (I) in 50 ml of methylene chloride[6] was added slowly over a period of 2 hr with stirring to a solution of 4.43 g (0.01 mol) of lead tetraacetate[7] in 40 ml of methylene chloride in a closed 125-ml erlenmeyer flask in an ice bath to maintain the reaction mixture at 0°. As the addition progressed the solution turned dark and a colorless precipitate of lead acetate appeared and was removed by filtration after standing at room temperature for 12 hr, 2.9 g (0.0089 mol), 89.1%. After successively washing the dark filtrate with water and sodium bicarbonate solution, drying over magnesium sulfate, filtering, and evaporating, a dark tarry residue was obtained and chromatographed over silica gel. Following elution of an unidentified yellow oil by hexane and benzene mixtures, 100 mg (0.5 mmol) of benzanilide (5% yield) was eluted by benzene–chloroform (6:1) and recrystallized from carbon tetrachloride as colorless needles: melting point and mixture melting point with an authentic sample, 162–163°.

A very dark oil (1.0 g) was eluted with benzene–chloroform (2:3) and slowly solidified, mp 90–95°. With a Rodder streaker instrument 250 mg was deposited on a thin layer (2 mm thick) chromatographic silica gel plate. Plate development with benzene–ethyl acetate (5:1) produced eight colored bands, only one of which, R_f 0.5, consisted of an appreciable amount of material from which 80 mg of light yellow solid, mp 108–111°, was isolated and recrystallized from benzene–hexane (1:4) as colorless needles, mp 116–117°. Combined product from different tlc runs at this stage gave 248 mg (0.78 mmol) (15.6% yield) of the O-benzoyl derivative (V) of the oxime of benzanilide. Comparison with an authentic sample revealed an identical ir spectrum, an identical nmr spectrum, and undepressed mixture melting point. Hydrolysis of V in 5% sodium hydroxide produced the oxime I in 87% yield and benzoic acid in 81% yield.

B. N-Bromosuccinimide.—To a stirred solution of 1.6 g (7.5 mmol) of the oxime (I) in 50 ml of $CHCl_3$ cooled in an ice bath to 0° a solution of 1.35 g (7.5 mmol) of N-bromosuccinimide in 50 ml of carbon tetrachloride, mp 169–171°, was added dropwise as a brown color developed and colorless crystals separated. Stirring was continued for 1.5 hr at 0° and 12 hr at room temperature. Succinimide, 227 mg (2.3 mmol), 30.6%, mp 124°, was separated by filtration. Trituration with carbon tetrachloride of a dark oil obtained from the filtrate on evaporation brought about the separation of a colorless solid which after separation by filtration, was dissolved in water and treated with excess sodium carbonate. From an ether extract after drying over magnesium sulfate and evaporation, the colorless oxime (I) was recovered: mp 134–136°; yield 300 mg (1.4 mmol, 18.7%).

The carbon tetrachloride solution was extracted with 5% sodium carbonate, washed with water, dried over calcium chloride, filtered, and evaporated. A dark oil residue was chromatographed over silica gel. A small quantity of an unidentified yellow oil was eluted with benzene followed by a colorless solid which recrystallized from carbon tetrachloride as needles, mp 162–163°, 50 mg (0.25 mmol) of benzanilide (4.2% yield based on recovered I).

Benzene–chloroform (4:1) eluted a light yellow solid which recrystallized from hexane–benzene as fine colorless needles, mp 116–117°, 120 mg (0.379 mmol) of the O-benzoyl derivative (V) of the oxime of benzanilide (13% yield based on recovered I). In comparison with an authentic sample ir and nmr, respectively, were identical and a mixture melting point was undepressed.

Further elution gave a dark unidentified oil and ether–chloroform (1:1) eluted a brown solid which recrystallized from benzene–hexane as colorless I, mp 133–135°, 50 mg (0.23 mmol) (3%). Further elution with ether gave a dark tar.

C. Diethyl Azodicarboxylate.—An orange solution of 1.80 g (8.4 mmol) of the oxime (I) and 1.46 g (8.4 mmol) of diethyl azodicarboxylate[8] in 50 ml of chloroform was kept at room temperature in a 125-ml erlenmeyer flask for 12 hr as the color deepened to red-brown. Combined 2 *N* hydrochloric acid extracts were carefully neutralized by the addition of potassium hydroxide pellets. From the slightly basic solution a white solid separated from which ether extracted 0.16 g (0.75 mmol), mp 135–136°, of recovered oxime (I) (8.9%).

The chloroform layer gave a brown-red oil after drying over magnesium sulfate, filtering and evaporating. On addition of 50 ml of ether a light yellow solid separated which deposited as colorless needles, 340 mg (1.93 mmol) (25.2% based on recovered I), mp 129–131°, on recrystallization from carbon tetrachloride and identified as diethyl hydrazodicarboxylate.[8] An unidentified brown solid, 15 mg, mp 280–290°, remained insoluble in hot carbon tetrachloride and was separated.

The ether solution was chromatographed over 70 g of silica gel. A few milligrams of unidentified yellow oils were eluted by benzene–hexane. A colorless solid was then eluted with chloroform–benzene (1:6) and recrystallized from benzene–hexane as 3,4-diphenyl-1,2,4-oxadiazolone-5, mp and mmp 166–167°,[4] 35 mg (0.14 mmol), 1.9% yield. Its ir spectrum from chloroform was identical with that obtained from authentic material: 3060, 3020, 1785 vs, 1605, 1595, 1565, 1510, 1455, 1415, 1330, 1320, 1150, 1075, 1030, 1010, 1000, 975, 890, 610 cm^{-1}.

Next benzene–chloroform (6:1) eluted a colorless solid, mp 160–161°, identified as benzanilide, 75 mg (0.38 mmol, 4.9% yield). With an authentic sample the melting point was undepressed and an identical ir spectrum was obtained. Continued elution produced 0.70 g (2.21 mmol, 57.7%) of pale yellow needles, mp 112–115°, which recrystallized from benzene–hexane as colorless needles, mp 116–117°, of V. Comparison with authentic material produced identical ir spectra and an undepressed mixture melting point.

Chloroform–benzene (3:1) then eluted a brown oil, apparently a mixture of V and diethyl hydrazodicarboxylate according to tlc and ir, followed by a colorless solid, mp 130–132°, 450 mg (2.55 mmol, 33.3% yield based on recovered I), identified as diethyl hydrazodicarboxylate.[8] Ether eluted a dark red band as an unattractive black oil and ethyl acetate eluted an additional dark brown oil.

Oxidation of N-Phenylhydroxylamine by Diethyl Azodicarboxylate.—To an orange solution of 8.70 g (0.05 mol) of diethyl azodicarboxylate in 50 ml of ether externally cooled to −30° by a Dry Ice–acetone bath, a solution of 5.45 g (0.05 mol) of N-phenylhydroxylamine[9] in 50 ml of ether was added dropwise with magnetic stirring over a period of 1 hr during which time a green color rapidly developed and a colorless precipitate appeared. The solution was stirred an additional 2 hr at room temperature. Infrared absorption identical with that for an authentic sample and an undepressed mixture melting point identified the separate colorless solid as diethyl hydrazodicarboxylate, 6.4 g (0.0363 mol, 72% yield), mp 131–133°.

(4) H. Muller, *Ber.*, **19**, 1669 (1886).

(5) C. Grundmann, *J. Org. Chem.*, **31**, 157 (1966).

(6) Distilled from phosphorus pentoxide.

(7) Recrystallized from acetic acid and washed with hexane immediately before use.

(8) J. C. Kauer, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 411. Commercial sample had $n^{20}D$ 1.4245.

(9) O. Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p 445.

A green solid remained after evaporation of the ether filtrate and was steam distilled. Combined ether extractions of the distillate were dried over calcium chloride, filtered, and evaporated leaving a green liquid which solidified to colorless crystals, mp 63–65° (green melt) of nitrosobenzene, 3.8 g (0.0356 mol, 71% yield). In comparison with authentic material, identical ir spectra were obtained and a mixture melting point was undepressed.

Benzonitrile Oxide and the Oxime (I) of Benzanilide.—After 12 hr at room temperature a solution of 2.12 g (0.01 mol) of the oxime (I) in 30 ml of chloroform and 0.0042 mol of benzoni rile oxide[10] in ether added dropwise became pale yellow. Combined 2 *N* hydrochloric acid extracts were carefully neutralized by the addition of potassium hydroxide pellets whereupon a colorless precipitate separated and was extracted with ether. The ether extracts were dried over magnesium sulfate, filtered, and evaporated leaving a residue of 1.60 g (0.0075 mol) of recovered I, mp 135–136°.

The ether–chloroform substrate after acid extraction was dried over magnesium sulfate, filtered, and evaporated to leave a brown oil which was chromatographed over silica gel. Hexane–benzene (3:1) eluted a colorless solid, mp 112–114°, 110 mg (0.46 mmol, 21.9%) identified as diphenylfuroxan.[11]

Next benzene–chloroform (6:1) eluted 45 mg (0.22 mmol) of benzanilide, mp 160–161° (8.8% yield based on recovered I or 5.2% based on benzonitrile oxide).

Continued elution with benzene–chloroform (6:1) removed 0.60 g (1.89 mmol) of V, mp 114–116°, as colorless needles (75.8% yield based on recovered I or 45.0% based on benzonitrile oxide). A brown band remained on top of the column.

Registry No.—I, 3488-57-1; lead tetraacetate, 546-67-8; N-bromosuccinimide, 128-08-5; diethyl azodicarboxylate, 1972-28-7; N-phenylhydroxylamine, 100-65-2; benzonitrile oxide, 873-67-6.

(10) From 0.65 g (0.0042 mol) of benzhydroxamoyl chloride and alkali according to P. Rajagopalan and B. G. Advani, *J. Org. Chem.*, **30**, 3369 (1965).

(11) A. Werner and H. Buss, *Ber.*, **27**, 2193 (1894).

Synthesis of (−)-(1*R*)-*cis*- and (+)-(1*S*)-*trans*-2-Isopropylidene-(5*R*)-N,N-trimethylcyclopentanemethylamines and Their Dideuterio Derivatives[1]

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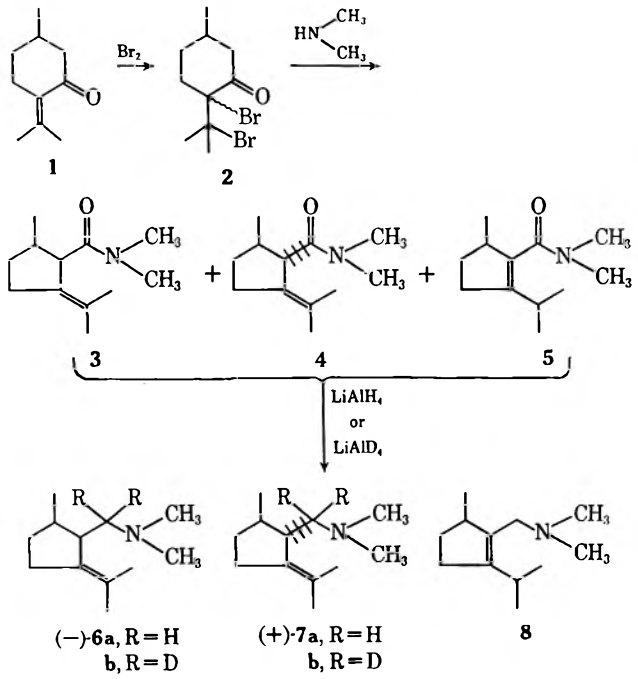
Received February 26, 1968

(−)-(1*R*)-*cis*-2-Isopropylidene-(5*R*)-N,N-trimethylcyclopentanemethylamine (**6a**) and (+)-(1*S*)-*trans*-2-isopropylidene-(5*R*)-N,N-trimethylcyclopentanemethylamine (**7a**) and their dideuterio derivatives (**6b** and **7b**) provided excellent model compounds for instrumental and chemical reaction comparisons with the elimination products obtained from Hofmann elimination reactions applied to α-, β-, γ-, and δ-skytanthines.[3] We now report the preparation of **6a**, **6b**, **7a**, **7b**, and **8** from (+)-pulegone (**1**) as shown in Scheme I.

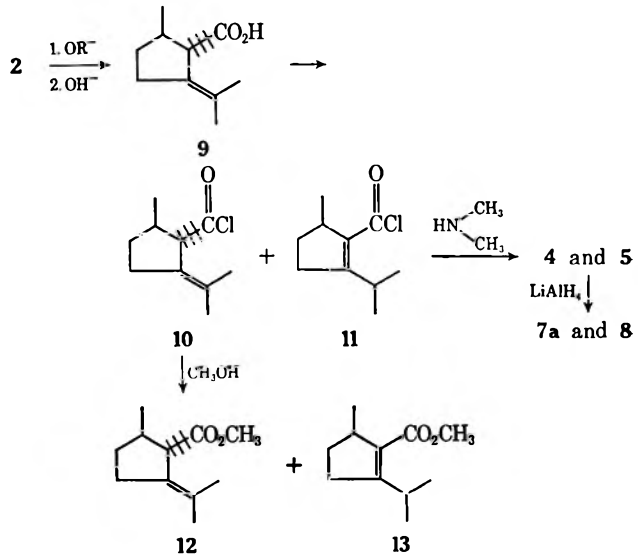
Scheme I is a useful alternate route to the earlier synthesis of **7a** and **8** shown in Scheme II.[4] The major

SCHEME I



advantages in using Scheme I are a low yield of **8** and the formation of **6a** as the major product (**6a**:**7a**:**8** = 11:7:1) in three steps from **1**. In comparison, Scheme II requires five steps, and if carried out on pure **9**, does not provide **6a** in significant yield and does produce considerable unwanted **8**. In our hands, Scheme II provided **7a**:**8** = 5:1.

SCHEME II



We used Scheme II to prepare authentic (+)-*trans* **7a** to serve as a reference compound in the assignment of stereochemistry and absolute configuration to (−)-**6a**, **6b**, (+)-**7a**, and **7b** from Schemes I and II. A stereochemical and absolute configuration assignment to (+)-*trans* **7a** had not been made. However, the data obtained from Schemes I and II are adequate to make this assignment. The major product of Favorskii rearrangement of **2** with aqueous alkali has been shown to be *cis*-pulegenic acid.[5] By analogy, the

(1) Supported by the National Science Foundation Grant GB-5607.

(2) Address correspondence and reprint requests to this author at the Department of Chemistry.

(3) H. Auda, H. R. Juneja, E. J. Eisenbraun, G. R. Waller, W. R. Kays, and H. H. Appel, *J. Amer. Chem. Soc.*, **89**, 2476 (1967).

(4) J. Wolinsky, B. Chollar, and M. D. Baird, *ibid.*, **84**, 2775 (1962).

(5) S. A. Achmad and G. W. K. Cavill, *Aust. J. Chem.*, **16**, 858 (1963).

Favorskii rearrangement of **2** in dimethylamine (Scheme I) can be expected to give mainly *cis* **3**. *cis* products **3**, **6a**, and **6b** were shown by gas chromatography to be present in the products derived from Scheme I but not among those from Scheme II. Scheme II was shown to give the expected *trans* products **4**, **7a**, and **12** by comparing **12** with an authentic sample,[6] obtaining the nmr spectrum of the mixture of **4** and **5**, and comparing this with a reported nmr spectrum which showed a single $-N(CH_3)_2$ group δ 2.85 (6 H). However, the nmr spectrum of the mixture of **3**, **4**, and **5** from Scheme I showed two different $-N(CH_3)_2$ groups at δ 3.18 and 2.85 in the ratio **3**:**4** = 3:2. This ratio is maintained in the reduction products **6a** and **7a**. It is of interest that the ratio of **12**:**13**, **4**:**5**, and **7a**:**8** remained 5:1 throughout the reactions in Scheme II. These data support the stereochemical assignments shown in Schemes I and II and allow assignment of absolute configuration to (−)-*cis* **6a** and *cis* **6b** as 1*R*, 5*R*, and (+)-*trans* **7a** and *trans* **7b** as 1*S*,5*R*.[7]

The presence of the parent ions *m/e* 181 in the mass spectra of **6a** and **7a** and **8** and *m/e* 183 for **6b** and **7b** confirms the molecular weights.

Experimental Section[8]

Pulegone Dibromide (2).[9]—To a well stirred solution of **76** g (0.5 mol) of (+)-pulegone at ice-bath temperature in 200 ml of glacial acetic acid was added dropwise 80 g (0.5 mol) of bromine during 30 min. The reaction mixture was stirred for another 30 min and then poured onto 100 g of crushed ice, and extracted with eight 100-ml portions of low-boiling petroleum ether. The combined petroleum ether fractions were washed with a dilute sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered. The resulting solution containing crude **2** was used without further treatment.

***cis*- and *trans*-2-Isopropylidene-(5*R*)-N,N-trimethylcyclopentanecarboxamides (3 and 4).**—All of the solution containing crude **2** (estimated 156 g, 0.5 mol) was added in one portion to 100 g (2.1 mol) of dimethylamine, which was previously cooled in a Dry Ice–acetone bath. Precipitation of dimethylamine hydrobromide occurred immediately after the addition. The flask was stoppered and allowed to come to room temperature, and the contents were stirred for an additional 5 hr. The stopper was removed and the excess dimethylamine was evaporated. The resulting mixture was stirred with 200 ml of ether and filtered, and the ether was washed with three 50-ml portions of 5% solution of hydrochloric acid and then with distilled water until the washings were neutral to litmus paper. The ether solution was dried over anhydrous magnesium sulfate, filtered, and distilled to yield 80 g (82%) of a mixture (**3**:**4**:**5** = 64:33:3): bp 75° (0.2 mm); nmr (CCl_4) δ 3.10 and 2.85 (6 H, 2 s, two $-N(CH_3)_2$ in ratio 3:2), 1.59 (3 H, s), 1.49 (3 H, s), an envelope centered at 2.2 (6 H), and 1.02 and 0.90 ppm (3 H, 2 d, J = 6 Hz); ν_{max}^{film} 2950, 2900, 1655, 1490, 1460, 1400, 1310, 1290, 1270, 1165, 1125, and 1060 cm^{-1}.

(−)-*cis*- and (+)-*trans*-2-Isopropylidene(5*R*)-N,N-trimethylcyclopentanemethylamine (6a and 7a).—To a well-stirred solution of 4 g (0.11 mol) of lithium aluminum hydride in 100 ml of anhydrous ether was added dropwise 11 g (0.06 mol) of a mixture of amides **3**, **4**, and **5** prepared above. The solution was heated at reflux temperature for 4 hr. The solution was cooled; the excess lithium aluminum hydride was destroyed with water; and the salts were filtered out and washed with ether. The ether fractions were combined, washed with three 50-ml portions of distilled water, dried over anhydrous magnesium sulfate, filtered, and concentrated to yield 7.8 g (76%) of a 3:2 mixture of (−)-**6a** and (+)-**7a**, bp 45° (0.3 mm), which showed 20- and 15.5-min retention times, respectively, on a 15 ft × 0.25 in. column of base-washed Chromosorb W coated with 15% Carbowax 20M operating at 120°.

The fraction due to **6a** was separated by preparative gas chromatography on the previously mentioned gas chromatography column and collected; it showed nmr (CCl_4) δ 2.15 (6 H, s), 1.65 (3 H, s), 1.59 (3 H, s), and 0.91 ppm (3 H, d, J = 6 Hz); $\nu_{max}^{CHCl_3}$ 2950, 2850, 2800, 2775, 1460, 1380, 1330, 1290, 1265, 1235, 1200, 1165, 1125, 1100, 1040, 1005, 995, 865, 835, 805, and 775 cm^{-1}; *m/e* 181 (parent ion) and 58 (100%); $[\alpha]^{23}D$ −48° (*c* 0.49, $CHCl_3$).

Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.63; H, 12.50; N, 7.54.

The fraction due to **7a** was also collected and it showed nmr (CCl_4) δ 2.15 (14 H, envelope), 1.60 (6 H, broad s), and 0.90 ppm (3 H, d, J = 6 Hz); ν_{max}^{neat} 2950, 2850, 2775, 1450, 1370, 1265, 1180, 1170, 1155, 1100, 1060, 1045, 1030, 895, 862, 840, and 785 cm^{-1}; *m/e* 181 (parent ion) and 58 (100%); $[\alpha]^{23}D$ +68° (*c* 0.17, $CHCl_3$).

(1*R*)-*cis*- and (1*S*)-*trans*-2-Isopropylidene-(5*R*)-N,N-trimethylcyclopentanedideuteriomethylamine (6b and 7b).—The procedure for the preparation of **6a** and **7a** was repeated using 2 g (0.01 mol) of a mixture of the amides **3** and **4** and 0.4 g (0.01 mol) of lithium aluminum deuteride in 20 ml of tetrahydrofuran to give 1.5 g (82%) of deuterated amines **6b** and **7b**. These were separated by preparative gas chromatography as described for **6a** and **7a**. The fraction (20-min retention time) due to **6b** showed nmr (CCl_4) δ 2.15 (12 H, envelope), 1.65 (3 H, s), 1.55 (3 H, s), and 1.05 ppm (3 H, d, J = 7 Hz); ν_{max}^{neat} 2950, 2850, 2800, 2775, 2200, 2150, 2000, 1460, 1380, 1265, 1120, 1110, 1100, 1080, 1045, 995, 910, 895, 830, 820, and 775 cm^{-1}; *m/e* 183 (parent ion) and 60 (100%).

The fraction due to **7b** (15.5-min retention time) was also collected and showed nmr (CCl_4) δ 2.15 (12 H, envelope), 1.61 (3 H, s), 1.57 (3 H, s), and 0.90 ppm (3 H, d, J = 7 Hz); ν_{max}^{neat} 2950, 2850, 2800, 2775, 2200, 2070, 1465, 1380, 1285, 1270, 1240, 1175, 1160, 1120, 1100, 1050, 1000, 895, 825, and 815 cm^{-1}; *m/e* 183 (parent ion) and 60 (100%).

Registry No.—**3**, 17943-81-6; **4**, 17943-82-7; **6a**, 17943-83-8; **6b**, 17943-84-9; **7a**, 17943-85-0; **7b**, 17943-86-1.

(6) We thank Dr. C. Brandenburg for a sample and nmr spectrum of pure methyl pulegenate.

(7) (a) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955); (b) R. S. Cahn, V. Prelog, and C. K. Ingold, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).

(8) The analyses of the amines were made on the combination mass spectrometer–gas chromatography apparatus (prototype of the LKB-9000) using a 16 ft × 0.25 in. glass column packed with 120-mesh, base-washed firebrick coated with 20% Carbowax 20M. The operating conditions were column at 120°, injection port at 200°, and helium flow of 45 ml/min. The nmr spectra were obtained on a Varian A-60 spectrometer.

(9) J. Wolinsky and D. Chan, *J. Org. Chem.*, **30**, 41 (1965).

Reactions of Nitro Alcohols. III. The Reaction of 2,2,2-Trinitroethanol and Phosgene in the Presence of Some Tertiary Amines

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Received March 26, 1968

The esterification of 2,2,2-trinitroethanol (**1**) by acyl chlorides has been reported to proceed both with[1] and without[2] a catalyst. Since none of these methods is particularly suitable for the preparation of bis(2,2,2-trinitroethyl) carbonate (**2**) from **1** and phosgene, it was decided to use the pyridine-catalysis method developed by Kissinger, *et al.*,[3] for the esterification of 2,2-dinitropropanol by phosgene.

The desired biscarbonate was indeed obtained by

(1) (a) M. H. Gold and K. Klager, *Tetrahedron, Suppl. 1*, **19**, 77 (1963); (b) M. B. Frankel, *J. Org. Chem.*, **27**, 331 (1962).

(2) (a) H. Feuer, H. B. Haas, and R. D. Lowery, *ibid.*, **25**, 2070 (1960); (b) N. S. Marans and R. P. Zelinsky, *J. Amer. Chem. Soc.*, **72**, 5329 (1950).

(3) L. W. Kissinger, T. M. Benzinger, H. E. Ungnade, and R. K. Rowher, *J. Org. Chem.*, **28**, 2491 (1963).

this method in a yield of 51%, using a molar ratio of pyridine to **1** of one. Since the crude product was contaminated by pyridinium trinitromethide (**3**) the use of a base weaker than pyridine seemed desirable.[4] As expected the use of 4-nitropyridine or pyridine 1-oxide in place of pyridine eliminated **3** and increased the yield of **2** to 59 and 72%, respectively. Increasing the molar ratio of pyridine to **1** was found to cause nucleophilic attack of pyridine on **1** and resulted in the formation of a new compound, **4**, with the structure $[(C_6H_5N^+—CH_2O—)_2C{=}O][(NO_2)_3C^-]_2$ (see Experimental Section).

Experimental Section

All chemicals were reagent grade except the phosgene gas (99%, The Matheson Co.) and the pyridine 1-oxide (technical grade, Reilly Tar and Chemical Co.). 4-Nitropyridine was made by deoxygenating 4-nitropyridine[5] 1-oxide with PCl_3.[6] The citation in ref 4 gives the methods for preparing 2,2,2-trinitroethanol and trinitromethane. The following instruments were used: a Varian HR-100 nmr spectrometer, a Bendix time-of-flight mass spectrometer, Beckman DU, Beckman IR-4, and Cary Model 14 spectrophotometers. The Cary was used for the CH_2O equivalent weight.

Bis(2,2,2-trinitroethyl) Carbonate (2).—Following the method of Kissinger,[3] 10.0 g of 2,2,2-trinitroethanol (0.0552 mol) was dissolved in 6 ml of methylene chloride and 13 ml of chloroform; 4.44 g of pyridine (0.0561 mol) was added; and phosgene was bubbled into the stirred solution at 18 cc/min until 40% excess had been introduced, keeping the temperature near 27°. The reaction mixture was allowed to stand for 1 hr at ambient temperature. The crude product was precipitated by the addition of *n*-hexane and was then stirred with water for 16 hr to remove **3**,[7] collected and air dried. The yield of **2**, mp 113–115°, was 5.44 g (51%). Two recrystallizations from chloroform raised the mp to 116–117°. A mull of **2** showed the expected absorption: a C=O doublet at *1783*[8] and *1795* cm^{-1}, C—O stretching at 1235 cm^{-1},[9] asymmetic and symmetric NO_2 stretching in nonsalt *gem*-dinitro compounds at 1595 and 1345 cm^{-1}, respectively, and C—H stretching at *2882* and *2967* cm^{-1}.

Using this procedure, with a reduction of the stirring period to 1 hr, 6.96 g of 4-nitropyridine (0.0561 mol) in place of the pyridine gave 6.29 g (59%) of **2**, and 5.34 g of pyridine 1-oxide in place of the pyridine gave 7.68 g (72%) of **2**.

Anal. Calcd for $C_5H_4N_6O_{15}$: C, 15.47; H, 1.04; N, 21.65. Found: C, 15.45, 15.50; H, 1.28, 1.41; N, 21.48, 21.54.

Pyridinium Trinitromethide (3).—Reaction of equimolar quantities of pyridine and trinitromethane in chloroform gave a yellow precipitate which had the absorption, as a mull, expected for **3**: 1900 and 2400 cm^{-1} for C=N+H of the pyridinium ion, 1613 and 1640 cm^{-1} for C=C, C=N stretching, 1050 and 1203 cm^{-1} for C—H deformation, and 3060 cm^{-1} for C—H stretching of the pyridine ring, 737, 787, 870, 1128, 1260, 1410, and 1544 cm^{-1} for a carbanion of the type $Z(NO_2)_2C^-$.[10]

Anal. Calcd for $C_6H_6N_4O_6$: C, 31.31; H, 2.63; N, 24.35. Found: C, 31.49, 31.32; H, 2.77, 2.83; N, 23.91, 24.17.

Compound 4, $[(C_5H_5N^+—CH_2O—)_2C{=}O][(NO_2)_3C^-]_2$, Data.

A. Preparation.—Phosgene (0.11 mol) was bubbled at 18 cc/min into a stirred solution of 4.00 g of **1** (0.020 mol) in a mixture of 20 ml of pyridine and 0.40 ml of water, keeping the temperature of the solution near 27°. Stirring the reaction mixture into 80 ml of ice–water caused the precipitation of a yellow solid which was collected, washed with 35 ml of ice–water, and air dried. The yield was 3.85 g of **4** (64%). The analytical sample, made by recrystallizing the crude product twice from acetonitrile, decomposed over a wide range (*ca.* 130–175°).

Anal. Calcd for $C_{15}H_{14}N_8O_{15}$: C, 32.97; H, 2.58; N, 20.51. Found: C, 32.29, 32.83; H, 2.58, 2.45; N, 20.31, 20.60.

B. Spectral Measurements.—A mull of **4** showed the absorption expected: *3106*,[8] *3067*, and *3053* cm^{-1} for C—H stretching of the pyridine ring; *2924* and *2841* cm^{-1} for the methylene C—H stretching; *1773* cm^{-1} for C=O stretching of a carbonate; 1640, 1632, and 1540 cm^{-1} for C=C, C=N stretching of the pyridine ring (1-methylpyridinium iodide used for comparison); 1247 cm^{-1} for C—O stretching in a carbonate;[8,9] 778, 1054, and 1210 cm^{-1} for C—H deformation of the pyridine ring; 737, 785, 870, 1155, 1265, 1414, and 1540 cm^{-1} for a carbanion of the type $Z(NO_2)C^-$.

Strong evidence that **4** contains the quaternized pyridine ring was obtained from the pmr spectrum. τ values in parts per million and relative intensities for **4** in acetone were 0.88 (2), 1.72 (2), 1.19 (1), and −0.10 (2).[11] For comparison, 1-methylpyridinium iodide in acetone-d_6 gave 0.70 (2), 1.72 (2), and 1.27 (1) for the 2-, 3-, and 4-ring H, and 5.23 (3) for the methyl H.

C. Equivalent Weights.—Aqueous solutions of **4** were analyzed spectrophotometrically for $(NO_2)_3C^-$, using ϵ 14,418,[12] and for formaldehyde, using the method developed by Nash,[13] ϵ based on a sulfite-standardized[14] CH_2O solution and an optical density corrected for absorption by $(NO_2)_3C^-$. The amount of pyridine distilled from a basic solution of **4** was determined spectrophotometrically,[15] and the amount of gas generated by the acidification of a basic degassed solution of **4** was determined in a volume-calibrated system by the ideal gas law. Mass spectrographic analysis of the gas generated showed it to be at least 99.9% CO_2. The equivalent weights thus determined were $(NO_2)_3C^-$, 276; pyridine, 273; CH_2O, 283, CO_2, 543.

A single crystal of **4** was shown to have a density of 1.70 g/cc, a unit cell volume of 1097 Å,[3] and a unit cell molecular weight of 1123. These data required that the molecular weight of **4** be 281 or 562. A molecular weight of 562, the molecular weight required by the empirical formula $C_{15}H_{14}N_8O_{15}$ (546), in addition to the spectral data and equivalent weights justify the structure given for **4**.

Registry No.—**1**, 918-54-7; phosgene, 75-44-5; **2**, 17943-76-9; **3**, 17943-77-0; **4**, 17943-78-1.

Acknowledgments.—Grateful appreciation is expressed to Dr. J. R. Holden for determining the molecular weight of the unit cell; Dr. J. R. Holden and Mr. C. W. Dickinson for the X-ray powder diffraction measurements; Dr. W. B. Moniz and Dr. F. E. Saalfeld, of the U. S. Naval Research Laboratory, Washington, D. C., for the nmr and mass spectrographic analysis, respectively; Professor M. A. Aldridge, American University, Washington, D. C., for the microanalyses.

(4) Increasing the basicity of the solvent increases the extent to which **1** is dissociated into $(NO_2)_3C^-$ and CH_2O. See T. N. Hall, *J. Org. Chem.*, **29**, 3587 (1964).

(5) Made by nitrating pyridine 1-oxide according to E. Ochiai, *ibid.*, **18**, 534 (1953).

(6) M. Hamana and H. Yoshimira, *J. Pharm. Soc. Jap.*, **72**, 1051 (1952).

(7) Shown to be present by X-ray powder diffraction.

(8) A LiF prism assembly was used for the italicized frequencies and a NaCl prism assembly for the frequencies not italicized.

(9) J. L. Hales, J. I. Jones, and W. Kynaston, *J. Chem. Soc.*, 618 (1957).

(10) M. J. Kamlet, R. E. Oesterling, and H. A. Adolph, *ibid.*, 5838 (1965).

(11) A value of −0.10 for the methylene protons is unusual, but not unreasonable, for **4** if one considers that both oxygen and positively charged nitrogen are strongly deshielding.

(12) See footnote *c*, Table I, in citation of ref 4.

(13) T. Nash, *Biochem. J.*, **55**, 416 (1953).

(14) J. F. Walker, "Formaldehyde," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1964, p 486.

(15) H. D. LeRosen and J. T. Wiley, *Anal. Chem.*, **21**, 1175 (1949).

Conformations of *cis*- and *trans*-2,5-Diphenyl-1,4-dioxanes

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Received June 13, 1968

Bryan, Smedley, and Summerbell[1] obtained two compounds melting at 122 (I) and 173° (II) from the

(1) L. A. Bryan, W. M. Smedley, and R. K. Summerbell, *J. Amer. Chem. Soc.*, **77**, 2206 (1950).

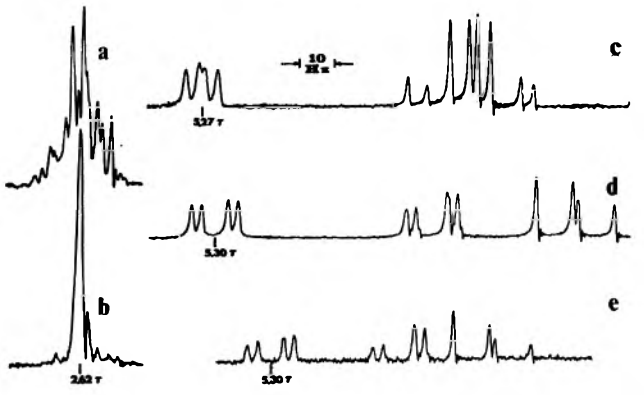

Figure 1.—The 60-MHz aromatic proton spectra of (a) I and (b) II. The 100-MHz ring-proton spectra of (c) I and (d) II. The 60-MHz ring-proton spectra of (e) II. Magnetic field increases left to right. All sweep scales are equal.

reaction of phenylmagnesium bromide with 2,5-dichloro-1,4-dioxane. (These same two compounds can be obtained using styrene oxide as a starting material and anhydrous stannic chloride as catalyst.[2]) They identified the compounds as the two isomeric 2,5-diphenyl-1,4-dioxanes and, on the basis of the melting points, assigned the *cis* structure to I and the *trans* structure to II.

The 60- and 100-MHz proton spectra of I and II as their 10% solutions in $CDCl_3$ are shown in Figure 1. The aromatic region of I at 60 MHz is a broad, complicated multiplet while that of II is much narrower and simpler (Figures 1a and b) indicating the phenyl rings in I may be more hindered that in II, although neither spectrum was temperature dependent. The ring protons of I at 60 MHz form an ABC system which has been analyzed in detail to yield the two vicinal coupling constants of 5.8 and 3.1 Hz and a geminal coupling constant of −11.9 Hz.[3] These values are consistent with the 100-MHz spectrum shown in Figure 1c. The ring protons of II form an ABX system (by comparison of 100- and 60-MHz spectra in Figures 1d and e) with vicinal coupling constants of 10.4 and 2.9 Hz and a geminal coupling constant of −11.5 Hz (the choice of signs being made by analogy to the assignments for I). The values for the vicinal coupling constants obtained from ring-proton spectra of I and II in dimethyl sulfoxide at 30 and 140° are the same.

Making the reasonable assumption of a chair geometry for both I and II[4] and using the fact that for vicinal coupling constants in these kinds of rings $J_{ea} \sim J_{ae} \sim J_{ee} < J_{aa}$,[5] the observed nmr data are consistent with the assignment of *cis* (Ph_e, $Ph_a \rightleftarrows Ph_a$, Ph_e) to I and *trans* (Ph_e, Ph_e) to II, so that the vicinal coupling constants are given by $(J_{aa} + J_{ee})/2 = 5.8$ Hz and $(J_{ea} + J_{ae})/2 = 3.1$ Hz in I, and $J_{aa} = 10.4$ Hz and $J_{ea} = 2.9$ Hz in II. The only other way to assign chair conformations to the isomers consistent with the nmr data involves the unreasonable assumption of a rigid *cis* structure and a rapidly interconvering *trans* structure.

(2) R. K. Summerbell and M. J. Kland-English, *J. Amer. Chem. Soc.*, **77**, 5095 (1955).
(3) C. Altona and E. Havinga, *Tetrahedron*, **22**, 2275 (1966).
(4) G. Gatti, A. L. Segre, and C. Morandi, *ibid.*, **23**, 4385 (1967).
(5) See, for example, E. L. Eliel and C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

There is little possibility that the bulky phenyl groups cause the *cis* isomer to assume twist–boat conformations[6] in which both phenyls are exclusively in equitorial orientations with respect to the ring. If this were the case, the *cis* isomer would display a large vicinal coupling constant. However, only one vicinal coupling constant greater than 6 Hz is observed so that if a twist–boat conformation is adopted for the *cis* isomer, the *trans* structure must be either in a twist–boat conformation itself or undergoing rapid chair interconversions. Either situation is unlikely. Furthermore, any room-temperature dynamic equilibrium involving substantial amounts of boat and chair forms is unlikely since the spectra of both isomers are unchanged at higher temperatures.

Thus, the original structural assignments given by Summerbell are correct and the *cis*- and *trans*-2,5-diphenyl-1,4-dioxanes are, in fact, an example of the higher melting of two geometrical isomers being the one with the greater molecular symmetry.

Registry No.—I, 13217-26-0; II, 5888-95-9.

(6) R. D. Stolow and M. N. Bonaventura, *ibid.*, **85**, 3636 (1963); E. W Garbisch, Jr., and D. B. Patterson, *ibid.*, **85**, 3228 (1963); H. Booth and E. O. Gidley, *Tetrahedron Lett.*, 1449 (1964). These authors discuss this possibility for cyclohexane derivatives with large *cis* substituents at C-1 and C-4.

Ionization Constants of Squaric Acid[1]

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Squaric acid, $C_4H_2O_4$ (1,2-dihydroxycyclobutenedione), is an unusually strong organic acid, so strong that its first ionization constant cannot be easily measured, and until now there seems not to have been any serious attempt to do so. Its second ionization constant has been variously reported as $pK_2 = 2.2$[3] and as $pK_2 = 3.0$.[4] The availability of a digital-computer program[5] designed for the precise evaluation of the pK values of a dibasic acid from experimental titration data made it feasible to do an accurate determination of the pK values of squaric acid, the results of which are reported in this communication.

Experimental Section

The experimental data (shown in Table I) were obtained by measuring with a Radiometer pH meter (using a type G202B glass electrode and a type K401 calomel reference electrode) the pH of a 0.173 F aqueous solution of squaric acid (squaric acid supplied by Chemische Werke Hüls, A.G., and used after drying for 1 hr at 110°) thermostated to 25.0 ± 0.1° as successive increments of 2.00 N KOH were added to it from a micrometer syringe buret. The pH meter and electrodes were calibrated

(1) This work was sponsored by the Air Force Office of Scientific Research, AFOSR (SRC)-OAR, USAF, under Grant No. AF-AFOSR-994-66.
(2) Address correspondence to U. S. Bureau of Mines, Reno Metallurgy Research Center, Reno, Nev. 89505.
(3) S. Cohen, J. R. Lacher, and J. D. Park, *J. Amer. Chem. Soc.*, **81**, 3480 (1959).
(4) J. D. Park, S. Cohen, and J. R. Lacher, *ibid.*, **84**, 2919 (1962).
(5) A copy of the program, written in FORTRAN II, with a description of how it works, will be sent on request to interested individuals.

TABLE I
TITRATION OF 296 mg OF SQUARIC ACID IN 15.00 ml OF AQUEOUS SOLUTION WITH 2.00 *N* KOH

pH	Equiv of KOH per mol of squaric acid
1.01	0.000
1.04	0.077
1.09	0.154
1.11	0.232
1.14	0.308
1.20	0.386
1.24	0.463
1.30	0.540
1.38	0.617
1.46	0.695
1.58	0.772
1.70	0.848
1.86	0.925
2.04	1.003
2.25	1.080
2.42	1.158
2.59	1.233
2.73	1.311
2.87	1.389
3.00	1.466
3.12	1.542
3.27	1.620
3.40	1.698
3.59	1.774
3.81	1.851
4.20	1.929

against standard buffer solutions[6] having pH's of 1.68 and 4.01 at 25°. Duplicate titrations done in this manner yielded nearly identical results, from which the following values (and their standard deviations) were calculated: $pK_1 = 1.2 \pm 0.2$ and $pK_2 = 3.48 \pm 0.02$ (at 25.0 ± 0.1° and corrected to zero ionic strength by use of the Davies equation[7] for activity coefficients). The sum of these p*K* values, *i.e.*, $pK_1 + pK_2$, equals 4.7 ± 0.2.

In principle, a more precise measurement of pK_1 could be obtained by using a larger concentration of squaric acid, but its limited solubility (about 2 wt % or 0.176 *F* at 20°) makes that approach impracticable.

Discussion

The acidity of squaric acid is similar to that of oxalic acid, a substance which squaric acid resembles structurally. For oxalic acid at 25°, $pK_1 = 1.28$,[8] $pK_2 = 4.27$,[9] and $pK_1 + pK_2 = 5.55$.

For both acids, a part of the free-energy change during ionization reflects an entropy effect caused by the change in symmetry number, *i.e.*, $\sigma = 4$ for the oxalate ion and $\sigma = 8$ for the more symmetrical squarate ion. This rotational entropy effect therefore contributes to the *difference* in $pK_1 + pK_2$ between oxalic acid and squaric acid, an amount $T\Delta S = 298\ R \ln 2 = 0.4$ kcal/mol of free energy, a relatively small but not insignificant quantity.

A larger part of the difference in acidity between squaric acid and oxalic acid depends on the extra delocalization energy possessed by the squarate ion. According to West and Powell,[10] molecular orbital calculations indicate that this delocalization energy amounts to 0.240β for each of two π electrons. If it is assumed that β is about 18 kcal/mol, then the delocalization energy of squarate would be about 9 kcal/mol. If delocalization energy were the major energy factor in the ionization of squaric acid, then the difference $[(pK_1 + pK_2)_{squaric} - (pK_1 + pK_2)_{oxalic}]$ should equal 6.05. It is remarkable that this difference is actually only 0.85 ± 0.2. This discrepancy can be explained on the basis of a difference in the hydration energy of the two types of dianions. Ionization of oxalic acid is relatively favored by the concentration of negative charge on the oxygen atoms of the oxalate ion, a concentration of negative charge which results in a relatively large hydration energy. In the squarate ion, however, the hydration energy should be relatively smaller, to the extent that the charge delocalization extends over a larger region of space, *i.e.*, over the four-carbon ring in addition to the four oxygen atoms. If this analysis is correct, then the hydration energy for the squarate ion must be less than that for the oxalate ion by about 7.0 kcal/mol.[11]

Registry No.—Squaric acid, 2892-51-5.

(6) Prepared as described by R. G. Bates, "Electrometric pH Determinations," John Wiley & Sons, Inc., New York, N. Y., 1954, p 74.

(7) J. N. Butler, "Ionic Equilibrium: A Mathematical Approach," Addison-Wesley, Reading, Mass., 1964, p 437.

(8) L. S. Darken, *J. Amer. Chem. Soc.*, **63**, 1007 (1941).

(9) G. D. Pinching and R. G. Bates, *J. Res. Nat. Bur. Stand., A*, **40**, 405 (1948).

(10) R. West and D. L. Powell, *J. Amer. Chem. Soc.*, **85**, 2577 (1963).

(11) NOTE ADDED IN PROOF.—It has recently come to the author's attention that another paper has been published [by D. T. Ireland and H. F. Walton, *J. Phys. Chem.*, **71**, 751 (1967)] containing data in agreement with those described here. The author regrets that his literature search was not thorough enough to permit location of Ireland's and Walton's work prior to the time this Note was submitted for publication.

Catalyzed Rearrangements of 2-Alloxypyridine and 2-Crotoxypyridine

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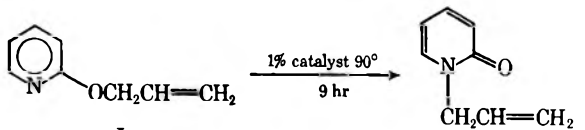
The rearrangement of alloxypyridine has been the subject of several recent investigations.[2-4] These reactions, carried out above 240°, were generally characterized by low yields of all possible "Claisen type" rearranged products.

We found that several Lewis acids facilitated rearrangement of 2-alloxypyridine (I) exclusively to 1-allyl-2-pyridone (II) in high conversion at moderate reaction temperatures.



I II

The thermal rearrangements[2,3] of I were classified as ortho-Claisen rearrangements as a result of the nature of the products formed and the experimental

(1) To whom all correspondence should be addressed at the Department of Chemistry, University of Wisconsin, Madison, Wis. 53706.

(2) R. B. Moffett, *J. Org. Chem.*, **28**, 2885 (1963).

(3) F. J. Dinan and H. Tieckelman, *ibid.*, **29**, 892 (1964).

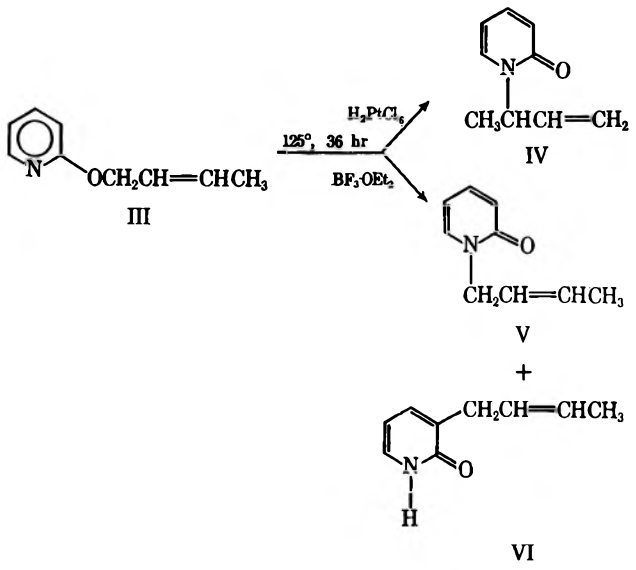
(4) B. S. Thyagarajan, *Advan. Heterocycl. Chem.*, **8**, 143 (1967).

conditions required.[5] Our catalyzed reactions differed in several respects from previously reported results: (1) lower reaction temperatures were permitted for rearrangement, 90 *vs.* 240°; (2) only the N-allyl rearrangement product was formed; (3) a high degree of conversion to the rearranged product was obtained, 90 *vs.* 30–60%; (4) the rearrangement proceeded well, even with impure I, to afford clean reaction mixtures from which the products were easily isolated.

The catalysts which performed best in the neat rearrangement of I to II were soluble Lewis acids. Platinum complexes, boron trifluoride etherate and tin(IV) chloride gave excellent conversions into II during the reaction period. Insoluble species such as aluminum chloride, platinum(0) black, alumina, and nickel(II) chloride (anhydrous) were poor catalysts when used in a similar manner.

The reaction mechanism was investigated by studying the rearrangement of 2-crotoxypyridine (III) (Scheme I). It was established that different products

SCHEME I



could be obtained from the reaction, depending on the nature of the catalyst used. Reactions catalyzed by chloroplatinic acid provided essentially quantitative conversion to the normal Claisen product, 1-(1-methylallyl)-2-pyridone (IV). The formation of this compound suggests that platinum complexes with III in a manner analogous to 2-allylpyridine and Pt(II),[6] in which the allylpyridine acts as a bidentate ligand. Such a complex could facilitate the intramolecular allyl rearrangement to nitrogen by a pseudo-Claisen cyclic mechanism. Reactions catalyzed by boron trifluoride etherate proceed by an entirely different mechanism, because the two abnormal Claisen products, 1-crotyl-2-pyridone (V) and 3-crotyl-2-pyridone (VI), were obtained in yields of 82 and 18%, respectively. A possible explanation for the formation of these products is that the boron trifluoride coordinates with the ether oxygen of III, providing a pathway for a 1,3-allyl shift, preferably to nitrogen.

These results suggest that other types of Claisen rearrangements might be catalyzed by metal complexes to afford conversion to fewer isomeric products using moderate reaction conditions.

Experimental Section

2-Alloxypyridine (I) was used as obtained from K & K Laboratories, Inc., Plainview, N. Y. 11803. Glpc analysis[7] of I showed that 2-chloropyridine (5%) was present as an impurity. Its presence did not affect our experimental results.

2-Crotoxypyridine (III) was prepared using the procedure of Dinan and Tieckelman.[3] Its ir and nmr spectra were consistent with the proposed structure, bp 92° (11 mm).

Rearrangement of 2-Alloxypyridine (I) to 1-Allyl-2-pyridone (II).—In a large-scale reaction a mixture of I (340 g, 2.5 mol) and a 4.2% H_2PtCl_6–isopropyl alcohol solution (4.8 g, 4.9 × 10^{-4} mol) were heated at 90–150° in a nitrogen atm for 9 hr. The reaction was followed by glpc analysis and at the end of this period no I could be detected. Distillation of the reaction mixture through a 30-cm Vigreux column gave II (289 g, 85% of theory) in good yield. The identity of II was confirmed by ir and nmr analysis.[3]

Rearrangement of I to II in Sealed Tubes.—I (2.0 g) was heated at 140° in sealed 6-mm glass tubes with 1% catalyst for 40 hr. The catalysts which gave excellent conversions to II (>85%) were H_2PtCl_6, Na_2PtCl_4, $BF_3 \cdot Et_2O$ and $SnCl_4$; and Pd on C gave 55% II. Less than 15% II was obtained with $AlCl_3$, alumina, $NiCl_2$ and Pt (black). Compound I alone did not rearrange under similar reaction conditions. Analyses of the reactions were obtained by glpc using internal standards. Area percentages were taken as a measure of the degree of conversion.

Rearrangement of 2-Crotoxypyridine (III) with H_2PtCl_6.—III (1.5 g, 0.01 mol) and a 4.2% H_2PtCl_6–isopropyl alcohol solution (0.1 g, 1 × 10^{-5} mol) were mixed under nitrogen and sealed in a 6-mm glass tube. The cloudy, light yellow solution was heated at 125 ± 1° for 36 hr. A glpc of the clear light orange reaction mixture showed only one peak eluting above 100°. An nmr[8] of this crude sample revealed a large doublet at τ 8.55 (J = 7.0 cps) and a smaller upfield doublet at 8.80 (J = 6.0 cps). The former is consistent with that found for 1-(1-methylallyl)-2-pyridone (IV).[3] The latter may be due to a complex formed between IV and platinum. The reaction mixture was distilled to dryness with only one pure component being isolated (1.4 g), bp 97° (1.2 mm). The nmr spectra of this material was identical with IV. The ir spectrum was also consistent with this proposed structure.

Rearrangement of 2-Crotoxypyridine (III) with $BF_3 \cdot Et_2O$.—III (1.5 g, 0.01 mol) and freshly distilled $BF_3 \cdot Et_2O$ (0.1 g, 7.0 × 10^{-4} mol of BF_3) were mixed under nitrogen and sealed in a 6-mm glass tube. This clear solution was heated at 125 ± 1° for 36 hr. A glpc of the crude reaction mixture showed two peaks, both eluting after III or IV, with relative areas of 82–18.[9] (The 82% component was the first to elute.) This solution was distilled to dryness with the main fraction taken at (1.35 g) 105° (0.5 mm). The area ratio of the compounds in the distillate had not changed. The two compounds were separated by preparative glpc and examined by nmr and ir analysis. The data for the larger component were found to be consistent for 1-crotyl-2-pyridone (V)[3] with the methyl protons appearing as distorted quartet (due to independent splitting by two vinylic protons) at τ 8.28 (J = 3.8, 1.0 cps). The smaller component was identified as 3-crotyl-2-pyridone (VI),[3] *via* the distorted methyl quartet at τ 8.32 (J = 3.3, 1.1 cps), and the absence of the ring three proton doublet at τ 3.40. The ir spectra of both compounds were consistent with these structures.

Registry No.—I, 5831-77-6; III, 17953-65-0; H_2PtCl_6, 16941-12-1; $BF_3 \cdot Et_2O$, 109-63-7.

(5) For an excellent review of the Claisen rearrangement, see S. J. Rhoads, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 655.

(6) R. E. Yingst and B. E. Douglas, *Inorg. Chem.*, **3**, 117 (1964).

(7) All glpc analyses were done using a 3/8 in. × 20 ft 25% Dow Corning DC 200 fluid on 40–60 mesh, Chromosorb W column. The temperature was programmed from 75 to 300° at 15°/min with a helium flow rate of 200 ml/min.

(8) All nmr spectra were obtained using a Varian A-60A spectrometer. Solution samples were made with chloroform or deuteriochloroform using tetramethylsilane as an internal standard.

(9) Other small peaks were detected which represented less than 10% of the total area.

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