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Nitration by Aroyl Nitrates

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Aroyl nitrates, prepared from the corresponding aroyl chloride and silver nitrate, were allowed to react with toluene in acetonitrile solvent. Nitrotoluenes were produced, the isomeric pattern of which varied depending on the conditions. At lower temperatures (25–60°), or with acid promoters, benzoyl nitrate underwent ionic decomposition, probably by way of dinitrogen pentoxide. The invariability in the resulting nitrotoluene distribution using a variety of para-substituted benzoyl nitrates and benzoyl nitrate with a number of acid catalysts and the similarity of this orientation to literature values indicates that the nitronium ion is the electrophile responsible for the aromatic substitution process. At higher temperatures (80°) or in the presence of added peroxides, radical products became more evident from the benzoyl nitrate–aromatic reaction. With *o*-xylene, small yields of 4-benzoyloxy-*o*-xylene were obtained implicating direct reaction between *o*-xylene and the aroyl nitrate. Spectral analyses on benzoyl nitrate solutions were performed. The mechanism of these reactions is discussed.

Despite the rather common use of benzoyl and acetyl nitrate (*i.e.*, nitric acid–acetic anhydride mixtures) as aromatic nitrating agents, mechanistic studies have led to conflicting reports concerning the mechanism of these reactions. A number of equilibria (eq 1 and 2) have been demonstrated[2-4] for these reagents in

$$2RCONO_3 \rightleftharpoons (RCO)_2O + N_2O_5 \quad (1)$$

$$N_2O_5 \rightleftharpoons NO_2^+ + NO_3^- \quad (2)$$

solution and evidence has been obtained for the formation of N_2O_5[5,6] from the nitrate under certain conditions. The acyl nitrate itself, N_2O_5, and NO_2^+ have each been suggested as the reagent responsible for the nitrating action of acyl nitrates.[2,3,7,8]

Most of the more recent investigations have utilized the acetic anhydride–nitric acid combination as a source of acetyl nitrate leading in many cases to the possibility of yet a fourth nitrating agent, protonated acetyl nitrate (eq 3). Not only has this species been

$$RCONO_2 \xrightarrow[\text{slow}]{H^+} RC(=O)-\overset{+}{O}(H)NO_2 \xrightarrow[\text{fast}]{ArH} ArNO_2 \quad (3)$$

proposed as the electrophile in nitrations,[9] but it has also been intimated as the substance responsible for the concomitant nitration and acetoxylation of *o*-xylene.[10] Recent MO calculations support this contention.[11,12]

In addition to ionic decomposition, benzoyl nitrate has been shown to decompose thermally to radical intermediates.[13] Among the products found in the presence of aromatics were the corresponding nitrated compounds, but no isomer distributions were reported. It seems possible that radical nitration is occurring, the mechanism of which has been reviewed extensively by Titov.[14]

Since there is still uncertainty concerning the mechanism of acyl nitrate reactions, our purpose was to study them further in the hope of clarifying the manner in which they exert their nitrating action.

Results and Discussion

We decided to investigate reactions of benzoyl nitrate, since systematic structural changes could be conveniently accomplished with this reagent.

Stock solutions of benzoyl nitrate in acetonitrile were prepared by the method of Francis[15] (eq 4) and some re-

$$C_6H_5COCl + AgNO_3 \xrightarrow{CH_3CN} C_6H_5CONO_3 + AgCl\downarrow \quad (4)$$

(1) Taken in part from the M.S. thesis of L. T. A. Yang, Illinois State University, Normal, Ill., 1972; presented at the Great Lakes Regional Meeting of the American Chemical Society, Houghton, Mich., June 23, 1972.

(2) V. Gold, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2467 (1950); G. A. Benford and C. K. Ingold, *ibid.*, 929 (1938); E. D. Hughes, C. K. Ingold, and R. I. Reed, *ibid.*, 2400 (1950).

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(11) N. Bodor and M. J. S. Dewar, *Tetrahedron*, **25**, 5777 (1969).

(12) P. Kriemler and S. E. Buttrill, Jr., *J. Amer. Chem. Soc.*, **92**, 1123 (1970).

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(14) A. I. Titov, *Tetrahedron*, **19**, 577 (1963).

(15) F. E. Francis, *J. Chem. Soc.*, **89**, 1 (1906).

actions were performed utilizing these solutions. This method proved unsatisfactory for substituted benzoyl nitrates owing to their ready hydrolysis and decomposition upon aging.

To circumvent this problem, many of the reactions of aroyl nitrates were performed *in situ* from silver nitrate and aroyl chloride under the reaction conditions desired. Acetonitrile was selected as solvent. This method provided for the preparation and immediate reaction of benzoyl nitrates, ensuring a known concentration of the nitrate ester. Quantitative determinations of the original benzoyl nitrate concentration were performed by the gravimetric analysis of the silver chloride precipitate at the end of each reaction.

Several preliminary studies of the reaction of benzoyl nitrate, prepared *in situ*, with toluene gave as products nitrotoluenes, benzaldehyde, and benzoic acid. Since the yield and isomer pattern of the nitrotoluenes was somewhat erratic, a number of reaction variables were checked to determine the best standard conditions. In Table I is shown the effect of carrying out the reaction at different temperatures.

TABLE I
TEMPERATURE EFFECT ON THE REACTION OF TOLUENE WITH BENZOYL NITRATE[a]

	Products					
Temp,	C_6H_5-	C_6H_5-	Nitrotoluenes			
°C	CHO	CH_2NO_2	% yield	*o*-	*m*-	*p*-
25[b]			51	62	4	34
35			50	62	4	34
50	1	2	44	58	6	36
60	3	1	41	57	5	38
80[c]	7[d]	3	13	54	13	33[e]

[a] Benzoyl nitrate, prepared *in situ*, was allowed to react at the appropriate temperature for 18–96 hr until all of the nitrate was consumed; see Experimental Section. [b] No difference in yields of isomers for reactions performed under oxygen or under nitrogen. [c] By blanketing the reacting mixture with nitrogen, yields of up to 25% (ortho:meta:para 59:8:33) could be accomplished. [d] Benzyl alcohol (3%) and nitrobenzene (2%) were also found. [e] The average of six runs with varying isomer composition (ortho, 49–58; meta, 8–24; para, 27–38).

A progressive decrease in yield with a slight increase in *m*-nitrotoluene distribution was noted as the reaction temperature was raised to 80°. The lower yields of nitration product were consistent with the observed increase in nitrogen dioxide fume evolution at the higher temperatures. These refluxing reactions were quite susceptible to the type of atmosphere under which they were run, with lower yields and a higher proportion of meta derivative formed when oxygen was present. On the other hand, benzoyl nitrate–toluene interaction at room temperature was little affected, regardless of whether it was run under nitrogen or oxygen. The effect of oxygen on this reaction at high temperatures suggests that radical intermediates might be involved, since free-radical reactions are often inhibited by oxygen.[16] At lower temperatures, seemingly ionic decomposition (not nearly so sensitive to air) was predominant.

As the amount of nitrotoluenes dropped off at higher temperatures, the by-products, benzaldehyde, benzyl alcohol, α-nitrotoluene, and nitrobenzene, began to appear. Their presence along with that of nitrogen dioxide would tend to further indicate the intervention of radical intermediates.

There are two potential sources of these by-products, both involving radicals: (a) the homolysis of benzoyl nitrate (eq 5) ultimately leading to nitrogen dioxide and

$$C_6H_5CONO_3 \longrightarrow C_6H_5CO_2\cdot + NO_2 \quad (5)$$

phenyl radicals (eq 6), or (b) breakdown of dinitrogen

$$C_6H_5CO_2\cdot \longrightarrow C_6H_5\cdot + CO_2 \quad (6)$$

pentoxide present in the system (eq 1) to dinitrogen tetroxide (eq 7)[17] which could occur by way of an

$$2N_2O_5 \rightleftharpoons 2N_2O_4 + O_2 \quad (7)$$

initial homolysis (eq 8).

$$N_2O_5 \rightleftharpoons NO_2 + NO_3 \quad (8)$$

The former pathway (eq 5 and 6) does not appear to be involved under these conditions, as no carbon dioxide was produced from a number of representative toluene–aroyl nitrate reactions at 60 and 80°. Also no phenylation products or other higher boilers were noted in any of these cases.

The possible involvement of dinitrogen pentoxide was scrutinized by performing a temperature study with toluene and the nitrogen oxide itself under analogous conditions (Table II). Nitration was achieved with this reagent and the same aromatic by-products were also formed. The nitrotoluene yields ranged near 20% in most cases and the isomer distributions stayed quite constant and similar to that attributed to the nitronium ion (*vide infra*).

Use of a mixture of dinitrogen pentoxide–benzoic anhydride or of dinitrogen tetroxide instead of the pure pentoxide led to similar results. Thus apparently either of these oxides of nitrogen could account for much of the nitration observed at the higher temperatures but cannot account totally for the room-temperature reactions of benzoyl nitrate with toluene.

Whatever the radicals first generated, side-chain abstraction from toluene would produce benzyl radicals capable of reacting with nitrogen dioxide to produce either α-nitrotoluene (eq 9) or benzyl nitrite (eq 10).

$$\text{Rad}\cdot + C_6H_5CH_3 \longrightarrow C_6H_5CH_2\cdot \xrightarrow{\cdot NO_2} C_6H_5CH_2NO_2 \quad (9)$$

$$C_6H_5CH_2\cdot \xrightarrow{\cdot ONO} C_6H_5CH_2ONO \quad (10)$$

This latter compound was not found, but could break down to form benzyloxy radicals (eq 11) and

$$C_6H_5CH_2ON{=}O \xrightarrow{-NO} C_6H_5CH_2O\cdot \quad (11)$$

ultimately benzaldehyde and benzyl alcohol (eq 12).

$$2C_6H_5CH_2O\cdot \longrightarrow C_6H_5CHO + C_6H_5CH_2OH \quad (12)$$

The isomer distribution of nitrotoluenes from the lower temperature studies in this research was quite similar to that noted for electrophilic aromatic nitration (*vide infra*). This suggests that at low temperature benzoyl nitrate undergoes ionic decomposition.

Thus the temperature study suggests that benzoyl nitrate or dinitrogen pentoxide derived thereof can undergo both an ionic and radical mode of decomposi-

(16) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 522.

(17) A. R. Cooksey, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, **26**, 5101 (1970).

TABLE II

TEMPERATURE EFFECT ON THE REACTION OF DINITROGEN PENTOXIDE WITH TOLUENE[a]

	Products						
					Nitrotoluenes		
Temp, °C	C_6H_5CHO	$C_6H_5CH_2OH$	$C_6H_5CH_2NO_3$	% yield	*o*-	*m*-	*p*-
25	<1	1	0	11	63	3	34
25[b]	1	2	0	20	64	3	33
50	13	7	0	19	68	4	28
60	3	1	1	19	62	4	34
60[c]	8	1	9	9	61	6	33
80	1	2	18	40	62	4	34

[a] Dinitrogen pentoxide was allowed to react at the appropriate temperature for 72–96 hr until all of the oxide was consumed (see Experimental Section). [b] N_2O_5 (0.0045 mol) + $(C_6H_5CO)_2O$ (0.005 mol). [c] Dinitrogen tetroxide was used instead of dinitrogen pentoxide.

TABLE III

REACTION OF BENZOYL NITRATE WITH TOLUENE AND DIISOPROPYL PEROXYDICARBONATE

		Products[a]					
			Nitrotoluenes				
Temp, °C	Peroxide/$C_6H_5CONO_3$ molar ratio	% yield	*o*-	*m*-	*p*-	C_6H_5CHO[b]	Tolyl isopropyl carbonates
35	0	50	62	4	34	0	
35	0.5	37	58	9	33	6	3
35	1	43	53	15	32	4	6
35	2	26	56	18	26	14	8
50	0	44	58	6	36	1	
50	0.5	39	55	11	34	3	3
50	1	45	55	13	32	4	3
50	2	25	48	26	26	5	9
50	1[c]	15	43	30	27	36[d]	34[e]
60	0	41	57	5	38	3	
60	1	22	59	17	24	2	6
60	2	34	53	20	27	5	8
60	1[c]	20	33	55	12	27[f]	48[g]
80	1[h]	7	34	52	14	10	
80	0.5[i]	6	49	20	31	3	
80	0.5[j]	8	53	19	28	11	

[a] Benzoyl nitrate was prepared *in situ* with the peroxide and toluene in acetonitrile at the appropriate temperature; yields are based on moles of product per mole of nitrate; see Experimental Section. [b] Trace amounts of benzyl alcohol were also found in most cases. [c] Dinitrogen pentoxide was used in place of benzoyl nitrate. [d] Benzyl alcohol (16%) and α-nitrotoluene (9%) were also found. [e] Ortho:meta:para = 53:18:29. [f] Benzyl alcohol (19%) and α-nitrotoluene (16%) were also found. [g] Ortho:meta:para = 55:15:30. [h] Benzoyl peroxide was used instead of diisopropyl peroxydicarbonate. [i] Azobisisobutyronitrile used instead of the peroxydicarbonate. [j] *tert*-Butyl perbenzoate was used instead of the peroxydicarbonate.

tion. At higher temperatures the latter reaction predominates.

Confirmation of radical involvement in benzoyl nitrate decompositions was sought by examining the effect of radical initiators on the nitrating properties of benzoyl nitrate. Diisopropyl peroxidicarbonate was selected as the radical source owing to its ready formation of radicals even at lower temperatures.[18]

The addition of increasing proportions of radicals would be expected to favor the radical decomposition pathway. As can be seen from Table III, the proportion of *m*-nitrotoluene increased steadily with increasing peroxide concentrations at all the temperatures studied. The less selective pattern reflected in the nitrotoluene isomer distributions under these conditions indicates either the involvement of a homolytic aromatic substitution pathway which is generally characterized by more statistical, less selective isomeric compositions than ionic substitutions,[19] or the production of a different nitrating agent from the peroxide–nitrate interaction.[20]

The yield of nitrotoluenes produced with increased radical initiator concentrations in general was lower, and greater amounts of the side products, benzaldehyde and tolyl isopropyl carbonates, were found. Interestingly, no sign of α-nitrotoluene was found in these cases. Utilization of dinitrogen pentoxide in place of benzoyl nitrate led to some nitration with characteristically high proportions of meta, but also to much larger amounts of α-nitrotoluene, benzaldehyde, and benzyl alcohol. This difference in product amounts suggests that dinitrogen pentoxide itself cannot solely account for benzoyl nitrate reactions.

Having established that benzoyl nitrate can react with aromatics by both radical and ionic pathways, we sought to investigate more closely the nature of the substituting entity under ionic conditions.

A number of potential substituting moieties have been proposed for both benzoyl and acetyl nitrate systems: the nitronium ion, dinitrogen pentoxide, protonated acyl nitrate, or even the acyl nitrate itself.[11,21] Our approach to the problem was to nitrate toluene with a series of substituted benzoyl nitrates and study the electronic effects of substituents on the pattern of nitration. It was hoped that this would allow us to distinguish between nitration intermediates formed

(18) W. A. Strong, *Ind. Eng. Chem.*, **12**, 33 (1964).

(19) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960.

(20) Recently (M. E. Kurz, unpublished work) it has been shown that the decomposition of peroxydicarbonates with nitric acid in the presence of toluene leads to aryl esters and nitrotoluenes. The predominance of the meta isomer in the latter product suggests a nitrating agent other than the nitronium ion in this case.

(21) J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity," Cambridge University Press, London, 1971.

TABLE IV

REACTIONS OF PARA-SUBSTITUTED BENZOYL NITRATES WITH TOLUENE[a]

Registry no.	p-$XC_6H_4CONO_2$, X =	Nitrotoluenes % yield[b]	o-	m-	p-	$k_{toluene}/k_{benzene}$[c]
39835-16-0	NO_2	34	60.9	5.4	33.7	26.9
39835-17-1	Cl	31	61.4	5.3	33.3	22.3
	H	41	61.1	4.8	34.1	27.1
39835-18-2	OCH_3	40	60.7	5.3	34.0	25.9
39247-26-2	CH_3	30	60.9	5.3	33.8	26.4
	N_2O_5[d]	19	63	5	32[e]	21

[a] Acetonitrile solvent, 60°. [b] Benzaldehyde, 1–7%, and α-nitrotoluene, trace–2%, were also found as well as the appropriately substituted benzoic acid. [c] The average of competition experiments carried out at toluene to benzene ratios of 0.83 and 0.207. [d] N_2O_5 was used instead of $C_6H_5CONO_2$. [e] Duplicate values were in poorer agreement in this case; values are ±2%.

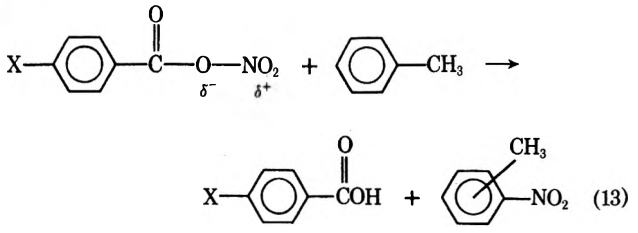
from the acyl nitrate and those actually involving the intact acyl nitrate structure.

A series of aroyl nitrates was prepared *in situ* from silver nitrate and substituted aroyl chloride in the presence of toluene at 60°. The results (Table IV) showed essentially constant nitrotoluene yields and isomer distributions (*i.e.*, ortho:meta:para = 61:5:34). Small amounts of α-nitrotoluene and benazldehyde also were produced. Reactions were also performed at 80° with lower but erratic yields found in all cases.

Subsequently, the competitive method of rate determinations was employed to determine the relative rate of benzene and toluene nitration, using substituted benzoyl nitrates. A large molar excess of both toluene and benzene in a variety of starting ratios was subjected to the nitrating agent. The results (Table IV) showed high substrate selectivity (*i.e.*, $k_{toluene}/k_{benzene}$ of 25 ± 3) accomplished with high positional selectivity (low meta isomer content).

In all of the cases investigated, *i.e.*, *p*-nitrobenzoyl, *p*-chlorobenzoyl, benzoyl, *p*-methoxybenzoyl, and *p*-methylbenzoyl nitrate, essentially the same nitration orientation was observed. Furthermore, the relative rate of nitration in each case was very similar.

If the aroyl nitrate itself is the nitrating agent under these conditions, one would expect the electronic influence of the substituents to affect the electrophilicity of the aroyl nitrate to different degrees and cause the ratio of isomeric nitrotoluenes to be different (eq 13). With electron-withdrawing groups sub-



(13)

stituted in the para position of benzoyl nitrate, the polarity of the O–N bond should be enhanced, resulting in a higher proportion of *o*- and *p*-nitrotoluenes. On the other hand, electron-donating groups should decrease the electrophilicity of the aroyl nitrate, as would be evidenced by higher meta nitration.

Since we found no change with the different agents, it appears that a common intermediate is involved in each case. It would seem, therefore, that the aroyl nitrate itself is not the actual nitrating species with toluene.

Nitration by dinitrogen pentoxide under similar conditions (Table IV) gave relative rate and isomer values reasonably similar to those from the aroyl nitrate reactions. Furthermore, these values compared closely to typical toluene nitration values in the literature ($k_{toluene}/k_{benzene}$ = 21–27, and ortho:meta:para = 57–61:3–5:37–40) for nitric acid,[22,23] mixed acid,[24] acetyl nitrate,[17,22] and benzoyl nitrate.[25] The similarity of our isomer distributions and relative rates with these literature values, which in some cases have been attributed to the nitronium ion,[22,23] suggests that this same species formed by way of dinitrogen pentoxide (eq 1 and 2) is the actual nitrating entity from benzoyl nitrates.

To determine whether protonated benzoyl nitrate can be involved in these reactions, nitrations were also carried out with acid catalysts (Table V).

TABLE V

ACID-PROMOTED REACTION OF BENZOYL NITRATE WITH TOLUENE[a]

Acid promoter	% yield	Nitrotoluenes o-	m-	p-	$k_{toluene}/k_{benzene}$[b]
None[c]	41	59.6	4.3	36.1	28.1
$HClO_4$	53	56.3	4.4	39.3	18.6
H_2SO_4	64	62.1	3.4	34.5	35.3
$AlCl_3$[d]	45[e]	60.6	3.2	36.2	32.3
BF_3[d,f]	55	66.4	2.7	30.9	58.0

[a] Catalyst: benzoyl nitrate molar ratio 2:1, acetonitrile (73%)–aromatic (27%) solvent, 25°. [b] The average of at least duplicate runs performed at toluene to benzene molar ratios of 0.83 and 0.207. [c] No difference in isomer distribution and relative rates for reactions carried out in predominantly acetonitrile or predominantly aromatic solvent. [d] Acetonitrile (33%)–aromatic (67%) solvent. [e] Chlorotoluenes produced in fair amounts. [f] Below 0°, BF_3 concentration unknown, but in excess of benzoyl nitrate.

Although the reaction rate was accelerated with all of the acid catalysts, rather minor differences in the nitration products resulted. The slight isomer distribution changes with boron trifluoride and aluminum chloride may in part be due to changes in the medium as well as to the lower reaction temperature in the latter case.

A number of benzoyl nitrate reactions with *o*-xylene both with and without added catalyst were studied to see if benzoyloxylation, analogous to the acetoxylation reported for acetyl nitrate,[10] could occur (Table VI). Even without catalysts, a small amount of benzoyl-

(22) C. K. Ingold, A. Lapworth, E. Rothstein, and D. Ward, *J. Chem. Soc.*, 1959 (1931).

(23) H. Cohn, E. D. Hughes, M. H. Jones, and M. G. Peeling, *Nature (London)*, **169**, 291 (1952).

(24) P. H. Griffiths, W. A. Walkey, and H. B. Watson, *J. Chem. Soc.*, 631 (1934).

(25) W. W. Jones and M. Russell, *J. Chem. Soc.*, 921 (1947).

TABLE VI
REACTION OF BENZOYL NITRATE WITH o-XYLENE

Catalyst (ratio)	Temp, °C	Products[a] Nitro-o-xylenes[b]	4-Benzoyloxy-o-xylene	o-Tolualdehyde	2-Methylbenzyl alcohol
None	0	17	3	1	1
None	25	22	7	5	4
None	50	22	4	4	1
BF_3[c]	25	38	14	3	0
$AlCl_3$ (2.0)	50	59	0	0[d]	0
$HClO_4$ (2.0)	50	53	0	10	10

[a] Benzoyl nitrate (0.00125 mol) was added to the solution of o-xylene and catalyst in acetonitrile at the appropriate temperature. [b] Isomeric mixture of varying composition containing predominantly 3- and 4-nitro-o-xylene contaminated with some α-nitro-o-xylene. [c] Exact amount not known; an excess of BF_3 was used. [d] 4-Chloro-o-xylene (135%) was also formed.

oxylation (3–7%) accompanied the expected nitration. This result would tend to indicate that the aroyl nitrate structure itself is interacting with the aromatic to some extent, as it is hard to visualize the ester product arising from dinitrogen pentoxide and benzoic anhydride.

Addition of boron trifluoride at 25° enhanced the aryl ester yield as well as that of the nitroxylenes. On the other hand, only nitroxylenes were produced with aluminum chloride and perchloric acid at 50°.

In this case, some sort of benzoyl nitrate–boron trifluoride complex analogous to that proposed with acetyl nitrate[11,12] might be involved in both the nitration and benzoyloxylation processes.

In an effort to learn more about the possible nitrating species available in these aroyl nitrate systems, nmr and uv spectra were observed for a variety of potential moieties in acetonitrile.

The aromatic region of the benzoyl nitrate nmr spectrum, when compared to that of benzoic anhydride and benzoic acid, indicated that these latter compounds are not present to a great extent in benzoyl nitrate solution. Addition of dinitrogen pentoxide alone or with a trace of benzoic acid to the benzoic anhydride did not substantially alter the anhydride's nmr spectrum. A more sensitive probe for the presence of benzoic acid (a by-product of benzoyl nitrate decomposition) was integration of the hydroxyl proton (11.3 ppm) *vs.* the total aromatic signal. Using this method, we found that, while fresh solutions of benzoyl nitrate contained just trace amounts of benzoic acid, its concentration steadily increased with solution aging.

The uv spectra of a variety of potential species in the benzoyl nitrate system are shown in Figure 1. A fresh solution of benzoyl nitrate in acetonitrile at room temperature showed two broad bands of equal intensity ($\epsilon \sim 500$) at 272 and 279 nm. Benzoic acid gave absorption bands at 272 nm ($\epsilon \sim 910$) and 279 (~ 690) also, but of considerably different intensity.[26] Aged solutions of benzoyl nitrate (*e.g.*, 2 weeks), still containing active nitrating power, gave spectra very much resembling that of benzoic acid.

(26) D. Pasto and C. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 101.

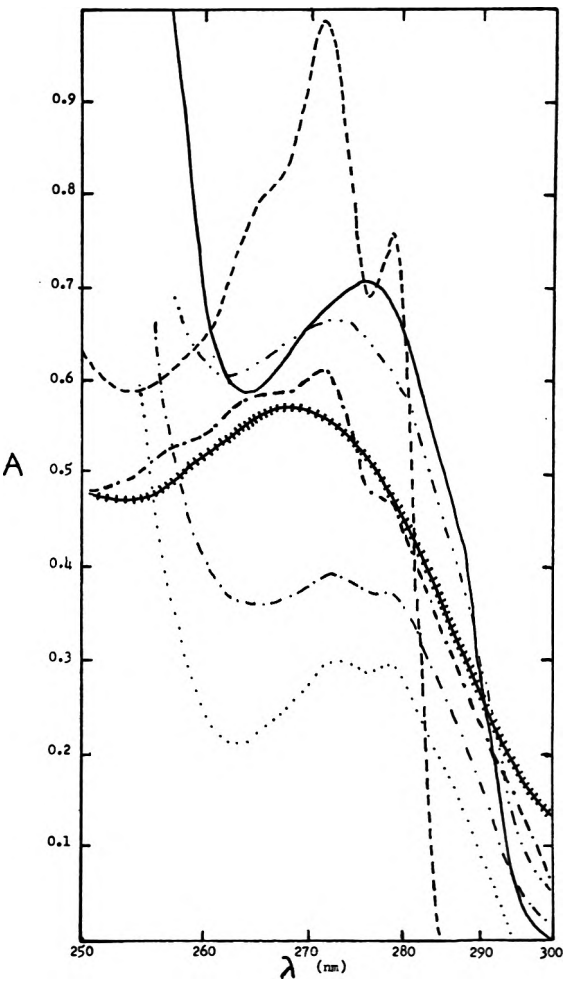


Figure 1. –Uv spectra in acetonitrile of ·····, benzoyl nitrate (0.0005 *M*), fresh; – – · – –, benzoyl nitrate (0.0005 *M*), aged; ——, benzoic anhydride (0.00025 *M*); ‖‖‖‖‖‖‖‖‖‖‖‖, dinitrogen pentoxide (0.0012 *M*); · · —· · –, benzoic anhydride:dinitrogen pentoxide (1:2); – · — · —, benzoic anhydride:dinitrogen pentoxide:benzoic acid (2:2:1); – – – –, benzoic acid (0.0009 *M*).

Pure dinitrogen pentoxide absorbed at 269 nm ($\epsilon \sim 475$) while benzoic anhydride showed a broad absorption [λ_{max} 277 nm ($\epsilon \sim 2830$)]. Synthetic mixtures of dinitrogen pentoxide–benzoic anhydride showed only a single absorption maxima which gradually shifted from 277 (pure anhydride) to 270 nm as higher dinitrogen pentoxide:anhydride ratios were utilized. However, when benzoic acid was added to this mixture, the resulting spectrum resembled that of benzoyl nitrate. Although the uv data is consistent with either benzoyl nitrate or anhydride as the main component in solution with benzoic acid as a contaminant, the combined uv–nmr studies would tend to favor the former case.

These findings are consistent with the previous work of Ingold and coworkers,[2] who showed that the equilibrium (eq 1) which is actually comprised of two steps (eq 14 and 15) is shifted to the left.

$$PhCOH + PhCONO_2 \rightleftharpoons (PhC)_2O + HNO_3 \quad (14)$$

$$HNO_3 + PhCONO \rightleftharpoons PhCOH + N_2O_5 \quad (15)$$

Discussion

Reactions involving aroyl nitrates are complicated by a series of possible equilibria (eq 1, 2, 13, 14) involving the nitrate itself and dinitrogen pentoxide–benzoic anhydride. In the temperature range studied (0–80°) various lines of evidence, including uv and nmr spectra, point toward the presence of both the aroyl nitrate and dinitrogen pentoxide with a predominance of the former. With *o*-xylene seemingly the aroyl nitrate interacts directly with the aromatic, leading to benzoyloxylation in addition to nitration, a process which can be enhanced with boron trifluoride. Whether both substitution reactions proceed by way of a common intermediate was not ascertained. With toluene, on the other hand, only nitration occurred, and dinitrogen pentoxide appeared to be the crucial intermediate. At temperatures of 60° and less, nitration proceeded by an ionic pathway, and involved the nitronium ion as evidenced by (1) the similarity in relative rates and isomer distributions of this reaction to others in which the nitronium ion is responsible, (2) the invariance of substitution patterns from a series of para-substituted benzoyl nitrates and benzoyl nitrate with acid catalysts, and (3) the fact that dinitrogen pentoxide itself led to similar products under simulated reaction conditions. At 80° the decreased yield of nitrotoluenes is thought to arise from radical breakdown of dinitrogen pentoxide to dinitrogen tetroxide and oxygen. No evidence of homolytic cleavage of benzoyl nitrate itself was found. Addition of radical initiators to benzoyl nitrate did lead to a different type of nitration pattern, but it is suggested that intermediates from the peroxide–nitrate interaction may be responsible for this.

Experimental Section

Materials.—Toluene, *o*-xylene, benzene (AR grade), and acetonitrile (Mallinckrodt Nanograde) were used directly. The aroyl chlorides and benzoic anhydride (Aldrich) used came from freshly opened bottles and were not purified further. The diisopropyl peroxidicarbonate[27] was found to be about 95% pure by titration.

Stock Solution of Benzoyl Nitrate. General Procedure.—Basically the procedure of Francis[2] was used with slight modification. A solution of freshly dried, powdered silver nitrate in acetonitrile was loaded into a flask fitted with a drying tube, a dopping funnel, and a thermometer, and stirred mechanically while cooling in an acetone–Dry Ice bath. After being cooled to −20°, an equimolar amount of benzoyl chloride was slowly added since the reaction was somewhat exothermic. Immediate silver chloride precipitation occurred, the solution turned yellow, and a small amount of brown fumes evolved. The temperature was maintained at −15 to −20° for at least 3 hr. At the end of this time, the solid material was filtered off and the filtrate was kept below −40° in a tightly capped bottle. For many reactions (*e.g.*, acid-catalyzed decompositions) the appropriate amount of benzoyl nitrate solution was pipetted into a mixture containing a twofold molar excess of catalyst in either pure aromatic (aluminum chloride) or in aromatic with acetonitrile solvent (H_2SO_4, $HClO_4$, or BF_3) at the appropriate temperature.

In a similar fashion, stock solutions of various para-substituted benzoyl nitrates were also produced using the corresponding para-substituted benzoyl chloride.

Owing to the ready decomposition of benzoyl nitrate to benzoic acid in the presence of moisture, the stock solution of benzoyl nitrate generally deposited a white precipitate upon aging and the nmr indicated the presence of benzoic acid. This problem was particularly acute in the case of a number of the substituted benzoyl nitrates. Since the exact concentration of benzoyl nitrate in the stock solutions was hard to determine, an alternative method of making benzoyl nitrate was utilized in many cases.

Aromatic Nitration with Benzoyl Nitrate Prepared *in Situ*. General Procedure.—The appropriate benzoyl chloride (0.02 mol) in acetonitrile (10 ml) was added dropwise to a rapidly stirred solution of silver nitrate (3.4 g, 0.02 mol) in acetonitrile (50 ml) containing toluene (10 ml, 0.094 mol) at reflux. Silver chloride precipitated immediately, the solution turned yellow, and brown fumes of nitrogen dioxide were evolved. The reaction mixture was stirred for an additional 18–96 hr at this temperature until no fumes remained. At the end of this period of time, the heterogeneous mixture was filtered *in vacuo* and the silver chloride solid was dried and weighed to determine the completeness of the benzoyl nitrate formation (eq 4). In all cases examined, conversion of the benzoyl chloride to the nitrate was found to be 95–100% complete by this gravimetric silver chloride method.

Qualitative and quantitative analysis of the products was carried out directly on the organic phase by gas chromatography.

Yields were based on moles of product per mole of benzoyl nitrate, and in all cases the table entries represent an average of at least duplicate runs in close agreement.

For reactions under nitrogen or oxygen, an additional gas inlet bringing in a slow flow of the gas was provided. Reactions at temperatures other than 80° were performed in constant-temperature baths and occasional shaking was used instead of mechanical stirring. Control runs with and without stirring showed no difference in product yields.

The benzoyl nitrate–toluene runs with added diisopropyl peroxydicarbonate or acid catalysts were done according to the general procedure with the catalyst being added to the silver nitrate solution just prior to addition of benzoyl chloride.

Competitive Nitration. General Procedure.—A solution of toluene (0.094 mol) and benzene (0.112 mol) in 40 ml of acetonitrile containing silver nitrate (0.85 g, 0.005 mol) was preheated to 60°. The solution of acid chloride (0.005 mol) in acetonitrile was added with vigorous shaking. Upon completion, a sample of the reaction mixture was analyzed by gas chromatography to determine the relative amounts of nitrotoluenes and nitrobenzene as well as the isomer distribution of the former. Competitive runs were also carried out at benzene–toluene ratios of 4:1. The toluene–benzene product ratios corrected to equimolar reactant concentrations were used directly as a measure of the relative rate.[28]

Preparation of Dinitrogen Pentoxide.—A literature method[29] with some modification was used. Fuming nitric acid (50 g) was degassed with dry oxygen until colorless, and then frozen in a flask. Phosphorus pentoxide (62 g) was added all at once, and a flow of ozone in oxygen (P. S. I. Model LOA4 Corona) was continuously run into the flask. The solution was allowed to warm up with occasional stirring, and the dinitrogen pentoxide was distilled out into a preweighed receiver held at −75°. At the end this flask was reweighed (3 g) and then flushed out with the appropriate amount of acetonitrile. The resulting stock solution of dinitrogen pentoxide was used immediately in a variety of reactions.

Analytical Procedures. A. Gas Chromatography.—Glpc was used extensively for quantitative product yield determinations. Varian Models 1400 and 600D with flame ionization detectors were used with 10 ft × 0.125 in. 20% SE-30/Chromosorb W-DMCS columns. The inlet pressure for the nitrogen carrier gas was 50 psig for the 1400 and 20 psig for the 600D model, resulting in carrier gas flow rates of about 20 cc/min. The column temperature was 175–180°.

B. Product Identification.—From a thermal decomposition of benzoyl nitrate (25 mmol) in toluene, sodium carbonate extraction yielded benzoic acid (3.07 g, 25.1 mmol). The remaining organic solution was concentrated and products were separated by preparative glpc (Varian 90-P, thermal conductivity detector, 6 ft × 0.25 in. 20% SE-30/Chromosorb P). Benzaldehyde and *o*- and *p*-nitrotoluene were identified by their ir spectra.

(27) We are grateful to the Pittsburg Plate Glass Co., Barberton, Ohio, and B. F. Goodrich Co., Henry, Ill., for samples of this compound.

(28) For a recent critical evaluation of competitive methods in aromatic nitration, see S. R. Hartshorn, R. B. Moodie, and K. Shofield, *J. Chem. Soc. B*, 1256 (1971).

(29) N. S. Gruenhut, M. Goldfrank, M. L. Cushing, and G. V. Caesar, *Inorg. Syn.*, **3**, 78 (1950).

The latter product was contaminated with the meta isomer, which was collected along with it. α-Nitrotoluene was identified by comparison of its retention time to that of an impure α-nitrotoluene sample prepared from benzyl bromide and silver nitrite.[30]

As a control, solutions of benzoyl nitrate in either acetonitrile or toluene were analyzed directly by glpc, with nitrobenzene (~1–2%) appearing as the only detectable pyrolysis product.

C. Quantitative Analysis.—Reaction product yields and isomer distributions were determined by adding a known quantity of a marker (*p*-chloroanisole) to a one-tenth portion (0.002 mol) of the reaction mixture and analyzing by glpc. The appropriate correction factors were used to convert area ratios to molar ratios and ultimately to product yields. To correct for detector response, mixtures containing known amounts of *p*-chloroanisole and nitrotoluenes were analyzed by glpc under the standard conditions. The slope of the straight line resulting from a plot of the relative area ratio against mole ratio for each product *vs.* the marker was the correction factor.

D. Relative Rates.—The reaction mixtures were analyzed directly by glpc. The molar ratio of isomeric nitrotoluenes to nitrobenzene was determined after correcting the peak areas for detector response.

E. Uv Spectroscopy.—A Beckman Model DK-2A spectrophotometer was used. Freshly prepared solutions were diluted to concentrations ranging from 0.00025 to 0.0015 *M* in acetonitrile for determination of their spectra.

F. Nmr Spectroscopy.—A Perkin-Elmer Model R-20 nmr spectrometer (60 MHz) was utilized, and spectra were determined in acetonitrile solvent.

Registry No.—Toluene, 108-88-3; benzoyl nitrate, 6786-32-9; dinitrogen pentoxide, 10102-03-1; diisopropyl peroxydicarbonate, 105-64-6; *o*-xylene, 95-47-6.

(30) N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).

Benzoyl Nitrate Reduction with Halide Ions

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Benzoyl nitrate, prepared from benzoyl chloride and silver nitrate, was treated with a twofold excess of halide ions in the presence of aromatics. The normal nitrating action was altered as the acyl nitrate was rapidly reduced to nitrite ion and molecular halogen. In the chloride and bromide ion reactions halogenated aromatics subsequently resulted. The fact that nearly 2 mol of haloaromatic was produced/mol of benzoyl nitrate under optimum conditions was explained by the further interaction of nitrous acid with hydrogen halide to generate more molecular halogen. The chlorotoluene isomer distributions and cyclohexene products from this system when compared to those of other chlorinating agents indicated that nitryl chloride, and not benzoyl hypochlorite, was formed as an intermediate in the overall reduction process. This was capable of chlorinating directly or reacting further with more chloride ion to generate chlorine. Nitryl chloride arises either from direct displacement by chloride ion on benzoyl nitrate, or on dinitrogen pentoxide present in equilibrium with the nitrate.

Although acyl nitrates (*e.g.*, acetyl and benzoyl nitrate) have found considerable use as mild nitrating agents, relatively few other reactions of these reagents have been studied.[2,3] This may be due in part to the relative instability of this class of compounds, which are often prepared *in situ*. The nitrating action of these species appears to occur by way of the nitronium ion formed from a series of equilibria involving heterolytic acyl nitrate breakdown to dinitrogen pentoxide (eq 1).[3–6] Recently Barlow reported that benzoyl

$$2C_6H_5CONO_3 \rightleftharpoons (C_6H_5CO)_2O + N_2O_5 \quad (1)$$

nitrate undergoes homolysis upon heating, giving rise to products best explained in terms of radical intermediates (eq 2).[7] The weakness of the O–N bond in the

$$C_6H_5\overset{\overset{O}{\|}}{C}ONO_2 \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}O\cdot + NO_2 \quad (2)$$

acyl nitrate structure which allows for this homolysis reaction suggests that this class may behave analogously to peroxides. Consequently, we have set out to look at other "peroxide-type" reactions of these molecules. It is known that peroxides are readily reduced by halide ions;[8–10] indeed this reaction has proved quantitatively useful for analysis.[11] We would like to report here on the reaction between benzoyl nitrate and halide ions.

Results and Discussion

Benzoyl nitrate solutions in acetonitrile were prepared from benzoyl chloride and silver nitrate.[12] Appropriate amounts of the nitrate were pipetted from fresh stock solutions into acetonitrile containing toluene and the appropriate source of halide. Table I summarizes the results from such a study using hydrogen halides as well as aluminum chloride. The products (51% nitrotoluenes and quantitative benzoic acid) from the reaction of benzoyl nitrate with toluene in the absence of any additives[3] are included for comparison. This reaction, which generally required some 2–3 days to complete at room temperature, can be represented by the stoichiometry shown in eq 3.

$$C_6H_5CONO_3 + C_6H_5CH_3 \longrightarrow C_6H_5CO_2H + O_2NC_6H_4CH_3 \quad (3)$$

Addition of aluminum chloride and the hydrogen halides caused a virtually instantaneous reaction at room temperature and below. With aluminum chloride, the nitrotoluene yield dropped off, and halotoluenes became evident in the product mixtures.

(1) Presented at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 31, 1972.

(2) G. A. Olah and S. J. Kuhn, "Friedel-Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter 43.

(3) See M. E. Kurz, L. T. A. Yang, E. P. Zahora, and R. C. Adams, J. *Org. Chem.*, **38**, 2271 (1973), and references cited therein.

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(6) R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3030 (1961); J. R. Knowles and R. O. C. Norman, *ibid.*, 3888 (1961).

(7) L. R. Barlow, *Tetrahedron*, **24**, 4913 (1968).

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(9) J. K. Kochi, B. M. Graybill, and M. Kurz, *J. Amer. Chem. Soc.*, **86**, 5257 (1964).

(10) N. J. Bunce and D. D. Tanner, *ibid.*, **91**, 6096 (1969).

(11) *E.g.*, H. A. Flaschka, A. J. Barnard, Jr., and P. E. Sturrock, "Quantitative Analytical Chemistry," Vol. I, Barnes and Noble, New York, N. Y., 1969, p 325.

(12) F. E. Francis, *J. Chem. Soc.*, **89**, 1 (1906).

TABLE I

BENZOYL NITRATE–HALO ACIDS–TOLUENE IN ACETONITRILE[a]

Catalyst	Temp, °C	Nitrotoluenes Yield, %	o-	m-	p-	PhCHO	$PhCH_2X$	Other
None	25	51	62	4	34	0	0	
$AlCl_3$	0	16	61	3	36	Trace	Trace	60[b]
HBr (aq)	25	0				2	6[c]	190[d]
HCl (aq)	25	0				0	Trace[e]	170[b]
HI (aq)	25	0				0	0	6[f]

[a] Toluene:acid catalyst:$C_6H_5CONO_3$ = 7.5:2:1 in acetonitrile (50 ml); see Experimental Section. [b] Chlorotoluenes. [c] Benzyl alcohol. [d] Bromotoluenes. [e] Benzyl chloride. [f] Unidentified.

TABLE II

BENZOYL NITRATE–TOLUENE–BROMIDE IN ACETONITRILE[a]

Catalyst	Molar ratio catalyst: nitrate	Temp, °C	Days	BrC_7H_7 Yield, %	o-/p-	$C_6H_5CH_2Br$	Total bromotoluenes	$O_2NC_6H_4CH_3$	C_6H_5CHO	$C_6H_5CH_2OH$	Other
HBr (aq)[b]	2	25	4	190	33/67	0	190	0	2	6	1[c,d]
HBr (aq)	2	60	1	136	33/67	31	167	0	10	10	
HBr (aq)	2	80	3	62		19	81		13	46	6[c,d]
HBr (aq)[e]	2	25	6	190	33/67	0	190	0	Trace	Trace	
HBr (g)[f]	2	60	1	82	38/62	35	117	5	10	12	4
HBr (g)	1	60	1	83	41/59	24	107	5	3	7	
HBr (g)	2	25	10	155	36/64	15	170	0	0	12	3
HBr (g)	1	25	12	65	37/63	7	72	3[g]	1	1	6[c]
HBr (g)[h]		60	1	0		0		0	0	0	d
LiBr[e]	2	60	1	40	49/51	8	48	Trace	4	18	27[k]
LiBr[e,i]	2	60	1	37	49/51	17	54	Trace	2	7	
LiBr[e,j]	2	60	1	10	41/59	5	15	Trace	1	12	4[k]
Br_2[l]		25	10	48	34/66	16	64				
Br_2[l]		60	1	37	34/66	8	45				
HBr(g)–$NaNO_2$[m]	2	60	1	5	37/63	24	29		13	8	
HBr(aq)–HNO_2[n,o]	2	60	1	107	34/66	11	118	0	26	10	
HBr(aq)–HNO_2[n,o]	2	25	7	14		0	14	0	1	3	
HBr(aq)–N_2O_5[o]	2	60	2	163	32/68	10	173	0	5	8	
HBr(aq)–HNO_3[o]	2	60	2	147	32/68	37	184	0	9	1	

[a] Toluene (0.094 mol), $C_6H_5CONO_3$ (0.0125 mol) in acetonitrile (50 ml); see Experimental Section. [b] 48% aqueous HBr. [c] Benzyl benzoate. [d] NH_4Br precipitated from the reaction mixture but was not determined quantitatively. [e] Mixed solvent of acetonitrile (25 ml) and acetic acid (25 ml) was used. [f] Reaction was run in acetonitrile (25 ml) and excess toluene (30–40 ml) solvent. [g] Ortho:meta:para = 65:5:30. [h] Control run, no $C_6H_5CONO_3$. [i] Run under nitrogen. [j] H_2O (0.09 mol) added. [k] Benzyl acetate. [l] Bromine (0.0125 mol), no $C_6H_5CONO_3$. [m] $NaNO_2$ (0.0125 mol) in H_2O (5 ml), no $C_6H_5CONO_3$. [n] From equimolar $NaNO_2$–$HClO_4$. [o] No $C_6H_5CONO_3$.

Hydrogen halides were immediately oxidized to molecular halogens, as evidenced by the yellow to dark red solutions formed upon mixing. The hydrochloric and hydrobromic acid reaction mixtures were allowed to stand until the halogen color disappeared, and analysis then showed chloro- and bromotoluenes to be produced in large amounts with virtually no nitrotoluenes found. No aromatic substitution products resulted in the hydriodic acid system.

With the acid catalysts being used, two competing benzoyl nitrate decomposition pathways seem possible: acid-catalyzed heterolysis of the benzoyl nitrate or dinitrogen pentoxide[3] yielding the nitronium ion

$$C_6H_5\overset{\overset{O\text{—}HX\ (MX_3)}{\|}}{C}ONO_2 \longrightarrow C_6H_5CO_2H + X^- + NO_2^+ \qquad (4)$$

(eq 4), and nitrate reduction by halide ion resulting in molecular halogen (eq 5).

$$C_6H_5\overset{\overset{O}{\|}}{C}ONO_2 + 2X^- \longrightarrow C_6H_5CO_2^- + NO_2^- + X_2 \qquad (5)$$

With aluminum chloride, both pathways were apparently operative, whereas the ionized Brønsted acids reacted preferentially by halide ion reduction (eq 5).

The bromide ion–benzoyl nitrate system was scrutinized in more detail using both hydrobromic acid and LiBr as halide ion sources (Table II). In all cases studied, the deep red coloration of bromine occurred immediately upon mixing, and the reactions were subsequently allowed to react until the bromine was consumed. Bromotoluenes were the major organic products of all runs involving benzoyl nitrate with hydrobromic acid in both the aqueous and gaseous form. Other products besides stoichiometric quantities of benzoic acid were varying amounts of benzaldehyde and benzyl alcohol and in a few of the reactions some nitrotoluenes. The following observations concerning the HBr–benzoyl nitrate system can be gleaned from Table II: (1) a 2:1 ratio of acid to nitrate led to bromotoluene yields approaching 200% based on benzoyl nitrate as the limiting reagent; (2) the ring bromination yield fell off at higher reaction temperatures and increased amounts of benzyl bromide and other products from the side chain of toluene were formed; (3) no change in the reaction path occurred when a mixed acetic acid–acetonitrile solvent was utilized; (4) the isomeric composition of bromotoluenes in aqueous HBr was the same as that obtained from molecular bromine under the same conditions and the

ortho–para distribution in the gaseous HBr system was more erratic; (5) a control run with HBr in the absence of benzoyl nitrate led to no aromatic substitution products.

Similar reactions performed with LiBr–benzoyl nitrate also produced bromotoluenes, albeit in lower yield. In these cases which were run in mixed acetic acid–acetonitrile solvent, benzyl acetate was also produced as by-product. Although the product mixture from reactions run under nitrogen or air showed little difference, the addition of water to the system caused a marked decrease in bromotoluenes from about 40% to 10%. The ortho:para ratio of the substitution product showed a higher percentage of ortho than that formed from bromine.

The mechanism suggested for the bromination reaction is shown below for the HBr–benzoyl nitrate system. Stoichiometrically 2 mol of HBr are required to generate 1 mol of bromine (eq 6), which in turn can

$$C_6H_5CONO_3 + 2HBr \longrightarrow C_6H_5CO_2H + HONO + Br_2 \quad (6)$$

react with toluene to form 1 mol of bromotoluenes (eq 7). To explain the nearly 200% yield of the

$$Br_2 + C_6H_5CH_3 \longrightarrow BrC_6H_4CH_3 + HBr \quad (7)$$

brominated aromatic under optimum conditions it is suggested that nitrous acid arising from the nitrate reduction (eq 6) can interact with HBr from eq 7 to generate more bromine (eq 8). The reactions (eq 7 and

$$2HBr + 2HONO \longrightarrow Br_2 + 2H_2O + 2NO \quad (8)$$

8) can then reoccur until all the nitrous acid and/or hydrobromic acid are consumed. This could theoretically lead to 2 mol of brominated product/mol of benzoyl nitrate. Reduction by iodide is a known quantitative method for determining nitrous acid;[10,11] so the analogous reactions (eq 8) with other halide ions seem reasonable. Similar reductions have been proposed as steps in the gas-phase reduction of nitrogen dioxide with HBr[13] and HCl.[14] To actually test this theory, a 2:1 mixture of HBr:HONO was mixed with toluene in acetonitrile at 60° under simulated reaction conditions and led to a good yield of bromotoluenes having the characteristic isomer distribution as from molecular bromine (Table II). The brominated products were also produced, although in much lower yield, from a similar reaction at 25° and a gaseous HBr–$NaNO_2$ run at 60°. These experiments verified the feasibility of eq 8.

The lower yields of bromotoluenes from benzoyl nitrate–HBr at higher temperatures may well result from loss of HBr from the reaction mixtures. Radical process also began to occur, as attested to by the formation of benzyl bromide and other products of the benzyl radical. One can also attribute the lower yield in the lithium bromide runs to the fact that the nitrite ion is much less susceptible to reduction than nitrous acid.

Subjection of N_2O_5 with a twofold molar excess of HBr to similar conditions in the presence of toluene led to results still consistent with 2 mol of halotoluenes/mol of oxidant. Nitric acid–hydrochloric acid under standard reaction conditions also produced nearly 2 mol of halotoluene/mol of nitric acid as had been previously reported.[15]

A more detailed study (Table III) of benzoyl nitrate with chloride ion led to similar results. Chlorotoluenes were the major aromatic substitution products, again accompanied by varying amounts of benzyl radical products and in some cases nitrotoluenes. As in the bromide ion study, use of HCl at lower temperatures gave higher yields of chlorotoluenes than did the higher temperature HCl and all of the LiCl runs. Control reactions also demonstrated that chlorine could be formed from nitrous acid, nitric acid, or dinitrogen pentoxide in the presence of HCl (Table III).

TABLE III

TOLUENE CHLORINATION WITH BENZOYL NITRATE–CHLORIDE[a]

	Products			
	$ClC_6H_4CH_3$[b]			$O_2NC_6H_4CH_3$
Catalyst	Yield,[c] %	o-	p-	
HCl (g)[d]	104	54	46	22[e]
HCl (aq)[d]	69	52	48	0
HCl (aq)[d,f]	170			0
LiCl	60	56	44	8
LiCl[g]	34	56	44	13
HCl–HONO[h,i]	44	55	45	0
HCl–HNO_3[d,i]	48	53	47	0
HCl–N_2O_5[d,i]	137	52	48	0

[a] Toluene (0.094 mol), $C_6H_5CONO_3$ (0.0125 mol), catalyst (0.025 mol) in acetonitrile (25 ml)–acetic acid (25 ml) solvent, 60°, 1 day. [b] Small amounts of benzyl chloride (up to 2%) were noted in many cases. [c] Based on 1 mol of product/mol of nitrate. [d] Acetonitrile solvent (50 ml). [e] Ortho:meta:para = 60:5:35. [f] 25°, 7 days. [g] Run under nitrogen or with added water (0.09 mol). [h] From equimolar $NaNO_2$–$HClO_4$. [i] No $C_6H_5CONO_3$.

Although it is clear that halide ions are capable of reducing benzoyl nitrate, it is of interest to determine the actual stepwise breakdown of the oxidant. With the aroyl nitrate, theoretically, two pathways are conceivable, leading to the possible reactive intermediates benzoyl hypohalite (eq 9) or nitryl halide (eq 10).

$$X^- + C_6H_5\overset{O}{\overset{\|}{C}}ONO_2 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}X + NO_2^- \quad (9)$$

$$X^- + C_6H_5\overset{O}{\overset{\|}{C}}ONO_2 \longrightarrow C_6H_5CO_2^- + NO_2X \quad (10)$$

In addition, if dinitrogen pentoxide, in equilibrium with benzoyl nitrate,[3,4] reacts with the halide, nitryl halide would be expected to be formed (eq 11). We

$$X^- + O_2NONO_2 \longrightarrow O_2NX + NO_3^- \quad (11)$$

attempted to determine whether benzoyl hypohalite or nitryl halide was involved as an intermediate in the toluene–benzoyl nitrate–chloride ion case by carefully determining the isomer distribution of chlorotoluenes and comparing them to known halogenating agents (Table IV).

The isomer composition from benzoyl nitrate with a twofold excess of chloride ion was the same as that from molecular chlorine under the same conditions. However, as the amount of halide:nitrate was lowered gradually to 0.25:1, the ortho:para ratio changed slightly to 55:45. Benzoyl hypochlorite has been

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TABLE IV
CHLORINATION OF TOLUENE WITH VARIOUS CHLORINATING AGENTS

Chlorinating agent[a]	Molar ratio	Chlorotoluenes Yield, %	o-	p-	Benzyl chloride
$HCl(g)-C_6H_5CONO_3$[b]	2:1	104	54.0	46.0	
$LiCl-C_6H_5CONO_3$	2:1	60	56.7	43.3	
$LiCl-C_6H_5CONO_3$	0.97:1	41	56.0	44.0	10[c]
$LiCl-C_6H_5CONO_3$	0.51:1	26	55.2	44.8	10[c]
$LiCl-C_6H_5CONO_3$	0.25:1	*i*	54.7	45.3	*i*
$LiCl-Cl_2$	2:1	83	56.7	43.3	
$LiCl-(C_6H_5CO_2)_2$[d]	2:1	15	57.5	42.5	22[e]
$LiCl-(C_6H_5CO_2)_2$	0.5:1	5	*i*	*i*	9[e]
NO_2Cl		41	55.3	44.7	
NO_2Cl[b]		31	54.6	45.4	5
$LiCl-NO_2Cl$	0.85:1	47	55.6	44.4	
$HCl-N_2O_5$[b]	2:1	137	52.1	47.9	
$HCl-HNO_3$	2:1	78	57.9	42.1	
$HBr-NO_2Cl$	1:1	2[f]			
$HBr-NO_2Cl$[g]	1:1	1[h]			

[a] Generally 0.0125 mol of chlorinating agent was used with toluene (0.094 mol) in acetonitrile (25 ml)–acetic acid (25 ml) solvent at 60°; see Experimental Section. [b] Acetonitrile solvent (50 ml). [c] Trace of benzyl acetate was also formed. [d] Air was bubbled through reacting mixture. [e] Other products (methylbiphenyls, bibenzyl, and benzyl benzoate) were produced. [f] Bromotoluenes, 28%, benzyl alcohol, 8%. [g] 25°. [h] Bromotoluenes, 51%. [i] Not determined.

demonstrated to be an intermediate in the reaction between benzoyl peroxide and chloride ion.[8-10] Two lithium chloride–peroxide runs were performed in an attempt to make benzoyl hypochlorite,[9] but the isomer distribution of the chlorotoluenes resulting indicated that either the hypochlorite had a similar selectivity in aromatic substitution to chlorine or that under the conditions used (even at low chloride:peroxide ratios) it reacted further with more chloride (eq 12) before it

$$C_6H_5\overset{O}{\overset{\|}{C}}OCl + Cl^- \longrightarrow Cl_2 + C_6H_5CO_2^- \qquad (12)$$

could react with the aromatic. Nitryl chloride proved to be an effective chlorinating agent under similar conditions and gave an isomeric composition of around 55% ortho and 45% para. Addition of lithium chloride to the nitryl chloride caused a slight shift in isomers toward that of molecular chlorine, indicating the probability of halogen formation as in eq 13. The

$$NO_2Cl + Cl^- \longrightarrow Cl_2 + NO_2^- \qquad (13)$$

chlorination isomer distribution from dinitrogen pentoxide–HCl was actually lower in ortho content than nitryl chloride, perhaps owing partly to the difference in the solvent utilized. Even though nitryl chloride, molecular chlorine, and benzoyl hypochlorite generated *in situ* do not differ too much in their selectivity toward toluene, the closer similarity of the benzoyl nitrate–chloride ion isomer distribution under optimum conditions to that of nitryl chloride suggests that this species is generated initially (eq 10 or 11). Nitryl chloride is known to preferentially chlorinate rather than nitrate aromatics.[16] In many instances at which higher lithium chloride:benzoyl nitrate ratios were used, molecular chlorine, formed subsequently (eq 13), probably served as the actual halogenating agent.

To determine how readily nitryl chloride can react with halide ion, equimolar amounts of hydrobromic acid and nitryl chloride were treated with toluene, and virtually only bromotoluenes resulted. This indicated that with bromide at least nitryl chloride reduction very favorably competed with aromatic chlorination.

It is interesting to note that with hydrochloric acid–benzoyl nitrate reactions the isomer distribution even at high acid:nitrate ratios was quite similar to that from nitryl chloride.

In a further attempt to distinguish between nitryl chloride and benzoyl hypochlorite as the initially formed reduction product, the benzoyl nitrate–chloride ion system was treated with cyclohexene. Previously, nitryl chloride had been reported to yield 2-chloro-1-nitrocyclohexane, 1,2-dichlorocyclohexane, 2-chlorocyclohexanol, and cyclohexen-3-ol as well as other minor products.[17,18] Presumably, radicals from homolysis of the nitryl halide add to the double bond or abstract an allylic hydrogen to account for these products,[17-20] although ionic intermediates have also been proposed.[21] In contrast, the major products recorded from cyclohexene–benzoyl hypochlorite (from tetramethylammonium chloride and benzoyl peroxide) were 2-chlorocyclohexyl benzoate (34%) and 1,2-dichlorocyclohexane (27%).[10] The former product is characteristic of the Prevost reaction.[22]

In the present study, the products from benzoyl nitrate and cyclohexene with both an excess and deficiency of chloride ions in mixed acetic acid–acetonitrile solvent were compared to those from cyclohexene with nitryl chloride–lithium chloride and benzoyl peroxide–lithium chloride under analogous conditions (Table V). The complex product mixture from benzoyl nitrate (which contained cyclohexen-3-ol acetate, 1,2-dichlorocyclohexane, 2-chlorocyclohexyl acetate, and 2-chloro-1-nitrocyclohexane as major products) very much resembled that from nitryl chloride, suggesting the intermediacy of nitryl chloride as the initial reduction product from the nitrate with

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TABLE V
CYCLOHEXENE TRAPPING REACTIONS[a]

Products	Retention time[b]	Reactants: $C_6H_5CONO_3$ + LiCl[c]	Reactants: NO_2Cl[d]	Reactants: $C_6H_5CO_2Cl$[e]
f	4.0	m[g]	m	m
f	4.3	m	m	m
Cyclohexen-3-ol acetate	6.6	M[g]	M	M
1,2-Dichlorocyclohexane[h]	7.8 + 8.8	M	M	<1
1-Nitrocyclohexene	9.9	m	m	
2-Chlorocyclohexyl acetate	12.8	M	M	M
2-Chloro-1-nitrocyclohexane	13.6	M	M	
f	17.4	m	m	<1
2-Chlorocyclohexyl benzoate	23.3[i]	*j*	*j*	M

[a] Cyclohexene:LiCl:oxidizing agent = 10:0.3–2:1, acetonitrile (25 ml)–acetic acid (25 ml) solvent, 60°, 24 hr. [b] On glpc column A, 160°; see Experimental Section. [c] Similar results with LiCl:nitrate ratios of 0.67 and 1.95. [d] Similar results with LiCl:NO_2Cl = 0.38 or NO_2Cl alone. [e] Similar results with LiCl:$(C_6H_5CO_2)_2$ = 0.63 and 2.02. [f] Not identified. [g] m = minor product (<10%); M = major product (>10%). [h] Mixture of cis and trans. [i] Programmed at 170–250° at 10°/min. [j] No higher boilers noted upon programming to 250°.

chloride. Apparently, benzoyl hypochlorite is not formed in the nitrate reduction; if it had been produced, 2-chlorocyclohexyl benzoate (a major product from the benzoyl hypochlorite–cyclohexene control, Table V) would have been noted.

Experimental Section

Reactions involving benzoyl nitrate were carried out using freshly prepared stock solutions in acetonitrile as described elsewhere.[3,12] Nitryl chloride was prepared according to a published procedure,[23] and also used as a stock solution in acetonitrile as was dinitrogen pentoxide.[3] In all reactions, the oxidant solution was added last to a solution of all the other components at the temperature desired. Although all reactions involving benzoyl nitrate–halide ion gave instantaneous indication of molecular halogen formation, they were allowed to react at the designated temperature until halogen decomposition was complete. At the end of the reactions the mixtures were analyzed directly by gas chromatography.

Varian Models 1400 and 600D (with flame ionization detectors) were used with the following columns: (A) 10 ft × 0.125 in. 20% SE-30/Chromosorb W-DMCS, 60/80 mesh; (B) 10 ft × 0.125 in. 10% OV-225/Suprelcoport, 80/100 mesh; (C) 6 ft × 0.125 in. 20% DEGS/Chromosorb W, 60/80 mesh.

Reaction product yields were determined by adding a known quantity of marker (*p*-chloroanisole, *p*-bromoanisole, or *p*-bromotoluene) to a one-tenth portion of the reaction mixture and analyzing by glpc (column A, 160–180°). The appropriate correction factors were used to convert area ratios to molar ratios and ultimately to product yields.[3] Yields were based on moles of product/mole of benzoyl nitrate (benzoyl peroxide, halogen, or nitryl chloride), and in all cases the table entries represent an average of at least duplicated runs in close agreement. Benzoic acid yields were determined in a number of representative reactions by titration, and were found to be quantitative based on starting aroyl nitrate.

Bromo- and chlorotoluene isomers were analyzed on glpc column B (100–150°) and column C (100°).

The products from the cyclohexene reactions were collected by way of preparative glpc (Varian Model 90-P, thermal conductivity detector, 6 ft × 0.25 in. 3% SE-30/Chromosorb W, 60/80 mesh) on concentrated reaction mixtures. Ir and nmr spectra were used to identify the products with comparison to authentic spectra performed where available. Semiquantitative amounts of each product (Table V) were obtained using glpc column A at 160°, with programming to higher temperatures in some cases.

Registry No.—Benzoyl nitrate, 6786-32-9; chloride ion, 16887-00-6; bromide ion, 24959-67-9; nitryl chloride, 13444-90-1.

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The Stereochemistry and Ultraviolet Spectra of Simple Nitrate Esters[1a]

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Eight simple representative nitrate esters (methyl nitrate, ethyl nitrate, *n*-propyl nitrate, isopropyl nitrate, *n*-butyl nitrate, *tert*-butyl nitrate, benzyl nitrate, and β-phenethyl nitrate) have been investigated by the extended Hückel molecular orbital (EHMO) method. The uv spectra of this set of compounds were recorded in heptane and resolved into a number of component bands as suggested by the EHMO calculations. The charge distributions of these molecules were calculated by an iterative charge consistency method.

Nitrate esters are used as propellants and explosives and as drugs for the relief of hypertension and *angina pectoris*. In synthetic work, the nitrato group (ONO_2) is frequently employed for blocking hydroxyl groups in molecules while the manipulation of other functional groups is carried out.

The physical and chemical properties of this interesting π-electron system have so far, however, received only brief attention in tne literature.[2] We report here theoretical and experimental investigations of the stereochemistry and uv spectra of methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, benzyl-, and β-phenethyl nitrates.

(1) (a) Presented in part at the 50th Canadian Chemical Conference of the Chemical Institute of Canada, June 4–7, 1967, Toronto. (b) On leave during 1971–1972 at the Department of Chemistry, University of York, Heslington, York, England.

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The well-known extended Hückel molecular orbital (EHMO) method[3] was applied to the above compounds; the input data consisted of the geometrical parameters of the molecules together with the exponents and matrix elements for the atomic orbitals. The bond lengths for the *C*-nitrato group (*C*-ONO_2) measured on methyl nitrate[4] were used (C–O = 1.43 Å, O–N = 1.36 Å, and N–O = 1.26 Å) and the data for alkyl and aryl groups were taken from published tables.[5] Bond angles were taken as either tetrahedral or 120° with the exception of the CON angle and the apical angle of the NO_2 portion of the nitrato group which were varied to calculate optimum values. The orbital exponents were estimated by Slater's rule[6] as H(1s) = 1.000, C(2s,sp) = 1.625, N(2s,2p) = 1.950, and O(2s,2p) = 2.275, and the matrix elements were taken as the negative of reported[7,8] ionization potentials (Table I). The results obtained by the EHMO method

TABLE I
ATOMIC ORBITAL IONIZATION POTENTIALS (eV) AS DIAGONAL MATRIX ELEMENTS

H	C[a]	N[b]	O[b]
1s, −13.60			
2s	−21.40	−26.00	−32.30
2p	−11.40	−13.40	−14.80

[a] Reference 6. [b] Reference 7.

were then used in the conformational and spectroscopic calculations. To obtain chemically meaningful net charges and dipole moments a previously proposed[9] charge iteration technique was employed.

The eight compounds were prepared according to published techniques.[10a] The uv spectra of the carefully purified samples were recorded from 30,000 to 47,500 cm^{-1} on 10^{-2}, 10^{-3}, and 10^{-4} molar solutions in heptane with a UNICAM SP. 800 spectrophotometer. The spectra were digitalized at 100-cm^{-1} intervals and then resolved into Gaussian component bands by a least-squares technique suggested by Stone.[10b] The number and to some degree the positions and intensities of the component bands were suggested by the EHMO results.

Results and Discussion

Stereochemistry.—To conserve computer time, complete potential surfaces were not calculated. Instead, the conformation of minimum energy was determined by the sequence of variations. For methyl nitrate the CON angle, β, was varied in conjunction with the ONO apical angle α and the rotation of the NO_2 group by the angle ϕ. A minimum was obtained with $\alpha = 122.8°$, $\beta = 130.2°$, the methyl group staggered, and the plane of the NO_2 group in the plane of the molecule. This predicted conformation of methyl nitrate is in agreement with that proposed by Dixon and Wilson.[11] The barrier to rotation of the nitrate group (ϕ) by 180° is 3.23 kcal/mol and the barrier to rotation of the methyl group (ϕ) by 120° is 0.20 kcal/mol.

For ethyl nitrate, θ_1, describing the rotation of the C–O bond, was also varied in addition to α, β, and ϕ. The terminal methyl group was assumed to be staggered ($\theta_2 = 60°$). A minimum was obtained for a completely staggered molecule with the nitrate group again in the plane of the C–C–O chain and $\alpha = 122.8°$, $\beta = 130.8°$. The barrier to rotation of the nitrate group (ϕ) by 180° is 3.53 kcal/mol.

On the basis of the results for methyl and ethyl nitrates the NO_2 group was assumed to be coplanar for *n*-propyl and *n*-butyl nitrates, α was assumed to be 122.8°, and β was taken to be the average of the results for methyl and ethyl nitrates, 130.5°. The methyl groups were assumed to be fully staggered. Only two isomers were considered for these two nitrates, the trans form ($\theta_2 = 0°$) and the gauche form ($\theta_2 = 120°$). The trans form was lower in energy by 0.36 kcal/mol for *n*-propyl nitrate and by 3.66 kcal/mol for *n*-butyl nitrate.

To select the minimum energy conformation of isopropyl nitrate the CON angle θ was again varied and the O–N and C–O bonds were rotated by ϕ and θ_1 respectively. The ONO apical angle was again assumed to be 122.8° and the methyl groups were staggered. The minimum was found for the NO_2 group coplanar with the C–O bond and the C–O bond rotated 29.5° out of a fully staggered conformation with $\beta = 133°$. The barrier to rotation of the nitrate group by 180° is 3.20 kcal/mol. The minimum with $\theta_1 = 29.5°$ is 0.08 kcal/mol below the energy for $\theta_1 = 0°$.

Only the CON angle β and rotation about the C–O bond were considered for *tert*-butyl nitrate. The conformation of minimum energy is a fully staggered molecule with the nitrate group coplanar and $\beta = 140°$.

The optimum value for the CON angle β increases with the size of the nitrate ester when varied. However, an increase or decrease in the optimum value for β by 2° raises the energy less than 0.05 kcal/mol.

Benzyl nitrate and β-phenethyl nitrate were considered in this study as examples of aryl nitrates and as phenyl-substituted methyl and ethyl nitrates, respectively. With increasing size of the molecule the computation becomes lengthy; hence calculations of only individual extreme conformations were performed, with $\alpha = 122.8°$ and $\beta = 130.5°$. For benzyl nitrate four conformations were considered, two with the benzene ring coplanar with the C–C–O–N chain and the nitrate group either coplanar or perpendicular to the plane of the C–C–O–N chain. The conformation of minimum energy was found to be that with the benzene ring and the nitrate group coplanar with the C–C–O–N chain. The two conformations with the plane of the benzene ring perpendicular to the plane of the nitrate group were at nearly the same energy and were 3.3 kcal/mol above the minimum. The maximum occurred when the plane of the benzene ring and the plane of the nitrate group were perpendicular to

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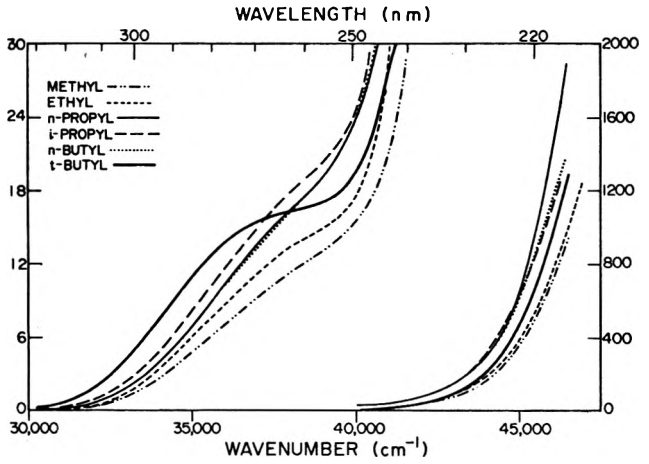

Figure 1.—Uv spectra of alkyl nitrate esters in heptane.

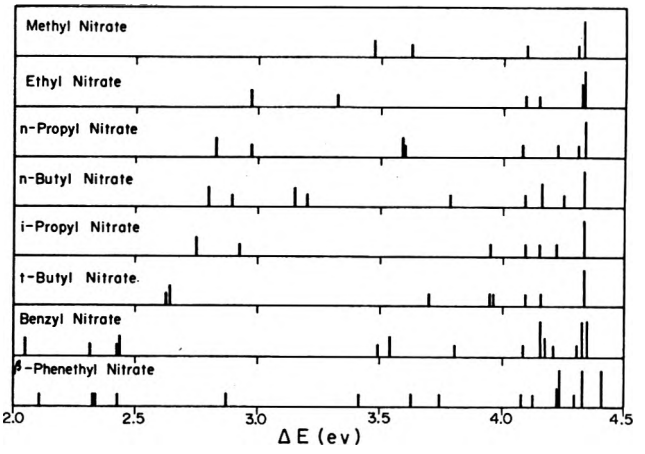

Figure 2.—Theoretical spectra of eight nitrate esters. Four classes of intensity are used. The lowest corresponds to $\pi_N^* \leftarrow \sigma$ excitations, the next highest to $\pi_N^* \leftarrow \pi'$, the 3rd highest to $\pi_N^* \leftarrow \pi$ or $\phi^* \leftarrow \phi$.

the plane of the C–C–O–N chain and was 6.9 kcal/mol above the minimum.

In the case of β-phenethyl nitrate it was assumed that the nitrate group was coplanar and two conformations were considered, one with the plane of the benzene ring perpendicular to the plane of the C–C–C–O–N chain and one with it coplanar. The conformation with the benzene ring perpendicular was lower in energy by 9.7 kcal/mol.

For the optimum conformations of all eight compounds as well as the sequence of geometrical optimization, see footnote 12.

Electronic Spectra.—The uv spectra of the six alkyl nitrates studied are presented in Figure 1. On inspection, a number of characteristics become apparent: (1) a progression can be seen with increasing *n*-alkyl chain length with the curves for *n*-propyl and *n*-butyl nitrates almost superimposable; (2) with increasing substitution on the α carbon (*i.e.*, methyl, ethyl, isopropyl, and *tert*-butyl nitrates) progression occurs for the first three compounds but the spectrum of *tert*-butyl nitrate is quite different from the others. This effect is easily explained if we assume the presence of a low intensity band progressively shifted to lower energy through the series methyl, ethyl and isopropyl nitrates. This would have the effect of increasing the intensity of the "bump" on the high intensity band and for *tert*-butyl nitrate the shift would be sufficient to appear as a band separation, with decreased intensity in the intermediate region.

The uv spectra of the two aralkyl nitrates studied (not shown in Figure 1) have the added complication that a benzenoid absorption possessing vibrational fine structure is superimposed on the excitation pattern associated with the nitrato group.

To analyze the spectra, the molecular orbital energy levels were used to construct theoretical spectra. Estimates of the relative intensities of the transitions were made from inspection of the coefficient matrices. All of these compounds except isopropyl nitrate possess a plane of symmetry in the plane of the carbon chain and nitrate group. The MO's can be classified as σ or π with respect to this plane. Among the π MO's several different types could be distinguished; those localized on the nitrato group were designated as π_N, those delocalized over the molecule as a whole but with larger coefficients on the nitrato group were classified as π, those delocalized over the whole molecule but with larger coefficients on the carbon atoms as π′, and those localized on the benzene ring were designated by φ. Some MO's localized on the nitrato group were also identified as being similar to n type MO's of the nitrate ion[13] and hence were classified as n. Other MO's which were delocalized over the entire molecule were classified as σ MO's.

The theoretical spectra of the eight nitrate esters, presented schematically in Figure 2, were calculated by taking all possible differences of the MO energy levels listed in Table II. The intensity scale shown is arbitrary; however, three classes of intensities were selected on the basis of MO type (σ, n, π_N, π, π′, or φ). The highest corresponds to $\phi^* \leftarrow \phi$ or $\pi_N^* \leftarrow \pi$ type excitations, the medium to $\pi_N^* \leftarrow \pi'$, and the lowest to $\pi_N^* \leftarrow \sigma$, $\pi_N^* \leftarrow$ n, or $\phi^* \leftarrow$ n excitations.

The resolved spectra of the six aliphatic nitrates are shown in Figure 3. The first $\pi_N^* \leftarrow \pi$ excitation was assumed to correspond to the high intensity absorption at the high energy end of the spectra and hence the bands used to resolve the spectra were cut off at this point. The resolution of the spectra of the aralkyl nitrates was considerably more complex owing to the vibrational structure in the benzenoid absorption. For this reason the vibrational bands of the corresponding alcohols plus a high energy electronic band probably corresponding to a $\phi^* \leftarrow \phi$ type excitation were resolved as shown in the two upper diagrams of Figure 4 and the band parameters are summarized elsewhere.[12]

The same number of vibrational bands was then assumed for the corresponding aralkyl nitrates in addition to the electronic bands suggested by the MO pattern (Table II). The first predicted $\phi^* \leftarrow \phi$ excitation for the nitrates was assumed to give rise to

(12) Optimized conformations, net atomic changes, and geometry variations (Figures A and B) as well as band parameters resolved from the experimental uv spectra of selected nitrate esters (Tables A–F) will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2281.

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TABLE II

EXCITATION ENERGIES OF NITRATE ESTERS (UP TO 5 eV) PREDICTED FROM THE EHMO ENERGY LEVELS[a]

Methyl		Ethyl		Benzyl		β-Phenethyl	
Transition	ΔE, eV	Transition	ΔE, eV	Transition	ΔE, eV	Transition	ΔE, eV
$2\pi_N^* \leftarrow 3\pi'$	3.40	$2\pi_N^* \leftarrow 4\pi'$	2.969	$3\pi_N^* \leftarrow \phi_{+1}$	2.051	$3\pi_N^* \leftarrow \phi_{+1}$	2.112
$2\pi_N^* \leftarrow 9\sigma$	3.622	$2\pi_N^* \leftarrow 12\sigma$	3.319	$3\pi_N^* \leftarrow 19\sigma$	2.315	$3\pi_N^* \leftarrow 21\sigma$	2.330
$2\pi_N^* \leftarrow 2n$	4.095	$2\pi_N^* \leftarrow 1n$	4.087	$3\pi_N^* \leftarrow 18\sigma$	2.424	$3\pi_N^* \leftarrow \phi_{-1}$	2.333
$2\pi_N^* \leftarrow 1n$	4.313	$2\pi_N^* \leftarrow 11\sigma$	4.141	$3\pi_N^* \leftarrow \phi_{-1}$	2.431	$3\pi_N^* \leftarrow \phi_0$	2.431
$\pi_N^* \leftarrow 1\pi_N$	4.336	$2\pi_N^* \leftarrow 3\pi$	4.319	$3\pi_N^* \leftarrow 17\sigma$	3.493	$3\pi_N^* \leftarrow 20\sigma$	2.869
$2\pi_N \leftarrow 8\sigma$	5.057	$2\pi_N^* \leftarrow 1\pi_N$	4.337	$3\pi_N^* \leftarrow 3\pi$	3.540	$3\pi_N^* \leftarrow 19\sigma$	3.415
		$2\pi_N^* \leftarrow 10\sigma$	4.524	$3\pi_N^* \leftarrow 16\sigma$	3.807	$3\pi_N^* \leftarrow 18\sigma$	3.632
		$2\pi_N^* \leftarrow 9\sigma$	4.611	$3\pi_N^* \leftarrow 3n$	4.087	$3\pi_N^* \leftarrow 17\sigma$	3.741
				$\phi_{-2} \leftarrow \phi_{+1}$	4.157	$3\pi_N^* \leftarrow 3n$	4.077
				$3\pi_N^* \leftarrow 2\pi'$	4.173	$3\pi_N^* \leftarrow 2n$	4.128
				$3\pi_N^* \leftarrow 15\sigma$	4.210	$3\pi_N^* \leftarrow 1\pi'$	4.224
				$3\pi_N^* \leftarrow 2n$	4.308	$\phi_{-2} \leftarrow \phi_{+1}$	4.224
				$3\pi_N^* \leftarrow 2\pi_N$	4.335	$3\pi_N^* \leftarrow 1n$	4.296
				$\phi_{+2} \leftarrow \phi_{+1}$	4.396	$3\pi_N^* \leftarrow 2\pi_N$	4.336
				$\phi_{-2}^* \leftarrow 19\sigma$	4.421	$\phi_{+2} \leftarrow \phi_{+1}$	4.409
				$\phi_{-2}^* \leftarrow 18\sigma$	4.530	$\phi_{-2} \leftarrow 21\sigma$	4.442
				$\phi_{-2}^* \leftarrow \phi_{-1}$	4.537	$\phi_{-2}^* \leftarrow \phi_{-1}$	4.445
				$3\pi_N^* \leftarrow 1n$	4.577	$3\pi_N^* \leftarrow 2\pi$	4.470
				$\phi_{+2}^* \leftarrow 19\sigma$	4.660	$\phi_{-2}^* \leftarrow \phi_0$	4.543
				$\phi_{+2}^* \leftarrow 18\sigma$	4.769	$\phi_{+2} \leftarrow 21\sigma$	4.627
						$\phi_{+2}^* \leftarrow \phi_{-1}$	4.036

n-Propyl		n-Butyl	
Transition	ΔE, eV	Transition	ΔE, eV
$2\pi_N^* \leftarrow 5\pi'$	2.831	$3\pi_N^* \leftarrow 5\pi'$	2.793
$2\pi_N^* \leftarrow 13\sigma$	2.970	$3\pi_N^* \leftarrow 14\sigma$	2.889
$2\pi_N^* \leftarrow 4\pi'$	3.587	$3\pi_N^* \leftarrow 4\pi'$	3.151
$2\pi_N^* \leftarrow 12\sigma$	3.592	$3\pi_N^* \leftarrow 13\sigma$	3.195
$2\pi_N^* \leftarrow 2n$	4.079	$3\pi_N^* \leftarrow 12\sigma$	3.788
$2\pi_N^* \leftarrow 11\sigma$	4.216	$3\pi_N^* \leftarrow 3n$	4.089
$2\pi_N^* \leftarrow 1n$	4.309	$3\pi_N^* \leftarrow 3\pi$	4.160
$2\pi_N^* \leftarrow 1\pi_N$	4.337	$3\pi_N^* \leftarrow 2n$	4.255
$2\pi_N^* \leftarrow 3\pi$	4.770	$3\pi_N^* \leftarrow 2\pi_N$	4.336
$2\pi_N^* \leftarrow 10\sigma$	4.982	$3\pi_N^* \leftarrow 1n$	4.547
		$3\pi_N^* \leftarrow 11\sigma$	4.959

Isopropyl		tert-Butyl	
Transition	ΔE, eV	Transition	ΔE, eV
$3\pi_N^* \leftarrow 1\pi'$	2.776	$3\pi_N^* \leftarrow 19\sigma$	2.628
$3\pi_N^* \leftarrow 16\sigma$	2.928	$3\pi_N^* \leftarrow 1\pi'$	2.637
$3\pi_N^* \leftarrow 15\sigma$	3.947	$3\pi_N^* \leftarrow 18\sigma$	3.705
$3\pi_N^* \leftarrow 2n$	4.090	$3\pi_N^* \leftarrow 17\sigma$	3.951
$3\pi_N^* \leftarrow 1n$	4.152	$3\pi_N^* \leftarrow 16\sigma$	2.963
$3\pi_N^* \leftarrow 14\sigma$	4.221	$3\pi_N^* \leftarrow 2n$	4.098
$3\pi_N^* \leftarrow 2\pi_N$	4.338	$3\pi_N^* \leftarrow 1n$	4.164
$3\pi_N^* \leftarrow 13\sigma$	4.338	$3\pi_N^* \leftarrow 2\pi_N$	4.336
$3\pi_N^* \leftarrow 12\sigma$	4.699	$3\pi_N^* \leftarrow 15\sigma$	4.487
$3\pi_N^* \leftarrow 11\sigma$	4.930	$3\pi_N^* \leftarrow 14\sigma$	4.551
		$3\pi_N^* \leftarrow 13\sigma$	4.949

[a] Only those modes of excitation which are above the rules were included in the spectral resolution.

TABLE III

DIPOLE MOMENTS (DEBYE) OF EIGHT NITRATE ESTERS

		Calcd[a]				Exptl[b]
Registry no.	Compd	M_x	M_y	M_z	$\|M\|$	$\|M\|$
598-58-3	Methyl nitrate	−4.58	0	2.29	5.12	2.88[c,d]
625-58-1	Ethyl nitrate	−5.02	0	2.03	5.42	2.96[e]
627-13-4	*n*-Propyl nitrate	−5.07	0	2.20	5.53	2.98[d]
928-45-0	*n*-Butyl nitrate	−5.10	0	2.13	5.53	2.99[d]
1712-64-7	Isopropyl nitrate	−5.18	−0.22	2.04	5.57	
926-05-6	*tert*-Butyl nitrate	−5.12	0	2.22	5.58	
15285-42-4	Benzyl nitrate	−4.42	0	2.15	4.91	
39835-32-0	β-Phenethyl nitrate	−4.42	0	2.08	5.43	

[a] Calculated from the point charges which in turn were obtained by the charge iteration technique. [b] Measured in benzene. [c] Dixon and Wilson[11] measured a value of 3.10 D in the gaseous phase. [d] Reference 17. [e] Reference 18.

the vibrational structure and so was not included in the resolution as a separate electronic transition. The second predicted $\phi^* \leftarrow \phi$ excitation which occurs after the first $\pi_N^* \leftarrow \pi$ excitation was thought to be the electronic transition which was assumed to be present in the alcohol spectra. Thus the high intensity of the high energy absorption of the aralkyl nitrates is due to both the $\pi_N^* \leftarrow \pi$ and the $\phi^* \leftarrow \phi$ excitations. The vibrational bands of the nitrate esters after optimization are given in the two lower diagrams of Figure 4. The broken lines on these spectra correspond to the gross absorption minus that of the vibrational bands. The component Gaussian bands associated with the absorption of the nitrato chromophore (the broken lines in Figure 4) are reproduced in Figure 5. A schematic representation of all the spectral resolution work is shown in Figure 6 and the detailed characteristics of the spectral components are listed elsewhere.[12]

It cannot, of course, be conclusively demonstrated in this manner that the simple-looking experimental curves (Figure 1) have indeed such unique complex structures as shown (Figures 3 and 5) (*e.g.*, that *tert*-butyl nitrate has eight bands). However, conversely, we do demonstrate that a complex band pattern can have a simple envelope curve. The error curves (observed–calculated curve) were less than 0.5 intensity unit for the curve

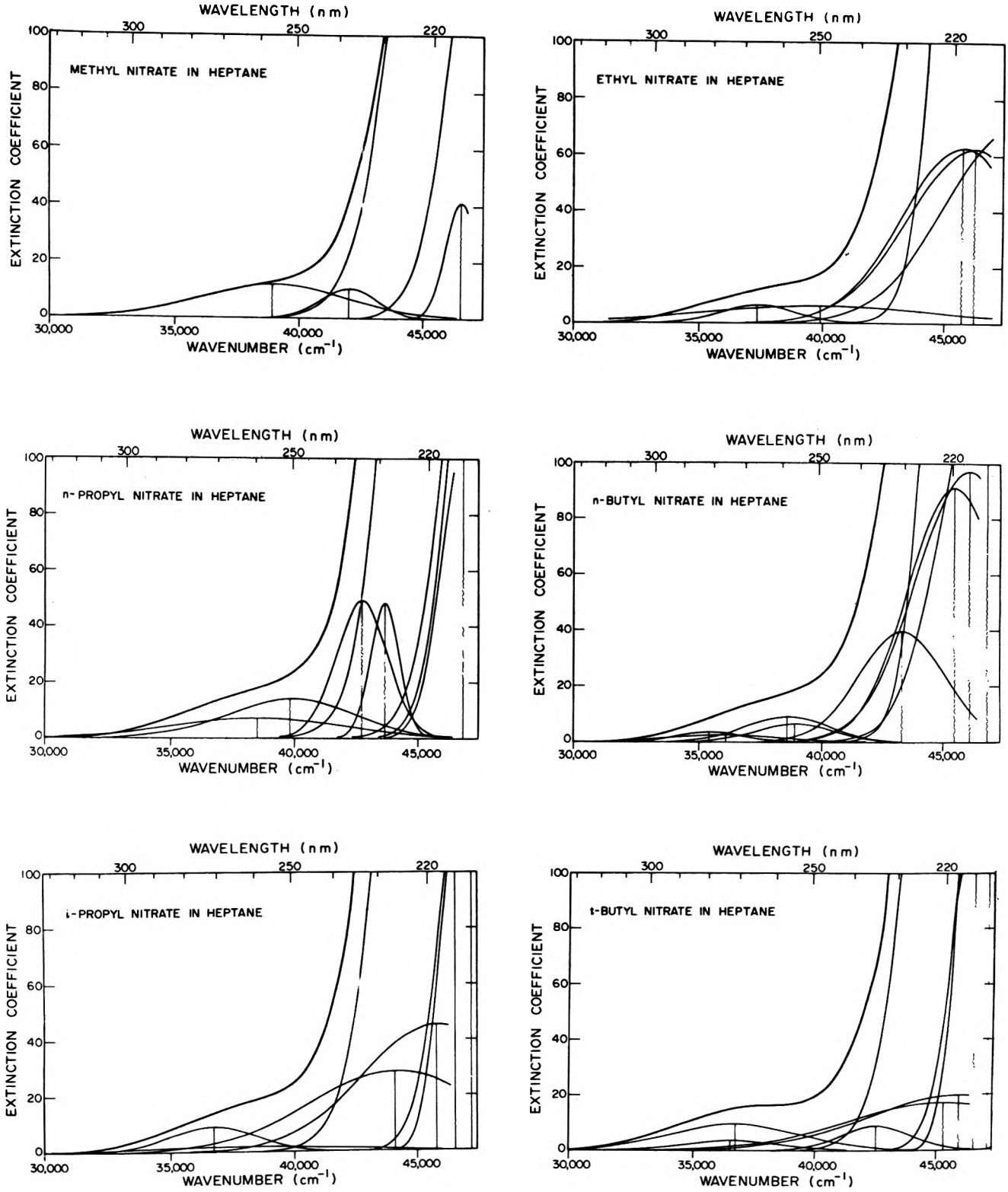

Figure 3.—Uv spectra of the aliphatic nitrate esters resolved to Gaussian component bands corresponding to the individual modes of excitation.

with $\epsilon < 200$ and not more than 5 intensity units for the entire curve up to ϵ 1400–2000.

As previously stated the number of bands was chosen to agree with the number predicted by the EHMO calculation keeping in mind the previous success of the EHMO method in this area.[14-16]

(14) K. S. Sidhu, I. G. Csizmadia, O. P. Strausz, and H. E. Gunning, *J. Amer. Chem. Soc.*, **88**, 2412 (1966).

(15) S. A. Houlden and I. G. Csizmadia, *Tetrahedon*, **25**, 1137 (1969).

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Charge Distribution.—The total electron distributions, which are of the same shape as the molecules, are of no particular interest. However the net charges, as obtained by Mulliken's population, have been computed and they are in agreement with expectations.[12]

The numerical values of the dipole moments (calculated from the point charges) are summarized in Table III. As might be expected the computed dipole moments are systematically larger than the experi-

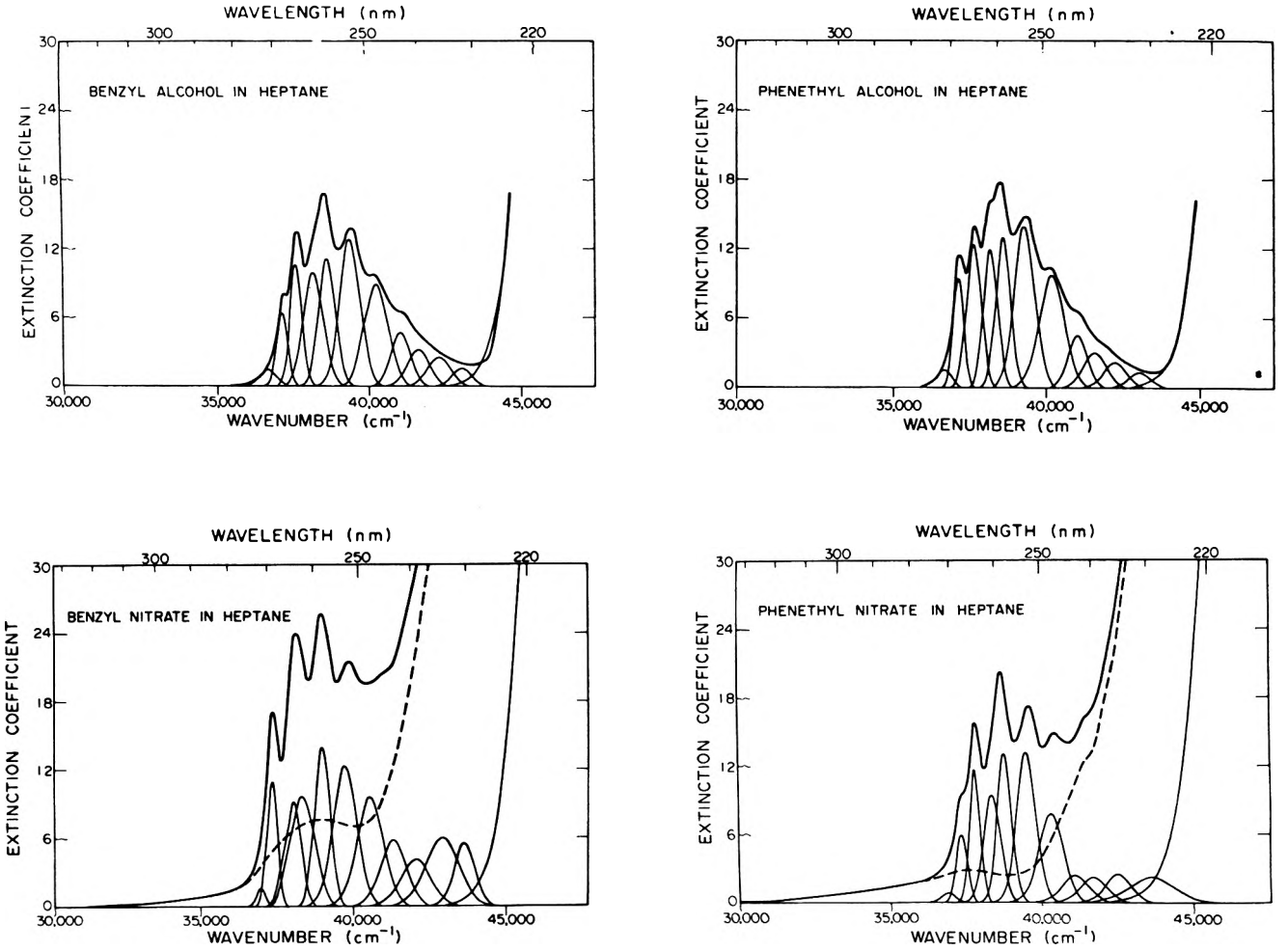

Figure 4.—Vibrational structure plus an electronic band of the benzenoid absorption in aryl alcohols and their corresponding nitrates. The broken line represents the total absorption associated with the nitrato group.

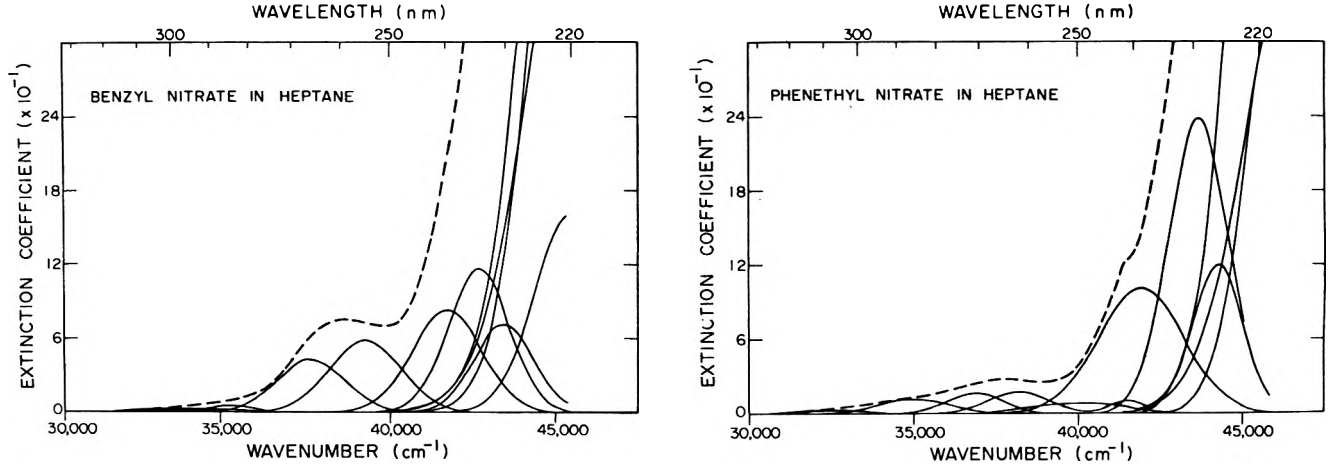

Figure 5.—Gaussian component bands of the nitrato absorption in aralkyl nitrates.

mental values;[17,18] nevertheless they show the same tendency to increase with the length of the alkyl chain as is apparent in the experimentally measured values.

Conclusions

A number of problems have been raised and possible answers have been offered in this paper.

One question concerns the preferred conformation of nitrate esters. For some time it was established[4,19-21] that the α-carbon atom in nitrate esters lies in a plane perpendicular to the nitrato group. Later Dixon and Wilson[11] suggested that the α carbon in methyl nitrate is coplanar with the ONO_2 moiety. The present results are in agreement with the latter observations.

Secondly it has been suggested that the tail of the long wavelength absorption in the uv spectrum is due to

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(21) T. C. W. Mak and J. Trotter, *Acta Crystallogr.*, **17**, 367 (1964).

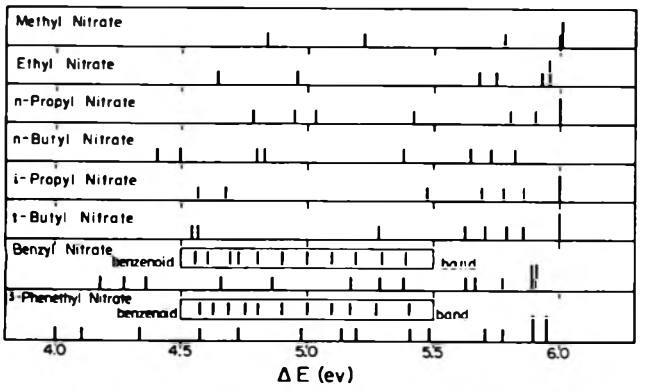

Figure 6.—A schematic representation of the nitrato absorption in aralkyl nitrates. High intensity bands correspond to $\pi_N^* \rightarrow \pi_N$ and $\phi^* \leftarrow \phi$ excitations.

the $\pi_N^* \leftarrow$ n mode of excitation.[22,23] Very recently the discovery of a second, higher energy, $\pi_N^* \leftarrow$ n band in the circular dichroism spectrum has been reported.[24] The present work indicates the presence of still more low intensity bands in this region, some of which are associated with a charge transfer from the alkyl or aryl group to the nitrato π_N^* orbitals. From this viewpoint the photochemical reactions[25-28] of nitrate esters ($RONO_2$) may be associated with an excited dipolar species $R^{\delta+}ONO_2^{\delta-}$, the chemical behavior of which must be *more* than a mere superimposition of the properties of the cation (R^+ONO_2) generated in the mass spectrometer and the anion ($RONO_2^-$) generated by electrolytic or chemical reductions. It is hoped that the information provided here will aid in the interpretation of the photochemical reactions.

Finally the electron distribution which indicated a net positive charge on nitrogen and carbon as well as α and β hydrogens is in agreement with the reaction mechanistic conclusions[29-32] of base-catalyzed reactions while the net negative charge on the three oxygen atoms predicts the sites of protonation which occur during acid catalyzed reactions.

Registry No.—Benzyl alcohol, 100-51-6; β-phenethyl alcohol, 60-12-8.

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Reactions of Enaminonitriles with Phosgene. Synthesis of Enaminocarboxylic Acid Chlorides

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Reactions of enaminonitriles with phosgene have been investigated. Enaminonitriles with an α hydrogen or α halogen gave enaminocarboxylic acid chlorides in moderate to good yields together with low yields of isocyanates. Reactions of enaminonitriles with an α-cyano or α-ethoxycarbonyl group resulted in the quantitative recovery of the starting materials. The acid chlorides obtained were characterized by spectral analyses and by conversion to derivatives such as esters and amides.

Halleux and Viehe[1] have recently reported the formation of enaminocarboxylic acid chlorides from reactions of tertiary enamines with phosgene in the presence of triethylamine. However, isolation of the acid chlorides was unsuccessful because of their instability, and therefore they were identified by conversion to derivatives such as esters and amides.

In the course of our studies on the reactions of enaminonitriles with phosgene,[2] we have found that enaminonitriles possessing an α halogen gave relatively stable enaminocarboxylic acid chlorides. We have succeeded in their isolation and have characterized them by spectral analyses and by conversion to esters or amides.

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Results and Discussion

Treatment of enaminonitriles **1a–f** with phosgene in refluxing ethyl acetate gave enaminocarboxylic acid chlorides **2a–d** in moderate to good yields (Table I). It is of much interest that in addition to **1a** enaminonitriles **1e** and **1f** possessing an α halogen also gave acid chloride **2a**. However, reactions of **1i** and **1j** with phosgene resulted in the quantitative recovery of the starting materials. The acid chlorides **2a–d** are either

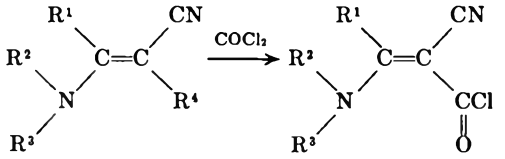
TABLE I

ENAMINOCARBOXYLIC ACID CHLORIDES[a]

Compd[b]	Yield, %	State	Mp,[c] °C	Ir,[d] cm⁻¹ C≡N	C=O	C=C	Nmr,[e] δ (ppm)	λmax (CH3CN), nm (ε × 10⁻⁴) Acid chloride	Starting nitrile (no.)
2a	64 (from 1a) 48 (from 1e) 31 (from 1f)	Powder	130–132	2220	1700	1655	2.34 (s, 3 H), 7.20 (br, 0.7 H) 8.90 (br, 0.7 H)	288 (1.63)	(1a)[g] 255 (1.24) (1e) 254 (1.66)
2b	72	Powder	140	2216	1690	1625	*ca.* 7.55 (m, 5 H), 8.45 (br, 0.7 H), 9.25 (br, 0.7 H)	306 (1.52), 243 (sh) (0.47)	(1b) 289 (1.02), 225 (1.08)
2c	67	Needles	~140	2212 (2220	1710 1682	1570 1577)	2.34 (s, 3 H), 7.30 (m, 5 H), 11.35 (br s, 1 H)	308 (2.09), 222 (1.17)	(1c) 287 (1.64), 225 (sh) (0.83)
2d	88	Needles	85–87	2210	1690	1585	2.40 (s, 3 H), 4.60 (d,[f] 2 H, J = 6.0 Hz), 7.25 (m, 5 H), 10.10 (br s, 1 H)	301 (2.03)	(1d) 258 (1.98), 205 (0.74)
2g		Viscous liquid		2205	1708	1565	2.50 (s, 3 H), 3.34 (s, 6 H)		
2h		Viscous liquid		2205	1713	1550	2.54 (s, 3 H), 3.22 (s, 3 H), 4.78 (s, 2 H)		

[a] Satisfactory analytical values (±0.3% for C, H, and N) were obtained for **2a–d**. [b] Recrystallization solvents: **2a–c**, AcOEt; **2d**, C_6H_6–CCl_4 2:1 (v/v). [c] **2a**, **2b**, and **2d** decompose at their melting points. **2c** begins to decompose at *ca.* 140° without melting. [d] **2a–d**, KBr; **2g**, **2h**, and **2c** (data in parentheses), $CDCl_3$. [e] Solvents: **2a**, liquid SO_2 (measured at −25°); **2b**, AcOEt; **2c**, **2d**, **2g**, and **2h**, $CDCl_3$. [f] Coupling with a NH proton. [g] J. J. Conn and A. Taurins, *Can. J. Chem.*, **31**, 1211 (1953).

powder-like or crystalline solids and all of them decompose at their melting points. In addition, **2a** and **2b** are very sensitive to moisture. Results are summarized in Table I.



1a–j cis or trans **2a–d, 2g, 2h**

a, $R^1 = CH_3$; $R^2 = R^3 = R^4 = H$ **b**, $R^1 = C_6H_5$; $R^2 = R^3 = R^4 = H$
c, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = R^4 = H$ **d**, $R^1 = CH_3$; $R^2 = C_6H_5CH_2$; $R^3 = R^4 = H$
e, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = Cl$ **f**, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = Br$
g, $R^1 = R^2 = R^3 = CH_3$; $R^4 = H$ **h**, $R^1 = R^2 = CH_3$; $R^3 = C_6H_5CH_2$; $R^4 = H$
i, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = CN$ **j**, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = CO_2C_2H_5$

The structures of the acid chlorides **2** were confirmed on the basis of ir, nmr, uv, and mass spectra and elemental analyses. Ir spectra of **2a–d** showed conjugated C≡N, C=O, and C=C stretching bands at 2210–2220, 1690–1710, and 1585–1655 cm^{-1}, respectively. The unusually low frequencies of the absorptions due to the carbonyl groups compared to ordinary acid chlorides are reasonable in view of their conjugations with double bonds of enamines. The ir spectrum of **2a** (CH_3CN solution) showed two NH absorptions at 3250 and 3390 cm^{-1} characteristic of primary amines.

Nmr spectra of **2a–d** showed one or two broad signals assignable to NH protons in low fields. Further, all the nmr spectra of **2a**, **2c**, and **2d** showed a singlet assignable to methyl protons attached to a double bond carbon atom. This shows that the acid chlorides are composed of only one geometrical isomer (cis or trans).

Uv absorption maxima of **2a–d** were observed at longer wavelengths than those of the corresponding starting enaminonitriles as a result of spread of conjugated systems.

Mass spectra of **2a–c** showed molecular ion peaks, and molecular weights of **2c** and **2d** measured by VPO (benzene solutions) agreed closely with the calculated values.[3]

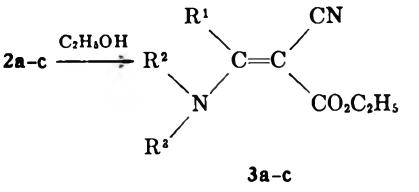
Reactions of **2a–c** with ethanol gave the corresponding enamino esters **3a–c** in high yields (Table II). Ester

TABLE II

ENAMINO ESTERS[a]

Compd	Yield, %	Mp, °C	Recrystn solvent
3a	86	192–193[b]	EtOH
3b	95	125–126	EtOH
3c	93	82–85	*n*-Hexane

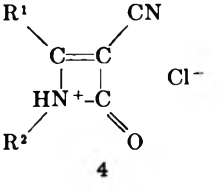
[a] Satisfactory analytical values (±0.3% for C, H, and N) were obtained for **3a–c**. Ir, nmr, and mass spectral data were consistent with the enaminoester structures. [b] Mp 190°: R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 357 (1946).



3a–c

3a was identified by comparison with an authentic sample[4] and others were characterized by their ir, nmr, and mass spectra and elemental analyses.

It is concluded, on the basis of the above data, that the products have enaminocarboxylic acid chloride structures. The alternative structure **4** when $R^3 = H$, can be excluded on the basis of the low carbonyl stretch-



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(3) Molecular weight: **2c**, found 217 (calcd 221); **2d**, found 224 (calcd 235).

(4) R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 357 (1946).

It may be explained in the same way that the acid chlorides **2**, in spite of the high reactivity between carboxylic acid chlorides and amines, can possess an amino group in the same molecule without further cyclization to azetinone hydrochloride **4**.

It is of much interest to know interactions between amino and chloroformyl group of the acid chlorides in solid states. Thus, the analysis of their crystal structures by X-ray diffraction is now in progress.

Experimental Section[15]

Materials.—Enaminonitriles **1a–d**[16,17] and **1g–j**[4,9,10] were prepared according to the known methods: **1d**, mp 78–80°, **1i**, 230–231°; **1g**, bp 110–113° (2.5 mm), **1h**, 150–155° (0.15 mm). **1e** (mp 120–121°) was obtained by chlorination of **1a** with NaOCl in water. **1f** (mp 120–123°) was prepared by reaction of **1a** with Br_2 in aqueous Na_2CO_3.

Reaction of Enaminonitrile with Phosgene.—A typical procedure is as follows. In a 100-ml round-bottomed four-necked flask, equipped with a stirrer, a condenser, a dropping funnel, and a gas inlet tube, 30 ml of AcOEt was placed and it was saturated with phosgene under reflux. Enaminonitrile **1d** (4.3 g, 25 mmol) in 20 ml of AcOEt was added to the solution in 15 min; then the reaction mixture was heated under reflux with stirring for an additional 35 min. The introduction of phosgene was continued throughout these procedures. After phosgene was purged with dry N_2, the solvent was removed under reduced pressure to give a yellow solid, which was washed with a small amount of CCl_4 and dried *in vacuo*, giving a yellow powder of **2d** (5.2 g, 88%). The acid chloride was recrystallized from C_6H_6–CCl_4 (2:1, v/v) to give colorless needles.

The solvent was removed from the CCl_4 washings to give a viscous liquid, which was extracted with hexane to give benzyl isocyanate (**12**) (0.12 g) after removal of the solvent. The isocyanate was treated with aniline (0.3 g) in CCl_4 to give *N*-benzyl-*N'*-phenylurea (0.18 g, 3%).

Crystallizations of all the acid chlorides were carried out in a dry atmosphere.

Reaction of Acid Chloride 2 with EtOH.—A typical procedure is as follows. EtOH (5.1 g) was rapidly added to a solution of acid chloride **2b** (0.5 g, 2.4 mmol) in 10 ml of AcOEt at room temperature; then the mixture was stirred for 1 hr. After evaporation of the solvent under reduced pressure, the resulting residue was washed with water and dried *in vacuo*, giving a yellow powder of **3b** (0.5 g, 95%).

Reaction of 1g with Phosgene. Isolation of 5 and 6.—Treatment of nitrile **1g** (3.0 g, 27 mmol) with phosgene in AcOEt gave 3.3 g of a reddish viscous liquid (**2g**). The product was dissolved in 20 ml of CH_2Cl_2 and was added to a solution of aniline (5.3 g, 57 mmol) in 20 ml of CH_2Cl_2 in 30 min at room temperature; then the mixture was allowed to stand overnight at room temperature. The aniline hydrochloride formed was filtered off and the solvent was removed under reduced pressure, giving a viscous liquid. A small amount of CCl_4 was added to it and the solution was allowed to stand overnight in a refrigerator. The precipitates formed were filtered, washed with water, and dried *in vacuo*, giving a yellow powder of **5** (0.52 g), which was recrystallized from *i*-PrOH to give yellow prisms, mp 141–142° dec. After evaporation of CCl_4 from the filtrate, the residue was dissolved in a small amount of AcOEt, the solution being allowed to stand overnight in a refrigerator. The precipitates formed were filtered and dried *in vacuo*, giving 2.3 g of a mixture of **5** and **6** (content of **5**, 0.46 g, content of **6**, 1.84 g) (determined by nmr), which was crystallized from I-PrOH to give yellow prisms of **6**, mp 139–142° dec.

Anilide **5** had ir (Nujol) 2170 (C≡N), 1663 (C=O), 1598, 1563, and 1526 cm^{-1}; nmr ($CDCl_3$) δ 2.42 (s, 3 H), 3.13 (s, 6 H), 7.0–7.6 (m, 5 H), and 7.7 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 229 (21, M^+), 212 (10), 61 (100), and 56 (15).

Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.15; H, 6.66; N, 18.63.

Anilide **6** had ir (Nujol) 2185 (C≡N), 1635 (C=O), 1592, 1573, and 1523 cm^{-1}; nmr ($CDCl_3$) δ 2.28 (s, 3 H), 6.9–7.1 (m, 10 H), 7.65 (br s, 1 H), and 12.42 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 277 (48, M^+), 185 (64), 118 (16), 93 (100), and 77 (19).

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.77; H, 5.41; N, 15.17.

Reaction of 1h with Phosgene.—Treatment of **1h** (3.7 g, 20 mmol) with phosgene in AcOEt gave 5.3 g of a reddish, viscous liquid (**2h**).

3-Isocyanato-2,2,3-trichlorobutyronitrile (**8**).—Enaminonitrile **1e** (11.7 g, 100 mmol) was treated with phosgene in AcOEt by the same method as described above. On removal of the solvent from the reaction mixture was obtained a yellow, moist solid, which was washed with 50 ml of CCl_4 and dried *in vacuo*, giving a yellow powder of **2a** (6.0 g, 48%). The solvent was removed from the CCl_4 washings to give a yellow liquid, which was distilled under reduced pressure to give isocyanate **8** (colorless liquid) (3.9 g, 18%): bp 80–82° (20 mm); ir (liquid film) 2260 cm^{-1} (NCO); nmr (CCl_4) δ 2.25 (s); mass spectrum (70 eV) *m/e* (rel intensity) 178 (8, $M^+ + 2 - HCl$), 176 (22, $M^+ - HCl$), 142 (49, $M^+ - Cl_2$), and 141 (100, $M^+ - HCl - Cl$).

Anal. Calcd for $C_5H_3N_2OCl_3$: C, 28.13; H, 1.42; N, 13.12; Cl, 49.83. Found: C, 28.46; H, 1.26; N, 13.44; Cl, 49.60.

***N*-Phenyl-*N'*-phenylcarbamoylacetamidine** (**10**).—A solution of aniline (1.3 g, 14 mmol) in 5 ml of CCl_4 was added to a solution of isocyanate **8** (0.94 g, 4.4 mmol) in 20 ml of CCl_4 in 5 min under ice cooling and the solution was stirred for 30 min. Then the reaction mixture was allowed to stand overnight at room temperature. The precipitates formed were filtered, washed with CCl_4 and water successively, and dried *in vacuo*, giving a tan powder of **10** (0.79 g, 77%), which was recrystallized from CH_3CN and MeOH successively, giving colorless needles: mp 186–189°; ir (Nujol) 1715, 1650, 1600, and 1565 cm^{-1}; nmr (DMSO-d_6) δ 2.07 (s, 3 H), 6.2–7.8 (m, 10 H), and *ca.* 9.5 (br, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 253 (8, M^+), 134 (39), 119 (100), 93 (64), 91 (11), and 77 (36).

Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.99; N, 16.59. Found: C, 71.14; H, 5.80; N, 16.62.

Preparation of Amidine 10 from *N*-Phenylacetamidine and Phenyl Isocyanate.[12]—A solution of phenyl isocyanate (0.6 g, 5.0 mmol) in 2 ml of ether was added to a solution of *N*-phenylacetamidine[18] (0.7 g, 5.2 mmol) in 10 ml of ether in 5 min at room temperature; then the reaction mixture was stirred for 30 min. The precipitates formed were filtered, washed with ether, and dried *in vacuo* to give 1.2 g (94% based on phenyl isocyanate) of **10**, mp 189–190° (from MeOH).

Registry No.—**1a**, 1118-61-2; **1b**, 1823-99-0; **1c**, 25354-49-8; **1d**, 39603-75-3; **1e**, 39603-76-4; **1f**, 39603-77-5; **1g**, 39603-78-6; **1h**, 39603-79-7; **2a**, 39603-80-0; **2b**, 39603-81-1; **2c**, 39603-82-2; **2d**, 39603-83-3; **2g**, 39603-84-4; **2h**, 39603-85-5; **3a**, 39603-86-6; **3b**, 3336-69-4; **3c**, 22990-46-1; **5**, 39603-89-9; **6**, 39603-90-2; **8**, 39603-91-3; **10**, 32772-96-6; phosgene, 75-44-5; ethanol, 64-17-5.

(15) Melting points were determined on a Yanagimoto micromelting point apparatus and were corrected. Boiling points were uncorrected. Nmr spectra were obtained using a JNM-G-60 spectrometer (Japan Electronic Optics Laboratory Co.) with tetramethylsilane as an internal reference. Ir spectra were recorded on a Japan Electroscopic IR-E spectrophotometer or on a Hitachi 225 spectrophotometer equipped with gratings. Mass spectra were recorded on a Hitachi RMU-6E spectrometer. Uv spectra were recorded on a Shimadzu UV-200 spectrometer.

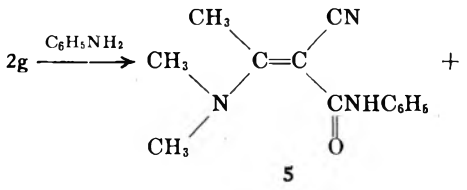
(16) H. Adkins and G. M. Whitman, *J. Amer. Chem. Soc.*, **64**, 150 (1942).

(17) J. Kuthan, V. Jehlička, and E. Hakr, *Collect. Czech. Chem. Commun.*, **32**, 4309 (1967).

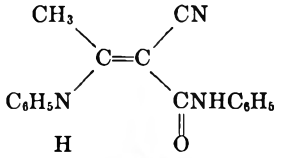
(18) *N*-Phenylacetamidine was prepared by the method of Oxley and Short: P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946).

ing frequencies[5,6] and the fact that addition of **2c** to a 10^{-3} *N* solution of $LiClO_4$ in CH_3CN did not increase the conductance of the solution, whereas the addition of tetraethylammonium bromide increased the conductance of the solution by a factor of about 9.[7,8]

The reaction was extended to enaminonitriles with a tertiary nitrogen atom. Reactions of **1g** and **1h** with phosgene gave corresponding acid chlorides **2g** and **2h**, which were very viscous liquids and could not be purified. Their ir spectra revealed characteristic absorptions of acid chlorides already described. Their nmr spectra also support the acid chloride structures. In addition, treatment of **2g** with aniline gave anilides **5** and **6** in 13 and 24% yield (overall), respectively; **6** was apparently formed by the reaction of **5** with aniline.[9,10]

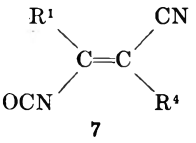


5



6

By-products of the reaction were also examined. Enaminonitriles **1a** and **1b** gave corresponding unsaturated isocyanates **7a** ($R^1 = CH_3$; $R^4 = H$) (trace) and **7b** ($R^1 = C_6H_5$; $R^4 = H$) (23%, determined by nmr),[11] respectively. Enaminonitrile **1e** afforded, instead of **7e**



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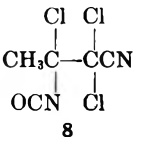
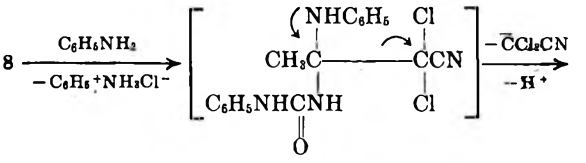


8

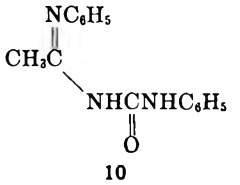
($R^1 = CH_3$; $R^4 = Cl$), 3-isocyanato-2,2,3-trichlorobutyronitrile (**8**) in 18% yield. **8** was probably produced by addition of chlorine formed during the reaction (*vide infra*) to initially formed isocyanate **7e**.

Isocyanate **8** was identified by ir, nmr, and mass spectra and elemental analyses. The assigned structure was supported by the fact that the isocyanate gave on treatment with an excess of aniline a 77% yield of *N*-phenyl-*N'*-phenylcarbamoylacetamidine (**10**), which was probably formed *via* intermediate **9**. Amidine **10** was characterized by spectral and elemental analyses and by independent synthesis from *N*-phenylacetamidine and phenyl isocyanate.[12]

In the case of **1c** and **1d**, phenyl isocyanate (**11**)



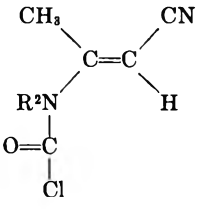
9



10

(8%)[13,14] and benzyl isocyanate (**12**) (3%)[13] were obtained, respectively. They were characterized by respective conversion to *N*,*N*-diphenylurea and *N*-benzyl-*N'*-phenylurea by reaction with aniline.

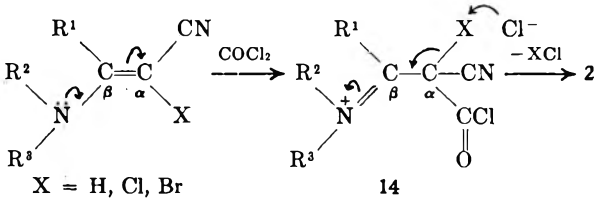
The formation of isocyanates **11** and **12** may be visualized to occur by the following two pathways: (a) decomposition of acid chlorides **2c** and **2d** *via* azetinone hydrochloride **4**; (b) decomposition of carbamoyl chloride **13**. Pathway a is excluded on the basis of the



13

fact that treatment of acid chloride **2c** with phosgene in refluxing ethyl acetate resulted in the quantitative recovery of **2c**. Thus, the isocyanates were probably formed by pathway b, although no evidence for the intermediacy of carbamoyl chloride **13** was obtained and the decomposition mechanism of **13** has not been clarified.

The formation of acid chloride **2** is evidently initiated by the α carbon attack of phosgene as follows.



X = H, Cl, Br

14

Since two very electronegative groups, a cyano and a chloroformyl group, are attached to the α carbon, the iminium salt **14** easily loses a proton or a positive halogen from the α carbon to give **2**.

Whereas reactions of enaminonitriles possessing an α alkyl group with phosgene have been found to give good yields of unsaturated isocyanates *via* initial N-phosgenation,[2] enaminonitriles with an α hydrogen or an α halogen give acid chlorides **2** as the major products. Predominance of C-phosgenation over N-phosgenation in the present cases may be due to a decrease in the nucleophilicity of the nitrogen atom of enaminonitriles on replacement of an α alkyl group by a more electronegative substituent such as hydrogen or halogen.

(5) Carbonyl stretching bands of azetinones and azetidinones appear around 1750 cm^{-1}. Since **4** has a protonated nitrogen adjacent to the carbonyl group, its carbonyl stretching band is expected to appear at a much higher frequency than 1750 cm^{-1}.

(6) D. Cook, *Can. J. Chem.*, **40**, 2362 (1962).

(7) Product **2c** and tetraethylammonium bromide were added to the solution so that their concentrations became 10^{-2} mol/l.

(8) The authors wish to express their thanks to Professor Hideo Tamura, Mr. Masayuki Tsunaga, and Mr. Mikio Miyake for their assistance in the measurement of the conductance.

(9) H. Ahlbrecht, *Tetrahedron Lett.*, 211 (1969).

(10) R. Helmers, *Angew. Chem.*, **83**, 756 (1971).

(11) Ir spectra (liquid film): **7a**, 2250 (NCO), 2210 (C≡N), and 1640 cm^{-1} (C=C); **7b**, 2250 (NCO), 2210 (C≡N), and 1610 cm^{-1} (C=C).

(12) A. J. Hill and I. Rabinowitz, *J. Amer. Chem. Soc.*, **48**, 732 (1962).

(13) Isolation yields (based on the enaminonitrile) as phenylureas.

(14) Ir spectrum of **11** agreed with that of an authentic sample.

Isoquinolines. 4.[1] The Synthesis of C(α)-Hydroxylated Tetrahydrobenzylisoquinolines and Related Compounds Using the 4-Oxazolin-2-one System as a Protecting Group[2a]

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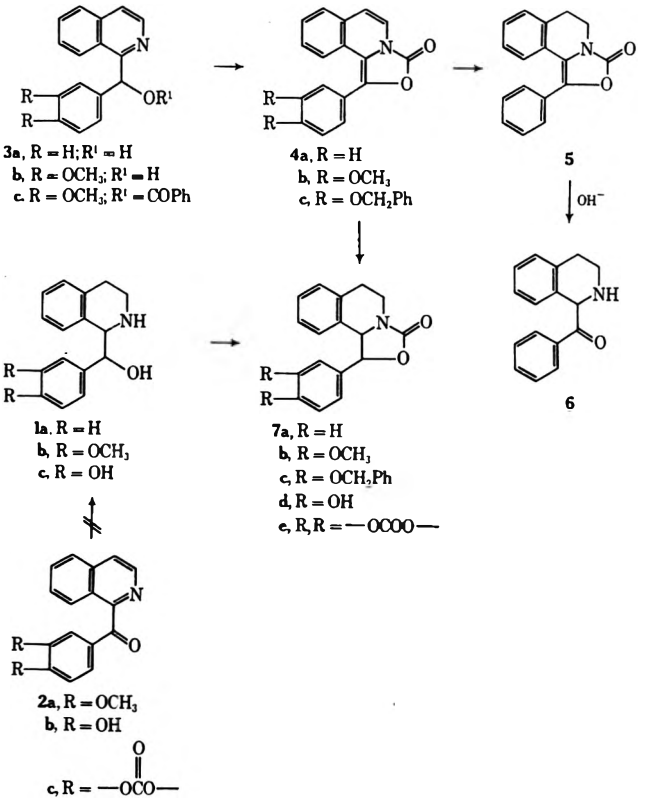
Received February 12, 1973

A convenient synthesis of the unstable 3,4-dihydroxybenzylmethanolamine (1) was devised by way of the 4-oxazolin-2-one system (4) as a protecting group. These compounds were prepared from the corresponding 1-(α-hydroxybenzyl)isoquinolines 3 by treatment with phosgene. These oxazolines were stable, recrystallizable intermediates which could be selectively reduced to the 5,6-dihydro (5) or 1,5,6,10b-tetrahydro (7) derivatives. Hydrolysis (acidic or basic) yielded the corresponding 1-(α-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines (1) or the 1-benzoyl-1,2,3,4-tetrahydroisoquinolines (6), respectively.

The benzylisoquinoline alkaloids are abundantly found in nature and have been the subject of extensive chemical and pharmacological investigations.[3] The related α-hydroxy-1-benzyltetrahydroisoquinoline alkaloid types have not been found in nature nor have they been thoroughly examined either in their methods of synthesis or for their biological activity. This investigation was initiated to develop methods for the synthesis of the 1,2-diaryl-2-aminoethanol system as shown in structure **1**, by incorporating the reactive carbinolamine into a more stable 4-oxazolin-2-one ring system. It was further considered that, if successful, this method would also serve as a means for the stereoselective synthesis of the C-7 hydroxy aporphine alkaloids. We have found the 4-oxazolin-2-one ring system[4] to be a versatile protecting group for such secondary amino nitrogens containing a β hydroxyl group that may be removed by mild hydrolysis conditions at the terminal stage of the synthesis. This method has been utilized in our laboratory for the synthesis of 7-hydroxyaporphine and 7-hydroxynoraporphine[5] and for the attempted synthesis of phenanthrene amino alcohols *via* photochemical cyclization of 4,5-diphenyloxazolin-2-one.[6] In the present report we wish to describe the details of our studies in the isoquinoline series.

Our initial effort in the synthesis of the α-hydroxytetrahydroisoquinoline **1c** (Scheme I) was directed at the reduction of 3,4-dihydroxyphenyl-1-isoquinolyl ketone (**2b**) and the cyclic carbonate **2c** to the desired

SCHEME I



1c under a variety of reduction conditions. In all instances the desired product proved to be extremely sensitive to air and could not be isolated. Similarly, the reduction of 3,4-dimethoxyphenyl-1-isoquinolylcarbinyl benzoate (**3c**)[7] with platinum in acetic acid yielded a mixture of compounds from which no crystalline compound could be isolated. However, saponification of the crude reaction mixture gave the alcohol **1b** in 46% yield. Attempts to demethylate **3c** with hydriodic acid in acetic acid[8] yielded only tarry, acid-insoluble material plus mixtures which eluded isolation.

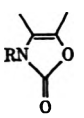
Unable to effect these reductions satisfactorily, we abandoned this route and developed an alternative synthesis which involved the oxazolone **4** in which the methanolamine functions were protected during the reduction and subsequent ether cleavage. Compound **4a** was prepared from the known alcohol **3a**[9] with

(1) K. K. Weinhardt and J. L. Neumeyer, *J. Med. Chem.*, **16**, in press.

(2) (a) Presented in part at the Seventh International Symposium on the Chemistry of Natural Products, Riga, June 1970, Abstract E 82. (b) To whom inquiries should be addressed at the Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Mass. 02115.

(3) For reviews on the benzylisoquinoline alkaloids see V. Deulofeu, J. Comin, and M. J. Vernego in "The Alkaloids," Vol. 10, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 401; M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N. Y., 1972, p 45.

(4) Reviewed by R. Filler in *Advan. Heterocycl. Chem.*, **4**, 103 (1965). The skeletal structure for the oxazolone, the *Chemical Abstracts* nomenclature (listed first), and the names with more common usage are shown below.



4-oxazolin-2-one
2(3*H*)-oxazolone

(5) J. L. Neumeyer and F. E. Granchelli, *Tetrahedron Lett.*, 5261 (1970).

(6) A. S. Dey and J. L. Neumeyer, 2nd Northeastern Regional Meeting of the American Chemical Society, Providence, R. I., Oct 1970, Abstract 122.

(7) F. D. Popp and W. E. Williams, *J. Amer. Chem. Soc.*, **79**, 3773 (1957).

(8) J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, *J. Pharm. Sci.*, **59**, 1850 (1970).

(9) L. Walters, N. Iyer, and W. E. McEwen, *J. Amer. Chem. Soc.*, **80**, 1177 (1958).

phosgene in triethylamine to give the oxazolone[10] in 91% yield. Catalytic hydrogenation of **4a** with platinum oxide in glacial acetic acid–tetrahydrofuran can be terminated after 1 mol of hydrogen has been absorbed, resulting in reduction of only the endocyclic isoquinoline double bond in **4** to give **5**. However, when the reduction was allowed to go to completion, **7a** was obtained which was converted without isolation to **1a** when treated with trifluoroacetic acid (TFA). However, when the oxazolone **5** was treated with potassium hydroxide in absolute ethanol, the ketone **6** was isolated in 86% yield. The oxazolone **4b** was prepared by reduction of the ketone **2a** without isolation of the intermediate alcohol. The catalytic reduction of **4b** over platinum oxide followed by hydrolysis with TFA gave 70% of **1b** hydrochloride. The successful synthesis of **1a** and **1b** encouraged us to prepare **4c** and its reduction product **7c**. We briefly examined the hydrogenolysis of **7c** to the phenol **7d** over palladium on charcoal in tetrahydrofuran. The hydrogenolysis product **7d** could not be purified sufficiently to permit a satisfactory identification, but the nmr spectrum clearly showed that the benzyl ether groups had been cleaved. Thus, in order to protect the sensitive pyrocatechol system, the carbonate ester **7e** was prepared *in situ* with phosgene and pyridine. 1-(3,4-Dihydroxyphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one cyclic carbonate (**7e**) was isolated and characterized as a crystalline solid which could be readily converted to the catecholamine **1c** by mild hydrolysis with TFA.

We contemplate that this method will provide the basis for stereoselective syntheses of both such phthalideisoquinoline alkaloids as narcotine and hydrastine and such C-7 hydroxylated aporphines as ushinsunine and norushinsunine.

Experimental Section[11]

1-Phenyl-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4a).—To a solution of 1.64 g of phenyl-1-isoquinolylcarbinol[9] in 100 ml of methylene chloride was added 2 ml of triethylamine and 100 ml of 8% aqueous sodium bicarbonate. The two phases were vigorously stirred as phosgene was bubbled into the mixture. When a vigorous evolution of CO_2 began, the addition was stopped. After stirring for 10 min, the layers were separated and the organic layer was washed with aqueous bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated until crystallization ensued. The resulting yellow product was recrystallized from methylene chloride–methanol to give 1.66 g (91%) of **4a**, mp 165–166° (lit.[10] mp 166–168°).

1-(3,4-Dimethoxyphenyl)-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4b).—To a rapidly stirred suspension of 1 g of 3,4-dimethoxyphenyl-1-isoquinolyl ketone in 30 ml of ethanol was added 0.5 g of sodium borohydride in small portions. The mixture was stirred for 2 hr, then 2 ml of water was added and stirring was continued for an additional 30 min. The inorganic solids were filtered off and the filtrate was evaporated under vacuum to give a gummy oil, which was extracted with ether. The ether extracts were combined, washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and evaporated to dryness to give an oil, **3b**, that could not be induced to crystallize. The oil was dissolved in anhydrous ether, 20 ml of triethylamine was added, and then a solution of about 7 g of phosgene in 75 ml of anhydrous ether was added dropwise. A vigorous reaction ensued, a heavy precipitate formed, and the solution turned bright yellow. After standing overnight the mixture was poured into water to give a dense yellow precipitate. The precipitate was filtered off, and the ether and water filtrates were separated. The ether layer was washed with water, aqueous hydrochloric acid, and finally aqueous sodium bicarbonate. It was then dried over magnesium sulfate, filtered, and evaporated to dryness. The residue and the precipitate already collected were combined and dissolved in methylene chloride, and 10 ml of ethanol was added to the solution. Methylene chloride was distilled from the mixture until crystallization occurred. There was obtained 0.87 g (79%) of **4b**: mp 178–181°; ν^{KBr} 1748 cm^{-1} (s); λ_{max}^{EtOH} 325 mμ (ε 22,300), 227 (12,800), 352 (12,000); nmr ($CDCl_3$) δ 3.84 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 6.2 (1 H, d, J = 8 Hz), 7.1 (7 H, m, PhH), 7.8 (1 H).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.84; H, 4.70; N, 4.23.

1-[3,4-Bis(benzyloxy)phenyl]-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (4c).—To a solution of 11.9 g of 2-benzoyl-1,2-dihydroisoquinaldonitrile[12] and 14.5 g of 3,4-dibenzyloxybenzaldehyde[13] in 150 ml of dimethylformamide cooled to −40° was added 3.5 g of 54% sodium hydride dispersion in oil. This mixture was stirred under nitrogen and allowed to warm to −20°, where it was maintained for 1 hr. Then the temperature was raised and held at 0° for another hour. The mixture was allowed to warm to room temperature overnight with good stirring. The solution was diluted with 300 ml of water and extracted with ether. The ether extract was washed with water, then with saturated sodium chloride solution. It was evaporated to dryness and the residual oil was dissolved in ethanol. The alcohol solution was treated with 2 g of sodium borohydride and stirred for 1 hr. To this mixture was added 10 ml of 50% aqueous potassium hydroxide and the mixture was refluxed for 2 hr. The solvent was evaporated and the residue was taken up in ether and water. The aqueous layer was separated and the ether layer was treated with a little dilute sulfuric acid, which immediately gave a gummy precipitate. The ether was removed by decantation and the gum was washed with water and then with ether. The coagulated semisolid was redissolved by shaking with aqueous sodium hydroxide and ether. The ether layer was separated, washed twice with water and once with saturated salt solution, and then dried over magnesium sulfate. After filtration and evaporation of the ether solution, the residue was dissolved in a mixture of 75 ml of dry methylene chloride and 20 ml of triethylamine. This solution was treated dropwise with 9 g of phosgene dissolved in methylene chloride. A vigorous exothermic reaction took place and the resulting mixture was allowed to stand overnight. The mixture was extracted twice with water, twice with dilute hydrochloric acid, once with sodium bicarbonate, and once with saturated salt solution. After the methylene chloride solution had been dried over magnesium sulfate and been evaporated to dryness, the residue was crystallized from methylene chloride–methanol to give 8.96 g (41%) of product **4c** as yellow needles: mp 135–137°; ν^{KBr} 1762 cm^{-1}, no absorption for OH; λ_{max}^{EtOH} 243 mμ (ε 22,800), 258 (s, 15,000), 277 (13,400), 353 (12,600); nmr δ 5.12 (s, 2 H, $PhCH_2O$), 5.17 (s, 2 H, CH_2O), 6.15 (d, J = 7.5 Hz, 1 H, CH=CHN), 7.3 (m, 6 H, PhH), 7.8 (d, J = 7.5 Hz, 1 H, CH=CHN).

Anal. Calcd for $C_{31}H_{23}NO_4$: C, 78.63; H, 4.90; N, 2.96. Found: C, 78.63; H, 4.87; N, 2.93.

5,6-Dihydro-1-phenyl-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5).—A solution of 0.52 g (2 mmol) of **4a** in 10 ml of tetrahydrofuran and 10 ml of glacial acetic acid was hydrogenated over 50 mg of platinum oxide until about 2 mmol of hydrogen had been absorbed. The catalyst was filtered off and the solvents were evaporated under vacuum. The residue was crystallized first from methanol and then from ethyl acetate, yielding 0.32 g (62%) of **5**, mp 155–157°.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 79.63; H, 7.94; H, 5.80. Found: C, 79.56; H, 8.09; N, 5.95.

(10) F. D. Popp, L. E. Katz, C. W. Klinowski, and J. M. Wefer, *J. Org. Chem.*, **33**, 4447 (1968). These authors prepared this compound in 13% yield from the Reissert compound derived from ethyl chloroformate and benzaldehyde.

(11) Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded with a Beckman grating spectrophotometer, Model 521, ultraviolet spectra were recorded with a Beckman Model DK-1A1, and the nmr spectra were determined on a Varian A-60 spectrophotometer with TMS as the internal standard.

(12) J. Weinstock and V. Boekelheide, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 641.

(13) H. S. Mahal, H. S. Roi, and K. Venkataraman, *J. Chem. Soc.*, 866 (1935).

1-Benzoyl-1,2,3,4-tetrahydroisoquinoline (6).—A solution of 0.238 g (1.0 mmol) of **5** and 0.250 g (4.5 mmol) of potassium hydroxide in 10 ml of absolute ethanol was allowed to reflux under nitrogen until thin layer chromatography no longer indicated the presence of **5** (about 2 hr). The volume was reduced to 2 ml and 5 ml of 10% aqueous hydrochloric acid was added. The volume was again reduced to about 5 ml and the hot solution was set aside. The resulting salt was recrystallized from water, yielding 0.205 g (86%) of **6**, mp 184–186° dec.

Anal. Calcd for $C_{16}H_{16}NOCl$: C, 70.19; H, 5.89; N, 5.12. Found: C, 69.85; H, 5.92; N, 4.91.

Phenyl-1-(1,2,3,4-tetrahydroisoquinolyl)methanol (1a).—A solution of 0.52 g (2 mmol) of **4a** in 5 ml of tetrahydrofuran and 10 ml of glacial acetic acid was hydrogenated over 50 mg of platinum oxide until hydrogen uptake ceased. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in 5 ml of trifluoroacetic acid and 2 ml of water. The solution was refluxed until no hydrogenation product was visible on thin layer chromatography. The solvent was removed and the residue was warmed with 10% sodium carbonate and extracted into ether. The ether was evaporated and the residue was crystallized twice from hexane to give 0.32 g (69%) of product, mp 90–93°.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.53; H, 7.27; N, 6.08. Found: C, 80.30; H, 7.16; N, 5.85.

3,4-Dimethoxyphenyl-1-(1,2,3,4-tetrahydroisoquinolyl)methanol Hydrochloride (1b HCl).—A solution of 0.64 g (2 mmol) of **4b** in 10 ml of tetrahydrofuran and 10 ml of glacial acetic acid was hydrogenated over 60 mg of platinum oxide until about 4 mmol of hydrogen had been absorbed. The catalyst was filtered and the solvent was evaporated to dryness. The residue was dissolved in 5 ml of trifluoroacetic acid and 1 ml of water and allowed to reflux until thin layer chromatography indicated complete hydrolysis. The solvent was evaporated to about 2 ml and the residue was taken up in 5 ml of 10% aqueous hydrochloric acid. The product was recrystallized from water, yielding 4.7 g (70%) of **1b** HCl, mp 219–221° dec.

Anal. Calcd for $C_{18}H_{22}NO_3Cl$: C, 64.37; H, 6.60; N, 4.17. Found: C, 64.46; H, 6.80; N, 4.08.

1-[3,4-Bis(benzyloxy)phenyl]-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (7c).—A solution of 5.0 g of 1-(3,4-dibenzyloxyphenyl)-3*H*-oxazolo[4.3-*a*]isoquinolin-3-one (**4c**) in 25 ml of tetrahydrofuran and 25 ml of acetic acid was hydrogenated over 0.5 g of platinum oxide at 60 psi for 32 hr. The catalyst was filtered off and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in ether and the solution was thoroughly washed with aqueous bicarbonate and saturated salt solution. The ether solution was dried over magnesium sulfate, evaporated to about 10 ml, and allowed to deposit 4.3 g of solid, which was recrystallized from ethyl acetate to give 3.75 g (74%) of **7c**: mp 139–149°; ν^{KBr} 1740 cm^{-1}; nmr ($CDCl_3$) δ 2.5–3.2 (m, 3, H, $PhCH_2CH_2$ and $CH_2CH_1H_aN$), 4.1 (m, 1 H, $CH_2CH_1H_aN$), 4.84 (s, 2 H, PhCHO), 4.98 (s, 2 H), PhCHO), 5.25 [d, J = 9 Hz, 1 H, PhCH[CH]N], 5.74 [d, J = 9 Hz, 1 H, PhCH(CH)O], 6.52–6.91 (m, 6 H, PhH), 7.34 (s 10 H, PhH), 6.64 (s, 1 H).

Anal. Calcd for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93. Found: C, 77.96; H, 5.71; N, 2.84.

1-3,4-(Dihydroxyphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo-[4,3-*a*]-isoquinolin-3-one Cyclic Carbonate (7e).—A solution of 9.42 g (19.7 mmol) of **7c** in 75 ml of tetrahydrofuran was hydrogenated over 5 g of 10% Pd on carbon. The hydrogenation was stopped after the uptake of about 40 mmol of hydrogen (about 2 hr). The catalyst was filtered and the filtrate was treated with 40 ml of pyridine. The solution was cooled to 5° and phosgene was added until a distinct yellow color developed. The solution was poured into ice and dilute hydrochloric acid and extracted with methylene chloride. The organic filtrates were washed, dried, and evaporated until crystallization occurred. Ethyl acetate was added to complete the crystallization, yielding 3.28 g (51%) of **7e**, mp 189–192°.

Anal. Calcd for $C_{18}H_{13}NO_5$: C, 66.64; H, 4.10; N, 4.23. Found: C, 66.87; H, 4.05; N, 4.33.

3,4-Dihydroxyphenyl-1-(1,2,3,4-tetrahydroisoquinolyl)carbinol Hydriodide (1c HI).—To a solution of 0.86 g (2.7 mmol) of **7e** in 5 ml of trifluoroacetic acid was added 5 ml of water. The solution was allowed to reflux gently until the volume was reduced to 5 ml. Dilution with 5 ml of water and refluxing was repeated and to the warm solution was added 1 ml of 50% hydriodic acid and charcoal. The solution was filtered and set aside to cool, yielding 0.56 g (60%) of **1c**, mp 139–141° dec.

Anal. Calcd for $C_{16}H_{18}NO_3I \cdot H_2O$: C, 46.05; H, 4.83; N, 3.36. Found: C, 46.23; H, 4.80; N, 3.40.

3,4-Dimethoxyphenyl-1-isoquinolyl Ketone (2a).—To a hot solution of 5 g (12.5 mmol) of **3c**[7] in 50 ml of alcohol was added a solution of 1.75 g (43.8 mmol) of sodium hydroxide in 100 ml of water. The solution was heated on a steam bath for 6 hr, partially evaporated to remove the ethanol, and allowed to cool to room temperature. The oil which separated was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated. The oily residue was dissolved in 60 ml of glacial acetic acid and a solution of 2.0 g (6.6 mmol) of sodium dichromate dihydrate in 20 ml of glacial acetic acid was slowly added. The solution was allowed to stand for 5 min at room temperature, then it was heated on a steam bath for 5 min. When the solution had been cooled to room temperature, 10 ml of methanol was added. The solvent was removed under reduced pressure and to the resulting gum was added 5 ml of concentrated hydrochloric acid and 20 ml of water. The acid solution was treated with aqueous ammonium hydroxide until the pH was about 5. The brownish gummy solid which precipitated from the solution was filtered and washed with water. The solid was redissolved in 5 ml of concentrated hydrochloric acid with 10 ml of water, treated with charcoal, and filtered. The aqueous filtrate was treated with aqueous ammonium hydroxide until crystallization ensued at about pH 2. After the product was collected and washed with water and methanol, 2.65 g (72%) of **2a** was obtained, mp 145–147°. An analytical sample was prepared by recrystallization from ethanol, mp 145–146°.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.76; H, 5.26; N, 4.66.

1-Isoquinolyl-3,4-dihydroxyphenyl Ketone (2b).—One gram of 3,4-dimethoxyphenyl-1-isoquinolyl ketone (**2a**) was dissolved in 25 ml of dry methylene chloride. The solution was placed under a nitrogen atmosphere and 0.9 ml of boron tribromide was added dropwise. A vigorous reaction ensued and the solution turned a dark purple color. The mixture was stirred for 6 hr at room temperature. The excess boron tribromide was destroyed by the cautious addition of 20 ml of water, whereupon the purple color was discharged to give an orange-yellow solution.

The methylene chloride was removed by evaporation on a steam bath. The solids which had precipitated were brought into isolation by the addition of 10 ml of methanol. The hot solution was treated with charcoal and filtered, and the methanol was removed by distillation. The hot aqueous solution was treated with a saturated solution of ammonium acetate to reduce the pH to about 3. The resulting pale yellow crystals were collected and washed with water and finally with methanol to give 0.71 g (78%) of **2b**, mp 257–262° dec.

Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.31; H, 4.25; N, 4.83.

1-Isoquinolyl-3,4-dihydroxyphenyl Ketone Cyclic Carbonate (2c).—Diphenyl carbonate (6 g, 28 mmol) and 3,4-dihydroxyphenyl-1-isoquinolyl ketone (**2b**) (3.8 g, 14 mmol) were fused at 200° under a stream of nitrogen for 45 min. The melt was allowed to cool and the resulting glass was crushed with ether. The solid was filtered, washed with ether, and dissolved in chloroform. The hot chloroform solution was treated with charcoal, filtered, and reduced to a volume of about 10 ml. The resulting crystals were collected and washed with a little chloroform to give 2.96 g (71%) of **2c**, mp 165–167°.

Anal. Calcd for $C_{17}H_9NO_4$: C, 70.10; H, 3.12; N, 4.81. Found: C, 70.31; H, 3.25; N, 4.83.

Registry No.—**1a**, 39949-72-9; **1b** HCl, 39949-73-0; **1c** HI, 39949-74-1; **2a**, 39971-69-2; **2b**, 39949-75-2; **2c**, 39949-76-3; **3c**, 39971-70-5; **4a**, 17954-30-2; **4b**, 39949-78-5; **4c**, 39949-79-6; **5**, 39949-80-9; **6** HCl, 39949-81-0; **7c**, 39949-82-1; **7e**, 39949-83-2; phenyl-1-isoquinolylcarbinol, 10175-00-5; 2-benzoyl-1,2-dihydroisoquinaldonitrile, 844-25-7; 3,4-dibenzyloxybenzaldehyde, 5447-02-9; diphenyl carbonate, 102-09-0.

The Physical Organic Chemistry of Benzisoxazoles. I. The Mechanism of the Base-Catalyzed Decomposition of Benzisoxazoles

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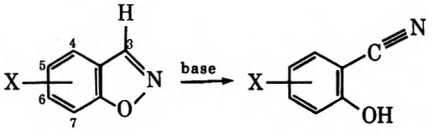
The mechanism of reaction of 5-, 6-, and 7-substituted benzisoxazoles with hydroxide or amines has been established as a concerted E2 elimination yielding *o*-cyanophenolate anions. With hydroxide in ethanol–water mixtures, these reactions have been shown to have a ΔH° in the range of -35 to -39 kcal/mol. The effects of salts and temperature on rates are considered, and the significance of the benzisoxazole system as a new kind of leaving group is discussed.

As has been extensively documented hitherto,[1] isoxazole derivatives bearing a 3 substituent which can act as an electron-deficient leaving group decompose rapidly and irreversibly to form an α-cyano ketone or its enol. Although this characteristic reaction has provided solutions for a number of synthetic problems,[2] its possible mechanistic significance has received small attention.[3] In this paper we present experimental evidence which defines the mechanism of base-catalyzed isomerizations of simple benzisoxazoles to *o*-cyanophenols.



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We were led to carry out a thorough investigation of this mechanism through the hope that the 3-benzisoxazolyl moiety may prove to be a useful leaving group for a variety of physical organic studies. Most attempts to vary the reactivity of a portion of a chemical system encounter the fundamental difficulty that secondary effects resulting from reactivity-increasing structural changes render quantitative interpretations ambiguous; a classical example is the curvature (or linearity) of a Brønsted plot which results from the inclusion of acids of differing structural types.

$$YL \longrightarrow Y^{+} + L^{-}$$

It would be useful to have a class of anionic leaving groups, L, which provide a substantial range of reactivities, but which have minimal steric or unpredictable electronic interaction with the reacting bonds of the group Y. In the summary section, we consider reasons for believing the 3-benzisoxazolyl grouping to be a good approximation to an ideal, noninteracting leaving group.

Before conclusions of this sort can be offered, the mechanism must be firmly established as a simple, intermediateless E2 elimination process.

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(3) For mechanistic discussion of these reactions, see P. Piriono, A. Scartabelli, and E. Lombardi, *Rend. Ist. Lomb. Sci. Lett.*, **87**, 229 (1954), and ref 4 and 5.

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(5) D. S. Kemp and K. Paul, *J. Amer. Chem. Soc.*, **92**, 2553 (1970).

Experimental Section[6]

Materials.—Trimethylamine hydrochloride (Eastman) was recrystallized twice from absolute ethanol and dried under vacuum, mp 279.0–280.0° dec (lit.[7] mp 277–280°). Methyldiethanolamine (Aldrich) was distilled through a spinning band column and the middle fraction was collected, bp 89.0° (0.35 mm). Baker reagent grade KCl, Eastman Spectrograde acetonitrile, and Columbia Organic deuterium oxide (99.5%) were used without further purification. Baker reagent grade KOH was dissolved in boiled, distilled water, and the solution was standardized using potassium hydrogen phthalate. Hydroxylammonium *O*-sulfonate was freshly prepared by the procedure of Matsuguma and Audrieth[8] and was used only if iodometric titration revealed better than 89% purity.

4-Chloro- and 5-methoxysalicylaldehydes were prepared from the corresponding phenols by means of the Duff reaction;[9] 4-methoxysalicylaldehyde was prepared by methylation of 2,4-dihydroxybenzaldehyde,[10] while 4-nitrosalicylaldehyde was prepared from 2-acetoxy-4-nitrotoluene.[11] The properties of these substances corresponded to those reported in literature.

General Benzisoxazole Synthesis.—A modification of the procedure of Kemp and Woodward[12] was followed. In a 125-ml erlenmeyer flask, 2 g of the salicylaldehyde was dissolved in ethanol (*ca.* 10 ml) such that the solution was saturated at 25°. To this stirred solution was added 2 g (*ca.* 1.5 equiv) of hydroxylammonium *O*-sulfonate. After several minutes, 50 ml of dichloromethane was added, the mixture was cooled in ice, and a solution of 3 g of sodium bicarbonate in 25 ml of water was added. If a chloro- or nitrobenzisoxazole was prepared, this suspension was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with three 10-ml portions of dichloromethane, returned to the reaction flask, and stirred for 30 min with 50 ml of dichloromethane. The extraction was then repeated. If a methyl- or methoxybenzisoxazole was prepared, the solution was allowed to stir for 30 min before the initial extraction and an additional 90 min before the final extraction. The dichloromethane solutions were pooled, dried, and evaporated under vacuum. The resulting benzisoxazoles (Table I) were found to be free of parent aldehyde as judged by ir and tlc.

Crystalline benzisoxazoles were recrystallized to constant melting point, dried under vacuum, and stored in a desiccator at 3° in foil-wrapped vials. Benzisoxazoles which are liquid at

(6) Details concerning experiments with benzisoxazoles and carboxybenzisoxazoles may be respectively found in the following theses: Martha T. Link, Ph.D. Thesis, M. I. T., Cambridge, Mass., 1968; Kenneth G. Paul, Ph.D. Thesis, M. I. T., Cambridge, Mass., 1969. Synthetic details for benzisoxazoles and salicylonitriles will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2294.

(7) I. Heilbron, A. H. Cook, H. M. Bunsbury, and D. H. Hey, "Dictionary of Organic Chemistry," Vol. 5, Oxford University Press, London, 1965, p 3156.

(8) "Inorganic Synthesis," Vol. 5, McGraw-Hill, New York, N. Y., 1957, p 122.

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TABLE I

BENZISOXAZOLES PREPARED BY THE GENERAL PROCEDURE

Registry no.	Benzisoxazole	Yield, %	Recrystn solvent	Mp or bp (mm), °C	Uv max (water), nm (ε)
39835-05-7	6-Methoxy[a]	75	Ether	66 (0.1)	219 (9320)
				ca. 15	251 (7520)
					283 (5690)
					291 (5340)
39835-06-8	5-Methoxy[a]	78	Ether	71 (0.1)	236 (8380)
				ca. 5	306 (3490)
39835-07-9	6-Chloro[a]	90	EtOH	70.0–71.0	244 (9940)
					284 (2960)
39900-62-4	5-Chloro[a]	92	EtOH	65–67	236 (8940)
				(lit. 70)[b]	293 (3170)
39835-08-0	6-Nitro[a]	94	Acetonitrile	133.5–134.5	275 (15,000)

[a] Satisfactory combustion analytical data (±0.3%) for C, H, N, Cl were provided for these compounds and are reported in the microfilm edition (see footnote 6): Ed. [b] G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, 89, 1009 (1959).

room temperature were distilled in a short-path still (1 mm) within 1 month of use.

Benzisoxazole was prepared by the method of Kemp and Woodward[12] and was distilled twice in a Hickman still before use.

[3-^{2}H]Benzisoxazole was prepared from [*formyl*-^{2}H]salicylaldehyde[13] by the above procedure. Mass spectroscopic analysis showed that the sample contained 97% monodeuterated material.

5-Nitrobenzisoxazole was prepared in 90% yield by nitration of benzisoxazole following the procedure of Lindemann and Thiele.[14] The product was recrystallized from acetonitrile three times and dried under vacuum for 12 hr, mp 127.0–128.0° (lit. mp 126.5–127.5°).[14]

[3-^{2}H]-5-Nitrobenzisoxazole was prepared analogously, mp 126.5–127.5°; nmr analysis showed the sample to contain >95% deuterium in the 3 position.

5,7-Dinitrobenzisoxazole.—A solution of 5-nitrobenzisoxazole (1.0 g, 6.1 mmol) in 8 ml of sulfuric acid was cooled to 0° and treated with 1.5 g of nitric acid. After 30 min of stirring at 25°, the solution was stirred for 10–15 hr at 50–60°. When starting material could no longer be detected in the reaction mixture by tlc, the mixture was poured on ice, and the product was collected and washed with ice water. The crude product (1.1 g, 86%) was recrystallized twice from acetonitrile, then was dissolved in dichloromethane. The resulting solution was extracted three times with 30 ml of cold, commercial pH 4.0 buffer and twice with water; the solution was dried and evaporated; and the residue was dried for 6 hr under vacuum at 25°, mp 122.0–123.0°. *Anal.* Calcd for $C_7H_3N_3O_5$: C, 40.20; H, 1.45; N, 20.10. Found: C, 40.40; H, 1.48; N, 20.30. It had λ_{max} (water, pH 3) 255 nm (ε 14,200), 305 (4080). [3-^{2}H]-5,7-Dinitrobenzisoxazole was prepared analogously; nmr analysis showed the sample to contain >95% deuterium in the 3 position.

General Procedure for the Preparation of Salicylonitriles.[15]—A solution of 0.5 g of benzisoxazole in 5–8 ml of ethanol and 5 ml of water was mixed with 15 ml of 2 *N* NaOH solution and allowed to stand for 10 min, at which time HCl was added to bring the pH to 1, and the solution was extracted with three 10-ml portions of dichloromethane which were pooled, dried, and evaporated. The residue was recrystallized (water, water–ethanol, or acetonitrile), dried under vacuum for 6 hr, and stored in foil-wrapped vials in a desiccator. In the case of the 3,5-dinitrosalicylonitrile, acidification was carried out immediately after addition of base. All melting points were in good agreement with literature values.

Test of the Products of Benzisoxazole Decompositions.—All nitriles could be isolated from the hydroxide- or amine-catalyzed reactions in at least 90% yield. Salicylonitriles which had been kept in 0.1 *N* sodium hydroxide solution for more than 1500 half-lives of the corresponding benzisoxazole decomposition were recovered by acidification and found to show no extraneous infrared absorption; moreover, decomposition of benzisoxazole tritiated in the 5 or 7 positions by triethylamine or diethanolamine buffers in the presence of salicylamide carrier yielded salicylamide with no detectable tritium content; the product therefore contains less than 0.3% salicylamide. All benzisoxazole decompositions carried out at uv concentrations gave products whose spectra were superimposable with those of the corresponding nitrile (Table II).

TABLE II

ULTRAVIOLET SPECTRA OF SALICYLONITRILES

Registry no.	Nitrile	Uv max (water), nm (ε) pH 2	pH 10
611-20-1	Salicylonitrile	232 (8300)	241 (7130)
		295 (4040)	325 (5980)
39835-09-1	5-Nitro	219 (18,900)	327 (8160)
		223 (18,700)	380 (15,800)
		306 (10,900)	
25844-84-2	3,5-Dinitro	226 (19,900) (30% H_2SO_4)	326 (10,800)
		255 (14,500)	359 (15,200)
		328 (5700)	
39835-11-5	4-Methoxy	250 (16,400)	252 (10,200)
		291 (5260)	313 (7000)
39900-63-5	5-Methoxy	233 (8280)	241 (6680)
		319 (4670)	347 (5880)
30818-28-1	4-Chloro	240 (13,600)	246 (8720)
		299 (4760)	327 (6770)
13589-72-5	5-Chloro	232 (10,100)	251 (9500)
		308 (3950)	339 (5650)
39835-14-8	4-Nitro	214 (12,700)	234 (17,000)
		237 (7010)	264 (10,300)
		271 (8840)	404 (2870)
		342 (3140)	

Kinetic Measurements.—Absorbance measurements were made with a Zeiss PMQ II spectrophotometer fitted with a constant-temperature cell block through which water was circulated by means of a Haake Model F constant temperature circulator. Control experiments using a Beckman thermometer indicated that the water temperature was maintained within ±0.05°. Rates were followed at the longest wavelength absorption maximum of the cyanophenol. All substances of the study were found to obey Beer's law at the wavelengths employed. Buffer solutions were prepared by weighing out the appropriate amount of the amine or amine hydrochloride. In the former case standard HCl solution, and in the latter, standard KOH solution were added to give the desired buffer ratio, and boiled, distilled water was added to bring the solution to the mark. The concentration of amine in the buffer was determined by titration with 1.00 *M* HCl using a Radiometer titration assembly (pH meter 25, ABU 16 buret, and SBR 2C Titrigraph). The latter values were used in all calculations. For a given run, appropriate volumes of buffer stock solutions were measured by buret into 100 ml volumetric flasks containing sufficient KCl to bring the final ionic strength to 0.100, and the flasks were filled to within 3–4 ml of the mark and equilibrated at 30°. If necessary (pH >9) the solutions were each adjusted to the pH observed for the 0.010 *M* buffer by the addition of 0.5 *M* KOH solution. All precise pH measurements were performed using a Radiometer Model 4 pH meter equipped with a thermostated 30° cell bath and Radiometer G202C glass and K401 calomel electrodes. The meter was standardized before each measurement with a Fisher pH 6.98 phosphate buffer, and before each series of measurements with Fisher pH 4.01 and 9.90 buffers.

For a kinetic run, 1–2 μl of an acetonitrile solution of benzisoxazole was introduced by syringe into a cuvette containing thermally equilibrated buffer. (For the 6-nitrobenzisoxazole, the substrate was introduced into an upper layer formed from one or two microdrops of acetonitrile, and the solution was then stirred.) Identical A_∞ measurements were obtained after 10 half-lives or by terminating the reaction after 3 half-lives by the addition of one quarter pellet of KOH. Pseudo-first-order rate constants were obtained as the slope of a graph of $\ln (A_\infty - A_0/A_\infty - A_t)$ as a function of time; a minimum of eight measurements were used. Hydroxide catalytic constants were obtained from the zero intercepts of graphs of k_{obsd} as a function of amine concentration, using hydroxide concentrations calculated from pH and the data of Harned and Owen.[16]

(13) D. S. Kemp, *J. Org. Chem.*, **36**, 202 (1971).

(14) H. Lindemann and H. Thiele, *Justus Liebigs Ann. Chem.*, **449**, 76 (1926).

(15) For additional data, see ref 6.

(16) H. S. Harned and R. B. Owen, "The Physical Chemistry of Electrolyte Solutions," Reinhold, New York, N. Y., 1943, pp 638, 752.

Determination of pK_a Values of Salicylonitriles.—Spectrometric measurements in amine buffer solutions brought to ionic strength 0.1 with KCl were used for pK_a determinations. Measurements were taken at a wavelength at which un-ionized phenol showed no absorption, usually the long-wavelength maximum of phenolate. Tertiary amine buffers whose pK_a values were close to those of the phenol were chosen.[6]

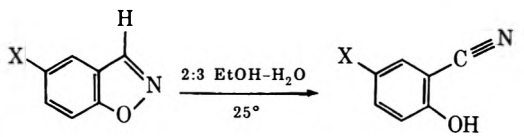
Calorimetric Measurements.—Crude measurements of $\Delta H°$ of reaction of benzisoxazoles and cyanophenols with sodium hydroxide were carried out as described by Daniels,[17] using 3 × 11 in. dewar flasks equipped with stirrer and Beckman thermometers. Reactions were carried out in 2:3 (v/v) ethanol–water, and the apparatus was calibrated by neutralizing NaOH with HCl solutions. For the experiments involving benzisoxazole or cyanophenol, roughly 10 mmol of substrate was contained in 100 ml of solvent and treated with 100 ml of 0.2 *M* NaOH solution; temperature increases lay in the range of 1.5° for benzisoxazole and 0.5° for the phenol. In the nitro series, the quantity of benzisoxazole was reduced by 7–8-fold.

Decompositions of Benzisoxazoles in the Presence of Exchangeable Tritium.—Three different tritium concentrations were employed in these experiments—0.025, 1.3, and 19 μCi/mmol of exchangeable hydrogen. (A fourth experiment utilized the catalytic efficacy of tetrabutylammonium acetate in dry or nearly dry acetone for benzisoxazole decompositions;[18] the exact tritium level for this experiment is not known, but must lie in the range of 50–70 μCi/mmol of exchangeable hydrogen.) No tritium incorporation into unreacted benzisoxazole could be detected in any of these experiments. For example, 10 ml of acetonitrile containing 1.0 g of 5-nitrobenzisoxazole was combined with a solution of 0.48 g of aminotri(hydroxymethyl)methane (Tris) in 1.5 ml of 1 *M* HCl, 2 ml of methanol, and 0.5 ml of water containing 4.3 mCi of tritium. The reaction was quenched at 17 min by the addition of HCl; uv monitoring at 380 nm indicated that 40% decomposition had occurred. The benzisoxazole was recovered after lyophilization, solution in CH_2Cl_2, and repeated extractions with pH 7 buffer and water. The recovered product was recrystallized from ethanol and decomposed with excess sodium methoxide in methanol. The methanol was isolated by bulb-to-bulb distillation and transferred to a liquid scintillation vial containing dioxane-based counting solution. The resulting count was indistinguishable from that of background: background, 23.6 cpm; methanol sample, 24.5 cpm. A control experiment with [3-^{3}H]benzisoxazoles established this procedure as quantitatively reliable for measuring tritium in the benzisoxazole 3 positions. Similar experiments were carried out at lower initial tritium levels using aqueous methanolic methyldiethanolamine and 3,4-lutidine buffers, applied respectively to benzisoxazole and 5,7-dinitrobenzisoxazole.

Results

General Properties of the Base-Catalyzed Benzisoxazole Decomposition.—From the product studies outlined in the Experimental Section, we conclude that the base-catalyzed decompositions of 3-unsubstituted benzisoxazoles in water, pH 5–13, consist of clean, quantitative conversions to salicylonitriles or their anions.

Approximate calorimetric measurements of the heats of reaction of benzisoxazole, 5-nitrobenzisoxazole, and the corresponding salicylonitriles with sodium hydroxide in 2:3 ethanol–water mixtures yielded values for $\Delta H°$ reported in Table III. It may be noted that



X = H, $\Delta H°$ = −27 kcal/mol
X = NO_2, $\Delta H°$ = −28 kcal/mol

(17) F. Daniels, J. H. Mathews, J. W. Williams, P. Bender, and R. Alberty, "Experimental Physical Chemistry," McGraw-Hill, New York, N. Y., 1956, p 37.

(18) D. S. Kemp and D. D. Cox, unpublished observations.

TABLE III
HEATS OF REACTION OF BENZISOXAZOLES AND SALICYLONITRILES WITH SODIUM HYDROXIDE[a]

Compd	$\Delta H°$, kcal/mol
Benzisoxazole	−35.1 ± 2.0[b]
2-Hydroxybenzonitrile	−8.4 ± 0.3
5-Nitrobenzisoxazole	−39.0 ± 1.5
2-Hydroxy-5-nitrobenzonitrile	−11.4 ± 0.3

[a] Temperature 25°, 2:3 (v/v) ethanol–water. [b] Estimates of precision are standard deviations based on 3–5 measurements.

the values obtained for heats of neutralization of phenols lie in the range which has been observed for phenols of comparable acidity.[19]

An estimate of the pK_a value of the conjugate acid of benzisoxazole was needed to determine the role of this species in base-catalyzed decomposition of the heterocycle. The uv spectrum of benzisoxazole in 92% sulfuric acid shows maxima at 259 nm (ε 13,800) and 300 (3500), which are in excellent accord with those observed for the 2-ethylbenzisoxazolium cation in water at pH 1 [258 nm (ε 13,000) and 297 (2900)].[12] In sulfuric acid–water mixtures spectra were quantitatively represented as linear combinations of protonated and free benzisoxazole spectra, with isosbestic points at 244, 278, and 287 nm. Benzisoxazole is found to be half-protonated in 62% sulfuric acid and thus can be assigned a pK_a value of −4.7 under the assumption that the H_0 function defines acidity for this substance. From this result it is clear that the conjugate acids of benzisoxazoles are irrelevant to the chemistry observed at a pH greater than 5.

Kinetics of the Base-Catalyzed Decomposition of Benzisoxazoles.—As indicated in the Experimental Section, the salicylonitriles formed from benzisoxazole decomposition under basic conditions show intense ultraviolet absorption maxima in the range of 310–400 nm, and reactions can therefore be followed conveniently at *ca.* 10^{-4} *M* substrate concentration. Table IV presents catalytic constants for the reaction of eight

TABLE IV
CATALYTIC CONSTANTS FOR BENZISOXAZOLE DECOMPOSITIONS AND pK_a VALUES FOR SALICYLONITRILES[a]

Benzisoxazole	k_{OH^-}, M^{-1} sec^{-1}	pK_a of salicylonitrile
5-Methoxy	1.8×10^{-1}	7.4
Unsubstituted	3.3×10^{-1}	6.9
6-Methoxy	3.8×10^{-1}	6.6
5-Chloro	9.2×10^{-1}	6.4
6-Chloro	1.2	6.1
6-Nitro	5.3	5.2
5-Nitro	1.5×10	4.1
5,7-Dinitro	1.5×10^3	0.6

[a] Temperature 30.0°, water, μ 0.10 (KCl).

substituted benzisoxazoles with hydroxide ion, along with pK_a values for the nitrile products.

The proton transfer step for reactions of hydroxide ion and tertiary amines with 5-nitrobenzisoxazole and 5,7-dinitrobenzisoxazole is rate determining and irreversible, for the 3-^{2}H derivatives show kinetic isotope effects in the range of 4–6, and, when reactions were carried out in tritiated water, recovered starting ma-

(19) C. T. Mortimer, "Reaction Heats and Bond Strengths," Pergamon Press, Elmsford N. Y., 1962, p 169.

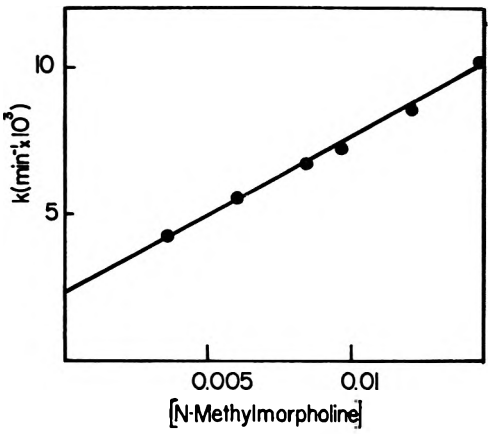


Figure 1.—Variation of pseudo-first-order rate constant for 5-nitrobenzisoxazole decomposition as a function of *N*-methylmorpholine concentration: 30°, water, μ 0.10, pH 8.00, buffer ratio 3:1 amine to amine salt.

terials showed no tritium incorporation. The conditions of the experiment allow one to conclude that, for benzisoxazole, conversion to salicylonitrile anion must occur at least 10^6 times faster than formation of tritiated starting material. For the nitro compounds the bound is at least 10^5, and at the highest tritium level, 10^7.

As shown in Figure 1, reactions conducted in amine buffers at high ratios of amine to amine salt concentrations show the linear dependence of pseudo-first-order rate constant on amine concentration expected for general catalysis. On the other hand, at low buffer ratios, more complex behavior is observed, typified by Figure 2.

A number of workers, for example Jencks and Gilchrist and more recently Salomaa and coworkers,[20] have noted that a change in cation from alkali metal to alkylammonium can result in rate changes which can mask or complicate the observation of general catalysis by amines. Such an effect might be expected to be important in the above cases, for, while the data points of Figure 1 correspond to a range of contributions of potassium ion to total cation of 99.7–85.0%, for Figure 2 the corresponding range is 90–40%. That the behavior of Figure 2 is indeed the result of a salt effect and not the consequence of mechanistic complexities follows from the observations of Table V.

From part A of Table V it is clear that anomalous behavior is observed only when potassium is the added cation; if tetramethylammonium chloride is used to maintain constant ionic strength, identical amine catalytic constants are observed at high and low buffer ratio. The first two entries of part B provide another example of the effect of mixing potassium and ammonium cations—neither the amine nor the hydroxide catalytic constant is invariant to a change in buffer ratio. The third entry establishes that this variance may be attributed to the cation; for it, as for the first entry, the buffer ratio is 2.6, but sufficient tetramethylammonium chloride has been added to simulate the salt environment characteristic of the second entry. The catalytic constants for the second and third entries are seen to be in reasonable agreement.

One can conclude that the base-catalyzed decompositions of benzisoxazoles exhibit general base catalysis, and that accurate catalytic constants can be obtained

(20) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 104 (1966); P. Salomaa, A. Kankaanpera, and M. Lahti, *ibid.*, **93**, 2085 (1971).

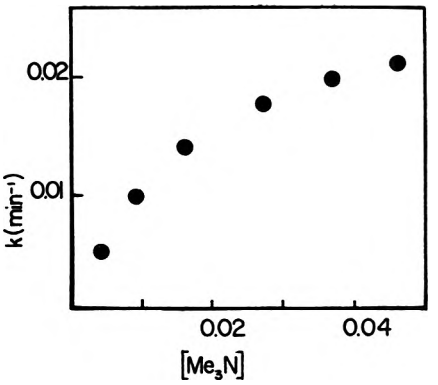


Figure 2.—Variation of pseudo-first-order rate constant for benzisoxazole decomposition as a function of trimethylamine concentration: water, 30°, μ 0.10, pH 9.36, buffer ratio 1:2.5 amine to amine salt.

TABLE V

EFFECTS OF CATION ON CATALYTIC CONSTANTS[a]

A. Effect of Salt on the Reaction of Benzisoxazole with Trimethylamine

$[Me_3N]/[Me_3N^+H]$	$[Me_3N]$ range $\times 10^3$	Salt added[b]	k_{Me_3N}, M^{-1} sec^{-1c} $\times 10^3$
3.0	2–12	$Me_4N^+Cl^-$	8.0 ± 0.7
0.43	3–13	$Me_4N^+Cl^-$	7.6 ± 0.5
2.8	4–14	KCl	9.2 ± 0.9
0.4	4–50	KCl	Nonlinear plot (Figure 2)

B. Effect of Salt on the Reaction of 5-Nitrobenzisoxazole with Methyldiethanolamine

$[R_2N]/[R_2N^+H]$	Salt added	k_{R_2N},[c] M^{-1} sec^{-1} $\times 10^2$	k_{OH^-}, M^{-1} sec^{-1}
2.6	KCl	3.80 ± 0.1	15.4
0.31	KCl	3.22 ± 0.1	19.5
2.6	KCl, Me_4N^+Cl[d]	3.28 ± 0.2	20.6

[a] Water, 30.0°, *ca.* 10^{-4} *M* substrate. [b] μ 0.1. [c] Error estimates are standard deviations obtained by a least-squares analysis. [d] $[R_3N]/([R_3NH^+] + [Me_4N^+]) = 0.31$.

from the conventional plots of pseudo-first-order rate constants as functions of buffer amine, provided that amine cations are used to maintain constant ionic strength, or provided that an alkali metal cation is allowed to dominate the cation composition.

Table VI[21,22] lists the effects of total ionic strength, solvent and kinetic isotope, and temperature on catalytic constants. Included in part A are data from Harned and Owen[21] which indicate that 0.5 *M* KCl is the concentration most favorable for the ionization of water. It is not unreasonable to expect, therefore, that the reaction of benzisoxazole with hydroxide, which results in charge dispersion at the transition state, would show a minimum in catalytic constant at this salt concentration, as is in fact observed.

Discussion

Given the evidence of a substantial kinetic isotope effect, general base catalysis, and the failure of benzisoxazoles to incorporate tritium from solvent in the presence of bases, one must regard the mechanism of reaction of bases with benzisoxazoles as a concerted elimination of the E2 type (eq 1) or as an E1cB elimi-

(21) Reference 16, p 578.

(22) P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 1 (1964).

TABLE VI

IONIC STRENGTH, KINETIC AND SOLVENT ISOTOPE AND TEMPERATURE EFFECTS ON CATALYTIC CONSTANTS FOR BENZISOXAZOLE DECOMPOSITIONS[a]

A. Effect of KCl Concentration on the Reaction of 5-Nitrobenzisoxazole with Methyldiethanolamine

μ	k_{R_3N},[b] M^{-1} sec^{-1} × 10^2	k_{OH^-},[b] M^{-1} sec^{-1} × 10	$\frac{\gamma_{OH^-} - \gamma_{H^+}}{a_{H_2O}}$[c]
0.10	3.80 ± 0.13	1.53 ± 0.06	0.627
0.30	4.10 ± 0.25	1.41 ± 0.20	0.561
0.50	4.18 ± 0.10	1.36 ± 0.03	0.533
0.75	4.65 ± 0.18	1.45 ± 0.03	0.560
1.00	4.35 ± 0.10	1.55 ± 0.02	0.587

B. Kinetic Deuterium Isotope Effects for Reactions of 3-Deuteriobenzisoxazoles with Bases[a]

Base	k_H/k_D Benzisoxazole	5-Nitrobenzisoxazole	5,7-Dinitrobenzisoxazole
Hydroxide	4.59	4.36	6.08
Trimethylamine	4.16	4.75	
N-Methylmorpholine	3.85	4.72	5.94

C. Solvent Deuterium Isotope Effect for the Reaction of 5-Nitrobenzisoxazole with Methyldiethanolamine[c]

$$\frac{k_{OD^-}}{k_{OH^-}} = \frac{24.5 \pm 0.7}{15.3 \pm 0.7} = 1.60 \pm 0.11$$

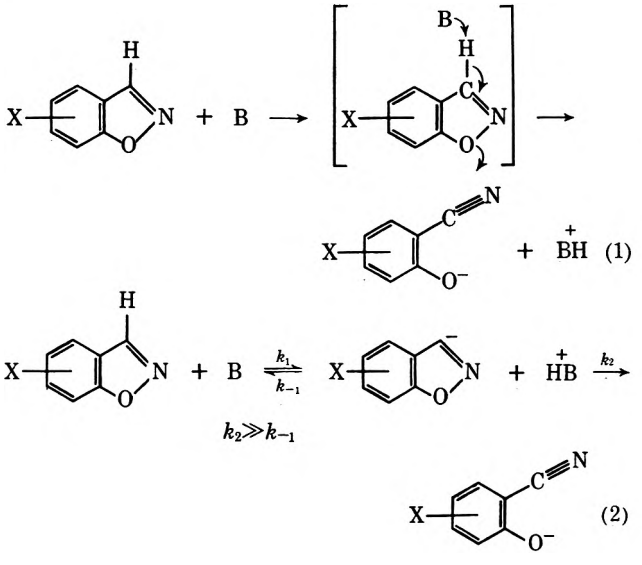
$$\frac{k_{R_3N(D_2O)}}{k_{R_3N(H_2O)}} = \frac{(3.35 \pm 0.1) \times 10^{-2}}{(3.90 \pm 0.13) \times 10^{-2}} = 0.86 \pm 0.08$$

D. Activation Parameters for the Reactions of Benzisoxazoles with Bases[d]

Substrate	Base	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/deg mol, 30°
Benzisoxazole	Hydroxide	14.6 ± 1.7	−12.8 ± 5.6
Benzisoxazole	Trimethylamine	18.7 ± 0.4	−6.2 ± 1.3
5-Nitrobenzisoxazole	Hydroxide	11.5 ± 1.7	−15.2 ± 5.6
5-Nitrobenzisoxazole	Methyldiethanolamine	14.5 ± 2.0	−17.5 ± 6.6

[a] Water, 30.0°. [b] Error estimates are standard deviations based on a least-squares analysis. [c] Solvent isotope effects were calculated assuming a ratio of ion products of H_2O and D_2O of 6.5 and a glass electrode correction pD = pH − 0.60: P. Saloman, L. L. Schlaeger, and F. A. Long, *J. Amer. Chem. Soc.*, 86, 1 (1964). [d] Activation parameters were calculated from an Arrhenius plot using catalytic constants measured at 20, 25, 30, and 35°. [e] Reference 21.

nation (eq 2) in which isomerization of an intermediary anion occurs much faster than reprotonation.



(1)

$k_2 \gg k_{-1}$

(2)

The E1cB class of elimination mechanism has been believed to have few examples and to require a resonance or inductively stabilized intermediary anion,[23] but it should also be recalled that both ylide and simple anionic intermediates which lack resonance stabilization have been encountered in the proton exchange reactions of five-ring heterocycles.[24] Moreover, Bordwell has recently drawn attention to the inconclusive evidence concerning the mechanisms of many elimination reactions and has affirmed that many reactions hitherto regarded as concerted E2 eliminations in fact belong to one of the several E1cB categories.[25]

There appear to be two independent, conclusive arguments which establish an elimination mechanism as E2. One, noted by Bordwell,[25] involves demonstration of both a sizable deuterium isotope effect for C–H cleavage and substantial dependence of rate on the nature of the leaving group. The other uses a measured rate of back exchange and Eigen's reprotonation rate data to exclude anionic intermediates as too unstable to contribute to the given elimination process. Both arguments can be applied definitively to the benzisoxazole isomerizations.

Both E2 and E1cB mechanisms predict that electron-withdrawing benzo substituents should accelerate the isomerization rate. However, not only should the effect be much smaller for the 3 anion of the E1cB mechanism, but the meta–para correlation expected for 5- and 6-substituted benzisoxazoles should be reversed from that expected for the incipient oxyanion of the E2 mechanism. The data of Table IV indicate that the rate of reaction of benzisoxazoles with hydroxide ion is strongly accelerated by electron-withdrawing substituents and that the effect is of the magnitude expected for development of partial negative charge on oxygen at the rate-determining transition state. (It may be noted that the effects of ionic strength on rate, the solvent isotope effects, and the activation parameters are all in accord with a process in which appreciable charge delocalization has occurred at the transition state.)

Data presented in Figure 3 permit comparison of the relative effectiveness of 5 and 6 substituents at stabilizing the transition state for benzisoxazole decomposition. Clearly, the assignment of σ_{meta} to 6 and σ^-_{para} to 5 substitutents gives a simple linear correlation with log k_{OH^-}, while the reverse assignment, σ_{meta} to 5 and σ_{para} to 6, gives an unsatisfactory correlation. This observation is best explained by a transition state in which substantial negative charge has appeared on oxygen.

It could, of course, be argued that the above conclusion is premature without an adequate model for

(23) D. J. McLennan, *Quart Rev., Chem. Soc.*, **21**, 491 (1967).

(24) R. A. Olofson, T. M. Landesberg, K. M. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966); R. Olofson and J. M. Landesberg, *ibid.*, **88**, 4263 (1966); R. A. Olofson, J. S. Michelman, and W. R. Thompson, *ibid.*, **86**, 1865 (1964); H. W. Wanzlich, *Angew. Chem.*, **74**, 127 (1962); R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, **26**, 685 (1970).

(25) F. G. Bordwell, *Accounts Chem. Res.*, **5**, 374 (1972), and references cited therein. Assignment of an E1cB mechanism to the benzisoxazole cleavages might seem especially appropriate in the light of Bordwell's view[25] that most HC=EY eliminations belong to this class. However, we do not regard Miller's observations[26] on the experimentally difficult and possibly atypical case, *cis*-1,2-dibromoethylene, as convincing evidence for a prototypic judgment.

(26) S. I. Miller and W. G. Lee, *J. Amer Chem. Soc.*, **81**, 6313 (1959); W. K. Kwok, W. G. Lee, and S. I. Miller, *ibid.*, **91**, 468 (1969).

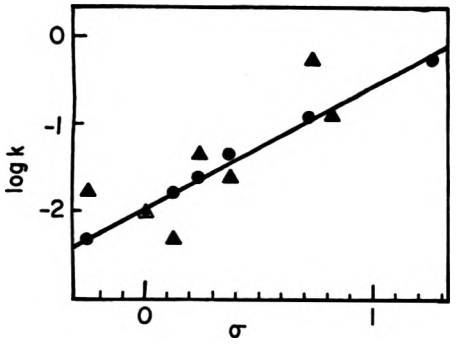
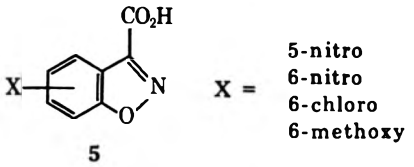


Figure 3.—Log k_{cat} for *N*-methylmorpholine-catalyzed decomposition of 5- and 6-monosubstituted benzisoxazoles as functions of Hammett values: ▲ points are plotted as functions of σ_{meta} for 5 substituents and σ_{para} for 6 substituents (test of charge localization at C-3); ● points are plotted as functions of σ^-_{para} for 5 substituents and σ^-_{meta} for 6 substituents (test of charge appearance at oxygen).

the positional effects of benzo substituents on the stability of charge at the 3 position of an intact benzisoxazole. Such a model is available in the form of pK_a values for 3-carboxybenzisoxazoles (**5**) prepared in



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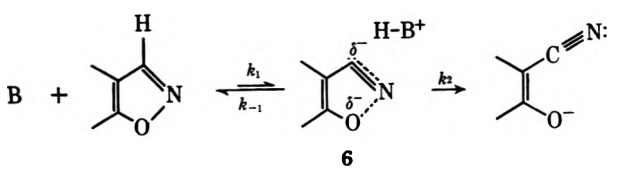
connection with another study.[5,6] A Hammett plot of these pK_a values, using σ_{para}^- for the 6 substituents and σ_{meta} for the 5-nitro compound, gives a ρ value of 0.29, with a correlation coefficient of −0.997. Clearly a localized benzisoxazole 3 anion should be more stabilized by an electron-withdrawing substituent in the 6 position, and the correlations of Figure 3 do correctly test the two mechanistic cases. The plots of Figures 4 and 5 establish this point more directly. Figure 4 plots log k_{OH^-} as a function of the pK_a value of the salicylonitrile formed as product of the reaction. Figure 5 plots log k_{OH^-} as a function of the pK_a value of the corresponding benzisoxazole-3-carboxylic acid. For the first case, a linear correlation is observed, while, for the second, the points for the critical nitro substituents deviate widely from linearity. Clearly, the transition state for the benzisoxazole decompositions has little of the character of an inductively stabilized, localized 3 carbanion, and very much the character of a salicylonitrile anion.

Although the above arguments establish by isotope and substituent effects that both C–H and N–O bonds are extensively cleaved at the rate-determining transition state, one could still argue that an extensively delocalized 3 carbanion such as **6** is not excluded by these



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findings. Evidence pertinent to this possibility is available from tritium exchange experiments.

The conditions of the exchange experiments with tertiary amines allow one to assert that, if an E1cB

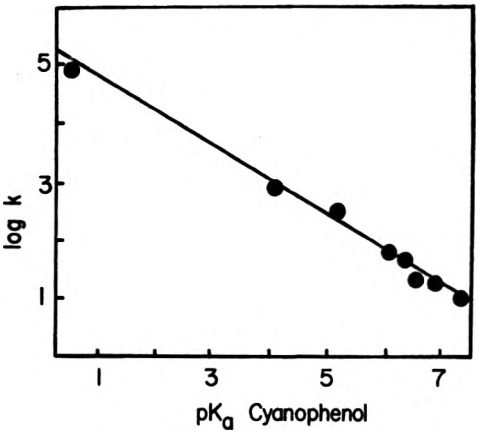


Figure 4.— Log k_{OH^-}, M^{-1} min^{-1}, for decomposition of benzisoxazoles as a function of salicylonitrile pK_a. Points from left to right correspond to 5,7-dinitro, 5-nitro, 6-nitro, 6-chloro, 5-chloro, 6-methoxy, H, 5-methoxy.

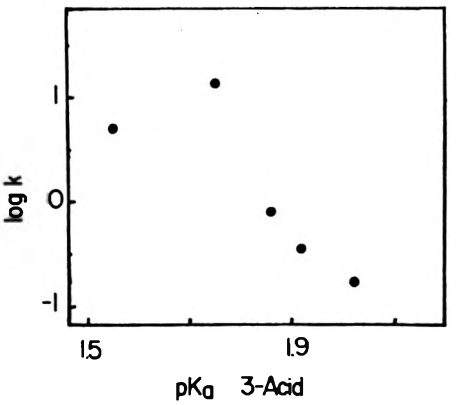


Figure 5.—Log k_{OH^-}, M^{-1} sec^{-1}, for decomposition of benzisoxazoles as a function of pK_a of benzisoxazole-3-carboxylic acid. Points from left to right correspond to 6-nitro, 5-nitro, 6-chloro, H, 6-methoxy.

mechanism is involved in benzisoxazole decompositions, for benzisoxazole in methyldiethanolamine buffer, k_{-1}/k_2 must be smaller than 10^{-6}; with 5-nitrobenzisoxazole in methyldiethanolamine buffer and with 5,7-dinitrobenzisoxazole in 3,4-lutidine buffer, the corresponding ratio must be less than 10^{-5}. Since no tritium incorporation was detected in any of these experiments, the magnitudes of these bounds are set by the experiment, and the limiting ratios may well be orders of magnitude smaller. If one assumes that a benzisoxazole 3 carbanion would react with methyldiethanolammonium ion at diffusion-controlled rates, a reasonable assumption for a localized carbanion in the light of Eigen's work[27] and recent observations concerning heterocyclic ylides,[28] then, since the concentration of ammonium ion was *ca.* 0.1 *M* in these experiments, one can estimate k_{-1} to lie in the range of 10^9–10^{10} sec^{-1}, whereupon k_2 is calculated as 10^{15}–10^{16} sec^{-1}, which is impossibly fast for a unimolecular decomposition.

Could the occurrence of tight ion pairing and resulting internal return drastically reduce the effectiveness of the tritium exchange probe as a test for intermediary anions? Cram has extensively investigated fluorenyl and indenyl systems which permit assessment of relative

(27) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(28) D. S. Kemp and J. T. O'Brien, *J. Amer. Chem. Soc.*, **92**, 2554 (1970).

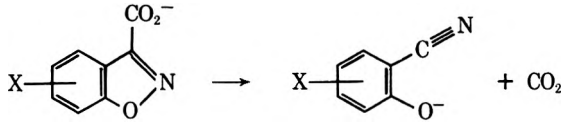
rates of internal isomerization and exchange *vs.* external exchange.[29] The results of Cram and coworkers can be briefly and qualitatively summarized. (1) In media of low dielectric constant and with tertiary amines as catalysts, isomerization can be as much as 300 times faster than external exchange. (2) In polar media, external exchange competes effectively with internal isomerization processes. (3) With primary amines as catalysts, exchange is always competitive with isomerization, presumably because the rate-determining step for exchange is reduced to a slight rotation of the cation component of a tight ion pair.

Although internal return processes seem unlikely in the polar media of our study, we carried out a final exchange experiment with 5-nitrobenzisoxazole and an acetonitrile–methanol–water solution of aminotris(hydroxymethyl)methane, a primary amine catalyst which is expected to maximize exchange within a tight ion pair. Using an order of magnitude higher tritium concentration than with the previously described experiments, we observed no exchange; under these conditions, k_{-1}/k_2 would have to be smaller than 10^{-7}.

In the light of the above evidence, we confidently conclude that the mechanism of base-catalyzed benzisoxazole decomposition is a concerted, intermediateless E2 elimination.

A further mechanistic point concerns the possible importance of subsidiary catalytic effects, such as acid catalysis or hydrogen bonding at the benzisoxazole oxygen.

Recently we gave a preliminary account of a related study[5,6] of the mechanism of decarboxylation of benzisoxazole-3-carboxylic acids in which it was shown that loss of carbon dioxide also occurs concertedly with N–O bond cleavage. The rate of the reaction in water was found to be proportional to the concentration of acid anion, and, remarkably, no general acidic catalysis



could be detected, even under conditions for which protonation of the cyanophenolate intermediate is thermodynamically favorable by a factor of 10^5.

From the similarity of mechanism and dependence of reactivity on substitution, it seems likely that the chemistry of proton transfer and decarboxylation of these two benzisoxazole systems are closely related, and one may therefore conclude that general acid catalysis is unlikely to play a role in accelerating the reactions of benzisoxazoles with bases.

Two points which are unrelated to the rate and mechanism problem arise from the data of the preceding section and seem worthy of comment. The pK_a value of -5 for the N-protonated conjugate acid of benzisoxazole contrasts with those of simple isoxazoles. Albert quotes values of 1.3 and 2.3 for the pK_a of protonated isoxazole and 5-methylisoxazole,[30] and, while benzo fusion is expected to result in an increase in acid strength, the change is usually only one to two pK_a units,[31] rather than the six or seven here observed. On the other hand, the very low basicity of benzisoxazole correlates well with its abnormal inertness toward alkylating agents,[32] and it might be noted that the conjugate acids of oximes have pK_a values near zero,[33] and an oxime with electronegative substituents, such as a benzisoxazole, should be materially less basic. It appears, therefore, that benzisoxazole in fact has the basicity expected by analogy with acylic relatives, and that the abnormality is the high basicity of simple isoxazoles.

The availability of an estimate of $\Delta H°$ for the isomerization of benzisoxazoles to salicylonitriles permits a reexamination of the question of the degree of resonance stabilization of isoxazoles. If one takes the value 48 kcal/mol for the normal O–N bond strength,[34] then, using standard values of the strengths of other bonds, one obtains an estimate of -30 kcal/mol for the heat of isomerization, which may be compared with the observed value of -27 kcal/mol. Strain in the isoxazole ring should not exceed 3–5 kcal/mol, and if included would render the estimated $\Delta H°$ more negative. Although there is appreciable uncertainty in these estimates, largely arising from the value for the O–N bond strength, it seems clear that benzisoxazole is roughly as resonance-stabilized as its isomer, salicylonitrile, and early estimates of a substantial resonance stabilization for isoxazoles are in error.[35]

Summary

The reaction of 3-unsubstituted benzisoxazoles with bases has been shown to be a quantitative, irreversible, highly exothermic process, proceeding by a concerted E2 mechanism. Rate depends on the concentration of base, and catalysis has been shown, by analogy with a related system, to be involved only in removing the 3 proton. The reaction is strongly accelerated by electron-withdrawing substituents, and is markedly sensitive to the strength of the base. Two other studies have shown that an identical mechanism applies to the decomposition of 2-alkylbenzisoxazolium salts[5] and to the decomposition of benzisoxazole-3-carboxylic acids.[4] Although final proof must await further mechanistic studies, we conjecture that clean E2 cleavage with marked sensitivity of rate to benzo substituents will be a characteristic feature of the decomposition of any benzisoxazole which bears a 3 substituent which can act as an electron-deficient leaving group.

Considered as an anionoid leaving group, the benzo-substituted 3-benzisoxazolyl function has several unique and desirable features. In all cases studied, the reactions appear to be clean and quantitative. The reactions can be easily monitored, for the uv properties of the system permit detection at very low substrate con-

(29) D. J. Cram, W. T. Ford, and L. Gosser, *J. Amer. Chem. Soc.*, **90**, 2598 (1968); W. T. Ford and D. J. Cram, *ibid.*, **90**, 2606 (1968); W. T. Ford and D. J. Cram, *ibid.*, **90**, 261 (1968); J. Almy and D. J. Cram, *ibid.*, **91**, 4459 (1969).

(30) A. Albert, "Heterocyclic Chemistry," 2nd ed, Oxford University Press, London, 1968, p 442. These values seem more reasonable than earlier values quoted by Quilico, ref 1, pp 41 and 53.

(31) Compare, for example, imidazole, $pK_a = 7.0$, with benzimidazole, $pK_a = 5.5$.

(32) E. P. Kohler and W. F. Bruce, *J. Amer. Chem. Soc.*, **53**, 644 (1931).

(33) E. M. Arnett in "Progress in Physical Organic Chemistry," S. Cohen, A. Streitweiser, Jr., and R. Taft, Ed., Interscience, New York, N. Y., 1963, p 282.

(34) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworths, London, 1958, p 278.

(35) See, for example, R. A. Barnes in "Heterocyclic Compounds," Vol. 5, R. A. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 453; also see G. Del Re, *Tetrahedron*, **10**, 81 (1960).

centrations. The direct correlation between reaction rate constant and salicylonitrile pK_a provides a built-in measure of the expected effects of substitution on reactivity. (In fact, if more refined thermodynamic measurements can establish that substituent effects on the benzisoxazole–salicylonitrile equilibrium constant are very small, then the salicylonitrile pK_a values must provide an exact measure of the effect of substituents on equilibria for the conversion of benzisoxazoles to salicylonitrile anions.) The predictability of the effect of benzo substitution on rate, together with the rigidity of the benzisoxazole function and the large separation of the 3 position and the reactivity-influencing benzo sites, implies that the leaving group properties of the benzisoxazole can be varied predictably and independently, with minimal idiosyncratic interaction with the region of reacting bonds adjacent to the 3 position. Because of this property, we feel that families of substituted benzisoxazoles offer much promise as experimental tools for the analysis of a variety of subtle mechanistic questions. In an initial study of this kind,[6,36] we have approached the problem of the existence of intrinsic curvature of Brønsted plots by determining the joint effects of base strength and ring substitution on the rates of proton transfer from benzisoxazoles. Other studies of solvent effects have been completed or are in process.[6,18] The ready availability of 3-acylbenzisoxazoles and their rapid cleavage by nucleophiles suggest an obvious application to acyl transfer chemistry which remains to be explored.

(36) D. S. Kemp and M. L. Casey, submitted to *J. Amer. Chem. Soc.*

Registry No.—Hydroxylammonium *O*-sulfate, 2950-43-8; 4-chlorosalicylaldehyde, 2420-26-0; 5-chlorosalicylaldehyde, 635-93-8; 5-methoxysalicylaldehyde, 672-13-9; 4-methoxysalicylaldehyde, 673-22-3; 4-nitrosalicylaldehyde, 2460-58-4; benzisoxazole, 271-95-4; 5-nitrobenzisoxazole, 39835-28-4; [3-^{2}H]-5-nitrobenzisoxazole, 39835-29-5; [*formyl*-^{2}H]-5-nitrosalicylaldehyde, 39835-30-8; 5,7-dinitrobenzisoxazole, 39835-31-9; trimethylamine, 75-50-3; methyldiethanolamine, 105-59-9.

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Chemistry of Diarylazoalkanes. IV. Effect of Substituents on the Thermal Decomposition of Symmetrically Disubstituted 1,1′-Diphenyl-1,1′-azoethanes[1,2]

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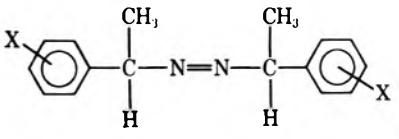
The effect of substituents upon the first-order thermal decomposition of symmetrically disubstituted 1,1′-diphenyl-1,1′-azoethanes was studied in *p*-cymene using a spectroscopic method. The observed effects can best be explained in terms of the relative importance of inductive and resonance effects (including hyperconjugation). Steric factors resulting from electrostatic repulsions are also involved in some cases. The importance of steric effects was especially evident in the increased rate of decomposition with an *o*-methoxy substituent on each phenyl group. The substituted α-phenylethyl radicals, formed by thermal decomposition of the respective azo compounds in *o*-dichlorobenzene, coupled to form disubstituted 2,3-diphenylbutanes. Minor amounts of substituted ethylbenzenes were also produced, probably by disproportionation. The corresponding substituted styrenes were not found and presumably were polymerized under the conditions of the reaction. Activation parameters were determined for most of the thermal decompositions.

Shelton and coworkers[2,3] investigated the effect of substituents upon the thermal decomposition of disubstituted azocumenes $[XC_6H_4(CH_3)_2CN{=}]_2$, X = H, *p*-CH_3, *p*-CH_3CH_2, *p*-$(CH_3)_2CH$, *p*-$(CH_3)_3C$, *p*-F, *p*-Br, *p*-Cl, and *m*-Cl, as part of their continuing study of the behavior of radical species.[4] The effects of the substituents upon the rates were small but significant, as also observed in the similar systems of the previous investigations.[5]

The availability in this laboratory of a modified synthetic method[6] suggested the possible preparation of a series of symmetricaly disubstituted 1,1′-diphenyl-1,1′-azoethanes (A) by oxidation with freshly made mercuric oxide of appropriately substituted hydrazines.



A, X = H, *o*-CH_3O, *p*-CH_3, *p*-CH_3CH_2, *p*-Cl, *p*-F, *p*-CH_3O, *m*-CH_3, *m*-CH_3O, *m*-Cl, *m*-F, *m*-CF_3

It was the purpose of this study to investigate the effects of the various substituted groups on the rate of decomposition and product distributions of these azo compounds. Some known derivatives are included in the series as a basis for comparison with prior studies.[5]

(1) Taken from the Ph.D. Thesis of C. K. Liang, Case Western Reserve University, 1969.

(2) Paper III of the series: P. Kovacic, R. R. Flynn, J. F. Gormish, A. H. Kappelman, and J. R. Shelton, *J. Org. Chem.*, **34**, 3312 (1969).

(3) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968).

(4) J. R. Shelton and C. W. Uzelmeier, *J. Amer. Chem. Soc.*, **88**, 5222 (1966).

(5) S. G. Cohen, S. J. Groszes, and D. B. Sparrow, *J. Amer. Chem. Soc.*, **72**, 3947 (1950); S. Solomon, C. H. Wang, and S. G. Cohen, *ibid.*, **79**, 4104 (1957).

(6) J. R. Shelton and C. K. Liang, *Synthesis*, (4), 204 (1971).

TABLE I

THERMAL DECOMPOSITION OF DISUBSTITUTED 1,1′-DIPHENYL-1,1′-AZOETHANES IN *p*-CYMENE

Registry no.	X in $[XC_6H_4CH(CH_3)N=]_2$	$k_1 \times 10^5$, sec^{-1} 85°	95°	105°	Rel reactivity 95°	Rel reactivity 105°
32234-19-8	*m*-CH_3O		1.53[a]	6.91 ± 0.04	0.56	0.84
32234-16-5	*p*-F	0.55 ± 0.12	2.35 ± 0.02	7.85 ± 1.10	0.86	0.96
5661-68-7	H		2.74 ± 0.06	8.21 ± 0.01	1.00	1.00
32234-18-7	*m*-CH_3			8.17 ± 0.07		1.00
32234-14-3	*p*-CH_3CH_2		3.02 ± 0.05	9.14 ± 0.13	1.10	1.11
32234-13-2	*p*-CH_3		3.06 ± 0.19	9.35 ± 0.10	1.12	1.15
32234-15-4	*p*-CH_3O		3.56 ± 0.03	10.90 ± 0.09	1.30	1.33
32234-20-1	*m*-F			11.21 ± 0.01		1.37
32234-21-2	*m*-Cl		4.13 ± 0.02	12.18 ± 0.01	1.51	1.46
32234-22-3	*m*-CF_3[b]		4.13	13.57	1.51	1.66
32234-17-6	*p*-Cl	1.45 ± 0.00	4.82 ± 1.20	16.50 ± 0.00	1.75	2.01
32234-23-4	*o*-CH_3O	1.69[c]	6.11 ± 1.00	19.75 ± 0.25	2.23	2.42

[a] Value may be low on the basis of higher relative rate observed at 105°. [b] Compound melted at 9–10° and was not recrystallized. [c] Measured at 84.6°.

Results and Discussion

Thermal Decomposition Rates.—Cohen and coworkers[5] studied the rates of decomposition of para,para′-disubstituted 1,1′-diphenyl-1,1′-azoethanes by measuring gas evolution. In our study, rates of decomposition were determined by following the disappearance of visible absorption due to the azo linkage of this series of compounds, which has a characteristic wavelength of 359 mμ and follows Beer's law.[7] No absorbance was shown in this region by either the solvent, *p*-cymene, or the decomposition products. In order to minimize the possible absorption interference due to a trace of acetophenone azines resulting from oxidation of azo compounds, the Guggenheim method[8] was employed to calculate the rate constants. The kinetic results are shown in Table I.

It is of particular interest that the rate of decomposition of 1,1′-diphenyl-1,1′-azoethene at 105° observed in this laboratory agrees with the previous findings,[5,9] within 3%. Molecular models indicate that the cis configuration of this compound would exhibit considerable steric strain, and it is generally accepted that the trans azo configuration is preferentially formed.[9]

It is helpful to compare the results obtained previously in this laboratory[2,3] for the thermal decomposition of disubstituted azocumenes (shown in Table II) with the data obtained in this study (Table I). It can be seen that the effects of the substituents in both systems on the rates of decomposition are relatively small (as expected for a radical mechanism) but significant. The results obtained in both studies indicated that the Hammett relation was not applicable, since there was mutual conjugation between the substituents and the reaction center (developing radical) in the transition state for the decomposition of the para-substituted azo compounds.

TABLE II

RELATIVE REACTIVITIES FOR THERMAL DECOMPOSITION OF DISUBSTITUTED AZOCUMENES AT 42.8° IN TOLUENE[a]

X in $[XC_6H_4(CH_3)_2N=]_2$	Rate constant $k_1 \times 10^5$, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[b] cal/deg mol	Relative reactivity
H	1.13	29.3	11.4	1.00
p-$(CH_3)_2CH$	1.13	29.7	14.9	1.00
p-$(CH_3)_3C$	1.16	29.5	13.9	1.02
p-CH_3CH_2	1.29	29.0	14.6	1.13
p-F[c]	1.31	27.7	9.0	1.16
p-CH_3	1.66	28.8	10.2	1.46
m-Cl[c]	2.46	27.7	7.6	2.18
p-Br	2.72	28.1	8.7	2.40
p-Cl[c]	2.90	26.9	6.5	2.67

[a] Reference 3. [b] Reference 10a. [c] Reference 2.

The relative reactivities in Tables I and II show that for those substituents which produced significant changes in the rate of thermal decomposition the relative order is the same in both series: azocumene series, *p*-Cl (2.7) > *m*-Cl (2.2) > *p*-CH_3 (1.5) > H (1.0); azo-α-phenylethane series, *p*-Cl (2.0) > *m*-Cl (1.5) > *p*-CH_3, H (1.0).

Comparing the relative effect of a given substituent in the two series shows a much greater effect upon the rate of thermal decomposition of an azocumene as compared to the same substituent on the phenyl groups of a 1,1′-diphenyl-1,1′-azoethane. This trend has been confirmed by Timberlake[10a] and extended to include a series of phenylazomethanes which exhibit even smaller substituent effects. These results are contrary to the order which would be expected from consideration of activation energies, which predict more bond breakage in the transition state for phenylazomethanes and phenylazoethanes as compared to the azocumenes. It seems probable that steric factors may account for the faster rates and greater susceptibility to substituent effects as methyl groups replace hydrogen on the methylene groups of the phenylazomethanes. Overberger and coworkers[11] used a steric argument to rationalize the increased rate observed with isobutyl compared to *n*-butyl in azonitriles.

The α-methylbenzylic radicals generated in the present system would be expected to be more reactive than the cumyl radicals (generated from the azocumenes), since the latter radicals have an additional methyl group to aid in the stabilization. Weiner and Hammond[12] found that the relative rate of bimolecular

(7) S. Seltzer, *J. Amer. Chem. Soc.*, **83**, 2625 (1961).
(8) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).
(9) S. Seltzer and E. R. Hamilton, Jr., *J. Amer. Chem. Soc.*, **88**, 3775 (1966).
(10) (a) J. W. Timberlake, private communication. (b) J. W. Timberlake and M. L. Hodges, *Tetrahedron Lett.*, 4174 (1970).
(11) C. G. Overberger, M. T. O'Shaughnessy, and H. Shalit, *J. Amer. Chem. Soc.*, **71**, 2661 (1949).
(12) S. A. Weiner and G. S. Hammond, *J. Amer. Chem. Soc.*, **91**, 986 (1969).

combination plus disproportionation is $C_6H_5\dot{C}HCH_3$ (5.0)/$C_6H_5\dot{C}(CH_3)_2$ (1.0).

The rates of decomposition of the symmetrically disubstituted 1,1′-diphenyl-1,1′-azoethanes in Table I decrease in the order *o*-CH_3O > *p*-Cl > *m*-CF_3 > *m*-Cl > *p*-CH_3O, *m*-F > *p*-CH_3, *p*-CH_3CH_2 > *m*-CH_3, H, *p*-F > *m*-CH_3O.

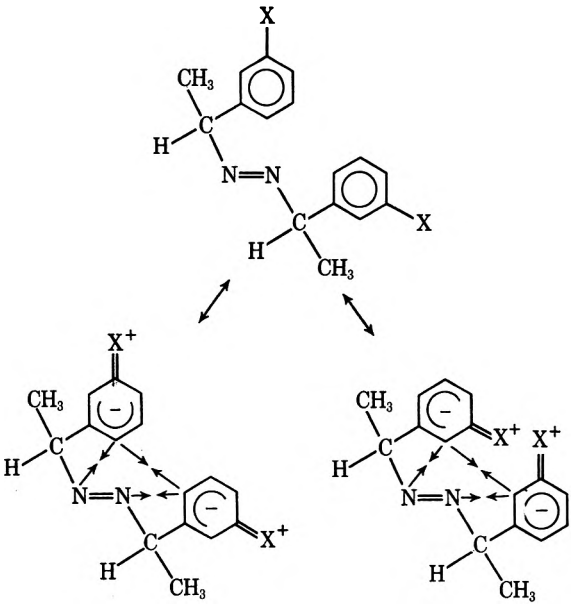
The net effect upon rate appears to be the resultant of a combination of inductive, resonance, and steric effects. A detailed analysis is not justified in view of the small differences observed, but some interpretation can be made consistent with the comparable effects observed in the azocumene work.[2,3]

The net outcome from the combined inductive and resonance influences appears to determine the observed rate order for the para-substituted azo compounds. The favorable resonance contribution of *p*-Cl and *p*-CH_3O outweighs the adverse inductive effect. The lesser effect of the methoxy group is consistent with a recent observation by Timberlake "that the stabilizing effect of the methoxy group in a pure radical system is small."[10] In the case of *p*-F any stabilization from resonance appears to be offset by induction; so the observed rate is very close to that of the parent compound, as was also observed in the azocumene study (Table II).

It is interesting that the *m*-F, *m*-Cl, and *m*-CF_3 substituted azo-α-phenylethanes decomposed at rates comparable to the *p*-Cl and *p*-CH_3O derivatives. In our discussion of the similar activating effect of *m*-Cl in azocumene,[2] we noted two possible hypotheses: (1) the adverse inductive effect should be negligible when the halogen is attached to a carbon which does not possess radical character in the transition state; and (2) a resonance effect may be indirectly involved.

The effects of meta substituents, often thought to be mainly inductive factors, may result in part from the charges, positive or negative, which they inject into the benzene rings to which they are attached. In symmetrically substituted diarylazoalkanes, the resulting electrostatic repulsions between the two halves of the molecule, as indicated in structures **1**, could contribute to the observed increased rate of decomposition observed with the *m*-F, *m*-Cl, and *m*-CF_3 compounds. In the latter case, C–F hyperconjugation[13] would impart a positive charge on the benzene rings with a resultant electrostatic repulsion. Alternatively, direct repulsions due to the electrons surrounding the halogen atoms may be a more important factor in the observed activating effects of *m*-F, *m*-Cl, and *m*-CF_3 substituents. Marvel and coworkers[14] observed a similar activating effect of *m*-Cl in the decomposition of hexarylethanes, which they explained in terms of electrostatic repulsions resulting from resonance interactions of the type illustrated in **1**.

The somewhat slower rate of decomposition of the *m*-CH_3O derivative than the parent compound is not consistent with the above resonance interpretation. Marvel[14] observed a similar lower reactivity for methoxy compared to other substituents in hexarylethanes [*m*-Cl (8.18)/*m*-CH_3O (1.27)]. Thus, direct repulsions between the halogen atoms in these meta derivatives may be the major factor in the observed activating effects rather than an indirect effect involving partial charges resulting from resonance delocalization.



1

(→ ←) = electrostatic repulsion
X = Cl, F

The *o*-methoxy derivative was the most reactive of the compounds studied. The much faster rate of decomposition as compared to *p*-CH_3O suggests a rather large steric effect. This view is supported by the unexpected doubling of the nmr spectra of the *o*-CH_3O derivative, as shown in Figure 1.[15] Doubling was also observed in the nmr spectra of the *m*-CF_3 compound (Figure 2).[15] In both cases, the methyl protons α to the azo group gave two sets of doublets which were centered at δ 1.38 and 1.42 for the *o*-CH_3O compound and at δ 1.50 and 1.56 for the *m*-CF_3 derivative. In contrast, all the other azo compounds in the series showed only the expected doublet for the corresponding methyl protons, as shown in Figures 3 and 4[15] for the *m*-Cl and *m*-CH_3O compounds. The methoxy protons appeared as the expected singlet in Figure 4 and also in the *p*-CH_3O isomer, but two singlets are seen in Figure 1, centered at δ 3.71 and 3.76, for the *o*-CH_3O protons. The methine protons are not affected and appear as the expected quartet centered at δ 4.70 and 5.07 for *m*-CF_3 and *o*-CH_3O, respectively.

Similar doubling of nmr spectra has been observed by others. This is an expected effect "when the rate of rotation about a given bond is intermediate between free rotation about unhindered bonds and the severely hindered rotation about formal double bonds, so that the nmr spectrum usually consists of a superposition of

(13) W. A. Sheppard and C. M. Shorts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, Chapter 3.

(14) M. F. Roy and C. S. Marvel, *J. Amer. Chem. Soc.*, **59**, 2622 (1937); C. S. Marvel, J. F. Kaplan, and C. M. Himel, *ibid.*, **63**, 1892 (1941); C. S. Marvel, J. Whitson, and H. W. Johnston, *ibid.*, **66**, 415 (1945); C. S. Marvel, F. C. Deitz, and C. M. Himel, *J. Org. Chem.*, **7**, 392 (1942).

(15) Figures 1–4 showing the nmr spectra of *o*-CH_3O, *m*-CF_3, *m*-Cl, and *m*-CH_3O disubstituted 1,1′-diphenyl-1,1′-azoethane will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2301.

spectra resulting from the two (or more) rotational isomers that are present in equilibrium." [16]

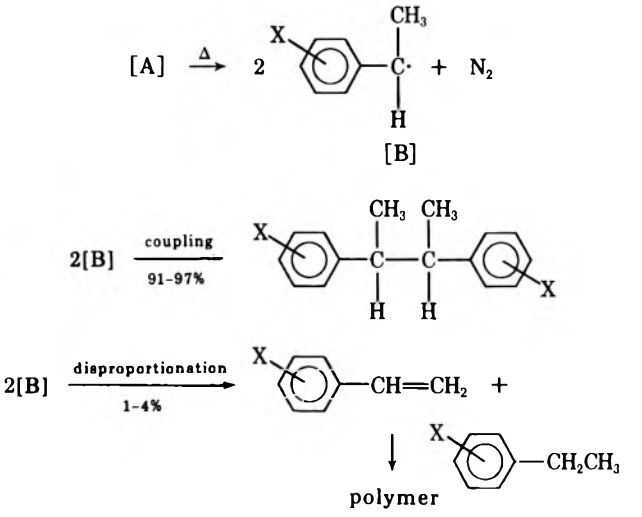
Alternatively, the observed doubling of the nmr spectra in the present study could be due to a mixture of meso and *dl* isomers which, having magnetically nonequivalent methyl groups, would give rise to two sets of doublets. It is possible that pure meso compounds were isolated in all the other cases, since they would be expected to be the least soluble of the diastereoisomers.[17] The presence of a second diastereoisomer in the *m*-CF_3 case is probable in view of the low melting point (9–10°)[6] and the weak intensity of one of the doublets, consistent with contamination by a small amount of another isomer. In contrast, both methyl doublets and the two methoxy singlets observed with *o,o'*-dimethoxy-1,1'-diphenyl-1,1'-azoethane are major peaks, and this compound was a crystalline solid (mp 56.5–58°).[6] It seems improbable that the same experimental procedures would yield essentially pure isomers of all the other crystalline compounds, and a mixture of diastereoisomers in this one case.

In order to test the restricted rotation hypothesis in this case, nmr spectra were also determined at other temperatures. Lowering the temperature produced no change, and higher temperatures caused decomposition, which gave very complex spectra. The nmr data are thus inconclusive, but the evidence of a rather large steric contribution to the increased rate of decomposition of the *o*-CH_3O disubstituted diphenylazoethane supports the interpretation that nonbonding interactions between these ortho methoxy groups and the azo α-methyl group may be strong enough to restrict rotation and cause the α-CH_3 to give rise to two different sets of doublets, and the CH_3O group to show two singlets as seen in Figure 1.[15]

Activation parameters for the thermal decomposition of disubstituted 1,1'-diphenyl-1,1'-azoethanes were calculated for all compounds in Table I for which rate constants were determined at two or more temperatures. The relative reactivity increases going down in Table I, and both enthalpy of activation and entropy of activation tend to lower values going down the series in the same order in Table III. (The values for the *m*-CH_3O compound are less reliable than the others, since the rate constant at 95° in Table I may be low.) The values for the *p*-F, *p*-Cl, and *o*-CH_3O compounds are the most reliable, as they represent rate constants determined at three temperatures over a wider range.

Bartlett and Hiatt[18] observed a similar tendency for a lowering of the activation energy associated with a lowering of activation entropy in their study of perester decomposition. Since these effects oppose each other, the net result in their series, and in the present study of the decomposition of diarylazoalkanes, was found to be in the direction indicated by the enthalpies of activation.

Product Analysis.—The organic products of the thermal decomposition of disubstituted 1,1'-diphenyl-1,1'-azoethanes in *o*-dichlorobenzene are mainly the coupling products of the substituted α-phenylethyl radicals plus some disproportionation products. A reaction scheme similar to that proposed for the azocumene system[3,19] follows.



The products were analyzed by gas–liquid partition chromatography (glpc) and only disubstituted 2,3-diphenylbutanes and minor amounts of substituted ethylbenzenes were observed in the reaction mixtures. Any substituted styrenes, formed by disproportionation, were evidently polymerized, since the α-phenylethyl radicals are excellent initiators, as was demonstrated in the polymerization of styrene by Cohen and coworkers.[5]

The distribution of the substituted α-phenylethyl radicals to observed products is listed in Table IV. Coupling to form substituted diphenylbutanes accounted for 91–97% of the radicals produced. This is in good agreement with a similar study done by Seltzer[7] with the deuterio derivative, 1,1'-diphenyl-1,1'-azoethane-*1,1'-d*$_2$. He found that the atom % D in the only identified product, 2,3-diphenylbutane-*2,3-d*$_2$, from the thermal decomposition of the azo compound in ethylbenzene is the same, within 15%, as that in the starting material. He did not detect the disproportionation product, since it would have been the same as the solvent, ethylbenzene. The formation of up to 2% of the substituted ethylbenzene in the present study indicates that up to 4% of the

TABLE III

ACTIVATION PARAMETERS FOR THERMAL DECOMPOSITION OF DISUBSTITUTED 1,1'-DIPHENYL-1,1'-AZOETHANES IN *p*-CYMENE

X in [$XC_6H_4CH(CH_3)N{=}]_2$	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[a] cal/deg mol	$\Delta\Delta H^{\ddagger}$, kcal/mol	$\Delta\Delta S^{\ddagger}$, cal/deg mol
m-CH_3O	41.0[b]	30.3[b]	11.4	29.7
p-F	35.1	15.0	5.5	14.4
H	29.6	0.6	0.0	0.0
p-CH_3CH_2	29.9	1.6	0.3	1.0
p-CH_3	30.2	2.3	0.6	1.7
p-CH_3O	30.2	2.8	0.6	2.2
m-Cl	29.2	0.4	−0.4	−0.2
m-CF_3	32.2	8.5	2.6	7.9
p-Cl	32.0	8.2	2.4	7.6
o-CH_3O	32.4	9.7	2.8	9.1

[a] Estimated error ± 2 cal/deg mol. [b] See footnote *a* in Table I.

(16) J. R. Dyer, "Application of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 113.

(17) F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Amer. Chem. Soc.*, **92**, 867 (1970).

(18) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

(19) S. F. Nelson and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).

TABLE IV

DISTRIBUTION OF RADICALS[a] TO OBSERVED PRODUCTS. THERMAL DECOMPOSITION OF DISUBSTITUTED 1,1′-DIPHENYL-1,1′-AZOETHANES IN *o*-DICHLOROBENZENES, 120°

X in [$XC_6H_4CH(CH_3)N=$]$_2$	$XC_6H_4CH_2CH_3$, %	[$XC_6H_4CH(CH_3)-$]$_2$, %	Overall yield, %
m-CH_3O	*b*	97 ± 0.2	97
p-F	<2	96 ± 0.6	98
H	2.2	91 ± 3	93
m-CH_3	<2	93 ± 1	95
p-CH_3CH_2	*b*	97 ± 1	97
p-CH_3	1.3	96 ± 1	97
m-F	<2	95 ± 0.5	97
m-Cl	*b*	97 ± 1.5	97
p-CH_3O	*b*	92 ± 0.5	92
o-CH_3O	*b*	93 ± 2	93

[a] Mole percentage of radicals accounted for after 24 hr of decomposition based on amount of azo compounds before reactions. [b] Glpc showed no peak for this product, estimated to be less than 1%.

radicals were involved in disproportionation, since an equivalent amount of the substituted styrene would be expected. It is also apparent that the effect of the substituents on the product distribution is negligible, consistent with the azocumene findings.[3]

Experimental Section

Syntheses of the azo compounds are reported elsewhere by Shelton and Liang,[6] including yields, melting points, analysis, and nmr data.

Decomposition Rate Measurements.—The solvent, *p*-cymene (Fisher), was distilled over calcium hydride and the middle fraction, bp 174–174.5°, was collected. Nitrogen, passed through a drying tube filled with Drierite, was bubbled through the *p*-cymene for at least 30 min at room temperature to expel the oxygen. A 180-ml portion of this *p*-cymene was transferred to the reaction vessel which was immersed in a constant-temperature bath (Lauda Thermostat, Type NBss15122) and purged with nitrogen throughout the entire reaction. After the temperature of the whole system was equilibrated, a 20-ml solution of azo compound (0.4–0.5 g, recrystallized before use, in 20 ml of pure dried *p*-cymene) was injected with a 50-ml syringe into the reaction vessel through a septum. After the contents came to temperature equilibrium with the bath (generally 5 min), sampling was started using a 10-ml syringe with a 12-in. needle.

Ten samples were taken at intervals of 30 min by puncturing the septum and withdrawing approximately 8 ml of the reaction mixture. The samples were transferred immediately into small brown bottles and quenched in an ice–water bath. The second set of ten samples was obtained in the same manner after about 1–2 half-lives. Then each sample was transferred to an uv cell (2-cm quartz) and absorbance was measured at a fixed wavelength, 359 mμ, with an A. P. C. Cary 14 recording spectrophotometer.

Excellent linear first-order plots were obtained using the Guggenheim method[8] by plotting ln $(A_t - A_{T+t})$ *vs.* time, where A is absorbance at 359 mμ, T is the time between the starts of the two series of samples, and t is the time interval (30 min). From these data rate constants were calculated. Activation parameters were obtained from decomposition rates measured at 105, 95, and in some cases 85°.

Product Analysis.—A 10–15-ml sample of the disubstituted 1,1′-diphenyl-1,1′-azoethane in *o*-dichlorobenzene solution (concentration ~0.07 *M*) was placed in a 50-ml flask fitted with reflux condenser and nitrogen inlet to give approximately 0.7–1.0 mmol of the azo compound. This flask was flushed with nitrogen and then immersed in a constant-temperature oil bath (120°) for about 24 hr under positive nitrogen pressure.

The raw reaction mixtures were analyzed by a Matronic Model 500 dual-column gas chromatograph. For the high-boiling products, a 2 ft × 0.25 in. column packed with 20% SF-96 on acid-washed Chromosorb P (30–60 mesh) was used, and, for the lower molecular weight materials, a 10 ft × 0.125 in. column packed with 5% diisodecyl phthalate and 5% Bentone-34 on Chromosorb G (60–80 mesh) was employed.

The reaction products from the decomposition of *p,p*′-dimethyl-1,1′-diphenyl-1,1′-azoethane and the parent compound were identified by comparison of glpc retention times with those of authentic samples which were either made by other routes or obtained commercially. Based on this information, the coupling and disproportionation products for the other derivatives could be easily identified by the reltaive retention times observed in each case. The coupling products of the methoxy isomers, for example, showed the following retention times: *p*-CH_3O (2.7 min)/*m*-CH_3O (2.1 min)/*o*-CH_3O (2.0 min). Since only a single peak was observed on each gas chromatogram, the identification was definite in every case.

Acknowledgment.—The authors are indebted to Miss Frances Chang for her contribution in obtaining rate data at additional temperatures for several of the azo compounds to permit calculation of the activation parameters. This work is part of a series of studies of free-radical reactions supported by the Goodyear Tire and Rubber Co., Akron, Ohio.

The Oxymercuration of Cycloalkenes

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The hydroxymercuration and methoxymercuration reactions of the eight stable unsubstituted cycloalkenes from C_4 through C_9 are reported. Near-ir hydroxy shift measurements and nmr methoxy shift measurements were used to assign product configurations of the β-hydroxymercurials and β-methoxymercurials, respectively. While the six *cis*-cycloalkenes underwent clean trans addition of the reagents, both *trans*-cyclooctene and *trans*-cyclononene reacted in an exclusively cis fashion. The tendency of an olefin to oxymercurate *via* a trans mechanism can be directly related to its ability to form the normal anti transition state. If for either steric or twist-strain reasons this transition state is made energetically unfavorable, cis addition will prevail.

Of the simple cyclic alkenes, only a few have received attention in the literature with respect to their oxymercuration products. One special problem of this reaction has been to assign the stereochemistry of the resultant alkoxy- or hydroxy-substituted organomercurial.

The product from methoxymercuration of cyclohexene was identified as the trans isomer by X-ray diffraction,[1] deoxymercuration studies,[2] and pmr methoxy shift data.[3] The hydroxymercuration product of cyclohexene was likewise identified as the trans isomer by pmr spin–spin coupling data[4] as well as ir hydroxy shift data.[5] The latter technique also identified the trans β-hydroxyalkylmercurial from cyclopentene.[5] Finally, both the ir technique and chemical methods proved cis-methoxymercuration and -hydroxymercuration of *trans*-cyclooctene.[6]

Since the stereochemical outcome for oxymercuration of cyclic alkenes necessarily sheds light on the transition state for this unique reaction, it was decided to enlarge the above list to include all the stable cycloalkenes from C_4 to C_9. Thus, the six cis olefins plus *trans*-cyclooctene and *trans*-cyclononene were allowed to react with mercuric acetate in both acetone–water and methyl alcohol solvents. The ir hydroxy shift and pmr methoxy shift techniques were used to prove the stereochemistry of hydroxymercuration and methoxymercuration, respectively.

Results

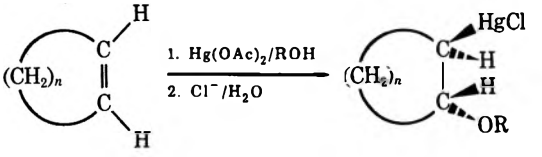
Table I outlines the results of the hydroxy- and methoxymercuration reactions for the C_4–C_9 unsubstituted cyclic alkenes.[7]

As noted in Table I, the *cis*-cycloalkenes from cyclobutene to cyclononene underwent both hydroxymercuration and methoxymercuration in an exclusively trans manner. Only the one product could be detected from each of the 12 reactions (eq 1).[8]

TABLE I

Cycloalkene	Stereochemistry of hydroxymercuration	Near-ir value $\Delta\nu$(OH),[a] cm^{-1}	Stereochemistry of methoxymercuration	Nmr value $\Delta\nu$-(OCH_3),[b] cps
Cyclobutene	Trans	11.9	Trans	7.2
Cyclopentene	Trans[c]	14.0	Trans	5.5
Cyclohexene	Trans[c,d]	12.0	Trans[e]	7.8
Cycloheptene	Trans	14.4	Trans	7.9
cis-Cyclooctene	Trans	20.7	Trans	8.5
trans-Cyclooctene	Cis[f]	20.3	Cis[f]	8.5
cis-Cyclononene	Trans	11.8	Trans	9.7
trans-Cyclononene	Cis[g]	11.8	Cis[g]	9.7

[a] See ref 5; ±2.5 cm^{-1}. [b] See ref 3; ±0.1 cps. [c] See also ref 5. [d] See also ref 4. [e] See also ref 1, 2, and 3. [f] See also ref 6. [g] See ref 9.



(1)

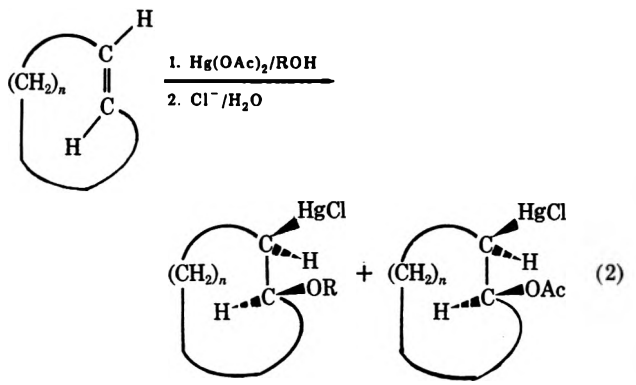
n = 2–7 and R = H or CH_3

In contrast to the cis olefins, both *trans*-cyclooctene[6] and *trans*-cyclononene[9] reacted with both sets of reagents in an exclusively cis fashion. Also, in addition

(1) A. G. Brook and G. F. Wright, *Acta Crystallogr.*, **4**, 50 (1951).
(2) M. M. Kreevoy and F. R. Kowitt, *J. Amer. Chem. Soc.*, **82**, 739 (1960).
(3) W. L. Waters, *Tetrahedron Lett.*, No. 43, 3769 (1969).
(4) M. M. Anderson and P. M. Henry, *Chem. Ind. (London)*, No. 50, 2053 (1961).
(5) T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963).
(6) V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, 136 (1966).
(7) All attempts to oxymercurate cyclopropenes resulted in ring opening. Although the structures of the reaction products were not proven conclusively, it was definite that no simple β-hydroxy- or methoxycyclopropylmercury compounds were produced.
(8) In the case of methoxymercuration the raw β-methoxycycloalkylmercuric acetate was analyzed by nmr spectroscopy. Although it has been our experience that the easily exchangeable acetates on the mercury atom always produce one acetate line for a mixture of isomers, the methoxy singlet has been a reliable indication of isomeric purity.[3] Thus the area immediately adjacent to the observed methoxy singlet was carefully analyzed under increased spectrum amplitude conditions. Also, the total line shape of the methoxy singlet was noted. In each case not only were there no neighboring singlets to be seen but also the methoxy singlet itself was perfectly symmetrical and the peak at half-height approached natural line width.

As for the isomeric purity of the hydroxyoxymercuration products, only the recrystallized β-hydroxycycloalkylmercuric chloride products were subjected to ir measurement.[6] Although not a good indication of isomer distribution in the raw product, it should be noted that only one sharp hydroxyl peak could be seen in the ir of each of the reaction products listed. Isomeric purification to this extent by mere recrystallization seems unlikely.
(9) Professor Reutov's group has also found cis-oxymercuration in the case of *trans*-cyclononene. This and other results are the subject of a paper in preparation by V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov.

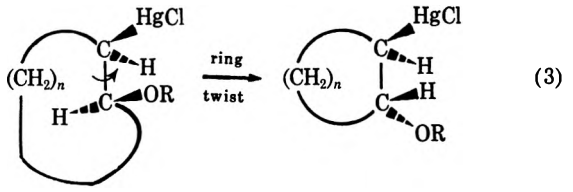
to the usual β-hydroxy or β-methoxy products, β-acetoxy products were sometimes formed[10] (eq 2).



(2)

n = 6, 7 and R = H or CH_3

The strained cis-addition products can undergo immediate ring flipping to give the more stable trans conformers (eq 3). These compounds, once in their



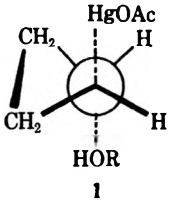
(3)

R = H, CH_3, or Ac

more stable trans conformations, are identical with the products from the cis olefins. Their structural and configurational assignments are therefore made extremely easily.

Discussion

Several contributing factors which can control the stereochemistry of electrophilic addition reactions were considered in some detail by Traylor.[11] Of these, the "twist–strain" theory[11] most adequately explains the results for oxymercuration of the simple *cis*-cycloalkenes. This theory deals with the transition-state stereochemistry for electrophilic addition and predicts that *only* cyclopropene of all the *cis*-cycloalkenes should undergo cis-oxymercuration.[7] In the case of a three-membered carbon ring the necessary anti transition state for normal addition is prohibited. However, cyclobutene, the next higher homolog, should accommodate the necessary 180° coplanar transition state as pictured in **1**, and should even



1

reflect a relief of ring strain compared to the parent olefin.[11]

The results listed in Table I for the C_4–C_9 *cis*-cycloalkenes support the twist–strain theory fully. Whenever there are no other interceding factors, *e.g.*, steric, etc., and whenever there is a decrease—or at least *no increase*—in the strain of a system when going from olefin to an anti transition state, the oxymercuration reaction will occur exclusively *via* a trans mechanism

In contrast to the *cis*-cycloalkenes, it can be noted that both *trans*-cyclooctene and *trans*-cyclononene undergo oxymercuration in an exclusively cis fashion. Although it might be argued that the increased strain involved in the anti transition state for these olefins prevents trans addition, the overriding factor is probably one of steric control. The back side of the π bond, and hence the back side of any intermediate mercurinium ion, is completely shielded toward attack by a nucleophile. Hence, addition can only be exo and cis to cycloalkenes such as these.

In light of the above, one would predict an increasing amount of trans-oxymercuration with larger and larger *trans*-cycloalkenes. In these olefins, the carbon skeletons would be much less rigid, thereby reducing ring strain and virtually eliminating any steric effect. In support of this expectation, Sokolov reports competing cis- *and* trans-oxymercuration for *trans*-cyclodecene and exclusive trans-oxymercuration for *trans*-cyclododecene.[12]

Unfortunately, this work does not settle any of the questions currently being raised about mercurinium ions.[13] However, when added to the results for the rigid and semirigid bicyclic olefins,[11] it does present a unified and very useful stereochemical picture of the overall oxymercuration reaction. Thus, the reaction involves the trans stereospecific addition of a mercury salt and alcohol or water solvent across a carbon–carbon multiple bond *except* in cases where an anti transition state is prohibited by steric and/or "twist–strain" reasons. The dividing lines for these two limitations appear to be *trans*-cyclodecene[12] and bicyclooctene,[13,14] respectively.

Experimental Section

Melting points were taken on a Thomas-Hoover and Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were taken on Perkin-Elmer Infracord 137B and Beckman IR-33, IR-5A, and IR-7 spectrophotometers. Overtone hydroxyl stretching frequencies in the near-ir were measured with a Cary 14 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained with Varian HR-60, A-60, and HA-60 instruments. Vapor phase chromatography (vpc) was performed with Varian A-700 and 1720 gas chromatographs.

Oxymercuration of Cycloalkenes. General Procedure.—To a solution of 1 *M* Hg $(OAc)_2$ in 25% acetone–water or methanol was added an equimolar amount of the cycloalkene (*ca.* 1–10 mmol). The reaction mixture was stirred at room temperature until a test portion failed to give a precipitate of HgO on treatment with 2 *M* NaOH. The reaction mixture was then neutralized by pouring it into an aqueous solution of excess NaCl and $NaHCO_3$, and the β-hydroxy- (or methoxy-) cycloalkylmercuric chloride was isolated by filtration or $CHCl_3$ extraction. The raw solid (or oily) product was then analyzed by ir or nmr spectroscopy to determine isomeric purity.[8] Simple recrystallization from an appropriate

(10) Professor Reutov's group also noted the β-acetoxy products: ref 6 and V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov, *J. Organometal. Chem.*, **17**, 323 (1969). The authors believe that the initial oxymercuration products of *trans*-cycloalkenes are the β-acetoxy compounds, which then react with water or alcohol to give the β-hydroxy- or β-alkoxycycloalkylmercurials.

(11) T. G. Traylor, *Accounts Chem. Res.*, **2**, 152 (1969).

(12) Personal communication from V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov, INEOS, Moscow, U. S. S. R. (paper in preparation).

(13) See, for example, R. D. Bach and R. F. Richter, *J. Amer. Chem. Soc.*, **94**, 4747 (1972).

(14) T. G. Traylor, *J. Amer. Chem. Soc.*, **86**, 244 (1964).

solvent yielded the desired mercury compound suitably pure for elemental analysis or mass spectroscopic studies.

Configurational Assignment of Hydroxymercuration Products.—Approximately 2 mmol of the β-hydroxycycloalkylmercuric chloride was added to *ca.* 30 mmol of $NaBH_4$ in 25 ml of water and stirred overnight at room temperature. The aqueous mixture of the parent alcohol and elemental mercury was then extracted with ether, the extract was dried over $MgSO_4$, and the solvent was removed on a rotary evaporator.

The first overtone hydroxyl stretching frequencies of the alcohols and hydroxymercurials were determined with *ca.* 0.02 *M* CH_2Cl_2 solutions of the sample in 1-cm silica cells. Scale expansion and slow scanning speeds were used to ensure large symmetrical peaks. All overtone frequencies were calibrated relative to phenol, using 7013.1 cm^{-1} as an arbitrary standard reference value. Finally, the cis and trans assignments were made by the generalization that the *trans*-β-hydroxymercurials have $\Delta\nu_{OH}$ values (compared to the parent alcohol) of 10–25 cm^{-1}, while the *cis*-β-hydroxymercurials have $\Delta\nu_{OH}$ values in the range of 29–35 cm^{-1}.[15]

Configurational Assignment of Methoxymercuration Products.—Approximately 2 mmol of the β-methoxycycloalkylmercuric chloride was dissolved in *ca.* 10 ml of 0.5 *M* NaOH at 0°. To the stirred basic solution was added an equivalent amount of $NaBH_4$ as a 1 *M* solution in 0.5 *N* NaOH. After 15 min of additional stirring the product cycloalkyl methyl ether was extracted with *ca.* 1 ml of CCl_4, washed repeatedly with H_2O until neutral, and dried over $MgSO_4$. To the clear CCl_4 solution of the cycloalkyl methyl ether was added a small amount of the β-methoxycycloalkylmercuric chloride and an nmr spectrum was then taken of the mixture (each compound *ca.* 2%). The frequency difference of the two methoxy lines was measured with a frequency counter on an expanded sweep width spectrum. Finally, the cis and trans assignments were made by the generalization that the trans-methoxymercuration products of cyclic olefins have $\Delta\nu_{OCH_3}$ values of 3–10 cps, while the *cis*-β-methoxycycloalkylmercurials have $\Delta\nu_{OCH_3}$ values of 10–13 cps.[3]

Cycloalkenes. Cyclobutene was prepared by the method of Cope[16] from the pyrolysis of the adduct[17] of acetylenedicarboxylic acid methyl ester to cyclooctatriene. The cyclobutene was condensed into a cold trap at −80° and used directly by recondensing it into a reaction solution at −80°. It should be noted that in some cases pyrolysis of the Diels–Alder adduct also produced 1,3-butadiene in about 10% yield.

Cyclopentene, cyclohexene, cycloheptene, and cyclooctene were obtained commercially (Aldrich Chemical Co.) and used without any further purification.

***trans*-Cyclooctene** was prepared by pyrolysis of cyclooctyltrimethylammonium hydroxide, as described by Cope.[18] The olefin, separated by extraction with 20% aqueous $AgNO_3$, was shown to be pure by vpc analysis on a 20 ft × 0.375 in. 20% DEGS column and by comparison of its ir spectrum with that reported.[18] Yield of the trans olefin was 33% of theory.

***cis*-Cyclononene** was prepared by P. G. Marsh using the method of Gardner.[19] Catalytic hydrogenation was chosen as the method for reduction of 1,2-cyclononadiene. The ir spectrum of the product was identical with that reported in the literature.[20]

***trans*-Cyclononene** was prepared by the method of Cope.[21] P. G. Marsh prepared cyclononylamine hydrochloride from dimethyl azelate. The amine hydrochloride was then converted to the usual tetraalkylammonium hydroxide and pyrolyzed at 100° (1 mm). The raw product mixture contained 98% *trans*-cyclooctene by vpc analysis using a 10 ft × 0.25 in. 20% DEGS column. The trans olefin was purified by preparative vpc using a 20 ft × 0.375 in. DEGS column. The ir spectrum of the product matched that in the literature.[20]

Oxymercuration Reactions. Cyclobutene.—Hydroxymercuration of cyclobutene under conditions described above gave a 33% yield of crude *trans*-2-chloromercuricyclobutanol. Recrystallization from chloroform–*n*-heptane gave a white, crystalline solid, mp 95.5–96.0°. *Anal.* Calcd for C_4H_7OHgCl: C, 15.64; H, 2.30; Hg, 65.31. Found: C, 15.75; H, 2.56; Hg, 63.57. The first overtone of the hydroxyl stretching frequency appeared at 7028.3 cm^{-1} (±1.5 cm^{-1}). Reduction of the organomercurial with $NaBH_4$ as outlined above gave cyclobutanol. Its ir spectrum was identical with that of an authentic sample,[17] and its first overtone hydroxyl frequency was found at 7040.2 cm^{-1}.

Methoxymercuration of cyclobutene gave a 65% yield of *trans*-1-methoxy-2-chloromercuricyclobutane, oil at room temperature: mass spectrum molecular ion at *m/e* 320; nmr ($CDCl_3$) τ 5.73 (m, 1), 6.73 (s, 3), 6.9–7.6 (m, 1), 7.8–8.2 (m, 4); spin decoupling *via* saturation at τ 8.0 produced a singlet at τ 5.73, therefore J[C(OMe)H–C(HgX)H] ≅ 0, and ∠CH–CH ≅ 90°. Reduction of the organomercurial with $NaBH_4$ gave cyclobutyl methyl ether (nmr, ir), whose methoxy line (nmr) had shifted 7.2 cps upfield compared to the parent organomercurial.

Contaminating 1,3-butadiene (noted above) produced 1,4-dichloromercuri-2,3-dimethoxybutane (nmr), mp 162.5–165.0° dec, from $CHCl_3$ (lit.[22] mp 165–166°), which separated quickly from all recrystallization solvents.

Cyclopentene.—Hydroxymercuration of cyclopentene gave *trans*-2-chloromercuricyclopentanol as described previously.[5] Reduction of the organomercurial with $NaBH_4$ yielded cyclopentanol (ir) with $\Delta\nu_{OH}$ = 14.0 cm^{-1}.

Methoxymercuration of cyclopentene gave an 85% yield of *trans*-1-methoxy-2-chloromercuricyclopentane: mp 83.0–83.5° from EtOH–H_2O (lit.[23] mp 83.3–83.7°); mass spectrum molecular ion at *m/e* 334; nmr (CCl_4) τ 5.89 (m, 1), 6.73 (s, 3), 7.29 (m, 1), 7.7–8.7 (m, 6). $NaBH_4$ reduction gave cyclopentyl methyl ether (ir, nmr) with $\Delta\nu_{OCH_3}$ = 5.5 cps.

Cyclohexene.—Hydroxymercuration of cyclohexene gave *trans*-2-chloromercuricyclohexanol as described previously.[5] $NaBH_4$ reduction gave cyclohexanol (ir) with $\Delta\nu_{OH}$ = 12 cm^{-1}.

Methoxymercuration of cyclohexene gave an 89% yield of *trans*-1-methoxy-2-chloromercuricyclohexane: mp 113.5–114.5° from EtOH–H_2O (lit.[24] mp 113.5–114.5°); mass spectrum molecular ion at *m/e* 348; nmr ($CDCl_3$) τ 6.66 (s, 3), 6.70 (m, 1), 7.18–9.10 (m, 8). $NaBH_4$ reduction gave cyclohexyl methyl ether (ir, nmr) with $\Delta\nu_{OCH_3}$ = 7.8 cps.

Cycloheptene.—Hydroxymercuration of cycloheptene gave *trans*-2-chloromercuricycloheptanol in 64% yield, mp 78.0–78.5° from chloroform–*n*-heptane. *Anal.* Calcd for $C_7H_{13}OHgCl$: C, 24.07; H, 3.75; Hg, 57.44. Found: C, 24.14; H, 4.02; Hg, 57.51. The first overtone of the hydroxyl stretching frequency appeared at 7025.4 cm^{-1}. $NaBH_4$ reduction gave cyclopentanol (ir), having a first overtone hydroxyl frequency of 7039.8 cm^{-1}.

Methoxymercuration of cycloheptene gave an 80% yield of *trans*-1-methoxy-2-chloromercuricycloheptane: mp 45.0–45.5° from hexane; mass spectrum molecular ion at *m/e* 362; nmr (CCl_4) τ 6.70 (m, 1), 6.78 (s, 3), 7.25 (m, 1), 7.8–8.8 (m, 10). $NaBH_4$ reduction gave cycloheptyl methyl ether (ir, nmr) with $\Delta\nu_{OCH_3}$ = 7.9 cps.

***cis*- and *trans*-Cyclooctene.**—Hydroxymercuration of *cis*- and *trans*-cyclooctene gave *trans*-2-chloromercuricyclooctanol in 59 and 83% yields, respectively, mp 96.5–97.0°[25] from chloroform–*n*-heptane (lit.[6] mp 96–97°). *Anal.* Calcd for $C_8H_{15}OHgCl$: C, 26.45; H, 4.16; Hg, 55.22. Found: C, 26.44; H, 4.35; Hg, 55.19. Ir spectra (CS_2) of the products from the two reactions were identical. The first overtones of the hydroxyl stretching frequencies appeared at 7022.5 cm^{-1} for the product from cis olefin and 7022.9 cm^{-1} for the product from *trans*-cyclooctene. $NaBH_4$ reduction gave cyclooctanol (ir), having a first overtone hydroxyl frequency of 7043.2 cm^{-1}.

Methoxymercuration of *cis*- and *trans*-cyclooctene gave *trans*-1-methoxy-2-chloromercuricyclooctane in 65 and 70% yields, respectively: mp 58.0–59.5° from EtOH–H_2O (lit.[6] mp 60–61°); mass spectrum molecular ion at *m/e* 376; nmr (CCl_4) τ 6.50

(15) The first overtone differences are approximately twice the primary frequency differences listed in ref 5.

(16) Method of W. R. Moore, private communication adapted from A. C. Cope, A. C. Haven, F. L. Rump, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **74**, 4867 (1952).

(17) Generously supplied by W. R. Moore.

(18) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3212 (1953).

(19) P. D. Gardner and M. Narayana, *J. Org. Chem.*, **26**, 3518 (1961).

(20) A. T. Bloomquist, L. H. Liu, and J. C. Bohrer, *J. Amer. Chem. Soc.*, **74**, 3643 (1952).

(21) A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, **87**, 3644 (1965).

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(25) It should be noted that recrystallization of the organomercurial from chloroform gave a white, crystalline solid, mp 93.5°. Remelting of this melting point sample occurred at 96.5–97.0°. A careful ir and thermal study of this compound revealed the existence of two crystalline polymorphic forms, the higher melting one being the more stable.

(m, 1), 6.68 (s, 3), 7.08 (m, 1), 7.7–8.8 (m, 12). $NaBH_4$ reduction gave cyclooctyl methyl ether (ir, nmr) with $\Delta\nu_{OCH_3}$ = 8.5 cps.

In the nmr spectrum of the raw β-methoxycyclooctylmercuric chloride, some β-acetate product was seen. Although investigation of this minor constituent was not carried out, it is certainly the identical product as isolated by Sokolov.[6]

cis- and *trans*-Cyclononene.—Hydroxymercuration of *cis*- and *trans*-cyclononene gave *trans*-2-chloromercuricyclononanol in 25 and 57% yields, respectively, mp 127–128° from chloroform–pentane. *Anal.* Calcd for $C_9H_{17}OHgCl$: C, 28.65; H, 4.54. Found: C, 28.53; H, 4.27. Ir spectrum ($CHCl_3$) of the products from the two reactions were identical. The first overtone hydroxyl stretching frequency was 7020.2 cm^{-1} for both products. $NaBH_4$ reduction gave cyclononanol (ir), having a first overtone hydroxyl frequency of 7032.0 cm^{-1}.

Methoxymercuration of *cis*- and *trans*-cyclononene gave *trans*-1-methoxy-2-chloromercuricyclononane in 54 and 65% yields, respectively: mp 86.5–87.5° from CH_3OH–H_2O; ir spectra (KBr) of the products from the two reactions were identical; mass spectrum molecular ion at *m/e* 490; nmr (CCl_4) τ 6.37 (m, 1), 6.64 (s, 3), 7.02 (m, 1), 7.7–8.6 (m, 14). $NaBH_4$ reduction gave cyclononyl methyl ether (ir, nmr) with $\Delta\nu_{OCH_3}$ = 9.7 cps.

Registry No.—Cyclobutene, 822-35-5; *trans*-2-chloromercuricyclobutanol, 39837-13-3; *trans*-1-methoxy-2-chloromercuricyclobutane, 39837-14-4; cyclopentene, 142-29-0; *trans*-2-chloromercuricyclopentanol, 39849-94-0; *trans*-1-methoxy-2-chloromercuricyclopentane, 29581-86-0; cyclohexene, 110-83-8; *trans*-2-chloromercuricyclohexanol, 29581-85-9; *trans*-1-methoxy-2-chloromercuricyclohexane, 5274-83-9; cycloheptene, 628-92-2; *trans*-2-chloromercuricycloheptanol, 39837-19-9; *trans*-1-methoxy-2-chloromercuricycloheptane, 39837-20-2; *cis*-cyclooctene, 931-87-3; *trans*-cyclooctene, 931-89-5; *trans*-2-chloromercuricyclooctanol, 5185-85-3; *trans*-1-methoxy-2-chloromercuricyclooctane, 5185-84-2; *cis*-cyclononene, 933-21-1; *trans*-cyclononene, 3958-38-1; *trans*-2-chloromercuricyclononanol, 39837-23-5; *trans*-1-methoxy-2-chloromercuricyclononane, 39837-24-6.

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A Direct ^1H and ^{19}F Nuclear Magnetic Resonance Study of Boron Trifluoride Complexes with Cycloalkanones[1]

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A direct ^1H and ^{19}F nmr study of BF_3 complexes of several cycloalkanones (cyclobutanone through cyclodecanone) has been completed. At temperatures below −80°, exchange is slow enough to permit the observation of separate sets of resonance signals for coordinated and bulk ketone molecules. The appearance of the α-CH_2 pmr peaks of coordinated cyclohexanone and cycloheptanone reflect the slowing of an additional kinetic process, possibly cis–trans isomerization at the carbonyl oxygen. The ^{19}F nmr signals of mixtures of the cycloalkanones with BF_3 were used to evaluate the relative basicities of this series of molecules. The basicities decreased in the order $C_8 > C_5 > C_7 > C_6 \simeq C_9 > C_{10} \gg C_4$, a trend which was interpreted primarily in terms of steric effects.

Boron trihalide mixtures with a variety of organic bases have been studied by calorimetric[3–7] and spectroscopic[8–17] techniques to evaluate the energetics and structural features of the complexes formed. The organic bases involved in several representative studies of BF_3 adducts include pyridines,[3,11] alkyl ethers, amines, and sulfides,[4] dimethyl sulfoxide and ethyl acetate,[5] cyclic ketones,[6] triethylamine,[7] ethers,[8] dimethylformamide,[9] benzophenone,[10] ureas and thioureas,[12] water,[13] trimethylamine,[14] diethyl ketone,[15] aromatic amine 1-oxides,[16] and benzaldehydes.[17] In most of the nuclear magnetic resonance (nmr) studies, the components were mixed in a 1:1 mole ratio, and the ligand chemical shifts were compared to pure base.

Recently, a direct, low-temperature nmr technique has been refined and applied to studies of boron trihalide complexes.[18–24] In the presence of excess base, and at temperatures low enough to reduce the rate of ligand exchange, it is possible to observe separate resonance signals for bulk and coordinated ligand molecules. This observation leads to an accurate measure of the ^1H, ^{11}B, ^{19}F, and even ^{13}C[25] chemical shifts produced by complex formation, the stoichiometry of the complex, steric hindrance to complex formation, and the ligand preference of a boron trihalide in a system containing more than one base. These features have been evaluated for amines and

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TABLE I
HYDROGEN-1 AND FLUORINE-19 CHEMICAL SHIFT AND COORDINATION DATA FOR BORON TRIFLUORIDE COMPLEXES WITH CYCLOALKANONES

Registry no.	Base	Mole ratios BF3	Base	CH2Cl2	Temp, °C[a]	δ (1H), ppm[b] B	C	δ (19F), ppm[c]	Coord no.
39209-65-9	C_4	1	3.0	30	−100	3.20	3.72	12.6	0.98
39684-87-5	C_5	1	2.9	30	−85	2.17	2.94	11.2	0.94
29684-87-5	C_5	1	2.9	15	−90	2.15	2.96	11.6	1.04
29684-90-0	C_6	1	2.8	30	−90	2.34	2.93	14.8	1.04
	C_6	1	3.0	15	−90	2.38	2.97	15.0	0.95
39209-67-1	C_7	1	2.6	80	−85	2.52	3.12	13.4	0.95
	C_7	1	3.1	30	−90	2.55	3.18	13.7	0.92
39209-68-2	C_8	1	2.9	30	−90	2.42	3.05	14.1	0.98
39837-95-1	C_9	1	3.0	30	−80	2.48	3.05	14.9	0.96
39837-96-2	C_{10}	1	3.1	35	−80	2.57	3.15	15.0	0.89

[a] These temperatures apply to the ^1H measurements which were made within a 5° range of the value shown. The ^{19}F spectra were recorded within a 10° range of these values. [b] The chemical shifts of the α-CH_2 peaks were measured with respect to internal tetramethylsilane. [c] The chemical shifts were measured with respect to internal hexafluorobenzene, which appeared at higher field in all cases.

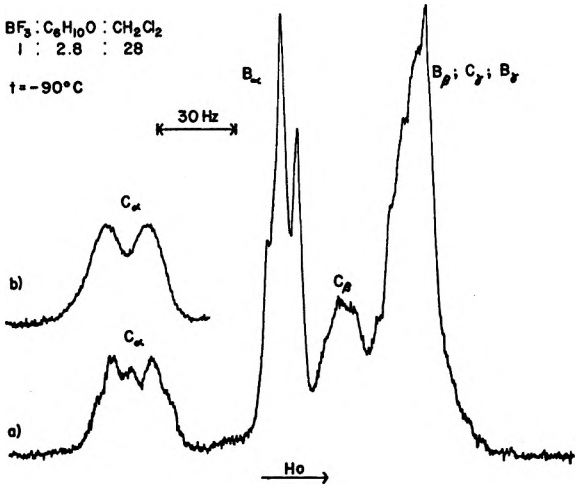

Figure 1.—The proton magnetic resonance spectrum of a mixture of BF_3 and cyclohexanone in methylene chloride, recorded on a Varian HA-100 spectrometer, is shown. The signals arising from coordinated (C) and bulk (B) cyclohexanone molecules are labeled and the particular protons are identified by the subscripts. The C_α signals in portion b result from decoupling of these protons from the C_β protons of the base. Mole ratios also are shown.

phosphines,[18] oxygen-containing bases,[19,20,25] pyridines,[21,22] nitrogen heterocycles,[23] keto esters,[24] several cyclic ketones,[26,27] and methanol.[28] The present study involves a series of cycloalkanones as the Lewis bases for BF_3 complexation. These compounds, cyclobutanone through cyclododecanone, have the same carbonyl functional group; yet they differ in ring size and strain, basic strength, and possible conformations. Thus, the influence of these parameters on complex formation could be evaluated. It was anticipated that a correlation of these results with available proton basicity data[29] would be possible, again demonstrating the utility of this direct nmr method as a complementary tool for basicity studies.[30]

Experimental Section

Methods.—The boron trifluoride was CP grade and 99.5% pure. The cycloalkanones, acetone, and dichloromethane solvent were at least reagent grade and they were used after drying over $CaSO_4$. Proton magnetic resonance (pmr) area measurements and gas chromatography revealed a noticeable impurity only in the case of cyclononanone. Although attempts to purify this compound by vacuum distillation were unsuccessful, the presence of this impurity did not hamper the measurements. The dryness of each sample was verified by the absence of a resonance signal for BF_3–H_2O adduct in the ^{19}F nmr spectrum. The boron trifluoride was fractionated twice at −100° and condensed *in vacuo* in the nmr sample tube. The tube was sealed, warmed in an acetone–Dry Ice mixture to dissolve the components, and stored in liquid nitrogen until the spectrum could be recorded. To avoid possible decomposition, the samples were not allowed to reach temperatures above −60°. With these precautions, decomposition was negligible in these systems as indicated by the lack of any extraneous ^1H or ^{19}F nmr signals, even when measurements were repeated after a period of several days.

The nmr chemical shift and area measurements were made on a Varian A-60 and a Varian HA-100 spectrometer, the latter operating at 94.1 MHz for ^{19}F nuclei. Both spectrometers are equipped with variable-temperature accessories for measurements from −150 to 200°. The procedure is described in more detail elsewhere,[19-24] and it consists essentially of cooling the sample in the probe to reduce the rate of ligand exchange. When separate coordinated and bulk ligand pmr signals, or ^{19}F nmr signals for base mixtures, are observed, the temperature is adjusted to maximize spectral resolution. The complete spectrum is recorded at this point for chemical shift data, and area integrations are measured electronically.

Results.—The ^1H and ^{19}F nmr chemical shift and area results for each boron trifluoride–cycloalkanone complex are listed in Table I, and representative pmr spectra are shown in Figures 1 and 2. The cycloalkanones are identified in Table I by the number of carbon atoms in the molecule, and each entry results from measurements of at least three samples. The quantities δ_B and δ_C are the separations in parts per million of the α-CH_2 pmr signals for bulk and coordinated base, respectively, with respect to internal TMS. The ^{19}F nmr chemical shifts were referred to the internal C_6F_6 signal, which appeared upfield (lower frequency) in all cases. The δ values were calculated using the expression $10^6[(\nu_S - \nu_R)/\nu_0]$, where ν_S is the resonance frequency of the cycloalkanone or BF_3, ν_R is the reference TMS or C_6F_6 resonance frequency, each taken as zero, and ν_0 is 60 or 100 MHz for protons and 94.1 MHz for ^{19}F nuclei. Since the α-CH_2 pmr multiplets usually were not symmetrical (see Figures 1 and 2), the center of each pattern was approximated for the chemical shift measurements. The ^1H and ^{19}F δ values are precise to within 0.05 ppm.

As seen in Figures 1 and 2 and implied by the data in Table I, only the α-CH_2 pmr signal of the coordinated cycloalkanone could be identified unambiguously, and, consequently, this signal was used in the chemical shift and area calculations. Also, signal overlap of the bulk α-CH_2 signal with the signals from the other bulk CH_2 protons usually precluded a direct comparison of the bulk and coordinated α-CH_2 signal areas. However, the total area due to coordinated ligand was deduced from the coordinated α-CH_2 signal. The number of base molecules bound per BF_3,

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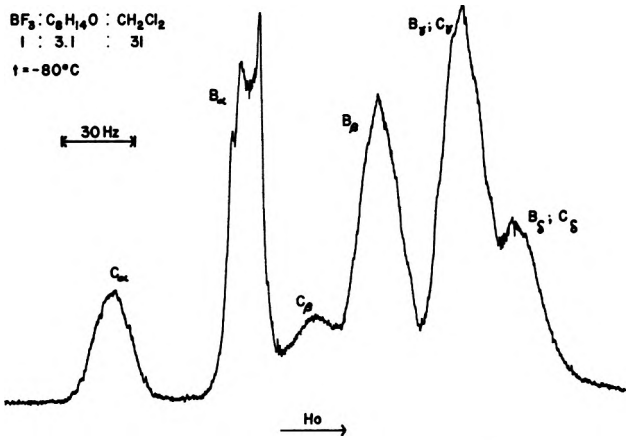

Figure 2.—The proton magnetic resonance spectrum of a mixture of BF_3 and cyclooctanone in methylene chloride, recorded on a Varian HA-100 spectrometer, is shown. The signals arising from coordinated (C) and bulk (B) cyclooctanone molecules are labeled and the particular protons are identified by the subscripts. Mole ratios also are shown.

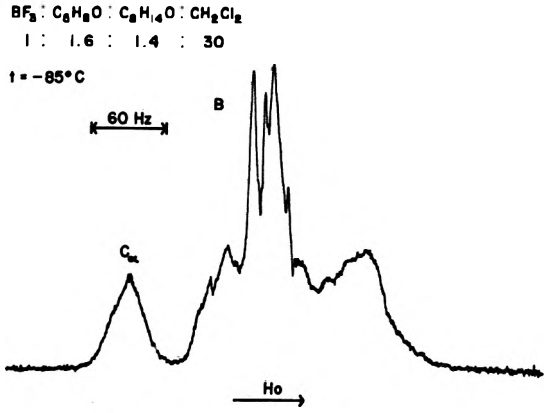

Figure 3.—The proton magnetic resonance spectrum of a mixture of BF_3, cyclopentanone, and cyclooctanone in methylene chloride, recorded on a Varian A-60 spectrometer, is shown. The signals arising from coordinated (C) and bulk (B) base molecules are labeled. Mole ratios are shown.

the BF_3 "coordination number," was calculated from the expression (moles of base/mole of BF_3)·(coord base area/total base area). A precision of 5% was typical for these area results. The coordination number results indicate that 1:1 complexes were formed in all cases, although low (0.9) values were obtained in the cycloheptanone and cyclodecanone solutions. Since gas chromatography, pmr areas, and ^{19}F nmr spectra showed no evidence for the presence of impurities, the two low results must be due to the more extensive signal overlap which prevails in the pmr spectra of these solutions.

The nmr chemical shift and area data for all possible pair mixtures of the cycloalkanones are listed in Table II. In these mixtures, the overlap of the coordinated α-CH_2 signals for each base, exemplified by Figure 3 for the cyclopentanone–cyclooctanone combination, prevented an evaluation of the amount of BF_3 complexed by each ligand. Thus, from pmr spectra, only the total amount of BF_3 complexed could be determined (last column). The fractions of BF_3 complexed, listed in columns 6 and 7 of Table II, were easily measured from the much simpler ^{19}F nmr spectra, an example of which is shown in Figure 4 for the same cyclopentanone–cyclooctanone solution. Since it was difficult to prepare solutions containing the exact base mole ratios desired, the concentrations and BF_3 fractions complexed were normalized to the values shown. Although only small changes (~5%) were involved, a detailed justification will be presented later.

The ^{19}F δ value assignments listed in Table II were aided by the chemical shift results for the single base systems summarized in Table I. The identities of the complexes were made easily in all cases except the cyclohexanone–cyclononanone, cyclohexanone–cyclodecanone, and cyclononanone–cyclodecanone combinations. As seen in Table I, the ^{19}F chemical shifts of the complexes of these bases differed only slightly. However, from the δ value of 14.6 ppm observed for the boron trifluoride–cyclohexanone adduct in the cyclobutanone through cyclooctanone mixtures, the assignment for this species in the remaining mixtures was made. The assignment of the cyclononanone and cyclodecanone complexes was based on a comparison of the data of Table II involving these ligands. The boron trifluoride–cyclononanone complex ^{19}F nmr signal consistently appeared at higher field than that of the cyclodecanone adduct by about 0.1 ppm.

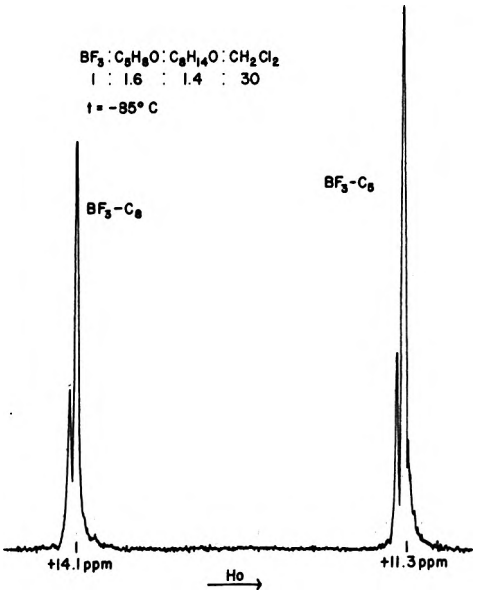

Figure 4.—The fluorine-19 nuclear magnetic resonance spectrum of a mixture of BF_3, cyclopentanone, and cyclooctanone in methylene chloride, recorded at 94.1 MHz on a Varian HA-100 spectrometer, is shown. The complexes of the bases with BF_3 are labeled, the shifts in parts per million to lower field from internal C_6F_6 are given, and mole ratios of all components are shown.

Discussion

The observation of bulk and coordinated ligand pmr signals in these cycloalkanone solutions is due to the reduced rate of intermolecular exchange at low temperatures. This observation was possible with all ketones studied, in contrast to the reported inability to achieve this slow exchange condition in BF_3 solutions of cyclohexanone.[26] From the chemical shift displacements produced by complex formation with these compounds, and the relationship $\tau \sim 10/2\pi\Delta\nu$, the lifetime of a base in a particular environment must be ~0.05 sec.

The more significant features of the pmr spectra of these boron trifluoride–cycloalkanone solutions at low temperature are (a) a chemical shift displacement of about 0.6 ppm, with two exceptions, for the α-CH_2 protons of coordinated base, with an attenuation of this effect at sites further from the carbonyl group; (b) an increased line width for the bound ligand signals, again more noticeable for the α-CH_2 proton peaks; and (c) a similar appearance of the bound and bulk ligand signals in all but two cases. The chemical shift change, represented by $\delta_{CB} = \delta_C - \delta_B$, induced at the α-CH_2 position of these cycloalkanones, was ~0.6 ppm except in the cyclobutanone (0.5 ppm) and cyclopentanone (0.8 ppm) solution spectra. A comparison of the δ_C values shows that in reality only the cyclobutanone result could be considered anomalous.

TABLE II
HYDROGEN-1 AND FLUORINE-19 CHEMICAL SHIFT AND COORDINATION DATA FOR BORON TRIFLUORIDE COMPLEXES IN MIXTURES OF CYCLOALKANONES

Base		Mole ratios					δ (¹⁹F), ppm[b]		BF_3 Fraction comp		
A	B	BF_3	A	B	CH_2Cl_2	Temp, °C[a]	A	B	A	B	Coord no.[c]
C_4	C_5	1	1.5	1.5	30	−90	12.8	11.3	0.02	0.98	0.95
C_4	C_6	1	1.5	1.5	30	−90	12.8	14.6	0.05	0.95	0.93
C_4	C_7	1	1.5	1.5	30	−90	12.8	13.6	0.02	0.98	0.90
C_4	C_8	1	1.5	1.5	30	−90	12.7	14.1	0.02	0.98	1.01
C_4	C_9	1	1.5	1.5	30	−90	12.7	14.9	0.02	0.98	0.90
C_4	C_{10}	1	1.5	1.5	30	−90	12.7	15.0	0.12	0.88	0.75
C_5	C_6	1	1.5	1.5	30	−90	11.4	14.6	0.67	0.33	1.01
C_5	C_6	1	1.0	2.0	35	−90	11.3	14.6	0.50	0.50	0.98
C_5	C_7	1	1.5	1.5	30	−90	11.4	13.6	0.57	0.43	0.99
C_5	C_7	1	1.4	2.9	30	−90	11.4	13.7	0.38	0.62	1.03
C_5	C_8	1	1.5	1.5	30	−90	11.3	14.1	0.45	0.55	0.96
C_5	C_8	1	1.7	2.9	25	−90	11.3	14.1	0.37	0.63	1.04
C_5	C_9	1	1.5	1.5	30	−90	11.3	14.9	0.67	0.33	0.99
C_5	C_9	1	1.5	3.0	30	−90	11.3	15.0	0.50	0.50	1.00
C_5	C_9	1	3.0	1.5	30	−90	11.4	15.0	0.83	0.17	0.97
C_5	C_{10}	1	1.5	1.5	30	−90	11.3	15.0	0.72	0.28	0.96
C_5	C_{10}	1	1.5	3.0	30	−90	11.3	15.1	0.64	0.36	1.04
C_6	C_7	1	1.5	1.5	30	−90	14.7	13.7	0.35	0.65	0.99
C_6	C_8	1	1.5	1.5	30	−90	14.6	14.1	0.32	0.68	0.99
C_6	C_9	1	1.5	1.5	30	−90	14.6	14.9	0.50	0.50	1.04
C_6	C_{10}	1	1.5	1.5	30	−85	14.6	15.1	0.57	0.43	0.89
C_7	C_8	1	1.5	1.5	30	−85	13.6	14.1	0.44	0.56	0.98
C_7	C_9	1	1.5	1.5	30	−85	13.6	15.0	0.61	0.39	0.93
C_7	C_{10}	1	1.5	1.5	30	−90	13.6	15.1	0.67	0.33	0.93
C_8	C_9	1	1.5	1.5	30	−90	14.1	14.9	0.78	0.22	0.96
C_8	C_{10}	1	1.5	1.5	30	−85	14.1	15.0	0.75	0.25	0.89
C_9	C_{10}	1	1.5	1.5	30	−85	14.9	15.0	0.60	0.40	0.90

[a] All shift and area measurements were made within a 5° range of the temperature shown. [b] The chemical shifts were measured with respect to internal hexafluorobenzene, which appeared at higher field in all cases. [c] These coordination numbers are based on ¹H spectra.

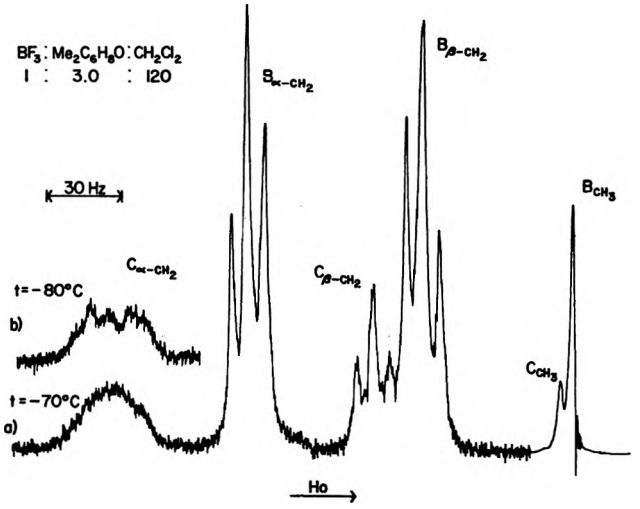

Figure 5.—The proton magnetic resonance spectrum of a mixture of BF_3 and 4,4-dimethylcyclohexanone in methylene chloride, recorded on a Varian HA-100 spectrometer, is shown. The signals arising from coordinated (C) and bulk (B) 4,4-dimethylcyclohexanone molecules are labeled and the particular protons are identified by the subscripts. The signal amplitude was reduced by a factor of 10 when recording the methyl group signals. Mole ratios also are shown.

For example, in the boron trifluoride–cyclopentanone solution spectra, the inordinately high field position of the bulk α-CH_2 pattern is responsible for the large δ_{CB} value. As will be discussed in detail later, the unusual complexing behavior of cyclobutanone is due to the severe ring strain in this molecule. The compounds in this series differ in basicity, and presumably should form complexes of varying strength. Calorimetric studies of the cyclopentanone and cyclohexanone systems, for instance, show marked differences in the heats of formation of their BF_3 complexes.[6] Thus, the lack of dependence of the δ_{CB} values with ring size rules out a correlation of pmr chemical shift with interaction strength. Rather, complex formation produces the same extent of deshielding at the α-CH_2 sites. Similarly there is no observable trend of ^{19}F nmr chemical shifts with molecular structure in this series of BF_3 complexes.

The line width characteristics of the coordinated ligand pmr signals are due to interactions with the quadrupole moment of the boron nucleus of BF_3. At the low temperatures required in this study, the solution viscosity is high and the lifetime of ligand molecules in the "coordination shell" of BF_3 is relatively long. Consequently, the coupling between the ^{11}B nuclei and bound ligand protons is effective, the proton T_1 values are reduced, and signal broadening results. As expected, this effect diminishes with distance from the ^{11}B nucleus.

The most interesting spectral features are exhibited by the BF_3 complexes of cyclohexanone and cycloheptanone, for which the coordinated α-CH_2 pmr peaks appear as more complicated patterns. This is illustrated in Figure 1 for the cyclohexanone complex and in Figure 5 for the BF_3 adduct of 4,4-dimethylcyclohexanone, which produces a much simpler spectrum.[31] It also appears that two processes, one in-

(31) The authors are indebted to Professor Paul McMaster of Holy Cross College for a sample of this compound and for many helpful suggestions regarding this aspect of the study.

volving ligand exchange and another causing the pattern of the bound α-CH_2 pmr signals, are involved. As seen in Figure 5, at $-70°$, ligand exchange is slow enough to observe distinct sets of signals for all protons, even those of the methyl groups, for bulk and coordinated 4,4-dimethylcyclohexanone molecules. The broadness of the coordinated α-CH_2 peak contrasts with the sharp, well-defined β-CH_2 triplet and indicates that these molecules are still involved in some process which has a greater influence at the carbon atoms closest to the carbonyl group. Although not completely resolved, the coordinated α-CH_2 pattern at lower temperatures (see Figures 1 and 5) seems to be a set of overlapping triplets, producing peaks with approximate area ratio 1:2:2:2:1. The three central peaks are well defined but the outer two are shoulders. If this assignment is correct, the two sets of coordinated α-CH_2 triplets would be duplicates of the parent bulk signal. When the coordinated β-CH_2 protons are decoupled, the coordinated α-CH_2 multiplets collapse into two singlets of equal area.

These features could result from a reduced rate of cis–trans isomerization at the boron trifluoride–carbonyl linkage. This process would produce two coordinated α-CH_2 triplets of equal area, since there is no thermodynamic preference for either isomer. A precedent is provided by the diethyl ketone–boron trifluoride adduct, for which cis–trans isomerization is slow at $-120°$.[15] Although a carbonyl group is involved in both cases, the structural differences between this ketone and the cycloalkanones can account for the ability to observe slow isomerization at higher temperatures in the latter systems. It is not clear why this process should be more rapid in the larger (C_8–C_{10}) cycloalkanones, a situation which seems to prevail.

A slow chair–chair interconversion also might give rise to the spectra of Figures 1 and 5, but several points minimize this possibility. Ring strain produces an essentially planar configuration for cyclobutanone[32-34] and a rigid, "half-chair" structure for cyclopentanone,[35] precluding this kind of conformational motion in these smaller members of the series. In the larger members, barriers to interconversion are very low and this motion proceeds easily. For example, interconversion is slow on the nmr time scale only at $-160°$ for cyclooctanone ($\Delta H^{\ddagger} \cong 7$ kcal)[36,37] and all attempts to slow chair–chair interconversion for cyclohexanone have been unsuccessful, even at $-170°$.[38,39] These results led to a postulate of a barrier of only 5 kcal for interconversion of this molecule. Unless the hybridization of the carbonyl carbon in the BF_3 complex resembles that of cyclohexane, where chair–chair interconversion proceeds with a $\Delta H^{\ddagger}$ of about 10 kcal,[40,41] this process does not seem to be the cause of the spectra observed with cyclohexanone and cycloheptanone. This process also should produce a more complex α-CH_2 spectrum as a result of axial–equatorial coupling, although this could be obscured by coupling with the boron quadrupole.[42] Measurements with substituted cyclohexanones are planned in an attempt to clarify these points.

The coordination data of Table II emphasize the utility of this direct nmr method for evaluating in a qualitative manner the relative basic strengths of a series of compounds toward a common Lewis acid.[18-24] As will be discussed later, at equal concentrations of each base, the fraction of BF_3 complexed depends only on the basicity of the ligand. For example, in all mixtures, cyclobutanone was able to complex only a small fraction of the BF_3, a good indication that it is the weakest base in this series. Cyclopentanone binds more than half of the BF_3 in the presence of any other member of this series except cyclooctanone. From a comparison of such results obtained with mixtures containing bases at equal concentrations, the following trend of decreasing relative basicity toward BF_3 can be constructed for these cycloalkanones.

$$C_8 > C_5 > C_7 > C_6 \sim C_9 > C_{10} \gg C_4$$

Here the subscript indicates the number of carbon atoms in the ring. This trend may be compared to the available protonation data for this series, which yield the following order of decreasing basicity expressed as pK_{BH^+} values at 25°.[29]

$$C_8\ (-6.2) > C_7\ (-6.6) > C_6\ (-6.8) > C_5\ (-7.5) > C_4\ (-9.5)$$

It is evident that, in both systems, cyclobutanone is the weakest base. This can be attributed to the effect of the severe ring strain of this molecule on the nature of the carbonyl bond. It has been suggested that the C–C–C bond angle at the carbonyl group in cyclobutanone produces an increase in the s character of the carbon–oxygen σ bond, and a consequent decrease in the basic strength of the oxygen atom.[43] This effect decreases with increasing ring size, but it probably is the cause of the relatively low pK_{BH^+} value of cyclopentanone.

In contrast to the smooth increase of basicity with ring size toward the proton, the order with respect to BF_3 is much more complicated. The main difference between the two groups of studies is the steric factor introduced by the use of the more bulky BF_3. For example, the position of cyclononanone and cyclodecanone in this BF_3 basicity series is not surprising when the conformational possibilities for these molecules are considered. The size of these two rings may introduce steric hindrance to complex formation at the carbonyl group, by methylene groups at the opposite end of the molecule. This steric hindrance also should prevail in the cyclooctanone ring but to

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(42) The authors are indebted to the referees for several comments concerning this aspect of the work.
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a lesser extent. Also, the preferred conformations of this molecule place the carbonyl group in a somewhat favorable position for complex formation.[34,36] Since these steric effects would be minimal in smaller rings, one would predict that cycloheptanone and cyclohexanone, respectively, should follow cyclooctanone in the BF_3 basicity series.

Thus, as a result primarily of steric factors, cyclopentanone emerges as a strong complexing agent for BF_3, in spite of its low proton basicity as compared to other members of this series. Previous studies in these laboratories[20-24] have implied that, if pK_{BH^+} values for two bases differ by one or more units, essentially all the BF_3 will be complexed by the stronger ligand. Since cyclopentanone can compete with all the larger cycloalkanones in BF_3 solution, steric factors reduce the effective basicity of the latter by at least a factor of 10.

In addition to the relative basicity, which is a fundamental molecular property, the fraction of BF_3 complexed by each base in a mixture depends on the concentration of the components. For instance, when cyclopentanone and cyclohexanone are mixed in equal concentrations, cyclopentanone complexes approximately two-thirds of the BF_3. However, these bases complex equal fractions when the cyclohexanone concentration is twice that of cyclopentanone (see Table II). In other words, the relationship, $f \propto b \cdot c$, where f is the BF_3 fraction complexed, b is the relative basicity of the molecule toward BF_3, and c is the base concentration, seems to hold for these systems. Thus, at equal concentrations, $f_1/f_2 = b_1/b_2$ provides a measure of the relative basic strength of these compounds. Assuming that basicity is not concentration dependent, the fraction of BF_3 complexed at various base concentrations can be estimated from f_1/f_2 = constant (c_1/c_2). This relationship holds within 10–20% when tested in these mixtures and it provides a justification for the normalization procedure used in the development of the Table II data.

Registry No.—Adduct of BF_3 and 4,4-dimethylcyclohexanone, 39209-78-4.

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On the Dehydroxylation of Phenols by Cleavage of Their Diethyl Phosphate Esters with Alkali Metals in Liquid Ammonia[1]

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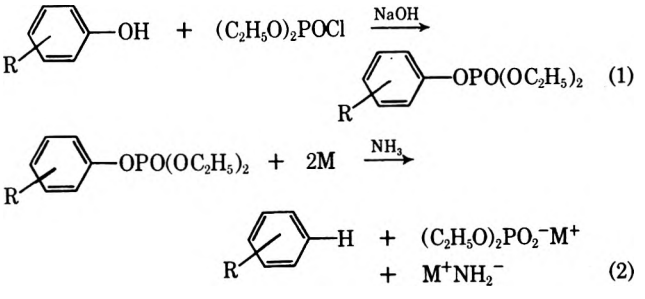
In a method due to Kenner and Williams, the phenolic hydroxyl group is replaced by hydrogen in a two-step process: the phenol is converted to an aryl diethyl phosphate ester, which is then cleaved with an alkali metal in ammonia. Reinvestigation of the method with use of glpc shows it to be convenient and to give high yields of dehydroxylation products. Complications are encountered in the dehydroxylation of 1-naphthol, but allyl, acetyl, and (in part) nitro substituents survive the procedure unscathed.

A communication by Musliner and Gates,[3] announcing a new method for the dehydroxylation of phenols, started with the sentence: "Up to the present time, no general method has been available for the removal of phenolic hydroxyl groups." The communication goes on to describe the method they developed, which involves conversion of phenols to heterocyclic ethers (especially 1-phenyl-5-tetrazolyl ethers) which are then cleaved by hydrogenolysis over 5% palladium on carbon. However, it fails to mention an attractive method of considerable generality which had been described 11 years earlier. We have reinvestigated the older method, and have formed a high opinion of it.

The method to which we refer, due to Kenner and Williams,[4] involves conversion of the phenol to the corresponding aryl diethyl phosphate ester, and then cleavage of the latter with an alkali metal in liquid ammonia. The modification of it which we employed is sketched in eq 1 and 2. Kenner and Williams reported high yields of dehydroxylation products from several alkoxy-, alkyl-, or acetamido-substituted phenols.



The method was also studied and employed by Pelletier and Locke[5] for the small-scale dehydroxylation of several phenols, most of which were derived from polycyclic aromatic systems. The yields that they ob-

(1) Research supported in part by the National Science Foundation.

(2) Grateful recipient of a fellowship from the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

(3) W. J. Musliner and J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **88**, 4271 (1966).

(4) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(5) S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958).

tained were modest (17–50%). They pointed out that the yields reported by Kenner and Williams were of crude products. In the case of the dehydroxylation of β-naphthol, Kenner and Williams reported naphthalene yields of 88 and 95%, but Pelletier and Locke carefully examined the crude product and found that only about half of it was actually naphthalene. Critics have perhaps drawn the inference that the method is one of mediocre worth.

Some closely related reactions, the cleavage of alcohol and enol diethyl phosphate or tetramethylphosphorodiimidate esters in fashion analogous to eq 2, have been reported by Ireland and coworkers.[6,7]

The investigations of Kenner and Williams and of Pelletier and Locke were conducted without benefit of gas–liquid partition chromatography. Making use of this technique, we have been able to reexamine with ease the question of product purity. We have also extended the method to phenols with substituents not involved in previous studies. We conclude that the method is an excellent one. However, it has some limitations, which we shall discuss.

Preparation of Phosphate Esters.—Kenner and Williams[4] converted phenols to the corresponding aryl diethyl phosphates in high yields by reaction with diethyl phosphite and triethylamine in CCl_4 solution; diethyl phosphorochloridate, $(C_2H_5O)_2POCl$, is apparently formed *in situ* and then reacts with the aryloxide ion much as in eq 1. We performed the esterification according to eq 1, after Bliznyuk, *et al.*[8] This straightforward method also gives high yields, as summarized in Table I.

The Step of Reductive Cleavage.—The general procedure is to dissolve the aryl diethyl phosphate in liquid ammonia with diethyl ether as cosolvent, cool the solution to −78°, and add small chunks of lithium, sodium, or potassium metal with stirring until a faint blue color persists. For phosphate esters with substituents, such as alkyl and alkoxy groups, that are resistant to solvated electrons and amide ions, the ester (in ether solution) may alternatively be added to excess alkali metal in ammonia. The mixture is then acidified by addition of solid NH_4Cl and products are isolated by standard techniques. A number of reductive cleavages are summarized in Table II. In most cases yield determination was by glpc, but in a few it was by isolation and weighing.

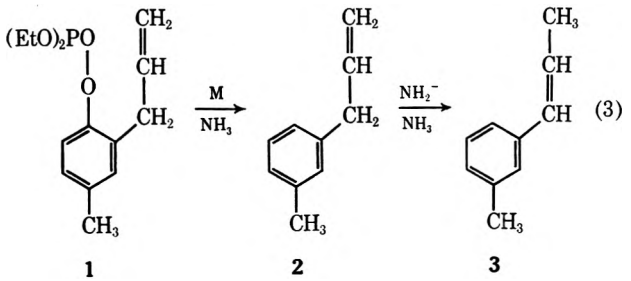
The aryl diethyl phosphate (aryl DEP) esters derived from phenol, 2,6-dimethylphenol, and 2-methoxy-4-methylphenol were reduced respectively to benzene (77%), *m*-xylene (92%), and *m*-methoxytoluene (77%). By the alternative procedure in which the ester is added to excess potassium metal in ammonia, 2,6-dimethylphenyl DEP gave *m*-xylene in 88% yield.

However, when 2-biphenylyl DEP was treated with potassium metal according to the usual procedure, not only biphenyl (85%) but also a dihydrobiphenyl (13%) were obtained. Biphenyl itself is reduced by alkali metals in liquid ammonia,[9a] and it readily accepts an electron to form a radical anion which is relatively stable in the absence of good proton donors.[10] Acting on the hypothesis that some biphenyl radical anion was formed under reduction conditions and that it was converted to a dihydrobiphenyl during acidification with NH_4Cl, we tried adding sodium benzoate to the reaction mixture before NH_4Cl. Sodium benzoate has a high affinity for electrons, and it has been used in other studies as an "electron mop."[11,12] When sodium benzoate was added, there was an immediate color change, from green to orange-yellow, and then to colorless on addition of NH_4Cl, and the product obtained was biphenyl (96%) free of dihydrobiphenyl.

From this experience, and with attention to the work of Pelletier and Locke[5] as well as the known affinity of naphthalene for electrons,[10] it was anticipated that similar problems would be encountered in the reductive cleavage of 1-naphthyl DEP. Therefore sodium benzoate was added before NH_4Cl in all runs. Extensive reduction to 1,4-dihydronaphthalene nevertheless occurred. In three runs, the highest yield of naphthalene obtained was 25%; it was always accompanied by 1,4-dihydronaphthalene, in yields as high as 41%, but the sum of yields of these two products never exceeded 43% in any run. The further products were not identified.

Reduction of *m*-acetylphenyl DEP with sodium metal afforded acetophenone in 71% yield. It is noteworthy that the carbonyl group survived in such an electron-rich environment. Nonenolizable ketones readily accept electrons to form ketyls, but enolizable ketones tend to form enolate ions instead.[13] It is probable that the enolate ion of *m*-acetylphenyl DEP was rapidly formed and that the carbonyl group remained protected in that way until acidification with NH_4Cl at the end of the process.[14]

Dehydroxylation of 2-allyl-4-methylphenol was a challenge because conceivably the double bond of the allyl group might shift into conjugation with the ring under the rather basic conditions of the dephosphation step.[15] If so, the double bond might also be reduced.[9b] Both complications were experienced when 2-allyl-4-methylphenyl DEP (**1**) was reductively cleaved by excess potassium metal without sodium benzoate aftertreatment; besides 28% of the product of straight-



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(15) *Cf.* E. A. Rabinovich, I. V. Astaf'ev, and A. I. Shatenshtein, *Zh. Obshch. Khim.*, **32**, 748 (1962), and references cited therein.

TABLE I
ARYL DIETHYL PHOSPHATES[a] FROM PHENOLS

Phenol	Phenol Registry no.	Yield,[b] %	Ester Registry no.	$n^{23}D$	Bp, °C (Torr)
Unsubstituted	108-95-2	87	2510-86-3	1.4761[c]	135–136 (3)[d]
2,6-Dimethyl	576-26-1	72[e]	39604-15-4	1.4852	119–120 (0.2)
2-Phenyl	90-43-7	84	39835-01-3	1.5408	153–155 (0.15)
2-Allyl-4-methyl	6628-06-4	80	39835-02-4	1.4907	142–144 (1.5)
2-Methoxy-4-methyl	93-51-6	98	39538-67-5	1.4903	144.5 (0.8)
3-Acetyl	121-71-1	65[e]	17027-73-5	1.4937[f]	143–145 (0.08)[f]
4-Nitro	100-02-7	72[e,g]	311-45-5	1.5071	164–167 (0.75)
1-Naphthol	90-15-3	90[e]	33650-14-5	1.5444	152–154 (0.03)

[a] Satisfactory analyses for C and H, by Micro-Tech Laboratories, Skokie, Ill., were obtained for all new compounds. [b] Preparation according to eq 1. [c] Lit. $n^{17}D$ 1.475;[4] $n^{20}D$ 1.4829.[5] [d] Lit.[5] bp 135–136° (3 Torr). [e] Diethyl ether used as solvent in esterification. [f] $n^{20}D$ 1.4926; bp 139–140° (0.12 Torr): M. I. Gunar, T. N. Shumyatskaya, E. B. Mikhalyutina, K. D. Shvetsova-Shilovskaya, and N. N. Mel'nikov, *Zh. Obshch. Khim.*, **38**, 2254 (1968). [g] 40% conversion and 45% recovery of unreacted 4-nitrophenol.

TABLE II
REACTIONS OF ARYL DIETHYL PHOSPHATES WITH ALKALI METALS IN LIQUID AMMONIA–DIETHYL ETHER SOLUTION AT −78°[a]

Aryl moiety	Aryl DEP, mmol	K metal,[a] mmol	NH_3, ml	Ether, ml	Products	Yield, %[b]	Product identification[c]
Phenyl	50	125	70	20	Benzene	77	Glpc,* ir,* ms[l]
2,6-Dimethylphenyl	5	150	150	25	*m*-Xylene	92	Glpc,* ir,* ms
	32[d]	136	300		*m*-Xylene	88[d]	
2-Methoxy-4-methylphenyl	68	115	250	50	*m*-Methoxytoluene	77[e]	Ms, nmr, bp
2-Biphenylyl	20	44	350	50	Biphenyl	85[f]	Glpc,* ir,* ms, nmr,* mp
					Dihydrobiphenyl	13[f]	Ms, nmr
2-Biphenylyl	15	*g, h*	200	20	Biphenyl	96	
1-Naphthyl	36	*g, h*	400	50	Naphthalene	28 (22)[e]	Glpc,* nmr, mp
					1,4-Dihydronaphthalene	3	Ms, nmr, bp
1-Naphthyl	18	40[h]	330	33	Naphthalene	25	
					1,4-Dihydronaphthalene	15	
1-Naphthyl	18	130[h]	350	38	Naphthalene	2	
					1,4-Dihydronaphthalene	(30[e])	
3-Acetylphenyl	16	43[h,i]	400	50	Acetophenone	71 (52)[e]	Glpc,* ir,* ms, nmr, bp
4-Nitro	8	17[j]	200		Nitrobenzene	13	Glpc*
2-Allyl-4-methylphenyl	49	135	200	40	*m*-Propyltoluene	32[k]	Ir, ms, nmr
					m-Allyltoluene	28[k]	Ir, ms, nmr, bp, n_D
					1-(*m*-Tolyl)propene	15[k]	Ir, ms, nmr
2-Allyl-4-methylphenyl	13	*g, h*	250	30	*m*-Allyltoluene	65	
					1-(*m*-Tolyl)propene	20	
2-Allyl-4-methylphenyl	26	*g, h, j*	200	50	*m*-Allyltoluene	81 (77[e])	

[a] The metal is K unless otherwise noted. [b] Yield by glpc unless otherwise noted. [c] An asterisk denotes identity to authentic sample; boiling point, melting point, and n_D, where cited, were in agreement with literature values. [d] Alternative procedure used; see text. [e] Yield by isolation and weighing. [f] Isolated total yield of hydrocarbons, 92%. [g] Not determined. [h] Sodium benzoate added before NH_4Cl. [i] Sodium metal. [j] Lithium metal. [k] Isolated total yield of hydrocarbons, 76%. [l] Mass spectrum.

forward dephosphation, *m*-allyltoluene (**2**), there was obtained 15% of its isomer, 1-(*m*-tolyl)propene (**3**), and 32% of the further reduction product, *m*-propyltoluene.

The situation was much improved when the reaction mixture was treated with sodium benzoate before acidification with NH_4Cl; only *m*-allyltoluene (65%) and 1-(*m*-tolyl)propene (20%) were formed. In order to suppress the complication of double-bond migration, it was necessary to use lithium instead of potassium metal; now *m*-allyltoluene was obtained, free of isomers or further reduction products, in 81% yield. $LiNH_2$ is only slightly soluble in liquid ammonia and, although doubtless formed, was thereby kept out of contact with the *m*-allyltoluene product. The latter was consequently protected from amide ion catalyzed double-bond migration. Thus, dehydroxylation of the rather sensitive 2-allyl-4-methylphenol can be achieved cleanly and in good yield if lithium metal is used in the dephosphation step.

An even greater challenge was dehydroxylation of *p*-nitrophenol. Nitrobenzene has an enormous affinity for electrons, but *p*-nitrophenyl DEP seemed likely to accept electrons even more readily. It therefore was conceivable that dehydroxylation might be achieved by the Kenner–Williams method if the alkali metal were always in deficiency.

Another conceivable complication was reaction of the amide ion by-product with nitrobenzene to form benzenediazotate ion and other products.[16] Lithium metal was therefore employed in the attempt to reduce *p*-nitrophenyl DEP to nitrobenzene, because of the low solubility of $LiNH_2$.

In the event, *p*-nitrophenyl DEP was treated with 2 equiv of lithium metal, added in small bits for the purpose of minimizing local zones with excess electrons. The resulting product mixture was unattractive, but 13% of nitrobenzene was obtained, as determined by glpc. We do not think of this reductive cleavage as

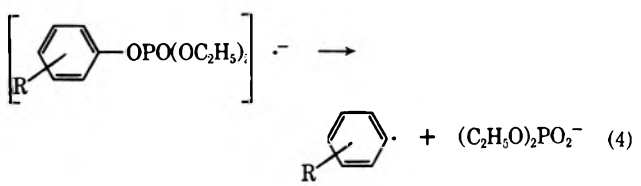
(16) F. W. Bergstrom and J. S. Buehler, *J. Amer. Chem. Soc.*, **64**, 19 (1942).

having preparative value, but rather as a demonstration that substituents exceedingly susceptible to reduction can at least partially survive.

Comparison with Other Dehydroxylation Methods.—Besides the method of Musliner and Gates,[3] mentioned in the introductory paragraph, the chief alternatives to the present method are procedures which involve conversion of the phenol to a diaryl ether, which is then cleaved by an alkali metal in liquid ammonia. The alkali metal cleavage of diaryl ethers was discovered by Sowa and coworkers,[17] and has been adapted for the purpose of dehydroxylating phenols by Sawa, Tsuji, and Maeda[18] and by Pirkle and Zabriskie.[19] The method of the latter workers, which is the more generally applicable, involves converting the phenol to its 2,4-dinitrophenyl ether, catalytic reduction to the 2,4-diaminophenyl ether, and finally cleavage with sodium metal in ammonia.

Both the method of Musliner and Gates[3] and that of Pirkle and Zabriskie[19] involve catalytic reduction steps which obliterate certain types of functionality, such as carbonyl groups, halogen and nitro substituents, and olefinic double bonds. The present method also involves strongly reducing conditions which can be expected to molest substituents sensitive to reduction, as well as partially to reduce polynuclear aromatic systems,[5] but it is to be noted that a carbonyl group, an olefinic double bond, and in part even a nitro group survived in cases we examined. On the whole, we consider the method outlined in eq 1 and 2 to be the most attractive, both for simplicity of operation and for the avoidance of complications, of those which are known.

Reaction Mechanism.—Solutions of alkali metals in liquid ammonia contain alkali metal cations and solvated electron anions, as well as aggregates of uncertain structure.[20] The immediate product of the acquisition of a solvated electron by an aromatic substrate is a radical anion.[21a] The radical anion may rupture according to eq 4, forming an aryl radical and a diethyl



(4)

phosphate anion,[21b] or conceivably it might acquire a second electron to form a dianion, which then undergoes somewhat analogous fission to an aryl anion and the same phosphate anion.[22] Reaction according to eq 4 is indicated by the fact that, when an aryl diethyl phosphate in liquid ammonia is treated with an alkali metal in the presence of a strong nucleophile such as the acetone enolate ion[23] or the amide ion,[24] a product representing combination of aromatic moiety with nucleophile is obtained.

We have obtained evidence in other studies[25] that an aryl radical is unable to abstract a hydrogen atom from ammonia fast enough to compete with other processes, but that hydrogen atom abstraction from isopropoxide ion occurs quite readily. We therefore judge that the aryl radical immediately formed in eq 4 either abstracts a hydrogen atom from the diethyl ether which was present in our reaction mixtures, or that it acquires an electron to form an aryl anion which then takes a proton from the ammonia solvent.[26] We suspect that both modes of hydrogen acquisition are utilized, but we are unable at this time to specify how much reaction occurs by each mode.

Toxicity of Aryl Diethyl Phosphates.—*p*-Nitrophenyl DEP is highly toxic, and should be handled with the greatest care. Aryl DEP with less strongly electron-attracting substituents are less toxic,[27] but prudence dictates that they be handled with precautions against inhalation, ingestion, or contact with the skin. We experienced no manifestations of toxicity in our work with these compounds.

Experimental Section

General.—Boiling points are not corrected. Nmr spectra were recorded on Varian A56/60A and JEOLCO 60 MHz nuclear magnetic resonance spectrophotometers with CCl_4 as solvent and all spectra are reported in parts per million relative to TMS (δ). All ir spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, using CCl_4 as solvent. Mass spectral measurements were obtained with a Hitachi Perkin-Elmer Model RMU-6E mass spectrophotometer. Glpc analyses were performed on a Varian Aerograph Model 200 with flame ionization detector. For determining yields, the molar responses of authentic samples were calibrated against those of suitable standards and peak areas were calculated using a Disc integrator. For preparative glpc, a Varian Aerograph Model A90-P3 was used with thermal conductivity detector using helium as carrier gas.

Reagents.—Diethyl phosphorochloridate (Aldrich Chemical Co.) and all phenols were commercially available and were used as received, except 2-methoxy-4-methylphenol and 2-allyl-4-methylphenol. Alkali metals were cut in small pieces and washed with dried pentane immediately before addition to reaction mixtures. Liquid ammonia was dried with potassium metal and distilled under nitrogen into the reaction flask. 2-Methyl-4-methylphenol was prepared from vanillin:[28] bp 101–102° (12 Torr) [lit.[28] bp 78–79° (4 Torr), 104–105° (13 Torr)]; nmr δ 2.05 (s, 3 H), 3.41 (s, 3 H), 6.18 (s, 1 H), and 6.3–6.8 (m, 3 H). *p*-Tolyl allyl ether was prepared from *p*-cresol:[29] bp 93–94° (13 Torr) [lit.[29] bp 91° (12 Torr)]; nmr δ 2.17 (s, 3 H), 4.28 (m, 2 H), 5.10 (m, 1 H), 5.20 (m, 1 H), 5.83 (m, 1 H), 6.60 (m, 2 H), and 6.83 (m, 2 H). Claisen rearrangement of this ether afforded 2-allyl-4-methylphenol:[29] bp 109–110° (9 Torr) [lit.[29] bp 112° (12 Torr)]; nmr δ 2.13 (s, 3 H), 3.25 (m, 2 H), 4.83 (m) and 5.05 (m, 2 H), 4.47 (s, 1 H), 5.83 (m, 1 H), and 6.4–6.8 (m, 3 H).

Esterification of Phenols.—Phenols were dissolved in toluene at 0–5°. Simultaneously were added from two separatory funnels diethyl phosphorochloridate and 20% aqueous NaOH, slowly and with good stirring, the temperature being kept at 5–10°. Addition time was about 2 hr, and the mixture was stirred for another 2 hr as it warmed to room temperature. When the phenol was not completely soluble in toluene, as with 1-naphthol, *m*-acetylphenol, and 2,6-dimethylphenol, ether was used as cosolvent. Esters were washed with 10% NaOH solution and with water; after drying, they were distilled under vacuum (see Table I).

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In an alternative preparation of phenyl DEP, phenol and a small excess of diethyl phosphorochloridate were dissolved in toluene at 3–5°, a 20% aqueous NaOH solution was slowly added with stirring, and then stirring was continued for 2 hr at room temperature. Product isolation as above afforded phenyl DEP in 81% yield.

Properties of Aryl Diethyl Phosphate Esters.—All the esters present a double triplet at δ 1.06–1.36, with J_{HH} = 6.7–7.2 and J_{HP} = 0.8–0.9 Hz, and a double quartet at δ 3.81–4.25 with J_{HH} = 6.9–7.2 and J_{HP} = 8.2–8.6 Hz, as well as the expected absorption due to the aryl groups. The infrared spectra of phenyl diethyl phosphate and its *p*-nitro derivative closely resembled those reported by Bellamy and Beecher;[30] the others showed characteristic absorption (as films) at 1267–1273 (P=O), 1183–1213 (POC, aromatic), 1156–1167 (POC, ethyl), 1095–1101 (?), 1028 (POC, aliphatic), and 955–964 cm^{-1} (?), assignments being after Bellamy.[31]

Reduction Reactions.—Dried liquid ammonia was condensed in a three-neck round-bottom flask (1 l.) under nitrogen at −78°; the flask was provided with a cold-finger condenser containing solid CO_2 in 2-propanol. Esters were dissolved in ether and added to the ammonia from a dropping funnel, with stirring. Alkali metal was added in small bits until a blue color persisted for at least 2 min. After 15 min, the reaction was quenched by adding solid NH_4Cl or sodium benzoate followed by NH_4Cl. The ammonia was then distilled off. When the product had substantial volatility and might codistil with the ammonia, ether (*ca.* 150 ml) was added immediately after the NH_4Cl and the ammonia was removed through a cold-finger condenser which was kept at −20° to −30° by adding small pieces of solid CO_2 to the 2-propanol. Products were isolated by standard techniques. Product structures were established and/or confirmed by physical property measurements as detailed in Table II.

In a typical experiment 18.6 g of 2-methoxy-4-methyl DEP dissolved in 50 ml of ether was added to 250 ml of dried liquid ammonia at −78°. Potassium metal (4.5 g) was added in pieces and the reaction solution was blue at the end. After 15 min of reaction it was quenched by adding NH_4Cl in excess and the solution became colorless. The liquid ammonia was distilled off, and the residue was treated with 150 ml of water and extracted with 100 ml of ether (twice). Ether extracts were washed with a saturated solution of NaCl in water and dried over anhydrous Na_2SO_4. The ether was removed and the residue was distilled under vacuum: bp 64–65.5° (12 Torr); yield 6.38 g (77%) of pure *m*-methoxytoluene; nmr δ 2.19 (s, 3 H), 3.53 (s, 3 H), 6.36 (m, 3 H), 6.36 (m, 3 H), and 6.75 (m, 1 H).

Cleavage of 2-Allyl-4-methyl DEP. Procedure A.—To 200 ml of liquid ammonia was added 13.9 g of ester dissolved in 40 ml of ether, and 5.2 g of K metal was added until a blue color persisted. The reaction was quenched with NH_4Cl and products were isolated much as described above, bp 67–85° (13 Torr), yield 4.90 g (76%). By glpc (20% Carbowax 20M on Chromosorb P, 130° isothermal, N_2 as a carrier gas, 3.2 mm × 1.22 m), three substances were found: *m*-propyltoluene (retention time 2.3 min, 32% yield), *m*-allyltoluene (retention time 2.9 min, 29% yield), and 1-(*m*-tolyl)propene (retention time 5.6 min, 15% yield). These compounds were separated by preparative glpc (10% Carbowax 20M on Chromosorb P, 6.4 mm × 1.22 m, 140°, He as carrier gas, 25 ml/min), and were identified by their nmr and mass spectra, as well as comparison of n_D values for *m*-propyltoluene[32] and 1-(*m*-tolyl)propene[33] with the literature. Also, for *m*-allyltoluene, ir 1640, 915, and 993 cm^{-1} (allylphenyl derivatives have absorption at 1640–1653, 905–925, and 985–1000 cm^{-1})[34] and $n^{23}D$ 1.5084; and for 1-(*m*-tolyl)propene, ir intense absorption in 965 cm^{-1} (probably the trans isomer).[33]

Procedure B.—To 200 ml of dried liquid ammonia at −78° was added 7.4 g of the ester dissolved in 50 ml of ether, and Li metal was added in small pieces until blue color persisted. Solid sodium benzoate was added to discharge the blue color and solid NH_4Cl was added as a proton source. The liquid ammonia was evaporated and the residue was worked up as usual, giving an 81% yield of *m*-allyltoluene, pure by glpc. By distillation was obtained 2.65 g (77%) of pure *m*-allyltoluene, bp 64–66° (12 Torr) [lit.[35] bp 60° (11 Torr)].

Registry No.—Potassium 7440-09-7; sodium, 7440-23-5; lithium, 7439-93-2; ammonia, 7664-41-7.

Acknowledgment.—We thank Professor Arthur G. Anderson, Jr., University of Washington, for helpful discussions.

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Synthetic Reactions by Complex Catalysts. XXX. Synthesis of Cyclic Compounds by Means of Copper–Isonitrile Complex. Copper(I) Carbenoid Intermediate

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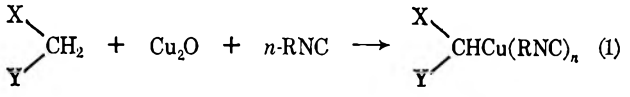
In the reaction of α-monohalo carbonyl and nitrile compounds such as chloroacetate, chloroacetonitrile, and chloroacetone with α,β-unsaturated carbonyl and nitrile compounds in the presence of cuprous oxide–isonitrile complex, cyclopropane derivatives (**3**) were produced. This reaction may be explained by the stepwise process involving the addition of α-halomethylcopper(I)–isonitrile intermediate (**2**), a new class of copper carbenoid, to the electron-deficient olefin which leads to the formation of the corresponding γ-haloorganocopper(I)–isonitrile (**11**), followed by the intramolecular ring closure. The cyclopropane synthesis by means of the cuprous oxide–isonitrile complex could be applied also to the reactions of α,α-dihaloacetate and of α,α-dihaloacetonitrile with an electron-deficient olefin leading to the corresponding monohalocyclopropane derivatives (**6**). In addition, the reaction of trichloromethyl compound, Cl_3CY (Y = Ph, CN, CO_2R), with electron-deficient olefin in the presence of metallic copper and isonitrile produces monochlorocyclopropane derivative. The key intermediate of this reaction is assumed to be an α,α-dichloromethylcopper–isonitrile complex (**5**), $Cl_2C(Y)Cu(RNC)_n$, a copper carbenoid which may be formed *via* an oxidative addition of the C–Cl bond to the copper(0)–isonitrile complex. The reaction of the so-called active methylene compound with α-haloacrylonitrile or α-haloacrylate was caused by the cuprous oxide–isonitrile complex, producing cyclopropane (**18**) and/or dihydrofuran (**19**) in moderate yields. These products were also explained in terms of γ-haloalkylcopper(I)–isonitrile (**16**) and δ-haloalkoxycopper(I)–isonitrile (**17**) intermediate.

Much attention has been centered on the chemistry of metal carbenoids in the last decade. Especially, zinc[1] and mercury carbenoids[2] have been intensively studied with the view of their synthetic utilities in the preparation of cyclopropane derivatives. Here, we wish to describe the three-membered ring synthesis, which involves a halomethylcopper(I)–isonitrile as a key intermediate, a new class of copper carbenoid.

In the continuation of studies[3] on copper(I)–isonitrile-catalyzed reactions, it has been established that the so-called active hydrogen compounds such as malonate and acetylacetone react with the cuprous oxide–isonitrile complex to produce the organocopper(I)–isonitrile complexes (**1**). The formation of **1** has



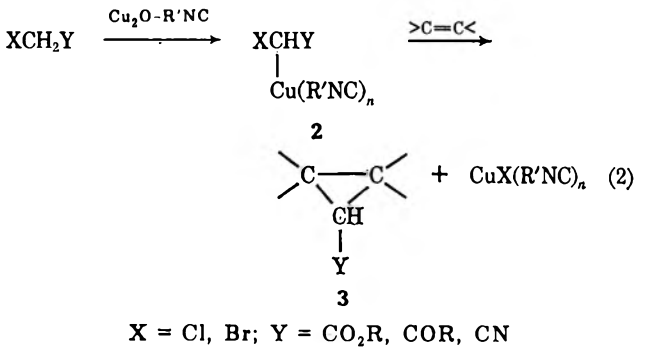
(1)

1

X, Y = CO_2R', COR', CN

been demonstrated by trapping experiments. For instance, the treatment of diethyl malonate with cuprous oxide–*tert*-butyl isocyanide in the presence of ethyl bromide produced diethyl ethylmalonate in 45% yield. Moreover, in the reaction of cyclopentadiene with the cuprous oxide–*tert*-butyl isocyanide complex, *penta-haptocyclopentadienylcopper(I) tert*-butyl isocyanide[3c] was successfully isolated as a stable crystalline solid.

In our preliminary paper,[4] we reported a new cyclopropane synthesis from an α-halo compound, olefin, and the cuprous oxide–isonitrile complex. In the scheme of this reaction, it has been assumed that α-halomethylcopper (**2**) is first formed by the reaction of the cuprous oxide–isonitrile complex with the α-halo compound, which then reacts with an electron-deficient olefin to yield the corresponding cyclopropane derivative (**3**) as shown in eq 2. We found another cyclopropane synthesis by means of a α,α-dihalomethylcopper–isonitrile complex **4** and/or **5** which may be formed by an

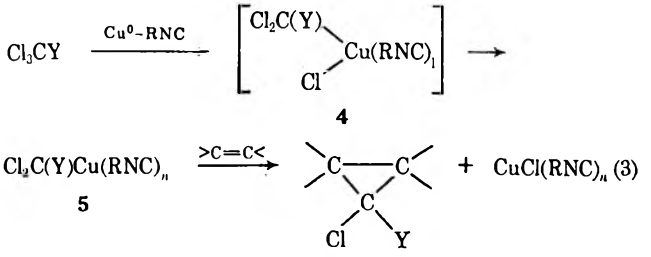


(2)

2

3

X = Cl, Br; Y = CO_2R, COR, CN



(3)

4

5

oxidative addition of a carbon–chlorine bond of trichloromethyl compounds onto a soluble complex of copper(0)–isonitrile. The intermediates **2** and **4** or **5** constitute a new class of copper carbenoids.

In the present paper, we wish to report some details of reaction 2 and reaction 3 as well as the related cyclic compound syntheses by means of copper–isonitrile complex.

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TABLE I

CYCLOPROPANE SYNTHESIS FROM α-MONOHALO COMPOUND, OLEFIN, AND CUPROUS OXIDE–ISONITRILE[a]

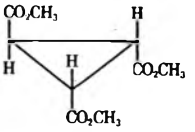
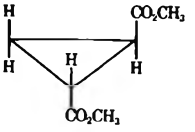
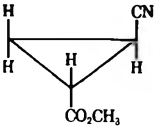
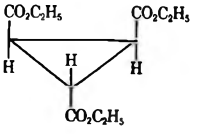
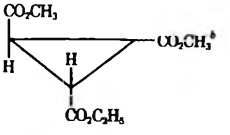
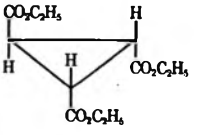
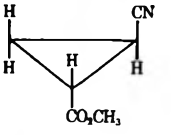
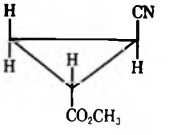
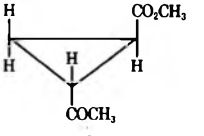
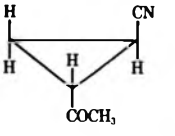
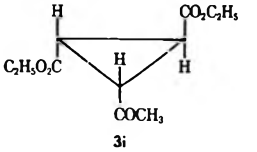
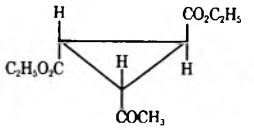
Registry no.	α-Monohalo compd	Registry no.	Olefin	Product (yield, %)	
96-34-4	$ClCH_2CO_2CH_3$		None	 3a	(34)
	$ClCH_2CO_2CH_3$	96-33-3	$CH_2{=}CHCO_2CH_3$	 3b	(22)
	$ClCH_2CO_2CH_3$	107-13-1	$CH_2{=}CHCN$	 3c	(31)
105-39-5	$ClCH_2CO_2C_2H_5$	141-05-9	*cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 3d	(29)
	$ClCH_2CO_2C_2H_5$	624-48-6	*cis*-$CH_3O_2CCH{=}CHCO_2CH_3$	 3e	(29)
	$ClCH_2CO_2C_2H_5$	623-91-6	*trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 3d	(53)
96-32-2	$BrCH_2CO_2CH_3$		$CH_2{=}CHCN$	 3f	(4)
107-14-2	$ClCH_2CN$		$CH_2{=}CHCO_2CH_3$	 3f	(10)
78-95-5	$ClCH_2COCH_3$		$CH_2{=}CHCO_2CH_3$	 3g	(21)
	$ClCH_2COCH_3$		$CH_2{=}CHCN$	 3h	(16)
	$ClCH_2COCH_3$		*trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 3i	(33)

TABLE I (*Continued*)

Registry no.	α-Monohalo compd	Olefin	Product (yield, %)[b]
	$ClCH_2COCH_3$	*cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 (15)

3i

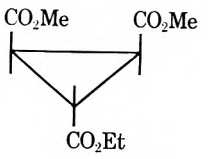
[a] Reaction conditions: A mixture of 20 mmol of an α-halo compound, 30 mmol of an olefin, 10 mmol of Cu_2O, and 60 mmol of *tert*-butyl isocyanide was stirred at 80° for 3 hr. [b] Cis and trans mixture.

Results and Discussion

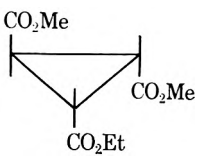
Reaction of α-Halocarbonyl and α-Halonitrile Compounds with Olefin by Cuprous Oxide–Isonitrile Complex.—On heating, cuprous oxide was dissolved in methyl monochloroacetate in the presence of *tert*-butyl isocyanide. From the reaction mixture, trimethyl cyclopropane-1,*cis*-2,*trans*-3-tricarboxylate was isolated in a yield of 34%. When this reaction was carried out in the presence of an electron-deficient olefin such as acrylate and acrylonitrile, the corresponding cyclopropane derivative in eq 2 was formed without being accompanied by the formation of trimethyl cyclopropanetricarboxylate. In the same way, monochloroacetone and monochloroacetonitrile react with electron-deficient olefins to produce the corresponding cyclopropane derivatives. This reaction is applied to electron-deficient olefins. However, no reaction occurred with electron-rich olefins such as cyclohexene and vinyl ethers.

Some representative results are shown in Table I. Spectral data and elemental analyses support the assigned structures of the products. The stereochemistry of the cyclopropanes produced is interesting. In all the reactions except for maleate and fumarate, only one of the stereoisomers, in which two polar substituents on the cyclopropane ring are oriented trans to each other, is selectively produced. A finding that cyclopropane-*cis*-dicarboxylic ester is readily isomerized to the more stable trans isomer under the reaction conditions suggests that the product stereochemistry is thermodynamically controlled.

The reaction of ethyl chloroacetate with methyl acrylate in the presence of sodium methoxide affords a cis–trans mixture of cyclopropanedicarboxylic acid ester in yields of 26 (cis) and 22% (trans), respectively.[5] On the other hand, when this reaction with a strong base was carried out in dimethylformamide or in hexamethylphosphoramide–benzene mixture, the trans isomer predominated.[5] In the reactions of ethyl chloroacetate with methyl maleate and with methyl fumarate in the presence of the cuprous oxide–isonitrile system, about a 1:1 mixture of the two stereoisomers, **3e** and **3e′**, was formed. This result may be



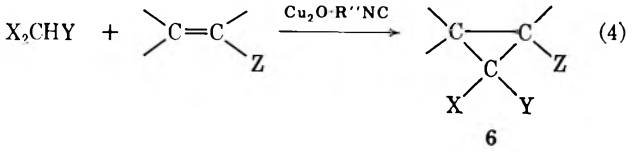
3e



3e′

rationalized on the basis of the thermodynamic stabilities of the products; *i.e.*, the carbomethoxy group and carbethoxy group are almost equivalent in steric bulk. In the reaction with methyl maleate, the isomerization of maleate to fumarate may have occurred prior to the formation of the cyclopropanetricarboxylate. In fact, both maleate and fumarate were recovered from the reaction mixture. However, the rapid equilibration between the isomers of the cyclopropane products seems to be the most important for the control of the **3e** to **3e′** ratio, because cyclopropane-*cis*-1,2-dicarboxylic acid ester was found to be isomerized rapidly into the trans isomer under the present reaction conditions.

Reaction of α,α-Dihalocarbonyl and α,α-Dihalonitrile Compounds with Olefin by Cuprous Oxide–Isonitrile Complex.—Cyclopropane synthesis by means of a cuprous oxide–isonitrile complex can be applied to the reactions of α,α-dihaloacetate and of α,α-dihaloacetonitrile with an electron-deficient olefin, leading to the corresponding monohalocyclopropane derivative **6** (eq 4). The results are summarized in Table II.



(4)

6

X = Cl, Br
Y = CO_2R, COR, CN
Z = CO_2R', CN

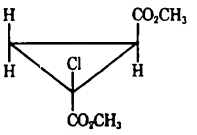
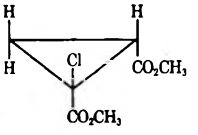
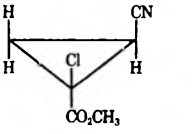
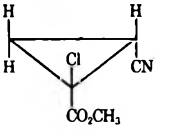
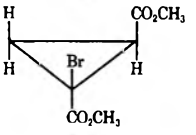
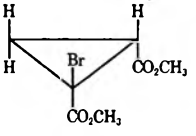
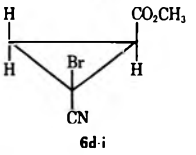
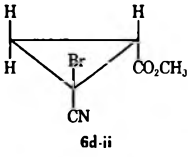
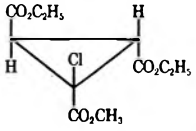
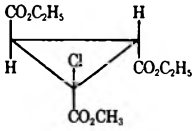
In the cases of acrylate (Z = CO_2R) and acrylonitrile (Z = CN) as the olefin component, the cyclopropane product consisted of the two stereoisomers in which Y and Z are either trans or cis. The combinations of methyl dichloroacetate with ethyl maleate and with ethyl fumarate gave a single product of 1-chloro-1-methoxycarbonyl-2,3-di(ethoxycarbonyl)cyclopropane in which the two ethoxycarbonyl groups from maleate and fumarate were oriented trans.

Reactions of Trichloroacetonitrile, Trichloroacetate, and Benzotrichloride with Olefins by Metallic Copper–Isonitrile Complex.—A solution freshly prepared by dissolving metallic copper in cyclohexyl isocyanide under nitrogen showed electron spin resonance (*g* value = 2.0041) which may be assigned to a zero-valent copper–isonitrile complex. Recently, electron spin resonance of Cu(0) species has been reported by Kochi, *et al.*[6] The mixture of metallic copper and isonitrile under nitrogen was treated at 80° with a mixture of a trichloromethyl compound and an electron-deficient olefin to produce chlorocyclopropane derivative (**7**) in a fair yield. This reaction was not catalyzed by the

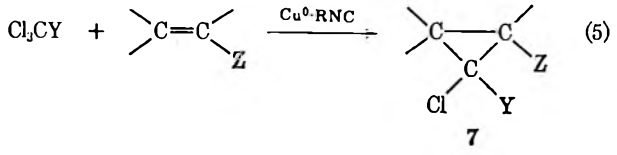
(5) L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568 (1958); **82**, 6416 (1960); **84**, 2246 (1962).

(6) K. Wada, M. Tamura, and J. K. Kochi, *J. Amer. Chem. Soc.*, **92**, 6656 (1970).

TABLE II.—CYCLOPROPANE SYNTHESIS FROM α,α-DIHALO COMPOUND, OLEFIN, AND CUPROUS OXIDE–ISONITRILE[a]

Registry no.	α,α-Dihalo compd	Olefin	Product (yield, %)[b]			
116-54-1	$Cl_2CHCO_2CH_3$	$CH_2=CHCO_2CH_3$	 6a-i	(11)	 6a-ii	(36)
	$Cl_2CHCO_2CH_3$	$CH_2=CHCN$	 6b-i	(14)	 6b-ii	(15)
6482-26-4	$Br_2CHCO_2CH_3$	$CH_2=CHCO_2CH_3$	 6c-i	(20)	 6c-ii	(12)
3252-43-5	Br_2CHCN	$CH=CHCO_2CH_3$	 6d-i	(9)	 6d-ii	(11)
	$Cl_2CHCO_2CH_3$	*trans*-$C_2H_3O_2CCH=CHCO_2C_2H_5$			 6e	(30)
	$Cl_2CHCO_2CH_3$	*cis*-$C_2H_5O_2CCH=CHCO_2C_2H_5$			 6e	(28)

[a] Reaction conditions: Cu_2O, 5 mmol; α,α-dihalo compound, 10 mmol; olefin, 30 mmol. [b] Yield is based upon α,α-dihalo compound.



Y = CO_2R', CN, Ph
Z = CO_2R', CN

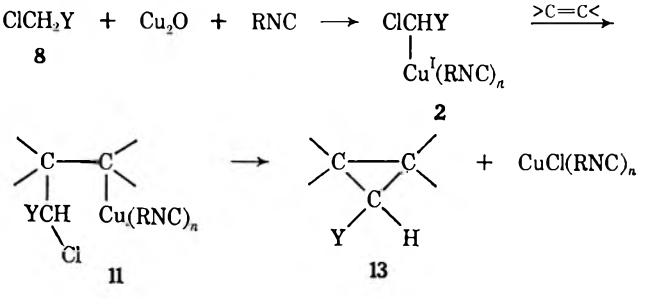
cuprous oxide–isonitrile complex. Results are summarized in Table III.

Products and their stereochemistry are almost the same as those of the reaction of α,α-dihalocarbonyl and α,α-dihalonitrile compounds with olefin by the cuprous oxide–isonitrile complex. These findings may suggest that both reactions involve a similar reaction intermediate.

Reaction Scheme.—These cyclopropane syntheses using cuprous oxide–isonitrile and copper(0)–isonitrile complexes may be explained by a stepwise process (Scheme I) involving the addition of α-halomethylcopper (I)–isonitrile intermediate **2** and **5**, a new class of copper carbenoid, to an electron-deficient olefin.

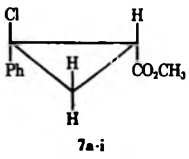
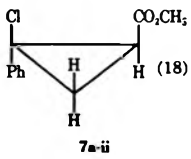
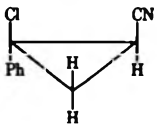
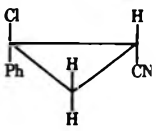
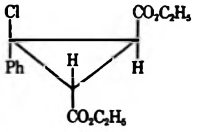
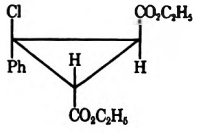
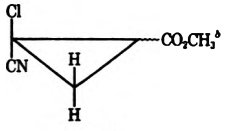
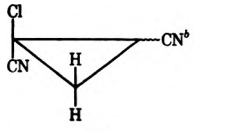
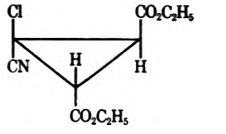
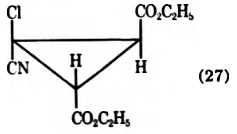
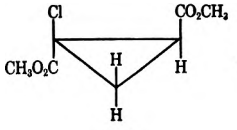
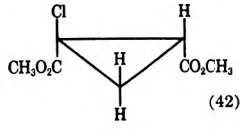
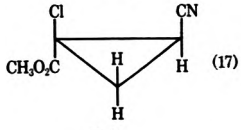
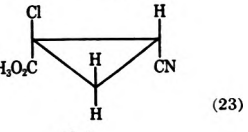
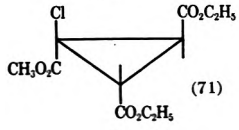
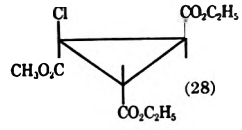
The copper carbenoid complexes are derived from the abstraction of the α hydrogen of **8** and **9** by the cuprous oxide–isonitrile complex and from the abstraction of the α chlorine of **10** by the copper(0)–isonitrile complex. The latter process may involve an oxidative addition of a carbon–chlorine bond of trichloromethyl compounds **10** to the copper(0)–isonitrile complex leading to copper(II) carbenoid–isonitrile complexes **4**, which are known[7] to be readily converted into copper(I)–isonitrile complexes **5**. The addition of α-halomethylcopper(I)–isonitrile intermediates **2** and **5** to an electron-deficient olefin leads to the formation of the corresponding γ-chloro–organocopper(I) complexes **11** and **12**, respectively, whose intramolecular ring closure brings about the cyclopropane product **13** and **14**.

SCHEME I

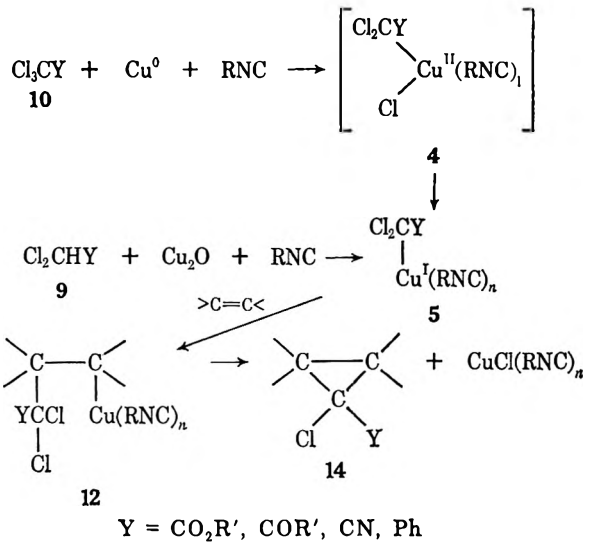


(7) R. W. Stephany and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **89**, 305 (1970).

TABLE III.—CHLOROCYCLOPROPANE SYNTHESIS FROM TRICHLOROMETHYL COMPOUNDS, OLEFIN, AND COPPER(0)–ISONITRILE[a]

Registry no.	Trichloromethyl compd	Olefin	Product (yield, %)
98-07-7	$PhCCl_3$	$CH_2{=}CHCO_2CH_3$	 (36)  (18)
			7a-i 7a-ii
	$PhCCl_3$	$CH_2{=}CHCN$	 (17)  (12)
			7b-i 7b-ii
	$PhCCl_3$	*trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 (35)
			7c
	$PhCCl_3$	*cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 (36)
			7c
545-06-2	Cl_3CN	$CH_2{=}CHCO_2CH_3$	 (66) (1:1.7)[c]
			7d
	Cl_2CCN	$CH_2{=}CHCN$	 (20) (1:1.4)[c]
			7e
	Cl_2CCN	*trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 (38)
			7f
	Cl_2CCN	*cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$	 (27)
			7f
598-99-2	$Cl_3CCO_2CH_3$	$CH_2{=}CHCO_2CH_3$	 (19)  (42)
			7g-i 7g-ii
	$Cl_3CCO_2CH_3$	$CH_2{=}CHCN$	 (17)  (23)
			7h-i 7h-ii
	$Cl_3CCO_2CH_3$	*trans*-$C_2H_5O_2CH{=}CHCO_2C_2H_5$	 (71)
			7i
	$Cl_3CCO_2CH_3$	*cis*-$C_2H_5O_2CCH{=}CHCOC_2H_5$	 (28)
			7i

[a] Trichloromethyl compound, 10 mmol; olefin, 30 mmol; Cu, 20 mg-atoms; and *tert*-butyl isocyanide, 40 mmol. [b] Cis and trans mixture. [c] Isomer ratio. [d] Cyclohexyl isocyanide was used instead of *tert*-butyl isocyanide.



Y = CO_2R', COR', CN, Ph

The intermediates, α-halomethylcopper(I)–isonitriles, have not been isolated. However, the following findings support the assumption of copper carbenoid intermediates **2** and **5**. When methyl trichloroacetate was treated with the copper(0)–isonitrile system in the presence of methyl iodide, methyl α,α-dichloropropionate was produced (eq 6). In addi-

$$Cl_3CCO_2CH_3 + Cu^0(RNC)_m \xrightarrow{CH_3I} CH_3CCl_2CO_2CH_3 \quad (6)$$

$$PhCCl_3 + Cu^0(RNC)_m \xrightarrow{t\text{-BuOH}} PhCHCl_2 \quad (7)$$

tion, benzal chloride was formed when benzotrichloride was treated with the copper(0)–isonitrile complex in *tert*-butyl alcohol solvent (eq 7). These findings are taken to support the transient formation of **5**.

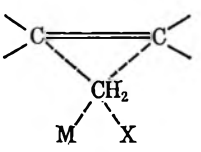
Hydrogen–deuterium exchange in the system of dichloroacetate and cuprous oxide–isonitrile may also support a transient copper carbenoid intermediate **2**. Deuterium was rapidly incorporated into dichloroacetate recovered from a short time reaction of dichloroacetate with the cuprous oxide–isonitrile complex in the presence of *tert*-butyl alcohol-d_1.

$$Cl_2CCO_2CH_3 \xrightarrow{t\text{-BuOD}} Cl_2CDCO_2CH_3 \quad (8)$$

$Cu(RNC)_n$

For the reaction of **2** and **5** with olefin, the one-step addition mechanism (Chart I) as in the cyclopropane

CHART I

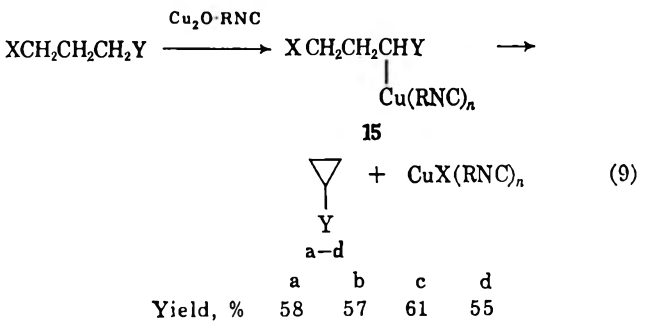


M = Zn, Hg
X = halogen

synthesis by means of zinc carbenoid[1] and mercury carbenoid[2] does not seem to be operating in the present reaction, because zinc and mercury carbenoids prefer to react with electron-rich olefins rather than with electron-poor olefins.

The stepwise reaction mechanism seems to be supported by the following findings. According to Scheme I, γ-halocarboxylic acid esters and nitriles having α-acidic hydrogen may undergo the cyclization reaction in the presence of the cuprous oxide–isonitrile complex, because they form a γ-haloorganocopper(I)–isonitrile complex resembling complexes **11** and **12**. In fact, methyl 4-chlorobutanoate, 5-chloropentan-2-one, and 4-chlorobutyronitrile were cyclized to the corresponding cyclopropane derivatives by the cuprous oxide–isonitrile complex in fairly good yields. This reaction is a good synthetic method.

A γ-haloorganocopper(I)–isonitrile complex (**15**) intermediate in the cyclization reaction (eq 9) is sup-

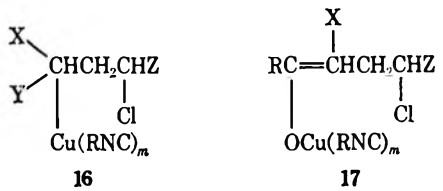


	a	b	c	d
Yield, %	58	57	61	55

a, X = Cl; Y = $CO_2C_2H_5$
b, X = Cl; Y = $COCH_3$
c, X = Cl; Y = CN
d, X = Br; Y = CN

ported by deuterium incorporation in the 4-chlorobutyronitrile recovered after a short time reaction of 4-chlorobutyronitrile with the cuprous oxide–isonitrile complex in the presence of *tert*-butyl alcohol-d_1.

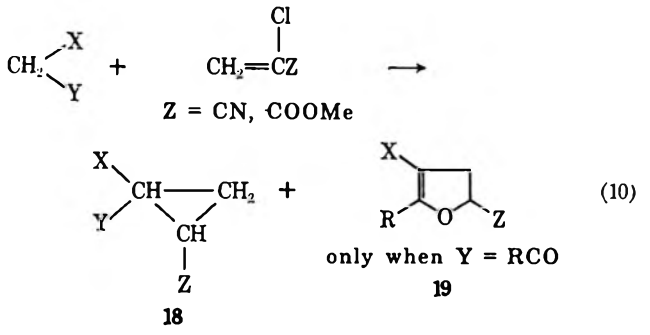
Reaction of α-Chloroacrylonitrile and α-Chloroacrylate with Active Methylene Compound by Cuprous Oxide–Isonitrile Complex.—We have hitherto mentioned a couple of cyclization reactions which involve the copper carbenoid isonitrile complexes as the key intermediates. These cyclization reactions are based upon a common elementary process of the intramolecular elimination of copper(I) halide–isonitrile complex from γ-haloalkylcopper(I)–isonitrile intermediates **11** and **12** formed by addition reaction of the copper carbenoid isonitrile complexes **2** and **5** to olefin. Now another combination leading to γ-haloalkylcopper(I)–isonitrile intermediate **16** and δ-haloalkoxycopper(I)–isonitrile intermediate **17** is presented, which gives



cyclopropane (**18**) and dihydrofuran (**19**) derivatives, respectively (eq 10). The reactions of α-chloroacrylonitrile and α-chloroacrylate with active methylene compounds such as dimethyl malonate and methyl cyanoacetate were carried out in benzene at 80° for 6 hr in the presence of Cu_2O and *tert*-butyl isocyanide. As the reaction proceeds, Cu_2O was dissolved progressively to form a homogeneous solution. The product was a mixture of cis and trans 1,1,2-trisubstituted cyclopropane (**18**) (eq 10). These reactions with malonate and cyanoacetate as the active methylene

component gave a single product of the cyclopropane derivative.

On the other hand, the reaction with active methylene compounds such as acetylacetone and phenylacetone, which have at least one acyl substituent, afforded dihydrofuran derivative (**19**) together with cyclopropane products (**18**) (eq 10).

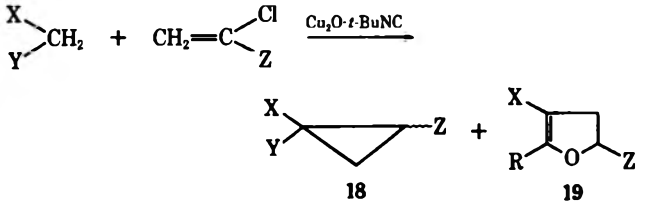


(10)

Results are shown in Table IV. The structures of all the products were established by nmr, mass, and ir

TABLE IV

REACTIONS OF α-CHLOROACRYLATE AND α-CHLOROACRYLONITRILE WITH ACTIVE METHYLENE COMPOUNDS BY MEANS OF CUPROUS OXIDE–*tert*-BUTYL ISOCYANIDE[a]



Registry no.	Run	X	Y	Z	Products yield, % 18 (isomer ratio)[b]	19
105-34-0	a	CN	CO_2Me	CO_2Me[c]	61 (100:0)	
108-59-8	b	CO_2Me	CO_2Me	CO_2Me	54 (100:0)	
140-29-4	c	CN	Ph	CO_2Me	55 (73:27)	
101-41-7	d	CO_2Me	Ph	CO_2Me	9 (86:34)	
109-77-3	e	CN	CN	CO_2Me	23	
105-53-3	f	CO_2Et	CO_2Et	CN[d]	29	
123-54-6	g	COMe	COMe	CO_2Me	8	68
141-97-9	h	COMe	CO_2Et	CO_2Me	10 (89:11)	53
103-79-7	i	COMe	Ph	CO_2Me	42 (95:5)	9
122-78-1	j	CHO	Ph	CO_2Me	62 (87:13)	9
	k	COMe	COMe	CN	33	5
	l	COMe	CO_2Et	CN	42 (88:12)	1
	m	COMe	Ph	CN	Trace	

[a] Reaction conditions: active methylene compound, 15 mmol; α-chloro olefin, 15 mmol; Cu_2O, 7.7 mmol; *tert*-butyl isocyanide, 24 mmol; benzene, 20 ml; 80°, 6 hr. [b] The stereoisomers ratio was determined by glpc. [c] Registry no., 80-63-7. [d] Registry no., 920-37-6.

spectra as well as elementary analyses. However, the stereochemistry of cyclopropane derivatives (**18**) remained unknown except for those of phenylcyclopropane derivatives (**18c**, **18d**, **18i**, and **18j**), of which the two isomers were differentiated from each other by nmr spectrum on the basis of a characteristic upfield shift of the proton cis to phenyl group on the cyclopropane ring.[8] In the products of phenylcyclopropanes, an isomer in which two polar substituents are oriented trans to each other is always predominating.

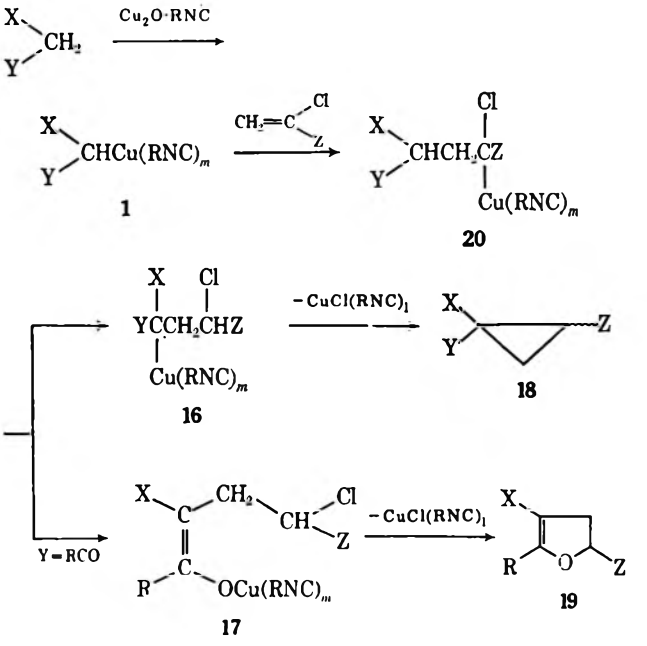
(8) G. A. Closs, R. A. Moss, and J. J. Coyle, *J. Amer. Chem. Soc.*, **84**, 4985 (1962).

The nmr spectra of 2,3,5-trisubstituted dihydrofurans exhibited a diagnostic long-range coupling[9] between 2 substituent and 4 protons. For example, 2-methyl-3-acetyl-5-methoxycarbonyldihydrofuran showed a strong triplet splitting ($J_{CH_3CH_3}$ = 1.5 Hz) on the 2-methyl absorption band owing to spin coupling with the 4-methylene protons.

As is seen in Table IV, the products ratio of dihydrofuran (**19**) to cyclopropane (**18**) formed in the reaction of the chloro olefin with the acyl-substituted methylene compound increases with the increasing acidity of the active methylene compound. The reaction of α-chloroacrylonitrile afforded lower yields of the products than the corresponding reactions of α-chloroacrylate, because α-chloroacrylonitrile was readily polymerized under these reaction conditions.

The present reaction may be explained by Scheme II, involving several organocopper(I)–isonitrile complexes

SCHEME II



as the intermediates. The addition of organocopper(I)–isonitrile (**1**) to an electron-deficient olefin leads to the formation of α-chloroalkylcopper(I)–isonitrile (**20**), which is converted intramolecularly or intermolecularly into γ-chloroalkylcopper(I)–isonitrile (**16**) and/or δ-chloroalkenyloxycopper(I)–isonitrile (**17**). The intramolecular eliminations of copper(I)chloride–isonitrile complex from **16** and **17** bring the products of **18** and **19**, respectively.

The following observation is consistent with the above mechanism (Scheme II). In the reaction of α-chloroacrylate with diethyl ethylmalonate, an addition product of **22** was given in a yield of 46%. No cyclization occurred in this case, because the α-chloroalkylcopper(I)–isonitrile (**21**) had no active hydrogen at the γ-carbon atom.

Finally, an alternative mechanism involving α elimination of copper(I) chloride–isonitrile from **20** producing an intermediate of carbene might be considered. The carbene mechanism, however, seems less probable from the fact that olefinic product (**23**)

(9) K. Ichikawa and S. Uemura, *J. Org. Chem.*, **32**, 493 (1967).

TABLE V

IDENTIFICATION DATA OF CYCLOPROPANE 3

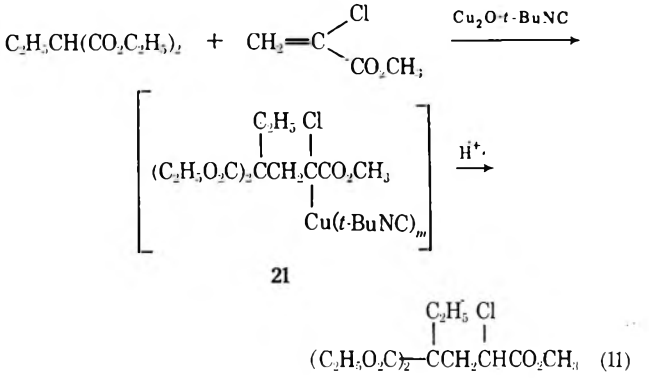
Compd	Ir, cm^{-1}	Nmr, τ			
3a	3050, 1725	6.27 (3 H, s)	6.30 (6 H, s)	7.52 (3 H, m)	
3b	3050, 1725	6.30 (6 H, s)	7.90–8.62 (4 H, m)		
3c	3090, 3040 2225, 1730	6.23 (3 H, s)	7.72 (1 H, m)	8.08 (1 H, m)	8.50 (2 H, m)
3d	3050, 1730	5.82 (6 H, q)	7.42 (3 H, m)	8.73 (9 H, t)	
3e	3055, 1730	5.91 (2 H, q)	6.36 (6 H, s)	7.53 (3 H, m)	8.74 (3 H, t)
3g	3050, 1730 1710	6.33 (3 H, s)	7.73 (3 H, s)	7.43–8.10 (2 H, m)	8.63–8.80 (2 H, m)
3h	3100, 3030 2230, 1710	7.63 (3 H, s)	7.27–7.53 (1 H, m)	7.90–8.20 (1 H, m)	8.37–8.67 (2 H, m)
3i	3050, 1730 1715	5.83 (2 H, q) 8.68 (3 H, t)	5.87 (2 H, q) 8.73 (3 H, t)	7.07–7.40 (3 H, m)	7.80 (3 H, s)

TABLE VI

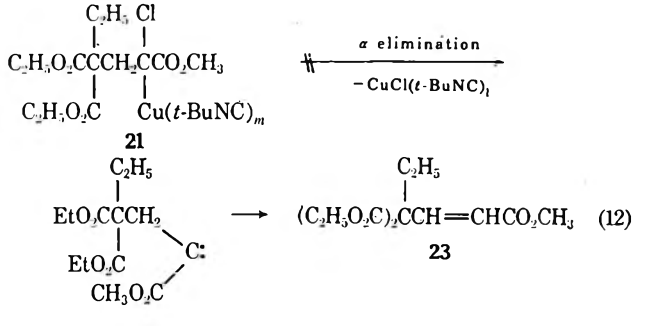
IDENTIFICATION DATA OF HALOCYCLOPROPANE 6

Compd	Ir, cm^{-1}	Nmr, τ			
6a-i	3100, 1735	6.27 (3 H, s)	6.33 (3 H, s)	7.53–8.05 (2 H, m)	8.30–8.53 (1 H, m)
6a-ii	3100, 1735	6.18 (3 H, s)	6.25 (3 H, s)	7.27–7.55 (1 H, m)	8.07–8.20 (2 H, m)
6b-i	3100, 2230, 1740	6.17 (3 H, s)	7.33–8.33 (3 H, m)		
6b-ii	3100, 2230, 1740	6.09 (3 H, s)	7.47–8.33 (3 H, m)		
6c-i	3080, 1740	6.27 (3 H, s)	6.30 (3 H, s)	7.50–8.52 (3 H, m)	
6c-ii	3090, 1740	6.24 (3 H, s)	6.29 (3 H, s)	7.36–7.65 (1 H, m)	8.00–8.24 (2 H, m)
6d-i	3100, 3050, 2230, 1745	6.16 (3 H, s)	7.34–8.32 (3 H, m)		
6d-ii	3090, 3050, 2225, 1740	6.14 (3 H, s)	7.24–8.08 (3 H, m)		
6e	3050, 1740	5.73 (2 H, q) 7.18 (1 H, d)	5.80 (2 H, q) 8.65 (3 H, t)	6.18 (3 H, s) 8.70 (3 H, t)	6.98 (1 H, d)

has not been detected in the reaction of α-chloroacrylate with ethyl malonate (eq 11). It has been known



that carbene, if it is formed as an intermediate, would have been rearranged into the olefinic compound (eq 12) according to the known behavior of carbene.[10]



Experimental Section

Reagents.—Cuprous oxide was a commercial reagent and was used without further purification. Copper was prepared by reducing[11] $CuSO_4$ with zinc powder and dried under nitrogen. *tert*-Butyl and cyclohexyl isocyanides were prepared by Ugi's procedure.[12] Methyl α-chloroacrylate[13] and α-chloroacrylonitrile[14] were synthesized according to the literature procedures and were distilled under nitrogen. All other commercially available reagents were distilled under nitrogen prior to use.

A. Reaction of Methyl α-Chloroacetate with Acrylonitrile Caused by the Cuprous Oxide–*tert*-Butyl Isocyanide Complex.—A mixture of 1.4 g (10 mmol) of Cu_2O, 5.0 g (60 mmol) of *tert*-butyl isocyanide, 2.2 g (20 mmol) of methyl chloroacetate, and 1.6 g (30 mmol) of acrylonitrile was stirred at 80° for 3 hr under nitrogen. As the reaction proceeded, Cu_2O gradually dissolved in the mixture to form a homogeneous system. The reaction mixture was treated with ether to remove the copper(I) chloride–*tert*-butyl isocyanide complex, and the ether solution was concentrated and distilled under 30 mm. *trans*-1-Cyano-2-methoxycarbonylcyclopropane was isolated from the distillate by preparative glpc. The stereochemistry of this product was determined by converting it by treatment with HCl–CH_3OH[15] into *trans*-1,2-dimethoxycarbonylcyclopropane, which exhibits a symmetrical A_2B_2 pattern in the region between τ 7.7 and 8.7. Spectral data are summarized in Table V. The other combinations of an α-monohalo compound and an olefin in Table I were treated similarly.

B. Reaction of Methyl Dichloroacetate with Methyl Acrylate Caused by Cuprous Oxide–*tert*-Butyl Isocyanide Complex.—To a stirred mixture of 0.7 g (5 mmol) of Cu_2O and 2.5 g (30 mmol) of *tert*-butyl isocyanide maintained at about 60°, a mixture of 1.4 g (10 mmol) of methyl dichloroacetate and 2.6 g (30 mmol) of methyl acrylate was added dropwise over 30 min. After the addition was complete, the reaction mixture was heated at 80° for 5 hr. The reaction mixture was treated with ether to remove the copper(I) chloride–*tert*-butyl isocyanide complex. The ether solution was concentrated, and the residue was distilled under reduced pressure. The distillate was analyzed by glpc, and two

(10) W. Kirmse and G. Wächtershäuser, *Tetrahedron*, **22**, 73 (1966).

(11) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 320.

(12) I. Ugi and R. Meyer, *Chem. Ber.*, **93**, 239 (1960).

(13) C. S. Marvel, H. G. Cooke, and J. C. Cowan, *J. Amer. Chem. Soc.*, **62**, 3496 (1940).

(14) H. Brintzinger, K. Pfannstiel, and H. Koddebusch, *Angew. Chem.*, **60**, 311 (1948).

(15) M. M. Rising and Tsoh-Wu Zee, *J. Amer. Chem. Soc.*, **50**, 1210 (1928).

stereoisomers of 1-chloro-1,2-dimethoxycarbonylcyclopropane were isolated separately by preparative glpc. The structures of 1-chloro-1,2-dimethoxycarbonylcyclopropanes were confirmed by reducing them with Zn–HCl to 1,2-dimethoxycyclopropanes, and comparing their nmr spectra with those of authentic samples. Spectral data are summarized in Table VI. The reaction of dichloroacetate with acrylonitrile was carried out in the same way.

C. Reaction of Methyl Dichloroacetate with Diethyl Fumarate Caused by Cuprous Oxide–*tert*-Butyl Isocyanide Complex.—To a stirred mixture of 0.7 g (5 mmol) of Cu_2O, 2.5 g (30 mmol) of *tert*-butyl isocyanide, and 5.2 g (30 mmol) of diethyl fumarate, 1.4 g (10 mmol) of methyl dichloroacetate was added dropwise over 30 min, and the reaction mixture was heated at 80° for 5 hr. Work-up was carried out in a similar way to that described in B.

D. Reaction of Benzotrichloride with Methyl Acrylate in the Presence of Metallic Copper and Isonitrile.—Under nitrogen, a mixture of 2.6 g (30 mmol) of methyl acrylate and 2.0 g (10 mmol) of benzotrichloride in 3 ml of benzene was added dropwise over 30 min to a preheated mixture of 1.3 g (20 mg-atom) of copper metal and 3.3 g (40 mmol) of *tert*-butyl isocyanide in 5 ml of benzene at 80°. Then the reaction mixture was heated with stirring for an additional 7 hr. Finally, the reaction mixture was extracted with ether to remove copper(I) chloride–*tert*-butyl isocyanide complex, and the extract was concentrated and subjected to glpc analysis. About a 1:2 mixture of cis (**7a**-ii) and trans (**7a**-i) isomers of methyl 2-chloro-2-phenylcyclopropanecarboxylate was produced in a total yield of 54%. (The geometrical isomerism is referred to the positions of a chlorine atom and a methoxycarbonyl group.) Each isomer was isolated by preparative glpc and their structures were convincingly confirmed by elementary analysis and spectra data (see Tables VII and VIII).

TABLE VII

IDENTIFICATION OF **7**

	Ir, cm^{-1} (neat)	Nmr (in CCl_4), τ
7a-i	>3000, 1735 750, 696	2.47–2.90 (5 H, m), 6.60 (3 H, s) 7.27–7.63 (1 H, m), 7.73–8.46 (2 H, m)
7a-ii	>3000, 1735 745, 696	2.43–2.93 (5 H, m), 6.23 (3 H, s) 7.57–8.43 (3 H m)
7b-i	>3000, 2215 755, 696	2.50–2.80 (5 H, m) 7.70–8.20 (3 H, m)
7b-ii	>3000, 2215 755, 695	2.37–2.73 (5 H, m) 7.60–8.20 (3 H, m)
7c	>3000, 1732 745, 692	2.50–2.83 (5 H, m), 5.73 (2 H, q), 6.10 (2 H, q) 6.97 (2 H, s), 8.67 (3 H, t), 8.92 (3 H, t)
7d	>3000, 2230 1736	6.20 (3 H, s) 7.20–8.30 (3 H, m)
7e	>3000, 2245	7.23–8.23 (m)
7f	>3000, 2230 1735	5.73 (4 H, q), 7.70 (2 H, m) 8.67 (6 H, t)

The reaction of the other combinations in Table III was carried out by a procedure similar to that mentioned above.

E. Reaction of Methyl Trichloroacetate with Copper Metal and *tert*-Butyl Isocyanide in the Presence of Methyl Iodide.—Under nitrogen, a mixture of 0.32 g (5 mg-atoms) of copper metal, 1.3 g (15 mmol) of *tert*-butyl isocyanide, and 1 ml of benzene was heated at 80° for 1 hr with stirring and then cooled to room temperature. To the stirred mixture, 0.9 g (5 mmol) of methyl trichloroacetate was added dropwise, and, after 1 hr, 4.26 g (30 mmol) of methyl iodide was added, and the solution was stirred for 1 hr at room temperature. The reaction mixture was treated with ether to remove copper(I)–*tert*-butyl isocyanide complex, the ether solution was concentrated, and the residue was analyzed by glpc. Methyl α,α-dichloropropionate was isolated in 30% yield by preparative glpc and identified by comparison with an authentic sample.

F. Cyclization of Methyl 4-Chlorobutanoate by Cuprous Oxide–Cyclohexyl Isocyanide Complex.—To a mixture of 0.7 g (5 mmol) of Cu_2O and 3.3 g (30 mmol) of cyclohexyl isocyanide, 1.4 g of methyl 4-chlorobutanoate was added dropwise with stirring at 80° and then the mixture was heated at 80° for 7 hr. The reaction mixture was treated with ether to remove the copper(I) chloride–cyclohexyl isocyanide complex, the ether solution was concentrated, and the residue was distilled under slightly reduced pressure. Methyl cyclopropanecarboxylate was isolated in 58% yield.

TABLE VIII

IDENTIFICATION OF **18** AND **19**

Compd	Mass, M^+	Ir (neat), cm^{-1}	Nmr (in $CDCl_3$), τ
18a	183	3100, 2230, 1735	6.10, 6.15 (s, 6 H, $COOCH_3$), 7.25 (q, 1 H), 7.90 (m, 2 H)
18b	216	3100, 1740, 1380	6.25, 6.29 (s, 9 H), 7.40 (q, 1 H), 8.20 (m, 2 H)
18c[a]	201	3080, 2218, 1740, 1225, 1250, 938	2.69 (5 H), 6.58 (s, $COOCH_3$), 7.25 (q, 1 H), ~7.90 (m, 2 H)
		3080, 2220, 1735 1050, 941	2.65 (5 H), 6.18 (s, $COOCH_3$), 7.70 (q, 1 H), ~8.00 (m, 2 H)
18d[a]	234	1738, 1435, 1095	2.70 (5 H), 6.30 (s, 3 H), 6.38 (s, 3 H), 5.7 (q, 1 H), ~7.3–7.4 (m, 2 H)
		1725, 1435, 1380, 1100, 925	2.71 (5 H), 6.21 (s, 3 H), 6.37 (s, 3 H), 7.25 (q, 1 H), 8.05 (m, 2 H)
18e	150	3100, 2243, 1740, 1442, 1388, 1018	6.15 (s, $COOCH_3$), 7.16 (q, 1 H), ~7.8 (m, 2 H)
18f	211	3098, 2225, 1735, 1375, 1015	5.70 (4 H), 7.51 (q, 1 H), ~8.2 (m, 2 H), 8.70 (6 H)
18g	184	3100, 1740, 1700	6.30 (s, 3 H, $COOCH_3$), 7.40 (q, 1 H), 7.68 (s, 3 H), 7.79 (s, 3 H), ~8.20 (m, 2 H)
	214	3080, 1740, 1710	5.73 (q, 2 H), 6.30 (s, 3 H, $COOCH_3$), ~7.40 (m, 1 H), 7.66 (s, 3 H, $COCH_3$), ~8.25 (m, 2 H), 8.68 (t, 3 H)
18h[a]		3080, 1735, 1710	5.75 (q, 2 H), 6.30 (s, 3 H, $COOCH_3$), ~7.40 (m, 1 H), 7.69 (s, 3 H, $COCH_3$), ~8.25 (m, 2 H), 8.7 (t, 3 H)
	218	3020, 1735, 1700, 1608, 980, 928	2.66 (5 H), 6.55 (s, 3 H, $COOCH_3$), 7.15 (q, 1 H), 8.00 (s, 3 H), 8.16 (m, 2 H)
18i[a]		3020, 1730, 1705, 1595, 975, 920	2.71 (5 H), 6.30 (s, 3 H, $COOCH_3$), 7.80 (q, 1 H), 7.94 (s, 3 H), 8.45 (m, 2 H)
18j[a]	204	3080, 1725, 1715, 1500, 1270, 1100, 1025, 950	1.49 (1 H, CHO), 2.7 (5 H), 6.60 (3 H, $COOCH_3$), 7.35 (q, 1 H), ~8.00 (m, 2 H)
		3080, 1728, 1701, 1195, 1170	1.45 (1 H, CHO), 2.75 (5 H), 6.23 (3 H, $COOCH_3$), 7.65 (q, 2 H), ~8.30 (m, 2 H)
18k[a]		3085, 2242, 1700, 1420, 1362, 920, 965	7.59, 7.72 (s, 6 H, $COCH_3$), 7.43 (q, 1 H), 7.87 (q, 1 H) 8.35 (q 1 H)
18l[a]	181	3098, 2228, 1720, 1370, 1310, 1250	5.62 (2 H), 7.54 (3 H, $COCH_3$), 7.48 (q, 1 H), 7.93 (q, 1 H), 8.40 (q, 1 H)
		3100, 2230, 1720, 1370, 1310, 1270	5.73 (2 H), 7.50 (3 H, $COCH_3$), 7.52 (q, 1 H), 7.85 (q, 1 H), 8.35 (q, 1 H)
19g	184	1755, 1675, 1630, 1200, 945, 920	4.95 (q, 1 H), 6.19 (s, 3 H), 6.85 (m, 2 H), 7.72 (t, 3 H), 7.79 (s, 3 H)
19h	214	1760, 1700, 1660, 1215, 1035, 965, 925	4.96 (q, 1 H), 5.84 (q, 2 H), 6.21 (s, 3 H, $COOCH_3$), 6.85 (m, 2 H), 7.75 (t, 3 H), 8.72 (t, 3 H)
19i	218	1750, 1660, 1595, 1510, 1195, 975, 955, 912	2.75 (5 H), 5.00 (q, 1 H), 6.20 (s, $COOCH_3$), ~6.70 (m, 2 H), 7.91 (t, 3 H)
19j	204	1750, 1640, 1601, 1495, 1440, 1100, 930, 910	2.0 (t, 1 H), 2.6 (5 H), 4.85 (q, 1 H), 6.19 (s, $COOCH_3$), 6.7 (m, 2 H)
19k	151	1700, 1680, 1630, 1420, 1380, 1360, 1205	4.72 (q, 1 H), 6.70 (m, 2 H), 7.75 (6 H, CH_3)

[a] Consisted of two isomers.

G. Deuterium Incorporation in 4-Chlorobutyronitrile.—A mixture of 0.7 g (5 mmol) of Cu_2O, 3.3 g (30 mmol) of cyclohexyl isocyanide, 1.0 g of 4-chlorobutyronitrile, and 1.5 g (20 mmol) of *tert*-butyl alcohol-d_1 was heated at 70° with stirring. After 1 hr, the reaction mixture was distilled under reduced pressure, and the recovered 4-chlorobutyronitrile was subjected to spectroscopic analyses. Nmr showed deuterium incorporation at the carbon α to the cyano group and the ir spectrum exhibited a new band at 2120 cm^{-1} which was assigned to ν_{C-D}.

H. Reaction of α-Chloroacrylonitrile with Active Methylene Compound Caused by Cuprous Oxide–*tert*-Butyl Isocyanide. General Procedure.—To a mixture of 7.7 mmol of Cu_2O, 15.0 mmol of an active methylene compound, and 20 ml of benzene, 15.0 mmol of α-chloroacrylate or α-chloroacrylonitrile was added, and then 24.0 mmol of *tert*-butyl isocyanide was added dropwise at room temperature with stirring under nitrogen. After

the mixture was heated at 80° for 6 hr, 30 ml of a mixture of petroleum ether (bp 30–60°) and diethyl ether (2:1) was poured into the cooled reaction mixture. The precipitated copper(I) chloride–*tert*-butyl isocyanide and some unreacted Cu_2O were removed by filtration. The filtrate was subjected to distillation and the residue was distilled *in vacuo*. Each fraction was analyzed by glpc. An analytical sample was purified by preparative glpc.

I. **Reaction of Methyl α-Chloroacrylate with Diethyl Ethylmalonate Caused by Cuprous Oxide–*tert*-Butyl Isocyanides.**—Reaction was carried out according to the procedure mentioned above. A main product of **22** [bp 123° (4 mm Hg); yield 46%] was accompanied by several minor by-products, whose nmr spectra exhibited no signal in the olefinic region. **22** (*Anal.* Calcd for $C_{13}H_{21}O_6Cl$: C, 50.57; H, 6.86; Cl, 11.48. Found: C, 50.85; H, 6.90; Cl, 11.30.) had nmr ($CDCl_3$) τ 5.2 (1 H, ClCH<), 5.75 (4 H, 2 × OCH_2CH_3), 6.21 (3 H, OCH_3), ~7.4 (2 H, >CCH_2CHCl), 8.01 (2 H, CH_3CH_2C<), 8.78 (6 H, 2 × OCH_2CH_3), 9.16 (3 H, CH_2CH_2C<).

Registry No.—**3a**, 717-69-1; **3b**, 826-35-7; **3c**, 34185-94-9; **3d**, 13949-99-0; (1α,2β,3β)-**3e**, 34185-95-0; (1α,2α,3β)-**3e′**, 34185-96-1; **3g**, 34185-98-3; **3h**, 39821-99-3; **3i**, 34185-99-4; **6a**-i, 39822-01-0; **6a**-ii, 39822-02-1; **6b**-i, 39822-03-2; **6b**-ii, 39822-04-3; **6c**-i, 30630-39-8; **6c**-ii, 30630-38-7; **6d**-i, 39822-06-5; **6d**-ii, 39822-07-6; **6e**, 39822-08-7; **7a**-i, 39822-09-8; **7a**-ii, 39822-10-1; **7b**-i, 39822-11-2; **7b**-ii, 39822-12-3; **7c**, 39822-13-4; *trans*-**7d**, 39822-14-5; *cis*-**7d**, 39822-15-6; *cis*-**7e**, 39822-16-7; *trans*-**7e**, 39822-17-8; **7f**, 39822-18-9; **18a**, 39822-24-7; **18b**, 22650-26-6; *cis*-**18c**, 39822-26-9; *trans*-**18c**, 39822-27-0; *cis*-**18d**, 39822-28-1; *trans*-**18d**, 39822-29-2; **18e**, 39822-30-5; **18f**, 714-92-1; **18g**, 39822-32-7; *cis*-**18h**, 39822-33-8; *trans*-**18h**, 39822-34-9; *cis*-**18i**, 39822-35-0; *trans*-**18i**, 39822-36-1; *cis*-**18j**, 39822-37-2; *trans*-**18j**, 39822-38-3; **18k**, 19930-90-6; *cis*-**18l**, 39822-41-8; *trans*-**18l**, 39822-42-9; **19g** (X = Ac; R = Me), 39822-40-7; **19h** (X = EtO_2C; R = Me), 39822-43-0; **19i** (X = Ph; R = Me), 39822-44-1; **19j** (X = Ph; R = H), 39822-45-2; **19k** (X = Ac; R = Me), 39822-46-3; **22**, 39822-47-4; cuprous oxide–*tert*-butylisonitrile complex, 39822-48-5; cuprous oxide–cyclohexylisonitrile complex 39822-49-6.

Reaction of α-Ketols and Other 21-Hydroxy Steroids with Phosgene. II. Structural Requirements in the Formation of 20-Chloro-20,21-cyclic Carbonates from 11-Deoxycorticosterone and 11-Dehydrocorticosterone[1]

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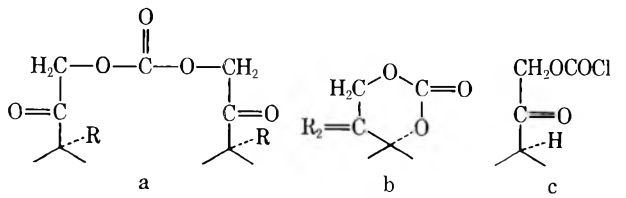
Reaction of 11-deoxycorticosterone (**1**) in pyridine with excess phosgene in benzene (condition B) affords the novel-20-chloro-20,21-cyclic carbonates **3a,b** as major products and the 21-chloride **2** as a minor product. In contrast, phosgenation of 11-dehydrocorticosterone (**9**) under condition B gives the 21-chloride **10** as a major product and the 20-chloro-20,21-cyclic carbonates **11a** and **11b** as minor products. Reduction of the 11-deoxy-cyclic chlorocarbonates **3a,b** with zinc in acetic acid furnishes both progesterone (**7**) and the epimeric 20-acetoxy-20,21-cyclic carbonates **8a** and **8b**, whereas similar reduction of **11a** and **11b** gives 11-ketoprogesterone (**12**) as the only significant product. Those structural features which are essential for cyclic chlorocarbonate formation have been determined by phosgenating under condition B a number of 17-deoxy-21-ols with various substituents at C-20. These include 11,20-dideoxycorticosterone (**16**) and the 3,20-bisethylene ketals of **1** and **9** as well as the analogous Δ^{16}-20-ketones and Δ^{16}-20-ethylene ketals. It was concluded from these studies that, although all steroidal 21-ols form 21-chlorocarbonates under condition B, hydrolysis to starting material occurs during the work-up in the absence of a carbonyl group at C-20 and a saturated D ring.

In the first paper of this series[2] we described the preparation of symmetrical and mixed 21,21′-bisteroidal carbonates (partial formula a, R = H or OH, Scheme I)

SCHEME I



by the slow addition of phosgene to excess α-ketols in pyridine (condition A). It was also reported that addition of cortisone (but not 11-deoxycortisol) and a number of nonketolic 17,21-diols to excess phosgene (condition B) affords 17,21-cyclic carbonates (partial formula b). This study has been extended to the phosgenation of 17-deoxy-α-ketols under condition B in the expectation that, in the absence of a hydroxyl group at C-17, 21-chlorocarbonates (partial formula c) would be major products. The results of this investigation, as well as a detailed examination of the influence of neighboring functional groups on reactions at C-21, are reported in the present paper.

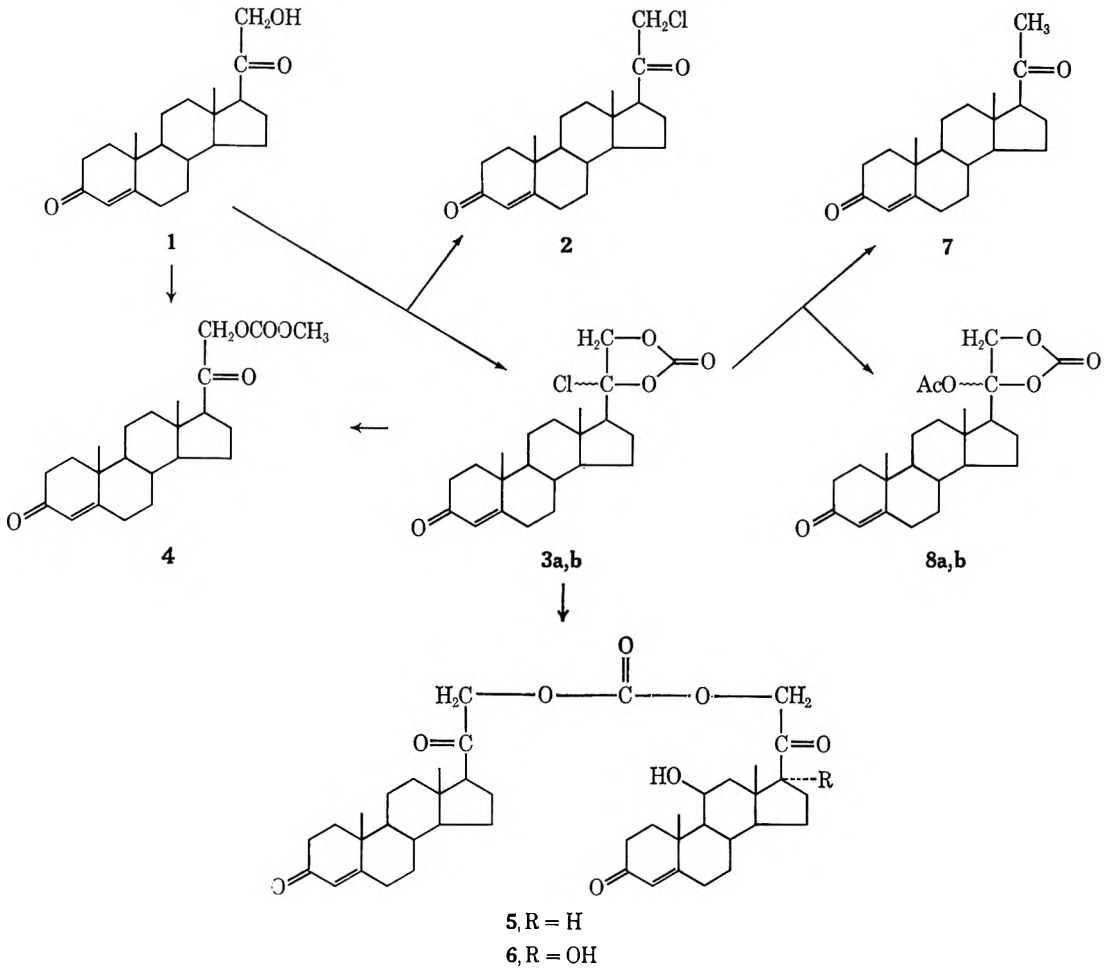
Treatment of 11-deoxycorticosterone (**1**, Scheme II) under condition B and tlc analysis of the reaction mixture showed that, in addition to small amounts of the bisteroidal carbonate and a component with the same mobility as 21-chloroprogesterone (**2**),[3] a major product with intermediate mobility is formed. The ketolic nature of the latter substance was evident from its rapid reduction of alkaline blue tetrazolium (BT). Column chromatography on silica gel gave the 21-chloride **2** in 14% yield, but resulted in nearly total destruction of the major product. It was found subsequently that repeated crystallizations from methylene chloride permitted direct isolation of this compound in 53% yield.

(1) This research was supported wholly by a grant, AM01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service. We are grateful to this institute for its continued and generous support of our work.

(2) M. L. Lewbart, *J. Org. Chem.*, **37**, 3892 (1972).

(3) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).

SCHEME II[a]



[a] In this and other schemes, the substituent at C-20 is α oriented in "a" compounds and β oriented in "b" compounds.

Since the major product is both Beilstein and BT positive, it was assumed to be the 21-chlorocarbonate. However, infrared analysis showed an intense carbonyl band at 1835 cm^{-1}, which is characteristic of five-membered ring cyclic carbonates,[4] but is of significantly higher frequency than the reported[5] range of 1780–1775 cm^{-1} for linear chlorocarbonates. The absence of a second carbonyl band near 1700 cm^{-1} (C-20 carbonyl) served further to rule out a 21-chlorocarbonate structure. Nmr analysis[6] revealed that the product is a roughly 1:1 mixture of closely related substances, as evidenced by splitting of the 18-CH_3 and 21-CH_2 signals. On the basis of these findings and the reactions to be described in this and the accompanying paper, the major phosgenation product from **1** under condition B is formulated as an epimeric mixture of 20-chloro-20,21-cyclic carbonates (**3a,b**). To our knowledge cyclic chlorocarbonates of this type have not been encountered either in the steroid or carbohydrate fields.

Isomerization of the cyclic chlorocarbonates **3a,b** to the open-chain form apparently is a necessary preliminary to reactions with alcohols, since substitution occurs only at C-21. For example, treatment of **3a,b** in pyridine at room temperature with an equivalent amount of methanol provided the 21-*O*-carbomethoxy (camylate) derivative **4** in 78% yield. The structure of **4** was confirmed by its independent synthesis from **1** by direct camylation. The synthesis of mixed carbonates of **1** with other α-ketols, which could be achieved only in low yields by phosgenating equivalent mixtures under condition A,[2] has been considerably improved by treating chlorocarbonates **3a,b** in pyridine with the appropriate substrate. For example, the mixed carbonates (**5** and **6**, respectively) of **1** with corticosterone and cortisol were recovered in yields averaging 70%. Presumably, any mixed carbonate of 11-deoxycorticosterone with a compound bearing a readily acylable hydroxyl can be prepared in this manner.

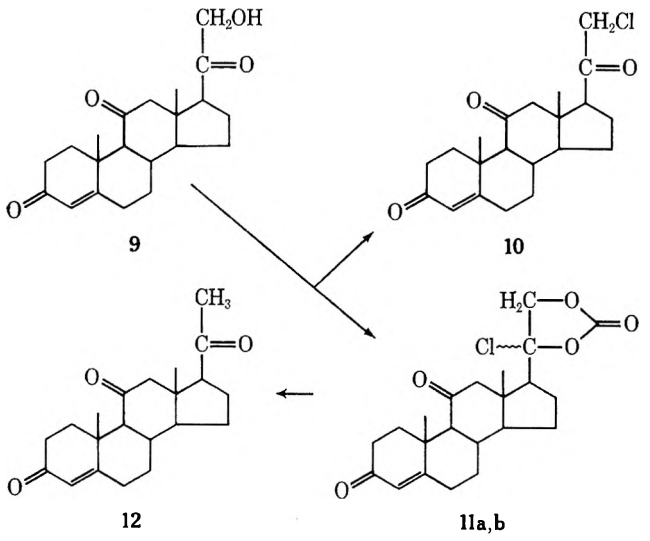
In order to obtain chemical evidence of the cyclic nature of **3a,b**, attempts were made to reduce them to halogen-free cyclic carbonates. Treatment with sodium borohydride in dimethylformamide gave a complex mixture, but reaction with zinc in acetic acid furnished what appeared to be two products. The mobile component, isolated after column chromatography on silica gel, was identified as progesterone (**7**). The more polar component was shown by spectral analyses to be a roughly 3:2 mixture of acetylated cyclic carbonates. Rechromatography on a partitioning-type column effected resolution of the mixture, and the pure components are formulated as the 20-acetoxy-20,-21-cyclic carbonates **8a** and **8b**. However, the evidence at hand does not permit individual configurational assignments. As an alternative preparative procedure the reaction mixture from **3a,b** was chromatographed directly on the partitioning column, affording pro-

(4) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).
(5) R. A. Nyquist and W. J. Potts, *Spectrochim. Acta*, **17**, 679 (1961).
(6) We wish to thank Dr. Byron H. Arison of the Merck Institute for the determination and interpretation of the nmr spectra.

gesterone (32%) and the mobile (11%) and polar (25%) acetoxy cyclic carbonates **8a** and **8b**. The presence of zinc is essential in the formation of the latter compounds, since a solution of **3a,b** in acetic acid alone is stable for at least several hours. The generation of two types of dehalogenation products from **3a,b** suggests that progesterone is formed to the extent that isomerization to the linear chlorocarbonate occurs, whereas that portion which remains cyclized undergoes direct substitution of acetate for chloride at C-20.

The phosgenation of 11-dehydrocorticosterone (**9**, Scheme III) under condition B was also studied,

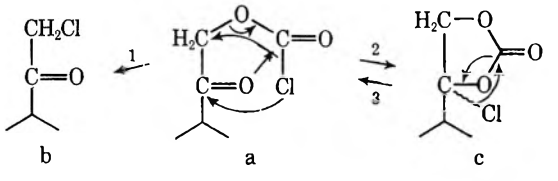
SCHEME III



Comparison of the tlc patterns of the reaction mixtures from **9** and **1** showed qualitative similarities but striking quantitative differences. In the 11-keto series the major product (subsequently isolated in 31% yield) is the 21-chloride **10**, and the cyclic chlorocarbonates are minor reaction products. In contrast to their 11-deoxy analogs **3a,b**, however, the 20-chloro-20,21-cyclic carbonates (**11a,b**) are separable on a silica gel column and, despite their limited stability under these conditions, could be isolated in pure form. Based on the nature of their dehydrohalogenation products (see accompanying paper) the more mobile component is formulated as 20β,21-cyclocarbonyldioxy-20α-chloropregn-4-ene-3,11-dione (**11b**) and the more polar component as 20α,21-cyclocarbonyldioxy-20β-chloropregn-4-ene-3,11-dione (**11a**). When **11a** and **11b** were treated with zinc in acetic acid only traces of products with the expected mobility of 20-acetoxy-20,21-cyclic carbonates were formed. The only recoverable common product from **11a** and **11b** was 11-ketoprogesterone (**12**) in yields of 40 and 48%, respectively. This finding suggests that under the reaction conditions isomerization to the linear chlorocarbonate prior to dehalogenation is more complete in the 11-keto series.

The formation of both 21-chlorides and cyclic chlorocarbonates from **1** and **9** under condition B can be understood in terms of a four-center type mechanism analogous to that proposed to explain the generation of a 20-methoxy-17,20-cyclic carbonate from a 17α-camyl-20-one.[2] There is little doubt that 21-chlorocarbonate a (Scheme IV) is the primary product. Decarboxylation of a, which has been shown to proceed by this

SCHEME IV



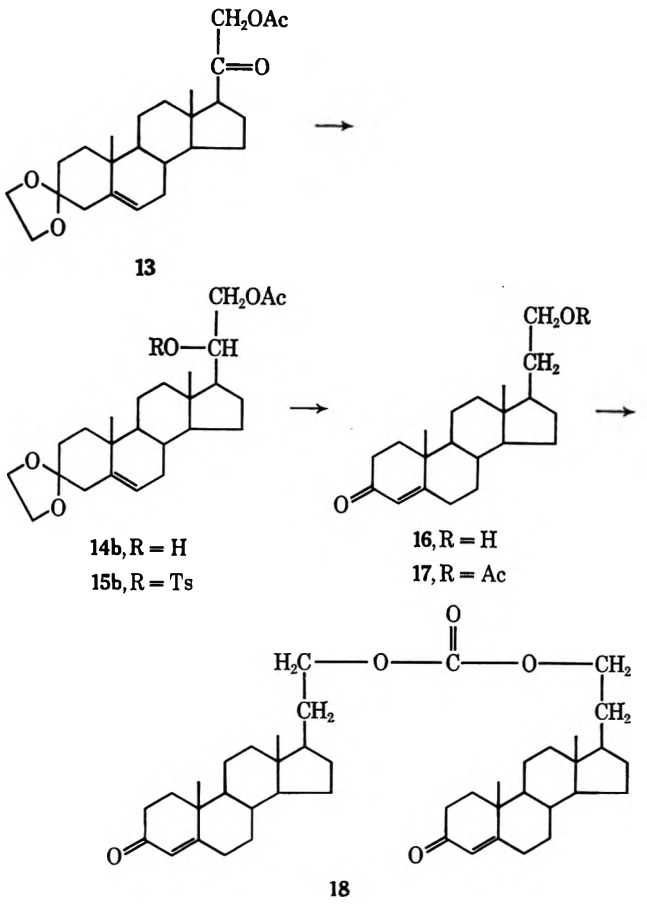
mechanism,[7] affords the alkyl chloride b *via* pathway **1**. If, however, attack by the C-20 carbonyl oxygen on the carbonate carbonyl occurs in conjunction with migration of chloride to C-20 (pathway 2), cyclic chlorocarbonate c results. The ready reversal of pathway 2, which results from attack by chloride on the carbonate carbonyl with simultaneous regeneration of the 20-carbonyl group (pathway 3), is evident from the nature of the C-21-substituted products previously discussed. In comparing the reactions of **1** and **9** under condition B, it is also evident that the presence of a carbonyl group at C-11 favors pathway 1, since the yield of the 11-keto 21-chloride **10** is more than twice that of its 11-deoxy analog **2**. Because free rotation is possible between all bonds in the side chain of the linear chlorocarbonate c, it is not surprising that random attack by chloride at C-20 in pathway 2 affords both possible cyclic chlorocarbonates.

The nature of phosgenation products from 17-deoxy-21-ols with substituents other than a carbonyl group at C-20 has also been examined. It was hoped that, if cyclic chlorocarbonate formation is precluded, stable 21-chlorocarbonates could be recovered. A synthesis of the simplest representative of this series, 11,20-dideoxycorticosterone (**16**, Scheme V) was therefore undertaken. Reduction of the ketal 21-acetate **13** with sodium borohydride in methanol afforded the 20β-hydroxy-21-acetate **14b**[8] in a yield of 79%. Conversion of **14b** to its 20β-tosyl derivative **15b**[8] (83% yield) followed by successive lithium aluminum hydride reduction and acid hydrolysis furnished the desired 20-deoxy-21-ol **16** in 40% yield. Phosgenation of **16** under condition B followed by the usual work-up (which involves addition of ice to the reaction mixture) gave starting material only. In order further to assess the reactivity of **16**, it was also phosgenated under condition A. There resulted an only modest yield (48%) of bisteroidal carbonate **18**, and a substantial amount (24%) of **16** was also recovered. It is evident that under both conditions the 21-chlorocarbonate is a major product, but under circumstances where cyclization is not possible, it is rapidly hydrolyzed to the parent 21-ol during the work-up.

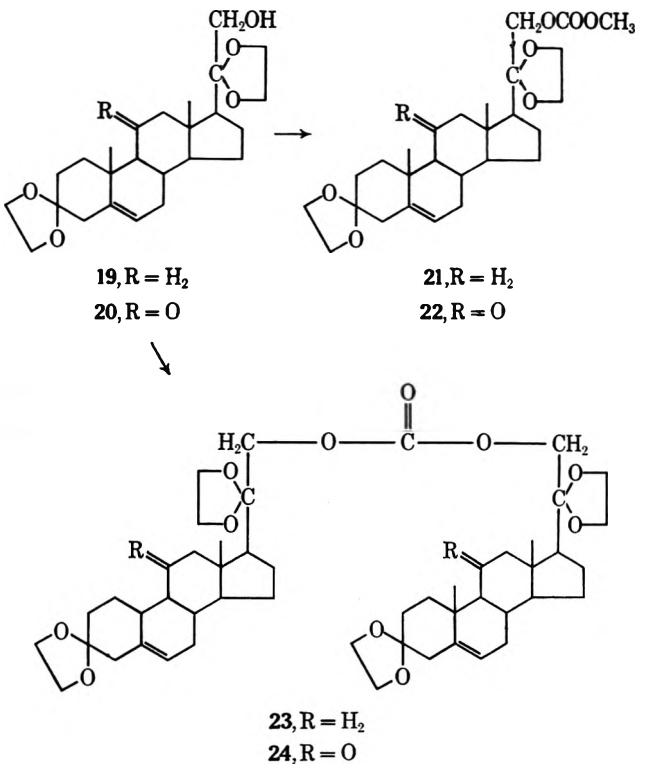
Another pair of 21-ols, the 3,20-bisketals from 11-deoxycorticosterone[9] and 11-dehydrocorticosterone[10] (**19** and **20**, Scheme VI), were also subjected to phosgenation. As in the case of **16**, treatment of **19** and **20** under condition B resulted in their nearly quantitative recovery from the reaction mixture. That 21-chlorocarbonate formation does occur was shown in a separate experiment by adding methanol instead of ice, whereby the 21-camylates **21** and **22** could be isolated in

(7) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956, p 458.
(8) D. N. Kirk and F. J. Rowell, *J. Chem. Soc. C*, 1498 (1970).
(9) J. von Euw, R. Neher, and T. Reichstein, *Helv. Chim. Acta*, **38**, 1423 (1955).
(10) S. Bernstein and R. H. Lenhard, *J. Amer. Chem. Soc.*, **77**, 2331 (1955).

SCHEME V



SCHEME VI

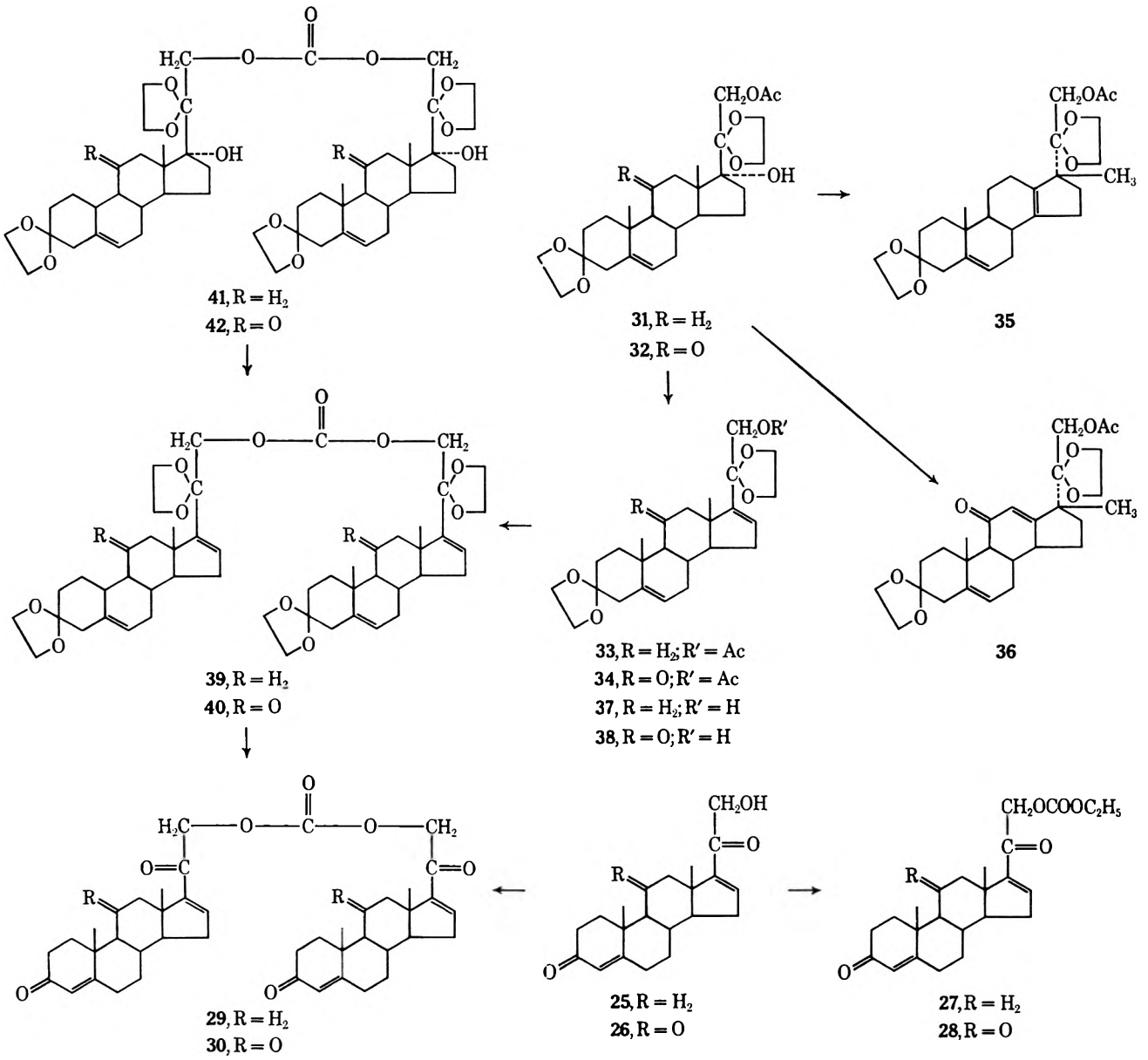


yields of 80 and 85%, respectively. Since treatment of bisketals **19** and **20** under condition A afforded the corresponding bisteroidal carbonates **23** and **24** in very low yields (9 and 24%, respectively), it is evident here also that, in the absence of a 20-carbonyl, 21-chlorocarbonate formation predominates.

It also seemed of interest to investigate Δ^{16} compounds analogous to **1** and **9** in order to determine what influence the proximity of a double bond has on the reaction of α-ketols with phosgene. Reaction of Δ^{16}-α-ketols **25** and **26** (Scheme VII) under condition B followed by the usual work-up furnished crude products whose infrared spectra closely resembled those of starting material, although weak bands at 1820, 1760, and 1730 cm^{-1}, characteristic of cyclic chlorocarbonates, bisteroidal carbonates, and 20-oxo-21-chlorides, respectively, were also noted. These results indicate that the presence of a C-16–C-17 double bond greatly inhibits cyclization of α-ketol 21-chlorocarbonates. There is no question that 21-chlorocarbonates are formed, since in a separate experiment addition of ethanol to reaction mixtures from **25** and **26** gave the 21-cathylates **27** and **28** in respective yields of 60 and 52%. Treatment of **25** and **26** under condition A provided their respective bisteroidal carbonates **29** and **30** in yields of 56 and 68%. As an extension of this study, the 3,20-bisketals (**37** and **38**) derived from **25** and **26** were also subjected to phosgenation conditions. For their preparation the 3,20-bisketal 21-acetates (**31** and **32**) from 11-deoxycortisol[11] and cortisone[12] were treated with thionyl chloride in pyridine under conditions similar to those used by Bernstein, *et al.*[13] In addition to the normal dehydration products **33** and **34**, which were obtained in yields of 41 and 75%, respectively, an isomeric by-product was also recovered from each reaction mixture. These have been formulated respectively as the $\Delta^{13,14}$- and $\Delta^{12,13}$-18-nor Wagner–Meerwein products **35** and **36**. The latter structural assignment was based on the observation that this by-product absorbs strongly in the ultraviolet region.[14] The formation of these rearrangement products serves in part to account for the modest yields of Δ^{16}-20-ketals reported by Bernstein, *et al.*,[13] in dehydrations of several 17α-ols. Phosgenation under A of **37** and **38**, obtained by saponification of **33** and **34**, furnished the corresponding bisteroidal carbonates **39** and **40** in yields of 81 and 75%, respectively. When these yields are contrasted with those of their D ring-saturated counterparts **23** and **24**, it is evident that the presence of the double bond exerts a beneficial influence on bisteroidal carbonate formation from 20-ethylenedioxy-21-ols. Correlation of **39** and **40** with the previously described[2] 17α-ols **41** and **42** was also sought. Treatment of the bis-11-one **42** with thionyl chloride in pyridine gave **40** in 76% yield. However, similar reaction of **41** afforded **39** as a minor product (8%). The major dehydration product (30%) is tentatively formulated as a Wagner–Meerwein product of bisteroidal carbonate **39**. When the behavior of the monomeric 21-acetate **33** and the bisteroids **41** and **42** under dehydration conditions are compared, it is apparent that the presence of a 21,21′-carbonate linkage in the absence of a carbonyl at C-11 favors generation of the abnormal product. The much greater resistance to mineral acids of carbonate over ethylene ketal bonds was demonstrated by the ready hydrolysis in methanolic sulfuric

(11) R. Antonucci, S. Bernstein, and R. H. Lenhard, *ibid.*, **76**, 2956 (1954).
(12) R. Antonucci, S. Bernstein, M. Heller, R. H. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).
(13) W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, **77**, 1028 (1955).
(14) N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

SCHEME VII



acid of the bisketal carbonates **39** and **40** to **29** and **30** in excellent yields.

It can be concluded from the experiments described in this and the preceding communication[2] that all steroidal 21-ols readily form 21-chlorocarbonates under condition B. However, only starting material will be recovered after the usual work-up in the absence of additional structural features which permit cyclization to stable products. The two features encountered thus far are (a) the presence of a 17α-hydroxyl leading to 17,21-cyclic carbonates, and (b) the presence of both a saturated D ring and C-20 carbonyl which provides cyclic chlorocarbonates.

The infrared spectral properties of the new cyclic chlorocarbonates **3a,b**, **11a**, and **11b** may be briefly summarized as follows. All three exhibit carbonate carbonyl bands ranging from 1836 to 1833 cm^{-1}. In addition they possess strong to very strong bands at 1282–1275, 1173–1165, 1065–1060, and 769–766 cm^{-1}.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined at 589 mμ (D line of sodium) in a Zeiss 0.005° photoelectric polarimeter. Unless noted otherwise, measurements were made in chloroform solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Infrared (ir) spectra were determined as KBr pellets with a Beckman IR-8 instrument. Nmr spectra were determined with a Varian HA-100D instrument in $CDCl_3$, using TMS as an internal standard. Ultraviolet (uv) spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. General procedures for chromatographic techniques on silica gel, including column dimensions, fraction size, and flow rate, as well as the processing of reaction mixtures, follow from earlier publications.[15] Unless otherwise indicated, tlc and column systems are indicated in the text by a number which corresponds to one of the following compositions [in each case the number is followed (in parentheses) by that volume of ethyl acetate which, diluted to 25 ml with isooctane (or, in the cases of systems 7, 8, and 9, with toluene), comprises the system]: 1 (10), 2 (12.5), 3 (8.8), 4 (15), 5 (13.8), 6 (7.5), 7 (3.1), 8 (6.2), 9 (7.5). Microanalyses were by A. Bernhard, Elbach über Engelskirchen, West Germany.

Phosgenation of 11-Deoxycorticosterone (1) under Condition B.—Repeated crystallizations from methylene chloride of the reaction mixture from 3.3 g (10 mmol) of steroid afforded 2.07 g (53%) of **20ξ,21-cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one (3a,b)**: mp 159–160°; $[\alpha]_D$ +109°; λ_{max} 241 mμ (ϵ 16,800); ν_{max} 1835 cm^{-1} (cyclic carbonate); nmr δ 9.13 and 9.03 (s, 3,

(15) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).

18-CH_3), 8.81 (s, 3, 19-CH_3), 5.43, 5.34, and 5.37, 5.29 (d, 2, J = 10.0 Hz, 21-CH_2).

Anal. Calcd for $C_{22}H_{29}O_4Cl$: C, 67.25; H, 7.44; Cl, 9.02. Found: C, 67.13; H, 7.47; Cl, 8.87.

The mother liquor was chromatographed on a silica gel column in system 1. This furnished **21-chloropregn-4-ene-3,20-dione** (2) as plates from ethyl acetate (470 mg, mp 204–205°; 25 mg, mp 200–201°) in a yield of 14%: $[\alpha]_D$ +220°; λ_{max} 240 mμ (ε 16,400) [lit.[3] mp 203–205°; $[\alpha]_D$ +210°; λ_{max} 242 mμ (log ε 4.15)].

21-*O*-Carbomethoxypregn-4-ene-3,20-dione (4) from 3a,b.—To a solution of 20ξ,21-cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one (79 mg, 0.2 mmol) in pyridine (1 ml) was added 85 μl (0.21 mmol) of methanol. After 66 hr at room temperature the product was recovered and crystallized from methanol as needles (48 mg, mp 160–162°; 12 mg, mp 155–158°) in a yield of 78%: $[\alpha]_D$ +196°; λ_{max} 240 mμ (ε 16,650); γ_{max} 1759, 1280, and 798 cm^{-1} (camylate).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3O, 7.99. Found: C, 71.19; H, 8.39; CH_3O, 8.03.

Treatment of 11-deoxycorticosterone (100 mg) in pyridine (1 ml) with methyl chlorocarbonate (75 μl) for 1 hr at room temperature afforded 110 mg (94%) of prisms from methanol, mp 156–158°. The ir spectrum was identical with that of the 21-camylate (4) prepared from **3a,b**.

3,20-Dioxopregn-4-en-21-yl 11β-Hydroxy-3,20-dioxopregn-4-en-21-yl Carbonate (5) from 3a,b.—A mixture of 20ξ,21-cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one (393 mg, 1 mmol) and corticosterone (381 mg, 1.1 mmol) was dissolved with slight warming in 1:1 pyridine–methylene chloride (6 ml). After 66 hr at room temperature the product was recovered and crystallized as rosettes from methanol (503 mg, mp 134–138°) in a yield of 68%. The ir spectrum was identical with that of the mixed carbonate prepared by phosgenating equivalent mixtures of the two α-ketols under condition A.[2]

3,20-Dioxopregn-4-en-21-yl 11β,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl Carbonate (6) from 3a,b.—Treatment of 20ξ,21-cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one with cortisol (402 mg 1.1 mmol) as in the preparation of **5** from **3a,b** afforded 551 mg, (71%) of needles from methanol, mp 154–156°, whose ir spectrum was identical with that of **6** prepared by phosgenation of the parent α-ketols.[2]

Reaction of 20ξ,21-Cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one (3a,b) with Zinc in Acetic Acid.—A solution of the chlorocarbonates (590 mg) in 3:1 acetic acid–methylene chloride (20 ml) was shaken with powdered zinc (1.2 g) for 1 hr. The insoluble material was filtered off and washed with acetone. The filtrate was concentrated nearly to dryness in a nitrogen stream, then partitioned between methylene chloride and dilute sodium bicarbonate. The reaction mixture was chromatographed on a Celite column in the system toluene–isooctane–formamide (95:205:20). Crystallization of the most mobile component from acetone–hexane gave prisms (117 mg, mp 130–131°; 35 mg, mp 127–129°) in a yield of 32%. The ir spectrum was indistinguishable from that of a reference sample of **progesterone** (7).

The intermediate fraction furnished the "mobile" **20ξ,21-cyclocarbonyldioxy-20ξ-acetoxypregn-4-en-3-one** as prisms from ethyl acetate (60 mg, mp 246–247°; 10 mg, mp 243–244°) in a yield of 11%: $[\alpha]_D$ +123°; λ_{max} 241 mμ (ε 17,300); ν_{max} 1820 (cyclic carbonate), 1760, 1225 cm^{-1} (acetate); nmr δ 9.07 (s, 3, 18-CH_3), 8.82 (s, 3, 19-CH_3), 7.89 (s, 3, CH_3CO), 5.63, 5.37 (q, 2, J = 10.5 Hz, 21-CH_2).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75; CH_3CO, 10.33. Found: C, 69.37; H, 7.58; CH_3CO, 10.17.

The least mobile fraction supplied the "polar" **20ξ,21-cyclocarbonyldioxy-20ξ-acetoxypregn-4-en-3-one** as prisms from ethyl acetate (138 mg, mp 247–247.5°; 18 mg, mp 243–244°) in a yield of 25%: $[\alpha]_D$ +104°; λ_{max} 241 mμ (ε 18,000); ν_{max} 1820 (cyclic carbonate), 1760, 1225 cm^{-1} (acetate); nmr δ 9.18 (s, 3, 18-CH_3), 8.82 (s, 3, 19-CH_3), 7.89 (s, 3, CH_3CO), 5.45 (s, 2, 21-CH_2).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75; CH_3CO, 10.33. Found: C, 69.06; H, 7.82; CH_3CO, 10.44.

Phosgenation of 11-Dehydrocorticosterone (9) under Condition B.—The reaction mixture from 1032 mg (3 mmol) of steroid was chromatographed on a silica gel column in system 4. Crystallization of the most mobile component from acetone gave **21-chloropregn-4-ene-3,11,20-trione** (10) as prisms (334 mg, mp 185–186.5°) in a yield of 31%: $[\alpha]_D$ +279°; λ_{max} 238 mμ (ε 15,800); ν_{max} 1731 cm^{-1} (20-ketone).

Anal. Calcd for $C_{21}H_{27}O_3Cl$: C, 69.50; H, 7.50; Cl, 9.77. Found: C, 69.68; H, 7.57; Cl, 9.78.

Two crystallizations from ethyl acetate of the intermediate fraction afforded **20β,21-cyclocarbonyldioxy-20α-chloropregn-4-ene-3,11-dione (11b)** as prisms (83 mg, 7%): mp 154.5–156°; $[\alpha]_D$ +193°; λ_{max} 238 mμ (ε 16,500); ν_{max} 1832 cm^{-1} (cyclic carbonate); nmr δ 9.17 (s, 3, 18-CH_3), 8.60 (s, 3, 19-CH_3), 7.20, 7.07 (d, 1, 12β H), 5.35 (s, 2, 21-CH_2).

Anal. Calcd for $C_{22}H_{27}O_5Cl$: C, 64.93; H, 6.69; Cl, 8.71. Found: C, 64.83; H, 6.58; Cl, 8.82.

The least mobile fraction gave, after two crystallization from ethyl acetate, 124 mg (10%) of **20α,21-cyclocarbonyldioxy-20β-chloropregn-4-ene-3,11-dione (11a)** as needles: mp 155–166°; $[\alpha]_D$ +146°; λ_{max} 237 mμ (ε 16,200); ν_{max} 1832 cm^{-1} (cyclic carbonate); nmr δ 9.05 (s, 3, 18-CH_3), 8.59 (s, 3, 19-CH_3), 7.04, 6.91 (d, 1, 12β H), 5.47, 5.34 (q, 2, J = 10.0 Hz, 21-CH_2).

Anal. Calcd for $C_{22}H_{27}O_5Cl$: C, 64.93; H, 6.69; Cl, 8.71. Found: C, 64.79; H, 6.64; Cl, 8.61.

Pregn-4-ene-3,11,20-trione (12) from 11a and 11b.—Solutions of 40 mg each of 20α,21-cyclocarbonyldioxy-20β-chloropregn-4-ene-3,11-dione and 20β,21-cyclocarbonyldioxy-20α-chloropregn-4-ene-3,11-dione in 3:1 acetic acid–methylene chloride (1.6 ml) were shaken with 80 mg of powdered zinc for 45 min. The crude products, recovered as in the reaction of **3a,b**, were chromatographed on Celite columns in the system toluene–isooctane–formamide (100:100:5). The major product from **11a** was obtained as prisms from methanol (10.1 mg, mp 176–177°; 2.9 mg, mp 173–175°) in a yield of 40%. The ir spectrum was identical with that of **11-ketoprogesterone** (12). Similarly, **11b** gave 15.4 mg (48%) of prisms, mp 177–178°; which possessed an ir spectrum identical with that of the reference compound. Continued development of both columns furnished only traces of BT-positive compounds.

3-Ethylenedioxypregn-5-ene-20β,21-diol 21-Acetate (14b) from 13.—To a solution of 21-acetoxypregn-5-ene-3,20-dione 3-ethylene ketal[16] (4.16 g, 10 mmol) in a mixture of methylene chloride (150 ml) and methanol (250 ml) at 0° was added sodium borohydride (600 mg, 16 mmol). After 20 min at 0° acetic acid (1.2 ml) was added and, after concentration of the solution to a small volume, the product was recovered by extraction with methylene chloride. Two crystallizations from methanol gave 3.29 g (79%) of needles: mp 157–158.5°; $[\alpha]_D$ −30.3°; ν_{max} 3510 (hydroxyl), 1741 and 1250 (acetate), and 1100 cm^{-1} (ketal) [lit.[8] mp 145–149°; $[\alpha]_D$ −12° (dioxane)].

Anal. Calcd for $C_{25}H_{38}O_6$: C, 71.74; H, 9.15. Found: C, 71.75; H, 9.11.

3-Ethylenedioxypregn-5-ene-20β,21-diol 20-Tosylate 21-Acetate (15b) from 14b.—To a solution of 3-ethylenedioxypregn-5-ene-20β,21-diol 21-acetate (3 g) in pyridine (15 ml) was added an equal weight of tosyl chloride. After 68 hr at room temperature the product was recovered in the usual manner and crystallized from acetone as platelets (3.36 g, mp 146.5–147.5°) in a yield of 83%: $[\alpha]_D$ −17.3°; ν_{max} 1748, 1235 (acetate), 1603, 1500, 1360, 1192, 1178, 681 (tosylate),[17] 1100 cm^{-1} (ketal) (lit.[8] no constants given).

Anal. Calcd for $C_{32}H_{44}O_7S$: C, 67.10; H, 7.74. Found: C, 67.04; H, 7.85.

21-Hydroxypregn-4-en-3-one (16) from 15b.—A solution of 3 g each of 3-ethylenedioxypregn-5-ene-20β,21-diol 20-tosylate 21-acetate and lithium aluminum hydride in tetrahydrofuran (190 ml) was refluxed for 2 hr and the crude product (1.6 g) was treated with 10:1 methanol–8% sulfuric acid (55 ml) for 19 hr at room temperature. The reaction mixture was chromatographed on a silica gel column in system 2. A mobile by-product crystallized from acetone as needles (142 mg, mp 160–163°) in a yield of 8.5%. Its ir spectrum was identical with that of a reference sample of **20α-hydroxypregn-4-en-3-one**. The major product (16) was obtained as needles from ether and ethyl acetate–*n*-hexane (450 mg, mp 125–127°; 200 mg, mp 121–122.5°) in 40% yield: $[\alpha]_D$ +132°; λ_{max} 242 mμ (ε 16,600); ν_{max} 3440 cm^{-1} (hydroxyl).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.83; H, 10.30.

Treatment of **16** with acetic anhydride–pyridine and crystallization of the product from *n*-hexane afforded **21-acetoxypregn-4-**

(16) R. Antonucci, S. Bernstein, R. H. Lenhard, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(17) M. L. Lewbart, *ibid.*, **33**, 1695 (1968).

en-3-one (17) as prisms: mp 118.5–119°; $[\alpha]D$ +112°; λ_{max} 241 mμ (ε 16,600); ν_{max} 1731, 1235 cm^{-1} (acetate).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.94; H, 9.59.

Bis(3-oxopregn-4-en-21-yl) Carbonate (18) from 16.—Phosgenation of 21-hydroxypregn-4-en-3-one (158 mg, 0.5 mmol) was carried out under condition A. Two crystallizations of the product from methanol gave 72 mg of needles: mp 193–195°; $[\alpha]D$ +124°; λ_{max} 241 mμ (ε 32,000); ν_{max} 1745, 1266, and 785 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{43}H_{62}O_5$: C, 78.37; H, 9.48. Found: C, 78.56; H, 9.57.

The mother liquor was chromatographed on a silica gel column in system 2. Following the recovery of an additional 8 mg of **18**, mp 186–190° (raising the yield of 48%), there was obtained 38 mg (24%) of starting material (**16**), mp 131–132°.

21-*O*-Carbomethoxypregn-5-ene-3,20-dione 3,20-Bisethylene Ketal (21) from 19.—Phosgenation of 21-hydroxypregn-5-ene-3,20-dione 3,20-bisethylene ketal[9] (84 mg, 0.2 mmol) under condition B was followed by addition of methanol (1 ml). Crystallization of the product from ethyl acetate gave 76 mg (80%) of prisms: mp 182–184°; $[\alpha]D$ −21.5°; ν_{max} 1755, 1265, and 791 (camylate), 1101 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.20; H, 8.26.

21-*O*-Carbomethoxypregn-5-ene-3,11,20-trione 3,20-Bisethylene Ketal (22) from 20.—Phosgenation of 21-hydroxypregn-5-ene-3,11,20-trione 3,20-bisethylene ketal[10] (86 mg, 0.2 mmol) under condition B was followed by addition of methanol (1 ml). Crystallization from methanol furnished 83 mg (85%) of prisms: mp 166–167°; $[\alpha]D$ +5.5°; ν_{max} 1754, 1265, and 791 (camylate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 66.27; H, 7.64.

Bis(3,20-bisethylenedioxypregn-5-en-21-yl) Carbonate (23) from 19.—The product from phosgenation of 21-hydroxypregn-5-ene-3,20-dione 3,20-bisethylene ketal (168 mg, 0.4 mmol) under condition A was chromatographed on a silica gel column in system 3. The desired product crystallized from ethyl acetate as needles (15 mg, mp 253–254°) in a yield of 9%: $[\alpha]D$ −17.7°; ν_{max} 1755, 1260, and 788 (bisteroidal carbonate), 1097 cm^{-1} (ketal).

Anal. Calcd for $C_{51}H_{74}O_{11}$: C, 70.97; H, 8.64. Found: C, 70.79; H, 8.52.

Bis(3,20-bisethylenedioxy-11-oxopregn-5-en-21-yl) Carbonate (24) from 20.—Treatment of 21-hydroxypregn-5-ene-3,11,20-trione 3,20-bisethylene ketal (173 mg, 0.4 mmol) as in the preparation of **23** from **19** and chromatography in system 5 gave 42 mg (24%) of needles from ethyl acetate: mp 286–287°; $[\alpha]D$ +1.21°; ν_{max} 1758, 1260, and 788 (bisteroidal carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{51}H_{70}O_{13}$: C, 68.74; H, 7.92. Found: C, 68.77; H, 7.70.

21-*O*-Carboethoxypregna-4,16-diene-3,20-dione (27) from 25.—Phosgenation of 21-hydroxypregna-4,16-diene-3,20-dione[13] (66 mg) under condition B was followed by addition of excess ethanol. The crude product was chromatographed on a silica gel column (system 1). The major component crystallized from methanol as needles (48 mg, mp 147.5–148.5°) in a yield of 60%: $[\alpha]D$ +147°; λ_{max} 240 mμ (ε 26,600); ν_{max} 1740, 1265, and 797 (cathylate), 1675 (C-3 and C-20 ketones), 1621 (Δ^4), 1588 cm^{-1} (Δ^{16}).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.10; H, 8.20.

Treatment of **25** (15 mg) in cold pyridine (0.5 ml) with ethyl chlorocarbonate (25 μl) for 2 hr at 5° and crystallization of the product from methanol gave 10.3 mg of needles, mp 149–150°. The ir spectrum was identical with that of the 21-cathylate **27** recovered after addition of ethanol to the phosgenation mixture.

21-*O*-Carboethoxypregna-4,16-diene-3,11,20-trione (28) from 26.—The crude product obtained after phosgenation of 21-hydroxypregna-4,16-diene-3,11,20-trione (68 mg) and addition of ethanol was chromatographed on a silica gel column in system 4. The major component crystallized from ethanol as needles (41 mg, mp 169–170°; 3 mg, mp 166–168°) in a yield of 52%: $[\alpha]D$ +222°; λ_{max} 238 mμ (ε 24,800); ν_{max} 1752, 1265, and 793 (cathylate), 1675 (C-3 and C-20 ketones), 1618 (Δ^4), 1591 cm^{-1} (Δ^{16}).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.58; H, 7.30. Found: C, 69.66; H, 7.34.

Treatment of **26** (15 mg) as in the cathylation of **25** afforded 13.4 mg of prisms from ethanol, mp 167–169°, whose ir spectrum was indistinguishable from that of the 21-cathylate **28** prepared *via* the 21-chlorocarbonate.

Reaction of 21-Acetoxy-17-hydroxypregn-5-ene-3,20-dione Bisethylene Ketal (31) with Thionyl Chloride in Pyridine.—To a solution of the bisketal acetate[11] (500 mg) in pyridine at −5° was added 2 ml of thionyl chloride. After 30 min at −12° the reaction mixture was carefully added to ice and water. Methylene chloride extraction of the resulting suspension followed by successive washing with dilute hydrochloric acid, 2 *N* sodium hydroxide, and water gave the crude, neutral product. Several crystallizations from ether furnished **21-acetoxypregna-5,16-diene-3,20-dione bisethylene ketal (33)** as needles, 174 mg, mp 131–132° (lit.[13] mp 131–132°). When the mother liquor was chromatographed on a silica gel column in system 7, only partial separation of the two components was achieved. The most mobile fraction gave an additional 25 mg of **33**, mp 131–133°, raising the yield to 41%.

Several crystallizations from methanol of the residue (156 mg) from later eluates supplied 105 mg (30%) of **21-acetoxy-17β-methyl-18-nor-17α-pregna-5,13(14)-diene-3,20-dione bisethylene ketal (35)** as prisms: mp 112.5–114.5°; $[\alpha]D$ −118°; ν_{max} 1739, 1250 (acetate), 1102 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.80; H, 8.35.

Reaction of 21-Acetoxy-17-hydroxypregn-5-ene-3,11,20-trione 3,20-Bisethylene Ketal (32) with Thionyl Chloride in Pyridine.—Dehydration of the bisketal acetate[12] (2 g) in pyridine (40 ml) with thionyl chloride (8 ml) was carried out for 3 hr at 5°. Crystallization of the product, recovered as in the preparation of **33** and **35** from **31**, gave **21-acetoxypregna-5,16-diene-3,11,20-trione 3,20-bisethylene ketal (34)** as prisms from methanol, 1.23 g, mp 116–117.5° (lit.[13] mp 114–115°). The mother liquor was chromatographed on a silica gel column in systems 8 and 9. The initial fraction gave an additional 0.19 g of **34**, mp 116–117.5°, raising the yield to 75%. Crystallization of the less mobile component afforded **21-acetoxy-17β-methyl-18-nor-17α-pregna-5,12(13)-diene-3,11,20-trione 3,20-bisethylene ketal (36)** as needles from ethyl acetate-*n*-hexane (122 mg, mp 119.5–122°) in 6% yield: $[\alpha]D$ −110°; λ_{max} 241 mμ (ε 10,400); ν_{max} 1741, 1240 (acetate), 1654 (conjugated 11-ketone), 1109 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.64; H, 7.61.

Bis(3,20-bisethylenedioxypregna-5,16-dien-21-yl) Carbonate (39) from 37.—Phosgenation of 21-hydroxypregna-5,16-diene-3,20-dione bisethylene ketal[11] (166 mg, 0.4 mmol) under condition A and crystallization of the product from methanol gave needles (139 mg, mp 194.5–195.5°) in a yield of 81%: $[\alpha]D$ −43.5°; ν_{max} 1758, 1260, and 788 (bisteroidal carbonate), 1622 (Δ^{16}), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{61}H_{70}O_{11}$: C, 71.30; H, 8.21. Found: C, 71.11; H, 8.15.

39 from 41.—To a solution of bis(17-hydroxy-3,20-bisethylenedioxypregn-5-en-21-yl) carbonate[2] (200 mg) in pyridine (4 ml) at −12° was added 0.8 ml of thionyl chloride. After 30 min at −12° the product was recovered as described previously and chromatographed on a silica gel column (system 6).

The major product, which is formulated as **bis(17β-methyl-3,-20-bisethylenedioxy-18-nor-17α-pregna-5,13(14)-dien-21-yl) carbonate**, was eluted first. Crystallization from methanol gave fine needles (53 mg, mp 131–134°) in a yield of 30%; $[\alpha]D$ −95°; ν_{max} 1755, 1260, and 788 (bisteroidal carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{51}H_{70}O_{11}$: C, 71.30; H, 8.21. Found: C, 71.15; H, 8.00.

The minor product, which followed, crystallized from methanol as needles (16 mg, mp 193–194°). The ir spectrum was identical with that of **39** prepared by phosgenation of **37** under condition A.

Bis(3,20-bisethylenedioxy-11-oxopregna-5,16-dien-21-yl) Carbonate (40) from 38.—Phosgenation of 21-hydroxypregna-5,16-diene-3,11,20-trione 3,20-bisethylene ketal[12] (172 mg, 0.4 mmol) under condition A and two crystallizations of the product from methylene chloride–methanol gave 133 mg (75%) of needles: mp 179–184°; $[\alpha]D$ −13.1°; ν_{max} 1758, 1265, and 788 (bisteroidal carbonate), 1625 (Δ^{16}), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{51}H_{66}O_{13}$: C, 69.05; H, 7.50. Found: C, 68.94; H, 7.50.

40 from 42.—To a solution of bis(17-hydroxy-3,20-bisethylenedioxy-11-oxopregn-5-en-21-yl) carbonate[2] (200 mg) in pyridine (4 ml) at −12° was added 0.8 ml of thionyl chloride. After 3 hr at 5° the product was recovered in the usual manner and crystallized from methanol, affording 147 mg (76%) of needles, mp 165–166°. A mixture melting point with **40** prepared by phosgenation of **38** was 168–174° and their ir spectra were identical.

Bis(3,20-dioxopregna-4,16-dien-21-yl) Carbonate (29) from 25.—Phosgenation of 21-hydroxypregna-4,16-diene-3,20-dione (66 mg, 0.2 mmol) under condition A followed by tlc analysis showed approximately 40% of starting material. The reaction mixture was therefore rephosgenated, and the recovered material was crystallized from methanol as plates (44 mg, mp 238–240°) in a yield of 65%: $[\alpha]D$ +152°; λ_{max} 240 mμ (ε 44,700); ν_{max} 1760, 1275, and 792 (bisteroidal carbonate), 1670 (C-3 and C-20 ketone), 1619 (Δ⁴), 1590 cm⁻¹ (Δ¹⁶).

Anal. Calcd for $C_{43}H_{54}O_7$: C, 75.63; H, 7.97. Found: C, 75.85; H, 8.10.

29 from 39.—To a solution of bis(3,20-bisethylenedioxypregna-5,16-dien-21-yl) carbonate (50 mg) in methylene chloride (10 ml) and methanol (15 ml) was added 8% aqueous sulfuric acid (2 ml). The mixture was boiled until most of the methylene chloride was gone, then refluxed for an additional 90 min. The product, recovered after concentration *in vacuo* and methylene chloride extraction, crystallized from methanol as needles, mp 238–242°, in quantitative yield. A mixture melting point with **29** prepared by phosgenation of **25** was 240–244° and their ir spectra were identical.

Bis(3,11,20-trioxopregna-4,16-dien-21-yl) Carbonate (30) from 26.—Phosgenation of 21-hydroxypregna-4,16-diene-3,11,20-trione (68 mg, 0.2 mmol) under condition A and crystallization of the product from methanol gave 48 mg (68%) of needles: mp 171–173°; $[\alpha]D$ +250°; λ_{max} 238 mμ (ε 48,500); ν_{max} 1760, 1272, and 786 (bisteroidal carbonate), 1670 (C-3 and C-20 ketones), 1619 (Δ⁴), 1591 cm⁻¹ (Δ¹⁶).

Anal. Calcd for $C_{43}H_{50}O_9$: C, 72.65; H, 7.09. Found: C, 72.43; H, 6.91.

30 from 40.—Acid hydrolysis of bis(3,20-bisethylenedioxy-11-oxopregna-5,16-dien-21-yl) carbonate (50 mg) as in the preparation of **29** from **39** and crystallization from methanol furnished 35 mg (88%) of needles, mp 176–178°. The ir spectrum was identical with that of **30** prepared by phosgenation of **26** under condition A.

Registry No.—**1**, 64-85-7; **2**, 26987-64-4; **3a**, 39703-91-8; **3b**, 39703-92-9; **4**, 39833-00-6; **5**, 39833-01-7; **6**, 36675-01-1; **7**, 57-83-0; **8a**, 39833-03-9; **8b**, 39833-04-0; **9**, 72-23-1; **10**, 39833-05-1; **11a**, 39704-16-0; **11b**, 39704-17-1; **12**, 516-15-4; **13**, 13382-00-8; **14b**, 26437-02-5; **15b**, 26437-04-7; **16**, 5598-02-7; **17**, 39833-10-8; **18**, 39833-11-9; **19**, 39833-12-0; **20**, 39833-13-1; **21**, 39833-14-2; **22**, 39900-65-7; **23**, 39833-15-3; **24**, 39833-16-4; **25**, 39833-17-5; **26**, 39833-18-6; **27**, 39833-19-7; **28**, 39703-59-8; **29**, 39833-21-1; **30**, 39833-22-2; **31**, 39833-23-3; **32**, 39900-66-8; **33**, 39833-24-4; **34**, 39833-25-5; **35**, 39833-26-6; **36**, 39833-27-7; **37**, 39833-28-8; **38**, 39833-29-9; **39**, 39833-30-2; **40**, 39833-31-3; **41**, 36675-03-3; **42**, 36623-32-2; bis(17β-methyl-3,20-bisethylenedioxy-18-nor-17α-pregna-5,13(14)-dien-21-yl) carbonate, 39833-32-4.

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Reactions of α-Ketols and Other 21-Hydroxy Steroids with Phosgene. III. Dehydrohalogenation Products from 20-Chloro-20,21-cyclic Carbonates[1]

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Dehydrohalogenation of the cyclic chlorocarbonate mixture (**1a,b**) from 11-deoxycorticosterone either in hot pyridine or acetone–sodium iodide–triethylamine affords the Δ²⁰,²¹-20,21-cyclic carbonate **2** and the trans and cis Δ¹⁷,²⁰-20,21-cyclic carbonates **3** and **4**, respectively. Sequential treatment of the cis isomer **4** with sodium borohydride and chromic anhydride–pyridine provides the 20β,21-cyclic carbonate **5b**, whereas similar reaction of the trans isomer **3** gives the 20β-hydroxy-21-camylate **6b**. Definitive configurational assignments for **3** and **4** were made by their independent synthesis *via* dehydration with thionyl chloride in pyridine of 17-hydroxy-20,21-cyclic carbonates of known orientation at C-20. Dehydrohalogenation of the cyclic chlorocarbonate mixture (**19a,b**) from 11-dehydrocorticosterone also provides three unsaturated cyclic carbonates (**20**, **21**, and **22**). The geometric isomers from **19a,b** were also synthesized *via* 17-hydroxy-20,21-cyclic carbonates. It was also found that Δ¹⁶ compounds, which are minor products in the dehydration of hydroxy cyclic carbonates, can be obtained in good yield when 17-hydroxy-20,21-diacetates are substrates. Structural correlations among Δ¹⁶-cyclic carbonates, Δ¹⁶-diacetates, and Δ¹⁶-α-ketols in both the 11-deoxy and 11-keto series were made *via* Δ¹⁶-20-hydroxy-21-camylates.

In the preceding paper[2] we reported that novel 20-chloro-20,21-cyclic carbonates are generated in the reaction of 11-deoxy- and 11-dehydrocorticosterone in pyridine with excess phosgene in benzene (condition B). The chlorocarbonates from the former α-ketol could be obtained only as an epimeric mixture (**1a,b**, Scheme I), but the corresponding 11-ketones (**19a** and **19b**, Scheme II) were isolated in pure form. Preliminary experiments directed toward purification of the epimeric mixture **1a,b** showed that loss of hydrogen chloride occurs readily, and the resulting products appeared to be of sufficient interest to warrant a separate, detailed investigation of their formation and reactions. In the present paper we describe the isolation and identification of the dehydrohalogenation products both from cyclic chlorocarbonates **1a,b** and **19a,b** as well as their independent syntheses. In the course of these studies a number of C-20-epimeric Δ¹⁶-20,21-diols and their derivatives were encountered. A description of their preparation and properties will also be presented.

As described earlier,[2] addition of either steroidal or nonsteroidal primary alcohols to a solution of **1a,b** in pyridine affords mixed carbonates in good yield. It

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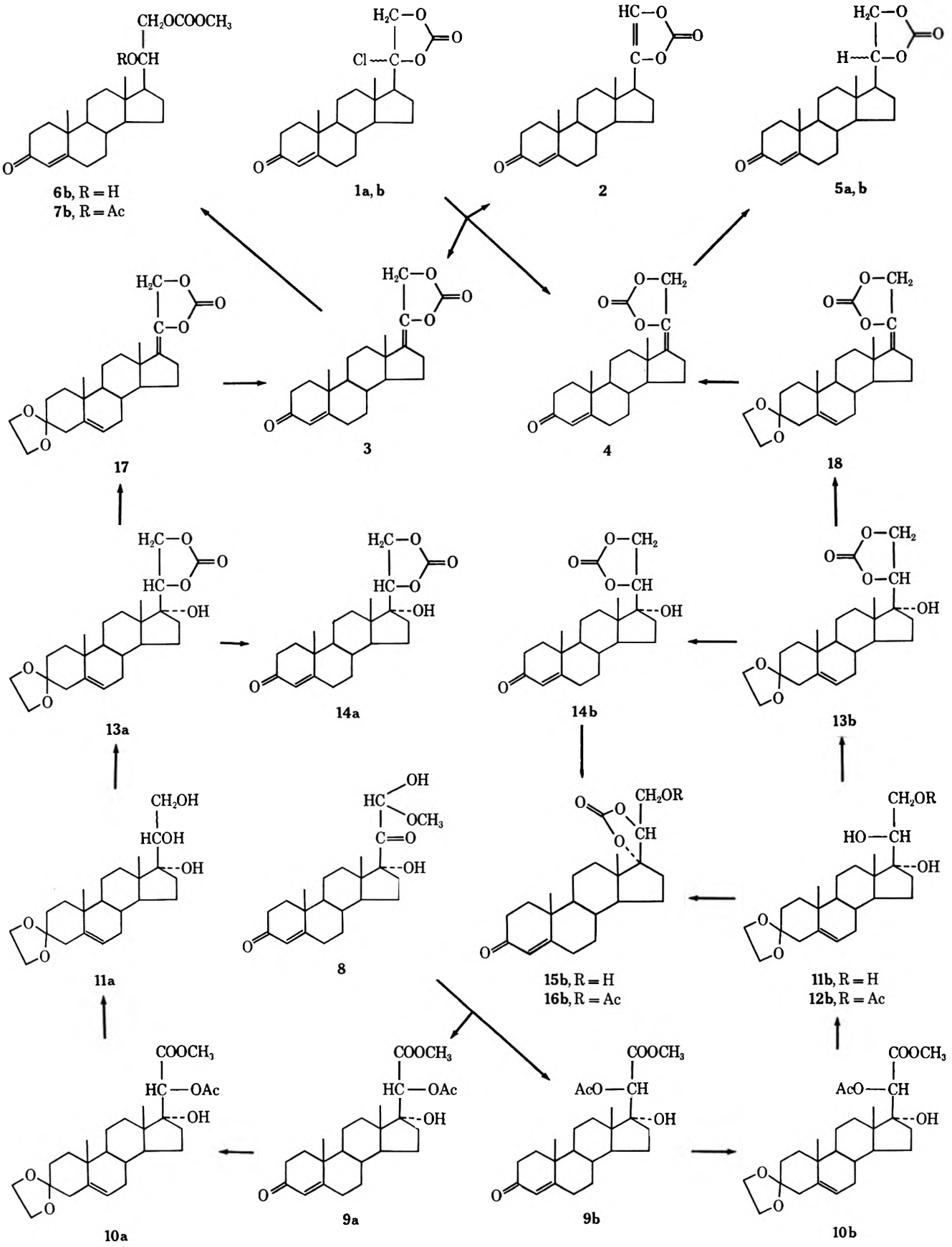
(2) M. L. Lewbart, *J. Org. Chem.*, **38**, 2328 (1973).

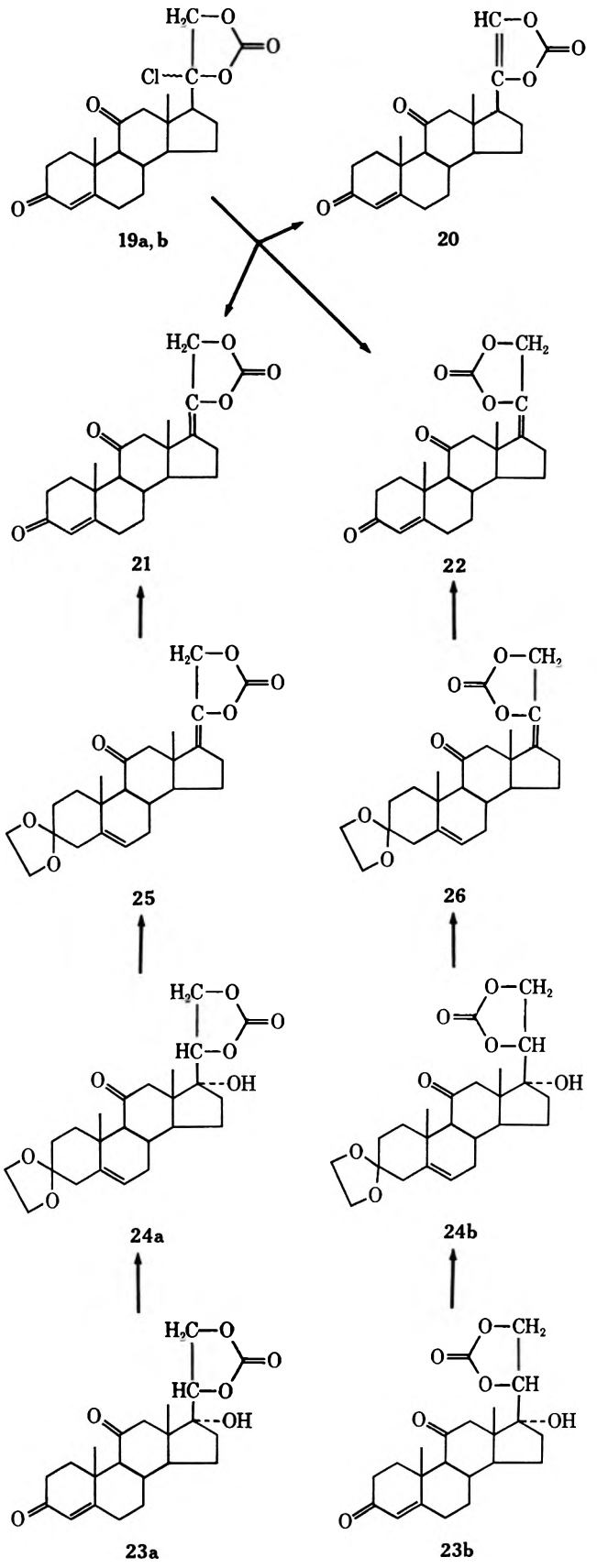
SCHEME I[a]



[a] In this and other schemes, the substituent at C-20 is a α oriented in "a" compounds and β oriented in "b" compounds.

was found in control experiments that, although a solution of **1a,b** in pyridine is relatively stable for prolonged periods at room temperature, heating on the steam bath brings about a heavy deposition of water-soluble crystals (presumably pyridinium chloride) within 15 min. Analysis of the reaction mixture by tlc showed, in addition to roughly 10% each of products with the same mobilities as the 21,21′-bisteroidal

SCHEME II



carbonate[3] and free 11-deoxycorticosterone, the presence of three more mobile products which also reduce alkaline blue tetrazolium (BT). Successive fractionation of the mixture on silica gel and partitioning-type columns[4] afforded the latter substances in yields (according to decreasing mobility) of 4.5, 20.0, and 5.7%. Dehydrohalogenation of **1a,b** with acetone–sodium iodide–triethylamine at room temperature afforded two of the products in considerably better yields (3.5, 50.6, and 9.3%, respectively). Alternatively, the crude product from phosgenation of 11-deoxycorticosterone under condition B was treated directly with the latter reagent, furnishing the three products in overall yields of 1.8, 28.6, and 7.2%, respectively. When this procedure was employed the halogen exchange product, 21-iodoprogesterone,[5] was also recovered in a yield of 12.5%. The close chemical relationship of the isomeric dehydrohalogenation products was shown by conversion of all three to 11-deoxycorticosterone acetate after sequential treatment with methanolic sodium hydroxide and acetic anhydride–pyridine. In addition, prolonged refluxing of each in methanol afforded another common product, namely 21-*O*-carbomethoxypregn-4-ene-3,20-dione.[2] The infrared spectra of all three compounds exhibited intense carbonyl bands above 1800 cm^{-1}, indicating that the five-membered cyclic carbonate ring was retained. The most mobile product possessed no other carbonyl band above 1700 cm^{-1}, but the intermediate and most polar products also showed absorption maxima in the vicinity of 1735 cm^{-1}. Nmr analysis proved especially helpful in establishing the structures of these products.[6] No 21-methylene signals were observed in the most mobile product, but the 21-methylene protons which are present in the two companion substances exhibit considerable fine structure which was attributed to long-range spin coupling. This view was confirmed when irradiation in the τ 7.5 region caused collapse of the multiplets in both compounds. The nmr spectra also strongly suggested the presence of a double bond in all three products somewhere between C-16 and C-21. Based on these spectral properties and the structures of the precursors **1a,b**, the most mobile dehydrohalogenation product was assigned the $\Delta^{20,21}$-20,21-cyclic carbonate structure **2**, and its companions have been formulated as the cis and trans $\Delta^{17,20}$-20,21-cyclic carbonates **3** and **4**. However, individual configurational assignments for **3** and **4** could not be made on the basis of spectral data. The latter formulations were made with some reluctance at the time because **3** and **4** exhibited an unexplained band in the carbonyl region of their infrared spectra. However, our attention was called to recent reports[7] that anhydrohirundigenin, a 15-oxa steroid which contains no carbonyl group, also exhibits a conspicuous band at 1715 cm^{-1} (in KBr) which was attributed to a trisubstituted, heteroannular enol ether (>C=CO–) grouping. It is not surprising, therefore, that cyclic carbonates **3** and **4**, which possess the same system but with the olefinic bond in an exocyclic position, the infrared spectra should not only contain such a band

(3) M. L. Lewbart, *J. Org. Chem.*, **37**, 3892 (1972).

(4) Control experiments showed that preliminary group separation on silica gel was essential (for reasons which are not apparent), since direct fractionation of the mixture on the Celite column led to both incomplete separations and formation of artifacts, resulting in much lower yields.

(5) T. Reichstein and O. Schindler, *Helv. Chim. Acta*, **25**, 669 (1940).

(6) The author is especially indebted to Dr. Byron H. Arison of the Merck Institute, whose determination and interpretation of the nmr spectra first made us aware of the structures of **2**, **3**, and **4**.

(7) (a) O. Kennard, J. K. Fawcett, D. G. Watson, K. A. Kerf, K. Stockel, W. Stocklin, and T. Reichstein, *Tetrahedron Lett.*, **35**, 3799 (1968); (b) K. Stockel, W. Stocklin, and T. Reichstein, *Helv. Chim. Acta*, **52**, 1175 (1969).

but that it is both intensified and displaced to a higher frequency.

Solution of the only remaining problem, the respective geometric isomerism of **3** and **4**, was attempted by chemical means. Initial experiments centered around relating them to side chain saturated cyclic carbonates of known configuration at C-20. Hydrogenation of **3** and **4** in the presence of platinum or palladium catalysts resulted in reduction of the A ring double band but not that in the side chain. Under more vigorous hydrogenation conditions reductive elimination of the C-3 oxygen also occurred. As a means of preventing this side reaction **3** and **4** were first treated with sodium borohydride in methanol in order to generate the more resistant Δ^4-3-ol system. It was found, however, that the side chain was also affected by this treatment, since the major products did not reduce BT. This finding was pursued by treating **3** and **4** successively with sodium borohydride and chromic anhydride–pyridine in order to regenerate the Δ^4-3-keto system. The identity of the major product (70%) from **4** as the 20β,21-cyclic carbonate **5b** was confirmed through its independent synthesis by phosgenation of 20β,21-dihydroxypregn-4-en-3-one.[8] In the expectation that **3** would afford the 20α,21-cyclic carbonate **5a**, this compound was also prepared by phosgenation of 20α,21-dihydroxypregn-4-en-3-one.[8] However, the major reduction–oxidation product from **3** is the 20β-hydroxy-21-camylate **6b**, which was also prepared by camylation of 20β,21-dihydroxypregn-4-en-3-one. Fixation of the camyl group at C-21 in **6b** followed from the demonstration that its acetylation product **7b** is identical with the camylation product of 20β,21-dihydroxypregn-4-en-3-one 20-acetate.[8] Proof that the cyclic carbonate **5b** is a direct hydrogenation product from **4** was forthcoming in a control experiment where successive sodium borohydride and chromic anhydride–pyridine treatment of the 21-camylate **6b** resulted in nearly complete recovery of starting material. The formation of **6b** from **3** suggests for this isomer initial methanolysis of the carbonate bond (which would be more accessible in the trans configuration) to the 20-oxo-21-camylate followed by reduction at C-20 in the normal manner It is noteworthy that the hydroxyl group in **6b** is not oxidized by chromic anhydride–pyridine, presumably because of steric hindrance imposed by the bulky camyl group at C-21.

The nature of the products obtained by sequential reduction and allylic oxidation of the $\Delta^{17,20}$-20,21-cyclic carbonates **3** and **4** suggests but by no means proves that they possess the trans and cis configurations, respectively. An independent synthesis of **3** and **4** was therefore considered essential for definitive structural assignments. A promising route appeared to be *via* dehydration of 17α-hydroxy 20,21-cyclic carbonates. Since the use of thionyl chloride in pyridine was anticipated, protection of ring A was a necessary preliminary.[9] A convenient starting point was the glyoxal hemiacetal **8**, prepared in 95% yield by oxidation of 11-deoxycortisol with methanolic cupric acetate.[10] Sequential reaction of **8** with sodium hydroxide, diazomethane, and acetic anhydride–pyridine as described in earlier papers,[11] followed by column chromatography, furnished the acetoxy methyl esters **9a** and **9b** in yields of 36 and 21%, respectively. Ketalization of **9a** and **9b** by the direct procedure of Bernstein and coworkers[12] provided the corresponding 3-ethylene ketals **10a** and **10b** in respective yields of 58 and 63%. Lithium aluminum hydride reduction of **10a** and **10b** gave the glycerol 3-ketals **11a** and **11b** in high yields. A superior route to **11b** was *via* sodium borohydride–dimethylformamide reduction of 21-acetoxy-17-hydroxypregn-5-ene-3,20-dione 3-ethylene ketal[12] to the 20β-hydroxy 21-acetate **12b** followed by saponification. Phosgenation of the glycerol 3-ketals **11a** and **11b** supplied the desired 20,21-cyclic carbonates **13a** and **13b**. As a convenient alternative the reaction sequence leading from glyoxal hemiacetal **8** to the cyclic carbonate 3-ketals can be carried out without isolating the intermediates. The overall yields of **13a** and **13b** by this procedure were 24 and 11%, respectively. Further characterization of **13a** and **13b** was accomplished by their deketalization in acetone–*p*-TSA to the corresponding Δ^4-3-ones **14a** and **14b**.[13] Since sodium borohydride reduction of 20-keto pregnanes gives 20β-ols almost exclusively,[15] the interrelationship of **12b** with the minor glycolic acid derivative **9b** speaks strongly for the 20β configuration in this series. Furthermore, it was shown that the deketalization product **14a** is identical with the phosgenation product from 17,20α,21-trihydroxypregn-4-en-3-one,[16] thus establishing unequivocally the 20α orientation of the major glycolic acid derivative **9a**.

Treatment of cyclic carbonates **13a** and **13b** with thionyl chloride in pyridine for 15 min at 5° afforded in each case a major, mobile BT-positive and a minor, polar BT-negative substance (for elucidation of the structures of the minor products, see below). Following column chromatographic separation on silica

(8) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **29**, 2559 (1964).

(9) C. C. Beard, "Organic Reactions in Steroid Chemistry," Vol. 1, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1972, p 322. The authors state that Δ^4-3-ketones are stable to thionyl chloride–pyridine at −30°, but that 17α-ols are not dehydrated at this temperature. Experience in this laboratory has shown that at the higher temperatures essential for dehydration of 17α-ols (−20 to 5°) almost quantitative loss of material from the neutral fraction occurs in the absence of a protecting group.

(10) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 2001 (1963).

(11) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, 1773 (1963).

(12) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *ibid.*, **18**, 70 (1953).

(13) The 20β,21-cyclic carbonates **13b** and **14b** appeared to undergo some alteration when methanol was used as a crystallizing solvent. It was later found that refluxing **14b** in methanol for 4 hr resulted in its almost complete conversion to a more polar hydroxy cyclic carbonate. Since treatment of **14b** with methanolic sodium hydroxide (a reagent known to isomerize 17α-hydroxy-20β,21-cyclic carbonates[14]) afforded in 86% yield the same product, the artifact was identified as the 17 20β-cyclocarbonyldioxy-21-ol **15b**. Confirmation of this structural assignment was obtained by showing that its acetylation product **16b** is identical with the phosgenation product from 21-acetoxy-17,20β-dihydroxypregn-4-en-3-one (M. L. Lewbart, unpublished synthesis). Further investigation showed that of three 11-oxygenated 17α-hydroxy-20β,21-cyclic carbonates,[14] only the 11β-ol undergoes isomerization in refluxing methanol to the 17,20β-cyclocarbonyldioxy-21-ol[14] in 92% yield. The other compounds which bear β-acetyl and carbonyl functions at C-11 and all four 17α-hydroxy-20α,21-cyclic carbonates are not affected by refluxing methanol. Isomerization of glycerol 20,21-cyclic carbonates is therefore limited to 20β-oriented compounds which are either unsubstituted or bear a β-hydroxyl group at C-11. The highly selective nature of the rearrangement which depends on long-range effects at C-11 is of some theoretical interest.

(14) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).

(15) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p 139.

(16) P. L. Julian, E. W. Meyre, W. J. Karpel, and W. Cole, *J. Amer. Chem. Soc.*, **73**, 1982 (1951). The 20α glycerol was prepared in this laboratory by an unpublished procedure which involves solvolysis of a 20β-tosyl-17α,21-diacetate.[17]

(17) D. K. Fukushima, N. S. Leeds, H. L. Bradlow, T. H. Kritchevsky, M. B. Stokem, and T. F. Gallagher, *J Biol. Chem.*, **212**, 449 (1955).

gel, the products from **13a** were isolated in yields of 40 and 24%. Similar fractionation of the mixture from **13b** gave the pure components in yields of 48 and 18%. Since deketalization in acetone–*p*-TSA of the major dehydration products from **13a** and **13b** gave Δ^4-3-ones identical with the dehydrohalogenation products **3** and **4**, their geometric isomerism at trans and cis,[18] respectively, can be assigned with certainty. These conclusions are valid because dehydrations involving thionyl chloride are known to occur stereospecifically.[19] The structures of the major dehydration products from **13a** and **13b** are therefore those of **17** and **18**, respectively.

A study of the dehydrohalogenation products from the 11-oxochlorocarbonates **19a** and **19b** (Scheme II) was also undertaken. For preparative purposes, it was found convenient to employ as substrate the crude product from phosgenation of 11-dehydrocorticosterone. After treatment of this material with acetone–sodium iodide–triethylamine and silica gel chromatography, a number of products could be isolated. A mobile, amorphous, Beilstein-positive component (21% yield) was identified as 21-iodopregn-4-ene-3,11,20-trione through its conversion with zinc in acetic acid to 11-ketoprogesterone. Thereafter emerged three Beilstein negative substances in overall yields (according to decreasing mobility) of 3.4, 2.0, and 16.7%. When dehydrohalogenation of the phosgenation mixture was effected in hot pyridine, only the mobile (4.4%) and polar (11.8%) products could be recovered. The companion substance with intermediate mobility was assigned the $\Delta^{20,21}$-20,21-cyclic carbonate structure **20** because its infrared spectrum is very similar to that of the 11-deoxy analog **2**.

Infrared analysis showed the remaining products to be the isomeric $\Delta^{17,20}$-20,21-cyclic carbonates **21** and **22**. Definitive configurational assignments followed from a reaction sequence similar to that used in the 11-deoxy series. Ketalization of the 20,21-cyclic carbonates **23a** and **23b**[14] afforded ketals **24a** and **24b**. Treatment of **24a** with thionyl chloride in pyridine gave a mobile BT-positive product in 55% yield and a polar BT-negative substance in 19% yield. Similar reaction of **24b** furnished in 62% yield a BT-positive compound. A more polar, unknown by-product which also reduced BT was recovered, but no significant amount of BT-negative material could be detected. Deketalization of the major dehydration products (**25** and **26**) from **24a** and **24b** gave Δ^4-3-ones indistinguishable from **21** and **22**, thus establishing their configurations as trans and cis, respectively.

At this point it seemed of interest to establish the configurations of the chlorocarbonates **19a** and **19b** by determining the nature of their dehydrohalogenation products. Treatment of the more mobile epimer with hot pyridine followed by tlc analysis indicated nearly quantitative conversion to a product with the same mobility as the cis $\Delta^{17,20}$-20,21-cyclic carbonate **22**. Under the same conditions the more polar chlorocarbonate gave a roughly 1:1 mixture of cis and trans isomers. Isomerization between cis and trans forms in hot pyridine was ruled out in control experiments. It is on the basis of these findings that the mobile chlorocarbonate, which appears to lose hydrogen chloride in a stereospecific manner, was assigned the 20β,21-cyclocarbonyldioxy-20α-chloro structure, and that the polar chlorocarbonate, which affords a significant quantity of the trans isomer, was assigned the 20α,21-cyclocarbonyldioxy-20β-chloro formulation.[2]

In the course of independent syntheses of the cis and trans $\Delta^{17,20}$-20,21-cyclic carbonates, BT-negative by-products were isolated after three of four dehydrations with thionyl chloride. Because of our general interest in the reactions of pregnan-17α-ols these substances were also investigated. On the assumption that the by-products are Δ^{16}-20,21-cyclic carbonates, efforts were directed toward devising conditions under which Δ^{16}-20,21-diols or their derivatives are major products. Dehydration of 17α-hydroxy-20,21-diacetates offered a logical approach to this series. Reaction of the acetylation products (**27a** and **27b**, Scheme III) from the glycerol 3-ketals **11a** and **11b** with thionyl chloride in pyridine afforded BT-negative products (**28a** and **28b**) in yields of 57 and 73%, respectively. Only small amounts of BT-positive products (presumably $\Delta^{17,20}$-20,21-diacetates) were detected. Saponification of **28a** and **28b** gave the glycols **29a** and **29b** in excellent yields. In order to relate the dehydration products from the glycerol diacetates to the minor dehydration products from 17-hydroxy-20,21-cyclic carbonates, and at the same time establish the location of the olefinic bond, additional transformations were carried out as follows. Treatment of glycols **29a** and **29b** with ethyl chlorocarbonate–pyridine gave the 21-cathylates **30a** and **30b** in yields of 54 and 58%, respectively. Cyclization of **30a** and **30b** in methanolic sodium hydroxide afforded in high yields the Δ^{16}-20,21-cyclic carbonates **31a** and **31b** which proved identical with the respective BT-negative by-products from **13a** and **13b**. Oxidation of 21-cathylates **30a** and **30b** with chromic anhydride–pyridine furnished a common product which was identified as the Δ^{16}-α-ketol 21-cathylate **32**, since successive saponification and acetylation gave the known Δ^{16}-α-ketol 21-acetate **33**.[20]

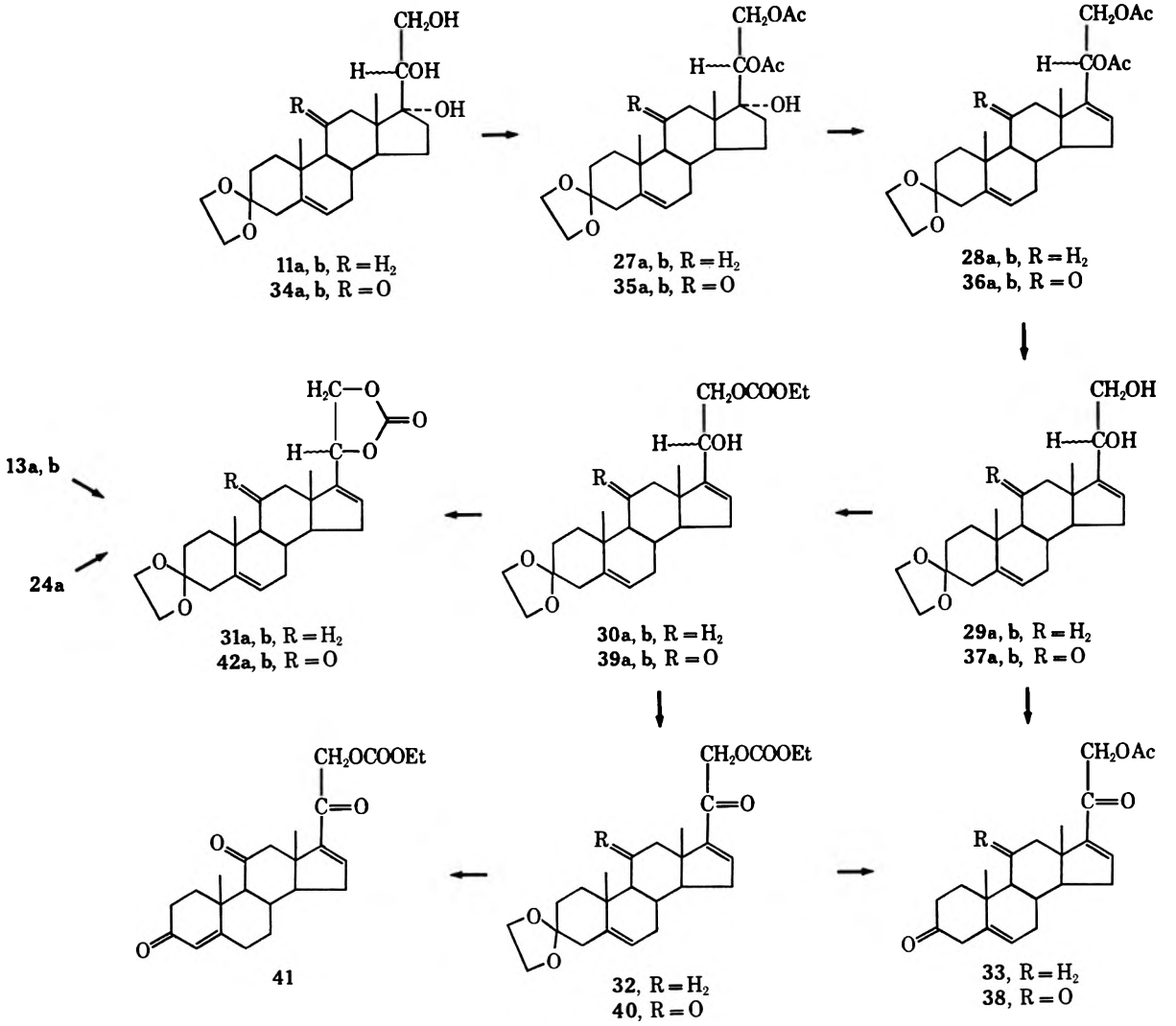
A similar reaction sequence was employed in the 11-keto series. Saponification of the cyclic carbonate 3-ketals **24a** and **24b** gave the glycerol 3-ketals **34a** and **34b**. Treatment of the acetylation product (**35a**) from **34a** with thionyl chloride gave in 78% yield the Δ^{16}-diacetate **36a** which could be saponified to the Δ^{16}-glycol **37a**. Similar dehydration of **35b** gave a major BT-negative and a minor BT-positive product which could not be separated by fractional crystallization or column chromatography. It was found, however, that following saponification of the mixture the Δ^{16}-20β,21-diol **37b** could be isolated directly in 79% yield. Acetylation of **37b** furnished a pure sample of Δ^{16}-diacetate **36b**. Structural correlation of the 11-keto Δ^{16}-glycols was accomplished in two ways. First, treatment of **37a** and **37b** with dichlorodicyanobenzoquinone (DDQ) in *tert*-butyl alcohol followed by acetylation gave in low yield a common product, namely the known Δ^{16}-α-ketol 21-acetate **38**.[20] Second, treatment of Δ^{16}-glycols **37a** and **37b** with ethyl chlorocarbonate–pyridine furnished the 21-cathylates **39a** and **39b** in yields

(18) It is understood that in $\Delta^{17,20}$-20,21-cyclic carbonates a trans configuration exists when the cyclocarbonyldioxy ring faces a direction opposite that of the angular methyl group at C-18, and that in a cis configuration the ring is oriented toward the C-18 methyl group.

(19) Reference 15, p 102.

(20) W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, **77**, 1028 (1955).

SCHEME III



of 54 and 75%, respectively. Oxidation of **39a** and **39b** with chromic anhydride–pyridine afforded the Δ^{16}-α-ketol 21-cathylate **40**. The structure of **40** was confirmed by demonstrating that its deketalization product **41** is identical with the cathylation product of 21-hydroxypregna-4,16-diene-3,11,20-trione.[20] Treatment of the 20α-hydroxy-21-cathylate **39a** with methanolic sodium hydroxide afforded the Δ^{16}-cyclic carbonate **42a** which is identical with the BT-negative by-product from **24a**. Similar reaction of **39b** gave the Δ^{16}-20β,21-cyclic carbonate **42b**, which had not been encountered previously.

When the optical rotatory properties of the four pairs of $\Delta^{17,20}$-20,21-cyclic carbonates were reviewed it was noted that in all cases the trans isomers are more levorotatory than the cis isomers by a margin of from -97 to -210 M_D units. Acetylation increments for the two pairs of Δ^{16}-20,21-diols described in this paper are of the order exhibited by D ring-saturated 20-ols,[21] namely negative shifts in M_D of -81 and -76 units in the 20α epimers and positive shifts of $+174$ and $+141$ units in the 20β epimers. An opposite effect was observed, however, when Δ^{16}-glycols are converted to cyclic carbonates. In the two available examples the 20α epimers undergo positive M_D shifts of $+48$ and $+64$ units, and the 20β epimers exhibit negative shifts of -150 and -326 units. This behavior of the Δ^{16}-20,21-cyclic carbonates is of interest, since no significant differences in M_D had been noted between epimeric 20,21-cyclic carbonates saturated in ring D.[14]

Comparison of the infrared spectral properties of the new side chain-unsaturated cyclic carbonates also proved interesting. In all four cis $\Delta^{17,20}$ isomers the carbonate carbonyl absorption is split into a major band at 1830 cm^{-1} and a minor band at 1815–1810 cm^{-1}, while in the trans $\Delta^{17,20}$ isomers carbonate carbonyl absorption appears as a single band in the range 1830–1810 cm^{-1}. Another point of difference in the infrared spectra of the $\Delta^{17,20}$ isomers lies in the location of the intense, displaced olefin band discussed earlier. The frequency range of this band is consistently higher (1741–1737 cm^{-1}) in the cis isomers than in the trans isomers (1732–1728 cm^{-1}). Other strong to very strong bands in the fingerprint region which are common to both isomers were found in the ranges 1376–1369, 1135–1124, 775–768, and 734–728 cm^{-1}. Both $\Delta^{20,21}$-cyclic carbonates exhibit moderately intense C=C stretch bands above 3100 cm^{-1} and split carbonate carbonyl bands. Other strong to very strong fingerprint bands common to both analogs appear at 1127 and 1067 cm^{-1}.

(21) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **33**, 1707 (1968).

Experimental Section

General experimental procedures are detailed in the previous paper.[2] Unless otherwise indicated, tlc and column systems are designated in the text by a number which corresponds to one of the following compositions [in each case the number is followed (in parentheses) by that volume of ethyl acetate which, diluted to 25 ml with isooctane (or, in the case of system 8, with toluene), comprises the system]: 1 (10), 2 (11.2), 3 (12.5), 4 (8.8), 5 (16.2), 6 (15), 7 (13.8), and 8 (3).

Reaction of 20ξ,21-Cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one (1a,b) with Hot Pyridine.—A solution of the chlorocarbonates (350 mg) in pyridine (3 ml) was heated in the rings of a steam bath for 1 hr. The reaction mixture was processed in the usual fashion and the crude product was chromatographed on a silica gel column in system 1. The mixture (130 mg) was rechromatographed on a Celite column in the system isooctane–toluene–formamide (260:40:5).

20,21-Cyclocarbonyldioxypregna-4,20(21)-dien-3-one (2).—The most mobile fraction afforded 14 mg (4.5%) of prisms from ethyl acetate: mp 185–186°; $[\alpha]_D$ +140°; λ_{max} 240 mμ (ε 17,400); ν_{max} 3180 (shoulder), 3160, 1837 (1808) cm^{-1} ($\Delta^{20,21}$-cyclic carbonate); nmr δ 9.30 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.21, 5.18 (d, 1, 21-methine).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.05; H, 7.77.

20,21-Cyclocarbonyldioxypregna-4,*cis*-17(20)-dien-3-one (4).—From the intermediate fraction was obtained 63 mg (20.0%) of prisms from ethyl acetate: mp 199–201°; $[\alpha]_D$ +165°; λ_{max} 240 mμ (ε 17,400); ν_{max} 1830 (1815), 1741 cm^{-1} (cis $\Delta^{17,20}$-cyclic carbonate); nmr δ 9.04 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.18, 5.16, 5.14 (m, 2, 21-CH_2).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.90.

20,21-Cyclocarbonyldioxypregna-4,*trans*-17(20)-dien-3-one (3).—The least mobile band supplied 17.6 mg (5.7%) of prisms from ethyl acetate: mp 253–254°; $[\alpha]_D$ +106°; λ_{max} 241 mμ (ε 17,150); ν_{max} 1810, 1728 cm^{-1} (trans $\Delta^{17,20}$-cyclic carbonate); nmr δ 9.07 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.0, 4.99, 4.97, 4.96, 4.93 (m, 2, 21-CH_2).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.10; H, 7.95.

Reaction of 1a,b with Sodium Iodide–Acetone–Triethylamine.—To a solution of the chlorocarbonates (350 mg) in acetone (23 ml) was added an equal volume of 10% sodium iodide in acetone and 0.175 ml of triethylamine. After 22 hr in the dark at room temperature most of the solvent was removed in a nitrogen stream and the residue was partitioned between methylene chloride and dilute hydrochloric acid. The crude product was chromatographed on a Celite column of the same composition as that used in fractionating the reaction mixture from hot pyridine, giving 15 mg (3.5%) of **2**, mp 184–185°, 158 mg (50.6%) of **4**, mp 199–201°, and 29 mg (9.3%) of **3**, mp 252–253°.

21-Iodopregn-4-ene-3,20-dione, 2, 3, and 4 from 11-Deoxycorticosterone.—Phosgenation of the α-ketol (1.65 g, 5 mmol) under condition B was followed by treatment of the reaction mixture in acetone (230 ml) with sodium iodide (11.5 g) and triethylamine (0.9 ml) for 20 hr. The crude product was chromatographed on a silica gel column (system 1). The 21-iodide emerged first and crystallized from acetone–*n*-hexane as rosettes [275 mg, mp 111.5° dec (on stage at 110°)] in a yield of 12.5%: $[\alpha]_D$ +217°; λ_{max} 241 mμ (ε 17,400); ν_{max} 1718 cm^{-1} (20-ketone) (lit.[5] no constants given).

Anal. Calcd for $C_{21}H_{29}O_2I$: C, 57.27; H, 6.64; I, 28.82. Found: C, 57.11; H, 6.68; I, 28.77.

Continued development of the column furnished the unsaturated cyclic carbonates (1.15 g). Rechromatography on the Celite column gave 32 mg (1.8%) of **2**, mp 183.5–185°, 509 mg (28.6%) of **4**, mp 198–200°, and 128 mg (7.2%) of **3**, mp 252–253°.

20β,21-Cyclocarbonyldioxypregn-4-en-3-one (5b) from 4.—To a solution of 20,21-cyclocarbonyldioxypregna-4,*cis*-17(20)-dien-3-one (50 mg) in methylene chloride (0.2 ml) and methanol (1.8 ml) was added 20 mg of sodium borohydride. After 30 min at 5° excess acetic acid was added and after dilution with methylene chloride the solution was washed successively with dilute sodium bicarbonate and water. To the crystalline residue in pyridine (3 ml) was added 50 mg of chromic anhydride and after 18 hr at room temperature the product was recovered in the usual manner. Crystallization from methanol gave prismatic needles (17 mg, mp 164–166°; 17 mg, mp 162–164°): $[\alpha]_D$ +93.9°; λ_{max} 239 mμ (ε 17,200); ν_{max} 1805 (1785), 780 cm^{-1} (cyclic carbonate[14]).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.59; H, 8.20.

5b from 20β,21-Dihydroxypregn-4-en-3-one.—Phosgenation of the glycol (332 mg, 1 mmol) under condition A and crystallization of the product from methanol gave prismatic needles (278 mg, mp 167.5–168°; 32 mg, mp 164–166°) in a yield of 87%. The ir spectrum was identical with that of **5b** prepared from **4**.

20α,21-Cyclocarbonyldioxypregn-4-en-3-one (5a).—Phosgenation of 20α,21-dihydroxypregn-4-en-3-one (25 mg) under condition A and crystallization from methanol gave 19 mg of prisms: mp 230–232°; $[\alpha]_D$ +101°; λ_{max} 240 mμ (ε 17,600); ν_{max} 1805, 786 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.56; H, 8.22.

21-*O*-Carbomethoxy-20β-hydroxypregn-4-en-3-one (6b) from 3.—Reduction of 20,21-cyclocarbonyldioxypregna-4,*trans*-17(20)-dien-3-one (25 mg) in 4:1 methanol–methylene chloride (2 ml) with 10 mg of sodium borohydride was followed by oxidation of the crude product with pyridine–chromic anhydride as in the preparation of **5b** from **4**. The reaction mixture was chromatographed on a silica gel column in system 1, affording 11.5 mg of needles from ethyl acetate: mp 190.5–192.5°; $[\alpha]_D$ +84.5°; λ_{max} 241 mμ (ε 16,800); ν_{max} 3480 (hydroxyl), 1756, 1275, and 798 cm^{-1} (camylate[14]).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.72; H, 8.77. Found: C, 70.74; H, 8.88.

6b from 20β,21-Dihydroxypregn-4-en-3-one.—Treatment of the glycol (100 mg) in pyridine (2 ml) at 0° with a mixture of methyl chlorocarbonate (0.2 ml) and benzene (1.8 ml) as in a condition A phosgenation and crystallization of the product from methanol gave 100 mg (85%) of needles, mp 201–203°. The ir spectrum was identical with that of **6b** prepared from **3**.

21-*O*-Carbomethoxy-20β-acetoxypregn-4-en-3-one (7b) from 6b.—Treatment of 21-*O*-carbomethoxy-20β-hydroxypregn-4-en-3-one (30 mg) with 0.1 ml each of pyridine and acetic anhydride for 3 hr at room temperature (with initial warming to effect solution) and crystallization of the product from methanol gave 21 mg of needles: mp 136–137°; $[\alpha]_D$ +115°; λ_{max} 241 mμ (ε 17,000); ν_{max} 1755, 1275, and 798 (camylate), 1740 (shoulder), 1237 cm^{-1} (acetate).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.52; H, 8.19.

7b from 20β,21-Dihydroxypregn-4-en-3-one 20-Acetate.—Camylation of the 20β-acetoxy-21-ol[8] (7.5 mg) as in the preparation of **6b** followed by purification on a silica gel column (system 1) gave 4.1 mg of platelets from acetone–*n*-hexane, mp 136–137°. The ir spectrum was identical with that of **7b** prepared from **6b**.

17,21-Dihydroxy-21-methoxypregn-4-ene-3,20-dione (8) from 11-Deoxycortisol.—Oxidation of the α-ketol (5.19 g, 15 mmol) in methanol (750 ml) with cupric acetate (750 mg) was carried out in the manner described previously.[10] The hemiacetal crystallized from methanol as rosettes (5.11 g, mp 113–116°; 0.23 g, mp 114–117°) in a yield of 95%: $[\alpha]_D$ +110°; λ_{max} 240 mμ (ε 16,900); ν_{max} 3545, 3440 (hydroxyl), 1732 cm^{-1} (20-ketone).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; CH_3O, 8.24. Found: C, 70.12; H, 8.35; CH_3O, 8.12.

Methyl 20α- (and 20β-) Acetoxy-17-hydroxy-3-oxopregn-4-en-21-oates (9a and 9b) from 8.—To a solution of 17,21-dihydroxy-21-methoxypregn-4-ene-3,20-dione (3.76 g, 10 mmol) in methanol (100 ml) at 0° was added 15 mmol of sodium hydroxide in 400 ml of water. After the clear solution stood for 1 hr at 0°, 1 *N* hydrochloric acid (17.5 ml) was added and the precipitate was extracted with ethyl acetate. The organic layer was washed with brine and concentrated to dryness. The crude acidic mixture was treated sequentially with excess ethereal diazomethane and acetic anhydride–pyridine as described earlier.[11] Several crystallizations from methanol gave **9a** as needles (820 mg, mp 185–186°): $[\alpha]_D$ +91.6°; λ_{max} 240 mμ (ε 16,900); ν_{max} 3570, 3530 (hydroxyl), 1750 (carbomethoxyl), 1750, 1240 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: 68.76; H, 7.97.

The mother liquor was chromatographed on a silica gel column in system 2. The initial fraction afforded an additional 692 mg of **9a**, mp 184–185°, raising the yield to 36%. Later eluates furnished **9b** as prisms from ethyl acetate (688 mg, mp 164–165°; 174 mg, mp 157–159°) in a yield of 21%: $[\alpha]_D$ +87.5°; λ_{max}

241 mμ (ε 17,100); ν_{max} 3500 (hydroxyl), 1750 (carbomethoxyl), 1750, 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.86; H, 8.29.

Methyl 20α-Acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (10a) from 9a.—Direct ketalization of methyl 20α-acetoxy-17-hydroxy-3-oxopregn-4-en-21-oate (1110 mg) for 11 hr was carried out as described in earlier publications.[8] The reaction mixture was treated with acetic anhydride–pyridine, since tlc analysis showed that some deacetylation had occurred. Two crystallizations from methanol gave 610 mg of platelets: mp 208–210°; $[\alpha]_D$ −30.9°; ν_{max} 3605 (hydroxyl), 1745 (carbomethoxyl), 1745, 1245 (acetate), 1092 cm^{-1} (ketal[20]).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.38; H, 8.38.

Silica gel chromatography of the moter liquor in system 3 afforded an additional 100 mg of product, mp 206.5–20.8.5°, raising the yield to 58%. Starting material (200 mg) was also recovered in later fractions.

Methyl 20β-Acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (10b) from 9b.—Ketalization of methyl 20β-acetoxy-17-hydroxy-3-oxopregn-4-en-21-oate (500 mg) as in the preparation of **10a** followed by silica gel column chromatography furnished the ketal as a filterable solid from aqueous methanol (360 mg, mp 128–130°) in a yield of 63%. Recrystallization from ethyl acetate–*n*-hexane gave small prisms: mp 185–187°; $[\alpha]_D$ −40.6°; ν_{max} 3530 (hydroxyl), 1750 (carbomethoxyl), 1750, 1230 (acetate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.68; H, 8.30.

3-Ethylenedioxypregn-5-ene-17,20α,21-triol (11a) from 10a.—An equal weight of methyl 20α-acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (850 mg) and lithium aluminum hydride was refluxed in tetrahydrofuran (100 ml) for 3 hr. The product was recovered in the usual manner except for omission of the acid wash. Crystallization from methanol gave plates (699 mg, mp 230–232°; 28 mg, mp 223–224°) in quantitative yield: $[\alpha]_D$ −51.2°; ν_{max} 3450 (hydroxyl), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.29; H, 9.32.

3-Ethylenedioxypregn-5-ene-17,20β,21-triol 21-Acetate (12b) from 11-Deoxycortisol 21-Acetate 3-Ethylene Ketal.—Reduction of the ketal acetate[12] (3.0 g) in a mixture of methylene chloride (75 ml) and dimethylformamide (150 ml) with sodium borohydride (225 mg) in the presence of sodium bicarbonate (450 mg) and water (15 ml) was carried out for 3 hr in the manner described previously.[8] Several crystallizations of the product from ethyl acetate gave 1.79 g (60%) of prisms: mp 193–194°; $[\alpha]_D$ −39.9°; ν_{max} 3480 (hydroxyl), 1729, 1240 (acetate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.24; H, 8.83.

Acetylation of the mother liquor followed by silica gel column chromatography (system 1) furnished 640 mg (19%) of the 20β,21-diacetate **27a** (*vide infra*) and 95 mg (3%) of the 20α,21-diacetate **27b** (*vide infra*).

3-Ethylenedioxypregn-5-ene-17,20β,21-triol (11b) from 12b.—To a solution of 3-ethylenedioxypregn-5-ene-17,20β,21-triol 21-acetate (868 mg, 2 mmol) in methanol (100 ml) was added 2.4 ml of 1 *N* sodium hydroxide. After 1 hr at room temperature the solution was concentrated *in vacuo* and the product was recovered by extraction with methylene chloride. Crystallization from methanol gave prisms (720 mg, mp 191–192°; 70 mg, 189.5–190°) in a yield of 97%: $[\alpha]_D$ −54.5°; ν_{max} 3450 (hydroxyl), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.51; H, 9.32.

11b from 10b.—Reduction of methyl 20β-acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (250 mg) with lithium aluminum hydride in tetrahydrofuran as in the preparation of **11a** and three crystallizations from methanol provided 100 mg of prisms, mp 198–200°. The ir spectrum was identical with that of **11b** prepared by saponification of **12b**.

20α,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13a) from 11a.—Phosgenation of 3-ethylenedioxypregn-5-ene-17,20α,21-triol (650 mg) under condition A and silica gel column chromatography (system 3) gave 417 mg (60%) of small platelets: mp 265–266°; $[\alpha]_D$ −62.8°; ν_{max} 3480 (hydroxyl), 1805, 778 (cyclic carbonate[14]), 1105 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.08; H, 8.31.

20β,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13b) from 11b.—Phosgenation of 3-ethylenedioxypregn-5-ene-17,20β,21-triol (784 mg) under condition A followed by silica gel column chromatography (system 1) gave a minor, mobile product (247 mg, mp 240–241°) which was not investigated further. The major, less mobile component crystallized from ethyl acetate as needles (418 mg, mp 224–227°) in a yield of 50%: $[\alpha]_D$ −80.3°; ν_{max} 3520 (hydroxyl), 1805 (1785), 779 (cyclic carbonate), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.78; H, 8.29.

20α,21-Cyclocarbonyldioxy-17-hydroxypregn-4-en-3-one (14a) from 13a.—To a solution of 20α,21-cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (25 mg) in acetone (10 ml) was added 5 mg of *p*-TSA. After 18 hr at room temperature the product was recovered and crystallized from methanol as needles (14.7 mg, mp 233–235°; 2.6 mg, mp 228–230°) in a yield of 77%: $[\alpha]_D$ +52.5°; λ_{max} 240 mμ (ε 17,400); ν_{max} 3450 (hydroxyl), 1800, 778 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.45; H, 8.15.

20β,21-Cyclocarbonyldioxy-17-hydroxypregn-4-en-3-one (14b) from 13b.—Deketalization of 20β,21-cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (25 mg) in acetone–*p*-TSA as in the preparation of **14a** gave 18 mg of rosettes from ethyl acetate: mp 191–194 and 240–243°; $[\alpha]_D$ +67.3°; λ_{max} 240 mμ (ε 16,400); ν_{max} 3450 (hydroxyl), 1805 (1785), 779 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.42; H, 7.91.

17,20β-Cyclocarbonyldioxy-21-hydroxypregn-4-en-3-one (15b) from 14b.—A solution of 20β,21-cyclocarbonyldioxy-17-hydroxypregn-4-en-3-one (100 mg) in methanol (50 ml) was refluxed for 4 hr. Crystallization of the residue from acetone afforded prismatic needles (71 mg, mp 254.5–256.5°; 16 mg, mp 253–255°) in a yield of 87%: $[\alpha]_D$ +103°; λ_{max} 240 mμ (ε 17,500); ν_{max} 3400 (hydroxyl), 1790, 778 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.68; H, 8.13.

Treatment of the 20β,21-cyclic carbonate **14b** (50 mg) in methanol (9.5 ml) with 0.1 *N* methanolic sodium hydroxide (0.5 ml) for 10 min at room temperature and crystallization of the product from acetone gave 43 mg (86%) of needles, mp 255–257°, which did not depress the melting point of **15b** prepared by refluxing **14b** in methanol, and their ir spectra were identical.

17,20β-Cyclocarbonyldioxy-21-acetoxypregn-4-en-3-one (16b) from 15b.—Treatment of 17,20β-cyclocarbonyldioxy-21-hydroxypregn-4-en-3-one (25 mg) with acetic anhydride–pyridine followed by crystallization of the product from methanol gave 26 mg of needles: mp 198.5–200°; $[\alpha]_D$ +83.5°; λ_{max} 239 mμ (ε 17,700); ν_{max} 1800, 772 (cyclic carbonate), 1749, 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.06; H, 7.71.

16b from 17,20β,21-Trihydroxypregn-4-en-3-one 21-Acetate.—Phosgenation of the 21-monoacetate[13] (78 mg) under condition A furnished 72 mg (87%) of product, mp 197.5–199°, whose ir spectrum was identical with that of **16b** prepared by acetylation of **15b**.

Reaction of 20α,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13a) with Thionyl Chloride in Pyridine.—Treatment of the cyclic carbonate 3-ketal (100 mg) in cold pyridine (1.5 ml) with thionyl chloride (0.1 ml) was carried out for 15 min at 5°. The reaction mixture was processed in the usual fashion and the crude product was chromatographed on a silica gel column (system 4). The initial band afforded **20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-dien-3-one ethylene ketal (17)** as needles from ethyl acetate (29 mg, mp 207–209°; 9 mg, mp 205–207°) in a yield of 40%; $[\alpha]_D$ −51.8°; ν_{max} 1825, 1731 (trans $\Delta^{17,20}$-cyclic carbonate), 1115 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.78; H, 7.93.

Later fractions contained a BT-negative by-product which crystallized from ethyl acetate (22 mg, mp 231–233°; 3 mg, 227–229°) in a yield of 24% (*vide infra*).

Reaction of 20β,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13b) with Thionyl Chloride in Pyridine.—Dehydration of the cyclic carbonate 3-ketal (100 mg) and silica gel chromatography of the product was performed as in the reaction of **13a**.

The mobile component, **20,21-cyclocarbonyldioxypregna-5,*cis*-17(20)-dien-3-one ethylene ketal (18)**, was obtained as needles from ethyl acetate (46 mg, mp 225–225.5°) in a yield of 48%: $[\alpha]_D$ −21.1°; ν_{max} 1830 (1810), 1739 (cis $\Delta^{17,20}$-cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.75; H, 7.89.

A BT-negative, less mobile by-product was recovered as needles from ethyl acetate (17.5 mg, mp 263–263.5°) in a yield of 18% (*vide infra*).

3 from 17.—Deketalization of 20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-dien-3-one ethylene ketal (20 mg) in acetone–*p*-TSA for 19 hr and crystallization of the product from ethyl acetate gave 14.2 mg of prisms, mp 242–253°. A mixture melting point with the least mobile dehydrohalogenation product from **1a,b** was 251.5–252.5° and their ir spectra were identical.

4 from 18.—Treatment of 20,21-cyclocarbonyldioxypregna-5,-*cis*-17(20)-dien-3-one ethylene ketal (20 mg) with acetone–*p*-TSA for 17.5 hr and crystallization from ethyl acetate afforded 14.0 mg of prisms, mp 197.5–199.5°. A mixture melting point with the intermediate dehydrohalogenation product from **1a,b** was 197–198.5° and their ir spectra were identical.

Sequential Reaction of 11-Dehydrocorticosterone with Phosgene and Sodium Iodide–Acetone–Triethylamine.—The crude product from phosgenation of the α-ketol (1.72 g, 5 mmol) under condition B was dehydrohalogenated as in the sequential reactions of 11-deoxycorticosterone described previously. The final reaction mixture was chromatographed on a silica gel column (system 3). The contents of the first band (0.5 g, 21%) could not be crystallized, but the Beilstein-positive compound was identified as **21-iodopregn-4-ene-3,11,20-trione** through its conversion with zinc (700 mg) in acetic acid (12 ml) to 300 mg of prisms (methanol), mp 176–178°, whose ir spectrum was identical with that of **11-ketoprogesterone**.

20,21-Cyclocarbonyldioxypregna-4,*trans*-17(20)-diene-3,11-dione (21).—The next band afforded prisms from ethyl acetate (59 mg, mp 255–257°; 4 mg, 250–254°) in a yield of 3.4%: $[\alpha]_D$ +157°; λ_{max} 238 mμ (ε 15,600); ν_{max} 1820, 1728 cm^{-1} (trans $\Delta^{17,20}$-cyclic carbonate).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.20; H, 7.15.

20,21-Cyclocarbonyldioxypregna-4,20(21)-diene-3,11-dione (20).—Succeeding fractions furnished 35 mg (2.0%) of prisms from ethyl acetate: mp 227–228°; [α] +204°; λ_{max} 238 mμ (ε 16,150); ν_{max} 3180, 1839 (1810) cm^{-1} ($\Delta^{20,21}$-cyclic carbonate).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.43; H, 7.09.

20,21-Cyclocarbonyldioxypregna-4,*cis*-17(20)-diene-3,11-dione (22).—The least mobile component crystallized as needles from ethyl acetate (367 mg, mp 193–195°; 26 mg, mp 189–192°) in a yield of 16.7%: $[\alpha]_D$ +189°; λ_{max} 238 mμ (ε 16,000); ν_{max} 1830 (1810), 1738 cm^{-1} (cis $\Delta^{17,20}$-cyclic carbonate).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.27; H, 7.12.

20α,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24a) from 23a.—Direct ketalization of 20α,21-cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione[14] (2.4 g) for 8 hr by the usual procedure and crystallization from methanol gave needles (1.95 g, mp 248.5–250°; 0.20 g, mp 238–240°) in a yield of 81%: $[\alpha]_D$ −40.0°; ν_{max} 3530 (hydroxyl), 1810 (1785), 776 (cyclic carbonate), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.68; H, 7.29.

20β,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24b) from 23b.—Ketalization of 20β,21-cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione[14] (2.4 g) for 8 hr followed by silica gel column chromatography in system 5 gave a total of 2.16 g (82%) as needles from methylene chloride–methanol: mp 291–293°; $[\alpha]_D$ −48.8°; ν_{max} 3460 (hydroxyl), 1790, 774 (cyclic carbonate), 1092 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.23; H, 7.65.

Reaction of 20α,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24a) with Thionyl Chloride in Pyridine.—Treatment of the cyclic carbonate 3-ketal (300 mg) in pyridine (4.5 ml) with thionyl chloride (0.3 ml) for 15 min at 5° and silica gel column chromatography in system 6 afforded **20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-diene-3,11-dione 3-ethylene ketal (25)** as prisms from ethyl acetate (132 mg, mp 220–224°; 26 mg, mp 218–221°) in a yield of 55%: $[\alpha]_D$ −57.5°; ν_{max} 1830, 1732 (trans $\Delta^{17,20}$-cyclic carbonate), 1110 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.54; H, 7.14.

A less mobile, BT-negative by-product was also recovered as needles from ethyl acetate (49 mg, mp 249–251°; 6 mg, mp 242–244°) in a yield of 19% (*vide infra*).

Reaction of 20β,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24b) with Thionyl Chloride in Pyridine.—Dehydration of the cyclic carbonate 3-ketal (300 mg) followed by silica gel column chromatography as in the preparation of **25** furnished **20,21-cyclocarbonyldioxypregna-5,*cis*-17(20)-diene-3,11-dione 3-ethylene ketal (26)** as leaflets from ethyl acetate–*n*-hexane (166 mg, mp 161.5–163°; 11 mg, mp 159–160°) in a yield of 62%: $[\alpha]_D$ −34.0°; ν_{max} 1829 (1810), 1739 (cis $\Delta^{17,20}$-cyclic carbonate), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.80; H, 7.43.

A less mobile, BT-positive by-product was also obtained as needles from ethyl acetate (31 mg, mp 277–278°; 17 mg, mp 267–270°). This material was not further characterized.

21 from 25.—Deketalization of 20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-diene-3,11-dione 3-ethylene ketal (25 mg) in acetone–*p*-TSA and crystallization of the product from acetone gave 18 mg (80%) of prisms, mp 256–260°. A mixture melting point with the most mobile dehydrohalogenation product from **19a,b** was 250–254° and their ir spectra were identical.

22 from 26.—Treatment of 20,21-cyclocarbonyldioxypregna-5,-*cis*-17(20)diene-3,11-dione 3-ethylene ketal (25 mg) with acetone–*p*-TSA afforded 18 mg (80%) of needles, mp 188.5–190.5°. A mixture melting point with the most polar dehydrohalogenation product from **19a,b** was 189.5–191.5° and their ir spectra were identical.

3-Ethylenedioxypregn-5-ene-17,20α,21-triol 20,21-Diacetate (27a) from 11a.—Acetylation of 3-ethylenedioxypregn-5-ene-17,20α,21-triol (790 mg) in the usual fashion and crystallization from methanol supplied platelets (680 mg, mp 219–222°; 180 mg, mp 220–222°) in a yield of 90%: $[\alpha]_D$ −72.7°; ν_{max} 3450 (hydroxyl), 1740, 1240 (acetate), 1110 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.02; H, 8.40.

3-Ethylenedioxypregn-5-ene-17,20β,21-triol 20,21-Diacetate (27b) from 11b.—Acetylation of 3-ethylenedioxypregn-5-ene-17,20β,21-triol (500 mg) and crystallization of the product from ethyl acetate gave prisms (450 mg, mp 200–202°; 70 mg, mp, 198–200°) in a yield of 95%: $[\alpha]_D$ +11.8°; ν_{max} 3580 (hydroxyl), 1740, 1240 (acetate), 1112 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.91; H, 8.51.

3-Ethylenedioxypregna-5,16-diene-20α,21-diol Diacetate (28a) from 27a.—Reaction of 3-ethylenedioxypregn-5-ene-17,20α,21-triol 20,21-diacetate (800 mg) in pyridine (12 ml) with thionyl chloride (0.8 ml) was carried out for 15 min at 5°. Crystallization of the product from methanol gave 380 mg of platelets: mp 149–151°; $[\alpha]_D$ −76.2°; ν_{max} 1738, 1240 (acetate), 1670 (Δ^5), 1632 (Δ^{16}), 1099 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.92; H, 8.44.

The mother liquor was chromatographed on a silica gel column in system 8, affording an additional 60 mg of **28a**, mp 146–148°, and raising the yield of 57%. From later fractions was recovered an amorphous, BT-negative by-product (280 mg) which after deketalization in acetone–*p*-TSA and crystallization from aqueous methanol gave 144 mg of needles, mp 97–100°. Since microanalysis showed a close fit for a diacetate with the empirical formula $C_{25}H_{34}O_5$ (*Anal.* Calcd: C, 72.43; H, 8.27; CH_3CO, 20.77. Found: C, 73.08; H, 8.13; CH_3CO, 19.98.), the less mobile companion is tentatively formulated as an isomeric Wagner–Meerwein rearrangement product.

3-Ethylenedioxypregna-5,16-diene-20β,21-diol Diacetate (28b) from 27b.—Dehydration of 3-ethylenedioxypregn-5-ene-17,20β,-21-triol 20,21-diacetate (1.0 g) as in the preparation of **28a** and crystallization of the product from *n*-hexane furnished 570 mg of prisms: mp 126–127°; $[\alpha]_D$ +3.54°; ν_{max} 1740, 1240 (acetate), 1670 (Δ^5), 1622 (Δ^{16}), 1090 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.52; H, 8.24.

Silica gel column chromatography of the mother liquor afforded an additional 130 mg of **28b**, mp 125–126°, raising the yield to

73%. A more polar, amorphous, BT-negative by-product (220 mg) was also recovered but was not examined further.

3-Ethylenedioxypregna-5,16-diene-20α,21-diol (29a) from 28a.—To a solution of 3-ethylenedioxypregna-5,16-diene-20α,21-diol diacetate (300 mg) in methanol (40 ml) was added 5 ml of 0.1 *N* methanolic sodium hydroxide. After 30 min at room temperature the reaction mixture was added to methylene chloride (300 ml) and the solution was washed with water. The crude product crystallized from ethyl acetate as platelets (176 mg, mp 215–217°; 41 mg, mp 212–213°) in a yield of 89%: $[\alpha]_D$ −71.7°; ν_{max} 3340 (hydroxyl), 1672 (Δ^5), 1625 (Δ^{16}), 1096 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.65; H, 9.14.

3-Ethylenedioxypregna-5,16-diene-20β,21-diol (29b) from 28b.—Saponification of 3-ethylenedioxypregna-5,16-diene-20β,21-diol diacetate (500 mg) in a mixture of methylene chloride (5 ml) and methanol (50 ml) with 0.1 *N* methanolic sodium hydroxide (5 ml) was carried out for 1 hr as in the preparation of **29a**. The product crystallized from ethyl acetate as platelets (327 mg, mp 198–200°; 41 mg, mp 194.5–197°) in a yield of 90%: $[\alpha]_D$ −42.3°; ν_{max} 3520 (hydroxyl), 1672 (Δ^5), 1621 (Δ^{16}), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.98; H, 9.24.

3-Ethylenedioxypregna-5,16-diene-20α,21-diol 21-Cathylate (30a) from 29a.—To a solution of 3-ethylenedioxypregna-5,16-diene-20α,21-diol (150 mg) in pyridine (1.5 ml) was added 50 μl of ethyl chlorocarbonate. After 19 hr at 5° the reaction mixture was chromatographed on a silica gel column (system 1). The major product was recovered as long needles from ethyl acetate–*n*-hexane (83 mg, mp 131–133°; 13 mg, mp 126–128°) in a yield of 54%: $[\alpha]_D$ −65.9°; ν_{max} 3520 (hydroxyl), 1741, 1270, and 792 (cathylate), 1096 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.87; H, 8.58.

3-Ethylenedioxypregna-5,16-diene-20β,21-diol 21-Cathylate (30b) from 29b.—Cathylation of 3-ethylenedioxypregna-5,16-diene-20β,21-diol (300 mg) in pyridine (3 ml) with ethyl chlorocarbonate (110 μl) proceeded for 19 hr at 5°. The major product, recovered as in the preparation of **30a**, crystallized as needles from ethyl acetate–*n*-hexane (205 mg, mp 163.5–165°; 3 mg, mp 159–162°) in a yield of 58%: $[\alpha]_D$ −29.6°; ν_{max} 3500 (hydroxyl), 1749 (1725), 1270 and 792 (cathylate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.13; H, 8.67.

20α,21-Cyclocarbonyldioxypregna-5,16-dien-3-one Ethylene Ketal (31a) from 30a.—Cyclization of 3-ethylenedioxypregna-5,16-diene-20α,21-diol 21-cathylate (25 mg) in methanol (3.8 ml) with 0.1 *N* methanolic sodium hydroxide (0.2 ml) for 5 min at room temperature and crystallization of the product from ethyl acetate gave 19.5 mg (87%) of needles: mp 230–233°; $[\alpha]_D$ −54.9°; ν_{max} 1800, 775 (cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.87; H, 8.18.

A mixture melting point with the minor dehydration product from **13a** showed no depression and their ir spectra were identical.

20β,21-Cyclocarbonyldioxypregna-5,16-dien-3-one Ethylene Ketal (31b) from 30b.—Cyclization of 3-ethylenedioxypregna-5,16-diene-20β,21-diol 21-cathylate (25 mg) as in the reaction of **30a** furnished 19.2 mg (86%) of needles from ethyl acetate: mp 262–264°; $[\alpha]_D$ −76.9°; ν_{max} 1794, 775 (cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.86; H, 7.92.

A mixture melting point with the minor dehydration product from **13b** was 263–264° and their ir spectra were identical.

21-*O*-Carboethoxypregna-5,16-diene-3,20-dione 3-Ethylene Ketal (32) from 30a.—Oxidation of 3-ethylenedioxypregna-5,16-diene-20α,21-diol 21-cathylate (25 mg) with chromic anhydride–pyridine by the usual procedure and crystallization of the product from ethyl acetate–*n*-hexane gave plates (13.1 mg, mp 173–175°; 7 mg, mp 170.5–172.5°) in a yield of 82%: $[\alpha]_D$ −19.8°; λ_{max} 240 mμ (ε 9000); ν_{max} 1751, 1265, and 794 (cathylate), 1679, 1588 (Δ^{16}-20-ketone), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.22.

32 from 30b.—Oxidation of 3-ethylenedioxypregna-5,16-diene-20β,21-diol 21-cathylate (100 mg) as in the reaction of **30a** furnished plates from ethyl acetate–*n*-hexane (65 mg, mp 173–175°; 21 mg, mp 166–168°) in a yield of 87%. The ir spectrum was indistinguishable from that of the chromic anhydride–pyridine product from **30a**.

21-Acetoxypregna-5,16-diene-3,20-dione 3-Ethylene Ketal (33) from 32.—To a solution of 21-*O*-carboethoxypregna-5,16-diene-3,20-dione 3-ethylene ketal (20 mg) in methanol (3 ml) was added 0.2 ml of 5% aqueous sodium bicarbonate. After 2 hr at room temperature the product was recovered by extraction with methylene chloride and treated with acetic anhydride–pyridine. The final product crystallized from acetone–*n*-hexane as rosettes (10.3 mg, mp 164–167°): $[\alpha]_D$ −19.9°; λ_{max} 240 mμ (ε 9200); λ_{max} 1750, 1240 (acetate), 1681, 1588 (Δ^{16}-20-ketone), 1097 cm^{-1} (ketal) [lit.[20] mp 190–192°; $[\alpha]_D$ −23°; λ_{max} 239.5 mμ (ε 8800)]. The ir spectrum was identical with that of a sample of **33** prepared by ketalization of **21-acetoxypregna-4,16-diene-3,20-dione**.[20]

17,20α,21-Trihydroxypregna-5-ene-3,11-dione 3-Ethylene Ketal (34a) from 24a.—Saponification of 20α,21-cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (2 g) in methanol (500 ml) with 0.2 *N* sodium hydroxide (50 ml) for 21 hr at room temperature and crystallization of the product from methanol gave needles (1.53 g, mp 200–201.5°; 0.19 g, mp 199–201°) in a yield of 92%: $[\alpha]_D$ −27.0°; ν_{max} 3430 (hydroxyl), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.03; H, 8.38.

20α,21-Diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (35a) from 34a.—Treatment of 17,20α,21-trihydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.72 g) with 2 ml each of pyridine and acetic anhydride for several hours at room temperature and crystallization of the product from methylene chloride–ethyl acetate gave platelets (1.6 g, mp 250–253°; 0.13 g, mp 248–251°) in a yield of 92%: $[\alpha]_D$ −30.6°; λ_{max} 3460 (hydroxyl), 1742, 1240 (acetate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.94; H, 7.75.

17,20β,21-Trihydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (34b) from 24b.—Saponification of 20β,21-cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (2.0 g) as in the preparation of **34a** and crystallization of the product from benzene gave prisms (1.20 g, mp 184–186°; 0.43 g, mp 182.5–184°) in a yield of 87%: $[\alpha]_D$ −20.8°; ν_{max} 3450 (hydroxyl), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_6 \cdot 0.5H_2O$: C, 66.48; H, 8.49. Found: C, 66.03; H, 7.95.

20β,21-Diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (35b) from 34b.—Acetylation of 17,20β,21-trihydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.0 g) in the usual fashion gave prisms from methanol (1.2 g, mp 261–263°) in a yield of 100%: $[\alpha]_D$ +22.8°; ν_{max} 3570 (hydroxyl), 1744, 1240 (acetate), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.96; H, 7.60.

20α,21-Diacetoxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (36a) from 35a.—Dehydration of 20α,21-diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.0 g) in pyridine (15 ml) with thionyl chloride (1 ml) for 15 min at 5° and crystallization of the product from *n*-hexane afforded needles (720 mg, mp 123.5–124.5°; 30 mg, mp 121.5–123°) in a yield of 78%: $[\alpha]_D$ −43.5°; ν_{max} 1745, 1230 (acetate), 1670 (Δ^5), 1635 (Δ^{16}), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.77; H, 7.72.

20α,21-Dihydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (37a) from 36.—Saponification of 20α,21-diacetoxypregna-5,16-diene-3,11-dione 3-ethylene ketal (500 mg) with methanolic sodium hydroxide as in the preparation of **29a** and crystallization of the product from ethyl acetate furnished platelets (310 mg, mp 176–178°; 59 mg, mp 173–176°) in a yield of 90%: $[\alpha]_D$ −33.5°; ν_{max} 3400 (hydroxyl), 1670 (Δ^5), 1626 (Δ^{16}), 1094 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.26; H, 8.23.

20β,21-Dihydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (37b) from 35b.—Dehydration of 20β,21-diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.0 g) as in the preparation of **36a** followed by tlc analysis of the reaction mixture in system 3 showed a major BT-negative product (R_f 0.20) and a minor BT-positive product (R_f 0.17). Saponification of the

mixture in methanolic sodium hydroxide and crystallization from ethyl acetate gave the glycol **37b** as needles (550 mg, mp 185.5–188°; 75 mg, mp 184–186°) in a yield of 79%: $[\alpha]_D$ −5.42; ν_{max} 3440 (hydroxyl), 1670 (Δ^5), 1625 (Δ^{16}), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.04; H, 8.32.

The mother liquor was treated with acetic anhydride–pyridine and the reaction mixture was chromatographed on a silica gel column in system 3. The most mobile component, **20β,21-diacetoxypregna-5,16-diene-3,11-dione 3-ethylene ketal (36b)**, was recovered as prisms from *n*-hexane (48 mg, mp 116–117°): $[\alpha]_D$ +25.4°; ν_{max} 1740, 1230 (acetate), 1670 (Δ^5), 1622 (Δ^{16}), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.53; H, 7.54.

The least mobile component, **21-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal**,[22] was obtained as needles from acetone (70 mg, mp 185–186.5°) in a yield of 8%: $[\alpha]_D$ +58.6°; ν_{max} 1751, 1230 (acetate), 1731 (20-ketone), 1672 (Δ^5), 1099 cm^{-1} (ketal) [lit.[22] mp 193.5–194°; $[\alpha]^{25}D$ +52°; λ_{max} 5.71, 5.77, 5.86 μ]. The generation of this by-product *via* saponification and acetylation reflects the extent to which $\Delta^{17,20}$ dehydration occurs in the diacetate **35b**.

21-Acetoxypregna-5,16-diene-3,11,20-trione 3-Ethylene Ketal (38) from 37a.—To a solution of 20α,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (100 mg) in *tert*-butyl alcohol (7 ml) was added an equal weight of DDQ. After 95 hr at room temperature the reaction mixture was added to methylene chloride (50 ml) and the solution was washed successively with cold, dilute sodium hydroxide and water. The crude product was treated with acetic anhydride–pyridine and the resulting mixture was chromatographed on a silica gel column (system 6). The initial band gave 14.3 mg of starting material as the diacetate **36a**; from later fractions was obtained the Δ^{16}-α-ketol acetate **38** as prisms from ether (26 mg, mp 159–160°). The ir spectrum was indistinguishable from that of a reference sample[20] of **38**.

38 from 37b.—Sequential allylic oxidation and acetylation of 20β,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (110 mg) followed by silica gel chromatography as in the preparation of **38** from **37a** gave 46 mg of the diacetate **36b** and 6.8 mg of the Δ^{16}-α-ketol acetate **38**, mp 155–157°, as confirmed by ir spectroscopy.

21-*O*-Carboethoxy-20α-hydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (39a) from 37a.—Cathylation of 20α,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (300 mg) in pyridine (3 ml) with ethyl chlorocarbonate (120 μl) for 19 hr at 5° was followed by silica gel column chromatography in system 7. The first fraction crystallized from ethanol as platelets (72 mg, mp 144.5–145°; 2 mg, mp 139–142°) in a yield of 18%. Because ir analysis of this mobile by-product showed no hydroxyl and intensification of the cathylate bands, it is designated as **20α,21-di-*O*-carboethoxypregna-5,16-diene-3,11-dione 3-ethylene ketal**: $[\alpha]_D$ −38.1°; ν_{max} 1750, 1275, and 792 (cathylate), 1668 (Δ^5), 1631 (Δ^{16}), 1092 cm^{-1} (ketal).

Anal. Calcd for $C_{29}H_{40}O_9$: C, 65.39; H, 7.57. Found: C, 65.24; H, 7.71.

The 21-cathylate **39a** emerged in later fractions and crystallized from ethanol–ether as needles (193 mg, mp 123–125°) in a yield of 54%: $[\alpha]_D$ −34.4°; ν_{max} 3530 (hydroxyl), 1742, 1265, and 790 (cathylate), 1675 (Δ^5), 1628 (Δ^{16}), 1092 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.90; H, 8.01.

The residue from the least mobile fraction furnished a second by-product as needles from aqueous ethanol (26 mg, mp 119–122°) in a yield of 7%. The presence of both hydroxyl and cathylate bands in its ir spectrum served to identify it as **20α-*O*-carboethoxy-21-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal**. However, since a moderate carbonyl band at 1810 cm^{-1} was also present (indicating that partial cyclization had occurred during manipulation), this product was not further characterized.

21-*O*-Carboethoxy-20β-hydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (39b) from 37b.—Cathylation of 20β,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (200 mg) in pyridine (2 ml) with ethyl chlorocarbonate (80 μl) as in the preparation of **39a** and two crystallizations of the product from ether gave needles (134 mg, mp 154–156°): $[\alpha]_D$ −10.6°; ν_{max} 3440 (hydroxyl), 1739, 1265, and 792 (cathylate), 1671 (Δ^5), 1629 (Δ^{16}), 1090 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.84; H, 7.86.

The mother liquor was chromatographed on a silica gel column (system 6). A mobile, minor dicathylate fraction was discarded; subsequent fractions afforded an additional 43 mg of the 21-cathylate **39b**, mp 157–160°, raising the yield to 75%.

20α,21-Cyclocarbonyldioxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (42a) from 39a.—Treatment of 21-*O*-carboethoxy-20α-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) with methanolic sodium hydroxide as in the synthesis of **31a** and crystallization of the product from ethyl acetate gave needles (11.7 mg, mp 248–250°; 6.7 mg, mp 243–248°) in a yield of 82%: $[\alpha]_D$ −15.8°; ν_{max} 1795, 772 (cyclic carbonate), 1670 (Δ^5), 1625 (Δ^{16}), 1096 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.54; H, 7.11.

A mixture melting point with the minor dehydration product from **24a** and 248–250° and their ir spectra were identical.

20β,21-Cyclocarbonyldioxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (42b) from 39b.—Cyclization of 21-*O*-carboethoxy-20β-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) as in the reaction of **39a** and crystallization of the product from ethyl acetate furnished 19.3 mg (86%) of platelets: mp 234–237°; $[\alpha]_D$ −79.0°; ν_{max} 1790, 770 (cyclic carbonate), 1675 (Δ^5), 1627 (Δ^{16}), 1090 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.39; H, 7.10.

21-*O*-Carboethoxypregna-5,16-diene-3,11,20-trione 3-Ethylene Ketal (40) from 39a.—Oxidation of 21-*O*-carboethoxy-20α-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) in pyridine (3 ml) with an equal weight of chromic anhydride for 17 hr and crystallization of the product from ether gave 22 mg (88%) of needles: mp 137–139°; $[\alpha]_D$ −6.20°; λ_{max} 236 mμ (ε 9450); ν_{max} 1752, 1265, and 792 (cathylate), 1695, 1591 (Δ^{16}-20-ketone), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 67.93; H, 7.58.

40 from 39b.—Oxidation of 21-*O*-carboethoxy-20β-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) with pyridine–chromic anhydride as in the reaction of **39a** and crystallization from ether afforded 20 mg of needles, mp 135–137°, in a yield of 80%. The ir spectrum was identical with that of **40** prepared from **39a**.

21-*O*-Carboethoxypregna-4,16-diene-3,11,20-trione (41) from 40.—To a solution of 21-*O*-carboethoxypregna-5,16-diene-3,11,20-trione 3-ethylene ketal (15 mg) in acetone (10 ml) was added 5 mg of *p*-TSA. After 18 hr the product was recovered and crystallized from ethanol as prisms (11.8 mg, mp 157–169°). A mixture melting point with the cathylation product from 21-hydroxypregna-4,16-diene-3,11,20-trione[2] showed no depression and their ir spectra were identical.

Registry No.—**1a**, 39703-91-8; **1b**, 39703-92-9; **2**, 39703-93-0; **3**, 39703-94-1; **4**, 39703-95-2; **5a**, 39703-96-3; **5b**, 39703-97-4; **6b**, 39703-98-5; **7b**, 39703-99-6; **8**, 39704-00-2; **9a**, 39704-01-3; **9b**, 39704-02-4; **10a**, 39704-03-5; **10b**, 39704-04-6; **11a**, 39704-05-7; **11b**, 39704-06-8; **12b**, 39704-07-9; **13a**, 39704-08-0; **13b**, 39704-09-1; **14a**, 39704-10-4; **14b**, 39704-11-5; **15b**, 39704-12-6; **16b**, 39704-13-7; **17**, 39704-14-8; **18**, 39704-15-9; **19a**, 39704-17-1; **20**, 39704-18-2; **21**, 39704-19-3; **22**, 39704-20-6; **23a**, 33487-68-2; **23b**, 33487-69-3; **24a**, 39704-22-8; **24b**, 39704-23-9; **25**, 39704-24-0; **26**, 39704-25-1; **27a**, 39704-26-2; **27b**, 39704-27-3; **28a**, 39704-28-4; **28b**, 39703-39-4; **29a**, 39703-40-7; **29b**, 39703-41-8; **30a**, 39703-42-9; **30b**, 39703-43-0; **31a**, 39703-44-1; **31b**, 39703-45-2; **32**, 39703-46-3; **34a**, 39703-47-4; **34b**, 39703-48-5; **35a**, 39703-49-6; **35b**, 39703-50-9; **36a**, 39703-51-0; **36b**, 39703-52-1; **37a**, 39703-53-2; **37b**, 39703-54-3; **38**, 39703-55-4; **39a**, 39703-56-5; **39b**, 39703-57-6; **40**,

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39703-58-7; **41**, 39703-59-8; **42a**, 39703-60-1; **42b**, 39703-61-2; phosgene, 75-44-5; sodium iodide, 7681-82-5; acetone, 67-64-1; triethylamine, 121-44-8; 21-iodopregn-4-ene-3,20-dione, 20576-46-9; 11-deoxycorticosterone, 64-85-7; 20β-21-dihydroxypregn-4-en-3-one, 298-35-1; 20α,21-dihydroxypregn-4-en-3-one, 26437-06-9; 20β,21-dihydroxypregn-4-en-3-one 20-acetate, 7676-48-4; 11-deoxycortisol, 152-58-9; 11-deoxycortisol 21-acetate 3-ethyleneketal, 39703-66-7; thionyl chloride, 7719-09-7; 21-iodopregn-4-ene-3,11,20-trione, 39703-67-8; 21-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal, 39703-68-9; 20α,21-di-*O*-carboethoxypregna-5,16-diene-3,11-dione 3-ethylene ketal, 39703-69-0; 20α-*O*-carboethoxy-21-hydroxypregna-5,16-diene-3,-11-dione 3-ethylene ketal, 39703-70-3; 17,20β,21-trihydroxypregn-4-en-3-one 21-acetate, 39703-74-7.

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The Reformatsky Reaction of Ethyl α-Bromo Esters with Bis(chloromethyl) Ether

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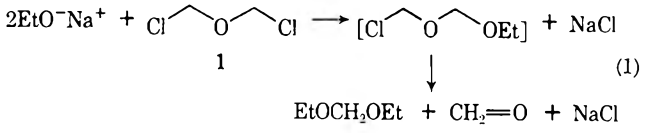
The Reformatsky reaction of ethyl α-bromoisobutyrate and several other α-bromo esters with bis(chloromethyl) ether has been studied to develop a synthetic procedure for the synthesis of α,α'-substituted dimethyl ethers. Using the techniques developed, the dineopentyl-substituted ether **7a** was synthesized in 66% yield. Less substituted ethers **7b** and **7c** were isolated in smaller yields. The side products of these reactions were isolated and characterized by spectra and alternate syntheses. A dual radical–ionic mechanism is postulated to account for the products observed. An interesting synthesis of **4a** *via* a β-lactone intermediate from β-chloropivalic acid is given.

Recently we reported[1] a new approach to the synthesis of dineopentyl ethers involving the reaction of 2 equiv of anion,[2] in our case Reformatsky reagents, with bis(chloromethyl) ether[3] (**1**). We would now like to report our complete results, including the reactions of ethyl α-bromoisobutyrate, ethyl α-bromopropionate, ethyl α-bromoacetate, and α,α'-dibromoisopropyl ketone with chloromethyl ether **1** and zinc.

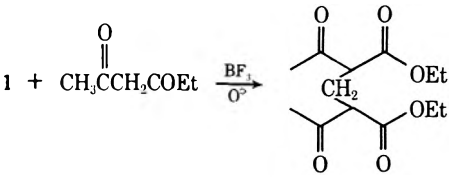
The first attempted dialkylation using chloromethyl ether **1** was reported in 1922 and involved the reaction of sodium ethoxide with the chloromethyl ether.[4] The desired diethoxy diadduct was not obtained but rather formaldehyde diethyl acetal and formaldehyde were isolated (eq 1).



(1)

In 1945 a second unsuccessful attempt at using chloromethyl ether **1** as a dialkylating agent was reported. In this case the enol of ethyl acetylacetate was to displace the bischlorides with the help of a Lewis acid catalyst.[5] This reaction, however, gave a methylene dimer of starting material (eq 2).

While bis(chloromethyl) ether and many monochloromethyl ethers have been employed as monoalkylating agents successfully,[6] it was not until our studies[1] and that reported by Gash[2] that successful didisplacements on bis(chloromethyl) ether were realized. The product studies reported here and recent mechanistic studies on the thermal[7] and metal-catalyzed[8] decomposition of chloromethyl ethers help to explain the earlier failures and the synthetic limits of this potentially useful type of dialkylation reaction, particularly in the synthesis of hindered ethers.



(2)

Results

Our initial studies were concerned with the reactions of ethyl α-bromoisobutyrate and various metals such as zinc and magnesium with chloro ether **1**. Several solvents were employed, including dry ether, glyme, and tetrahydrofuran (THF). Optimum conditions for maximum yield of the desired diadduct, ether diester **7a**, were found to include prior formation of the Reformatsky reagent at a low temperature (10°) in rigorously dried and N_2-degassed glyme (ether worked almost as well as glyme; however, THF gave a multi-

(1) (a) J. Zitsman and P. Y. Johnson, *Tetrahedron Lett.*, 4201 (1972); (b) Presented in part at the Seventh Middle Atlantic Regional Meeting of the American Chemical Society, Feb 14, 1972.

(2) Since that time a second successful dialkylation using bis(chloromethyl) ether and diethyl methylmalonate anion has been reported. See V. W. Gash, *J. Org. Chem.*, **37**, 2197 (1972).

(3) Chloromethyl ether **1** is a proven carcinogenic material and should be handled with care. See S. Laskin, *et al.*, *Arch. Environ. Health*, **23**, 135 (1971), for a report of its toxic properties. We wish to thank J. A. Vida for bringing this article to our attention.

(4) A. W. Dox and L. Yoder, *J. Amer. Chem. Soc.*, **44**, 649 (1922).

(5) R. Levine and C. H. Houser, *J. Amer. Chem. Soc.*, **67**, 2050 (1945).

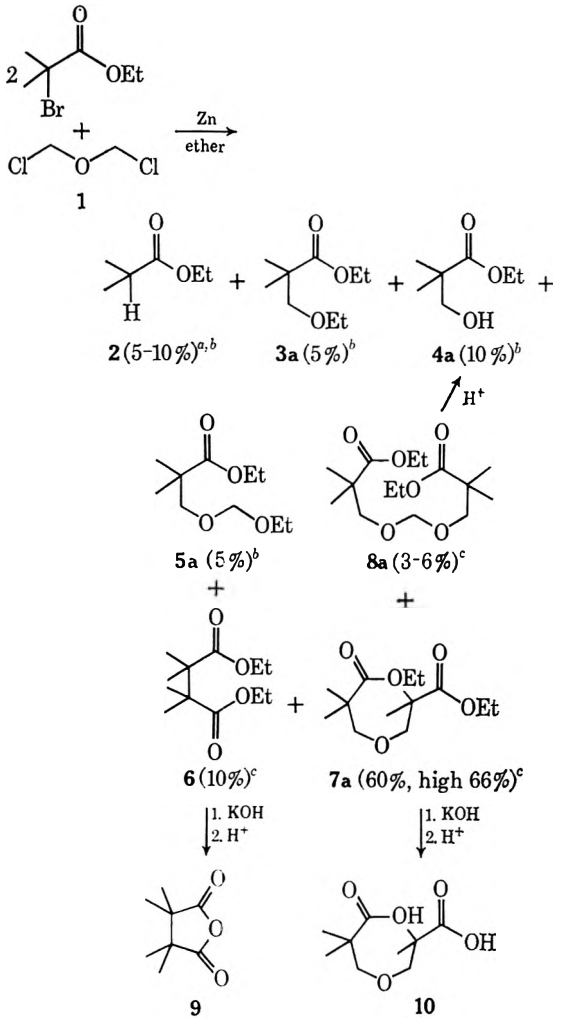
(6) (a) I. I. Lapkin and P. A. Lekseeva, *Zh. Org. Khim.*, **2**, 393 (1966); (b) I. I. Lapkin and F. G. Saitkulova, *ibid.*, **6**, 450 (1970); (c) I. I. Lapkin and L. S. Kozlova, *ibid.*, **6**, 453 (1970); (d) M. Jacobson, *et al.*, *J. Med. Chem.*, **14**, 236 (1971); (e) H. Bohme and P. H. Meyer, *Synthesis*, **3**, 150 (1971); (f) E. Vilsmaier and B. Hloch, *ibid.*, **11**, 590 (1971); (g) S. Nunomoto, M. Shinohara, and Y. Yamashita, *J. Chem. Soc. Jap.*, 1263 (1972); (h) J. Hayami, *et al.*, *Bull. Chem. Soc. Jap.*, **44**, 3091 (1971).

(7) (a) I. A. Kaye and R. S. Jaret, *J. Chem. Eng. Data*, **16**, 485 (1971); (b) K. Moedritzer and J. R. Van Wazer, *J. Org. Chem.*, **30**, 3920 (1965).

(8) (a) A. Z. Shikhmamedbekova and R. A. Sultanov, *Zh. Obshch. Khim.*, **40**, 77 (1970); (b) I. I. Lapkin and N. N. Pavlova, *Zh. Org. Khim.*, **4**, 803 (1968).

tude of products). Pretreating[9] the powdered zinc did not seem to affect the reaction but an excess of zinc beyond the 2 equiv required tended to lower the yield of diester **7a**. The fresh bis(chloromethyl) ether was added to the reaction mixture, which was stirred at 10° in the dark. After being allowed to react at 10° for 1 hr the mixture was warmed to 25° and finally heated at 50° for 1 hr. Under these conditions diester **7a** could be obtained in 66% yield. The products, which were isolated by careful distillation from the reaction after work-up, are shown in Chart I.

CHART I[d]

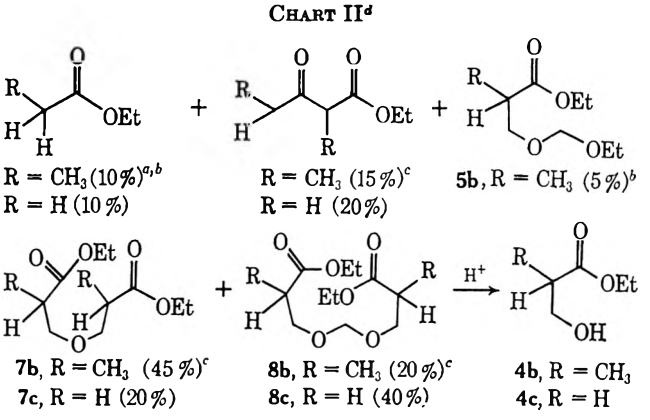


[a] Yields given are averages of several runs ranging from 0.2 to 0.4 mol scale. [b] Based on 1 equiv. [c] Based on 2 equiv. [d] Yields in these reactions were fairly consistent.

Conveniently, diester **7a** could be obtained nearly pure by precipitation of the zinc halide complex from the crude reaction mixture by addition of hexane to the reaction mixture[9,10] (see Experimental Section). Diester **7a** could also be separated from the crude oil obtained after normal work-up by addition of $ZnCl_2$ to an ether solution of the oil followed by precipitation of the formed complex with hexane and subsequent work-up of it. The presence of water greatly decreased the yield of diester **7a** and increased the yields of alcohol **4a** and its acetal **8a**.

Similar reactions with ethyl α-bromopropionate and ethyl α-bromoacetate gave lower yields of the desired ether diesters **7b** and **7c** and greatly increased yields of the acetals **8b** and **8c**. The lack of alcohols **4b** and **4c** is accounted for by the increased yield of acetals **8b** and **8c**.[7a] Coupled products observed in these reactions were not the α,α′ type, **6**, noticed in the isobutyrate case, but rather normal ester condensation products.[9] Ethyl α-chloroacetate did not form a Reformatsky reagent at 0–10° in our hands.[11] The products isolated from the above reactions are shown in Chart II.

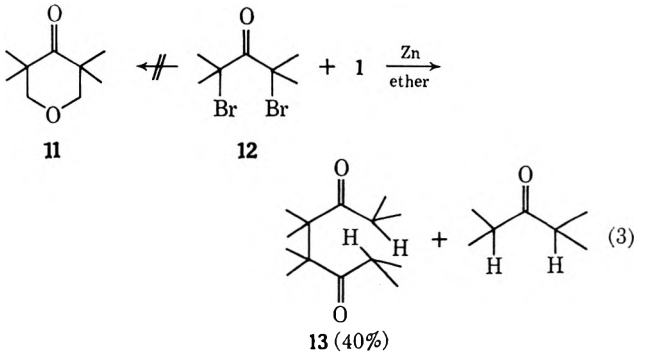
CHART II[d]



[a] Yields given are averages of several runs ranging from 0.1 to 0.4 mol scale. [b] Based on 1 equiv. [c] Based on 2 equiv. [d] Yields varied ±10% for major products with different runs.

Inverse or simultaneous addition of reagents in order to prevent ester condensation of these more reactive halo esters was not advantageous because of the decomposition of bis(chloromethyl) ether in the presence of zinc metal.[8b] The use of magnesium instead of zinc offered no advantages and greatly increased the amount of reduced and Claisen-type products.

Finally, attempts to make 3,3,5,5-tetramethyl-1-oxacyclohexan-4-one (**11**) by reaction of α,α′-dibromoisopropyl ketone (**12**) and chloromethyl ether **1** in the presence of zinc gave instead the monocoupled diketone **13** as the major product. Isopropyl ketone was also observed but not isolated for yield (eq 3).



(3)

As both SN1 (carbonium ion would be α to the carbonyl group) and SN2 (steric factors) reactions are unlikely to be operative in the above system, dimer **13** is most likely the result of radical coupling (also dimer

(9) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).

(10) J. F. Dippy and J. C. Parkins, *J. Chem. Soc.*, 1570 (1951).

(11) For a discussion of the effect of the halogen of halo esters in the Reformatsky reaction, see M. S. Newman, *J. Amer. Chem. Soc.*, **64**, 2131 (1942), and D. A. Shirley, *Org. React.*, **8**, 33 (1954).

product 6 in Chart I). Radical coupling reactions have recently been reported for these types of hindered molecules. 2,2-Dialkyl-substituted 2-bromo esters have been coupled using $Zn/CuCl_2$ to give tetraalkylsuccinate esters.[12] Anions of 2,2-dialkyl-substituted esters have also been shown to couple in the presence of an electron acceptor ($CuBr_2$) to give the substituted succinate esters.[13a] It seems possible that the non-Claisen-type coupled products formed in our studies and in earlier studies could have resulted from dimerization of radicals formed from either the bromo esters (ketones) or the generated Reformatsky reagents. Electron donors and acceptors Zn, ZnCl, and $ZnCl_2$ are all believed to be present in the zinc-catalyzed decomposition of chloromethyl ether 1.[8b] It has also been shown that isopropyl ketone can be coupled under radical conditions to give dimer 13.[13b,14]

Discussion

In 1965 Moedritzer and Van Wazer[7b] studied the thermal scrambling of the CH_2 group of labeled bis(chloromethyl) ether with the CH_2 group of trioxane and paraformaldehyde in the absence of catalyst. They found that the methylene (CH_2) groups scrambled readily at 120°, the temperature at which their studies were performed. They also noted that CH_2Cl_2 was not present in the mixture and that this scrambling occurred at all temperatures, the rate being slower at lower temperatures. Kaye and Jaret[7a] have reported that the thermal decomposition of cholesteryl chloromethyl ether gives dicholesteryl formal as well as some dioxymethylene and trioxymethylene dicholesteryl ether (eq 4). The above reactions are believed to be radical in nature.

$$ROCH_2Cl \xrightarrow{\Delta} RO(CH_2O)_nR \qquad \begin{matrix} ROH = \text{cholesterol} \\ n = 1 \text{ and } 2, 3 \end{matrix} \quad (4)$$

Lapkin and coworkers[8b] have shown that chloromethyl ethers are decomposed in the presence of metals, in particular zinc, and postulate a radical mechanism. They have trapped the formaldehyde formed with alcohols, thiols, and selenols as shown generalized below (eq 5).

$$ROCH_2Cl + Zn \longrightarrow ROCH_2\cdot + ZnCl\cdot$$

$$\downarrow$$

$$R\cdot + CH_2{=}O \quad (2R\cdot \longrightarrow R\text{–}R) \quad (5)$$

$$\uparrow$$

$$ZnCl\cdot + ROCH_2Cl \longrightarrow ROCH_2\cdot + ZnCl_2 \qquad R = CH_3, Et$$

$$2R'XH + CH_2{=}O \longrightarrow R'XCH_2XR' + H_2O \qquad X = O, S, Se$$

When the formaldehyde was not trapped, it formed trioxane, which has been shown to react with Reformatsky reagents to give, after work-up, hydroxymethyl adducts[15] (alcohol 4a, Chart I, is an example of such an adduct).

While most of the products shown in Charts I and II can be accounted for by the discussed radical processes, the desired dialkylated product does not fit into the radical scheme. In fact, it was obtained in highest yield when all precautions were taken to eliminate radical reactions. The following facts support the possibility of an ionic mechanism for its formation.

Russian workers[8a] have envisioned an ionic mechanism for the reaction of chloromethyl ethers and olefins in the presence of Lewis acids such as $ZnCl_2$ (eq 6).

$$\begin{matrix} (CH_3)_3SiCH{=}CH_2 \\ + \\ CH_3OCH_2Cl \end{matrix} \xrightarrow{ZnCl_2} \left[\begin{matrix} CH_3OCH_2^+ \\ CH_3O{=}CH_2 \end{matrix} \right] ZnCl_3^- \longrightarrow \text{products} \quad (6)$$

Japanese workers, using labeled chlorine, noted that monochloromethyl phenyl ethers readily exchanged chlorine with tetraalkylammonium chlorides in acetonitrile at a rate 10^5 times faster than does phenylethyl chloride. They discuss their results in terms of a facile SN2 displacement reaction.[6h]

Finally, another group of Japanese workers studied the reactions of organometallic reagents (metals studied were Li, Mg, Al) with chloromethyl methyl ether using various solvents.[6g] They found that the normal displacement products increased and the abnormal products decreased with increasing solvent basicity and ionic character of the metal ($Li^+ > Mg^{2+} > Al^{3+}$). While they did not study the reactions of organozinc reagents with chloromethyl ethers, their work supports an ionic mechanism for the normal displacement products in the zinc reactions reported here. Unfortunately, in our studies the more "ionic" metals caused ester condensation reactions and one of the more basic solvents, THF, caused a change in the reaction giving more than 20 products (vpc). Other groups have also noted unusual solvent effects when THF was used as the solvent in the Reformatsky reaction.[16]

To assure correct structure assignments and to allow spectral correlations between the isobutyrate, propionate, and acetate series of reactions, products **3a**, **5a** and **8a** were synthesized from the common intermediate **4a**.[17] While alcohol **4a** could be obtained by Fischer esterification of acid **16**,[18] it was also obtained in nearly 90% yield when β-chloropivalic acid (**15**)[19] was refluxed in ethanol containing 2 equiv of sodium. It seems clear in this case that **4a** was obtained by attack of sodium ethoxide on β-lactone **17** which was formed *in situ* as a result of SNi displacement of the chloride by the generated carboxylate anion. Acetals **8a** and **5a** were readily hydrolyzable back to alcohol **4a** in acidic aqueous ethanol. These reactions are shown in Chart III. Diethyl tetramethylsuccinate was converted to tetramethylsuccinic anhydride[20] and ether diester **7a** was hydrolyzed to the diacid **10**, corroborating its structure. Unsubstituted ether diester **7c** was synthesized from commercially available 2-

(12) C. Fouquey and J. Jacques, *Synthesis*, 306 (1971).

(13) (a) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 4605 (1971); (b) M. F. Ansell, W. J. Hickinbottom, and P. G. Holton, *J. Chem. Soc.*, 349 (1955).

(14) The isolation of **13** in this study and octamethyl cyclohexane-1,4-dione in a related study has prompted us to look more closely at this type of reductive dimerization.

(15) S. Reiffers, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 2339 (1971).

(16) (a) See ref 9; (b) Y. H. Stavel, H. Torabi, and R. L. Evans, *J. Org. Chem.*, **34**, 3792 (1969).

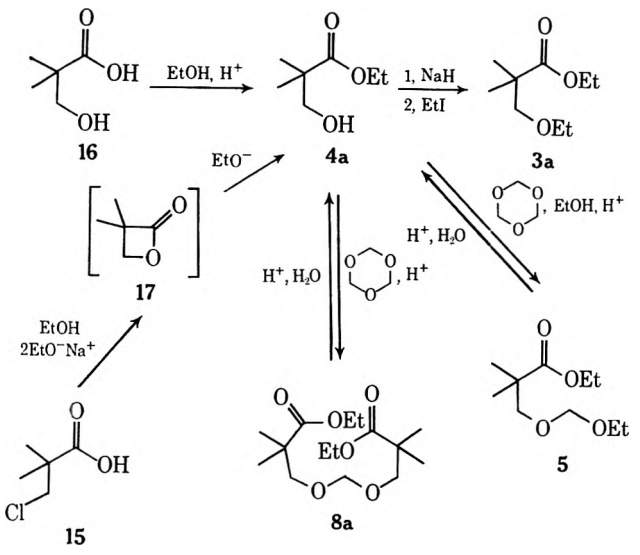
(17) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, London, 1965, p 1680.

(18) J. L. Greene and H. J. Hagemeyer, *J. Amer. Chem. Soc.*, **77**, 3016 (1955).

(19) M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 928 (1940).

(20) P. E. Verkade and H. Hartman, *Recl. Trav. Chim. Pays-Bas*, **52**, 951 (1933).

CHART III



cyanoethyl ether. The products isolated from the propionate reactions were identified from their spectra.

In conclusion, as long as ionic conditions are maintained, symmetrical, highly hindered diester ethers and their derivatives can be synthesized by the route discussed.

Experimental Section

Melting points were taken on a calibrated Mel-Temp apparatus. Infrared spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Vpc analyses were performed using program temperature control on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chromosorb P and 8 ft × 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reactions of Ethyl α-Bromoisobutyrate, Bis(chloromethyl) Ether,[3] and Zinc. A.—Into a flame-dried flask covered with tinfoil and containing 26.2 g (0.4 mol) of powdered zinc under N_2 was distilled 250 ml of glyme from NaH. After the flask was cooled to 0°, 78.0 g (0.4 mol) of ethyl α-bromoisobutyrate was added carefully dropwise. The mixture was stirred at 0–10° until nearly all the zinc had reacted (about 3 hr). On occasion it was necessary to add I_2 to start these reactions.

Bis(chloromethyl) ether, 23.0 g (0.2 mol), was then added dropwise to the flask over 1 hr and the mixture was allowed to warm to 25° over several hours,[21] after which time it was heated at 50° for 1 hr and cooled.

Aqueous NH_4Cl was added to the mixture and the aqueous layer was extracted with ample amounts of ether which were dried with K_2CO_3, filtered, and evaporated to give a crude oil. The crude oil was distilled on a spinning-band apparatus to yield 36 g (66%) of **7a**: bp 73–75° (0.1 mm); ir (CCl_4) 2960, 1730, 1460, 1380, 1360, 1157, and 1118 cm^{-1}; nmr (CCl_4) δ 1.15 (s, 12) 1.26 (t, 6), 3.41 (s, 4), 4.10 (q, 4); mass spectrum (70 eV) *m/e* (rel intensity) 274 (M^+, trace), 259 (trace), 229 (5), 219 (1), 213 (1), 201 (11), 200 (8), 159 (66), 147 (21), 129 (100), 101 (31), 73 (31), 59 (54), 57 (10), 56 (19), 55 (15), 43 (11); metastable peaks *m/e* 176.9, 104.8, 83.0, 79.1.

Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 61.45; H, 9.70.

The other products were isolated and characterized as given in Chart I.

B.—When dried ether was used as the solvent and the reaction was run as described above (0.2–0.4-mol[21] scales) similar results were obtained.

(21) One one occasion the reaction "took off" at this point, causing some damage. Care must be taken to ensure complete formation of the Reformatsky reagent at the lower temperatures!

Three work-ups were employed in these reactions. The first was a careful vacuum distillation of the crude products obtained as described above. Because of the closeness of the boiling points of some of the products, this method did not yield extremely pure material for several of the minor products.

The second procedure involved complexing several of the products, in particular the desired diester, from an ether solution of the crude products as the $ZnCl_2$ complex. In this case the crude products obtained after normal work-up were dissolved in ether and 1 molar equiv (0.2–0.4 mol) of anhydrous $ZnCl_2$ was added to the solution. The mixture was stirred until solution was accomplished (extra ether was added if necessary to accomplish solution). A volume of hexane equal to 25% of the volume of ether was added to the $ZnCl_2$–ether mixture and the contents were stirred thoroughly and then allowed to settle. The hexane layer was decanted off the brown "slurry" and saved. The "slurry" was mixed with another portion of hexane and the process was repeated. The combined hexane layers were washed with aqueous K_2CO_3 and H_2O, and then dried with K_2CO_3, filtered, and evaporated and the crude oil obtained was carefully vacuum distilled to give products **2**, **3a**, **5a**, **6**, and some **8a** (0–5%) in yields comparable to those given in Chart I for these products.

The "slurry" was partitioned with ether–H_2O, the ether was washed with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, filtered, and evaporated, and the residue was vacuum distilled to give **4a** (5–15%), diester **7a** (54–62%), and the remainder **8a** (5–0%).

A third, simpler procedure was generally used when ether was employed as the reaction solvent. In this case, as soon as the reaction was completed and cooled, hexane, 25% by volume, was added to the reaction flask and the mixture was stirred for 10 min. The above (second) procedure was then followed. Isolation of *pure* **7a** was easier when the $ZnCl_2$–complex procedures were used.

Hydrolysis of Diester 7a.—Diester **7a**, 5.48 g (0.02 mol), was hydrolyzed in aqueous KOH–ethanol by heating the mixture to 80° for 3 hr. Acidification of the basic mixture with cold HCl followed by ether extraction and evaporation gave 4.2 g (96%) of 2,2,6,6-tetramethyl-4-oxaheptanedioic acid (**10**): mp 134–135°; ir ($CHCl_3$) 3400–2800 (broad), 1170, 1495, 1310, 1258, 1133, and 1048 cm^{-1}; nmr (1:1 $CDCl_3$–pyridine) δ 1.22 (s, 12), 3.60 (s, 4).

Diacid **10** was easily converted back to diester **7a** using the Fischer esterification procedure.

Synthesis of Ethyl β-Hydroxypivalate (4a).—β-Hydroxypivalic acid,[18] 3.75 g (0.032 mol), was Fischer esterified using methanesulfonic acid as a catalyst giving, after work-up and distillation, a near quantitative yield of ester **4a**: bp 70–72° (3 mm); ir (CCl_4) 3520, 2980, 2940, 2875, 1720, 1380, 1360, 1215, 1145, 1062 cm^{-1}; nmr (CCl_4) δ 1.11 (s, 6), 1.21 (t, 3), 3.47 (s, 2), 3.55 (s, 1, exchanges with D_2O), 4.10 (q, 2); mass spectrum (70 eV) *m/e* (rel intensity) 146 (trace, M^+), 145 (1), 128 (6), 116 (74), 101 (18), 88 (69), 73 (100), 70 (40), 57 (10), 56 (19), 55 (52), 14 (45), 43 (28), 42 (18), 41 (32).

Preparation of Alcohol 4a from β-Chloropivalic Acid (15).—To a solution of sodium ethoxide in ethanol made by reaction of 1.2 g (0.051 mol) of sodium in 100 ml of ethanol under N_2 was added 3.4 (0.025 mol) of acid **15**. After the mixture was heated for 12 hr at 60°, it was poured onto ice. The resulting mixture was extracted with ether which was washed with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, filtered, and evaporated and the crude oil obtained was distilled to give 5.2 g (88%) of alcohol **4a**. No other products were recovered from this reaction.

Synthesis of Ethyl 2,2-Dimethyl-4-oxahexanoate (3a).—To a dry flask under N_2 was added 100 ml of dry THF, 2.92 g (0.02 mol) of alcohol **4a**, and 1.5 g (0.031 mol) of 50% sodium hydride in mineral oil. Ethyl bromide, 4.4 g (0.04 mol), was added to the mixture and it was refluxed for 1 hr, cooled, and extracted with ether which was washed with water, dried with K_2CO_3, filtered, and evaporated. The residue was distilled to give 3.25 g (93%) of **3a**: bp 28–29° (0.1 mm); ir (CCl_4) 1735, 1380, 1365, 1270, 1230, and 1037 cm^{-1}; nmr (CCl_4) δ 1.09 (t, 3), 1.10 (s, 6), 1.20 (t, 3), 3.32 (s, 2), 3.40 (q, 2), 4.05 (q, 2); mass spectrum (70 eV) *m/e* rel intensity) 174 (M^+, trace), 159 (2), 145 (7), 130 (17), 129 (11), 128 (16), 101 (19), 88 (14), 73 (29), 70 (10), 59 (100), 55 (17), 43 (10), and 41 (20).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.81; H, 10.60.

Synthesis of Ethyl 2,2-Dimethyl-4,6-dioxaoctanoate (5a).—To a flask was added 1.46 g (0.01 mol) of alcohol **4a**, 0.2 g (0.0067

mol) of trioxane, 1 ml of ethanol, 100 ml of dry benzene, and 5 drops of methanesulfonic acid. The mixture was stirred at 50° for 2 hr, at which time 50 ml of solvent was removed from the flask. After cooling, the mixture was partitioned with water–ether and the ether was washed with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, and evaporated to give a crude oil which was shown to contain 80% of the mixed acetal **5a** and 20% of *sym*-acetal **8a**. Distillation gave 1.55 g (76%) of **5a**: bp 50–51° (0.1 mm); ir (CCl_4) 2975, 2945, 2875, 1740, 1395, 1370, 1258, 1125, and 1058 cm^{-1}; nmr (CCl_4) δ 1.14 (s, 6), 1.15 (t, 3), 1.21 (t, 3), 3.48 (s, 2), 3.51 (q, 2), 4.10 (q, 2), 4.56 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 204 (none, M^+), 174 (2), 159 (11), 145 (11), 130 (17), 129 (12), 128 (9), 73 (12), 71 (11), 59 (100), 56 (12), 55 (10), 43 (15), 41 (18).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.79; H, 9.87. Found: C, 58.60; H, 10.06.

Synthesis of Diethyl 2,2,8,8-Tetramethyl-4,6-dioxanonanedioate (8a).—To a flask was added 1.46 g (0.01 mol) of alcohol **4a**, 0.60 g (0.02 mol) of trioxane, 100 ml of dry benzene, and 5 drops of methanesulfonic acid. The mixture was treated as described above for **5a** giving, after work-up and distillation, 2.40 g (79%) of **8a**: bp 108–112° (0.2 mm); ir (CCl_4) 2965, 2925, 2860, 1735, 1390, 1360, 1260, 1230, 1155, 1124, and 1058 cm^{-1}; nmr (CCl_4) δ 1.16 (s, 12), 1.22 (t, 6), 3.46 (s, 4), 4.11 (q, 4), 4.59 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 302 (none, M^+), 273 (trace), 259 (1), 231 (trace), 175 (3), 159 (100), 129 (48), 101 (14), 73 (20), 59 (53), 56 (18), 55 (11), 41 (11); metastable peak 104.8.

Acetal **8a** and mixed acetal **5a** were readily hydrolyzed in acidic aqueous ethanol to give alcohol **4a** as the only recoverable material.

Identification and Hydrolysis of Diethyl Tetramethylsuccinate (6). Formation of Tetramethylsuccinic Anhydride (9).—Product **6** was identified by its spectra: ir (CCl_4) 1725, 1395, 1375, and 1265 cm^{-1}; nmr (CCl_4) δ 1.19 (s, 12), 1.23 (t, 6), 4.09 (q, 4).

Hydrolysis of **6** in aqueous KOH–ethanol followed by acidification with HCl and extraction with ether, evaporation, sublimation, and recrystallization from ethyl acetate gave tetramethylsuccinic anhydride, mp 150–152° (lit. mp 152°).[20]

Reactions of Ethyl α-Bromopropionate, Bis(chloromethyl) Ether, and Zinc.—These reactions were performed as described above with the following modifications. I_2 was usually needed to start these reactions and was added to the zinc–glyme or ether mixture before the ethyl bromopropionate was added. The bromo ester (0.1–0.4 mol) was added to the flask at 0–10° over 0.5 hr and stirred until about $^2/_3$ of the zinc appeared to have reacted, at which time bis(chloromethyl) ether (0.05–0.2 mol) was added over 1–1.5 hr. (These conditions represent a compromise between ester condensation and chloromethyl ether decomposition.)[21]

Cold aqueous NH_4Cl work-up and vacuum distillation of the resulting oil gave varying results as shown in Chart II. Products were identified by spectra or conversion to known compounds. Ethyl 2-methyl-3-oxovaleroate[22] (**5b**) had bp 64–70° (0.3 mm); ir ($CHCl_3$) 1740 cm^{-1}; nmr (CCl_4) δ 1.09 (d, 3), 1.14 (t, 3), 1.20 (t, 3), 2.53 (hex, 1), 3.3–3.6 (multiplet, 2), 3.39 (q, 2), 3.97 (q, 2), 4.39 (s, 2). **7b** had bp 95–101° (0.3 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.07 (d, 6), 1.19 (t, 6), 2.53 (hex, 2), 3.2–3.7 (multiplet, 4), 3.95 (q, 4); mass spectrum (70 eV) *m/e* (rel intensity) 246 (none, M^+), 172 (10), 155 (18), 145 (13), 131 (11), 116 (14), 115 (39), 101 (8), 88 (12), 87 (37), 85 (15), 73 (15), 69 (57), 59 (100), 45 (23), 43 (22), 42 (23), 41 (31). **8b** had bp 112–119° (0.3 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.09 (d, 6), 1.19 (t, 6), 2.56 (hex, 2), 3.3–3.7 (multiplet, 4), 3.94 (q, 4), 4.40 (s, 2).

Acetal **8b** and mixed acetal **5b** were readily hydrolyzable to alcohol **4b** in acidic aqueous ethanol.

Reactions of Ethyl α-Bromoacetate, Bis(chloromethyl) Ether, and Zinc.—These reactions were performed as described above with the following modifications. I_2 was needed in every case to start these reactions. It was found that more consistent results could be obtained if 2–5% by weight of Mg was added to the zinc, I_2, glyme or ether mixture before the bromoacetate was added. The chloro ether was added 0.5–1 hr after the bromo ester was added. Cold aqueous NH_4Cl work-up and vacuum distillation of the resulting oil gave ethyl acetylacetate and two other major products as shown in Chart II.[21] **7c**[23] had bp 94–97° (0.1 mm); nmr (CCl_4) δ 1.27 (t, 6), 2.51 (t, 4), 3.72 (t, 4), 4.14 (q, 4). **8c** had bp 112–114° (0.1 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.22 (t, 6), 2.49 (t, 4), 3.72 (t, 4), 4.09 (q, 4), 4.58 (s, 2).

Reaction of α,α′-Dibromoisopropyl Ketone.—Reaction of the dibromo ketone,[24] 13.5 g (0.05 mol), bis(chloromethyl) ether, 5.75 g (0.05 mol), and zinc, 6.54 g (0.1 mol), in 50 ml of glyme as described above gave after work-up 7.4 g of crude material. Distillation gave 4.8 g (40%) of 2,4,4,5,5,7-hexamethyl-3,5-octanedione (**13**),[13b] bp 108–111° (6 mm), and an unidentified higher boiling product.[14]

Registry No.—**3a**, 34506-33-7; **4a**, 14002-73-4; **5a**, 34506-34-8; **5b**, 39837-83-7; **6**, 33367-54-3; **7a**, 34506-36-0; **7b**, 17615-31-5; **7c**, 17615-27-9; **8a**, 39837-87-1; **8b**, 39837-88-2; **8c**, 39837-89-3; **10**, 13987-64-9; **15**, 13511-38-1; ethyl α-bromoisobutyrate, 600-00-0; bis(chloromethyl) ether, 542-88-1; β-hydroxypivalic acid, 4835-90-9; ethyl α-bromopropionate, 535-11-5; ethyl α-bromoacetate, 105-36-2; α,α′-dibromoisopropyl ketone, 17346-16-6.

(22) H. B. Kagan and Y-H. Suen, *Bull. Soc. Chim. Fr.*, 1819 (1966).
(23) I. N. Nazarov, *et al.*, *Zh. Obshch. Khim.*, **24**, 329 (1954); *Chem. Abstr.*, **49**, 4515c (1955).
(24) G. Claeson and A. Thalen, *Acta. Chem. Scand.*, **17**, 1172 (1963).

Studies of the Photocyclization of Some 1-(Haloarylmethyl)pyridinium Salts

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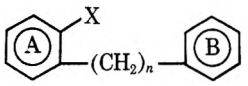
A series of 1-(2-halo-3-quinolylmethyl)- and 1-(2-chlorobenzyl)pyridinium salts were synthesized and photolyzed to investigate electronic factors governing photocyclodehydrohalogenation in π-deficient heteroaromatics and the orientation of the cyclization in unsymmetrically substituted rings. While the latter series gave photocyclization, the former did not. These results suggest that photocyclodehydrohalogenations between aromatic rings are not successful when both rings are electron-deficient heterocycles. Cyclization was favored at a position adjacent to a methyl substituent.

The photodehydrohalogenation reaction has been shown to be a highly successful synthetic method for forming polycyclic, aromatic heterocycles such as those found in alkaloids.[2] These reactions require a system (**1**) having a halogen attached to an aromatic



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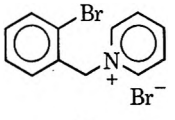
ring (A) connected by a chain to a second aromatic ring (B), the cyclization terminus. Although a large number of systems have been subjected to photolysis,[3] very little was known about the limitation of the electronic nature of the halogen-bearing ring (A), the cyclization terminus (B), the regioselectivity[4] relative to an unsymmetrical ring (B), or the generality of having a single methylene as the chain connecting A and B.

The lack of correlation of the structure of **1** with the success of cyclization can be illustrated. A system with a nitrogen's free pair of electrons unprotected failed to undergo cyclization; however, the corresponding proton salt underwent photocyclodehydrohalogenation.[2a] Similarly, cyclization into the electron-deficient pyridinium ring of 1-(*o*-bromobenzyl)-pyridinium bromide (**2**) has been reported. 2-Bromo-1-(2,5-dichlorobenzyl)pyridinium bromide (**3**), which



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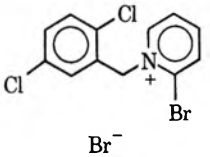

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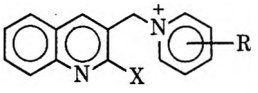
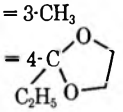
could give photocyclization to either ring, undergoes rupture of the pyridyl bromine bond with bond formation at the benzene ring.[5]

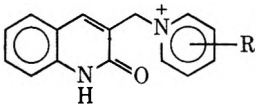
These results would suggest that successful cyclizations can be accomplished with a halogen-bearing ring A that is very electron deficient and cyclization to an electron-rich or poor aromatic ring (B) can occur equally well.

To test this generality a series of 1-(2-halo-3-quinolylmethyl)pyridinium salts (**4**) were prepared and subjected

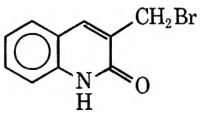


4a, X = Cl; R = 3-CH_3
b, X = Br; R = 4-CH_3
c, X = Br; R = 3-CH_3
d, X = Br; R = 4-





5a, R = 4-CH_3
b, R = 3-CH_3



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to photolysis (Table I). The uv absorption spectra of these salts showed maxima at ~267, 295, 308, and 322 nm. Photolysis using a Vycor filter should lead to excitation of those absorption bands due to both the quinoline and pyridinium chromophores (Figure 1). **4a** gave no reaction after 24 hr as evidenced by lack of change in the uv spectrum and isolation of the starting material from the photolysis mixture. **4b** in hydrobromic acid gave a change in the long-wavelength region of the spectrum after 26 hr of irradiation. Isolation of the product gave a solid with elemental analysis consistent with the formula $C_{16}H_{15}BrNO$. The spectral properties of the product showed it to be the quinolone **5a** (R = 4-CH_3) resulting from displacement of halogen by hydroxyl. An authentic sample of **5a** was prepared by reaction of 3-bromomethyl-2-quinolone (**6**) with 4-picoline, and this quinolone **5a** was identical with the photochemical product.

The formation of the quinolone **5a** was a photochemical process and not a simple hydrolysis, for stirring a solution of **4b** for 26 hr in the absence of irradiation caused no change in the uv spectrum. To gain some information about the manner in which the excited state of **4b** underwent reaction with solvent the photolytic reaction was carried out in acetic acid. No reaction occurred until benzophenone was added as a sensitizer. The uv absorption spectrum then began to change, indicating the formation of the quinolone (**5a**). The direct formation of the quinolone **5a** instead of the 2-acetoxy derivative strongly suggests that the solvent adds to form a 1,2-dihydroquinoline which

(1) This research was abstracted in part from the Ph.D. theses of M. J. K. and J. A. B. submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the degree requirements.

(2) (a) S. M. Kupchan, J. L. Moniot, R. M. Kanojia, and J. B. O'Brien, *J. Org. Chem.*, **36**, 2413 (1971); (b) R. J. Spangler and D. C. Boop, *Tetrahedron Lett.*, 4851 (1971); (c) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, **35**, 175 (1970); (d) J. L. Neumeyer, K. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *ibid.*, **34**, 3786 (1969); (e) S. M. Kupchan and R. M. Kanojia, *Tetrahedron Lett.*, 5353 (1966); (f) K. Wiesner, I. Jirkovsky, M. Fishman, and C. A. J. Williams, *ibid.*, 1523 (1967).

(3) T. Kametani and K. Fukumoto, *Accounts Chem. Res.*, **5**, 212 (1972).

(4) A. Hassner [*J. Org. Chem.*, **33**, 2684 (1968)] did not propose specifically that regiospecificity might apply to orientation in aromatic substitution reactions; however, this type of reaction falls within the scope of the definition of this term.

(5) C. K. Bradsher and C. F. Voigt, *J. Org. Chem.*, **36**, 1603 (1971).

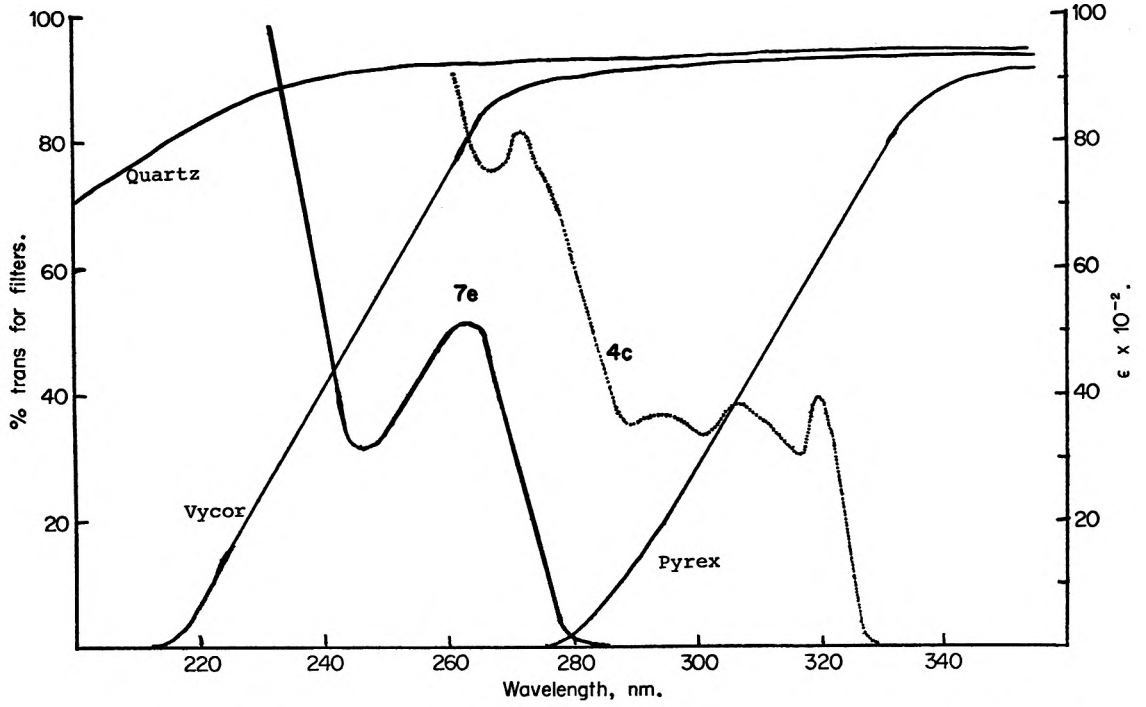


Figure 1.—A comparison of the uv absorption spectra of **4c** (· · · · ·) and **7e** (——) with the Pyrex and Vycor filters.

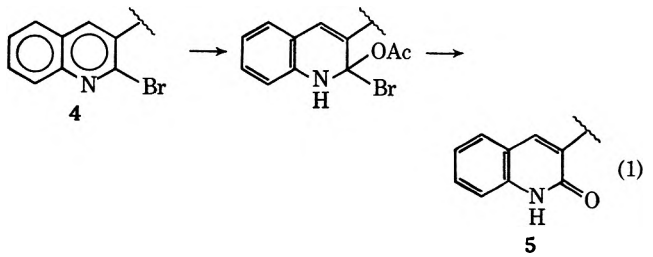
TABLE I

PHOTOLYSES OF 1-(2-HALO-3-QUINOLYLMETHYL)PYRIDINIUM BROMIDES (4)

Compd	X	R	$h\nu$ time, hr[a,b]	Solvent	Product	% yield
4a	Cl	3-CH_3	24	H_2O	s.m.[c]	25
4b	Br	4-CH_3	26	H_2O (HBr)	**5a**	47
4c	Br	3-CH_3	48	HOAc (Ac_2O)[d]	**5b**	43
4d	Br	4-(2-Ethyl-1,3-dioxolan-2-yl)	28	H_2O (HBr)[e]	s.m.	60
4e	Br	4-$COCH_3$	20[f]	H_2O	s.m.	[g]
4f	I	4-CH_3	17.5	H_2O	**5a**	50
4g	Cl	3,4-$(CH_3)_2$	140	22 *N* H_2SO_4	s.m.	[g]
4h	Cl	2-Br	24	H_2O	s.m.	[g]

[a] All photolyses were carried out with a Vycor filter unless otherwise specified. [b] See Experimental Section for the concentration of each solution. [c] Starting material was recovered. [d] The reaction was sensitized with benzophenone after 22 hr. [e] The reaction was sensitized with benzene after 22 hr. [f] The photolysis was carried out with the Srinivasan-type apparatus. [g] The uv absorption spectrum did not change during the photolysis indicating that no reaction had occurred.

then undergoes elimination to form **5a** as shown in eq 1.[6] Reaction of the solvent with an intermediate



(1)

radical formed by homolysis at the C–Br bond could not give 2-quinolone directly. Such *photohydration* of heterocycles has been observed previously.[7] The salts **4** listed in Table I gave either no reaction or photochemical hydration to the corresponding quinolone **5**, identified by spectral data and comparison with authentic samples. These results suggest that photodehydrohalogenation cyclizations are not successful when both aromatic rings are electron-deficient heterocycles.

Photolysis using a Pyrex filter should lead to excitation of only those maxima at ~295, 308, and 322 nm, and thus to selective excitation of the quinolone chromophore in the presence of the pyridinium ring. After 24 hr **4d** and **4e** showed spectral changes indicative of quinolone formation, but no bands at higher wavelength, expected for the cyclized product, were observed.

A number of cyclizations have been reported in which the cyclization terminus, B, is unsymmetrically substituted. In these cases the regiospecificity is biased by blocking one of the two favored positions with a substituent or by having a free phenolic substituent which leads to ortho or para regiospecificity regardless of ring size or presence of blocking group.[2,3] To study the effect of alkyl groups on the regioselectivity of this reaction the 1-(2-chlorobenzyl)pyridinium chlorides (**7**) were prepared and photolyzed, Table II.

(6) One referee proposed that the 2-acetoxyquinoline could be formed and undergo photolysis to the quinolone.

(7) (a) S. T. Reid, *Advan. Heterocycl. Chem.*, **11**, 1 (1970); (b) D. A. Nelson and D. W. Rowe, Abstracts of the First Rocky Mountain Regional Meeting of the American Chemical Society, Fort Collins, Colo., June 30, 1972, paper 4, p 32; (c) D. G. Crosby, *et al.*, in "Environmental Toxicology of Pesticides," F. Matsumura, G. M. Boush, and T. Misato, Ed., Academic Press, New York, N. Y., 1972, p 426.

TABLE II
PHOTOCYCLODEHYDROHALOGENATIONS OF 1-(*o*-CHLOROBENZYL)PYRIDINIUM CHLORIDES (7)

$$7 \xrightarrow[H_2O]{h\nu} 8$$

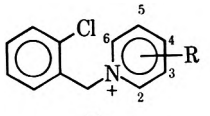
Compd	R	$h\nu$ time, hr	Product	R	% yield
7a	4-CH_3	19[a]	**8a**	3-CH_3	20
7b	3,5-$(CH_3)_2$	35[a]	**8b**	2,4-$(CH_3)_2$	30
7c	2,4-$(CH_3)_2$	7[b]	**8c**	1,3-$(CH_3)_2$	47
7d	3-CH_3	23[a]	**8d**	4-CH_3	33
7e	3,4-$(CH_3)_2$	78[a]	**8e** (33%)[c]	2,3-$(CH_3)_2$	20
			8f (67%)[c]	3,4-$(CH_3)_2$	

[a] Photolyzed in a 0.0224 *M* solution. [b] Photolyzed in a 0.0161 *M* solution. [c] Mixture.

The salts **7a** and **7b**, having a symmetrical ring B, were cyclized to give models for spectral identification, and **7c**, having one α position blocked, was used to check the blocking effect of a substituent on the reaction. The unsymmetrical systems **7d** and **7e** were studied to detect any regioselectivity.

The compounds **7** all gave uv absorption maxima below 280 nm which indicated that irradiation using a Pyrex filter, opaque below 280 nm, would prevent reaction. This was found to be true experimentally. Using a Vycor filter, opaque below 240 nm, or using a "Srinivasan" apparatus with 16 8-W lamps emitting 253.7-nm light gave cyclizations in both water and acetic acid. The reactions were considered to be complete when no further change in uv absorption occurred on further irradiation. The isolated yields of the cyclic compounds were low; however, there were no differences in the spectral properties of the crude reaction solutions and the purified products. The cyclic salts were all sensitive to basic reagents making isolation difficult.

The photolysis of **7d** gave only **8d** in which cyclization occurred adjacent to the methyl substituent. The



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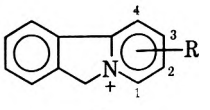

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photodehydrohalogenation of **7e** gave a cyclization product which appeared to be a mixture of **8e** and **8f**. The methyl group at lower field, 2.71 ppm, probably is deshielded by the adjacent aromtic ring and belongs to **8f**. The quantitative analysis of the mixture by nmr thus shows the photocyclization is regioselective to the extent of 67%, favoring reaction ortho to the methyl substituent in ring B as was observed with **7d**. The regioselectivity in these reactions compares with that observed for the Pschorr cyclization and may reflect similar controlling factors.[8]

Experimental Section

1-(2-Chloro-3-quinolylmethyl)-3-methylpyridinium Bromide (4a).—A mixture of 2.56 g (0.010 mol) of 2-chloro-3-bromomethylquinoline[9] and 0.93 g (0.010 mol) of β-picoline in 30 ml of sulfolane was stirred at room temperature for 4 days. After this time the mixture was diluted with ether, and the solid was separated by filtration and dried. Recrystallization of the solid from a 4:1 mixture of ethyl acetate–absolute ethanol gave 2.57 g (74%) of **4a** as tan crystals: mp 208–209°; pmr (CF_3COOH)[10] δ 9.16 (s, 1 H, het), 8.56 (br s, 2 H, het), 8.16–7.48 (m, 6 H, het), 6.00 (s, 2 H, CH_2), 2.36 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 267 nm (ϵ 6916), 293 (2957), 307 (3173), 321 (3287).

Anal. Calcd for $C_{16}H_{14}BrClN_2$: C, 54.95; H, 4.04; N, 8.01. Found: C, 55.29; H, 4.01; N, 7.99.

1-(2-Bromo-3-quinolylmethyl)-4-methylpyridinium Bromide (4b).—When the procedure above was used, 5.00 g (0.0166 mol) of 2-bromo-3-bromomethylquinoline[9] and 1.54 g (0.0166 mol) of γ-picoline in 40 ml of sulfolane gave, after 18 hr, 6.44 g (98%) of **4b**: mp 205–207°; pmr (CF_3COOH) δ 9.32 (s, 1 H, het), 8.90 (d, 2 H, het), 8.56–7.88 (m, 6 H, het), 6.00 (s, 2 H, CH_2), 2.88 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 240 nm (ϵ 67,213), 295 (4070), 308 (4486), 322 (4661).

Anal. Calcd for $C_{16}H_{14}Br_2N_2$: C, 48.75; H, 3.58; N, 7.07. Found: C, 48.86; H, 3.58; N, 7.06.

1-(2-Bromo-3-quinolylmethyl)-3-methylpyridinium Bromide (4c).—When the procedure to obtain **4a** was used, 5.00 g (0.0166 mol) of 2-bromo-3-bromomethylquinoline and 1.54 g (0.0166 mol) of β-picoline in 40 ml of sulfolane gave, after 18 hr, 5.58 g (84%) of **4c**: mp 204–206°; pmr (CF_3CO_2H) δ 8.81–7.43 (m, 6 H, Ar H), 5.93 (s, 2 H, CH_2), 2.25 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 267 nm (ϵ 7812), 295 (3448), 308 (3782), 322 (3900).

Anal. Calcd for $C_{16}H_{14}Br_2N_2$: C, 48.75; H, 3.59; N, 7.11. Found: C, 49.07; H, 3.50; N, 7.17.

1-(2-Bromo-3-quinolylmethyl)-4-(2-ethyl-1,3-dioxolan-2-yl)pyridinium Bromide (4d).—When the procedure to obtain **4a** was used, 5.00 g (0.0166 mol) of 2-bromo-3-bromomethylquinoline[9] and 2.98 g (0.0166 mol) of 4-(2-ethyl-1,3-dioxolan-2-yl)pyridine in 40 ml of sulfolane gave, after 3 days, 3.73 g (47%) of **4d**: mp 227–228°; pmr (CF_3COOH) δ 8.98 (s, 1 H, het), 8.64 (d, 2 H, het), 8.00–7.55 (m, 6 H, het), 6.01 (s, 2 H, CH_2N), 3.91–3.48 (m, 4 H, CH_2O), 1.68 (q, 2 H, CH_2C), 0.64 ppm (t, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 239 nm (ϵ 22,360), 295 (3616), 308 (3920), 322 (3960).

Anal. Calcd for $C_{20}H_{20}Br_2N_2O_2$: C, 50.01; H, 4.21; N, 5.84. Found: C, 50.06; H, 4.13; N, 5.82.

1-(2-Bromo-3-quinolylmethyl)-4-acetylpyridinium Bromide (4e).—When the procedure to obtain **4a** was used, 5.00 g (0.0166 mol) of 2-bromo-3-bromomethylquinoline[9] and 2.01 g (0.0166 mol) of 4-acetylpyridine in 40 ml of sulfolane gave, after 3 days, 6.84 g (98%) of **4e**: mp 204–205°; pmr (CF_3COOH) δ 9.10 (m, 3 H, het), 8.32 (d, 2 H, het), 8.18–7.72 (m, 4 H, het), 6.24 (s, 2 H, CH_2), 2.55 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 240 nm (ϵ 16,086), 275 (7609), 308 (4293), 322 (4130).

Anal. Calcd for $C_{17}H_{14}Br_2N_2O$: C, 48.36; H, 3.35; N, 6.64. Found: C, 48.20; H, 3.32; N, 6.67.

1-(2-Iodo-3-quinolylmethyl)-4-methylpyridinium Bromide (4f).—When the procedure to obtain **4a** was used, 2.00 g (0.0058 mol) of 2-iodo-3-bromomethylquinoline[9] and (0.0535 mol) of γ-picoline in 10 ml of sulfolane gave, after 24 hr, 1.90 g (75%) of **4f**: mp 221–223°; pmr (CF_3COOH) δ 8.60 (s, 1 H, het), 8.36 (d, 2 H, het), 8.00–7.32 (m, 6 H, het), 5.80 (s, 2 H, CH_2), 2.24 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 234 nm (ϵ 52,100), 311 (4980), 325 nm (5350).

Anal. Calcd for $C_{16}H_{14}BrIN_2$: C, 43.57; H, 3.20; N, 6.35. Found: C, 43.75; H, 3.22; N, 6.16.

1-(2-Oxo-1,2-dihydro-3-quinolylmethyl)-4-methylpyridinium Bromide (5a).—When the procedure to obtain **4a** was used, 2.00 g (0.0084 mol) of 3-bromomethyl-2-quinolone (**6**) and 0.78 g (0.0084 mol) of γ-picoline in 30 ml of sulfolane gave, after 0.5 hr, 2.60 g (94%) of **5a**: mp 255–258°; pmr (CF_3COOH) δ 8.86–8.66 (m, 2 H, het), 8.17–7.49 (m, 6 H, het), 5.95 (s, 2 H, CH_2), 2.69 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 225 nm (ϵ 33,500), 247 (11,140), 263 (8320), 275 (8400), 331 (6680).

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(10) Chemical shifts are relative to TMS as an external standard except where otherwise indicated: het, heterocyclic.

Anal. Calcd for $C_{16}H_{15}BrN_2O$: C, 58.01; H, 4.57; N, 8.46. Found: C, 58.13; H, 4.56; N, 8.58.

1-(2-Oxo-1,2-dihydro-3-quinolylmethyl)-3-methylpyridinium Bromide (5b).—When the procedure to obtain **4a** was used, 1.00 g (0.0042 mol) of 3-bromomethyl-2-quinolone (**6**) and 0.39 g (0.0042 mol) of β-picoline in 10 ml of sulfolane gave, after 2 days, 1.30 g (93%) of **5b**: mp 242–243°; pmr (CF_3COOH) δ 8.56–7.14 (m, 9 H, het), 5.56 (s, 2 H, CH_2), 2.28 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 223 nm (ε 32,320), 247 (10,911), 270 (12,486), 332 (7575).

Anal. Calcd for $C_{16}H_{15}BrN_2O$: C, 58.01; H, 4.57; N, 8.46. Found: C, 57.94; H, 4.43; N, 8.60.

1-(2-Chloro-3-quinolylmethyl)-3,4-dimethylpyridinium Bromide (4g).—When the procedure to obtain **4a** was used, 1.12 g (0.00437 mol) of 2-chloro-3-bromomethylquinoline[9] and 0.47 g (0.00437 mol) of 3,4-lutidine in 10 ml of sulfolane gave, after 8 hr, 1.53 g (96%) of **4g**: mp 243–244°; pmr (CF_3COOH) δ 9.06 (s, 1 H, het), 8.40 (s, 2 H, het), 8.10–7.43 (m, 5 H, het), 5.93 (s, 2 H, CH_2), 2.27 (s, 3 H, CH_3), 2.12 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 237 nm (ε 56,373), 262 (7779), 294 (3468), 307 (3740), 321 (3831).

Anal. Calcd for $C_{17}H_{16}BrClN_2$: C, 56.13; H, 4.44; N, 7.70. Found: C, 55.87; H, 4.28; N, 7.69.

1-(2-Chloro-3-quinolylmethyl)-2-bromopyridinium Bromide (4h).—When the procedure to obtain **4a** was used, 1.12 g (0.00437 mol) of 2-chloro-3-bromomethylquinoline and 0.69 g (0.00437 mol) of 2-bromopyridine in 10 ml of sulfolane gave, after 7 days and dilution with dry ether, 0.68 g (37%) of **4h**: mp 149–150°; pmr (CF_3COOH) δ 8.94 (d, 1 H, het), 8.66 (s, 1 H, het), 8.30–7.50 (m, 7 H, het), 6.21 ppm (s, 2 H, CH_2); $\lambda_{max}^{H_2O}$ 237 nm (ε 56,282), 274 (12,220), 307 (3770), 321 (3690).

Anal. Calcd for $C_{15}H_{11}Br_2ClN_2$: C, 43.45; H, 2.68; N, 6.76. Found: C, 43.13; H, 2.73; N, 6.66.

Photolysis Reactions.—The photolysis reactions were run in an Ace quartz apparatus using a 450-W, water-cooled high-pressure Hanovia lamp. The reactions were followed by monitoring changes in the uv absorption spectrum of aliquots withdrawn periodically from the reaction vessel. The solvent was water unless otherwise stated and the reactions were stirred and deoxygenated by passing a steady stream of nitrogen through the reaction mixture.

Photolysis of 4a.—A solution of 2.00 g (0.0057 mol) of **4a** in 650 ml of water was irradiated for 24 hr during which time the uv spectrum remained constant. Evaporation of the mixture and crystallization of the residue gave only recovered **4a**, identified by ir, pmr, uv, and melting points, in 25% yield.

Photolysis of 4b.—Hydrogen bromide gas was bubbled through a solution of 2.00 g (0.0051 mol) of **4b** in 100 ml of water until the pH ≃ 2. This solution was then diluted to 650 ml and photolyzed for 26 hr. After work-up, 766 mg of a tan crystalline solid, mp 252–253°, was obtained. The ir, pmr, and electronic spectra were all identical with those of an authentic sample of 1-(2-oxo-1,2-dihydro-3-quinolylmethyl)-4-methylpyridinium bromide (**5a**) described above. A mixture melting point was not depressed. This constitutes a 47% conversion to **5a**.

Attempted Hydrolysis of 4b.—Hydrogen bromide gas was bubbled into a solution of 0.33 g (0.00084 mol) of **4b** in 75 ml of water until the pH ≃ 2. The solution was then diluted to a volume of 110 ml and stirred at room temperature for 26 hr. No change in the uv absorption spectrum was observed during this time.

Photolysis of 4c.—A solution of 2.00 g (0.0051 mol) of **4c** in acetic acid containing a few drops of anhydride was photolyzed for 22 hr. No change in the uv spectrum was observed. Benzophenone (126 mg) was added and photolysis was continued for another 26 hr. The solution was concentrated under reduced pressure to give a brown oil which was dissolved in 300 ml of MeOH. The solution was treated with Norit and after standing for 3 hr was filtered through Celite. The clear filtrate was concentrated under reduced pressure to give a tan oil which crystallized on addition of EtOH and acetone. The solid, mp 227–230°, 730 mg (43%), gave identical uv and ir spectra with those of an authentic sample of 1-(2-oxo-1,2-dihydro-3-quinolylmethyl)-3-methylpyridinium bromide (**5b**). A mixture melting point with a crystallized (isopropyl alcohol) sample, mp 240–242°, of photolysis product was not depressed.

Photolysis of 4d, 4e, 4f, 4g, and 4h.—The photolyses were run as described for **4a** and **4b** with the solvents and results given in Table I.

1-(*o*-Chlorobenzyl)-4-methylpyridinium Chloride (7a).—A solution of 17.5 g (0.10 mol) of *o*-chlorobenzyl chloride and 9.3 g (0.10 mol) of γ-picoline in 20 ml of sulfolane was stirred at room temperature for 3 days. The mixture was diluted with ether, and the solid which separated was isolated by filtration and dried. Recrystallization of the solid from acetonitrile ether gave 21.2 g (84%) of **7a**: mp 208–209.5°; pmr (CF_3COOH) δ 7.93 (d, 2 H, α-pyr), 7.20 (d, 2 H, β-pyr), 6.88 (m, 4 H, Ar H), 5.27 (s, 2 H, CH_2), 2.25 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 256 nm (ε 3832), 275 sh (569).

Anal. Calcd for $C_{13}H_{13}Cl_2N$: C, 61.42; H, 5.16; N, 5.51. Found: C, 61.60; H, 5.15; N, 5.52.

1-(*o*-Chlorobenzyl)-3,5-dimethylpyridinium Chloride (7b).—When the procedure to obtain **7a** was used, 2.68 g (0.025 mol) of 3,5-lutidine and 4.40 g (0.025 mol) of *o*-chlorobenzyl chloride in 10 ml of sulfolane gave 6.30 g (94%) of **7b**: mp 233–234°; pmr (CF_3COOH) δ 7.84 (s, 2 H, α-pyr), 7.62 (s, 1 H, γ-pyr), 7.00 (s, 4 H, Ar H), 5.36 (s, 2 H, CH_2), 2.19 ppm (s, 6 H, CH_3); $\lambda_{max}^{H_2O}$ 273 nm (ε 6340).

Anal. Calcd for $C_{14}H_{15}Cl_2N$: C, 62.29; H, 5.65; N, 5.22. Found: C, 62.58; H, 5.44; N, 5.20.

1-(*o*-Chlorobenzyl)-2,4-dimethylpyridinium Chloride (7c).—When the procedure to obtain **7a** was used, 8.75 g (0.05 mol) of *o*-chlorobenzyl chloride and 5.36 g (0.05 mol) of 2,4-lutidine in 10 ml of sulfolane gave 10.80 g (81%) of **7c**: mp 210–211°; pmr (CF_3COOH) δ 7.98 (d, 1 H, α-pyr), 7.47–6.58 (m, 6 H, Ar H), 5.42 (s, 2 H, CH_2), 2.50 (s, 3 H, CH_3), 2.30 ppm (s, γ-CH_3); $\lambda_{max}^{H_2O}$ 262 nm (ε 5505).

Anal. Calcd for $C_{14}H_{15}Cl_2N$: C, 62.69; H, 5.64; N, 5.22. Found: C, 62.67; H, 5.62; N, 5.10.

1-(*o*-Chlorobenzyl)-3-methylpyridinium Chloride (7d).—When the procedure for the synthesis of **7a** was followed, 17.5 g (0.10 mol) of *o*-chlorobenzyl chloride and 9.3 g (0.10 mol) of β-picoline in 20 ml of sulfolane gave 18.0 g (71%) of **7d**: mp 128–130°; pmr (CF_3COOH) δ 8.18–7.83 (m, 3 H, α- and γ-pyr), 7.68–7.36 (m, 1 H, β-pyr), 7.10 (s, 4 H, Ar H), 5.47 (s, 2 H, CH_2), 2.18 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 267 nm (ε 4451), 275 sh (3336).

Anal. Calcd for $C_{13}H_{13}Cl_2N$: C, 61.42; H, 5.16; N, 5.51. Found: C, 61.24; H, 5.41; N, 5.43.

1-(*o*-Chlorobenzyl)-3,4-dimethylpyridinium Chloride (7e).—When the procedure to obtain **7a** was used, 2.68 g (0.025 mol) of 3,4-lutidine and 4.40 g (0.025 mol) of *o*-chlorobenzyl chloride in 10 ml of sulfolane gave 6.31 g (94%) of **7e**: mp 200–201°; pmr (CF_3COOH) δ 8.01–7.85 (m, 2 H, α-pyr). 7.31 (d, 1 H, β-pyr), 7.04 (s, 4 H, Ar H), 5.39 (s, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.18 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 262 nm (ε 4722).

Anal. Calcd for $C_{14}H_{15}Cl_2N \cdot {}^1/_2H_2O$: C, 60.65; H, 5.83; N, 5.05. Found: C, 60.74; H, 5.55; N, 5.05.

Photolysis of 1-(o-Chlorobenzyl)-4-methylpyridinium Chloride (7a).—A solution of 3.71 g (0.0146 mol) of **7a** in 650 ml of water was photolyzed for 19 hr using a Vycor sleeve as a filter. The solution was concentrated under reduced pressure leaving a brown syrup which was dissolved in 10 ml of methanol. Acetone (125 ml) was added, the flocculent precipitate was removed by filtration, and 300 ml of ethyl acetate was added. The precipitate was removed and recrystallized from ethyl acetate–absolute ethanol to give 0.62 g (20%) of **8a** as tan needles: mp 244° dec; pmr (CF_3COOH)[11] δ 8.74 (d, 1 H, α-pyr), 8.08–7.86 (m, 2 H, β-pyr), 7.69–7.44 (m, 4 H, Ar H), 5.64 (s, 2 H, CH_2), 2.63 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 223 nm (sh, ε 14,464), 250 (10,893), 257 (11,607), 308 (10,625).

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.71; H, 5.56; N, 6.43. Found: C, 71.54; H, 5.73; N, 6.19.

Photolysis of 7b.—According to the procedure for the photolysis of **7a**, 3.92 g (0.0146 mol) of **7b** was photolyzed in 650 ml of water for 35 hr. Recrystallization of the residue from ethyl acetate–absolute ethanol gave 1.02 g (30%) of **8b**: mp 206–210° dec; pmr (CF_3COOH) δ 8.50 (s, 1 H, α-pyr), 7.97 (s, 2 H, Ar H), 7.58 (m, 3 H, Ar H), 5.64 (s, 2 H, CH_2), 2.73 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3).

Anal. Calcd for $C_{14}H_{14}ClN \cdot {}^1/_2H_2O$: C, 69.84; H, 6.29; N, 5.81. Found: C, 69.55; H, 6.08; N, 5.65.

Photolysis of 7c.—According to the procedure for the photolysis of **7a**, 2.80 g (0.0105 mol) of **7c** was photolyzed in 650 ml of water for 7 hr. Recrystallization of the residue from ethyl acetate–absolute ethanol gave 1.15 g (47%) of **8c**: mp 290° dec; pmr (CF_3COOH) δ 8.15–7.45 (m, 6 H, Ar H), 5.68 (s, 2 H, CH_2), 2.90 (s, 3 H, CH_3), 2.76 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 253 nm (ε 10,867), 257 (11,907), 310 (14,104).

(11) The chemical shifts are reported relative to the ring CH_2 which was assumed to be 5.64 ppm downfield from TMS.

Anal. Calcd for $C_{14}H_{14}ClN$: C, 72.55; H, 6.10; N, 6.04. Found: C, 72.71; H, 6.06; N, 5.70.

Photolysis of 7d.—A solution of 3.71 g (0.0146 mol) of **7d** in 650 ml of water was photolyzed according to the procedure for the photolysis of **7a**, using a Vycor sleeve as filter to give 1.05 g (33%) of **8d**: mp 235° dec; pmr (CF_3COOH) δ 8.49 (d, 1 H, α-pyr), 8.11–7.82 (m, 2 H, β- and γ-pyr), 7.56–7.29 (m, 4 H, Ar H), 5.64 (s, 2 H, CH_2), 2.83 ppm (s, 3 H, CH_3); $\lambda_{max}^{H_2O}$ 250 nm (sh, ε 1200), 254 (13,304), 317 nm (12,152).

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.71; H, 5.56; N, 6.43. Found: C, 71.30; H, 5.57; N, 6.15.

Photolysis of 7e.—According to the procedure for the photolysis of **7a**, 3.92 g (0.0146 mol) of **7e** was photolyzed in 650 ml of water for 78 hr. Recrystallization of the residue from ethyl acetate–absolute ethanol gave 0.67 g (20%) of a mixture of **8e** and **8f**, mp 268° dec. The mixture was not separated. However, analysis of the mixture showed ~67% **8f** and 33% **8e** to be present: pmr (CF_3COOH) δ 8.40–7.18 (m, 6 H, Ar H), 5.64 (s, 2 H, CH_2), 2.71 (s, 2 H, $^2/_3CH_3$), 2.51 (m, 3 H, CH_3), 2.37 ppm (s, 1 H, $^1/_3CH_3$); $\lambda_{max}^{H_2O}$ 225 nm (ε 14,900), 252 (12,190), 260 (11,700), 311 (10,290).

Anal. Calcd for $C_{14}H_{14}ClN \cdot {}^1/_2H_2O$: C, 70.72; H, 6.22; N, 5.89. Found: C, 70.58; H, 5.99; N, 6.08.

Registry No.—**4a**, 39727-35-0; **4b**, 39727-36-1; **4c**, 39727-37-2; **4d**, 39838-38-5; **4e**, 39727-38-3; **4f**, 39727-39-4; **4g**, 39727-40-7; **4h**, 39727-41-8; **5a**, 39727-42-9; **5b**, 39727-43-0; **6**, 35740-85-3; **7a**, 39727-54-3; **7b**, 39727-55-4; **7c**, 39727-56-5; **7d**, 39727-57-6; **7e**, 39727-58-7; **8a**, 39727-59-8; **8b**, 39727-60-1; **8c**, 39727-61-2; **8d**, 39727-62-3; **8e**, 39727-63-4; **8f**, 39727-64-5; 2-chloro-3-bromomethylquinoline, 35740-82-0; β-picoline, 108-99-6; 2-bromo-3-bromomethylquinoline, 35740-83-1; γ-picoline, 108-89-4; 4-(2-ethyl-1,3-dioxolein-2-yl)pyridine, 39727-67-8; 4-acetylpyridine, 1122-54-9; 2-iodo-3-bromomethylquinoline, 35740-84-2. 3,4-lutidine, 583-58-4; 2-bromopyridine, 109-04-6; *o*-chlorobenzyl chloride, 611-19-8; 3,5-lutidine, 591-22-0; 2,4-lutidine, 108-47-4.

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Formation of Long-Lived Free Radicals from Acylpyridinium Salts with Alkali

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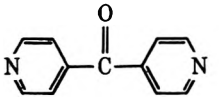
4-Acetylpyridinium methiodide reacted with concentrated aqueous alkali to yield a nonviologenic, stable, long-lived free radical whose esr spectrum indicated molecular symmetry. Several stable nonparamagnetic derivatives of the radical have been prepared and characterized. In contrast to the acetyl and valeryl derivatives, the bulkier alkyl analog 4,4-dimethylvalerylpyridinium salt reacted with hydroxide to yield dimethylviologen radical. On the other hand, di(4-pyridyl)methylcarbinol dimethiodide underwent a several-step transformation when dissolved in concentrated aqueous hydroxide to yield the same symmetrical stable radical as that obtained from 4-acetylpyridinium iodide. The reaction of the latter with sodium ethoxide in alcohol yielded still another radical which is different from that formed in hydroxide. The identity and esr spectra of the radicals and their derivatives and the overall mechanism of reaction are discussed.

We have recently reported[4-6] on the formation of several different long-lived free radicals from methiodide derivatives of di(4-pyridyl) ketone (**1**). The dimethiodide of **1**, in an unusual reaction, yielded rapidly the stable viologen cation radical **2** on simple mixing



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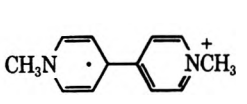

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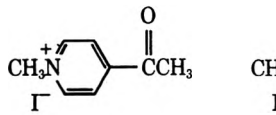
with concentrated aqueous hydroxide.[5] Since the long-lived pyridinyl radicals remain of high research interest because of their relevancy to basic chemical and biological reactions,[7-14] we have extended the study of N-heteroaromatic methiodides with bases to other acylpyridinium salts. In this paper, we report the formation of a nonviologen, stable, symmetrical radical from 4-acetylpyridinium methiodide **3** in aqueous alkali. Whereas the nonbranched homolog of **3**, 4-valerylpyridine methiodide (**4**), behaved analogous to **3**, its bulkier 4,4-dimethyl derivative **5** yielded dimethylviologen (**2**) with aqueous hydroxide in a manner resembling that of the dimethiodide of **1**. On the other hand, the same stable radical obtained



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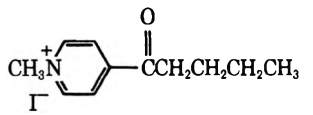

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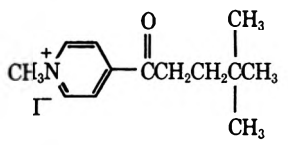

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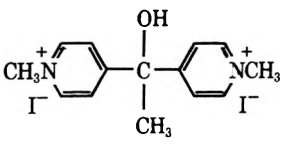

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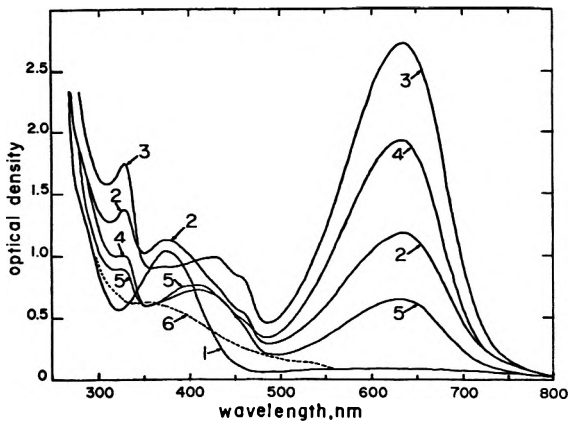
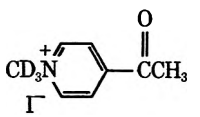


Figure 1.—Changes in the uv–visible absorption spectrum of a degassed 1.5×10^{-3} *M* solution of 4-acetylpyridine methiodide in ~1 *N* NaOH: (1) after mixing, (2) 3 hr, (3) 24 hr, (4) 212 hr, (5) 598 hr, (6) open to air.

from **3** was generated from an apparently unrelated compound, di(4-pyridyl)methylcarbinol dimethiodide (**6**), in the same reaction with aqueous hydroxide. Structurally different stable radicals were obtained from **3** with ethoxide in ethanol or with secondary amines in aprotic solvents.

Results

When crystalline methiodide **3** was mixed with 1 *N* sodium hydroxide in the absence of oxygen, a deep blue color developed progressively.[15] The colored solutions were intensely paramagnetic. Changes in the uv–visible absorption spectrum of a degassed 1.5×10^{-3} *M* solution of **3** in 1 *N* aqueous hydroxide are shown in Figure 1. It is apparent that the blue color is caused by the progressive formation of a visible absorbing species with a prominent band centered at 635 nm and several overlapping and less intense bands in the 300–500 nm regions. One can also see that after reaching a maximum, the concentration of the visible-absorbing species diminishes slowly in about 1 week following mixing. Although numerous curves have been recorded throughout this transformation, only a few are shown in Figure 1 for clarity. Sufficient spectra were recorded to determine accurately the kinetics of the radical disappearance and its half-life in the absence of oxygen. The esr spectrum of a blue solution prepared by dissolving crystalline **3** in aqueous hydroxide is shown at the top of Figure 2. The intensity of the esr signal paralleled the absorbance at 635 nm, suggesting that the blue color is associated with the paramagnetic species. On admission of air both the 635-nm absorption (curves 2–5, Figure 1) and esr signal disappeared. As expected, the *N*-methyl-d_3 analog of **3**, compound **7**, reacted with concentrated hydroxide to give uv–visible absorption spectra indistinguishable from those of **3** shown in Figure 1. On the other hand, the esr spectrum, shown at the top of Figure 3, was distinctly different from that obtained with **3**.



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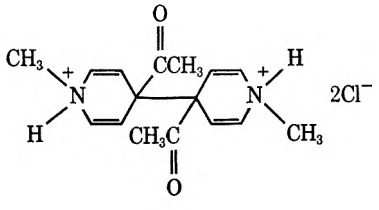
In order to uncover chemical evidence regarding the identity of the detected free radical, several large-scale (gram-size) reactions of **3** with 1 *N* sodium hydroxide have been carried out. When the concentrated blue solution prepared with 2 *N* sodium hydroxide was allowed to stand overnight, green crystals with metallic luster and weak paramagnetic properties precipitated. Although these crystals can be filtered in an inert atmosphere, their inherent instability in the presence of air prevented accurate elemental analysis and other direct analytical tests. A 10^{-4}–10^{-5} *M* solution of green crystals in degassed DMSO gave the visible absorption shown in Figure 4, curve 1 which changed progressively as indicated with decrease in the intensity of the band at 625 nm and concomitant increase in concentration of a component absorbing at λ_{max} 445 nm. The presence of an isosbestic point at 505 nm suggests a clean 1:1 transformation.

When redissolved, the emerald green solid melting at 236–238° reexhibited all the spectroscopic and chemical properties of its precursor blue free radical. In spite of its lability the green, crystalline compound could be preserved for several days under refrigeration in an inert atmosphere. It reacted vigorously with concentrated H_2SO_4, forming a stable red solution which gave the uv–visible absorption spectrum shown in Figure 5. The uv–visible spectrum remained unchanged for weeks and the solution was diamagnetic. The analogous red, crystalline hydrochloride prepared from the green solid and 0.5 *M* HCl was quite stable and therefore lended itself to thorough characterization. Elemental analysis, nmr (in D_2O), ir, and uv–visible spectra were all consistent with dihydrochloride structure **8**. In addition the nmr spectrum of the green solid in 100% D_2SO_4 agreed with trication structure **9**. Thus, comparison of the nmr spectra of **8** in D_2SO_4 and D_2O with that of **3** in DMSO-d_6 and D_2SO_4 allowed good assignments of individual nmr signals shown in Figure 6.



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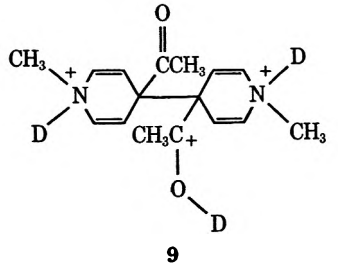


9

It is interesting that 4-acetylpyridinium iodide **3** yielded structurally different stable radicals when

(15) The requirement for absence of oxygen is not stringent for the formation of the radical. If the aqueous hydroxide was not degassed prior to mixing, the blue color of the radical develops after some initial delay. On the other hand, initial deoxygenation by numerous freeze–thaw cycles under high vacuum causes the immediate appearance of the blue color on mixing. Such samples were used for the recordings in Figure 1.

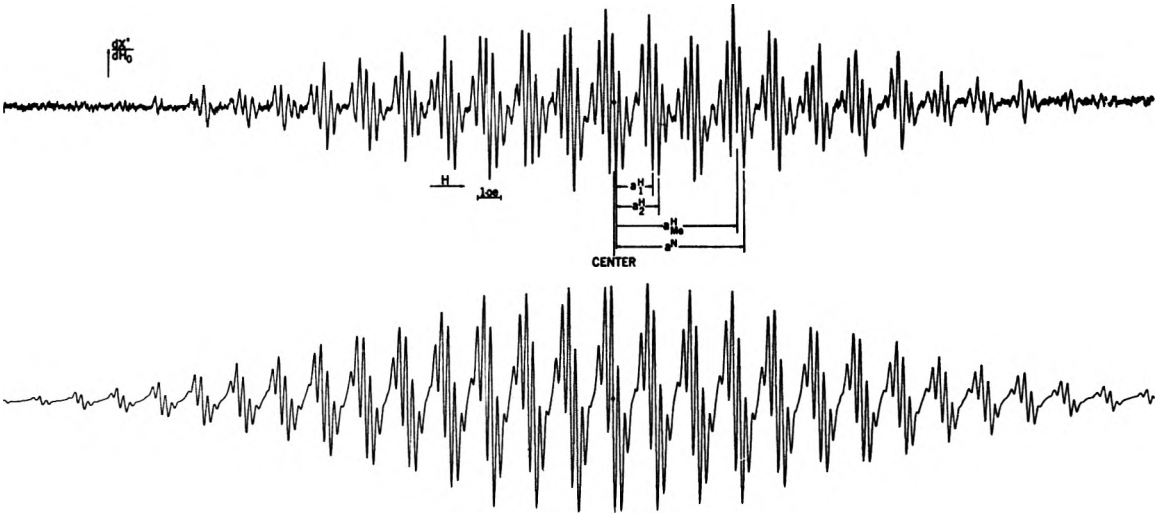


Figure 2.—Top: esr spectrum of 4-acetylpyridine methiodide in 1 *N* aqueous NaOH. Bottom: computer-simulated spectrum with hyperfine splitting constants $a^N = 5.39$, $a_1^H = 1.54$, $a_{CH_3}^H = 5.10$, and $a_2^H = 1.80$.

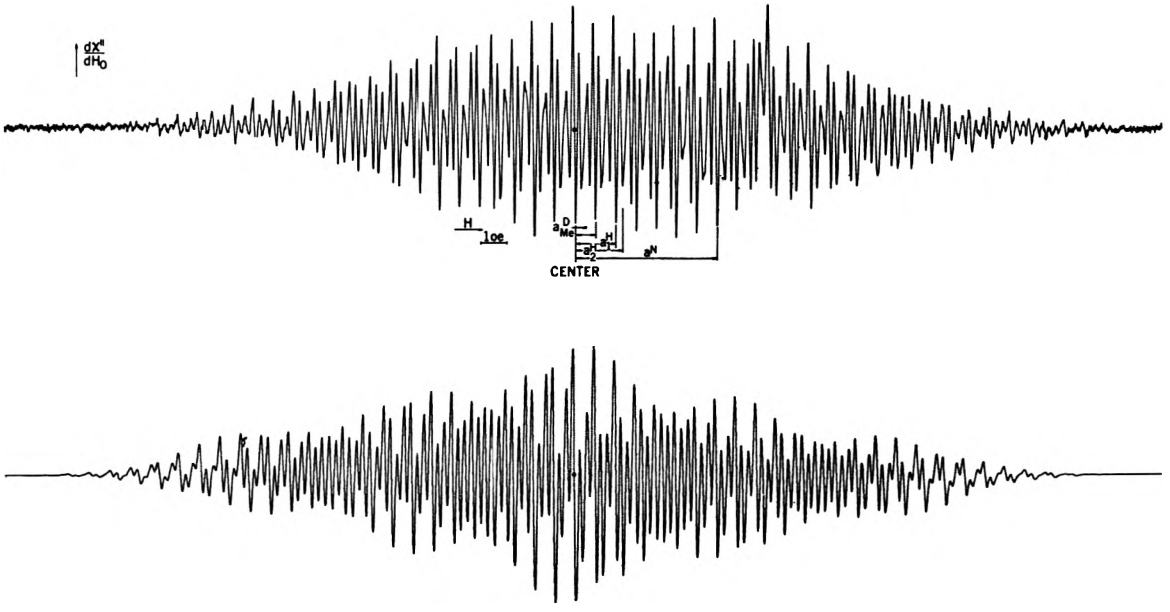


Figure 3.—Top: esr spectrum of *N*-methyl-d_3-4-acetylpyridinium methiodide (**7**) in 1 *N* aqueous NaOH. Bottom: simulated spectrum with hyperfine splitting constants $a^N = 5.39$, $a_1^H = 1.54$, $a_{CD_3}^D = 0.79$, and $a_2^H = 1.80$.

treated with ethoxide in alcoholic solution or with secondary amines in nonprotic solvents.

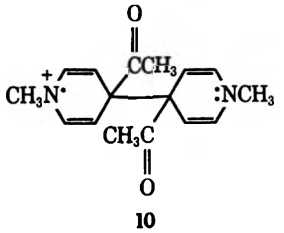
Both 4-acetylpyridine methiodide (**3**) and its CD_3 derivative **7** reacted with sodium ethoxide in ethanol to give the same brown-green free radical whose uv–visible absorption spectrum showed prominent bands at 326 and 435 nm and a weaker broad band around 735 nm. Its esr spectrum in approximately 1 *N* sodium ethoxide is displayed in Figure 7. Despite the fact that the line width is remarkably narrow, about 100 mOe, the complexity of the spectrum, showing approximately 250 distinct lines, did not allow accurate determination of the splitting constants.

The fact that both compounds **3** and **7** gave the same paramagnetic species in EtOH–NaOEt may be explained in two ways: either the CH_3 or CD_3 groups no longer exist in the free radical, or fast exchange of methyl deuterons takes place in the presence of the powerful alkoxide base. The behavior of **7** in ethoxide is mentioned here mainly to exhibit the contrast with its reaction in aqueous hydroxide.

The reaction of 4-acetylpyridinium iodide with pyrrolidine in deoxygenated dimethoxyethylene (DME) resembled more that with aqueous hydroxide, since **3** and **7** yielded two different stable radicals whose esr spectra are shown in Figure 8. Neither the radicals formed in alcoholic ethoxide nor those in DME–pyrrolidine were identical with those prepared in aqueous hydroxide.

Discussion

The reaction of 4-acetylpyridinium iodide with concentrated aqueous hydroxide yielded a long-lived new free radical for which we tentatively propose structure **10**. This structure was derived from a



10

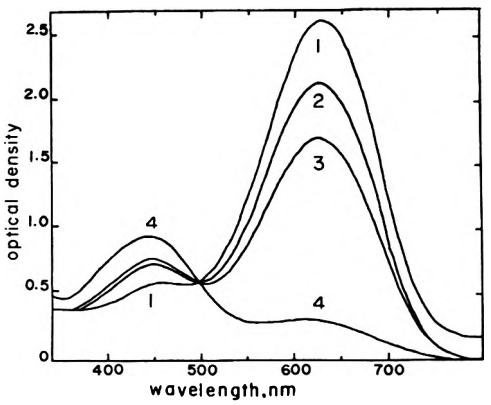


Figure 4.—Visible absorption of 12 in degassed dimethyl sulfoxide at different times: (1) after solubilization, (2) 135, (3) 195, and (4) 540 min later.

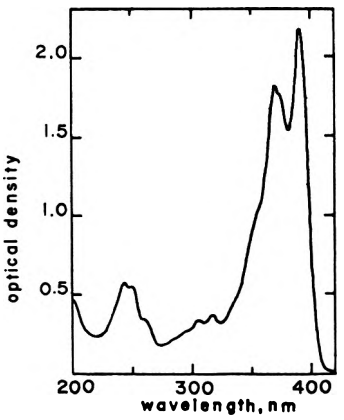


Figure 5.—Uv absorption spectrum of 12 in deoxygenated H_2SO_4.

variety of spectroscopic and other analytical tests on radical **10** itself and on some of its more stable derivatives such as dihydrochloride **8** and trication **9**.

It is conceivable that by reacting with the hydroxide counterion, the *N*-methylacetyl pyridinium cation undergoes reduction to a Kosower-type radical **11**, which in turn reacts with the pyridinium ion of **3** to give radical ion **10** (see Scheme I). Radical **10** can be further reduced to diamagnetic species **12**. The uv–visible absorption spectrum of **12** in DMSO (Figure 4) is very similar to that of radical **10** (Figure 1). This is compatible with their structural similarity. The fact that aqueous solutions of **12** were paramagnetic is readily understood in view of the reformation of radical **10** by either one of the two paths shown in Scheme I. The absence of both hydroxide and iodide ions in **12** was shown by the negative test with silver nitrate. Compound **12** reacted quickly with hydrochloric and perdeuterated sulfuric acids to form **8** and **9**, respectively.

Free radical **10** exhibited visible absorption with λ_{max} in the 600–700-nm range, which is characteristic of viologen-like radicals. Its ir spectrum retained the carbonyl stretching band at 1640 cm^{-1}. The nmr spectrum of diamagnetic trication **9** in D_2SO_4 was indistinguishable from that of the dihydrochloride **8** in D_2SO_4. Qualitatively, dihydrochloride **8** also showed evidence for preservation of the acetyl groups of **3** by forming 2,4-dinitrophenylhydrazone (mp 184°) and a positive iodoform test. Probably the most convincing evidence for structure **10** is the esr spectrum

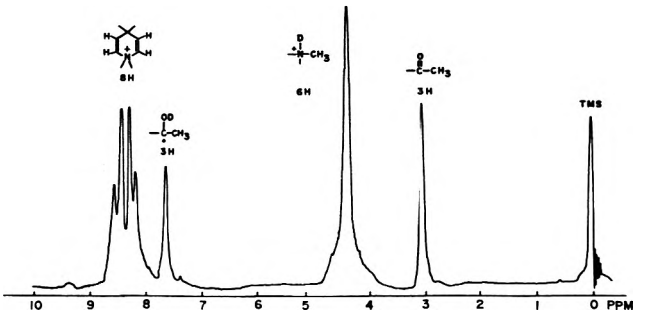
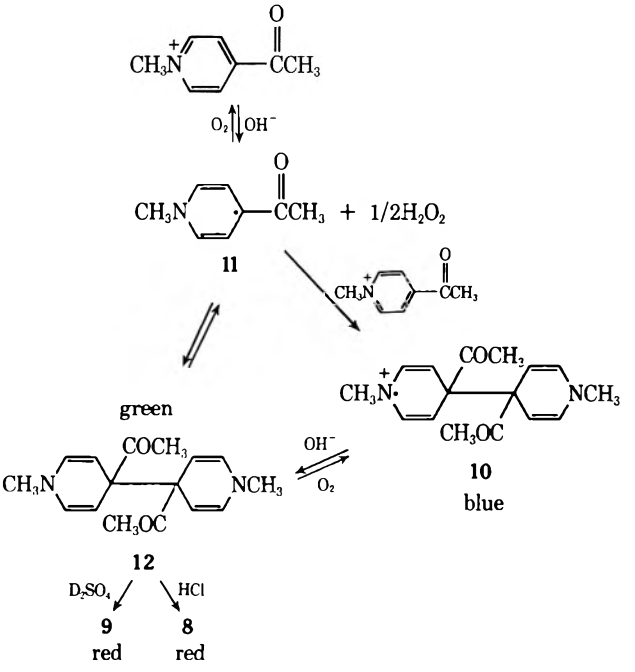
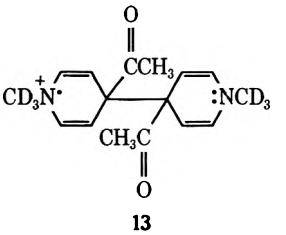


Figure 6.—Nmr spectrum of 12 in D_2SO_4. Identical spectrum obtained for 8 in D_2SO_4.

SCHEME I



of the blue aqueous solution shown in Figure 2. The hyperfine splitting constants indicated on the diagram were determined very accurately by computer analysis, since the fit between simulated and experimental curves is extremely sensitive to even very slight changes in the values of the hyperfine splitting constants. Very useful information was obtained from the comparison of esr spectra of **10** (NCH_3) with that of the free radical derived from the NCD_3 analog of **3**, structure **13**.



13

The spectrum of the radical cation **13** containing NCD_3 groups should differ from that containing NCH_3 groups only in the splitting constants of the deuterons. Indeed, the hyperfine splitting constants a^N = 5.39 Oe, a_1^H (α to N) = 1.54 Oe, and a_2^H (β to N) = 1.80 Oe are identical for the two free radicals derived from **3** and **7**, whereas $a^H_{CH_3}$ (from NCH_3) = 5.10 Oe in **10** and $a^D_{CD_3}$ = 0.79 Oe in **13**. Since $a^H_{CH_3}/a^D_{CD_3}$ should be equal to the gyromagnetic ratio of H to D,

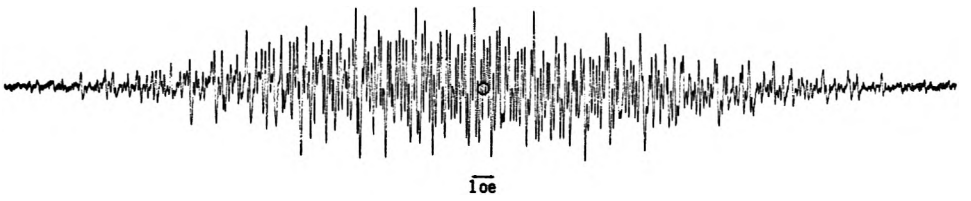


Figure 7.—Esr spectrum of 4-acetylpyridine methiodide in sodium ethoxide–ethanol solution.

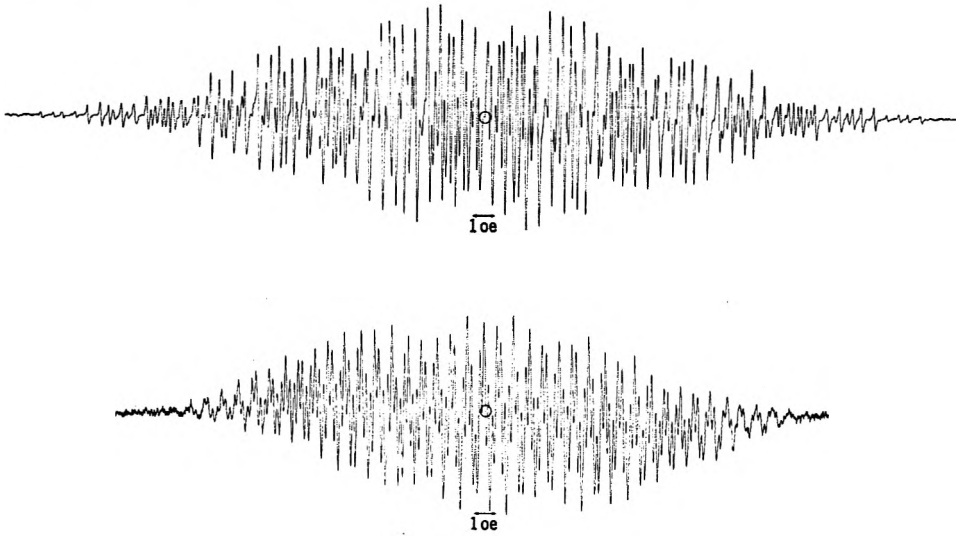
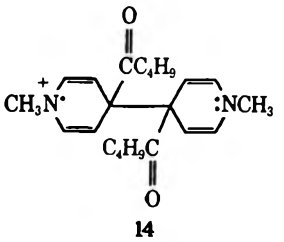


Figure 8.—Esr spectra of stable radicals generated from 4-acetylpyridine methiodide (3) (top) and its d_3 derivative 7 (bottom) in pyrrolidine–dimethoxyethylene solution.

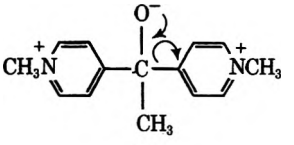
namely 6.51, one can easily verify that *there must be six deuterium atoms in the free radical derived from compound 7, or two equivalent CD_3 groups.* That implies that there are two 4-substituted *N*-methylpyridine groups in the paramagnetic species and no other atoms with nuclear magnetic moment within the delocalized domain of the unpaired spin. The esr spectra also indicate that the presence of the two acetyl groups in radical **10** does not interfere sufficiently with the π through-space delocalization to prevent the equal time-distribution of the unpaired spin on each of the two pyridine rings. On the other hand, it seems quite reasonable that there should be no additional splitting in the esr spectrum caused by the CH_3 groups of the acetyls, since any hyperconjugative structures suggestive of unpaired-spin proximity to the H's of those CH_3 groups would represent highly improbable configurations. In addition we found that the esr spectrum of the radical derived from *N*-methyl-4-valeryl iodide (**4**) in hydroxide, presumably **14**,



14

was virtually identical with that of **10**. In contrast, the bulky derivative 4,4-dimethylvaleryl pyridyl ketone methiodide (**5**) yielded a totally different stable radical in deoxygenated 1 *N* aqueous sodium hydroxide. The intensely blue solution exhibited characteristic dimethyl viologen radical uv–visible absorption[4] and esr spectrum indistinguishable from that of viologen **2** prepared from different reagents.[5,6] The only tentative explanation for the difference in behavior of **5** compared to **3** is that the bulkiness of the dimethylvaleryl group sterically inhibits the formation of a radical retaining the two acyl groups analogous to **10**. To support this argument the unsubstituted valeryl analog **4** yielded uv–visible and esr spectra consistent with **14**, a radical similar to **10**.

We find it worth mentioning that di(4-pyridyl)-methylcarbinol (**6**), prepared by treatment of di(4-pyridyl) ketone with methylmagnesium iodide and then with excess methyl iodide, also generated radical **10** when treated with hydroxide. Immediately after mixing crystals of **6** with aqueous concentrated hydroxide an intense red color developed which persisted for several minutes only to change abruptly into a more stable deep blue color. Both uv–visible and esr spectra of this blue solution were identical with those derived from 4-acetylpyridine methiodide (**3**) with base under the same conditions. Whereas the uv–visible absorption is only moderately indicative of minor changes in alkyl substituent, the hyperfine



15

↓

3

↓ OH^-

10

splitting in the esr spectrum is extremely sensitive to even minor changes in the molecule. Therefore, the superimposable identity of the paramagnetic signals of the blue radicals derived from both **3** and **6** in hydroxide testifies to the formation of the same stable radical **10** and the necessary cleavage adjacent to the carbinol carbon of **6**. It is quite possible that the observed red intermediate is ion **15** which subsequently cleaves to form **3**, which, in turn, reacts with hydroxide to generate radical **10**.

Experimental Section

Spectrograde solvents were used throughout. Alkoxide solutions were freshly prepared by dissolving metallic sodium in alcohol. Degassed solutions were prepared by repeated freeze–thaw cycles under high vacuum in either silica absorption cells or esr tubes provided with side reservoirs and constrictions for flame sealing. Degassing was carried out with the solvent in the side bulb and the crystals of solute in the sample compartment. Because of dielectric loss in the solvent, aqueous esr samples were placed in 1-mm i.d. quartz tubes and those in alcohol in 1-, 2-, or 3-mm i.d. tubes.

Uv–visible absorption spectra were recorded on the Cary spectrophotometer Model 15 in double-beam mode. Esr spectra were recorded on a modified Varian V-4502 spectrometer with 10-kHz modulation. The microwave bridge of the spectrometer consisted of a circulator in the sample arm and a precision attenuator and phase shifter in the bucking arm. Computer simulations were carried out on an IBM 360/91 computer and drawn by the Cal-Comp Associates Plotter; other calculations were performed on an IBM 360/50 computer.

Nmr spectra were recorded on a Hitachi Perkin-Elmer nmr spectrometer, Model R-20, with internal and in some cases external TMS standard. Infrared spectra were taken on a Perkin-Elmer 221 infrared spectrometer. Mass spectra were run on a Perkin-Elmer 270 GC mass spectrograph.

The preparation of di(4-pyridyl) ketone (**1**) and di(4-pyridyl)-methylcarbinol dimethiodide (**6**) was described previously.[4]

4-Acetylpyridinium Methiodide (3).—Treatment of 10 g (82.6 mmol) of 4-acetylpyridine (Aldrich) with excess CH_3I gave 19 g of orange, crystalline methiodide: yield 87%; mp 172–173°; ir (KBr) ν 1690 cm^{-1} (C=O); nmr (DMSO-d_6) δ 9.26 (2 H, doublet, 2,6-pyridinium H's), 8.47 (2 H, doublet, 3,5-pyridinium H's), 4.50 (3 H, singlet, NCH_3), 2.79 (3 H, singlet, acetyl H's).

Anal. Calcd for $C_8H_{10}NOI$: C, 36.5; H, 3.80. Found: C, 36.3; H, 3.90.

4-(4′,4′-Dimethylvaleryl)pyridine.—To a stirred solution of dry 4-cyanopyridine (41.0 g, 0.39 mol) dissolved in 300 ml of anhydrous ether under an N_2 atmosphere was added dropwise 1 *M* *tert*-butyllithium in *n*-pentane (200 ml, 0.39 mol). The dark red-brown solution was stirred for 8 hr, then hydrolyzed with dilute HCl. The organic layer was extracted with five 60-ml portions of dilute HCl; the combined aqueous extracts were made basic with concentrated NaOH and extracted with eight 50-ml portions of chloroform, which were then dried over $MgSO_4$. The $CHCl_3$ was evaporated off, leaving a red oil which was distilled at reduced pressure. The fraction of bp 96–98° (0.5 mm) showed only one peak upon vpc analysis and was identified as 4-(4′,4′-dimethylvaleryl)pyridine: yield 5 g (9.3%); ir (neat) ν 1685 cm^{-1} (C=O); nmr (neat) δ 8.35 (2 H, doublet, 2,6-pyridyl H's), 7.32 (2 H, doublet, 3,5-pyridyl H's), 2.60 (2 H, triplet, methylene adjacent to C=O), 1.22 (2 H, triplet, methylene adjacent to *tert*-butyl), 0.55 ppm (9 H, singlet, *tert*-butyl group); mass spectrum *m/e* (rel intensity) 191 (19, M^+), 176 (23), 135 (41), 134 (14), 122 (31), 107 (26), 106 (100), 79 (28), 78 (42), 57 (61), 51 (23), 41 (28).

4-Valerylpyridine was obtained by treatment of dry 4-cyanopyridine (10.4 g, 0.1 mol) with 2.67 *M* *n*-butyllithium in *n*-hexane (60 ml) followed by hydrolysis with dilute HCl and similar work-up as with 4-(4′,4′-dimethylvaleryl)pyridine: yield 5 g (30%); bp 94–96° (0.5 mm); ir (neat) ν 1694 cm^{-1} (C=O); nmr (neat) δ 8.20 (2 H, complex doublet, 2,6-pyridyl H's), 7.14 (2 H, complex doublet, 3,5-pyridyl H's), 2.51 (2 H, triplet, methylene adjacent to C=O), 1.07 and 0.50 ppm (7 H, multiplet, *n*-propyl group).

4-Valerylpyridinium Methiodide (4).—Treatment of 4-valerylpyridine (2.2 g, 13.5 mmol) with CH_3I (5 ml) in benzene gave the orange-red methyl iodide: yield 3.7 g (89%); mp 87–89°; ir (KBr) ν 1680 cm^{-1} (C=O); nmr (DMSO-d_6) δ 9.10 (2 H, doublet, 2,6-pyridinium H's), 8.36 (2 H, doublet, 3,5-pyridinium H's), 4.49 (3 H, singlet, NCH_3), 3.15 (2 H, triplet, methylene H's adjacent to carbonyl group), 1.41 and 0.90 ppm (7 H, multiplet, *n*-propyl group).

Anal. Calcd for $C_{11}H_{16}NOI$: C, 43.29; H, 5.28. Found: C, 42.77; H, 5.38.

4′,4′-Dimethylvalerylpyridine Methiodide (5). Treatment of 4-(4′,4′-dimethylvaleryl)pyridine (1.0 g, 5.24 mmol) with CH_3I (3 ml) in methyl ethyl ketone formed orange methyl iodide: yield 1.4 g (81%); mp 177.5–178.5°; ir (KBr) ν 1695 cm^{-1} (C=O); nmr (DMSO-d_6) δ 9.16 (2 H, doublet, 2,6-pyridinium H's), 8.42 (2 H, doublet, 3,5-pyridinium H's), 4.38 (3 H, singlet, NCH_3), 3.12 (2 H, triplet, methylene H's adjacent to carbonyl), 1.47 (2 H, triplet, methylene H's adjacent to *tert*-butyl group), 0.89 ppm (9 H, singlet, *tert*-butyl H's).

Anal. Calcd for $C_{13}H_{20}NOI$: C, 46.85; H, 6.05. Found: C, 46.23; H, 6.22.

***N*-Methyl-d_3-4-acetylpyridinium iodide (7)** was prepared with CD_3I (ICN Corp., 99.5%) by a procedure[16-18] similar to that described for **3** as orange crystals: yield 68%; mp 172.5–173.5°; ir (KBr) ν 1690 cm^{-1} (C=O); nmr (DMSO-d_6) δ 9.22 (2 H, doublet, 2,6-pyridinium H's), 8.49 (2 H, doublet, 3,5-pyridinium H's), 2.79 ppm (3 H, singlet, acetyl H's).

1,1′-Dimethyl-4,4′-diacetyl-1,1′-dihydro-4,4′-bipyridinium Dihydrochloride (8).—Radical cation **10** (1.1 g, 3.8 mmol) was suspended at room temperature in 30 ml of 0.5 *M* HCl. The green crystals turned red immediately. Within 25 min the crystals were completely dissolved. After the yellow solution was filtered, 5 ml of 1 *N* NaOH was added dropwise to pH ~9. The solution turned purple, violet, and then blue. The red crystals were reprecipitated with 37% HCl to pH 2. The crystals were suction filtered and washed with ethyl ether: yield 1.3 g (96.15%); mp 296–297°; uv (H_2SO_4) λ_{max} 390 nm (ϵ 16,900), 372 (14,600), 355 sh (8300), 316 (3000), 305 (2900), 295 sh (2600), 285 sh (2500), 262 sh (3400), 250 (5900), 244 (5800); ir (KBr) 1640 cm^{-1} (C=O); the nmr spectrum is shown in Figure 6.

Anal. Calcd for $C_{16}H_{22}N_2O_2Cl_2$: C, 55.62; H, 6.42; N, 8.11; O, 9.26; Cl, 20.53. Found: C, 55.92; H, 5.59; N, 8.29; O, 9.04; Cl, 20.96.

Preparation of 1,1′-Dimethyl-4,4′-diacetyl-1,1′-dihydro-4,4′-bipyridyl (12).—Work was done under N_2 atmosphere. *N*-Methyl-4-acetylpyridinium iodide (**3**) (5 g, 0.019 mol) was introduced into a 250-ml three-necked flask equipped with pressure-equalizing addition funnel and magnetic stirrer. Freshly prepared aqueous 2 *N* NaOH (30 ml) previously deaerated for 20 min by N_2 bubbling, was added dropwise at room temperature. A green solution developed and within 10–15 min a green precipitate appeared. After 2 hr the apparatus was transferred to a nitrogen glove box, and the precipitate was filtered off by suction and washed with ethyl ether, yield 1.5 g (54.74%); uv and nmr spectra are given in text.

Registry No.—**3**, 7630-04-8; **4**, 39833-34-6; **5**, 39833-35-7; **7**, 39833-36-8; **8**, 39833-37-9; **8** di-2,4-DNP, 39833-38-0; **10**, 39833-39-1; **12**, 39833-40-4; **13**, 39833-41-5; CH_3I, 74-88-4; CD_3I, 865-50-9; 4-acetylpyridine, 1122-54-9; 4-(4′,4′-dimethylvaleryl)pyridine, 39833-42-6; 4-cyanopyridine, 100-48-1; 4-valerylpyridine, 1701-73-1.

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Optically Active Heteroaromatic Compounds. VI. 3-Substituted Furans and Thiophenes from α,β-Unsaturated Aldehydes

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The hydroformylation of the acetals of the 2-substituted α,β-unsaturated aldehydes (1) in the presence of rhodium catalysts results in the exclusive formation of the monoacetals of the corresponding succinaldehydes (2) with 60–80% yield. Compounds 2 undergo cyclization reactions to the corresponding 3-substituted furans (4) and thiophenes (5) with satisfactory yields (40–77%). This synthesis is suitable for the preparation of optically active 3-*sec*-butylfuran (4a), thiophene (5a), and pyrrole (6). Although in the formation of 4a, 5a, and 6 racemization up to 26% was observed, the present method for obtaining such optically active heterocyclic compounds appears to be more convenient than others described in the literature.

Investigations of the steric course of the synthesis and of the chiroptical properties of simple optically active heteroaromatic systems[1-4] are in progress in our laboratories. The present report is concerned with 3-substituted furans and thiophenes, which are not readily accessible compounds and which represent the structural unit embodied in many natural products,[5-7] and are intermediates with increasing pharmacological interest.[8]

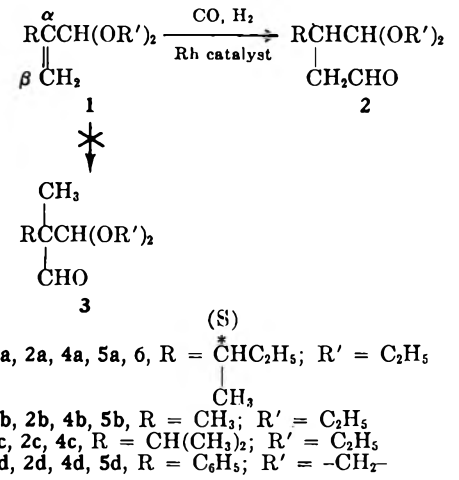
As previously pointed out by some authors,[5,7] the synthesis of a furan or thiophene ring bearing only a 3 substituent usually requires many steps with consequent low overall yields.[9,10] The best syntheses of such compounds appear to be those based upon the cyclization of suitable 1,4-dicarbonyl compounds or their derivatives.[6,11] Key precursors are the corresponding 2-substituted succinaldehydes, which are now readily available through rhodium-catalyzed hydroformylation[12,13] of suitable 2-substituted acrolein acetals.

We wish to describe here (1) examples of this convenient synthetic approach to 3-alkyl- or 3-aryl-substituted furans and thiophenes starting with the now easily available α,β-unsaturated aldehydes,[14] a method that may also be used for obtaining optically active 3-alkylfurans, thiophenes, and pyrroles; and (2) the relationship between the sign of the optical rotation, absolute configuration, optical purity, and rotatory power.

Results

Synthesis of Succinaldehyde Monoacetals (2).—The hydroformylation of α,β-unsaturated aldehyde acetals (1) was carried out in the presence of *trans*-bis(triphenylphosphine)carbonylchlororhodium(I)[15] as catalyst[12,16,17] and triethylamine in benzene solution.[16] The presence of the amine in the reaction mixture prevents side reactions during the hydroformylation. The hydroformylation of 1 in the presence of $RhCl(CO)(PPh_3)_2$ results in the exclusive formation of 2 (Scheme I), which corresponds to a β introduction of the formyl

Scheme I



group as confirmed by glpc and nmr analysis. The results obtained in hydroformylation experiments of 1 are summarized in Table I. Compounds 2, which were recovered by simple distillation from the reaction mixture in the presence of small amounts of sodium or potassium carbonate, are quite stable intermediates, at least at room temperature.

Cyclization to Heterocycles.—Distillation of 2 in the presence of aqueous sulfuric acid promotes cyclization to the corresponding furan 4 in a 40–80% yield[19]

(1) C. Botteghi, L. Lardicci, E. Benedetti, and P. Pino, *Chim. Ind. (Milan)*, **49**, 171 (1967).
(2) L. Lardicci, R. Rossi, S. Pucci, M. Aglietto, C. Botteghi, and P. Pino, *ibid.*, **50**, 227 (1968).
(3) L. Lardicci, C. Botteghi, and P. Salvadori, *Gazz. Chim. Ital.*, **98**, 760 (1968).
(4) C. Botteghi, E. Guetti, G. Ceccarelli, and L. Lardicci, *ibid.*, **102**, 945 (1972).
(5) M. A. Gianturco and P. Friedel, *Can. J. Chem.*, **44**, 1083 (1964).
(6) P. Bosshard and C. H. Eugster, *Advan. Heterocycl. Chem.*, **7**, 378 (1966), and references cited therein.
(7) S. R. Ohlsen and S. Turner, *J. Chem. Soc. C*, 1632 (1971).
(8) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 119 (1963), and references cited therein.
(9) N. Elming, *Acta Chem. Scand.*, **6**, 605 (1952).
(10) D. Miller, *J. Chem. Soc. C*, 12 (1969).
(11) M. E. Garst and T. A. Spencer, *J. Amer. Chem. Soc.*, **95**, 250 (1973); see also ref 8 and literature cited therein.
(12) C. Botteghi and L. Lardicci, *Chim. Ind. (Milan)*, **52**, 265 (1970).
(13) C. Botteghi, G. Consiglio, G. Ceccarelli, and A. Stefani, *J. Org. Chem.*, **37**, 1835 (1972), and ref 12 therein.
(14) L. Lardicci, F. Navari, and R. Rossi, *Tetrahedron*, **22**, 1991 (1966).
(15) D. Evans, J. A. Osborn, and G. Wilkinson, *Inorg. Syn.*, **11**, 99 (1968).
(16) D. Evans, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. C*, 3133 (1968).
(17) The advantage of using rhodium catalysts in the hydroformylation of acrolein acetals was recently pointed out by Maeda and Yoshida.[18]
(18) I. Maeda and R. Yoshida, *Bull. Chem. Soc. Jap.*, **41**, 2969 (1968).
(19) The best yields were obtained when 4 was distilled off from the reaction mixture as formed.

TABLE I

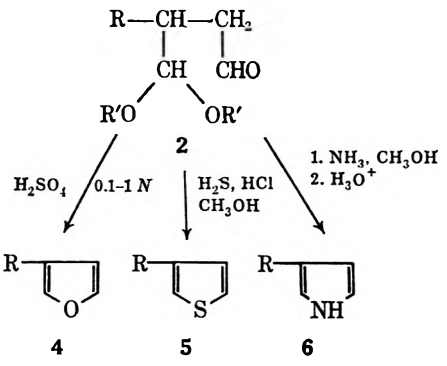
HYDROFORMYLATION OF α,β-UNSATURATED ACETALS (1) IN THE PRESENCE OF RHODIUM CATALYSTS TO THE CORRESPONDING ALKYL- AND ARYLSUCCINALDEHYDE MONOACETALS (2)

Substrate[a]	Concn, mol/l.	Catalyst	Concn, mmol/l.	Reaction pressure CO:H₂ 1:1, atm	Reaction temp, °C	Reaction time, hr	[α]²⁵D, deg (n-heptane)	Yield,[b] %
1a	1.23	RhCl(CO)(PPh₃)₂	5.82	100[c]	95	5	−6.94	85
	1.34		1.76	100[c]	80	*i*	−6.88	80
	1.50		2.10	100[c]	110	6	−6.84	79
	1.02		2.3	100[d]	80	6	*i*	80
1b	0.90	RhCl(CO)(PPh₃)₂	4.64	100[c]	75	50 min		70
	2.12		2.97	100[c]	80	2		76
	1.92		0.52	100[d]	80	24		70
1c	1.20	RhCl(CO)(PPh₃)₂	2.20	100[d]	105	5.5		75
	1.20		2.20	100[c]	110	5		60
	1.62	Rh[e,f]	4.00	10[c]	110	Very slow gas absorption		*i*
	1.62	Rh,[e] P(OPh)₃[g]	4.00	20[c]	110	73		60
1d	1.00	RhCl(CO)(PPh₃)₂	2.48	100[d]	90	5.5		80[h]

[a] The reaction mixture in benzene contains 0.7–0.75 mol of triethylamine per mol of substrate. [b] The yields are calculated on the isolated (by distillation) hydroformylation product. [c] Initial pressure at room temperature. [d] Experiment carried out at constant pressure at the reaction temperature. [e] 5% of rhodium on charcoal. [f] 0.5 ml of triethylamine was added to the reaction mixture. [g] 2.4×10^{-2} mol/l. [h] 15% of hydrogenation product was detected by nmr analysis. [i] Not determined.

(Scheme II). Cyclization of **2** to the corresponding thiophene **5** (50–60% yield) and pyrrole **6** (24% yield)

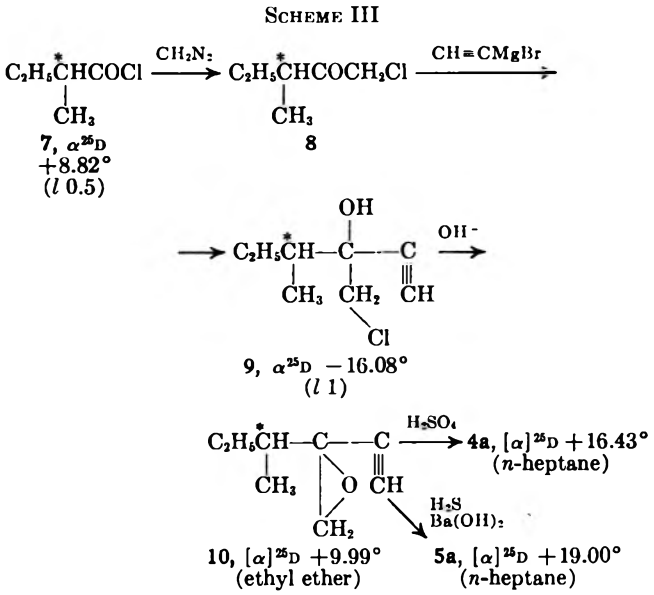
SCHEME II



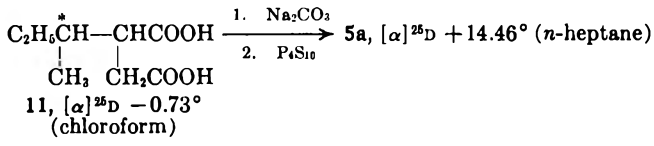
derivatives was accomplished in methanol solution by treatment with hydrogen sulfide and hydrogen chloride or by treatment with anhydrous ammonia followed by distillation in the presence of aqueous citric acid (Scheme II). The structures of **4**, **5**, and **6** were unequivocally confirmed by nmr and mass spectroscopy and, whenever possible, by direct comparison with authentic samples. The crude **4** and **5**, as recovered by distillation from the reaction mixture, were of satisfactory chemical purity (≥95% by glpc).[20] Table II gives results obtained in the cyclization of optically active **2** to the corresponding **4a** and **5a**.

Results of ring closures with the optically active compound **2a** were compared with prior art methods: (1) those of Miller[10] and Perveev,[21] shown in Scheme III, and (2) the ring closure of optically active *sec*-butylsuccinic acid[22] (**11**) which is available by resolution methods[23] (Scheme IV). The yields in the cyclization of **10** and **11** and the chemical purity of the products **4a** and **5a** were similar to those using Schemes I and II.

SCHEME III



SCHEME IV



Discussion

The results reported in Table I clearly point out that the synthesis of the 2-substituted succinaldehyde monoacetals (**2**) can be achieved in satisfactory yield (60–85%) and with a high degree of chemical purity (≥95%) through the hydroformylation of the α-alkylacrolein acetals **1**, which are readily available compounds.[24–26]

(20) In the cyclization of **2** to **5** a small amount of **4** (2–3% by glpc) was formed.

(21) F. Ya. Perveev and N. K. Kudryashova, *Zh. Obshch. Khim.*, **23**, 976 (1953); *Chem. Abstr.*, **48**, 8219 (1954); *Zh. Obshch. Khim.*, **23**, 1569 (1953); *Chem. Abstr.*, **48**, 10727 (1954).

(22) C. Botteghi, G. Ceccarelli, and G. Consiglio, *J. Prakt. Chem.*, **314**, 840 (1972).

(23) A. Fredga and U. Sahlberg, *Ark. Kemi*, **A18**, 8 (1944).

(24) J. A. Van Allan, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 21.

(25) R. Quelet and J. D'Angelo, *Bull. Soc. Chim. Fr.*, 1503 (1967).

(26) E. Elkik, *ibid.*, 283 (1968).

Table II

Cyclizations of the Optically Active 2-Alkylsuccinaldehyde Monoacetals (2a) to the Corresponding Furans (4a) and Thiophenes (5a)

2a $[\alpha]^{25}D$, deg (*n*-heptane)	Reaction conditions	Reaction time, hr	4a $[\alpha]^{25}D$, deg (*n*-heptane)	4a Yield, %	5a $[\alpha]^{25}D$, deg (*n*-heptane)	5a Yield, %
−6.94	H_2SO_4 0.1 *N*[a]	1	+18.24	77		
−6.88	H_2SO_4 0.1 *N*[a]	1	+19.86	73		
−6.84	H_2SO_4 0.5 *N*[a]	1	+17.91	72		
−6.94	H_2O–CH_3OH[b] H_2S–HCl	2			+24.86	60
−6.94	H_2O–CH_3OH[b] H_2S–HCl	2			+23.96	58

[a] The reaction mixture was heated to the boiling point and **4a** was distilled off as formed. [b] Water–methanol, 1:9 (v/v); reaction temperature 60°.

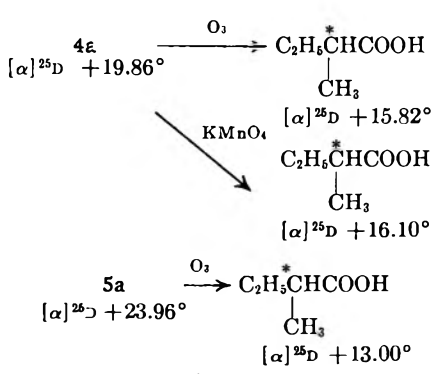
The nature of the α substituent in **1** does not seem to affect the reactivity of the double bond toward the addition of carbon monoxide and hydrogen.

It should also be noted that, while in the rhodium-catalyzed hydroformylation of similar substrates an appreciable extent of α addition can take place,[27,28] in the present case no significant amount ($\leqslant 2\%$) of α isomer was detected by glpc and nmr analysis.[29] Compounds **2** represent a very interesting class of 1,4-dicarbonyl compounds which have so far not been described in the literature and appear to be difficult to prepare by classical methods.

While the yields obtained in the cyclization of **2** to (+)-(*S*)-3-*sec*-butylpyrrole are very small (24%), because of the simultaneous formation of high-boiling by-products, they are quite satisfactory (50–60%) in the preparation of the furans **4** and thiophenes **5**. The reaction sequences of Schemes I and II are therefore competitive with those reported in the literature[6,10,11] for similar synthesis.

In order to obtain information on steric course in the preparation of the optically active heterocyclic compounds, **4a** and **5a** were cleaved by ozonolysis to (+)-(*S*)-2-methylbutanoic acid according to a previously described procedure[3,4] (Scheme V). On this basis a

Scheme V[a]



[a] $[\alpha]^{25}D$ measurements in *n*-heptane.

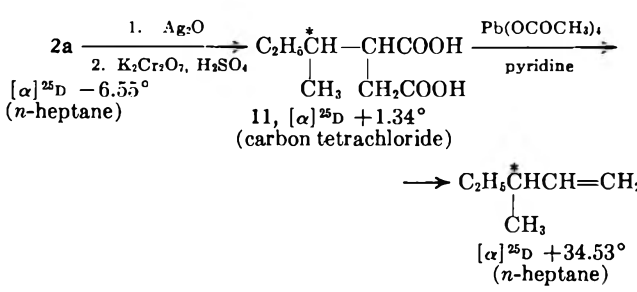
minimum optical purity of 65% for **5a** and 79% for **4a** was calculated; this last value was further confirmed by permanganate oxidation[30] (Scheme V).

The minimum optical purity of the (+)-(*S*)-3-*sec*-butylpyrrole,[31] prepared by us according to Scheme II, was estimated to be 73.5%.[32]

These results indicate, therefore, a 17–30% racemization with respect to the (+)-(*S*)-α-*sec*-butylacrolein[14] (optical purity ~96%) used as starting product.

Because the oxidative processes used have been successfully employed[3,4,30] in the breakdown of optically active heterocyclic systems and since a sample of **5a** does not racemize under the reaction conditions, it can be assumed that the overall racemization is to be attributed to the sequence (+)-(*S*)-α-*sec*-butylacrolein → **1a** → **2a** → **4a** or **5a**. In order to determine in which step of this sequence the maximum racemization takes place, a sample of (+)-(*S*)-α-*sec*-butylacrolein was converted *via* **2a** and its oxidation product, (*S*)-*sec*-butylsuccinic acid (**11**), to (+)-(*S*)-3-methyl-1-pentene[22] (Scheme VI). From the experimental data only

Scheme VI



a ~5% racemization was found; this result indicates that the hydroformylation process has no effect on the asymmetric carbon atom of **1a**. Thus, it is concluded that racemization primarily takes place during the cyclization process. This is confirmed by the following: (1) poor reproducibility of the rotation power of **4a** and **5a**, which arise from the same substrate **2a**; in all cases the optical purity of **5a** is lower than that of **4a** (Scheme V); (2) an obvious dependence of the optical purity of **4a** on the acidity of the medium (Table II); and (3) the considerable loss of optical activity in the preparation of **6** from **2a** (~18%). Although we are not yet able to postulate reasonable reaction interme-

(27) J. Falbe and N. Huppes, *Brennst.-Chem.*, **48**, 46 (1967).

(28) R. L. Pruett and J. A. Smith, *J. Org. Chem.*, **34**, 327 (1969).

(29) The hydroformylation product obtained under the same reaction conditions from the diethyl acetal of acrolein in practically quantitative yield contained the straight-chain and branched isomer in a 58:42 ratio (glpc).

(30) P. S. Skell and G. P. Bean, *J. Amer. Chem. Soc.*, **84**, 4660 (1962).

(31) J. M. Patterson, L. T. Burka, and M. R. Boyd, *J. Org. Chem.*, **33**, 4033 (1968).

(32) This is based on an $[\alpha]^{25}D$ of +26.98° for optically pure (+)-3-*sec*-butylpyrrole, a value derived from the oxidation experiments of Skell and Bean,[30] but with correction made using a more reliable $[\alpha]^{25}D$ value[33] for 2-bromobutane and a corrected value for (+)-(*S*)-2-methylbutanoic acid.[14]

(33) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4878 (1969), and ref 30 cited therein.

diates to account for the racemization of the 2-*sec*-butylsuccinaldehyde monoacetals (**2a**) in the cyclization process, it is tentatively concluded that species of considerable ionic character are involved in the ring-closure step, the observed partial racemization taking place in some way through these intermediates. In spite of the above-mentioned limitations, the method described provides a satisfactory synthetic approach to optically active 3-alkylfurans and thiophenes; in fact, using other optically active precursors and procedures already described[10,11,21] (Schemes III and IV), essentially lower optical yields (39–66%) in the preparation of **4a** and **5a** were obtained.

Experimental Section

Boiling points are uncorrected. Glpc analyses were performed on a Perkin-Elmer F-11 chromatograph, using the columns and the temperatures specified. Infrared spectral data were recorded on a Perkin-Elmer 221 spectrometer. Nmr spectra were recorded on a Varian A-60 spectrometer in CCl_4 solution (10%), with TMS as an internal standard (δ 0). Mass spectra were obtained with an Hitachi Perkin-Elmer RNU-6L mass spectrometer. All rotations were taken on a Perkin-Elmer 141 polarimeter in 1-dm or 0.1-dm tubes. Analyses were performed by the Microanalytical Laboratory of the Technical-Chemical Department of ETH (Zürich, Switzerland).

Acetals of 2-Substituted α,β-Unsaturated Aldehydes (1a–d).—Methacrolein from Fluka AG (Switzerland) was used without further purification. (+)-(*S*)-2-*sec*-Butylacrolein and 2-isopropylacrolein were prepared by a general method described in the literature.[14,34]

The corresponding ethyl acetals 1a–c were prepared according to the procedure described by Van Allan[24] and employed by other authors.[25] The dioxolane of atropic aldehyde (**1d**) was obtained by the method of Elkik[26] in 23% overall yield. The physical constants of **1b–d** were consistent with those reported in the literature.[12,25,26]

Pure **1a** showed bp 73–75° (12 mm); n^{25}D 1.4210; $[\alpha]^{25}$D +23.75° (*c* 2.901, *n*-heptane).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.58; H, 12.07.

Monoacetals of 2-Substituted Succinaldehydes (2a–d).—The following two procedures are representative of the hydroformylation experiments.

A.—Into a 0.2-l. autoclave, evacuated from air and containing $RhCl(CO)(PPh_3)_2$ (0.300 g), a solution of **1** (21.6 g, 0.1 mol) and triethylamine (8.42 g, 11.5 ml) in dry benzene (40 ml) was introduced by suction. A mixture of CO and H_2 (1:1) was then introduced to a pressure of 100 atm; the autoclave was then rocked and heated to 80–100°. Reaction started immediately and was allowed to proceed until no more pressure drop was observed. After cooling and release of the pressure, the slightly yellow reaction mixture was evaporated under reduced pressure (100 mm) and the residue was distilled under vacuum over K_2CO_3 to give compounds **2a–d** (60–80% yield) as colorless liquids (Table I).

B.—Following the same experimental procedure, **1c** (0.4 mol) in benzene (200 ml) was hydroformylated (73% yield) in a 0.5-l. autoclave in the presence of 5% Rh/C (2.0 g)[28] and triethylamine (0.5 ml) at 20 atm (CO:H_2 1:1) and 110°. Glpc analyses of **2a–d** (on a 2 m × 2.2 mm 15% polypropylene glycol column at 120–140°) showed only one peak.

The same results were obtained for **2a** and **2b** using a 16 m × 0.5 mm Carbowax 20M support coated column at 160 and 140°, respectively.

2a had bp 67–70° (0.6 mm); n^{25}D 1.4324; $[\alpha]^{25}$D −6.94° (*c* 3.786, *n*-heptane); ir (liquid film) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 9.64 (m, CHO), 2.21 (m, CH_2CHO).

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.59; H, 11.03.

2b had bp 80° (13 mm); n^{25}D 1.4190–1.4192; ir (liquid film) 1716 cm^{-1} (C=O); nmr (CCl_4) δ 9.70 (m, CHO), 2.38 (m, CH_2CHO).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.10; H, 10.39.

2c had bp 110–112° (12 mm); n^{25}D 1.4290; ir (liquid film) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 9.50 (m, CHO), 2.18 (m, CH_2CHO).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.60; H, 10.87.

2d had bp 108–112° (0.3 mm); ir (liquid film) 1718 cm^{-1} (C=O); nmr (CCl_4) δ 9.57 (m, CHO), 2.70 (m, CH_2CHO); 2,4-dinitrophenylhydrazone mp 217–219° (*m*-xylene).

Anal. Calcd for $C_{22}H_{18}N_8O_8$: C, 50.58; H, 3.47; N, 21.45. Found: C, 50.67; H, 3.68; N, 21.21.

Cyclization of 2a–c to 3-Alkylfurans (4a–c).—A sample of **2** (0.15 mol) was rapidly added to a boiling solution of 0.1 *N* sulfuric acid (1 l.) and the reaction product was distilled as formed through a short-path distillation apparatus. The liquid product was separated from the water and washed with concentrated solutions of calcium chloride and ammonium chloride. After drying (Na_2SO_4), the crude **4** was distilled over sodium to give a colorless liquid (40–80% yield); glpc analysis (on a 2 m × 2.2 mm 15% polypropylene glycol column at 40–90°) showed only one peak.

4a had bp 130°; n^{25}D 1.4415–1.4417; $[\alpha]^{25}$D +19.86° (*c* 3.020, *n*-heptane); nmr ($CDCl_3$) δ 6.36 (m, H-4), 7.30 (m, H-2), 7.46 (m, H-5); mass spectrum (70 eV) *m/e* (rel intensity) 95 (100), 67 (30), 41 (23.5), 124 (M^+, 22), 96 (16), 39 (15.5), 81 (11), 27 (9), 28 (8), 109 (7).

4b had bp 62–63° (730 mm); n^{20}D 1.4329–1.4330 (lit.[10] bp 65–66.5°, n^{21}D 1.4299); nmr ($CDCl_3$) δ 6.29 (m, H-4), 7.27 (m, H-2), 7.38 (m, H-5).

4c had bp 111°; n^{25}D 1.4348 (lit.[9] bp 111°, n^{25}D 1.4344); nmr (CCl_4) δ 6.21 (m, H-4), 7.11 (m, H-2), 7.25 (m, H-5); mass spectrum *m/e* (rel intensity) 95 (100), 67 (50.5), 110 (M^+, 47.5), 41 (37), 39 (27.5), 65 (13.5), 27 (11), 18 (10), 28 (8.5), 96 (7.5).

In another experiment **4a**, $[\alpha]^{25}$D +17.91° (*c* 1.87, *n*-heptane) (optical purity 71%), was prepared in 58% yield by cyclization of **2a**, $[\alpha]^{25}$D −6.84° (*c* 2.294, *n*-heptane), with 0.5 *N* sulfuric acid.

3-Phenylfuran (4d).—The method of Miller[10] for the cyclization of 3,4-epoxy-3-phenyl-1-butyne was used. A sample of **2d** (3.0 g, 0.0145 mol) in ethanol (15 ml) was added in one portion to 2 *N* sulfuric acid (20 ml), and the mixture was refluxed for 20 min with vigorous stirring. After cooling, the reaction mixture was diluted with water (50 ml) and the resulting oil was extracted exhaustively with pentane. The extracts were dried ($MgSO_4$) and the solvent was evaporated to leave yellow crystals of crude 3-phenylfuran. Sublimation at 60–70° (13 mm) gave pure **4d** (1.16 g, 55% yield): mp 58–59°;[10] nmr (CCl_4) 6.59 (m, H-4), 7.62 (m, H-2), 7.38 (m, H-5), 7.05–7.52 (m, equal to five phenyl ring protons); mass spectrum *m/e* (rel intensity) 115 (100), 144 (M^+, 82.5), 29 (61.5), 63 (16), 89 (15), 33 (15), 116 (13.5), 145 (9.5), 39 (8.5), 65 (7).

Cyclization of 2a–d to 3-Substituted Thiophenes (5a–d).—A sample of **2** (0.1 mol) was dissolved in 90% methanol (200 ml), and a slow stream of hydrogen sulfide was bubbled into the stirred solution during 1 hr at room temperature. The reaction mixture was heated at 50–60° and a stream of hydrogen chloride was allowed to flow onto the surface of the solution. After 2 hr the reaction was complete. The mixture was cooled, diluted with water (600 ml), and extracted with pentane (200 ml). The pentane extracts were dried ($MgSO_4$) and the solvent was removed, yielding a yellow-brown residue which was distilled over sodium to give **5a** and **5b** as colorless liquids (50–60% yield) or crystallized from ethanol to give **5d** as white plates (50% yield).

5a had bp 63° (12 mm); n^{25}D 1.5000; $[\alpha]^{25}$D +24.86° (*c* 2.88, *n*-heptane); nmr ($CDCl_3$) δ 7.28 (m, H-5), 6.88–7.08 (m, equal to two hydrogens, H-2 and H-4); mass spectrum *m/e* (rel intensity) 111 (100), 140 (M^+, 54.5), 45 (20.5), 97 (20), 77 (19.5), 112 (18), 39 (14), 67 (12), 41 (11), 125 (9).

5b had bp 114–115°; n^{26}D 1.5174 (lit.[35] bp 115.4°, n^{25}D 1.5175). This compound was identified by comparison of its physical constants and its nmr spectrum with those of a commercially available sample.

5d had mp 89° (lit.[36] mp 89.5–90.5°); mass spectrum *m/e* (rel intensity) 160 (M^+, 100), 115 (33), 161 (13), 116 (11), 128 (9.5), 80 (7), 89 (6), 67 (6), 63 (5.5), 45 (4.5).

(+)-(*S*)-**3-*sec*-Butylpyrrole (6).**—Into a solution of **2a** (0.1 mol), $[\alpha]^{25}$D −6.84° (*c* 2.294, *n*-heptane), in methanol (60 ml)

(34) M. B. Green and H. J. Hickinbottom, *J. Chem. Soc.*, 3266 (1957).

(35) H. D. Hartough in A. Weissberger, "The Chemistry of Heterocyclic Compounds," Interscience, New York, N. Y., 1952, p 72.

(36) S. Gronowitz and N. Gigs, *Acta Chem. Scand.*, **21**(3), 2823 (1967).

a stream of anhydrous ammonia was bubbled during 3 hr at 0°; then the mixture was heated for 1 hr at 40°. The resulting solution was added dropwise during 30 min to a boiling solution of citric acid (40 g) in 1.8 l. of water, and the reaction product was distilled as soon as formed. The recovered yellow oil (7 g) contained 43% of 6 and 36% of another compound (glpc). By preparative glpc at 170° (on a 3 m × 8 mm column packed with 15% polyglycol 4000 on Kieselgur, treated with potassium hydroxide) a pure sample of 6 was obtained:[31] bp 83° (12 mm); $n^{25}D$ 1.4870; $[\alpha]^{25}D$ +19.82° (neat) (optical purity 73%); nmr (CCl_4) δ 6.08 (m, H-4), 6.48 (m, H-2), 6.60 (m, H-5); mass spectrum *m/e* (rel intensity) 94 (100), 123 (M^+, 46), 80 (15.5), 67 (14.5), 108 (14), 93 (14), 95 (13.5), 41 (11.5), 39 (11), 28 (8).

The other compound proved to be recovered **2a** with $[\alpha]^{25}D$ −6.90° (*c* 2.78, *n*-heptane).

(*S*)-1-Chloro-3-methyl-2-pentanone (8).—To an ether solution of diazomethane at 0° was added during 2 hr 28.2 g (0.233 mol) of **7**, $\alpha^{25}D$ +8.82° (*l* 0.5).[37] The reaction mixture was allowed to stand for 12 hr and then saturated with hydrogen chloride at 0°. After stirring for an additional 8 hr at 0° the mixture was hydrolyzed by a described procedure[38] and the ether extracts were dried (Na_2SO_4). After removal of the solvent, distillation of the crude product yielded 16.24 g of **8** (51.5% yield), bp 62–63° (13 mm), $n^{25}D$ 1.4402.

(−)-(*S*)-3-*sec*-Butyl-4-chloro-1-butyn-3-ol (9).—A solution of ethylmagnesium bromide (0.160 mol) in dry THF was added dropwise to 70 ml of the same solvent saturated with acetylene. During this addition a stream of the gas was allowed to bubble into the solution. A sample of **8** (14.0 g, 0.104 mol) in THF (20 ml) was dropped (45 min) into the solution of ethynylmagnesium bromide at 0°. The reaction mixture was allowed to stand for 12 hr and then hydrolyzed by a cold saturated solution of NH_4Cl. The organic layer was separated, washed with water, and dried ($CaSO_4$). The solvent was removed and the residue was distilled, yielding 13.3 g (79.8%) of **9**: bp 83° (15 mm); $n^{25}D$ 1.4662–1.4664; $\alpha^{25}D$ −16.08° (*l* 1).

Anal. Calcd for $C_8H_{13}OCl$: C, 59.81; H, 8.15; Cl, 22.06. Found: C, 60.00; H, 8.06; Cl, 21.74.

(+)-(*S*)-3-*sec*-Butyl-3,4-epoxy-1-butyne (10).—A sample of **9** (13.0 g, 0.081 mol) in anhydrous ether (20 ml) was added during 3 hr to a stirred suspension of pulverized sodium hydroxide (15.8 g) in 60 ml of ether. After 5 hr, the reaction mixture was hydrolyzed by water at 0° and extracted with ethyl ether. After drying (Na_2SO_4) the solvent was evaporated, and distillation of the crude product afforded **10** (9.36 g, 93% yield): bp 133–134° (770 mm); $n^{25}D$ 1.4334; $[\alpha]^{25}D$ +9.99° (*c* 5.002, ethyl ether).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.20; H, 9.67.

Cyclization of 10 to (+)-(*S*)-*sec*-Butylfuran (4a).—A sample of **10** (5.68 g, 0.045 mol) was converted to the corresponding furan **4a** (3.93 g) by the procedure described by Miller[10] (69% yield). The fraction of bp 127–128° and $n^{25}D$ 1.4398 was 98.5% pure (glpc); $[\alpha]^{25}D$ +16.43° (*c* 3.166, *n*-heptane) (optical purity 66%).

Cyclization of 10 to (+)-(*S*)-3-*sec*-Butylthiophene (5a).—Into a stirred mixture of **10** (3.4 g, 0.027 mol) and barium hydroxide (1.3 g) in 15 ml of water a slow stream of hydrogen sulfide[21] was bubbled during 5 hr at 55–60°. After cooling, the reaction mixture was diluted by water (50 ml) and extracted with three 20-ml portions of *n*-pentane. The solvent was evaporated and the crude product was distilled over sodium to give **5a** as a colorless liquid (2.1 g, 50% yield): bp 65° (12 mm); $n^{25}D$ 1.5001; $[\alpha]^{25}D$ +19.00° (*c* 3.015, *n*-heptane) (optical purity 51%).

Oxidation of 2a to (*R,S*)- and (*S,S*)-*sec*-Butylsuccinic Acid (11).[39]—To a stirred mixture of **2a** (9.72 g, 0.045 mol), $[\alpha]^{25}D$ −6.55 (*c* 1.787, *n*-heptane), and $AgNO_3$ (25.3 g, 0.153 mol) in water (50 ml), 110 ml of a 7.0% aqueous solution of NaOH was added during 2.5 hr at room temperature. The reaction mixture was then stirred at 25° for 24 hr and at 50° for 7 hr. The silver was removed, and the alkaline solution was concentrated to 30 ml and extracted with four 30-ml portions of ether. The aqueous solution was then added dropwise during 1 hr to an oxidizing mixture, held at 20–25°, of 22.5 g of $K_2Cr_2O_7$ and 20 ml of 98% sulfuric acid in 100 ml of water. The mixture was stirred at 25° for 48 hr, and the organic layer was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent afforded crude **11** as a slightly yellow oil, which was shaken with pentane for 2 hr and allowed to stand at −10° for 3 days. The crystalline **11** (5.60 g, 71% yield) was filtered, washed with pentane, and dried under vacuum, mp 82–86°, $[\alpha]^{25}D$ +1.34° (*c* 0.723, CCl_4). Glpc analysis on a 100-m polyethylene glycol succinate capillary column at 100° showed the presence of both diastereoisomers, for which the following composition was determined:[22] (*R,S*), ~54%, (*S,S*), ~46%.

Oxidation of 11 to (+)-(*S*)-3-Methyl-1-pentene.—To a solution of **11** (4.4 g, 0.0253 mol) and dry pyridine (3.05 ml) in benzene (40 ml) was added under nitrogen atmosphere 13.17 g of lead tetraacetate (~85% chemical purity). The reaction mixture was stirred at 50–60° for 1 hr and at 75° for 3 hr while the volatile reaction products were swept out by a slow stream of dry nitrogen and collected in a trap cooled to −70°. The olefin (0.656 g, 32% yield from the corresponding dibromide) was ≥99% pure (glpc): bp 53–54°; $n^{20}D$ 1.3844; $[\alpha]^{25}D$ +34.53° (*c* 1.717, *n*-heptane) (optical purity 91%).[40]

Cyclization of 11 to (+)-(*S*)-3-*sec*-Butylthiophene (5a).—A sample of **11** (6.2 g, 0.0356 mol), $[\alpha]^{25}D$ −0.73° (*c* 0.745, $CHCl_3$), was neutralized (phenolphthalein) by a solution of 1.0 *N* sodium hydroxide and the water was completely evaporated. The resulting **11** sodium salt was carefully dried under vacuum, mixed with 7.0 g of P_4S_{10}, and introduced into a reaction vessel containing 20 ml of high-boiling oil. The stirred reaction mixture was then heated to 250° until the reaction started. A slow stream of dry nitrogen removed the reaction product as formed; it was collected in a trap cooled at −30°. The crude **5a** (3.5 ml) in pentane (10 ml) was washed twice with 10% sodium hydroxide (20 ml). The dried (Na_2SO_4) pentane extracts were distilled over sodium to give **5a** (2.1 g, 40% yield) (≥99% pure, glpc): bp 118–120°; $n^{25}D$ 1.5002; $[\alpha]^{25}D$ +14.46° (*c* 3.458, *n*-heptane) (optical purity 39%).

Ozonization of 4a.—A sample of **4a** (4.0 g, 0.032 mol), $[\alpha]^{25}D$ +19.86° (*c* 3.02, *n*-heptane), was dissolved in methylene chloride (70 ml) and a stream of oxygen containing 3% ozone was allowed to flow into the solution for 5 hr at 20°. The resulting ozonide was decomposed and (+)-(*S*)-2-methylbutanoic acid was recovered by the usual procedure[3,4] (2.1 g, 75.6% yield): bp 82–83° (15 mm); $n^{25}D$ 1.4042; $[\alpha]^{25}D$ +15.82° (*c* 2.863, *n*-heptane) (optical purity 79%).[3]

Oxidation of 4a.—The method of Skell and Bean[30] was employed. To a solution of 22.12 g (0.014 mol) of $KMnO_4$ in water (300 ml), **4a** (2.0 g, 0.016 mol), $[\alpha]^{25}D$ +19.86° (*c* 3.02, *n*-heptane), was added portionwise at 5–10°. By working up the reaction mixture in the usual manner,[30] (+)-(*S*)-2-methylbutanoic acid (0.2 g) was recovered (≥98% pure, glpc), $[\alpha]^{25}D$ +16.10° (*c* 1.006, *n*-heptane) (optical purity 81%).[3]

Ozonization of 5a.—A sample of **5a** (4.3 g, 0.03 mol), $[\alpha]^{25}D$ +23.96° (*c* 3.522, *n*-heptane), in methylene chloride (70 ml) was ozonized by the above procedure and (+)-(*S*)-2-methylbutanoic acid (32%) was obtained (≥98% pure, glpc): bp 80° (13 mm); $n^{25}D$ 1.4044; $[\alpha]^{25}D$ +12.99° (*c* 2.455, *n*-heptane) (optical purity 65%).

Racemization Attempt of (+)-(*S*)-3-*sec*-Butylthiophene (5a).—A 0.5 *M* solution of **5a**, $[\alpha]^{25}D$ +24.86° (*n*-heptane) (optical purity 67%), in methanol–water (9:1, v/v) was treated with a stream of hydrogen chloride and hydrogen sulfide for 15 min and then heated in a polarimeter tube at 62° for 5 hr. During this time no decrease of the optical activity was noticed, $[\alpha]^{62}D$ +22.39° (*c* 1.054) ($[\alpha]^{25}D$ +25.71°).

Registry No.—**1a**, 26871-36-3; **1b**, 23553-27-7; **1c**, 16627-19-3; **1d**, 16486-91-2; **2a**, 26871-37-4; **2b**, 26870-43-9; **2c**, 39542-01-3; **2d**, 39542-02-4; **2d** dinitrophenylhydrazone, 39542-03-5; **4a**, 26871-39-6, **5a**, 26871-40-9; **6**, 17289-43-9; **7**, 27763-54-8; **8**, 39542-08-0; **9**, 39542-09-1; **10**, 39542-10-4; (*R,S*)-**11**, 39497-75-1; (*S,S*)-**11**, 39542-12-6; (+)-(*S*)-3-methyl-1-pentene, 5026-95-9; (+)-(*S*)-2-methylbutanoic acid, 1730-91-2.

Acknowledgment.—The authors wish to thank Dr. Carlo Battistini for his helpful cooperation in the synthesis of acetylenic derivatives.

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Ionic and Free-Radical Bromination of 5,6-Dichloro-2-norbornenes

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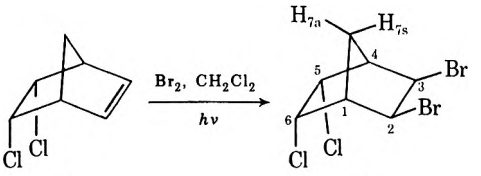
Free-radical bromination of *endo-cis*-5,6-dichloro-2-norbornene (**1**) with molecular bromine in methylene dichloride at 25° gave exclusively cis-exo dibromide **4**, whereas *exo-cis*-5,6-dichloro-2-norbornene (**2**) afforded a 10:1 mixture of trans (**5**) and cis (**6**) dibromides. *trans*-5,6-Dichloro-2-norbornene (**3**) gave a 1.5:1 mixture of cis (**8**) and trans (**7**) dibromides on free-radical bromination. Bromination of **2** and **3** under ionic conditions proceeded stereospecifically trans to afford **5** and **7**, respectively. The importance of steric effects and bridging in the free-radical and ionic pathways is discussed.

endo-cis-5,6-Dichloro-2-norbornene (**1**) brominated sluggishly under ionic conditions, although very facile stereospecific free-radical bromination with molecular bromine in methylene dichloride at 25° was realized.[1] The exo-cis dibromide **4** was the exclusive product.



1 **4**

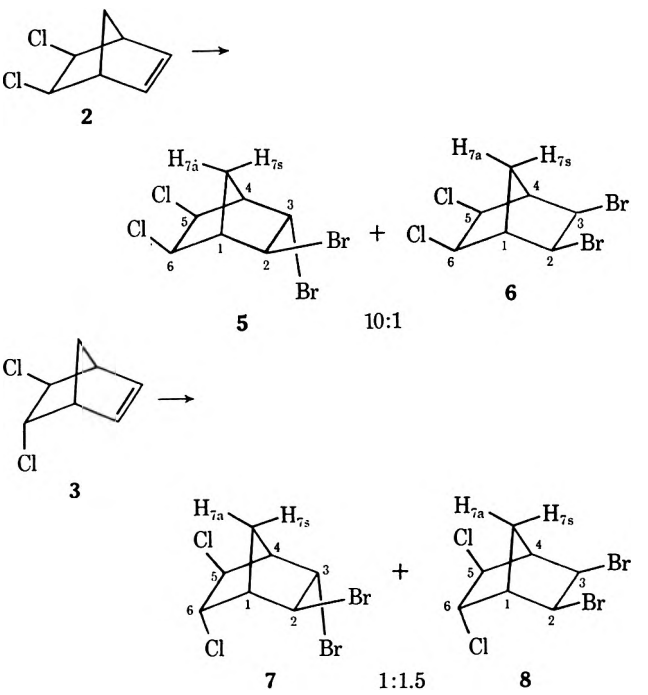
An endo-5,6-chlorine steric effect was suggested to explain these results.[1] The availability of the exo-cis dichloride **2**[2,3] and the trans dichloride **3**[3] isomers suggests a similar study for further investigation of the directing influence of the chlorine substituents in the free-radical brominations.

Ionic bromination of **2** and **3** was also noted, although no stereochemical results were presented.[1] A comparative study of the ionic and free-radical brominations of **2** and **3** therefore was undertaken to assess the influence of chlorine substitution on the respective product distributions. A further comparison with the ionic product distribution from the bromination of norbornene itself, where extensive 6,1- and 6,2-hydride shifts and Wagner–Meerwein rearrangement predominate,[4,5] was made.

Results

Bromination of olefins **2** and **3** in methylene dichloride solvent at 25° in a nitrogen atmosphere with molecular bromine and illumination with a 275-W sun lamp was instantaneous. Olefin **2** was converted to a mixture of two dibromide products which accounted for >98% of the products. The major product (89–94%) was identified as **5** and the minor product (6–11%) was the cis isomer **6**. The trans dichloride **3** afforded a 1.5:1 mixture of cis (**8**) to trans (**7**) products under these conditions. The dibromides **7** and **8** accounted for >98% of the products formed.

Olefins **2** and **3** slowly consumed bromine in methylene chloride solvent in the dark and under oxygen at 25° (ionic conditions). Olefin **2** afforded a single product (>99.5%) identified as the trans dibromide **5**.



2 **5** 10:1 **6**

3 **7** 1:1.5 **8**

The trans dibromide **7** was the sole product obtained from the bromination of **3** under ionic conditions.[6]

The dibromides were all stable to the reaction and analytical conditions and the respective product distributions are those of the kinetically controlled addition reactions.

Structural Assignments.—The respective dibromide structures were established by ^{1}H nmr. Tables I and II contain the chemical shift and coupling constant data. Appropriate double-resonance experiments allowed for the assignment of long-range couplings.[7]

The dibromide **4** gave a simple spectrum with the downfield vicinal protons adjacent to bromine (δ 4.88) split into a sharp doublet (J = 2.0 Hz). Long-range coupling with H_{7a} established the source of this splitting, and the protons adjacent to bromine are therefore cis-endo. The vicinal protons adjacent to chlorine (δ 4.41) appeared as a deceptively simple triplet with $J_{H_1H_6} + J_{H_4H_5} = J_{H_4H_5} + J_{H_1H_5} = 4.7$ Hz. The magnitude of these couplings suggests that protons H_5, H_6 are cis-exo.

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(6) Competitive experiments indicate that the relative rates of ionic bromination are **2** > **3** > **1** with $k_2/k_3 \cong 3.5$. A discussion of the bromination kinetics and halogen inductive effects is reserved for future publication.

(7) Nmr spectra (100 MHz) of dibromides **5**, **7**, and **8** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2366.

TABLE I

CHEMICAL SHIFTS[a] FOR DIBROMODICHLORONOBORNANES IN DEUTERIOCHLOROFORM

	Chemical shift				
Nucleus	4	5	6	7	8
H_1	2.90		2.86	2.74	2.87
		2.71[b]			
H_4	2.90		2.86	2.67	2.76
H_2	4.88	3.74	4.16	4.5[c]	4.70
H_3	4.88	4.39	4.16	4.5[c]	4.14
H_5	4.41	4.72	4.10	4.41	3.71
H_6	4.41	4.13	4.10	4.31	4.2[c]
H_{7s}	2.53	2.06		2.24	2.52
			2.28[b]		
H_{7a}	1.62	2.34		2.16	2.14

[a] All chemical shifts are in parts per million (δ) relative to internal tetramethylsilane. [b] Individual resonances not resolved. [c] Not determined accurately owing to interferences.

TABLE II

COUPLING CONSTANTS FOR DIBROMODICHLORONORBORNANES

	Coupling constant, Hz				
Nuclei	4	5	6	7	8
H_1H_2			c		
H_1H_6	a		b	4.5	4.5
H_2H_3		3.3			6.8
H_3H_4		5	c	3.2	
H_4H_5	a		b		
H_5H_6		6.6		3	3.0
$H_{7s}H_5$		1.9	b	2	2.7
$H_{7s}H_6$		1.9	b		
$H_{7a}H_2$	2.0	2	c	2	1.9
$H_{7a}H_3$	2.0		c		1.9
$H_{7s}H_{7a}$	11.8	11.8		11.8	11.6

[a] $J_{H_1H_6} + J_{H_4H_6} = J_{H_4H_5} + J_{H_1H_5} = 4.7$ Hz. [b] $J_{H_1H_6} + J_{H_4H_6} + J_{H_6H_{7s}} = J_{H_4H_5} + J_{H_1H_5} + J_{H_5H_{7s}} \cong 1.6$ Hz. [c] $J_{H_3H_4} + J_{H_1H_3} + J_{H_3H_{7a}} = J_{H_1H_2} + J_{H_2H_4} + J_{H_2H_{7a}} \cong 1.5$ Hz.

The vicinal protons H_2, H_3 and H_5, H_6 adjacent to halogen in **6** appeared as sharp multiplets ($W_{1/2} = 2.2$ Hz) in each case. These narrow resonances suggest that both sets of protons are cis-endo. The downfield resonance (δ 4.16) was assigned to protons H_2, H_3 adjacent to bromine while H_5, H_6 (δ 4.10) were adjacent to chlorine. These assignments were based on the reported downfield shift of protons geminal to bromine relative to chlorine in halogenated norbornanes and norbornenes.[8]

The protons H_5, H_6 vicinal to chlorine in **5** appeared as an AB quartet of doublets at δ 4.13 and 4.72 with $J_{H_5H_6} = 6.6$ Hz. The magnitude of this coupling is consistent with a cis orientation for these protons.[8-13] Long-range $H_{7s}H_{5,6}$ coupling of 2 Hz established the cis-endo orientation of H_5, H_6. The protons H_2 and H_3 adjacent to bromine appeared as a complex downfield multiplet at δ 4.39 and an apparent triplet at δ 3.74. The proton at δ 4.39 was coupled to a bridgehead proton at δ 2.70 by *ca.* 5 Hz, whereas the upfield proton showed no appreciable coupling with H_1 or H_4. The downfield proton H_3 is therefore exo. Proton H_2 (δ 3.74) was coupled to both H_3 and H_{7a} by 3.3 and *ca.* 2 Hz, respectively. The magnitude of $J_{H_2H_3}$ also is consistent with trans coupling in the norbornane system.[8,9,12,13] Proton H_3 showed no appreciable coupling with the bridgehead protons H_{7a}, H_{7s}.

The nmr spectrum of dibromide **8** can be similarly interpreted. Vicinal protons H_2, H_3 geminal to bromine (δ 4.70, 4.14) appeared as an AB quartet of doublets with $J_{H_2H_3} = 6.8$ Hz and $J_{H_{7a}H_{2,3}} = 1.9$ Hz. The endo proton at δ 3.71 adjacent to chlorine was an apparent triplet with $J_{H_{7s}H_6} = 2.7$ Hz and $J_{H_5H_6} = 3.0$ Hz, which suggests trans orientation for H_5 and H_6. Proton H_6 at *ca.* δ 4.2 was coupled to bridgehead proton H_1 (δ 2.87) by 4.5 Hz, which is consistent with exo assignment.

Adduct **7** gave a complex nmr spectrum which was further complicated by the overlap of two proton resonances at *ca.* δ 4.5 at 100 or 220 MHz. Decoupling experiments at 220 MHz established that the upfield proton (δ 4.31) was exo ($J_{H_1H_6} = 4.5$ Hz) and the δ 4.41 multiplet was an endo proton. The δ 4.41 multiplet resulted from a 2-Hz coupling with the methylene bridge proton H_{7s} at δ 2.24 and a trans coupling of ~3 Hz. One proton at δ 4.5 was coupled to the methine bridge proton (δ 2.67) by 3.2 Hz. Irradiation of the δ 4.5 multiplet also revealed a 2-Hz coupling with the methylene proton at δ 2.16. The assignment of the high-field exo proton geminal to chlorine (H_6) was based on the apparent greater shielding from bromine relative to chlorine in dichloronorbornanes[8] (compare also H_{3x} in **5** and H_{6x} in **8**). The endo protons H_2, H_5 adjacent to bromine and chlorine could not be unequivocally assigned. The small chemical shift difference between H_6 (δ 4.31) and the proton at δ 4.41 did not permit effective decoupling experiments. However, irradiation of H_6 did not appreciably alter the δ 4.5 multiplets. Proton H_{7a} was assigned at δ 2.16 based on the similar chemical shift of H_{7a} (δ 2.14) in **8**. The observed 2-Hz coupling of H_{7s} (δ 2.24) with the proton at δ 4.41 further suggests that the latter endo proton (H_5) is adjacent to chlorine.

Exo protons geminal to halogen normally appear downfield relative to endo protons in dihalonorbornanes.[8] This was also the case for H_5, H_6 in **8** and H_2, H_3 in **5**. However, for derivative **7** exo proton H_6 was upfield from the endo protons. This suggests appreciable shielding from Br_{3n} and Cl_{6n} on protons H_{5n} and H_{2n}, respectively. This proximity effect has been noted previously.[1] Comparison of derivatives **5** and **6** indicates that Br_{3n} deshields H_{5n} by 0.62 ppm (δ 4.72–4.10) while H_{6n} remains unperturbed (0.03 ppm). Comparison of **7** and **8** reveals a similar deshielding effect (δ 4.41–3.71 = 0.70 ppm). Deshielding by chlorine of *ca.* 0.7 ppm (H_{2n} in **4** and **6** and in **5** and **7**) was also evident. The effects are consistent with the suggested positive magnetic anisotropy of the carbon–halogen bond.[8,14]

Discussion

Free-radical bromination of olefins **1** and **2** involves initial attack by bromine from the exo side, which is unexceptional for large adducts,[1,12,13] to afford intermediate radicals **1a** and **2a**. The direction of subsequent attack by the propagating bromine molecule on **1a** or **2a** will be determined by the relative steric

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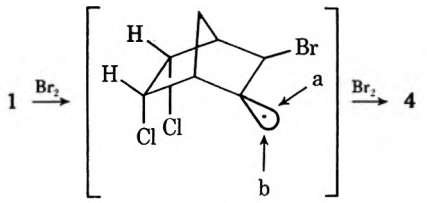
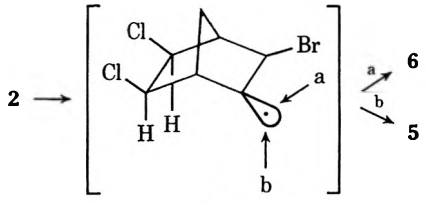


1a



2a

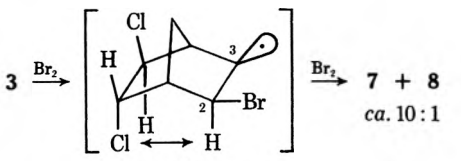
interactions of incoming bromine with the exo bromine substituent and with the endo substituents (Cl or H). For **2a**, nonbonded interaction with the exo bromine substituent is more severe than the endo hydrogen–bromine interaction and attack by path b is preferred. The 5:6 product ratio of 10:1 reflects these factors. However, the endo chlorine substituent provides substantial interference for attack by bromine from the endo direction on intermediate **1a** (path b) and attack from path a is now preferred. The exclusive formation of the exo-cis adduct **4** from olefin **1** is the result. Similar effects have been demonstrated for endo fluorine and endo methyl substituents in the free-radical addition of halogens[1,15] and polyhalomethanes[12,13,15,16] to norbornenes.

The bromination result for olefin **2** also suggests the appropriate stereochemistry for the radical bromination of norbornene itself. The distribution of dibromide products for the free-radical bromination of norbornene is unknown, although it has been suggested that the addition is predominantly trans.[1,4,15] Norbornene has an overwhelming preference for ionic bromination, even at −78°, which obviates any meaningful study of the radical pathway. Fortunately, the chlorine substituents in **2** sufficiently deactivate the double bond toward ionic bromination so that the radical process is favored, and the radical product distribution can be obtained with confidence. The 5,6-exo chlorine substituents in **1** are not anticipated to affect the stereochemistry of addition to the double bond, and the 10:1 preference for trans addition of **1** can be applied to the radical bromination of norbornene itself.

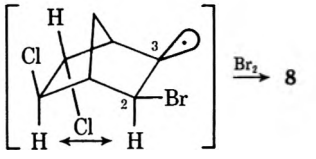
Initial addition of bromine to **3** can afford both intermediate radicals **3a** and **3b**. Subsequent attack by bromine on **3b** occurs from the exo direction, for the endo chlorine completely shields endo attack as in **1a**, with the formation of product **8**. Attack on **3a** by propagating bromine should exhibit stereospecificity similar to that for attack on **2a** with endo attack preferred by a factor of *ca.* 10:1. The observed product distribution of 60% **8** and 40% **7** can be used to calculate the **3b**:**3a** ratio, with the assumption that **3a** leads to 91% **7** and 9% **8**, which gives **3b**:**3a** = 1.4.

The preference for **3b** formation can be explained as follows. Attack at C_2 or C_3 on **3** results in the movement of the olefin hydrogen to an endo position as sp^3

(15) B. E. Smart, *J. Org. Chem.*, **38**, 2039 (1973).
(16) B. E. Smart, *J. Org. Chem.*, **38**, 2035 (1973).



3a

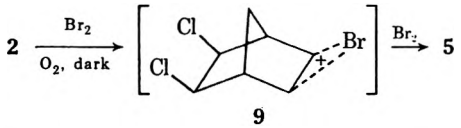


3b

development at the attacked carbon proceeds. The carbon atom which accommodates the odd electron retains its sp^2 configuration and little change in geometry is anticipated. Attack at C_2 (**3a**) therefore generates an endo,endo 1,3-H–Cl interaction, whereas attack at C_3 (**3b**) leads to an endo,endo 1,3-H–H interaction. Hence, attack at C_3 leading to intermediate **3b** is preferred.

The ionic brominations of **2** and **3** proceed slowly at 25° and are stereospecific. No nortricyclyl halide or Wagner–Meerwein rearrangement products are observed, as is the case for norbornene itself.[4,5] The electron-withdrawing chlorine substituents appreciably deactivate the C_1–C_6 bond toward σ participation and also eliminate hydride shifts where positive charge is developed adjacent to the chlorine substituent; hence, rearrangement becomes unfavorable.

The stereospecificity of the ionic brominations suggests bridged intermediates. Without bridging, bromination of **3** is anticipated to exhibit a mixture of cis (**8**) and trans (**7**) adducts as in the radical bromination. Formation of **7** at the exclusion of **8** requires the



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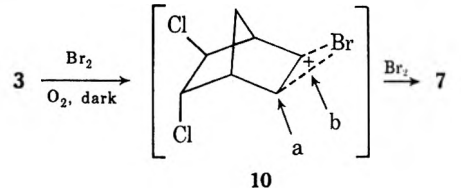

10

intermediacy of **10** and subsequent preferential attack endo and away from the endo chlorine substituent (path b). Attack *via* path a on **10** incurs severe nonbonded interaction of bromine with the endo chlorine substituent and is excluded. Intermediate **9**, with endo attack by bromine to give exclusively **5**, similarly explains the stereospecific ionic bromination of **2**.

Bridging in ions **9** and **10** provides a mechanism for charge delocalization when the normal σ participation for a norbornyl cation is unfavorable. Furthermore, bridging allows for the partial removal of positive charge to a greater distance from the electron-withdrawing chlorine substituents. These factors further support bridging in 3-bromo-5,6-dichloro-2-norbornyl cations.

In contrast, the lack of stereospecific free-radical addition to **3** argues against bridged bromine radicals. In fact, the preference is for cis addition with **8** as the major adduct. The radical addition results can be adequately explained by steric arguments without invoking bridged species.[17]

Experimental Section

Proton nmr spectra were recorded on a Varian Associates A-60, HA-100, or HR-220 MHz spectrometer. Homonuclear decoupling experiments at 220 MHz were performed by a track sweep method.[18] All compounds were run at 20–30% solutions in $CDCl_3$ at ambient temperature with tetramethylsilane as an internal reference.

All melting and boiling points are uncorrected. The gas chromatography work was performed on a Varian Aerograph Series 200 gas chromatograph fitted with a Brown Potentiometer recorder. The following columns were employed: column A, 5 ft × 0.25 in. 3% SE-30 on 100/120 Aeropak 30; column B, 8 ft × 0.375 in. 25% Triton X305 on Chromosorb W. *endo-cis*-5,6-Dichloro-2-norbornene (**1**) and *exo,cis*-5,6-dichloro-2-norbornene (**2**) were prepared by the procedure of Tanner and Gidley.[2] Two recrystallizations from *n*-hexane afforded pure **1**, mp 75–76° (lit.[3] mp 75–76°). Pure **2** was obtained by preparative vpc (column B, 150°). The procedure of Roberts and Carboni[3] afforded *trans*-5,6-dichloro-2-norbornene, bp 80–82° (20 mm) [lit.[3] bp 76–78° (17 mm)]. All dichloronorbornenes employed were >99.5% pure by vpc (column B).

Brominations. General Procedures.—The brominations under free-radical conditions in CH_2Cl_2 were performed as before.[1,16] Ionic brominations were conducted by treating a solution of the appropriate olefin in CH_2Cl_2 in the dark with bromine (1–1.1 equiv) at 25°. The reaction mixture was continuously purged with a slow stream of oxygen prior to work-up. After complete bromine addition, the reaction mixture was quenched in 5% aqueous sodium thiosulfate, washed with saturated aqueous sodium chloride, and dried over $MgSO_4$. Removal of the solvent on a rotary evaporator afforded the crude dibromide product, which was analyzed by vpc.

exo,cis-5,6-Dichloro-2-norbornene (**2**).—A solution of 1.63 g (10.0 mmol) of **2** in 9 ml of CH_2Cl_2 was treated dropwise with a solution of 1.60 g (10.0 mmol) of bromine in 1 ml of CH_2Cl_2. Irradiation was continued 5 min after complete bromine addition. Work-up afforded 3.08 g of semisolid product. Vpc analysis (column A, 165°) indicated a mixture of 89% **5** and 11% **6**. No unreacted starting material (>1%) was evident. The product mixture was treated with petroleum ether (bp 30–60°)–benzene, chilled to 0°, and filtered to afford 405 mg of solid containing 89% **6** and 11% **5** by vpc. Recrystallization from *n*-hexane afforded pure *exo-cis*-2,3-dibromo-*exo-cis*-5,6-dichloronorbornane (**6**), mp 227–228°. The filtrate was concentrated on a rotary evaporator to an oil (~98% **5**) and preparative vpc afforded pure *exo*-2-bromo-*endo*-3-bromo-*exo-cis*-5,6-dichloronorbornane (**5**), mp 57–58°.

Anal. Calcd for $C_7H_8Br_2Cl_2$: C, 26.04; H, 2.50; Br, 49.50; Cl, 21.96. Found (**5**): C, 26.31; H, 2.57; Br, 49.70; Cl, 21.93. (**6**): C, 26.02; H, 2.52.

Three runs of this reaction afforded 89, 91, and 94% **5** and an average **5**:**6** ratio of 10:1 is reported.

When the bromination of **2** was repeated on the same scale under ionic conditions, a 90% yield of **5** was obtained. No **6** (>0.5%) was present by vpc (column A, 150°).

trans-5,6-Dichloro-2-norbornene (**3**).—Treatment of 16.3 g (0.10 mol) of **3** in 90 ml of CH_2Cl_2 with a solution of 17.0 g (0.106 mmol) of bromine in 10 ml of CH_2Cl_2 under illumination afforded 30.2 g of a mixture of 60% **8** and 40% **7** (column A, 150°) which accounted for 98% of the products. Distillation at 0.5 mm afforded the following fractions: a, 5.9 g (100% **7**), bp 87–90°; b, 3.1 g (68% **7**, 32% **8**), bp 89–90°; c, 9.4 g (47% **7**, 53% **8**), bp 100–107°; d, 8.6 g (100% **8**), bp 109–111°. Each fraction solidified or partially solidified on collection. Recrystallization of fraction a from *n*-hexane gave pure *exo*-2-bromo-*endo*-3-bromo-*exo*-5-chloro-*endo*-6-chloronorbornane (**7**), mp 50–51°. Recrystallization of fraction d from *n*-hexane gave analytically pure *exo-cis*-2,3-dibromo-*exo*-5-chloro-*endo*-6-chloronorbornane (**8**), mp 56–58°.

Anal. Found (**7**): C, 26.29; H, 2.54; Br, 49.47; Cl, 21.90. (**8**) C, 26.26; H, 2.47; Br, 50.28; Cl, 21.61.

Bromination of **3** on the same scale under ionic conditions afforded a 90% yield of **7**. Vpc analysis (column A, 150°) indicated <0.5% **8**.

Control Experiments.—Pure samples of dibromides **5**, **7**, and **8** were not rearranged under the vpc conditions (column A, 150–180°). Solutions of 1 *M* dibromide in methylene chloride were individually irradiated for 30 min in the presence of bromine and were unchanged by nmr and vpc. Dibromide **8** was recovered unchanged after treatment with bromine in CH_2Cl_2 in the dark.

Registry No.—**1**, 2843-35-8; **2**, 14627-78-2; **3**, 2843-39-2; **4**, 39037-42-8; **5**, 39810-57-6; **6**, 39810-58-7; **7**, 39810-59-8; **8**, 39810-60-1; Br_2, 7726-95-6.

Acknowledgments.—The author is indebted to Mr. Lou Walther for performing the double-resonance experiments at 100 MHz and for Mr. Rou Rizzardi for similar experiments at 220 MHz.

(17) A recent publication describes similar electronic and steric effects of nitrile substituents on the stereochemistry of halogen addition to cyanonorbornene derivatives; see S. Kikkawa, *et al.*, *Bull. Chem. Soc. Jap.*, **45**, 2523 (1972).

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Alkyl Metal Asymmetric Reduction. III.[1,2] The Stereochemistry of Alkyl Phenyl Ketone Reductions by Chiral Organoaluminum Compounds

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The asymmetric reduction of a series of alkyl phenyl ketones by optically active organoaluminum compounds, having β-branched alkyl groups, has been studied. The reactions, which have been carried out at 0°, afforded (*S*)-alkylphenylcarbinols in good yield. The extent of the asymmetric reduction was found to depend on the structure of the ketone employed and to be affected by the presence of a donor ligand to the aluminum atom. Moreover the reduction of isopropyl phenyl ketone by chiral solvates of triisobutylaluminum occurs with low but definite asymmetric induction. The overall results, which are consistent with a β-hydride transfer from the alkyl group of the organoaluminum compound to the carbonyl carbon atom, are interpreted as indicating that, in the presence of ethers, the reaction occurs without prior dissociation of the ligand from the aluminum atom in cyclic six-membered-ring transition states. The stereoselectivity of the reduction process is rationalized in terms of steric and electronic interactions in competing transition states for the hydrogen-transfer step.

The steric course of asymmetric Grignard reductions has been extensively investigated during the last 20 years[3,4] to establish direct relationships among the extent of asymmetric induction and the nature of carbonyl substrates and chiral reducing agents. High stereoselectivity has been observed with chiral Grignard reagents having phenyl groups,[3f,5] while (+)-(*S*)-2-methylbutylmagnesium halides yield carbinols with lower extents of asymmetric reduction.[3d]

Although the ability of organoaluminum reagents to reduce carbonyl compounds has been well established,[6] this reaction has thus far attracted attention more for mechanistic aspects than for stereochemical implications.[7] Only recently has the occurrence of asymmetric induction phenomena in the reduction of prochiral ketones by optically active organoaluminum compounds been reported.[1,2,8]

In continuing our investigation[1,2] on this reaction we report now more accurate details on the stereochemistry of the reduction of alkyl phenyl ketones by (*S*)-2-methylbutylaluminum derivatives and triisobutylaluminum chiral solvates and, in this connection, on the role of the solvent.

Experimental Section

Materials.—*tert*-Butyl phenyl ketone was prepared (60% yield) by chromic oxidation[9] of *tert*-butylphenylcarbinol prepared in a 60% yield by the method of Winstein and Morse.[10] The other ketones were commercial products and were purified through the semicarbazone derivatives.[11] Triisobutylaluminum was obtained from Texas Alkyls, Inc., and was purified by distillation under vacuum. (+)-Tris[(*S*)-2-methylbutyl]aluminum and (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate of high optical purity were prepared as previously described.[12,13] (+)-Tris[(*S*)-2-methylbutyl]aluminum of low optical purity was obtained diluting the above mentioned samples with racemic product. All the organoaluminum compounds were distilled under nitrogen and stored in sealed glass vials, in weighed amounts.

Tetrahydrofuran was purified according to the procedure of Böhme and Schürhoff,[14] distilled, and stored over sodium wire. Glpc analyses were performed on a C. Erba Fractovap Model GT instrument with flame ionization detectors, using 200 × 0.30 cm columns packed with 10% butanediol succinate (BDS) on 60–80 mesh Chromosorb W, at 150°. All rotations, unless otherwise indicated, were taken on a Schmidt-Haensch polarimeter with sensitivity of ±0.005° in 0.5- and 1-dm tubes.

Asymmetric Reductions of Alkyl Phenyl Ketones. A. By (+)-Tris[(*S*)-2-methylbutyl]aluminum in Pentane. 1.—In a typical run, a solution of 0.780 g (5.26 mmol) of isopropyl phenyl ketone in 7 ml of anhydrous pentane was added rapidly, under nitrogen, to a solution of 1.414 g (5.88 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +24.82° (neat),[12] in 13 ml of pentane, cooled at 0°, in a flame-dried two-neck 100-ml flask fitted with a reflux condenser, a dropping funnel, and a magnetic stirrer. An immediate yellow-orange coloration developed and faded quickly. After 2 hr, the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid (pH 5) and the organic products were extracted with purified ether. The crude product was shown by glpc analysis to contain 3.6% of ketone. Distillation afforded 0.670 g (85%) of isopropylphenylcarbinol (96.5% pure by glpc analysis), bp 104° (18 mm), $n^{25}D$ 1.5114, $[\alpha]^{25}D$ −15.02° (*c* 4.68, ether).[3f]

2.—(+)-Tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +14.06° (neat), was treated at 0° with *tert*-butyl phenyl ketone in pentane to yield 99% of *tert*-butylphenylcarbinol (99.8% pure by glpc analysis), bp 111° (18 mm), mp 55°, $[\alpha]^{25}D$ −4.53° (*c* 4.86, ether).[3f]

Analogously, (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +6.89° (neat), afforded 88% of *tert*-butylphenylcarbinol (pure by glpc analysis), $[\alpha]^{25}D$ −2.21 (*c* 15.39, ether).

3.—At 0°, to 1.643 g (6.83 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +26.34° (neat), in 10 ml of pentane was added rapidly 1.038 g (6.40 mmol) of *tert*-butyl phenyl ketone in 10 ml of pentane. After 1 min, the reaction mixture was hydrolyzed and the organic product was recovered and distilled to give 0.879 g (84%) of the carbinol (99.6% pure), $[\alpha]^{25}D$ −8.46° (*c* 7.68, ether).

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B. By (+)-Tris[(*S*)-2-methylbutyl]aluminum Diethyl Etherate.—To 2.446 g (7.77 mmol) of (+)-tris[(*S*)-2-methylbutyl]-aluminum diethyl etherate, $[\alpha]^{23}D$ +22.20°,[13] $[\alpha]^{25}D$ +21.78° (*c* 4.68, pentane), in 15 ml of anhydrous pentane, was added at 0° 1.037 g (7.00 mmol) of isopropyl phenyl ketone in 10 ml of pentane. After 2 hr, the reaction mixture was worked up as above described. The crude carbinol, which was shown to contain 2.3% of ketone (by glpc analysis), yielded for distillation 0.955 g (91%) of isopropylphenylcarbinol (97.7% pure), $n^{25}D$ 1.5114, $[\alpha]^{25}D$ −15.76° (*c* 4.82, ether).

C. By Tris[(*S*)-2-methylbutyl]aluminum Tetrahydrofuranate.—To 1.748 g (7.27 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +24.82° (neat), in 10 ml of pentane was added 0.525 g (7.28 mmol) of tetrahydrofuran in 2 ml of pentane at 0°, and successively 0.970 g (6.55 mmol) of isopropyl phenyl ketone in 8 ml of pentane. Immediately the reaction mixture assumed an intense orange color, which faded slowly. After 2 hr the solution was decomposed with dilute sulfuric acid and extracted with ether. Distillation of the crude product, which contained ketone and carbinol in the ratio 1:6 (by glpc analysis), afforded 0.684 g of isopropylphenylcarbinol (86.0% pure), $n^{25}D$ 1.5119, $[\alpha]^{25}D$ −12.94° (*c* 5.64, ether).

Reduction of α-Tetralone by (+)-Tris[(*S*)-2-methylbutyl]-aluminum.—To 2.580 g (10.73 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +28.73° (neat), in 20 ml of pentane was added at 0° 1.412 g (9.66 mmol) of α-tetralone in 10 ml of pentane. After 2 hr the reaction mixture was hydrolyzed and the organic product was extracted with ether. The crude carbinol, after redistillation, yielded 0.878 g (61%) of α-tetralol (94% pure by glpc analysis on BDS columns at 170°), bp 87° (0.07 mm), $\alpha^{25}D$ (*l* 1) 0.00° (*c* 5.36, benzene).

Asymmetric Reduction of Isopropyl Phenyl Ketone by Chiral Solvates of Triisobutylaluminum. A. With (−)-Sparteine.—To a solution of 1.880 g (9.48 mmol) of triisobutylaluminum in 5 ml of dry pentane was added slowly at 0° 2.210 g (9.44 mmol) of (−)-sparteine, $[\alpha]^{25}D$ −16.27° (*c* 7.03, ethanol),[15] in 5 ml of pentane. The resultant mixture was then treated, at the same temperature, with 1.400 g (9.46 mmol) of isopropyl phenyl ketone in 10 ml of pentane. After 2 hr the reaction mixture was quenched with dilute hydrochloric acid (pH 3) and the organic layer was extracted with ether. After removal of the solvent, the crude carbinol (containing 5.3% of ketone, as shown by glpc analysis) was distilled and 1.170 g (82%) of isopropylphenylcarbinol (94.7% pure), $n^{25}D$ 1.5122, $[\alpha]^{25}D$ −3.55° (*c* 11.27, ether), was recovered.

B. With (+)-(*S*)-(1-Methylpropyl) Ethyl Ether.—To 0.497 g (4.86 mmol) of (+)-(*S*)-(1-methylpropyl) ethyl ether, $[\alpha]^{25}D$ +26.96° (*c* 4.02, isooctane), optical purity (o.p.) 78.7%,[16] was added at 0° a solution of 0.964 g (4.86 mmol) of triisobutylaluminum in 15 ml of pentane, followed by 0.713 g (4.82 mmol) of isopropyl phenyl ketone in 5 ml of pentane. The reaction mixture was hydrolyzed after 2 hr and worked up in the usual manner to give a crude product (95% conversion by glpc analysis) which, after redistillation, afforded 0.524 g (72%) of isopropylphenylcarbinol (95.1% pure), $n^{25}D$ 1.5118, $[\alpha]^{25}D$ −2.10° (*c* 10.48, ether).

C. With (+)-(3*S*,1′*S*)-3-(1′-Methylpropyl)tetrahydrofuran.—To 0.563 g (2.84 mmol) of triisobutylaluminum in 10 ml of anhydrous pentane was added at 0° a solution of 0.358 g (2.80 mmol) of (+)-(3*S*,1′*S*)-3-(1′-methylpropyl)tetrahydrofuran, $[\alpha]^{25}D$ +17.17° (*c* 1.18, *n*-heptane) [(*S*,*S*) ≥ 90%],[17] in 5 ml of pentane and then 0.400 g (2.70 mmol) of isopropyl phenyl ketone in 5 ml of pentane. The mixture, after hydrolysis (2 hr), was extracted continuously with ether to give a crude carbinol (92% conversion by glpc analysis), which, after accurate purification, yielded 0.234 g (58%) of isopropylphenylcarbinol, $[\alpha]^{25}_{589}$ −0.70° (*c*, 4.67, ether).

Results

The asymmetric reductions have been carried out at 0° for 2 hr, in pentane or ethereal solvent, using a slight excess (about 10%), with respect to the alkyl phenyl ketones, of tris[(*S*)-2-methylbutyl]aluminum[12] (Al2MB), tris[(*S*)-2-methylbutyl]aluminum diethyl etherate[13] (Al2MB·OEt_2), tris[(*S*)-2-methylbutyl]aluminum tetrahydrofuranate (Al2MB·THF), or chiral solvates of triisobutylaluminum (Al2MP·L*). The obtained results are summarized in Tables I and II.

It has been previously reported that organoaluminum compounds react with ketones to give addition, reduction, and enolization products.[6] The relative amounts of the addition and reduction products are dependent on the reaction temperature and on the reactants molar ratio, while the enolization reaction seems to be not affected.[6b,c] In the experimental conditions we have adopted, neither addition nor significant enolization reactions occur, the conversion (by glpc) in carbinols being generally ≥90% (Table I).

The reactions are very fast[18] in the absence of donor ligands (*e.g.*, the reduction of *tert*-butyl phenyl ketone is practically complete within 1 min), and also when Al2MB·OEt_2 in pentane is used, although an appreciable retardation is observed in ethereal solvent; however, the reaction rate drops substantially when THF is used.[19]

By inspection of Tables I and II, the following considerations can be made.

(1) All the carbinols have the absolute *S* configuration. The extent of asymmetric reduction is dependent on the structure of the alkyl group in the phenyl ketone employed, increasing in the order of CF_3 ≅ Me < Et < *t*-Bu < *i*-Pr.

(2) The stereoselectivity of the reduction is affected by the presence of a donor ligand, a large excess of which does not further change the extent of asymmetric induction.

(3) The decrease in the stereoselectivity of the reduction from isopropyl phenyl ketone to *tert*-butyl phenyl ketone is enhanced in the absence of donor ligands.

(4) The reduction of isopropyl phenyl ketone by Al2MP·L* in pentane solution occurs with low but definite asymmetric induction.

Discussion

Role of the Solvent.—It is generally accepted that, in the absence of donor ligands, the mechanism of the reduction of ketones by organoaluminum compounds with β-branched alkyls is based on the complexation of trialkylaluminum with the ketone (eq 1) followed by an intramolecular hydride transfer from the β carbon of the alkyl group bound to the aluminum to the carbonyl carbon (eq 2).[6b-d,7] Such a mechanism, adopted for the reduction of benzophenone by triisobutylaluminum in diethyl ether solvent,[6d] was recently tested by asymmetric induction studies carried out with optically active beryllium and aluminum compounds.[1]

(15) H. Nozaki, T. Aratani, T. Toraya, and R. Noyori, *Tetrahedron*, **27**, 905 (1971).

(16) E. Chiellini, private communication.

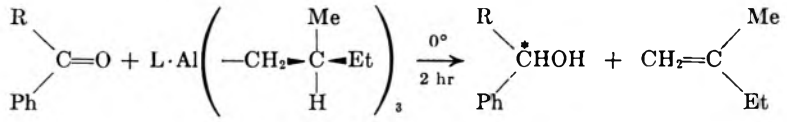
(17) C. Botteghi, G. Ceccarelli, and G. Consiglio, *J. Prakt. Chem.*, **314**, 840 (1972).

(18) According to previous observations of many workers,[6] when the ketone is added to the organoaluminum solution, a transient red-yellow color, which generally fades within a few minutes, is observed. Such a phenomenon should be related to an "ate-complex" [G. Wittig, *Quart. Rev., Chem. Soc.*, **20**, 191 (1966)], intermediate in product formation, although any consideration appears to be hazardous owing to other possible competing side equilibria.

(19) After 2 hr at 0° Al2MP·THF reduces isopropyl phenyl ketone in 89% conversion in pentane solution, and in conversion in 10% tetrahydrofuran as solvent.

TABLE I

ASYMMETRIC REDUCTION OF PHENYL ALKYL KETONES BY OPTICALLY ACTIVE ORGANOALUMINUM COMPOUNDS

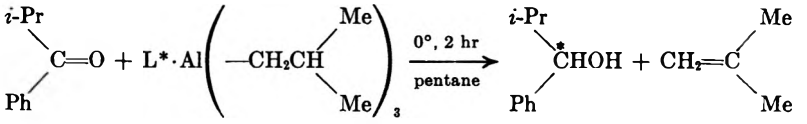


Run	R	Registry no.	L	Registry no.	Solvent	S Carbinol: Conversion [a] %	Chemical purity [b] %	Registry no.	Optical rotation: $\alpha^{25}D$, deg, ether (*l*, *c*)	Optical rotation: $[\alpha]^{25}D$	$[\alpha]^{25}D$ [c]	Optical purity, [d] %	Asymmetric reduction, [e] %
1[f]	Me	98-86-2		4023-25-0	Pentane	94	87.0	1445-91-6	−0.96 (0.5, neat)	−1.90	−2.18	5.0	5.9
2[g]			Et_2O	18902-57-3	Ether	95	99.4		−1.28 (0.5, neat)	−2.53	−2.55	5.8	5.9
3[h]	Et	93-55-0			Pentane	98	99.4	613-87-6	−2.54 (1, neat)	−2.56	−2.58	8.9	13.2
4[f]					Pentane	96	97.8		−1.56 (0.5, neat)	−3.15	−3.22	11.2	13.2
5[i]			Et_2O		Pentane	98	98.8		−1.42 (0.5, neat)	−2.86	−2.89	10.0	10.5
6[i]			Et_2O		Pentane	98	99.2		−1.32 (0.5, neat)	−2.66	−2.68	9.3	9.5
7[i]			Et_2O		Ether	97	96.8		−2.31 (1, neat)	−2.33	−2.41	8.4	8.7
8[i]			Et_2O		Ether	95	94.8		−1.06 (0.5, neat)	−2.14	−2.26	7.9	8.2
9[j]			THF	39814-22-7	Pentane	67	61.9		−0.25 (1, 9.15)	−2.73	−4.41	8.6[k]	11.7
10[h]	*i*-Pr	611-70-1			Pentane	96	98.4	34857-28-8	−0.71 (1, 5.04)	−14.07	−14.30	30.0	44.4
11[j]					Pentane	96	96.5		−0.73 (1, 4.86)	−15.02	−15.56	32.6	44.3
12[i]			Et_2O		Pentane	98	97.7		−0.76 (1, 4.82)	−15.76	−16.13	33.8	35.2
13[i]			Et_2O		Ether	98	97.7		−0.93 (1, 5.86)	−15.87	−16.24	34.0	35.4
14[j]			THF		Pentane	86	86.0		−0.73 (1, 5.64)	−12.94	−15.04	31.5[l]	42.8
15[h]	*t*-Bu	938-16-9			Pentane	99	99.3	15914-85-9	−0.70 (1, 9.66)	−7.24	−7.29	20.1	29.8
16[f]					Pentane	97	97.0		−0.45 (1, 5.02)	−8.96	−9.24	25.5	29.9
17[i]			Et_2O		Pentane	~100	~100		−0.86 (1, 7.54)	−11.40	−11.40	31.5	32.8
18[i]			Et_2O		Ether	97	97.1		−1.03 (1, 9.37)	−10.99	−11.31	31.2	32.6
19[j]			THF		Pentane	96	96.1		−0.90 (1, 9.13)	−9.85	−10.25	28.3	38.4
20[j]			THF		Pentane	89	~100		−0.46 (1, 4.49)	−10.24	−10.24	28.3	38.4
21[f]	CF_3	434-45-7			Pentane	~100	~100	340-06-7	+0.103 (1, 5.94, benzene)[m]	+1.73	+1.73	5.1[n]	6.0
22[f]					Pentane	~100	~100		+0.081 (1, 4.56, benzene)[m]	+1.77	+1.77	5.2[n]	6.1
23[i]			Et_2O		Pentane	~100	~100		+0.96 (0.5, neat)			4.7[o]	4.9

[a] Based on glpc analyses of the crude products. [b] Estimated from the gas chromatograms of the products after redistillation, other impurities being the ketone. [c] Corrected for the per cent purity of the carbinol. [d] See ref 3f. [e] Corrected for the minimum optical purity of the organoaluminum compound used. [f] (+)-Tris[(*S*)-2-methylbutyl]aluminum, o.p. 85.2%. [g] (+)-Tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, o.p. 98.0%. [h] (+)-Tris[(*S*)-2-methylbutyl]aluminum, o.p. 67.5%. [i] (+)-Tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, o.p. 96.9%. [j] (+)-Tris[(*S*)-2-methylbutyl]aluminum, o.p. 73.6%. [k] Assuming $[\alpha]^{25}D$ +51.1° (*c* 7.55, ether) for the enantiomerically pure carbinol in the presence of *ca.* 30% of the ketone. [l] This value, corrected on the basis of the rotatory power of an ethereal solution containing 86% of the carbinol (o.p. 28%) and 14% of the ketone, is 30.6. [m] Measured with a spectrophotometric polarimeter, Perkin-Elmer Model 141, at 365 nm. [n] Assuming $[\alpha]^{25}_{365}$ +34.0° (*c* 6.41, benzene) for the enantiomerically pure carbinol. [o] D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, **33**, 4242 (1968).

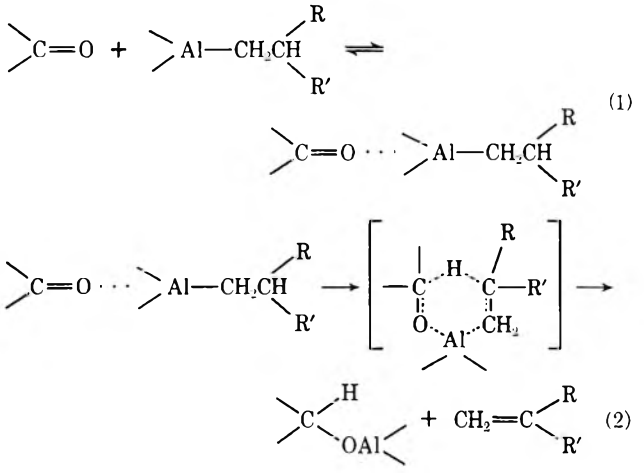
TABLE II

ASYMMETRIC REDUCTION OF ISOPROPYL PHENYL KETONE BY CHIRAL SOLVATES OF TRIISOBUTYLALUMINUM



Registry no.	L* [α]²⁵D, deg (c, solvent)	Conversion,[a] %	Chemical purity,[b] %	S carbinol: Optical rotation α²⁵D, deg, ether (l, c)		S carbinol: [α]²⁵D	S carbinol: [α]²⁵D[c]	Optical purity,[d] %
37349-76-1	(−)-Sparteine −16.30 (7.03, ethanol)	95	94.7	−0.80	(2, 11.27)	−3.55	−3.75	7.9
39814-23-8	(+)-(*S*)-*sec*-BuOEt +26.96 (4.02, isooctane)	95	95.1	−0.22	(1, 10.47)	−2.10	−2.21	4.6
39814-24-9	(+)-(3*S*,1′*S*)-3-*sec*-BuTHF +17.17 (1.18 *n*-heptane)	92	93.2	−0.033	(1, 4.67)[e]	−0.70	−0.75	1.6

[a] Based on glpc analyses of the crude products. [b] Evaluated from the gas chromatograms of the products after redistillation (other impurities are the ketone). [c] Corrected for the per cent purity of the carbinol. [d] See ref 3f. [e] Measured with a spectrophotometric polarimeter, Perkin-Elmer Model 141, at 589 nm.



Actually, in the presence of donor ligands, several alternative reaction pathways might be postulated for the reduction of ketones (Scheme I).[6d,20] While no doubt exists about the occurrence of a complex between the organoaluminum compound and the ketone,[6,20] the question arises whether the ligand is displaced from the aluminum alkyl prior to the formation of the complex or partakes in the transition state of the reaction in a pentacoordinate intermediate.

Although the dissociation of organoaluminum etherates (eq 3) does not seem probable, on the basis also of literature data,[21] both paths 3 and 4 could explain the decrease of the reduction rate when the etherates are used, especially in the presence of an excess of donor solvent. The reaction rate should be therefore in relation to the basic strength of the ligand; so the different stereoselectivity in the reduction of ketones by tris[(*S*)-2-methylbutyl]aluminum (Al2MB) and tris-[(*S*)-2-methylbutyl]aluminum etherates (Al2MB·OEt_2, Al2MB·THF) might be explained on the basis of a rate retardation. However, in a clear disagreement, while the reduction rate seems to be effectively related to the ligand basicity, *i.e.* Al2MB > Al2MB·OEt_2 > Al2MB·THF, the asymmetric induction extent does not always follow the same order (Table III).

On the other hand, using diethyl ether as solvent, the reduction rate of the ketones by tris[(*S*)-2-methylbutyl]aluminum diethyl etherate decreases appreciably but the percentage of asymmetric induction does not change (Table I). Moreover these mechanisms (eq 3, 4) are not consistent with the low but definite stereoselectivity observed in the reduction of isopropyl phenyl ketone by chiral solvates of triisobutylaluminum (Table II).

Such results are in better agreement with path 5 (Scheme I), which involves the formation of a penta-

SCHEME I

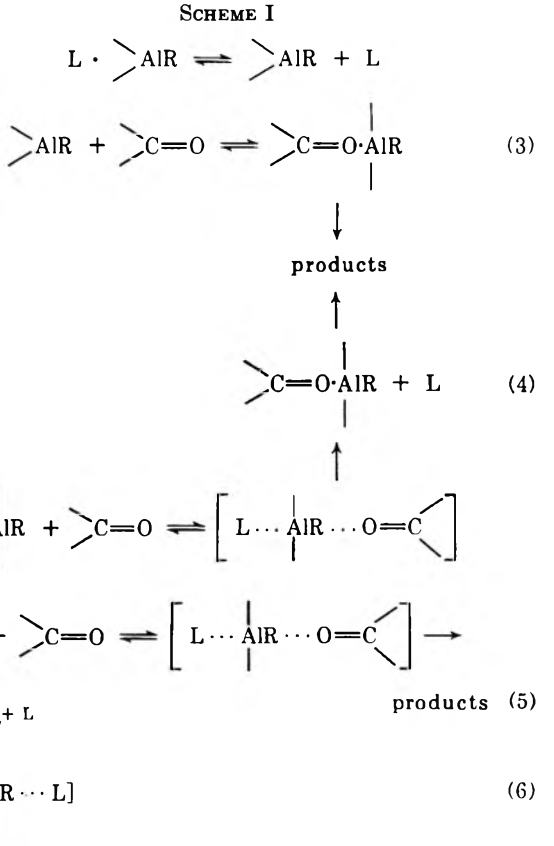


TABLE III

PER CENT ASYMMETRIC REDUCTION[a] OF ALKYL PHENYL KETONES BY OPTICALLY ACTIVE ORGANOALUMINUM COMPOUNDS

Ligand	Me	Et	*i*-Pr	*t*-Bu	CF_3
	6	13	44	30	6
Et_2O	6	9	35	33	5
THF		12	43	38	

[a] Average values.

(20) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37**, 1918 (1972).

(21) H. Lehmkuhl and K. Ziegler in "Methoden der Organischen Chemie," Houben-Weil, Ed., Vol. 13, Part 4, Georg Thieme Verlag, Stuttgart, 1970, pp 95–110.

coordinate aluminum in the transition state[6d,20,22] without loss of the initial solvating ligand, which in effect should not be split off but should still remain in the coordination sphere of the aluminum atom. Moreover, since ketone has a weaker basic strength than ether,[23] it seems more reasonable that a transition state having weak ether–aluminum–ketone bonds should proceed to trialkylaluminum etherate rather than to a complex between carbonyl and organoaluminum compounds.[24]

The different rates of the reduction of ketones by the various organoaluminum compounds used can be therefore rationalized on the basis of a different electronegativity of the aluminum atom in the aluminum alkyl and in the etherates.[25] The further decrease of the reduction rate in ethereal solvent might be explained in this case with a competition of ether and ketone in the solvating reaction of the organoaluminum etherate (eq 5, 6).[26]

In view of the above hypothesis the electronegativity of the aluminum atom should control its distance from the carbonyl oxygen in the transition state, since the stronger the coordination of the ligand the longer this distance. Therefore the steric interactions in the six-membered transition states (eq 2) and consequently the stereoselectivity of the reduction should change in relation to the Lewis base strength and to the steric bulk properties of the ligand (Table I).

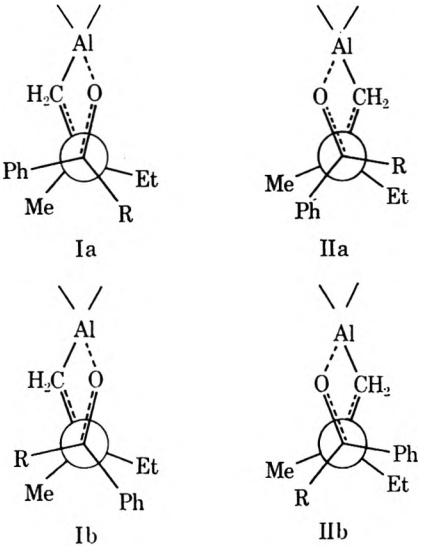
In any case, all the mechanisms (Scheme I) should involve a cyclic intramolecular hydride transfer (eq 2) rather than a reduction by dialkylaluminum hydride,[6d,7] formed either from trialkylaluminum or as a consequence of the ketone attack, since the monohydride species are in very low concentration at 0° in hydrocarbon solvents,[27,28] and quite absent in the presence of donor ligands; in fact, organoaluminum etherates do not form the corresponding hydride even at 90°.[29]

Conformational Analysis.—Table III reports the extent of asymmetric reduction of the alkyl phenyl ketones by optically active organoaluminum compounds. It is to be noted that the general trend in the extent of asymmetric reduction resembles that encountered in the reduction of the same series of ketones by (*S*)-2-methylbutylmagnesium halides.[3a-e]

Simple considerations of conformational analysis,[3,5] based on Whitmore's cyclic mechanism, permit the correct prediction of the absolute configuration of the predominant enantiomer, but they are not able to explain the trend in the series. In fact, if the extent of asymmetric reduction should depend on the difference in steric bulk between the phenyl and the alkyl group of ketones, the stereoselectivity of the reduction should decrease as the bulk of the alkyl group increases.[5] On the other hand, a conformational approach based on recent suggestions which take into account electronic interactions too[30] does not clarify the drop in the stereoselectivity when the alkyl is a *tert*-butyl group, even if it might explain the higher asymmetric induction in the phenyl alkyl series as the alkyl group changes from methyl to isopropyl.

On the basis of our previous considerations on the mechanism of the reduction, which involves a cyclic intramolecular hydride transfer (eq 2), and considering that the coordinate bond between aluminum and oxygen atom is to be relatively loose to minimize the rigidity consequent to a cyclic model,[30] only four reacting conformations, viewed along the C···H–C* axis, are to be considered (Scheme II).

SCHEME II



The transition states Ia and IIa lead to *S* carbinol; the first is reasonably the stablest both for steric and electronic requirements. In fact, in Ia the aluminum atom (CH_2–$Al^{\delta+}$) is placed between two negative dipoles (C–$O^{\delta-}$, C–$Ph^{\delta-}$)[30] and the phenyl group is in a quasi-anti position with respect to the ethyl group of the aluminum compound. On the contrary, Ib and IIb lead to *R* alcohol; for electronic reasons,[30] the conformation IIb has the lowest energy, although the steric interactions are similar in these two cases. Since the conformation Ia is more favored than IIb for steric requirements,[31] the carbinol from asymmetric induction must have the *S* configuration. This picture, however, does not satisfactorily predict the observed trend of asymmetric reduction. In this respect a helpful suggestion is to consider that, as the alkyl group increases in bulk, the conformational mobility of the phenyl group decreases, its size increasing formally. As confirmed by inspection of molecular models, the steric hindrance of the alkyl group prevents the free rotation of the phenyl group more in the conformation IIb than

(22) Although organoaluminum compounds appear generally to be tetracoordinate in donor solvents, the existence of pentacoordinate intermediates has been postulated, as transition states, in alkyl group exchange reactions[24] and observed as dimethyl sulfoxide adducts [C. A. Smith and M. G. H. Wallbridge, *J. Chem. Soc. A*, 2675 (1970)]. On the other hand, pentacoordinate organomagnesium compounds have been invoked to explain the influence on the addition rate of dimethylmagnesium to benzophenone [H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968)].

(23) T. Kagiya, Y. Sumida, and T. Inoue, *Bull. Chem. Soc. Jap.*, **41**, 767 (1968).

(24) (a) T. Mole, *Aust. J. Chem.*, **16**, 801 (1963); (b) T. Mole, *ibid.*, **18**, 1183 (1965); (c) N. S. Ham, E. A. Jeffery, T. Mole, and J. K. Saunders, *ibid.*, **20**, 2641 (1967).

(25) A. C. M. Wanders and E. Konijnenberg, *Tetrahedron Lett.*, 2081 (1967).

(26) It is noteworthy that a decrease in rate was observed in the alkyl group exchange reactions among different metal alkyls,[24c] as the ratio ether: organoaluminum compound is increased from 1:1.

(27) G. Pajaro and L. Baldi, *Gazz. Chim. Ital.*, **91**, 493 (1961).

(28) K. W. Egger, *J. Amer. Chem. Soc.*, **91**, 2867 (1969).

(29) L. Lardicci, L. Lucarini, P. Palagi, and P. Pino, *J. Organometal. Chem.*, **4**, 341 (1965).

(30) D. Nasipuri, C. K. Ghosh, P. R. Mukherjee, and S. Venkataraman, *Tetrahedron Lett.*, 1587 (1971).

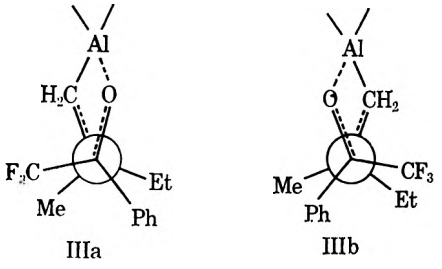
(31) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 138.

in Ia (Scheme II); thus the stereoselectivity should increase as the alkyl group changes from methyl to isopropyl (Table III). Considering that the free-energy differences among the transition states may be very sensitive to small changes in the nature of the groups which are compressed in these states, the effective sizes of the groups depend substantially on the ability of the angular and torsional strains in the cyclic transition state to minimize the van der Waals compressions.[32] Therefore the decrease in the stereoselectivity when the isopropyl is replaced by a *tert*-butyl group (Table III) might be explained supposing that the angular strains are no more able to diminish further the steric interactions among the groups which are compressed in the transition states; so the difference in free energy between Ia and IIb (Scheme II) drops down.

These suggestions seem to be confirmed by the lack of stereoselectivity in the reduction of α-tetralone, in which the phenyl group is effectively in a "frozen" conformation, both in Ia and IIb; therefore these diastereoisomeric states have very nearly the same energy.

On the basis of simple steric considerations[3,5] the reduction of trifluoromethyl phenyl ketone should lead to *R* carbinol.[33] On the contrary, opposite stereoselectivity is observed in the reduction of this ketone by (*S*)-2-methylbutylaluminum derivatives (Table I) in accordance with the data reported for the reduction by the comparable chiral Grignard reagent.[3b] Taking into account the conformational approach we have adopted, it is possible, however, to rationalize the stereochemistry of the reduction of trifluoromethyl phenyl ketone too. In fact the reacting conformations IIIa and IIIb (Scheme III) are the stablest since the

SCHEME III



$CH_2Al^{\delta+}$ is placed between the negative dipoles C–$O^{\delta-}$ and C–$CF_3^{\delta-}$.[34] However, IIIa should be reasonably the less hindered transition state, as the CF_3 is in a quasi-anti position with respect to the ethyl group, all the other interactions (Me ↔ Ph ↔ Et) being comparable both in IIIa and IIIb (Scheme III); so the *S* alcohol should be formed predominantly. In this connection it is not necessary to suppose that trifluoromethyl acts as if it were larger than phenyl group, this hypothesis being effectively incompatible with general evidence.[5]

(32) D. R. Boyd and M. A. McKervey, *Quart. Rev., Chem. Soc.*, **22**, 100 (1968).

(33) (*R*)-Trifluoromethylphenylcarbinol is configurationally related to (*S*)-methylphenylcarbinol.[5]

(34) We cannot exclude also the possibility that conformations IIIa and IIIb are further stabilized by intermolecular attractive forces between the fluorine and aluminum atoms, and these phenomena could be responsible for the relatively low extent of asymmetric reduction (Table III) in relation to a decrease of the difference between the free energies of the two diastereoisomeric states.

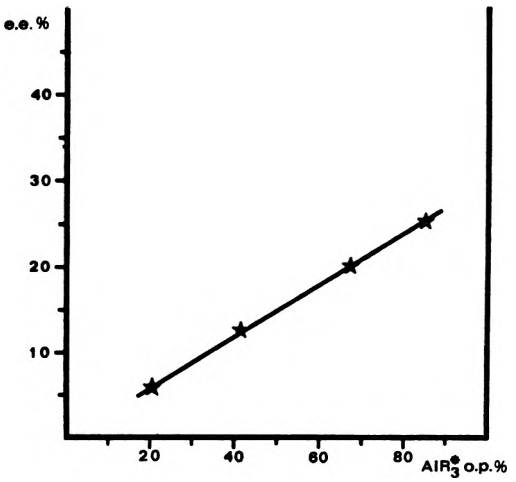
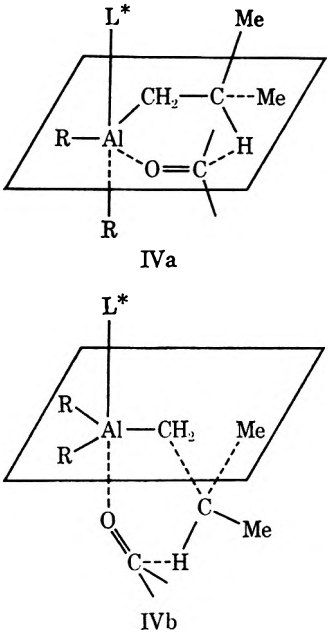


Figure 1.—Asymmetric reduction of *tert*-butyl phenyl ketone by (+)-tris[(*S*)-2-methylbutyl]aluminum: relationship between the carbinol e.e.% and aluminum alkyl optical purity.

When the optically active organoaluminum compounds are complexed with ethers the general trend of asymmetric reduction is not substantially changed, although the nature of the ligand seems to influence the stereoselectivity of the reaction (Table III). In fact, according to our previous suggestions, the ligand present in the transition state (as in IVa or IVb) should modify the relative steric interactions (Scheme IV).

SCHEME IV



The different electronegativity of aluminum atom, in relation to the basic strength of the ether employed,[25] will operate to make the cyclic transition state looser and so the mutual steric interactions will play a less important role, affecting therefore the extent of asymmetric reduction. On the other hand, the steric bulk properties of the ligand, which exerts itself a certain compression on the groups interacting in the transition states, should affect the stereoselectivity of the reaction and therefore the amount of *S* enantiomer would be expected to decrease, as a function of the bulk of the ligand, from THF to diethyl ether. These factors should act in opposition to each other, and in fact the

per cent of asymmetric reduction is greater in the presence of THF than of diethyl ether (Table III).

This conformational analysis was restricted only to the examination of the steric interactions between the alkyl phenyl ketone and the reacting 2-methylbutyl group bound to aluminum atom, although the other two optically active alkyl groups were able, in principle, to exert a further control on the stereochemistry of the reduction. The linear relationship we have observed between the per cent of enantiomeric excess of the carbinol and optical purity of (+)-tris[(*S*)-2-methylbutyl]aluminum in the reduction of *tert*-butyl phenyl ketone (Figure 1) excludes effectively that the two unreacting optically active alkyl groups control the asymmetric reduction of ketones. This result agrees with the data, previously reported, on the reduction of methyl *tert*-butyl ketone by bis[(*S*)-2-methylbutyl]magnesium and by the corresponding Grignard reagent, reduction which occurs with the same stereoselectivity.[35]

Registry No.—α-Tetralone, 529-34-0; α-tetralol, 530-91-6.

Acknowledgments.—This work was supported by the Consiglio Nazionale delle Ricerche, Roma. The authors are indebted to Dr. E. Chiellini (Istituto Chimica Organica Industriale, Pisa) for providing a sample of (+)-(*S*)-(1-methylpropyl) ethyl ether and to Dr. C. Botteghi (E. T. H. Technisch-Chemisches Laboratorium, Zürich) for samples of (+)-(3*S*,1′*S*)-3-(1′-methylpropyl)tetrahydrofuran.

(35) H. S. Mosher and P. K. Loeffler, *J. Amer. Chem. Soc.*, **78**, 4959 (1956).

Remote Oxidation with Photoexcited Nitrobenzene Derivatives

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Remote oxidation of unactivated carbon–hydrogen bonds by photoexcited nitrobenzene derivatives is described. The procedure is illustrated by the key step in the conversion of 5α-androstan-3α-ol (**3**) to 5α-androst-14-en-3-one (**6**). Introduction of unsaturation into the steroid D ring is accomplished by irradiation of the β-(*p*-nitrophenyl)propionate ester of **3** (compound **2**). As in previously reported remote oxidations utilizing benzophenone derivatives, the selectivity of the reaction is controlled by mutual orientation of the oxidizing agent and the substrate. The advantages and limitations of nitro compounds as reagents for remote oxidation are discussed.

Remote oxidation is a process in which unactivated carbon–hydrogen bonds are selectively oxidized at substrate sites remote from existing functionality.[1] Selectivity is achieved by attaching the substrate and oxidizing agent, thus mutually orienting them. The oxidation is then initiated by irradiation, and the reaction is carried out in sufficiently dilute solution that intramolecular reactions predominate. Previous examples have employed the benzophenone phototriplet as the oxidizing agent, and a common occurrence in such reactions is the formation of a new carbon–carbon bond which must then be cleaved to remove the residue of the oxidizing agent.

We have been seeking alternative remote oxidizing agents with which carbon–carbon bond formation would not be a problem, and we report here the first successful reaction with an attached reagent other than the benzophenone group.[2]

There is precedent in the literature for believing that the photoexcited aromatic nitro group would be able to abstract hydrogen from saturated carbon. Thus nitrobenzene is reduced when irradiated in "petroleum,"[3] and irradiation of 2,5-di-*tert*-butylnitrobenzene results in oxidation of one of the methyl carbons on the 2-*tert*-butyl group and reduction of the nitro group.[4]

Results and Discussion

To test the utility of the nitro function as a remote oxidizing agent, 5α-androstan-3α-yl *p*-nitrobenzoate (**1**) was first studied. Irradiation of **1** did not result in oxidation of the steroid at unactivated positions. Instead, reaction took place at the ester group to afford, after hydrolysis, the 3α and 3β alcohols, the 3 ketone, and the Δ^2 and Δ^3 olefins.

The next compound studied was 5α-androstan-3α-yl β-(*p*-nitrophenyl)propionate (**2**). It was believed that the methylene groups would decrease the reactivity of the ester function by isolating it from the nitroaromatic chromophore, and, at the same time, provide flexibility in the attachment of the oxidizing agent, a property shown to be of importance in the benzophenone reactions.[1b]

Irradiation of **2** was first carried out using a Corex filter. The reaction product was treated with iodine–acetic acid to dehydrate any tertiary alcohols, and the ester function was saponified. The nuclear magnetic resonance (nmr) spectrum of the neutral fraction thus obtained suggested the presence of 5α-androst-14-en-3α-ol (**5**) (vinyl signal at δ 5.18).[5] Hydroboration–

(1) (a) R. Breslow and M. A. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969); (b) R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); (c) R. Breslow and P. C. Scholl, *ibid.*, **93**, 2331 (1971); (d) R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971); (e) J. E. Baldwin, A. R. Bhatnagar, and R. W. Harper, *Chem. Commun.*, 659 (1970).

(2) There are reports in which selective oxidations are achieved by means other than direct attachment of reagent and substrate. Selective radical chlorination resulted when only one end of a straight-chain substrate was exposed to chlorine dissolved in CCl_4, the other substrate end being adsorbed on a solid surface: N. C. Deno, R. Fishbein, and C. Pierson, *J. Amer. Chem. Soc.*, **92**, 1451 (1970). Reports of intermolecular oxidations which are selective at steroid position 14 have also appeared: R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972); A. Rotman and Y. Mazur, *ibid.*, **94**, 6228 (1972).

(3) J. A. Barltrop and N. J. Bunce, *J. Chem. Soc. C*, 1467 (1968).

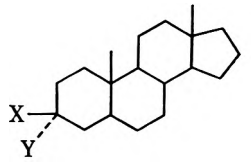
(4) D. Dopp, *Chem. Commun.*, 1284 (1968).

(5) L. Mamlok, *Bull. Soc. Chim. Fr.*, 3827 (1967).

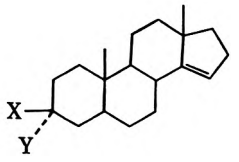
oxidation of this mixture and chromatography afforded 5α,14β-androstane-3,15-dione (7).

The yield of the remote oxidation product 7 was only 11%, even though isolation of only 18% of 5α-androstan-3-one (4) indicated that most (82%) of the starting steroid had undergone photooxidation.

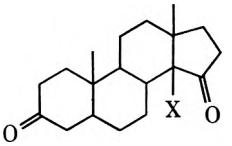
Two obvious difficulties existed with the above set of reactions, and no doubt contributed to the low yield. First, the photoreaction was not very "clean." Insoluble material had precipitated during the irradiation, requiring frequent cleaning of the lamp well, and much of the neutral fraction obtained upon work-up appeared to consist of a complex mixture of steroid components and polymer. The second difficulty was concerned with the sequence of reactions designed to aid the separation and characterization of products. The 14 olefin 5 was probably converted by the hydroboration–oxidation sequence into both 7 and its 14α epimer, 8. Compound 8, if produced, could not be isolated in pure form and characterized. Conditions for a "cleaner" photooxidation and an improved method of product characterization were therefore sought.



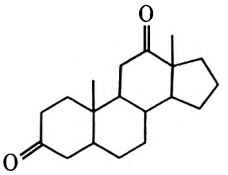
1, X = H; Y = $OCOC_6H_4NO_2$
2, X = H; Y = $OCOCH_2CH_2C_6H_4NO_2$
3, X = H; Y = OH
4, X, Y = O



5, X = H; Y = OH
6, X, Y = O



7, X = β-H
8, X = α-H



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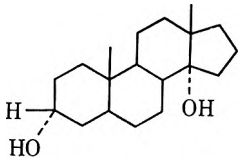

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The photoreaction of 2 could be effected under milder conditions (lower energy light) with a Pyrex filter. Under these conditions no solid separated, although the solution changed from colorless to deep yellow during the 12-hr reaction. Dehydration, saponification, and chromatography of the neutral fraction gave a mixture of 5α-androstan-3α-ol (3) and 5α-androst-14-en-3α-ol (5), and a mixture of more polar components. The mixture of 3 and 5 could not be separated, but the corresponding ketones 4 and 6, prepared by cautious Jones oxidation of the alcohol mixture, were readily separated by chromatography on silver nitrate impregnated silica gel.[6] This sequence afforded a 26% yield of 5α-androst-14-en-3-one (7) and 39% of 5α-androstan-3-one (4).

(6) Oxidation to ketones rather than the more common practice of masking the hydroxyl groups as acetates or methyl ethers was chosen since 6 is a known compound.

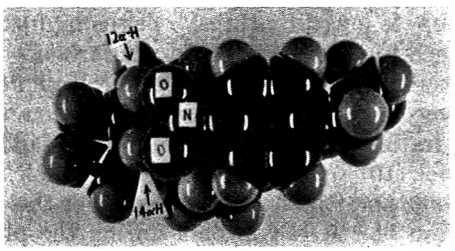

Figure 1.—Space-filling model of 5α-androstan-3α-yl β-(p-nitrophenyl)propionate (2) with the p-nitrophenyl moiety in position for oxidation of the steroid. View is from the α side of the steroid, with the D ring to the left and rotated slightly toward the viewer. Note the proximity of the nitro group oxygens and the steroid 12α and 14α hydrogens.

The more polar fraction isolated from the initial chromatography appeared to consist of a complex mixture of diols and polymer. Oxidation of this fraction with Jones reagent gave a mixture of diketones (and polymer). This mixture was complex, but the predominant isomer is probably 5α-androstan-3,12-dione (9) as evidenced by the position of the angular methyl signals in nmr spectra determined in deuteriochloroform and in benzene. Oxidation of the steroid 12 position in addition to position 14 is consistent with predictions based on space filling molecular models, as illustrated in Figure 1. Also, preference for oxidation at these positions has been observed in the analogous benzophenone photooxidation.[1b]

In addition to the above components isolated from the neutral fraction after saponification, it should be noted that *ca.* 10% of the steroid was found in the acid layer. This observation suggested that some of the steroid was undergoing multiple oxidation. It is likely that the more polar component of the neutral fraction also contained steroids which had undergone multiple oxidations. This conclusion was inferred from several vinyl proton signals, albeit faint, observed in the nmr spectrum, and from the polarity of the fraction which requires an oxygen function in addition to the 3α-hydroxyl group. The presence of both a second oxygen function and carbon–carbon unsaturation requires a multiple oxidation. This finding was not surprising, since the color of the solution after irradiation and the intense color of the acid fraction after saponification suggested reduction of the nitro group to azo- and/or azoxybenzene derivatives. Increasing the time of irradiation to 18, 24, or 48 hr resulted in more steroid undergoing photooxidation, as indicated by the isolation of smaller amounts of 4, but the yield of compound 6 was not improved, more tarry material being formed instead. In the 48-hr experiment, for example, 12% of 4 and 24% of 6 were obtained.

Material balances in these experiments were usually better than 90% when the steroid found in the acid fraction and the neutral polymeric material was included.

Acetonitrile appears to be the best solvent for the photoreaction. In acetone or benzene little oxidation of the steroid occurred, while in carbon tetrachloride, extensive chlorination of the steroid was observed.

The mechanism of the photoreaction has not been established. A reasonable pathway is abstraction of a hydrogen atom by one of the oxygen atoms of the

nitro group, followed by transfer of the hydroxyl group thus formed to the radical center on carbon. The 14α alcohol would be predicted as the initial photoproduct by this mechanism. Indeed, in a reaction in which the dehydration step was omitted, some 5α-androstane-3α,14α-diol (10) was observed. Some 14 olefin 5 was also present, and it is not known whether this arose by dehydration of the 14α alcohol during the photoreaction or whether the 14 double bond can be formed directly. Although the photoreactions were carried out in a nitrogen atmosphere, the reaction does not seem to be strongly inhibited by oxygen.

As a synthetic method, remote oxidation with nitro compounds must be compared with the reaction effected with benzophenone derivatives. The nitro function appears to be somewhat less selective between secondary and tertiary positions than benzophenone is. A more serious disadvantage is the inability to stop the reaction cleanly at a single (two-electron) oxidation of the substrate. The yield of well-defined remote oxidation products is therefore lower in the nitro oxidation than in some of the reported benzophenone reactions.[1b-d] However, the present study serves to extend the generality of the principle of remote oxidation to a nonbenzophenone case. More importantly, nitro compounds oxidize by the direct introduction of oxygen or unsaturation into the substrate. Formation of a carbon–carbon bond requiring further degradation, as frequently occurs in benzophenone cases, is thus avoided.

Experimental Section

5α-Androstan-3α-yl β-(*p*-Nitrophenyl)propionate (2).—A mixture of 1.28 g (5 mmol) of 5α-androstan-3α-ol (3), 1.10 g (5.6 mmol) of β-(*p*-nitrophenyl)propionic acid, and 0.35 g of *p*-toluenesulfonic acid in 300 ml of benzene was heated for 24 hr, with the refluxing benzene passing through a Soxhlet extractor containing anhydrous Na_2SO_4. The solution was cooled, washed with two 50-ml portions of $NaHCO_3$ solution followed by three 50-ml portions of brine, and dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the residue on 50 g of silica gel (ether–hexane) followed by recrystallization from aqueous CH_3CN afforded 1.45 g (64%) of compound 2, mp 116–118°. (*Caution*—An acid chloride route to 2 was first employed, but reaction of the acid with $SOCl_2$ resulted in the formation of tarry by-products. Purification of the acid chloride by vacuum distillation resulted in explosions several times.)

Photochemical Oxidation.—Photooxidations employed a 450-W Hanovia lamp, a Corex or a Pyrex sleeve, a quartz immersion apparatus (all from Ace Glass Co.), and a 2-l. reaction vessel. A solution of 906 mg (2.0 mmol) of compound 2 in 1980 ml of CH_3CN was purged with nitrogen for 1 hr prior to and during irradiation.

The solvent was removed, and the residue was treated with 75 ml of HOAc containing a trace of iodine. After heating at reflux for 4 hr, the HOAc was removed and the residue was treated with 100 ml of 1.0 *M* KOH in MeOH at reflux for 4 hr. Removal of the MeOH, addition of 100 ml of water, extraction with three 50-ml portions of hexane, washing the combined extracts with three 50-ml portions of brine, drying ($MgSO_4$), and evaporating afforded the crude photoproduct referred to below.

5α,14β-Androstane-3,15-dione (7).—A Corex filter had been used in a 24-hr protoreaction. The crude photoproduct was dissolved in 50 ml of dry tetrahydrofuran, and 0.600 g of finely powdered sodium borohydride was added, followed by 2.0 ml of boron trifluoride etherate. After 1 hr, water was added, followed by dilute sulfuric acid. Excess chromic acid reagent (prepared from 2.3 ml of concentrated H_2SO_4 and 2.7 g of CrO_3, diluted to 10 ml) was then added. After 15 min, 2-propanol was added, followed by brine and hexane. The organic layer was separated, washed with brine until neutral, and dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on 10 g of silica gel (ether–hexane) to afford 97 mg of 5α-androstan-3-one (4) (18%), 64 mg of 5α,14β-androstane-3,15-dione (7) (11%), and 40 mg of more polar material.

Compound 7, homogeneous by vpc (3% SE-30, 220°) and by tlc, exhibited mp 182–183.5°, unchanged upon recrystallization from aqueous acetone and from hexane; mass spectrum *m/e* 288.2085 ($C_{19}H_{28}O_2$ requires 288.2089), base peak *m/e* 97 (characteristic of 15-keto steroids[7]); nmr ($CDCl_3$) δ 0.983 (19-CH_3) and 1.200 (18-CH_3) (assigned structure requires δ 0.967 and 1.226[8]); ir 1742 and 1712 cm^{-1} (five- and six-membered cyclic ketones, respectively). The 14β stereochemistry is known to be preferred in 15-keto steroids lacking substitution at C-17.[9]

5α-Androst-14-en-3-one (6).—A Pyrex filter had been used in a 12-hr photoreaction. The crude photoproduct (488 mg) was chromatographed on 12 g of silica gel using gradient elution in which a flask of 250 ml of hexane fed the column and was in turn fed by a second flask containing 40% ether–60% hexane. A mixture of 358 mg of 5α-androstan-3α-ol (3) and 5α-androst-14-en-3α-ol (5) was eluted, followed by 123 mg of more polar material. The mixture of 3 and 5, dissolved in 30 ml of acetone and cooled to 0°, was treated with 15% excess of the chromic acid reagent described above. The excess oxidant was destroyed with 2-propanol after 4 min. The low temperature and short contact time were essential to prevent degradation of the double bond. Hexane and brine were added, the organic layer was separated, washed with brine until neutral, and dried ($MgSO_4$), and the solvent was evaporated to give 354 mg of a mixture of 5α-androstan-3-one (4) and 5α-androstan-14-en-3-one (6). This mixture was chromatographed on 20 g of 20% silver nitrate on silica gel, again using gradient elution with hexane and 20% ether–80% hexane, affording 213 mg of compound 4 (39%) and 140 mg of compound 6 (26%). Compound 6, recrystallized from aqueous CH_3CN, exhibited mp 117–118.5° (lit.[5] mp 118–119°); nmr ($CDCl_3$) δ 1.033 (18- and 19-CH_3's) (lit.[5] δ 1.033 for both CH_3's); ir 1715 cm^{-1} (six-membered cyclic ketone).

Analysis of the More Polar Neutral Fraction.—The more polar fraction (123 mg) obtained from chromatography of the crude photoproduct (12 hr photoreaction) presumably consisted of diols and polymer. Oxidation with excess Jones reagent (25° for 30 min), work-up with hexane and brine as described above, and vacuum sublimation afforded 60 mg of yellow material. The nmr spectra of this material exhibited several sharp singlets for angular methyl groups. The two largest singlets were found at δ 1.050 and 1.108 when the solvent was deuteriochloroform and at δ 0.733 and 0.533 when the solvent was benzene. The calculated peak positions for the 18- and 19-CH_3's of 5α-androstane-3,12-dione (9) are, respectively, δ 1.108 and 1.133 in deuteriochloroform and δ 0.748 and 0.523 in benzene.[8,10]

Registry No.—2, 39949-94-5; 3, 7657-50-3; 6, 17305-51-0; 7, 39949-97-8; β-(*p*-nitrophenyl)propionic acid, 16642-79-8.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to the Texas A & M University Chemistry Department, and to the Texas A & M University Research Council for support of this work.

(7) C. Djerassi, G. v. Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, **87**, 817 (1965).

(8) N. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy; Illustrations from the Steroid Field," Holden-Day, San Francisco, Calif., 1964, Table 2-3.

(9) C. Djerassi and G. v. Mutzenbecher, *Proc. Chem. Soc.*, 377 (1963).

(10) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).

Carbon-13 Magnetic Resonance Spectroscopy. The Spectrum of Proline in Oligopeptides

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The carbon-13 magnetic resonance spectra of a selection of simple proline derivatives are compared and discussed. The general features of such spectra are identified, with especial importance given to the problem of differentiation of cis and trans X-proline amide bonds. Spectra of the proline moiety in more complex oligopeptides are discussed in terms of the conclusions drawn from the spectra of simple compounds.

Because of the conformational requirements inherent in the pyrrolidine ring, proline has a unique place among the naturally occurring amino acids. Its occurrence in biologically active oligopeptides and proteins has important consequences upon the three-dimensional structures of these compounds.[1] As a result, proline and polypeptides containing proline have received extensive and detailed study by a wide variety of physical methods, including proton magnetic resonance (pmr) spectroscopy.[2]

Unlike the pmr spectrum of the proline residue, the fully proton-decoupled carbon-13 magnetic resonance (cmr) spectrum would be expected to be relatively simple. Furthermore, because of the importance of steric[3] and other proximity[4-6] effects in carbon-13 chemical shifts, one might expect that cmr spectroscopy would provide useful information regarding the conformation within and around the proline unit. We have therefore surveyed the cmr spectra of a number of proline derivatives and proline-containing oligopeptides. The purpose of the present paper is to identify and discuss the major features of the cmr spectrum of the proline unit.

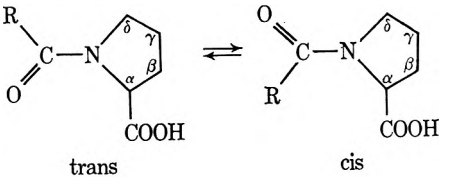
Experimental Section

The cmr spectra of the proline derivatives, all of which were commercially available, were measured as 10% (w/v) aqueous solutions, using a Varian XL-100 spectrometer adapted for Fourier transform spectroscopy.[7] Chemical shifts were measured relative to internal 1,4-dioxane, then referred to external carbon disulfide on the basis of the chemical shift of 1,4-dioxane relative to the reference (126.2 ppm).

Results

The cmr spectra of the proline derivatives studied are presented in Table I. The problem of peak assignments in such simple compounds is reduced to a minimum and can be based entirely upon the well-known correlations between carbon chemical shift and substitution.[8-10] These assignments are supported by comparisons within the series of proline deriviatives (*vide infra*), as well as by the proton-coupled ^{13}C nmr spectrum of proline.

The cmr spectra of the *N*-formyl and *N*-acetyl derivatives of proline (Table I) all show the peak doubling which would be anticipated because of the *cis–trans* isomerism of these compounds.[2,4-7,11] The major contributors to these mixtures have been clearly demonstrated by pmr spectroscopy[11] to be the trans conformers. Due to the general experience[4-6] that



trans cis

carbons syn to the carbonyl oxygen of amides are shielded relative to those which are anti, one would expect the α carbon of the trans conformer to be shielded relative to that of the cis. The δ carbon, however, would be expected to be more shielded in the cis, or minor, isomer. Such a situation should lead to a back-to-back[12] pattern for these resonances, as is observed in the case of *N*-acetylsarcosine.[6] As seen in the spectrum of *N*-acetylprolinamide (Figure 1), such is indeed the case. It is also evident from Figure 1 that a very similar pattern is observed for the β and γ resonances.[11b]

The carbons of the pyrrolidine ring throughout this series were assigned on the basis of (1) comparison to the spectrum of proline itself, and (2) the assumption that the trans conformer was the dominant species in each mixture.

The carbonyl resonances were assigned on the usual assumption that carbon chemical shift changes will be greatest near the site where substitution is altered. Comparison of the spectra of *N*-formyl- and *N*-acetylproline, for example, shows that both spectra have peaks near 16.5–17.0 ppm. Because the proline carboxyl might be expected to show only minor chemical shift changes in these two compounds, these peaks are assigned to that carbon. This leaves the peaks at about 28.5 and 20.3 ppm to be assigned to the formyl and acetyl carbonyls, respectively. These assignments are supported by other comparisons. Thus, in the acetylated proline and the analogous ester and amide, only the carboxyl carbon resonance should show large variations in chemical shift. Certainly the acetyl

(1) L. Mandelkern in "Poly-α-amino Acids," G. D. Fasman, Ed., Marcel Dekker, New York, N. Y., 1967, Chapter 13.

(2) *Cf.*, for example, F. A. Bovey, *et al.*, *Accounts Chem. Res.*, **5**, 193 (1972).

(3) D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315, 5319 (1967).

(4) W. McFarlane, *Chem. Commun.*, 418 (1970).

(5) G. C. Levy and G. L. Nelson, *J. Amer. Chem. Soc.*, **94**, 4897 (1972).

(6) D. E. Dorman and F. A. Bovey, *J. Org. Chem.*, **38**, 1719 (1973).

(7) H. Sternlicht and D. M. Zuckerman, *Rev. Sci. Instrum.*, **43**, 525 (1972).

(8) (a) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964); (b) L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).

(9) W. Horsley, H. Sternlicht, and J. S. Cohen, *J. Amer. Chem. Soc.*, **92**, 680 (1970).

(10) M. Christl and J. D. Roberts, *ibid.*, **94**, 4565 (1972).

(11) (a) W. A. Thomas and M. K. Williams, *J. Chem. Soc., Chem. Commun.*, 788 (1972). (b) This feature of the cmr spectra of proline derivatives has been noted in an independent study: K. Wüthrich, A. Tun-Kyi, and R. Schwyzer, *F.E.B.S. Lett.*, **25**, 104 (1972).

(12) F. A. Bovey, J. J. Ryan, and F. P. Hood, *Macromolecules*, **1**, 305 (1968).

TABLE I

CARBON CHEMICAL SHIFTS[a] OF SELECTED PROLINE DERIVATIVES

	Registry no.	Cis						Trans					
		CO	α	β	γ	δ	Other	CO	α	β	γ	δ	Other
Proline (zwitterion)	147-85-3							18.3	131.4	163.8	168.9	146.5	
N-Formylproline	13200-83-4	16.6	133.1	163.4	170.3	148.5	CHO 28.3	17.3	135.8	163.4	169.1	145.5	CHO: 29.4
N-Acetylproline	68-95-1	16.4	131.8	161.9	170.2	146.1	CO 19.7; CH_3 171.4	16.5	133.7	163.3	168.5	144.3	CO 20.0; CH_3 171.4
N-Acetylproline, methyl ester	27460-51-1	17.9	132.1	161.8	170.4	146.1	CO 20.0; CH_3 139.9	17.9	133.8	163.6	168.4	144.4	CO 20.0; CH_3 171.5; OCH_3 139.9
N-Acetylprolinamide	16395-58-7	15.5	131.5	161.1	170.3	145.8	CO 19.8; CH_3 171.3	15.5	133.0	162.7	168.7	144.2	CO 19.8; CH_3 171.5
Glycylproline	704-15-4	14.5	131.1	161.2	170.4	145.5	Gly(CO) 27.2; Gly(α) 152.3	13.8	130.8	163.2	168.5	146.1	Gly(CO) 27.8; Gly(α) 152.1
tert-Butoxycarbonylglycylproline[b]	14296-92-5	18.1	133.4	161.5	170.6	146.0	Gly(CO); 23.2; Gly(α) 150.0; Boc(CO) 35.5; C-quat 113.1; CH_3 165.1	18.1	133.4	163.8	168.2	146.6	Gly(CO) 23.7; Gly(α) 150.0; Boc(CO) 35.5; C-quat 113.1; CH_3 165.1
"Typical generalized proline"		14.5–18.5	131.1–133.4	161.1–163.4	170.2–170.6	145.5–148.5		13.8–18.3	130.8–135.8	162.7–163.8	168.2–169.1	144.3–146.6	

[a] Relative to external carbon disulfide. [b] D. A. Torchia, unpublished results.

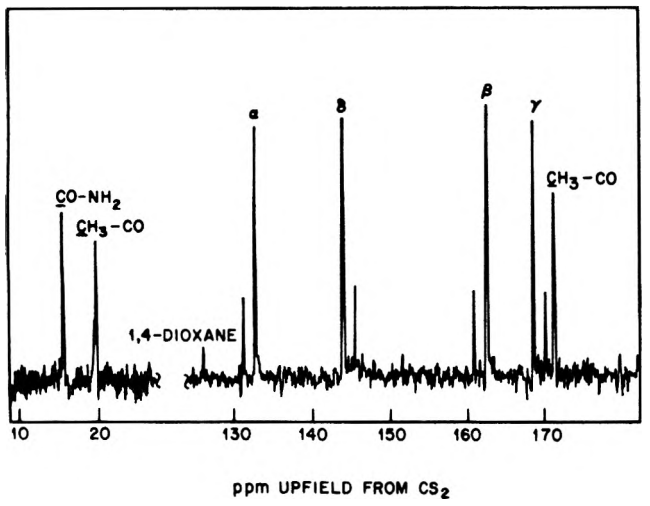


Figure 1.—The proton-decoupled cmr spectrum of *N*-acetylprolinamide. The resonances of the pyrrolidine ring carbons all show doubling due to cis–trans isomerism around the X-Pro bond. The methyl and carbonyl resonances also show this doubling, but only under conditions of higher resolution.

carbonyl resonances near 20 ppm appear to be unchanged in chemical shift throughout the series.

The acetyl methyl carbon resonance is assigned by elimination. It is evident that its chemical shift is unaffected by changes in the substitution at the carboxyl group. The assignment of the glycine resonances of the two glycylprolines is based on comparisons with earlier studies.[9,10] Peak assignments for other peptides discussed in this paper are available in the original articles.

Discussion

It is apparent from Table I that the spectra of these proline derivatives show many similarities. Most striking is that seen in the resonances assigned to the γ carbons. Throughout this series, the peak assigned to the γ-carbon resonance of the trans conformer is within the narrow range 168.6 ± 0.5 ppm. The analogous peak of the minor cis isomer occurs at 170.3 ± 0.3 ppm. This pattern in the γ-carbon resonances was noted very early in this work and formed the basis of the hypothesis that this chemical shift behavior could be used to determine the conformation about the peptide bond involving the proline nitrogen, the so-called X-Pro bond.[13]

A similar but more variable pattern is seen in the resonances of the β carbons (Table I). In the trans conformers, the chemical shifts of this carbon range from 162.7 to 163.8 ppm. With the exception of *cis*-*N*-formylproline, the β resonances of the cis conformers vary from 161.1 to 161.9 ppm. Unfortunately, the chemical shift of the β carbon is subject to conformational effects other than the cis–trans isomerism of the peptide bond (*vide infra*). For this reason this resonance is a less reliable guide in the determination of the conformation of the X-Pro bond.

On the basis of prior results with simple amides,[4-6] it is reasonable to suppose that the chemical shift differences observed at the α and δ positions (*vide supra*) would suffice to identify the peptide bond conformation. Such would certainly appear to be the case for the *N*-acetylproline derivatives (*cf.* Table I). The normal back-to-back pattern in these resonances are reversed, however, when the acyl group on the proline nitrogen is an amino acid, as is seen in the spectra of glycylproline derivatives (*cf.* Figure 2). Closer examination of Figure 2 leads to additional conclusions regarding the sources of chemical shift differences in these compounds. It is obvious that the chemical shift of the δ carbon of the cis isomer is broadly independent of the nature of R. This is as might have been expected on the grounds that R is relatively distant from this position. The δ resonance of the trans conformer, however, is seen to move upfield as the steric bulk of R increases (Figure 2). This shielding effect may result from steric perturbations.[3] The net result of this chemical shift effect, regardless of its origin, is that the δ-carbon resonances of *cis*- and *trans*-proline derivatives have very similar chemical shifts and are therefore not generally useful in the identification of the dihedral angle about the X-Pro bond.

An analogous change is observed in the α resonances. Comparison of the spectra of *N*-acetyl- and *tert*-butoxycarbonylglycyl-L-proline in Figure 2 shows that it is the α resonance of the cis conformer which moves upfield. Again, such a shift is consonant with a steric

(13) F. A. Bovey, "Proceedings of the Third American Peptide Symposium," Ann Arbor Science Publishers, Ann Arbor, Mich., 1972.

effect and leads to difficulties in interpretation of the α-carbon chemical shift in terms of conformation of the X-Pro bond. In the spectrum of glycyl-L-proline, this effect is masked by those resulting from ionization of the neighboring carboxyl group. The observed chemical shift change at the α position in the last compound is in accord with an earlier study of the effects of ionization of carboxylic acids,[14] which showed that the α carbons of even these simpler compounds were deshielded by ionization of the acid.

From these spectra we may conclude that the chemical shifts of the γ resonance provide a means by which the conformation of the X-Pro bond may be analyzed. In those spectra wherein the γ resonance cannot be observed or identified, the chemical shift of the β resonance can serve this function. To assess the reliability of these criteria, we have attempted to identify the sources of the chemical shift dependences at the β and γ positions upon the conformation of the X-Pro bond. From Table I it is seen that the γ resonances of a pair of X-Pro conformers differ in chemical shift by 1.5–2.0 ppm; similar differences are observed at the β position. In the spectra of *N*-formyl- and *N*-acetylpyrrolidine (Table II), in which

TABLE II

CARBON CHEMICAL SHIFTS OF *N*-FORMYL- AND *N*-ACETYLPYRROLIDINE

Pyrrolidine	C-2	C-3	C-4	C-5	CO	CH_3
N-Formyl	149.5	169.1	168.5	146.6	30.7	
N-Acetyl	147.0	168.7	167.5	144.9	21.0	171.6

the β and γ carbons differ in chemical shift solely by virtue of the amide group, we observe chemical shift differences of approximately 1 ppm at these positions. It therefore appears that to a large degree the dependence of these chemical shifts upon the conformation of X-Pro bonds arises from the direct influence of the peptide function.

Correlation with Other Results.—The above conclusions are based solely on the cmr spectra of relatively simple compounds. In no case, for example, is the proline carboxyl involved in a peptide bond to a second amino acid. It is possible, therefore, that some of our generalizations will fail when they are applied to more complex systems. Fortunately, there are available in the literature sufficient data to test our conclusions thoroughly. Indeed, in some cases the reevaluation of published data in the light of our generalizations leads to additional insight into the structures and conformations of these oligopeptides.

The simplest cases available for comparison are the di- and tripeptides studied by Christl and Roberts.[10] Perhaps because these authors were limited to the sensitivity available from a continuous wave spectrometer, they were unable to observe peak doubling due to cis–trans isomerism of the X-Pro bond. In the case of L-prolyl-L-phenylalanine (Table III), no such isomerism is possible. It is interesting that the chemical shifts of both the β and γ carbons of this compound occur in the ranges typical of trans X-Pro systems, as was observed for unsubstituted proline

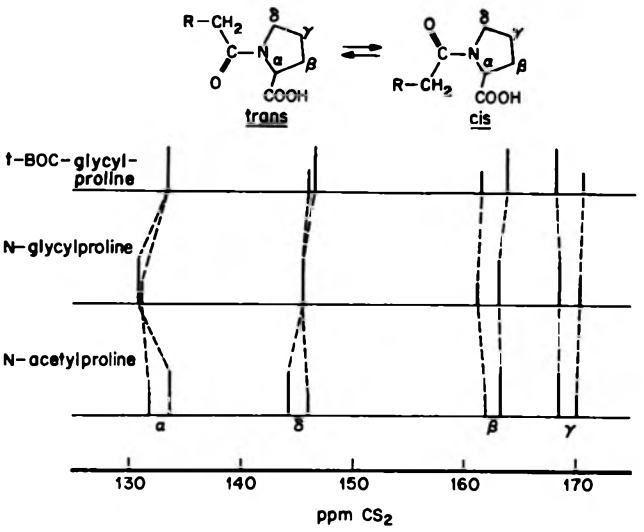


Figure 2.—Comparison of the cmr spectra of *N*-acetylproline, *N*-glycylproline, and *tert*-butoxycarbonylglycyl-L-proline. The peaks of the major trans conformer are denoted by the lines of greater height. Only the spectra of the pyrrolidine ring carbons are shown.

(Table I). This suggests that the chemical shifts of these carbons are not influenced by charge on the proline nitrogen or by substitution at the prolyl carboxyl. It is also notable that the prolyl carbonyl resonance of prolylphenylalanine comes into resonance at significantly higher field than in all previous examples, including *N*-acetylprolinamide. In previous studies of simple amides[6] it was noted that increasing substitution upon the amide nitrogen had a generally shielding effect at the carbonyl carbon. It is probable that the generally higher field position of the proline carbonyl carbon in peptides is due at least in part to this substituent effect.

A rather more interesting case is that of phenylalanyl-L-proline.[10] In acidic solutions, the spectrum of the pyrrolidine ring most closely corresponds to that of a trans X-Pro system (Table III). In neutral and alkaline solutions, however, the carbon chemical shifts suggest that the X-Pro bond is cis. Interpreted on the basis of our hypotheses, then, these results suggest that the X-Pro equilibrium in these compounds is pH dependent.

In the case of L-phenylalanyl-L-prolyl-L-arginine,[10] again only one species was observed. The chemical shifts of the β and γ resonances (Table III) are in better agreement with a trans X-Pro system. However, both these resonances appear at unusually high field. Problems in the peak assignments in this spectrum led the authors to suggest an alternative assignment by which the β and γ resonances occur at 163.0 and 168.4 ppm, respectively.[10] It will be noted that this latter assignment is in excellent agreement with a typical trans X-Pro spectrum. For this reason we consider the alternative assignment more reliable.

In pmr spectroscopy the diketopiperazines are not necessarily good models for polypeptides.[15] One might expect that ring strain and other effects associated with such structures would make their cmr spectra atypical.

(14) R. Hagen and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 4504 (1969).

(15) F. A. Bovey, "High Resolution NMR of Macromolecules," Academic Press, New York, N. Y., 1972, p 274.

TABLE III
CARBON CHEMICAL SHIFTS[a] OF PROLINE IN SELECTED OLIGOPEPTIDES

	CO	α	β	γ	δ	Solvent	Ref
Prolylphenylalanine (pH 0.9)	22.9	132.4	162.5	168.5	145.4	H_2O	10
Phenylalanylproline (pH 0.9)	17.3	132.5	163.6	167.7	144.8	H_2O	10
Phenylalanylproline (pH 5.5)	14.4	130.4	161.2	170.2	145.8	H_2O	10
Phenylalanylproline (pH 10.5)	13.5	130.4	161.2	170.0	145.6	H_2O	10
Phenylalanylprolylarginine (pH ~7)	19.6	131.4	165.8[c]	169.2[c]	144.6	H_2O	10
Polyproline-I	20.9	133.7	161.4	171.1	144.6	H_2O	23
Polyproline-II	21.3	134.3	164.9	168.2	145.2	H_2O	23
Glycyl-L-proline diketopiperazine	23.4	134.7	164.8	170.6	146.7	DMSO	16
L-Prolyl-L-proline diketopiperazine	26.8	133.0	165.5	169.8	148.1	DMSO	16
c-(Pro-Gly)$_3$	22.4	133.2	165.9	167.1	146.4	CH_2Cl_2	24
c-(Pro-Gly)$_3$	21.0	133.1	161.8	168.8	146.2	DMSO	24
	22.0	134.1[b]	162.3	169.8	147.1[b]		
	22.8		163.7	171.2			
c-(Pro-Gly)$_3$-Na	20.3	133.9	164.3	168.8	147.2	DMSO	25
c-(Pro-Ser-Gly)$_2$	21.9[b]	131.1	163.3	168.3	145.9	H_2O	25
Gramicidin S	*d*	132.6	163.4	168.5	146.1	DMSO	19
Gramicidin S	*d*	130.3	161.6	166.4	144.3	CH_3OH	19
Antamanide	*d*	131.5	161.0	167.6	144.3	CD_3CN	22
		131.7	161.6	167.6	144.7		
		133.5	163.7	170.4	145.8		
		133.8	164.0	171.2	145.9		
Antamanide-Na	*d*	133.8	160.9	167.2	144.5	CD_3CN	22
		134.0	160.9	167.9	145.2		
		134.2	163.7	170.1	145.5		
		134.2	164.3	170.5	145.5		
Actinomycin D	*d*	133.7	161.4	169.6	145.2	1,4-Dioxane-d_8	26
Actinomycin D	*d*	134.5	161.4[e]	170.2	145.7	DMF	26
Actinomycin D-deoxyguanosine	*d*	134.4	161.5[e]	170.0 170.2	145.8	DMF	26

[a] Relative to external carbon disulfide. [b] Double intensity. [c] Assignment tentative. [d] Not tabulated by original authors. [e] Peak position uncertain due to overlapping solvent resonances.

It is apparent from Table III, however, that the chemical shifts of the γ resonances of glycyl-L-proline and L-prolyl-L-proline diketopiperazines are quite close to the average shift of this carbon in a cis X-Pro system.[16] In contrast, the β-carbon resonances are shielded relative to the simpler derivatives. We believe this shielding to result from the proximity effect[4-6] of the carbonyl oxygen. In normal proline systems the angle ψ[17] is approximately 320° (the so-called trans′ conformation), and in such a situation the β carbon is not particularly close to the proline carbonyl group. In the diketopiperazines, however, the β carbon can be judged from models to be very nearly coplanar with the carbonyl group. Such a conformation is expected to shield the β carbon.[4-6] In possible accord with this notion are the unusually high chemical shifts observed for the proline carboxyl carbons of the diketopiperazines. Thus, for *N*-methylformamide[5,6] the chemical shifts of both carbons were found to be upfield in the trans isomer, indicating that syn interaction between the *N*-methyl and the carbonyl oxygen led to a general shielding effect. An analogous interaction with the β carbon could shield the carbonyl nucleus of proline in diketopiperazines.

Gramicidin S, a decapeptide antibiotic, is of particular interest in that the published conformational models[18] for this compound have the ψ angle of the proline units in the cis′ conformation (ψ ~ 120°). Such a conformation might be expected to lead to irregularities in the cmr spectrum as, for example, in the β resonances of the diketopiperazines. This does not appear to be the case. The cmr spectra of gramicidin S[19] in methanol and dimethyl sulfoxide are qualitatively very similar, both clearly showing the existence of C_2 symmetry in the molecule. As seen from Table III, the proline spectrum of gramicidin S in dimethyl sulfoxide is entirely consistent with that of a typical trans X-Pro peptide bond.[20] Clearly additional experiments are necessary before the effects of ψ upon the chemical shifts of the β and γ resonances can be properly assessed.

The decapeptide antamanide contains no element of symmetry, and its cmr spectrum is accordingly complex.[22] However, the grouping of the β- and γ-proline carbon resonances enables one to conclude that two of the four proline residues are cis and two are trans,[22] a conclusion which cannot be drawn from the proton data alone.

Conclusions

The present results show that carbon chemical shifts alone can be instrumental in the assignment of the conformation of the X-Pro bond. Application of this principle in these laboratories has led to the clarification of details of the conformation of poly-L-proline,[23] *cyclo*-(Pro-Gly)$_3$,[24] *cyclo*-(Pro-Ser-Gly)$_2$,[25] antamanide,[22]

(16) D. J. Patel, unpublished results.

(17) For an explanation of the conventions used in this paper describing dihedral angles in peptides, see J. T. Edsall, *et al.*, *Biopolymers*, **4**, 121 (1966); *J. Biol. Chem.*, **241**, 1004 (1966); *J. Mol. Biol.*, **15**, 399 (1966). Another convention has been more recently introduced: J. C. Kendrew, *et al.*, *Biochemistry*, **9**, 3471 (1970); *J. Biol. Chem.*, **245**, 489 (1970); *J. Mol. Biol.*, **52**, 1 (1970).

(18) (a) A. Stern, W. A. Gibbons, and L. C. Craig, *Proc. Nat. Acad. Sci. U. S.*, **61**, 734 (1968); (b) Y. A. Ovchinnikov, Y. T. Ivanov, V. F. Bystrov, A. I. Miroshnikov, E. N. Shepel, N. D. Abdullaev, E. S. Efremov, and L. B. Senyavina, *Biochem. Biophys. Res. Commun.*, **39**, 217 (1970).

(19) W. A. Gibbons, J. A. Sogn, A. Stern, L. C. Craig, and L. F. Johnson, *Nature*, **227**, 840 (1970).

(20) The spectrum reported[19] for gramicidin S in methanol is in very poor agreement with all other results. Comparison of the spectra of this compound in the two solvents shows that the entire spectrum appears to have been shifted downfield in methanol. This suggests the possibility of a systematic error. In accord with this notion is Figure 2 of ref 19, in which the methanol resonance is represented as occurring at about 142 ppm. In fact, the chemical shift of methanol referred to external carbon disulfide is 144.2 ppm.[21] If a +2 ppm adjustment is made in the spectrum of gramicidin in methanol, much better correspondence for the two different solvents is obtained.

(21) J. D. Roberts, F. J. Weigert, J. I. Kroschiwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970). These authors report chemical shifts relative to internal carbon disulfide, and their chemical shift data must be accordingly adjusted by +0.7 ppm.

(22) D. J. Patel, *Biochemistry*, **12**, 667, 677 (1973).

(23) D. E. Dorman, D. A. Torchia, and F. A. Bovey, *Macromolecules*, **6**, 80 (1973).

(24) C. M. Deber, D. A. Torchia, D. E. Dorman, F. A. Bovey, and E. R. Blout, Proceedings of the Third American Peptide Symposium, 1972.

(25) D. E. Dorman, A. I. Brewster, F. A. Bovey, C. M. Deber, and E. R. Blout, in preparation.

actinomycin D,[26] and oxytocin.[27] Only in the case of *cyclo*-(Pro-Gly)$_3$ in methylene chloride do these rules fail to agree with previous conclusions, and this failure may be due to an unusual dihedral angle ψ.[24] We believe this application of ^{13}C nmr spectroscopy will find great importance in future studies of oligo- and polypeptides.

(26) D. J. Patel, *et al.*, unpublished results.
(27) A. I. R. Brewster, V. J. Hruby, A. F. Spatola, and F. A. Bovey, *Biochemistry*, **12**, 1643 (1973).

Registry No.—*N*-Formylpyrrolidine, 3760-54-1; *N*-acetylpyrrolidine, 4030-18-6.

Zonarol and Isozonarol, Fungitoxic Hydroquinones from the Brown Seaweed *Dictyopteris zonarioides*[1]

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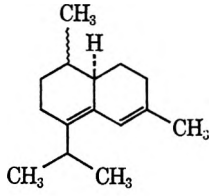
Zonarol and isozonarol, isomeric C_{21} hydroquinones, have been obtained each from separate methanol extracts of *Dictyopteris zonarioides* collected in the Pacific Ocean and in the Gulf of California. The structural assignments were made based upon spectral grounds and by degradation to dihydrotauranic acid and comparison with an authentic sample.

Previous investigations of members of the genus *Dictyopteris* (family Dictyotaceae) have led to the isolation of two new oxygenated sesquiterpenes[3,4] and a novel assortment of nonterpenoid C_{11} hydrocarbons and sulfur-containing compounds.[5-8] In an earlier paper[9] we described the structure of zonarene (**1**),



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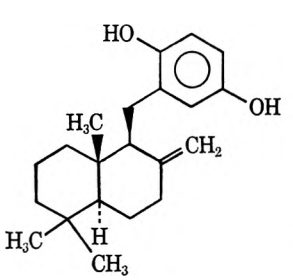
the major hydrocarbon component of the hexane extract of *D. zonarioides*, an alga indigenous to the Pacific Ocean near southern California and to the Gulf of California. We wish to report here the structures of zonarol (**2**) and isozonarol (**3**), hydroquinones obtained from the methanol extract of this alga. Zonarol was the exclusive isomer present in samples collected in the Pacific Ocean, while only isozonarol was obtained from the Gulf of California source. Both methanol extracts also contained **1** and small amounts of the corresponding quinones which are discussed below. Both **2** and **3** are moderately fungitoxic toward *Phytophthora cinnamomi*, *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, and *Sclerotium rolfsii*.



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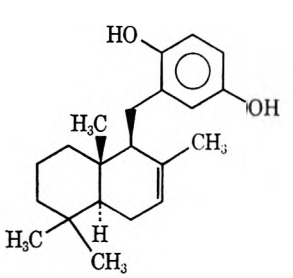

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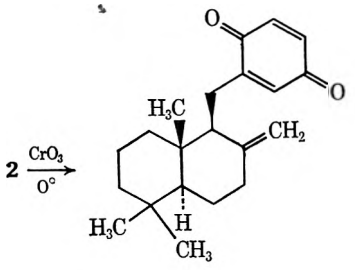
Column chromatographic separation of the methanol extract of *D. zonarioides*, collected in San Diego, Calif., gave zonarol (**2**) as a noncrystalline gum. All attempts to crystallize this material failed. The infrared absorptions of this compound clearly showed the presence of hydroxyl (3400 cm^{-1}) and an exocyclic double bond (1650 and 908 cm^{-1}). While **2** did not give a positive ferric chloride test, it was recognized as a monosubstituted hydroquinone by its eventual oxidation to the corresponding quinone. In addition, its nmr spectrum showed three aromatic protons at δ 6.55 as a complex band and two hydroxyl protons at solvent-dependent chemical shifts. Two exocyclic methylene protons were recognized by broad bands at δ 4.64 and 4.75. Multiple bands from δ 1.0 to 2.8 showed the molecule to contain a variety of saturated methylene hydrogen. Overlapping sharp signals centered at δ 0.80 indicated three quaternary methyl groups to be present. The mass spectrum of **2** and the integration of the nmr bands described above were consistent (P = *m/e* 314) in indicating the molecular formula $C_{21}H_{30}O_2$. The uv spectrum[10] also suggested the hydroquinone structure, λ_{max}^{MeOH} 211 nm (ϵ 8400) and 295 (3150). Treatment of **2** with Jones reagent[11]

(1) (a) Marine Natural Products. VII. For Part VI see W. Fenical, J. Sims, and P. Radlick, *Tetrahedron Lett.*, **4**, 313 (1973). (b) Presented in part at the Third International Conference on Food-Drugs from the Sea, Kingston, R. I., Aug 1972.
(2) Address correspondence to Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla, Calif. 92037.
(3) T. Irie, K. Yamamoto, and T. Masamune, *Bull. Chem. Soc. Jap.*, **37**, 1053 (1964).
(4) E. Kurosawa, M. Izawa, K. Yamamoto, T. Mosamune, and T. Irie, *Bull. Chem. Soc. Jap.*, **39**, 2509 (1966).
(5) R. E. Moore, J. A. Pettus, Jr., and M. S. Doty, *Tetrahedron Lett.*, **46**, 4787 (1968).
(6) J. A. Pettus, Jr., and R. E. Moore, *Chem. Commun.*, 1093 (1970).
(7) J. A. Pettus, Jr., and R. E. Moore, *J. Amer. Chem. Soc.*, **93**, 3087 (1971).
(8) P. Roller, K. Au, and R. E. Moore, *Chem. Commun.*, 503 (1971).
(9) W. Fenical, J. Sims, R. Wing, and P. Radlick, *Phytochemistry*, **11**, 1161 (1972).
(10) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Elmsford, N. Y., 1964.
(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

at 0° resulted in quantitative conversion to zonarone (**4**) which crystallized as long yellow needles from



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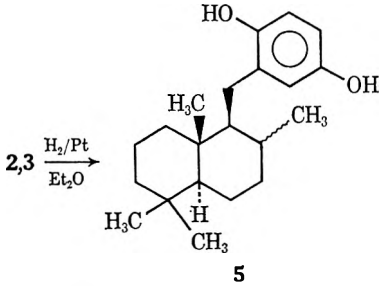
methanol, mp 125–127°. The uv of this quinone showed λ_{max}^{MeOH} 248 nm (ϵ 12,700) and 331 (790), consistent with its structure. The nmr spectrum of **4** exhibited a greater separation of bands and therefore showed more clearly the structural features of this system. Two aromatic protons appeared as a sharp band at δ 6.65 and the other aromatic as a more broad band at δ 6.40. The exocyclic olefinic protons appeared as two bands centered at δ 4.75 and 4.38. Methylene protons spanned between δ 2.7 and 1.0 and three singlets, sharply resolved at δ 0.92, 0.87, and 0.80, were assigned to the quaternary methyl groups. The coupling and chemical shifts observed in the nmr of **4** are entirely consonant with those reported for tauranin,[12] a disubstituted quinone with the identical sesquiterpenoid substituent.

Column chromatographic separation of the methanol extract of *D. zonarioides*, collected in the Gulf of California near Puerto Peñasco, Mexico, gave only the isomeric hydroquinone isozonarol (**3**).[13] Isozonarol was also obtained as a noncrystalline gum. Spectral information showed **3** to be isomeric with **2**, with the obvious difference being the loss of the exocyclic double bond features in both the infrared and nmr spectra. Hydrogenation of **2** and **3** served to confirm the double bond isomer relationship of these two hydroquinones. Each absorbed 1 mol of hydrogen to give a saturated hydroquinone epimeric mixture (**5**), *m/e* 316, $C_{21}H_{32}O_2$,



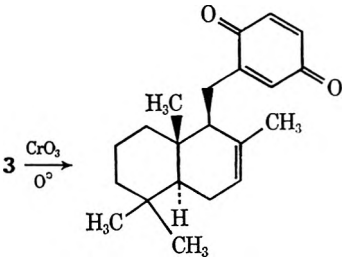
5

which were identical in all respects. Oxidation of **3** in an analogous fashion as with **2** gave isozonarone (**6**) as bright yellow plates from methanol, mp 111–112°. The spectral data for this isomer (Experimental Section) exhibited elements in confirmation of its structure.

The structural information gained from the spectral features of **2**–**6** clearly showed the molecules in question to be monosubstituted hydroquinones and quinones. The substituent in each case was a $C_{15}H_{25}$ fragment which contained two rings and a single double bond,

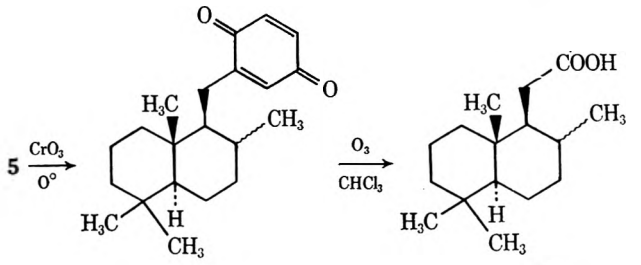
(12) K. Kawashima, K. Nakanishi, and H. Hishikawa, *Chem. Pharm. Bull.*, **12** (7), 796 (1964).

(13) The possibility that **3** is formed from **2** during work-up procedures is discounted since all samples were treated in an identical fashion.



6

exocyclic in one series and endocyclic in the other. Using a method analogous to that employed by Nakanishi in his structure proof of tauranin,[12] the hydroquinone moiety in zonarol was cleaved *via* an oxidative degradation. To accomplish this, zonarol was first hydrogenated to the saturated epimeric mixture **5**. This mixture was then oxidized with Jones reagent to yield the saturated quinone mixture **7**. Ozonation of **7** followed by oxidative work-up gave a carboxylic acid mixture **8** which crystallized from acetonitrile, mp



7 **8**

104–105°. This acid gave identical spectra with those reported[12] for the eutectic mixture of dihydrotauranic acids derived from tauranin and from the degradation of ambrein,[14] sclareol,[14] and manool.[15] A sample of authentic[16] dihydrotauranic acid and the eutectic mixture obtained above were converted to their methyl esters and compared by gas chromatography. Each sample was composed of a 60:40 mixture of epimeric esters whose behaviors were identical including retention times on mixed injection.

The results of mass spectral analysis of the quinones **4** and **6** are worthy of discussion. Under our conditions neither **4** nor **6** gave a clean parent ion. Instead, each quinone gives very large P + 2 and P + 4 peaks. For zonarone P + 2 was 40% parent and for isozonarone P + 2 was 128% parent intensity. This phenomenon has already been observed[17] with other quinones and is due to the formation of the corresponding hydroquinones *via* reduction upon electron impact. In order to probe the redox nature of these compounds, a cyclic voltametry study of **4** and **6** was initiated. The cyclic voltammagram shows two quasi-reversible electrochemical couples identical for each quinone. One couple has an E_{pc} of -0.525 V and an E_{pa} of -0.45 V while the other shows an E_{pc} of -1.35 V and an E_{pa} of -1.275 V. An E_{pc} defines the reduction potential for the reaction ox. + $ne^- \rightleftarrows$ red., and the

(14) C. C. Asselineau, E. Lederer, D. Mercier, and J. Polonsky, *Bull. Soc. Chim. Fr.*, 720 (1950).

(15) L. Ruzicka, O. Durst, O. Durst, and O. Jeger, *Helv. Chim. Acta*, **30**, 353 (1947).

(16) The authentic sample used was obtained from the degradation of tauranin.[12] We are grateful to Professor K. Nakanishi, Columbia University, for providing us with a sample of the dihydrotauranic acid epimeric mix.

(17) R. T. Alpin and W. T. Pike, *Chem. Ind. (London)*, 2009 (1966).

E_{pa} the oxidation potential of the reverse reaction. These results indicate two one-electron reductions from quinone to semiquinone and from semiquinone to hydroquinone. The low reduction potentials noted above and the reversible nature of the reduction are in complete accord with the ease of reduction under mass spectral conditions.

Experimental Section

General Methods.—All melting points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Infracord instrument either as thin films or in solvent-cancelling solution as noted. Ultraviolet absorptions were obtained in methanol solution using a Perkin-Elmer Model 202 spectrophotometer. ORD–CD spectra were obtained using a JASCO Model ORD-CD-UV-5 spectrometer. Nmr spectra were recorded in solutions at 60 MHz using a Varian Associates T-60 spectrometer. Mass spectral analyses were all obtained with a Finnigan 1015 SL mass spectrometer. All solvents used were Mallinckrodt AR grade and were used as received with the exception of hexanes, which required distillation. Gas chromatographic analyses were completed with an Aerograph Model A-90-P with the columns and conditions noted.

Methanol Extraction of *Dictyopteris zonarioides* (Pacific Ocean Source).—Air-dried *Dictyopteris zonarioides* (127 g) collected intertidally in San Diego, Calif., on September 30, 1970, was ground in a Wiley mill to 1 mm. Extraction was initiated with methanol in a Soxhlet extractor and allowed to continue for 48 hr. The methanol was then removed *in vacuo* and the resulting tar was taken up in an excess of diethyl ether. The ether was dried and concentrated to give 3.2 g of dark tar. The tar was taken up in petroleum ether (bp 30–60°) and chromatographed on a column (250 g) of Davison grade 62 silica gel eluting with petroleum ether, benzene, and varying amounts of diethyl ether in benzene; 3% diethyl ether in benzene eluted zonarol as a noncrystalline gum, 0.450 g. Thin layer chromatography on silica H with 5:1 benzene–ether showed one spot at R_f 0.80. Zonarol was then dissolved in benzene and precipitated by adding petroleum ether, resulting in solids but still noncrystalline ?. Zonarol had the following spectra, features: ir $\nu_{max}^{CHCl_3}$ 3550, 3400, 2960, 1650, 1490, 1440, 1170 and 910 cm^{-1}; uv λ_{max}^{MeOH} 211 nm (ϵ 8400), 295 (3150); nmr δ 3.3 (m, 3 H), 4.7 (s, 2 H), 4.75 (s, 1 H), 4.64 (s, 1 H), 2.60 (m, 2 H), 2.4–1.0 (m, 12 H), 0.85 (m, 9 H); mass spectrum *m/e* (rel intensity) 41 (25), 43 (11), 55 (27), 57 (8), 67 (18), 69 (32), 77 (12), 79 (14), 81 (28), 83 (10), 91 (15), 93 (15), 95 (49), 97 (11), 105 (12), 107 (24), 109 (43), 119 (12), 121 (29), 122 (10), 123 (90), 124 (20), 135 (21), 136 (16), 137 (24), 147 (8), 149 (14), 161 (29), 162 (8), 163 (18), 175 (18), 176 (10), 177 (16), 178 (21), 189 (14), 190 (16), 191 (100), 192 (18), 299 (6), 314 (52), 315 (10), 316 (2). In some earlier chromatography fractions very small amounts (~10 mg) of zonarone were found.

Oxidation of Zonarol (2).—2 (0.200 g) was dissolved in 20 ml of cold (0°) acetone and titrated to an oxidation end point with Jones reagent.[11] When the reaction was complete, the solution was poured onto ice and extracted with three 100-ml portions of diethyl ether.

The combined ether extracts were washed with water and dried with anhydrous magnesium sulfate, and the solvent was removed *in vacuo* to leave zonarone (4), 0.190 g, as bright yellow crystals. Crystallization from methanol gave 4 as long yellow needles, mp 126–127°.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.98; H, 9.02.

Zonarone had the following spectral features: ORD-CD (MeOH) $[\alpha]_{425}^{30}$ −178°, $[\alpha]_{498}^{30}$ +279°, $[\alpha]^{30}D$ +88.7°; ir $\nu_{max}^{CCl_4}$ 2940, 1660, 1600, 1455, 1430, 1375, 1300, 1210, 1180, 1115, 1075, 1050, 911 and 898 cm^{-1}; uv λ_{max}^{MeOH} 331 nm (ϵ 790), 248 (12, 700); nmr (CCl_4) δ 6.70 (s, 2 H), 6.45 (s, 1 H), 4.80 (s, 1 H), 4.40 (s, 1 H), 2.60 (m, 2 H), 2.50–1.00 (m, 12 H), 0.90 (s, 3 H), 0.84 (s, 3 H), 0.79 (s, 1 H); mass spectrum *m/e* (rel intensity) 27 (15), 28 (26), 29 (22), 32 (10), 36 (10), 39 (24), 41 (100), 42 (8), 43 (30), 51 (9), 53 (30), 54 (14), 55 (80), 56 (8), 57 (16), 65 (12), 66 (8), 67 (41), 68 (8), 69 (79), 77 (36), 78 (14), 79 (36), 81 (63), 82 (14), 83 (12), 91 (54), 92 (10), 93 (34), 94 (12), 95 (63), 97 (10), 103 (10), 105 (31), 107 (36), 108 (10), 109 (31), 115 (16), 117 (13), 119 (27), 120 (10), 121 (26), 122 (11), 123 (75), 124 (19), 128 (10), 129 (10), 131 (15), 133 (24), 134 (22), 135 (19), 136 (12), 137 (64), 138 (8), 145 (10), 147 (16), 149 (22), 157 (8), 159 (8), 160 (8), 161 (36), 162 (10), 163 (12), 173 (12), 174 (22), 175 (21), 176 (14), 188 (7), 189 (67), 190 (16), 191 (12), 201 (10), 227 (8), 312 (19), 313 (7), 314 (7).

Methanol Extraction of *Dictyopteris zonarioides* (Gulf of California Source).—Air-dried *Dictyopteris zonarioides* (3100 g) collected intertidally near Puerto Peñasco, Mexico, on March 27, 1971 was ground to 1 mm with a Wiley mill. The powdered plant was extracted for 48 hr with methanol in a Soxhlet extractor and the methanol was then removed. The resulting dark tar was taken up in diethyl ether, the solution was dried with anhydrous magnesium sulfate, and the ether was removed to yield 67 g of dark solids. This tar (25 g) was taken up in petroleum ether and chromatographed on 480 g of Davison grade 62 silica gel. Varying solvents from petroleum ether to ether in benzene gave a clean separation of isozonarol (3), 3.1 g, as a noncrystalline gum. In a prior fraction (benzene) 25 mg of isozonarone was obtained. Isozonarol showed the following spectral characteristics: ir $\nu_{max}^{CHCl_3}$ 3570, 3340, 2920, 1605, 1500, 1450, 1377, 1290, 1170, 1095, 955, and 872 cm^{-1}; uv λ_{max}^{MeOH} 209 nm (ϵ 8210), 296 (2700); nmr ($CDCl_3$) δ 6.80 (s, 1 H), 6.60 (s, 2 H), 5.45 (m, 1 H), 4.90 (m, 2 H), 2.60 (m, 2 H), 1.0–2.5 (m, 12 H), 0.90 (m, 9 H); mass spectrum *m/e* (rel intensity) 39 (17), 41 (76), 42 (7), 43 (39), 53 (15), 55 (55), 57 (13), 65 (11), 67 (41), 69 (43), 77 (22), 79 (23), 81 (23), 83 (10), 91 (29), 93 (21), 95 (57), 97 (11), 105 (19), 107 (29), 109 (72), 119 (15), 121 (32), 123 (74), 124 (13), 135 (29), 147 (9), 149 (10), (161) (24), 163 (11), 173 (11), 175 (32), 190 (13), 191 (100), 192 (13), 314 (17), 315 (5), 316 (1).

Oxidation of Isozonarol (3).—Isozonarol (1.0 g) was oxidized with Jones reagent in a fashion identical with that given above for zonarol. The yield of isozonarone (6) was essentially quantitative. Recrystallization from methanol gave 6 as bright yellow plates, mp 111–112°.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 9.15.

Isozonarone showed the following spectral characteristics: ORD–CD (MeOH) $[\alpha]_{424}^{30}$ −261°, $[\alpha]_{498}^{30}$ +341°, $[\alpha]^{30}D$ +95.2°; ir $\nu_{max}^{CHCl_3}$ 2940, 1660, 1595, 1445, 1375, 1300, 1075, and 910 cm^{-1}; uv λ_{max}^{MeOH} 248 nm (ϵ 21,500), 330 (1430); nmr ($CDCl_3$) δ 6.75 (m, 3 H), 5.47 (m, 1 H), 2.49 (m, 2 H), 1.0–2.3 (m, 13 H), 0.90 (m, 9 H); mass spectrum *m/e* (rel intensity) 39 (14), 41 (61), 43 (18), 53 (12), 55 (50), 65 (11), 67 (18), 69 (21), 77 (15), 79 (17), 81 (17), 83 (10), 91 (26), 93 (13), 95 (17), 105 (20), 107 (15), 109 (38), 119 (100), 120 (20), 121 (13), 124 (25), 125 (39), 133 (20), 147 (10), 161 (9), 173 (9), 189 (37), 190 (8), 312 (<1), 313 (<1), 314 (<1), 315 (<1).

Hydrogenation of Zonarol and Isozonarol (2 and 3).—The hydrogenations of both 2 and 3 were run in an identical fashion. In each case 0.1–1.0 g of 2 or 3 was dissolved in 50 ml of diethyl ether, 25 mg of platinum oxide was added, and the solution was placed in a 125-ml filter flask. The neck was fitted with a large serum cap and the side arm was fitted with a balloon to act as a hydrogen reservior. The flask and side arm were filled with hydrogen and stirred for 24 hr. The contents were then filtered and the solvent was removed *in vacuo* to give a saturated hydroquinone mixture. On prolonged sitting very fine needles were observed. Both 2 and 3 gave the identical saturated hydroquinone mixture (5), characterized by the following spectral information: parent *m/e* 316; ir $\nu_{max}^{CHCl_3}$ 3550, 3350, 2960, 1600, 1490, 1450, 1380, 1300, 1175, 1100, 975, 875, and 840 cm^{-1}; nmr ($CDCl_3$) δ 6.52 (m, 3 H), 2.50 (m, 2 H), 1.0–2.2 (m, 15 H), 0.70–1.00 (m, 12 H).

Oxidation of the Hydroquinone 5.—The oxidation of 5 was carried out as described for zonarol. In a typical run 0.500 g of hydroquinone was converted to the quinone mixture in quantitative yield. The crystalline mixture was confirmed as the saturated structure 6 by the following spectral information: ir $\nu_{max}^{CHCl_3}$ 1650, 1590, 1280, 1070, and 909 cm^{-1}; nmr δ 6.60 (m, 3 H), 2.50 (m, 2 H), 1.0–2.0 (m, 13 H), 0.90 (m, 12 H); parent *m/e* 314.

Ozonation of Quinone 6. Dihydrotauranic Acid (8)—The saturated quinone mixture 5 (0.400 g) was dissolved in 50 ml of ethanol-free chloroform. A stream of 1–2% ozone was directed into the flask, which was stirred and cooled to 0°. After 2 hr the solvent was removed at 0° under low pressure and the contents were mixed with 200 ml of 1% H_2O_2 and warmed for 1 hr on a

steam bath. Ether extraction gave 0.200 g of a viscous oil which crystallized from acetonitrile. Repeated recrystallization gave colorless needles of dihydrotauranic acid epimeric mixture, mp 104–105° (lit.[12] mp 107°).

The nmr of this product was identical with that reported;[12] δ ($CDCl_3$) 0.79 (d, 1.5 H), 0.82 (s, 3 H), 0.86 (s, 6 H), 1.02 (s, 1.5 H), 1.0–2.6 (m, 15 H), 9.98 (s, 1 H).

Gas Chromatography of Methyl Dihydrotauranates.—The samples of dihydrotauranic acid obtained above, mp 104–105°, and an authentic sample,[16] mp 107°, were converted to their respective methyl esters *via* treatment with thionyl chloride and anhydrous methanol. Analysis of each ester mixture by gas chromatography on a 0.25 in. × 3 m 10% DC-11 silicon grease on Chromosorb W 60/80 column at 200° showed a 60:40 mixture of two epimeric esters. At this temperature their retention times were 25.7 and 28.6 min. Equal amounts of the esters from each source were combined and injected; identical results were obtained. A comparison was also completed on a 0.25 in. × 2 m 15% butanediol succinate on Chromosorb P 60/80 column at 215°. The esters had identical retention times of 8.8 and 10.0 min.

Cyclic Voltammetry of Zonarone (4).—The cyclic voltammetric measurements were done using a three-electrode system in a degassed electrochemical cell with dimethyl sulfoxide as solvent and tetraethylammonium perchlorate (0.1 *F*) as supported electrolyte. A Beckman platinum-inlay electrode was employed as the working electrode. An aqueous silver–silver chloride electrode in 0.4 *F* tetramethylammonium chloride was used as a reference with a potential of 0.00 V *vs.* the saturated calomel electrode. Potentials recorded for two-electron reduction of zonarone were: E_{pc} −0.525 V, E_{pa} −0.450 V and E_{pc} − 1.350 V, E_{pa} −1.275 V.

Registry No.—**2**, 39707-54-5; **3**, 39707-55-6; **4**, 39707-56-7; **5** isomer A, 39707-57-8; **5** isomer B, 39707-58-9; **6**, 39707-59-0.

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The Pschorr Reaction by Electrochemical Generation of Free Radicals. II. Benzophenone Series. An Alternative Mechanism[1]

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Diazonium salts of 2-amino-R′-benzophenone (R′ = 4-CH_3, 4-OCH_3, 3-NO_2) were decomposed electrolytically, thermally, and by the iodide ion. Protic and aprotic solvents were employed, with a variety of catalysts and over a range of temperatures. Using our results and published data, a general inter- or intramolecular one-electron redox mechanism is proposed. Based on experimental results and theoretical calculations, this proposal alleviates many of the previously encountered difficulties in explaining the behavior of diazonium salts under varied conditions and specifically clarifies the Pschorr cyclization mechanism.

Phenyl radicals produced by the electrochemical reduction of benzenediazonium salts have been used for phenylation of aromatic substrates.[2] This technique was used in a new approach to the Pschorr reaction, in which intramolecular arylation occurred upon reduction of diazonium salts of 2-amino-α-(R′)-phenylcinnamic acids giving near quantitative yields of phenanthrene derivatives.[3] However, when this technique was applied to diazonium salts of 2-amino-R′-benzophenones to obtain fluorenone derivatives, some surprising results were obtained.

Various literature surveys[4-9] have revealed a long history of mechanistic studies on Pschorr-like systems. All agree that, depending on the reaction conditions, homolytic or heterolytic mechanisms, or a combination of the two, could explain the type and yield of products. However, aryl diazonium cations have been shown to be strong oxidizing agents,[10] which upon reduction (electrolytically or thermally) release nitrogen and produce aryl radicals. This redox model has been used to explain the salient fact of diazonium salt chemistry.[11]

We now believe there are indeed two mechanisms operating in the Pschorr reaction: one is the conventional homolytic mechanism and the other is a substitute for the classical heterolytic mechanism. Both mechanisms involve a one-electron redox reaction: the homolytic one results from external reduction of the diazonium moiety, while the other invokes an *internal* or intramolecular reduction in which the system goes through an intramolecular charge-transfer or redox state.

Results

A. Electrolytic Reductions of Unsubstituted Diazonium Salts (Table I).—Protic and aprotic media were employed at different potentials. In aprotic media at 0.0 V cyclization was poor, while abstraction and attack on the electrode produced the major products. At higher potential attack on the cathode was reduced,

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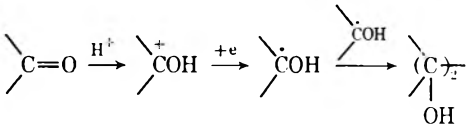
TABLE I
ELECTROLYTIC REDUCTION OF DIAZONIUM SALTS OF 2-AMINOBENZOPHENONE

Expt[a]	Conditions	Temp in °C, V[b]	Yields, % Fluorenone	Benzophenone	Mercury product	Other products
1	CH_3CN, Bu_4NClO_4	0–5, 0.0	5	38	55[c]	1 (2-F)
2	Sulfolane, Bu_4NClO_4	rt.[d] 0.0	2	46	42[c]	
3	CH_3CN, Bu_4NClO_4	0–5, 1.5	8	55	20[c]	
4	Sulfolane, Bu_4NClO_4	rt. 1.6	4	71	15[c]	
5	H_2SO_4 (0.6 *N*)	rt. 1.2	32	5	+	20[e]
6	H_2SO_4 (0.6 *N*)	rt. 1.6	42	7	+	23[e]
7	HF (anhyd)	0–5, 0.0	15	2		

[a] Note: in expt 1, 2, 3, 4, and 7, the counterion is BF_4^-; in expt 5 and 6, the counterion is HSO_4^-. [b] Cathodic potential *vs.* sce. [c] Bis(2,2)benzophenonemercury. [d] Room temperature. [e] Fluoropinacol.

hydrogen abstraction enhanced, and yield of cyclized product slightly improved. The slight difference between acetonitrile and sulfolane may be due to the reactivity of each solvent towards the phenyl radical.[12]

When protic media were employed, hydrogen abstraction yields dropped drastically and consequently cyclization increased. In expt 5 and 6, the last column gives fluoropinacol yields. The pinacol is formed by protonation and reduction followed by coupling, *i.e.*,



The sum of the first and last columns, which is the total yield of cyclized products, was as high as 65% at 1.6 V. In anhydrous HF, while cyclization was substantial, the reaction was not carried to completion because of the slow course of electrolysis, due to absorption phenomena, occurring in this medium.[13] The high yields of organomercury compounds are due to the interaction between the intermediate radical and the mercury cathode.[14]

B. Thermal Decomposition of Unsubstituted Diazonium Salts (Table II).—Protic and aprotic media, with or without catalysts, were employed. In protic media, adding copper (groups a and b) reduced the yield of cyclized products slightly and phenols considerably. In group c (Lewin and Cohen experiments[9]), addition of copper did not make any appreciable change, but cuprous oxide gave mainly cyclization. These results were explained by Lewin and Cohen.

Decomposition in acetone or sulfolane alone (group d) gave cyclization as the major product. Phenol in 15% yield in expt 17 is due to the presence of water which was very difficult to eliminate.[15] The absence of deamination product is of vital importance since this product would be expected from a σ-radical mechanism (by hydrogen abstraction from the aliphatic solvents, as occurred in electrolytic reductions, Table I, or when copper was added, expt 18). The very small yield of fluorinated products, 5% in expt 16 and traces in expt 17, decreases the chance of a conventional ionic mechanism.[16] A 65% yield of fluorenone, expt 17, strongly suggests some quite different mechanism.

Addition of copper (group e) reduced cyclization considerably and promoted abstraction. However, the high yield of benzophenone in the absence of copper, 90%, expt 20, strongly suggests that the cyclic ether tetrahydrofuran [I_p(THF) = 9.45 eV; see Discussion][17] might be playing an important role as a reducing agent. Group f results add support to the well-known fact of the absence of hydrogen abstraction from aromatic nuclei. The small effect of Cu illustrates the involvement of the two reaction mechanisms which will be discussed later.

Experiment 24 (Lewin and Cohen[9]) shows that Cu_2O is a strong reducing agent at moderate temperatures. This result, compared to expt 20 and 21, suggests that dioxane might also play a role as a reducing agent [I_p(dioxane) = 9.52 eV; see Discussion].[17]

Experiment 25 is significant. One would expect decomposition to occur *via* the cation since BF_4^- is conventionally thought to be a poor reducing agent. According to Schiemann,[16] we would then expect high yields of the fluoro compound. This was not the case. Thus there may be a redox mechanism and the discussion will deal with the nature of the reducing agent.

Experiments 26 and 27 emphasize the role of iodide ion as a strong reducing agent for diazonium salts.[3]

C. Substituent Effects (Table III).—Selected results of electrolysis and thermal decomposition of substituted benzophenonediazonium salts are collected in Table III.

As expected, the overall products and yields of 4-methoxy and 4-methyl compounds from electrolytic reduction were more or less the same as obtained from the unsubstituted salt. That is, activation by $-CH_3$ $-OCH_3$ groups in the *m* position is $\sim$1.[2a]

Activation by the nitro group resulted in higher cyclized yields from 3-NO_2 substituted benzophenones.[2a] The results of thermal decomposition in protic media gave higher cyclized yields with copper than without (compare expt 35 and 40 and 36 and 39), for the reasons previously given.

The ratio of 4-nitrofluorenone to 2-nitrofluorenone followed two patterns: (i) higher than 2 in electrochemical reduction and acid and Cu; (ii) lower than 1 (0.4) in acid, sulfolane, sulfolane and acid, and dry salt.

For the diazonium salt of 2-amino-β-benzoylnaphthalene, electrolytic reduction gave a ratio of angular to linear benzofluorenones similar to that from reactions which are considered pure free radical ($\sim$9).[9,18] The results of Huisgen and Zahler[18] and Lewin and Cohen[9] are in agreement with our results in the case of free-radical mechanisms (A/L $\simeq$ 9). Different conditions result in the same distribution ratio, a situation which will be explained in the following discussion.

Discussion

Two mechanisms have been invoked to explain Pschorr cyclization: (a) **ionic route** (Scheme I, 1-a)

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TABLE II

THERMAL DECOMPOSITION OF DIAZONIUM SALTS[a] OF 1-AMINOBENZOPHENONE WITH AND WITHOUT CATALYSTS

Group	Expt	Conditions	Temp, °C	Yield, % Fluorenone	Phenol	Benzophenone	Other products	Ref
a	8	H_2O	75	60	40			
	9	H_2O, Cu	75	51	<1			
	10	H_2O, Pyridine	75	57	22	3.5	8 (2-Py)[b]	
b	11	HBF_4, 10%	75	72	20		9 (2-F)	
	12	HBF_4·Cu	75	58	6	2.4	2 (2-F)	
c	13	H_2SO_4 (0.1 *N*)	45	68	31			9
	14	H_2SO_4 (0.1 *N*), Cu	45	67	33			9
	15	H_2SO_4 (0.1 *N*), Cu_2O	45	93	1	6		9
d	16	Acetone	Reflux	54			5 (2-F) + polymers	
	17	Sulfolane	75	65	15		+ (2-F)	
	18	Acetone, Cu	Reflux	7		30	42 (dimer)[c]	
e	19	THF (0.05 *M*)[d]	Reflux	25		50	10 (2-F)	
	20	THF (0.0033 *M*)[d]	Reflux	8		90	Traces	
	21	THF, Cu (0.05 *M*)[d]	Reflux	1.5		97		
f	22	Benzene	Reflux	58			18 (2-F), 10 (2-Ph)	
	23	Benzene, Cu	Reflux	67			21 (2-F), 7 (2-Ph)	
	24	Dioxane, Cu_2O	25			100		9
	25	Dry salt		54			36 (2-F)	
	26	Acetonitrile, Pr_4NI	5	1.5		2	95 (2-I)	
	27	Acetone, NaI	5	1		8	90 (2-I)	

[a] Note: all are fluoroborate salts. [b] Three isomers, α-, β-, and γ-benzophenonepyridine. [c] Bis(2,2′)benzophenone. [d] Molarity of diazonium salt in THF.

where the C–N bond cleaves heterolytically to produce an aromatic cation; (b) **radical route** (Scheme I, 1-b) in which the diazonium cation accepts an electron and the diazo radical, then decomposes to molecular nitrogen and an aromatic radical. Combinations of these mechanisms have also been suggested.[8]

In route 1-b the electron is supplied by $X^{(-)}$ which could be a cathode, copper or appropriate metal, metal salts, suitable anion (OH^-, Cl^-, Br^-, or I^-), or a neutral molecule such as pyridine. The free radical VII can cyclize or couple with Z· which can be, for example, X·, H· abstracted from the solvent, another radical VII, or the electrode (*i.e.*, Hg). As can be seen, coupling and cyclization processes are in competition. The result of this competition is affected by the rate of each process, which in turn is controlled by the reaction conditions.

The electrochemical reactions listed in Table I have product distributions typical of sp^2 free radicals (route 1-b).[2a] They proceed primarily by hydrogen abstraction or attack on the electrode. Very little cyclized product is obtained, although it can be made the major product by running the reaction at high potential in protic media. In the electrochemical expt 34 and 42 (Table III) where both the 3-nitro group and 2,3-fused ring activate the B ring, the distribution of cyclized products formed follows free-radical arylation patterns.[8]

In electrolytic reduction of diazonium salts of 2-amino-α-phenylcinnamic acid, where (a) the gap between the reactive sites is small and (b) the molecule is rigid, cyclization was nearly quantitative.[3] Reduction with iodide ion resulted in 90% cyclization and 10% iodide product. On the other hand, benzophenone radicals produced by this technique, owing to the absence of a and b, prefer to abstract hydrogen from the aprotic solvent or couple with the iodine atom to give up to 95% of the iodo derivative (expt 26 and 27, Table II). Waters[19] suggested this mechanism in 1942, and recently an added evidence of the redox nature of similar reactions was demonstrated.[3,20,21]

It was argued that in the absence of an external reducing agent an SN1 reaction, as in route 1-a, can take place. Here, an aromatic cation (II) results after the release of N_2 and this cation either couples with $Z^{(-)}$ or attacks ring B and cyclizes. In Table II, clearly, the high yields of cyclized products cannot be obtained from the radical process (route 1-b), because of the hydrogen abstraction as mentioned before. However, a cationic mechanism with a discrete SN1 step (route 1-a) fails to explain the results, *viz.*, the low yields of hydroxy, fluoro compounds and the isomer ratios in the cyclized products of the nitro- or naphthoyl-substituted systems (Table III). The discrete sp^2 cation would not allow for a considerable amount of orbital overlap leading to cyclization and isomer ratio distributions observed (see below). Abramovitch, in his review,[8] argued against this heterolytic mechanism and attempted to improve this scheme by introducing the phenyl diradical cation model of Taft.[22] Very recent work has proposed redox mechanisms as alternatives for SN1 and SN2 reactions of diazonium salts.[23]

As route 1-a stands, the two ring moieties A and B in I are taken to be independently solvated; the reaction does not occur in a solvent cage. Invoking the solvent cage implies the existence of a stabilizing interaction between the two ring moieties. As will be shown later,

(19) W. A. Waters, *J. Chem. Soc.*, 266 (1942).

(20) R. Kumar and P. R. Singh, *Tetrahedron Lett.*, 613 (1972).

(21) P. R. Singh and R. Kumar, *Aust. J. Chem.*, **25**, 2133 (1972).

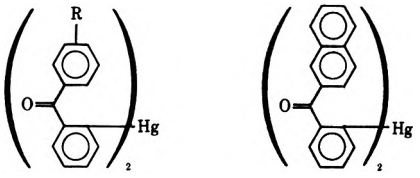
(22) R. W. Taft, *J. Amer. Chem. Soc.*, **83**, 3350 (1961).

(23) Rieker, *et al.* [*Tetrahedron Lett.*, 2581 (1972)] observed diazo radicals in ^{13}C-polarization experiments during reductive deamination of diazonium salts. Bubnov, *et al.*, published a series of papers and reviews on the one-electron transfer in organic reactions. The very recent one [N. N. Bubnov, *et al.*, *J. Chem. Soc., Chem. Commun.*, 1058 (1972)] which appeared during revision of this paper, showed that azo coupling proceeds *via* radical intermediates and previous work by this group [*Dokl. Akad. Nauk SSSR*, 583 (1970)] rules out the so-called SN1 nature of diazonium salt decomposition. The latter reference fully supports our suggested redox mechanism of diazonium salt reactions as proposed in our paper presented in Halifax (1971).[11] The work of the latter group was apparently stimulated by our polarographic measurements of the high oxidation potential (*sic*) of diazonium salts.[10]

TABLE III
EFFECT OF REACTION CONDITIONS ON DECOMPOSITION OF DIAZONIUM SALTS

Registry no.	Expt	R′	Reaction Conditions	Temp, °C	Yield, % Cyclization	Isomer ratio	Phenol	Deamination	Mercury products	Other products	Ref
			2-Amino-R′-benzophenonediazonium Salts								
39834-86-1	28	4-OCH_3	Elect. redn, CH_3CN, 0.0 V	0–5	1.5			23[f]	65[a]		
39834-87-2	29		H_2SO_4, Ag		80						4
342-63-2	30	4-CH_3	Elect. redn, CH_3CN, 0.0 V	0–5	2			32[g]	60		
39834-89-4	31		H_2SO_4 (1 *N*)	Reflux	61		35				*b*
	32		H_2SO_4 (1 *N*), Cu	rt	46		33	12			*b*
	33		H_2SO_4 (1 *N*), CuCl	rt	46		40	6			*b*
						4-/2-					
39834-90-7	34	3-NO_2	Elect. redn, CH_3CN, 0.0 V	0–5	18.5	2.4[c]		26.5[h]	50		
39834-91-8	35		H_2SO_4 (1 *N*), Cu	75	79	2.4	7	4			
	36		H_2SO_4 (1 *N*), only	75	57	0.4	41				
	37		Sulfolane	75	60	0.35	15			10 (2-F)	
	38		Dry salt		40	0.4				54 (2-F)	
	39		H_2SO_4 (1 *N*)	Heat	47		54				*b*
	40		H_2SO_4 (1 *N*), Cu	Heat	90		4	1			*b*
	41		H_2SO_4 (1 *N*), CuCl	Heat	74		2	19			*b*
			2-Amino-β-benzoylnaphthalenediazonium Salts								
						A/L[d]					
2264-63-3	42		Elect. redn, CH_3CN, 0.0 V	0–5	17	9.5		38	35[e]		
39834-93-0	43		H_2SO_4 (3 *N*)	100	50	2.3	+				18
	44		H_2SO_4 (3 *N*), Cu	100	54	4.4	+			22 (dimer)	18
	45		Acetone, Cu	100	17	4.6					18
	46		Nitrosoacylamine, THF	20	4	10		7			18
	47		Nitrosoacylamine, PhH	20	15	9.4					18
	48		H_2SO_4 (0.1 *N*)	25	57.6	2.3	42.4				9
	49		H_2SO_4 (0.1 *N*), Cu	25	82	9.5		18.1			9
	50		H_2SO_4 (0.1 *N*), Cu_2O	25	68.2	8.9		31.8			9
	51		Dioxane, Cu_2O	25	25	9		75			9

[a] See structure i. [b] D. F. De Tar and T. E. Whiteley, *J. Amer. Chem. Soc.*, **79**, 2498 (1957). [c] 4-/2-, 4-nitrofluorenone/2-nitrofluorenone. [d] A/L, angular/linear. [e] See structure ii. [f] Registry no., 39834-94-1. [g] Registry no., 39834-95-2. [h] Registry no., 39834-96-3.



i ii

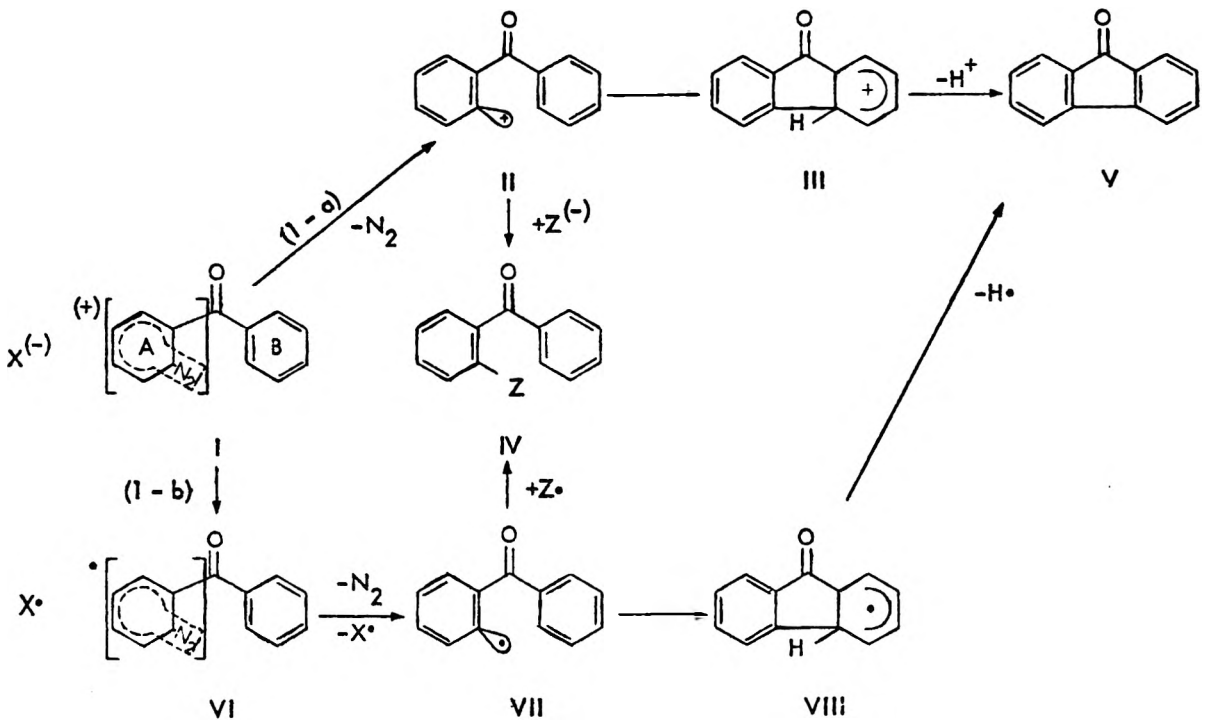
such interactions destroy the pure cationic character of 1-a. Now, when diazonium fluoroborate salts of 2-aminobenzophenone are heated in aprotic solvents, the yield of cyclized material is close to that in the much more polar media (expt 17 and 11). This, contrary to the expectations of route 1-a, implies that solvent effects are small for these reactions, provided, of course, that there are no obvious reducing agents present; *cf.* Scheme I (1-b). More notably, the isomer ratio is similar whether the thermal decomposition of 3′-nitro-2-benzophenone salts is carried out in strong acid, in aprotic solvents, or as the dry salt (expt 36, 37, and 38, respectively), a rather unusual coincidence if the mechanism of 1-a is invoked.

We wish to suggest an alternative mechanism to route 1-a based on studies of the redox behavior of diazotized aromatic amines conducted in this laboratory.[2,3,10] We believe that the reaction is taking place in a solvent cage and that reduction of the diazonium moiety is occurring with a simultaneous release of nitrogen. In the absence of external reducing agents, the only source of electrons for reducing the diazonium moiety is the attached ring B. This mechanism of *internal* or *intramolecular* redox is initially described by Scheme II. The more real situation is delineated in Figure 1 which treats the decomposition of IX → XI. In effect, the change of IX to the Wheland complex (intermediate) occurs concertedly. The structures X and XI in Scheme II merely symbolize that N_2 release occurs simultaneously with the transfer of electrons; they are by no means necessarily intermediates or transition states. The transition state most likely occurs between the path of XI to XII. This proposal goes a long way to unify the theory of diazonium salts decomposition.

The general idea of a charge-transfer (CT) or redox mechanism in heterolytic aromatic substitution is not new. Nagakura and Tanaka,[24] and Brown[25] have long advocated such an approach. The internal redox state is more commonly known as an internal

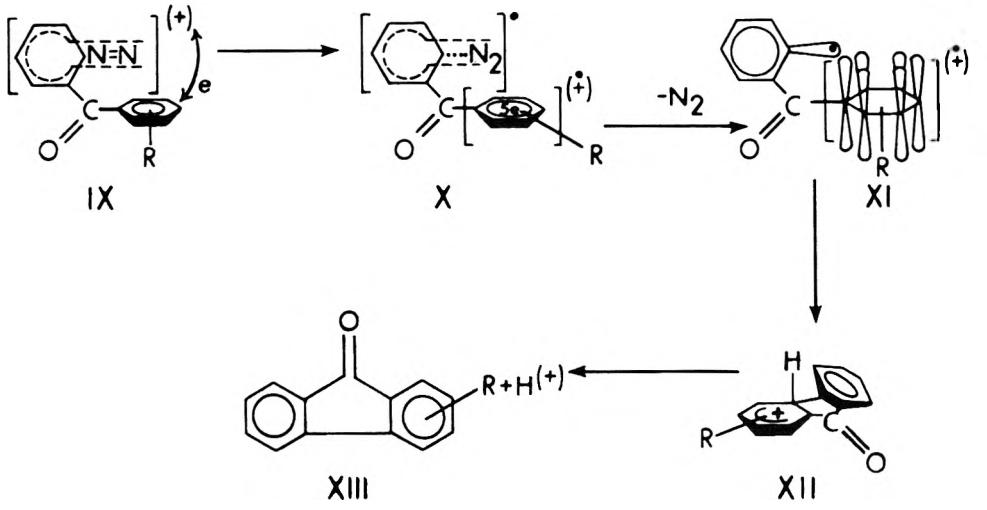
(24) S. Nagakura and J. Tanaka, *J. Chem. Phys.*, **22**, 563 (1954).
(25) R. D. Brown, *J. Chem. Soc.*, 2224, 2232 (1959).

SCHEME I[a]



[a] X·, Z·, and/or H· are atoms or radicals.

SCHEME II
INTRAMOLECULAR REDUCTION



charge-transfer state.[26] This would be X in Scheme II. Such a concept, where an external charge transfer may occur between the diazonium cation and $X^{(-)}$, is shown in route 1-b. Scheme II, which leads only to cyclization, is in the spirit of route 1-b, but is by no means a special case of it as the latter indicates external reduction. The two pathways, in fact, compete with each other, making the results complicated if one does not exercise careful control of experimental conditions. Let us now follow in detail the path for IX going to XI.

The stereochemistry of the diazonium salt of the 2-amino-3′-nitrobenzophenone cation is more precisely shown in Figure 2.[27] The geometry can be such that the N_2 moiety lies above the substituted benzene ring, B. This is also shown in IX. The N_2 group is approximately at the van der Waals distance[27] from the ring B which provides the maximum opportunity for orbital overlap between the B-ring π orbitals and the N_2 π orbitals in the plane of the A ring. For this molecule, solvation occurs as a solvent shell or cage. In this geometry the carbonyl group has lost conjugation with ring B. Furthermore, the carbonyl group should not affect drastically the electron affinity of the aryl diazonium moiety. In fact, by the inductive effect, it would increase the electron affinity. Thus, for determining the position of the internal CT state in an energy diagram, it is reasonable to assume that the two ring moieties behave independently of the carbonyl group. Therefore, the interaction energy of the rings can be considered in three steps (Figure 1): (A) both rings are infinitely far apart; (B) they are brought together to their equilibrium geometry and are allowed

(26) R. S. Mulliken and W. B. Person, "Molecular Complexes: A Lecture and Reprint Volume," Wiley, New York, N. Y., 1969.

(27) Fisher-Hirschfelder-Taylor, Atom Model Kit, U. S. Patent 2,308,402 (1943).

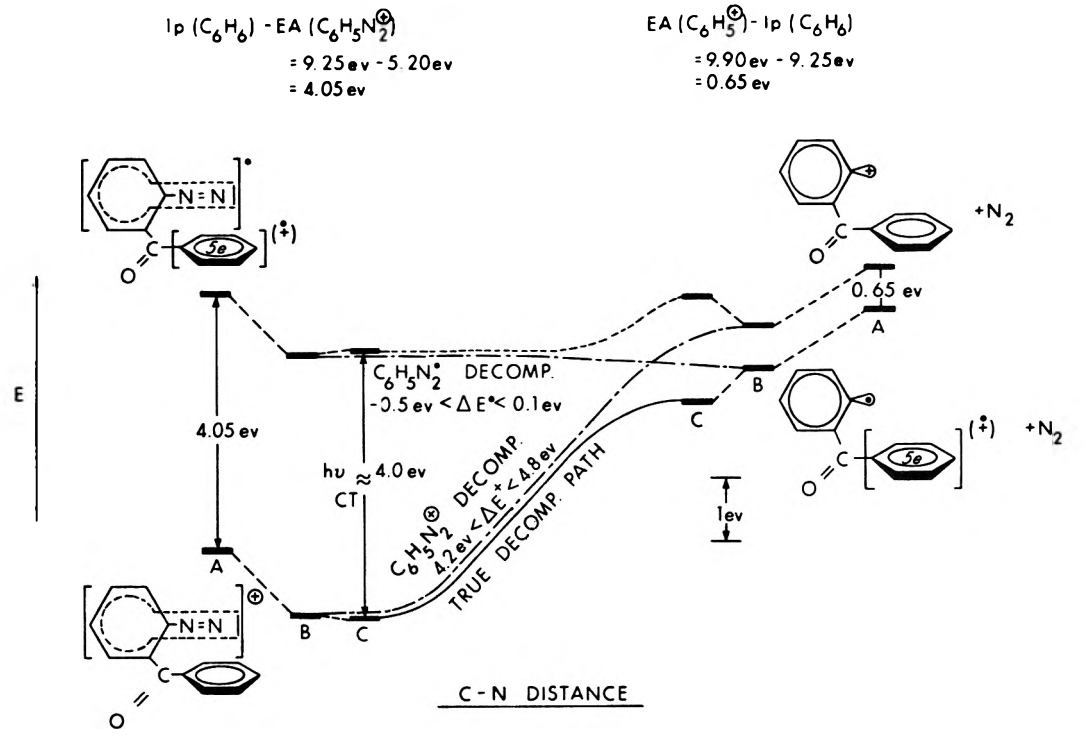


Figure 1.—Decomposition behavior of IX to XI.

to interact *without* inclusion of CT interaction but including the solvation shell; and (C) a more complete interaction is formed by including the CT contribution. It is assumed throughout that step B leads to stabilization and this seems reasonable on the basis of known complexing[28] power of aryl diazonium cations. Stages A, B, and C for the ground state and CT state of the diazonium system are shown on the left of Figure 1. For simplicity, the B ring is taken as unsubstituted. In stage A the CT state is above the ground state by an energy of $I_p(C_6H_6) - EA(C_6H_5N_2^+)$ where I_p and EA mean, respectively, the ionization potential and electron affinity. An all-valence-electron SCF-CI calculation gave an electron affinity of 5.20 eV for $C_6H_5N_2^+$ and the accepted ionization potential of benzene[17,29] is 9.25 eV. This makes the CT state 4.05 eV above the ground state.[30] Even if the carbonyl group is introduced in the ortho position of $C_6H_5N_2^+$, or if the calculated electron affinity of $C_5H_5N_2^+$ is in error by 30%,[31] the electron affinity should be below 9.25 eV; hence the CT state lies *above* the ground state. The energy decrease from stage A to stage B may be assumed to be the same for both states since orbital overlap is the same in both states and there is a solvation shell around the entire molecule. Thus there remains approximately the same separation between the two states for step B as in stage A.[32] This holds as well for stage C, since there will be very small CT interaction due to the large separation between the two states. It is assumed here that there will not be a

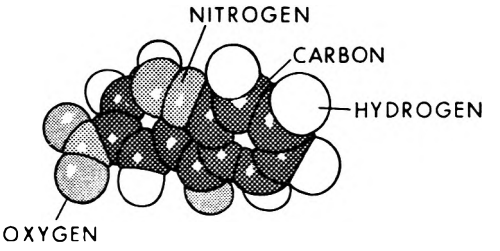


Figure 2.

significant change in solvation energy when state C is introduced. Thus for the left-hand side of Figure 1, the system IX is predominantly in the non-CT structure.

On the right-hand side of Figure 1, the dissociated species XI are considered. At stage A, the CT state lies below the non-CT state by an energy of $EA(C_6H_5^+) - I_p(C_6H_6) = 0.65$ eV. (The reported value for the electron affinity of $C_6H_5^+$ is 9.90 eV.[17]) In stage B it seems reasonable to assume that both states decrease the same amount as stage B at the left-hand side of Figure 1. In stage C, however, the small separation between the states makes the CT interaction very large.[26] Hence the lower energy state for XI is highly contaminated with CT structure. It should be noted that the two unpaired electrons depicted in Figure 1, or in X or XI, are only symbolic; the system must be in a singlet state (in order to have CT interaction) and thus these are really "paired" but in an excited state[26] (sometimes called singlet biradical).

Finally let us follow the decomposition by connecting the two sides of Figure 1. Decomposition without stage C is considered first. It has been shown[29] by an all-valence-electron calculation that the ground state of $C_6H_5N_2^+$ correlates with the ground state of the separated molecules $C_6H_5^+$ and N_2, and this correlation exists as well for the corresponding ground-state

(28) R. M. Elofson, A. A. Cantu, R. Ozubko, and F. F. Gadallah, to be published). See also Chr. Römming, *Acta Chem. Scand.*, **17**, 1444 (1963).

(29) Dr. S. Fraga, University of Alberta, Edmonton, Canada, private communication.

(30) Spectral and polarographic studies support the suggestion that the present compound exists largely as an internal CT complex. This will be reported in a subsequent paper.

(31) R. Carbo and S. Fraga, *An. Fis.*, LXVI, 270 (1970).

(32) It must be clearly understood that the CT complex contains none of the CT state but is merely a resonance hybrid of the CT and non-CT states.

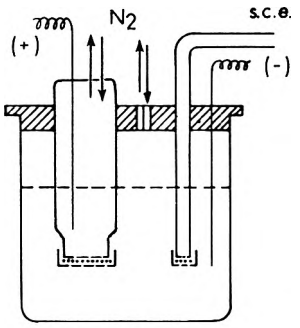


Figure 3.

radicals. The photochemical work of Sukigara and Kikuchi[33] provides some limits on the ΔE^+ for the dissociation of $C_6H_5N_2^+$ in solution. They found that the $^1B_1$ state, which is 4.20 eV above the ground state, fluoresces, while the higher $^1A_1$ state, which lies 4.79 eV above the ground state, leads to dissociation. They contended that the photoproduced $C_6H_5^+$ was reduced by BF_4^- to give the phenyl radical, but did not exclude the possibility that BF_4^- reduced the excited $^1A_1$ $C_6H_5N_2^+$ with decomposition to nitrogen and a phenyl radical (route 1-b). In any case, ΔE^+ is between 4.20 and 4.79 eV.[34] This, in turn, provided limits on the $\Delta E\cdot$ for the radical decomposition. Knowing the electron affinities of $C_6H_5N_2^+$ and $C_6H_5^+$, and assuming they both solvate to about the same extent, -0.5 eV $\leq \Delta E\cdot \leq 0.1$ eV. Thus, without considering CT contributions, in correlating the states there occurs *crossing*. Upon considering CT interaction (stage C), by the noncrossing rule, the crossing is avoided. Thus, in the decomposition, the system begins along a "heterolytic" path but ends up mainly along the internal-charge-transfer path. This, in turn, proceeds through a transition state to the Wheland complex and hence to the final cyclized product.

If the B ring is substituted and its ionization potential is still *less* than EA($C_6H_5^+$) = 9.90 eV, then Scheme II is still valid. This is the situation with most cases considered here:[17] $I_p(C_6H_5\text{–}OCH_3)$ = 8.56 eV, $I_p(C_6H_5\text{–}CH_3)$ = 8.82 eV, and I_p(naphthalene) = 8.12 eV. For nitrobenzene, a value of $I_p(C_6H_5\text{–}NO_2)$ = 10.18 eV has been reported.[35] For this case, the stage B curves will not cross but will be very close (0.28 eV). Hence the reaction embarks along a pathway that becomes highly contaminated with the CT state. A pure cationic mechanism, route 1-a, does not occur. It should be stated that the value of I_p of nitrobenzene quoted was determined by mass spectrometry and that an analysis of a series of such I_p values reveals an overestimate in value from previous values determined by electron-impact methods. Thus, it may still be possible that I_p(nitrobenzene) < 9.90 eV. Furthermore, the introduction of the carbonyl group on the phenyl cation would make the electron affinity greater than 9.90 eV. It is thus conceivable that in all cases the substituted B ring will have an I_p less than the EA of the A ring.

(33) M. Sukigara and S. Kikuchi, *Bull. Chem. Soc. Jap.*, **40**, 461 (1967).

(34) Sukigara and Kikuchi[33] did not consider the possibility that the $C_6H_5N_2^+$ may be complexing with the solvent (water–ethanol) or BF_4^- in which case the "excited" states may not correspond to just $C_6H_5N_2^+$ but to the complex. Consequently, the bounds determined for ΔE^+ and thus for $\Delta E\cdot$ may be wrong. This, however, does not affect the principal feature (avoided crossing) in Figure 1.

(35) G. F. Grable and G. L. Kearns, *J. Phys. Chem.*, **66**, 436 (1962).

The calculations represented in Figure 1 have an important consequence. Considering $C_6H_5N_2^+$ and a species X, if X is made to collide with $C_6H_5N_2^+$ forming a transient intimate pair, then the treatment of Figure 1 can be applied provided that $I_p(X) < 9.90$ eV. Such anions as BF_4^- or ClO_4^- [a value of $I_p(ClO_4^-)$ = 5.82 has been reported[17]] are capable of reducing $C_6H_5N_2^+$ (the yields of 2-F products in Table II, along with expt 37 and 38 in Table III, strongly support this concept). The general conclusions of this redox model of aromatic diazonium chemistry must be (1) that reduction, by either an external or internal source, of the aromatic diazonium cation is necessary for the facile release of nitrogen; (2) that, unless completely isolated, an aryl cation does not exist, since there is generally a reducing species available and the combination prefers to undergo a redox reaction to reach a lower state; (3) that, for the Pschorr reaction, there always exists potential competition between route 1-b and Scheme II.

Regarding the third point, thermal decomposition of the dry salts of unsubstituted and substituted benzophenonediazonium tetrafluoroborate (expt 25 and 38) produces the fluoro compounds which could only occur through route 1-b (Bubnov, *et al.*[23]). The other product is the cyclized material and this occurs through route 1-b and Scheme II (competition between coupling with F· and cyclization). On the other hand, when these decompositions are carried out in acetone and sulfolane (expt 16, 17, and 37), it seems reasonable to say that the high yields of cyclized products are due to Scheme II. Benzene was used as a reaction medium in expt 22 and 23 to stop hydrogen abstraction and promote cyclization. This was achieved by comparison with the runs where aliphatic hydrocarbons were used.

The behavior of the isomer distribution of the nitrofluorenone and naphthoylfluorenone derivatives requires comment. For the external reduction mechanism, route 1-b, the isomer distributions of these compounds agree with the normal arylation patterns[5] predicted by the usual reactivity indices: free valences, F_r, or radical localization energies, L_r. In the case of internal reductions, Scheme II, the reaction occurs in a solvent cage and in a concerted manner (since the entire redox process is assumed to occur along a singlet state manifold). The orientation properties are believed determined by the electronic interactions (electrostatic repulsions) occurring before internal redox occurs (stage B). For example, since the diazo moiety in ring A is partially positive, as is the nitro group in ring B, Figure 2, then internal redox and eventual coupling occurs better at the position where these two groups are further apart. Thus the 2′-nitrofluorenone derivative predominantes in the absence of an external reducing agent. This explains the reversal in going from route 1-b to Scheme II. Similarly, in the case of internal reduction of the 2-benzoylnaphthalenediazonium salts, the decrease, but not reversal, of the angular to linear ratio of the cyclized product follows the induced polarization effect of the diazonium moiety: it polarizes the naphthalene ring producing a partial positive charge on the outer ring (the one not attached to the carbonyl group). This partially positive charge then directs, in a manner weaker than the NO_2 group,

the diazonium moiety to the β-naphthalene position with the eventual result of a relative increase of linear cyclized product. These polar interaction arguments have been used previously by De Tar and Relyea,[36] but on the phenyl cation.

Experimental Section

Reagents.—All liquid reagents were purified by the methods described before.[2,3] Sulfolane was purified according to Jones,[37] by distilling under vacuum from NaOH, H_2SO_4, then solid NaOH, and twice from CaH_2. 2-Fluorobenzophenone was used as obtained commercially (98% pure)[38] for reference in glpc. Gatterman copper powder was prepared as mentioned before[3] and kept under vacuum. 2-Amino-4′-methoxy- and 2-amino-4′-methylbenzophenones were prepared according to Scheifele and De Tar.[39] 2-Amino-3′-nitro- and 2-hydroxy-3′-nitrobenzophenones were prepared according to De Tar and Whiteley.[40] 2-Nitrofluorenone was prepared by oxidizing 2-aminofluorenone.[41] 4-Nitrofluorenone was identified and estimated by mass spectrum and glpc. 2-*o*-Aminobenzoylnaphthalene and its products were prepared, identified and estimated according to Huisgen and Zahler.[18] 2-Phenylbenzophenone was prepared by Bradsher's method.[42] The three isomers of 2-pyridinobenzophenone were collected and were verified by mass spectrum. For quantitative work, 2-phenylbenzopheone was taken as their internal standard with an *f* value of 1. Boiling points, melting points, and mass spectra verified the purity of reagents, reference compounds, and products,

General Procedure for Electrolytic Reduction. A. In Aprotic Media.—Procedures and apparatus have been previously described.[2,3] Sulfolane or acetonitrile containing 0.1 *M* tetrabutylammonium perchlorate was used in both electrode compartments. The cathode compartment also contained 0.01 *M* diazonium tetrafluoroborate salt.

When the alkaline α-naphthol test was negative and output current dropped to less than 1 mA, the reaction was considered complete.

When acetonitrile was the solvent, the turbid reaction mixtures were separated from mercury, cooled, and filtered. The filtrates were concentrated, then chilled, and filtered again. The combined precipitates were washed with water, dried, and recrystallized from benzene yielding fine colorless needles, identified by mass spectrometry and elemental analysis as the organomercury compounds of bis(2,2′)benzophenonemercury or its derivative i (R = H, CH_3, OCH_3, NO_2; see footnote *a*, Table III). Elemental analyses and melting points (uncorrected) are as follows. *Anal.* Calcd for $C_{26}H_{18}O_2Hg$ (R = H; mp 162–163°): C, 55.46; H, 3.22. Found: C, 55.36; H, 3.37. *Anal.* Calcd for $C_{28}H_{22}O_2Hg$ (R = CH_3; mp 173–174°): C, 56.89; H, 3.75. Found: C, 56.65; H, 3.92. *Anal.* Calcd for $C_{28}H_{22}O_4Hg$ (R = 4-OCH_3; mp 176.7°): C, 53.97; H, 3.56. Found: C, 53.97; H. 3.57. *Anal.* Calcd for $C_{26}H_{16}N_2O_6Hg$ (R = 3-NO_2; mp 222–224°): C, 47.82; H, 2.47. Found: C, 47.73; H, 2.49. Ether was added to the mother liquor to precipitate the perchlorate. The filtrate was evaporated to dryness and the residue taken up in benzene for glpc analysis for the other products.

When sulfolane was the solvent, the reaction mixture was pretreated by the addition of 3 vol. of water and extraction with benzene. The benzene extract was evaporated to dryness, taken up in acetonitrile, and then subjected to the previous separation procedure.

B. In Protic Media.—(i) These reductions were carried out in dilute sulfuric acid. The amines were diazotized in dilute sulfuric acid and the solutions were used for electrolysis.

(ii) These reductions were carried out in anhydrous HF. The apparatus used consisted of two polyethylene jars with different diameters for cathode and anode compartments. The diaphragms between the two compartments and for the calomel bridge were Teflon (Millipore Cat. No. LSWPO). The calomel bridge was a polyethylene tube. The solutions were kept under N_2. A schematic diagram for the apparatus is shown in Figure 3.

General Procedure for Thermal Reactions. A. In Aprotic Media.—The diazonium salt was suspended or dissolved in the solvent and heated or refluxed until the test for diazonium cation was negative.

B. In Protic Media.—The diazonium salts were suspended with fast stirring at room temperature in the various media: fluoroboric acid (10%), acid and copper powder, water, water and copper powder, or water and pyridine. The temperature was increased to 75° in a short time (~5 min) and kept steady (±2°) until the test for diazonium cation was negative. The reaction mixtures were then cooled to room temperature and extracted with methylene chloride, extractions were washed with water, dried, and evaporated to dryness, and the residue was dissolved in benzene for analysis by glpc.

Reduction by Iodide Salts.—The diazonium salts were dissolved in acetonitrile or acetone at 5°. The solid iodide salt (10% excess) was added slowly with vigorous stirring under nitrogen. Fifteen minutes after the final addition, the diazonium cation test was negative and sodium thiosulfate solution (8% by weight) was added. Reaction mixtures were extracted with benzene, dried, and concentrated for the glpc analysis.

Thermal Decomposition of the Dry Salts.—Dry diazonium salts were placed in a flask fitted with a condenser guarded with a drying tube. Dry nitrogen stream was passed over it for 3 hr. Temperature was then increased gradually until decomposition commenced (maximum 150°) and kept constant for 15 min. The reaction mixtures were very dark. After the mixtures were cooled to room temperature, the condenser and flask were washed three times with benzene. The washings were concentrated and used for glpc analysis.

Identification and Estimation of Products.—All reaction mixtures were identified and estimated by glpc, using the internal standard method or the calibration curve method. Analyses were also performed with a directly coupled glpc–mass spectrometer combination, Bieman-Watson helium separator, and Nier-Johnson geometry. The reported yields are averages of duplicate or triplicate runs for each reaction.

Glpc Columns Used.—For compounds with R = H, 4′-CH_3, and 4′-OCH_3, a column of 6 ft × 1/8 in. polyester of diethylene glycol and tetrachlorophthalic acid (10% w/w) on Chromosorb W (acid washed), 60–80 mesh, at 220° was used. For compounds with R = 3′-NO_2, a column of 6 ft × 1/8 in. SE-30, 10% on Chromosorb W (acid washed), treated with hexamethyldisilazane, HMDS was used.

Registry No.—Benzophenone-2-diazonium tetrafluoroborate salt, 342-62-1; benzophenone-2-diazonium hydrogen sulfate salt, 39834-98-5; bis(2,2′)benzophenonemercury, 39834-99-6.

Acknowledgment.—The authors gratefully acknowledge Professor S. Fraga (University of Alberta, Edmonton, Canada) for his participation in all-valence-electron SCF-CI calculations and G. N. Spratt and J. K. Laidler for their technical assistance.

(36) D. F. De Tar and D. I. Relyea, *J. Amer. Chem. Soc.*, **76**, 1680 (1954).
(37) J. G. Jones, *Inorg. Chem.*, **5**, 1229 (1966).
(38) Aldrich Chemical Co., Inc.
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(41) N. Ishikawa and M. Hayashi, *Yuki Gosei Kagaku Kyokai Shi*, **15**, 40 (1957); *Chem. Abstr.*, **51**, 16379a (1957).
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A Novel Pschorr Reaction in the Papaverine Series

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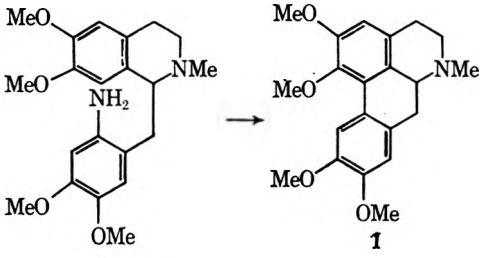
Diazotization of 6′-aminopapaverine (5) in dilute sulfuric acid, followed by treatment with copper, gave the indazole 7 as the major product; the oxoaporphine 8, derived from the normal Pschorr product 9, was the minor product. In contrast, diazotization of 5 in 46% sulfuric acid, followed by Pschorr cyclization, gave papaverine (10, 4.3%), the 1-oxoaporphine 12 (2.4%), and the indenoisoquinoline 11 (30%). Acid treatment of 11 affords 12 almost quantitatively. Chemical conversions of 11 and 12 to the known aporphine bases glaucine (1) and thaliporphine (18), respectively, are described.

The classical Pschorr synthesis of aporphine alkaloids consists of the copper-catalyzed decomposition of the diazonium salt derived from a 6′-amino-1,2,3,4-tetrahydroisoquinoline.[1] The original Gadamer synthesis of glaucine (1) from 6′-aminolaudanosine (2) exemplifies this synthesis.[2] The Pschorr procedure also takes an unexceptional course when applied to 6′-aminobenzoylisoquinolines, and affords a straightforward route to oxoaporphine alkaloids, *i.e.*, liriodenine (3) from amino ketone 4.[3]

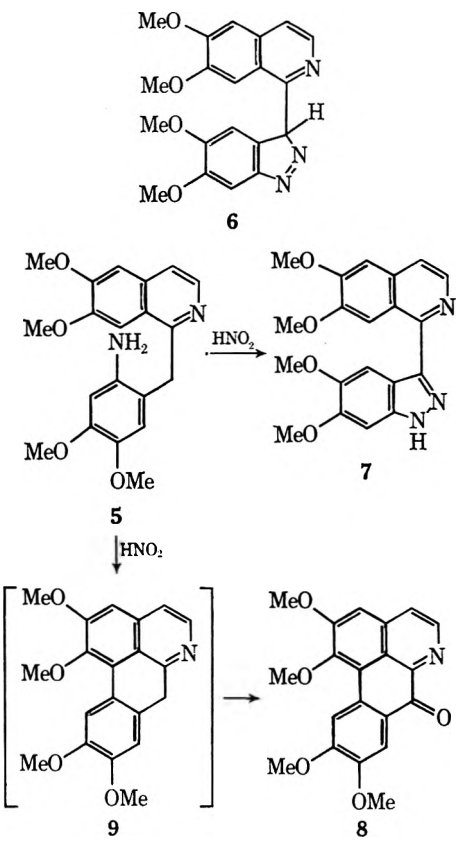


In 1904, Pschorr reported a very different result when he diazotized a typical 6′-aminoisoquinoline, 6′-aminopapaverine (5). Loss of nitrogen did not occur, and Pschorr isolated the stable "diazopapaverine," which he formulated as the isoindazole 6. No aporphine-related substance was obtained.[4]

In this paper, we report a reinvestigation of the diazotization of 6′-aminopapaverine, including the conversion of this amine to a novel and hitherto unknown type of Pschorr reaction product.

Results

Diazotization of 6′-aminopapaverine in dilute sulfuric acid–methanol, followed by treatment with copper, gave Pschorr's "diazopapaverine" as the major product. Since this compound shows an NH band in the infrared at 3.0 μ, and no nmr signal in the benzylic region, it may be reassigned the indazole structure 7. The residues afforded as a minor product (11%) the known 1,2,9,10-tetramethoxydibenzo[*de,g*]quinolin-7-one (8).[5] The oxoaporphine 8 presumably arises by the facile air oxidation of the unknown B-aromatic aporphine 9 during the work-up.[6]



In an attempt to suppress the formation of indazole 7, 6′-aminopapaverine (5) was diazotized in 46% sulfuric acid. Decomposition of the diazonium salt with copper in the cold, followed by the usual work-up, gave none of indazole 7, but a mixture of the deamination product papaverine (10, 4.3%), a pale yellow compound $C_{20}H_{19}NO_4$ (30%), and an orange compound $C_{19}H_{15}NO_4$ (2.4%). The latter compounds were assigned the novel structures 11 and 12, respectively, on the basis of the evidence presented below.

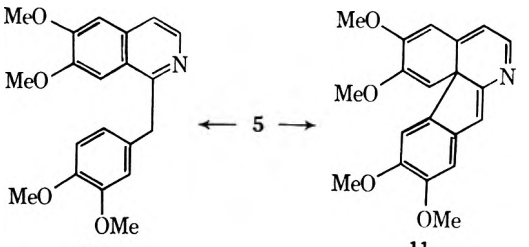
The yellow compound corresponds in composition to the B-aromatic aporphine 9, but nmr analysis immediately eliminated this structure in favor of the angular-coupled isomer 11. Whereas the planar molecule 9 should show a two-proton benzylic singlet and four methoxyls close to δ 4.0, the yellow compound

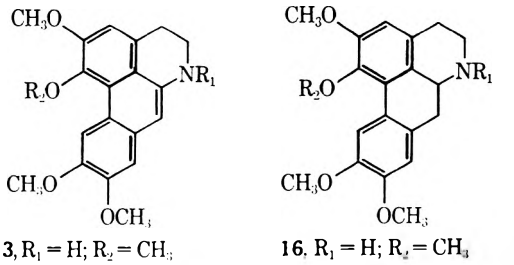
(1) D. F. DeTar, *Org. React.*, **9**, 409 (1957).
(2) J. Gadamer, *Arch. Pharm. (Weinheim)*, **249**, 680 (1911).
(3) W. I. Taylor, *Tetrahedron*, **14**, 42 (1961).
(4) R. Pschorr, *Ber.*, **37**, 1926 (1904).
(5) J. Cohen, W. Von Langenthal, and W. I. Taylor, *J. Org. Chem.*, **26**, 4143 (1961).
(6) A similar observation was reported recently in the synthesis of the oxoaporphine imenine: M. P. Cava and I. Noguchi, *J. Org. Chem.*, **38**, 60 (1973).

actually showed four methoxyls at δ 3.98, 3.67, 3.50, and 3.08. This is reasonable for structure **11**, in which two methoxyls are nonaromatic, and one of these is considerably shielded by the aromatic ring. In further accord with structure **11**, unsplit olefinic protons appeared at δ 4.97, 4.75, and 3.76; the latter proton represents that corresponding to C-8 of the original isoquinoline system, since a Dreiding model of **11** predicts this proton to be highly shielded by the aromatic nucleus below it.

Catalytic reduction of **11** under neutral conditions gave a dihydro derivative which proved to be the rearranged aporphine 6a,7-dehydronorglaucine (**13**). Ethyl chloroformate acylation of **13** afforded a product identical with synthetic *N*-carbethoxy-6a,7-dehydronorglaucine (**14**).[7] Furthermore, reduction of **13** by amalgamated zinc and acid afforded (±)-norglaucine (**16**), converted by formaldehyde and sodium borohydride to (±)-glaucine (**1**).

Reaction of the indenoisoquinoline **11** with warm 65% sulfuric acid brought about its conversion in high yield (94%) to the minor orange product originally isolated from the Pschorr reaction of 6′-aminopapaverine (**5**). The orange compound showed a conjugated carbonyl at 6.15 μ in the infrared; its nmr showed three similar methoxyls at δ 4.01, 4.08, and 4.13, all other protons falling into the aromatic region between δ 6.75 and 9.60. The formulation of this substance as the 1-oxoaporphine **12** followed from its chemical correlation with (±)-thaliporphine (**18**). Thus, catalytic reduction of **12** gave 6a,7-dehydronorthaliporphine (**15**), which was reduced by amalgamated zinc and acid to northaliporphine (**17**). Methylation of **17** by diazomethane gave (±)-norglaucine (**16**), whereas methylation of **17** by formaldehyde and sodium borohydride gave (±)-thaliporphine (**18**), identical with authentic synthetic material.[8]

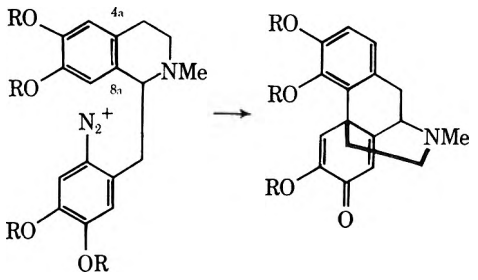




(7) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, **35**, 175 (1970).

Discussion

The Pschorr synthesis of the indenoisoquinoline **11** appears to be the first example of the formation of this unusual system, and involves a cyclization into the 8a position of an isoquinoline. Angular Pschorr cyclization into the 4a position of a 1,2,3,4-tetrahydroisoquinoline is, however, well documented and results in the formation of a morphinandienone, as shown below.[9] In the case of 6′-aminopapaverine (**5**), the



planarity of the aromatic isoquinoline system prevents attack at 4a for steric reasons and attack at 8a occurs instead.

The acid conversion of the indenoisoquinoline **11** to the 1-oxoaporphine **12** must involve selective demethylation at C-1, skeletal rearrangement to the aporphine system, and air oxidation to the quinone-like **12**; at present, the exact sequence of events cannot be specified. It may be noted, however, that **12** represents the first known 1-oxoaporphine. The stability of **12** suggests that compounds of this type will be found in nature.

Experimental Section

All melting points are uncorrected. Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Nmr spectra were measured on a Varian A-60A and a Varian HA-100 instrument in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise noted. Low-resolution mass spectra were measured on a Perkin-Elmer Model 270 instrument. Ultraviolet spectra were measured on a Perkin-Elmer 202 spectrophotometer.

6′-Aminopapaverine (5).—6′-Nitropapaverine[4] (6.7 g) was dissolved in tetrahydrofuran (300 ml) and hydrogenated below 10 psi pressure in the presence of 5% Pd/C (4.0 g) for 2 hr. Evaporation of the filtered solution followed by crystallization from ether gave colorless needles of **5** (5.8 g, 94%), mp 136–138° (lit.[4] mp 143°).

Pschorr Reaction of 6′-Aminopapaverine (5). A.—6′-Aminopapaverine (**5**) hydrochloride (400 mg) was dissolved in MeOH (30 ml) and 2 *N* H_2SO_4 (1.8 ml), and diazotized with 10% $NaNO_2$ (1.2 ml) at 0–5°. After the solution was stirred for 20 min at 0–5°, copper[10] (80 mg) was added and the mixture was stirred for 20 min at room temperature, warmed to 40° for 1 hr, and then basified (ammonia) to give a precipitate, which was extracted into $CHCl_3$. Usual work-up of the extract and crystallization from $CHCl_3$ gave 1-[3′-(5′,6′-dimethoxyindazolyl)]-6,7-dimethoxyisoquinoline (**7**) (156 mg, 42%), as colorless needles:

(8) (a) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967); (b) R. J. Spangler and D. C. Boop, *Tetrahedron Lett.*, 4851 (1971).

(9) The synthesis of morphinandienones by the Pschorr reaction has been reviewed: T. Kametani and K. Fukumoto, *J. Heterocycl. Chem.*, **8**, 341 (1971).

(10) Prepared from zinc dust and excess copper sulfate solution and stored under H_2O.

mp 271–273°; ir (KBr) 3.00 (NH), 6.10 μ (C=N); nmr (DMSO-d_6) δ 9.02 (1 H, s, $C_{7'}$ H), 8.58 (1 H, d, J = 6.0 Hz, C_3 H), 8.00 (1 H, s, $C_{4'}$ H), 7.68 (1 H, d, J = 6.0 Hz, C_4 H), 7.44 (1 H, s, C_8 H), 7.08 (1 H, s, C_5 H), 3.98, 3.94, 3.88, 3.84 (each 3 H, s, 4 OCH_3); uv λ_{max}^{EtOH} 245 nm (log ε 4.36), 307 (3.72), 341 (3.82); mass spectrum m/e 365 (M^+, base peak), 350 (M − 15), 334 (M − 31).

Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 66.00; H, 5.45; N, 11.72.

The residue from evaporation of mother liquors was purified by preparative tlc [silica gel, benzene–acetone (1:1) eluent] to give 1,2,9,10-tetramethoxydibenzo[*de,g*]quinolin-7-one (8) (42 mg, 11%) as yellow needles (from MeOH): mp 226° dec (lit.[1] mp 227–229°); ir (KBr) 6.10 μ (C=O); nmr δ 8.79 (1 H, d, J = 6.0 Hz, C_5 H), 8.69 (1 H, s, C_{11} H), 7.94 (1 H, s, C_3 H), 7.67 (1 H, d, J = 6.0 Hz, C_4 H), 7.10 (1 H, s, C_3 H), 4.03 (9 H, s, 3 OCH_3), 3.98 (3 H, s, OCH_3).

B.—6′-Aminopapaverine (5) (4.0 g) was dissolved in a precooled mixture of H_2SO_4 (65 ml) and H_2O (130 ml) and diazotized with a solution of $NaNO_2$ (760 mg) in H_2O (10 ml) at −5 to 0°. After the solution was stirred for 5 min at −5 to 0°, sulfamic acid (800 mg) and copper[10] were added to the mixture. The reaction was stirred for 30 min at 0–5° and then poured into cooled 20% NH_4OH and the precipitate was extracted into $CHCl_3$. Washing (10% NaOH and H_2O), work-up as usual, and crystallization from acetone (8 ml) yielded 2,3,10,11-tetramethoxyindeno[1,2-*j*]-isoquinoline (11) (1.12 g, 30%) as yellowish needles: mp 215° dec; ir (KBr) 6.15 μ (C=N and C=C); nmr δ 8.63 (1 H, d, J = 6.0 Hz, C_6 H), 8.04 (1 H, s, C_9 H), 7.41 (1 H, d, J = 6.0 Hz, C_5 H), 6.91 (1 H, s, C_{12} H), 4.97 (1 H, s, C_8 H), 4.75 (1 H, s, C_4 H), 3.76 (1 H, s, C_1 H), 3.98, 3.67 (each 3 H, s, 2 aromatic OCH_3), 3.50, 3.08 (each 3 H, s, 2 vinylic OCH_3); uv λ_{max}^{EtOH} 246 nm (log ε 4.17), 265 (sh, 4.00), 308 (sh, 3.33), 335 (sh, 3.28), 359 (3.38); mass spectrum m/e 337 (M^+), 322 (M − 15, base peak), 306 (M − 31).

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; m/e 337.1313. Found: C, 71.01; H, 5.55; N, 4.14; m/e 337.1301.

The residue from the mother liquors was purified by preparative tlc [silica gel, benzene–acetone (1:1 eluent)] to yield the following compounds.

2,9,10-trimethoxydibenzo[*de,g*]quinolin-1-one (12) was collected from the polar zone as orange needles (89 mg, 2.4%): mp 214° dec (from $CHCl_3$–ether); ir (KBr) 6.15 μ (C=O); nmr δ 9.60 (1 H, s, C_{11} H), 8.96 (1 H, d, J = 6.0 Hz, C_5 H), 8.76 (1 H, s, C_3 H), 7.43 (1 H, d, J = 6.0 Hz, C_4 H), 7.23 (1 H, s, C_8 H), 6.75 (1 H, s, C_7 H), 4.13, 4.08, 4.01 (each 3 H, s, 3 OCH_3); uv λ_{max}^{EtOH} 232 nm (log ε 4.54), 245 (sh, 4.49), 273 (sh, 4.22), 285 (sh, 4.13), 295 (sh, 4.04), 402 (3.98), 463 nm (3.92); mass spectrum m/e 321 (M^+), 306 (M − 15), 290 (M − 31, base peak).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36; m/e 321.1010. Found: C, 70.80; H, 4.76; N, 4.44; m/e 321.0972.

Work-up of the less polar zone gave papaverine (10) (164 mg, 4.3%), mp 146–147°.

6a,7-Dehydronorglaucine (13).—A solution of the spiro compound 11 (120 mg) in tetrahydrofuran (20 ml) was hydrogenated in the presence of platinum (from 120 mg of PtO_2) at atmospheric pressure for 20 hr. After filtration and the usual work-up, crystallization from ether afforded 13 (101 mg, 84%) as plates: mp 182° dec; ir (KBr) 3.05 (NH), 6.10 μ (C=C); nmr δ 9.05 (1 H, s, C_{11} H), 6.97, 6.92 (each 1 H, s, C_3 and C_8 H), 6.58 (1 H, s, C_7 H), 4.00 (6 H, s, 2 OCH_3), 3.98, 3.90 (each 3 H, s, 2 OCH_3), 3.60–3.20 (4 H, m, methylene protons): mass spectrum m/e 339 (M^+, base peak), 324 (M − 15); uv λ_{max}^{EtOH} 259 nm (log ε 4.81), 335 (3.89), 380 (3.35).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.77; H, 6.12; N, 4.18.

***N*-Carbethoxy-6a,7-dehydro-*N*-norglaucine (14).**—A solution of ethyl chloroformate (0.1 ml) in $CHCl_3$ (1 ml) was added dropwise to a stirred solution of 13 (50 mg) in $CHCl_3$ (10 ml) and triethylamine (0.1 ml) at 0–5°. After stirring for 2.5 hr at room temperature, the reaction mixture was washed (10% $NaHCO_3$ and H_2O) and dried ($MgSO_4$). Evaporation and crystallization of the residue from ether–hexane gave 14 (42 mg, 70%) as plates, mp 159–160° (lit. mp 162–163°[7], 156–157°[11]), ir (KBr), melting point, and mixture melting point identical with those of an authentic sample.

Norglaucine (16).—To a stirred mixture of zinc amalgam [prepared from 2 *N* HCl (10 ml), 2% $HgCl_2$ (10 ml), and zinc dust (1.0 g) as usual] was added a suspension of 13 (100 mg) in EtOH (10 ml). After the solution was heated at 60–70° for 30 min, 6 *N* HCl (5 ml) was added and heating was continued for an additional 30 min. The mixture was filtered and the filtrate was basified with ammonia. The free base was extracted with $CHCl_3$. The usual work-up of the extract gave 16 (78 mg, 79%) as an off-white gum: nmr δ 8.12 (1 H, s, C_{11} H), 6.77, 6.61 (each 1 H, s, C_3 and C_8 H), 3.89 (6 H, s, 2 OCH_3), 3.87, 3.67 (each 3 H, s, OCH_3). Amine 16 formed a colorless hydrochloride, mp 214° dec (from MeOH–ether), ir (KBr) 3.60–4.00 μ (≡NH^+). Its picrate had mp 218° dec (EtOH); uv λ_{max}^{EtOH} 280 nm (log ε 4.17), 303 (4.20), 315 (sh, 4.16), 356 (4.14).

Anal. Calcd for $C_{26}H_{26}N_4O_{11}$: C, 54.73; H, 4.59; N, 9.82. Found: C, 54.69; H, 4.77; N, 10.00.

(±)-Glaucine (1).—A solution of 16 (50 mg) in MeOH (5 ml) and 37% HCHO (1 ml) was warmed to 40–50° for 30 min. $NaBH_4$ (100 mg) was added portionwise to the mixture. The solvent was evaporated and the residue was extracted with benzene. The organic layer was washed with water and worked up as usual. Crystallization of the residue from ether afforded 1 (42 mg, 81%) as pale yellowish needles: mp 127–129°; ir (KBr) 3.70 μ (NMe); nmr δ 8.10 (1 H, s, C_{11} H), 6.80, 6.61 (each 1 H, s, C_3 and C_8 H), 3.93, 3.92, 3.90, 3.68 (each 3 H, s, 4 OCH_3), 2.55 (3 H, s, NCH_3); mass spectrum m/e 355 (M^+), 354 (M − 1, base peak), 324 (M − 31); uv λ_{max}^{EtOH} 280 nm (log ε 4.04), 301 (3.97). The picrate of 1 formed yellow needles, mp 199–200° dec (from EtOH) (lit.[7] mp 197–199°). The ir (KBr), melting point, and mixture melting point of 1 picrate were identical with those of an authentic sample.

2,9,10-Trimethoxydibenzo[*de,g*]quinolin-1-one (12).—A solution of 11 (1.4 g) in 65% H_2SO_4 (40 ml) was heated at 65° for 20 min. The reaction mixture was poured into ice–water and neutralized with ammonia. Extraction with $CHCl_3$ and the usual work-up gave 12 (1.25 g, 94%) as orange needles, mp 214° dec (from $CHCl_3$–ether), melting point and spectral properties identical with those of the authentic sample described above.

6a,7-Dehydronorthaliporphine (15).—A solution of 12 (1.1 g) in tetrahydrofuran (200 ml) was hydrogenated in the presence of platinum (from 1.1 g of PtO_2) at atmospheric pressure for 48 hr. Work-up as usual and crystallization from ether afforded 15 (850 mg, 77%) as gray plates: mp 197–199°; ir (KBr) 2.90, 3.00 (NH and OH), 6.10 μ (C=C); nmr (acetone-d_6) δ 9.26 (1 H, s, C_{11} H), 7.06, 7.00 (each 1 H, s, C_3 and C_8 H), 6.64 (1 H, s, C_7 H), 3.98 (3 H, s, OCH_3), 3.89 (6 H, s, 2 OCH_3); mass spectrum m/e 325 (M^+, base peak), 310 (M − 15); uv λ_{max}^{EtOH} 257 nm (sh, log ε 4.33), 266, (4.34), 310 (3.70), 335 (3.57), 380 (3.10).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.88; H, 5.88; N, 4.51.

Northaliporphine (17) from 15.—A suspension of 15 (530 mg) in tetrahydrofuran (40 ml) was added to a stirred suspension of zinc amalgam [prepared from zinc dust (6.0 g), 2% $HgCl_2$ (60 ml), and 2 *N* HCl (60 ml)]. The reaction was completed and worked up as for the reduction of 13.

Crystallization from MeOH afforded 17 (450 mg, 85%) as colorless needles: mp 214–216° dec; ir (KBr) 3.00 μ (NH); nmr δ 8.13 (1 H, s, C_{11} H), 6.77 (1 H, s, C_3 H), 6.58 (1 H, s, C_3 H), 3.91 (9 H, s, 3 OCH_3); mass spectrum m/e 327 (M^+), 326 (M − 1, base peak), 310 (M − 17); uv λ_{max}^{EtOH} 279 nm (log ε 4.04), 302 (4.07).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.56; H, 6.45; N, 4.36.

Norglaucine (16).—A solution of excess diazomethane in ether was added to 17 (27 mg) in MeOH (3 ml) and dioxane (0.5 ml) and the mixture was allowed to stand at room temperature for 20 hr. The excess diazomethane was decomposed with 2 *N* HCl, and the solvent was evaporated. Basification with 10% NaOH followed by usual work-up of the extract gave 16 as a colorless syrup, characterized as the hydrochloride (19 mg, 63%), mp 214° dec, ir (KBr) superimposable on that of the authentic sample prepared above.

(±)-Thaliporphine (18).—A solution of 17 (100 mg) in MeOH (20 ml), tetrahydrofuran (5 ml), and 37% HCHO (4 ml), was warmed to 65° for 30 min. $NaBH_4$ (500 mg) was added portionwise to the mixture. Work-up as for the methylation of 13 and crystallization from MeOH afforded 18 (64 mg, 64%) as color-

(11) N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966).

less needles: mp 188–190° (lit.[8] mp 190–192°); ir (KBr) 2.80 (OH), 3.60 μ (NMe); nmr δ 8.09 (1 H, s, C_{11} H), 6.80 (1 H, s, C_8 H), 6.55 (1 H, s, C_3 H), 3.91 (6 H, s, 2 OCH_3), 3.90 (3 H, s, OCH_3), 2.55 (3 H, s, NCH_3); mass spectrum *m/e* 341 (M^+), 340 (M − 1, base peak), 326 (M − 15), 310 (M − 31); uv λ_{max}^{EtOH} 279 nm (log ε 4.04), 304 (4.04). The spectral properties and mixture melting point of **18** were identical with those of authentic (±)-thaliporphine.

Northaliporphine (17) from 12.—A suspension of the oxoaporphine **12** (40 mg) in tetrahydrofuran (10 ml) was added to a stirred suspension of zinc amalgam [prepared from 2% $HgCl_2$ (15 ml), zinc dust (1.5 g), and 2 *N* HCl (15 ml)].

The reaction was completed and worked up as for the reduction of **15** to give a reddish residue. Purification by preparative tlc [silica gel, $CHCl_3$–MeOH (5:1) eluent] afforded **17** (21 mg, 52%) as colorless needles, mp 212–214° (from $CHCl_3$–ether–hexane), identical by spectral properties and mixture melting point with the sample prepared by reduction of **15**.

Registry No.—**1**, 5630-11-5; **5**, 39945-32-9; **5** HCl, 39945-33-0; **7**, 39945-34-1; **8**, 5574-24-3; **10**, 58-74-2; **11**, 39945-36-3; **12**, 39945-37-4; **13**, 39945-38-5; **15**, 39945-39-6; **16**, 39945-40-9; **16** HCl, 39945-41-0; **16** picrate, 39945-42-1; **17**, 39945-43-2; $NaNO_2$, 7632-00-0; formaldehyde, 50-00-0; sodium borohydride, 16940-66-2; diazomethane, 334-88-3.

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Purine *N*-Oxides. XLVII. Photochemistry of 1-Hydroxy- and 1-Methoxyhypoxanthines[1]

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The photochemistry of the cations, neutral species, and anions of 1-hydroxyhypoxanthine and 1-hydroxy-7-methylhypoxanthine is reported. Two types of reactions, rearrangement and reduction, occur upon uv excitation of these *N*-hydroxypurines. The influence of tautomeric structure and ionic state on the type and the extent of these two reactions is examined. 1-Methoxy-7-methylhypoxanthine, which undergoes photoreduction only, was used as a model for the un-ionized *N*-hydroxy species. It is deduced that deoxygenation is the primary reaction of the neutral *N*-hydroxy species, while rearrangement occurs from an excited state of the enolate anions of these 1-hydroxyhypoxanthines. Studies with triplet sensitizers in dioxane demonstrated that photoreduction of the neutral species of 1-hydroxy-7-methylhypoxanthine occurs through the triplet state, while in acetonitrile photoreduction of it takes place by a combination of triplet energy transfer and chemical sensitization. Photoreduction of 1-methoxy-7-methylhypoxanthine occurs from the excited singlet but it can also be accomplished by chemical sensitization with aromatic ketones. The enolate anions can also be photoreduced with aqueous acetone as sensitizer. Syntheses of the requisite 1-hydroxy-7-methyl- and 1-methoxy-7-methylhypoxanthines are described.

The photochemical sensitivity of purine *N*-oxides in solution has been reported[2-7] and products resulting from deoxygenation, rearrangement, and ring opening have been isolated. Study of a series of *N*-hydroxyxanthines showed that free radicals can be induced by ultraviolet irradiation of the dry solids.[8] These radicals are stable in the solid state, but are immediately reduced to the parent purines when dissolved in protic solvents. Irradiation of the same *N*-hydroxypurines in solution gave the deoxygenated derivatives as the primary photoproducts.[8] We have now studied the mechanism of photochemical reduction of *N*-hydroxypurines in solution, with consideration of the influence of the ionic and the tautomeric state on the photochemical behaviors of the irradiated compounds.

For initial study 1-hydroxyhypoxanthine[9] (**1**) and derivatives of it were selected. This system has the desired cyclic hydroxamic acid moiety, only one additional ionizable proton, and a minimal number of ionic species and tautomeric forms to be considered. In addition, the availability of 1-hydroxyinosine[9] (**12**) presented a route to the desired selectively methylated derivatives of **1**.

Results

Irradiations of 1-Hydroxyhypoxanthine (1).—The neutral species of **1** was studied at pH 3, which is more than 2 pH units from the first ionization p*K* of 5.65,[9] but above the protonation p*K* of 1.77 ± 0.05. Irradiation of **1** at pH 3 in the presence of O_2 resulted in rapid destruction of uv-absorbing components (expt 1–2, Table I); by 2 hr only 6% of the starting material could be accounted for, all as hypoxanthine (**8**). This loss could be greatly diminished by flushing with N_2 and all subsequent irradiations were done under N_2.

Irradiation of the neutral species of **1** under N_2 with a Corex filter (260-nm cutoff) for 30 min or more gave three isolable products (Scheme I): hypoxanthine (**8**) (40%), 2,6-dihydroxypurine (xanthine) (**10**) (9%), and 6,8-dihydroxypurine (**7**) (1%) (expt 8–10, Table I). Even under N_2 there was still a decrease in the total recovery of these products, based on uv absorption, as the photolysis proceeded (expt 5–10). The cation of **1**, irradiated in 3 *N* CF_3CO_2H (pH ~0) (expt 3–4), re-

(1) This investigation was supported in part by funds from the Atomic Energy Commission (Contract No. AT[11-1]-3521) and from the National Cancer Institute (Grant No. CA 08748).

(2) G. Levin and G. B. Brown, *Fed. Proc.*, **21**, 372 (1962).

(3) G. B. Brown, G. Levin, and S. Murphy, *Biochemistry*, **3**, 880 (1964).

(4) G. Levin, R. B. Setlow, and G. B. Brown, *ibid.*, **3**, 883 (1964).

(5) F. Cramer and G. Schlingloff, *Tetrahedron Lett.*, 3201 (1964).

(6) G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *J. Med. Chem.*, **8**, 190 (1965).

(7) A. Giner-Sorolla, C. Gryte, M. L. Cox, and J. C. Parham, *J. Org. Chem.*, **36**, 1228 (1971).

(8) J. C. Parham, I. Pullman, and G. B. Brown, *Radiat. Res.*, **47**, 242 (1971); *Tetrahedron*, **29**, in press.

(9) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **31**, 966 (1966).

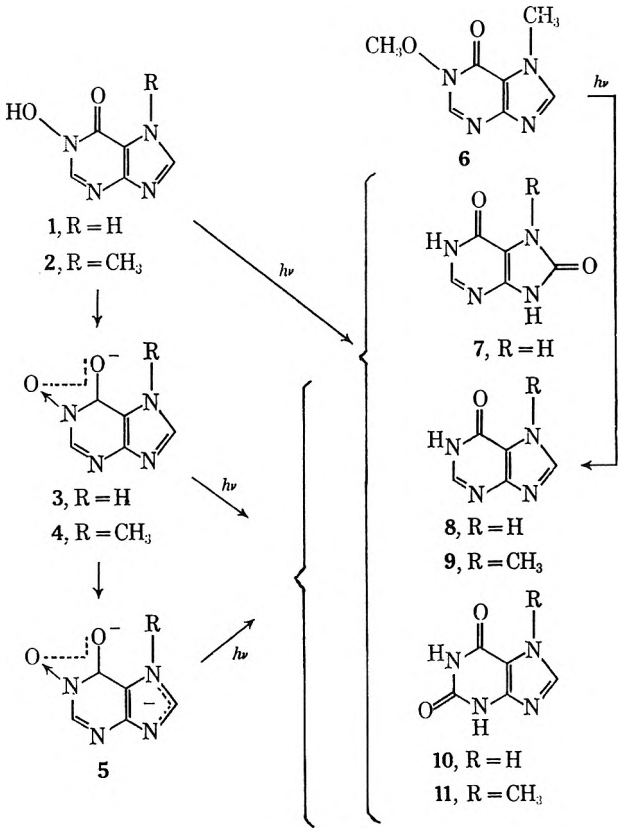
TABLE I

PHOTOLYSIS OF 1-HYDROXYHYPOXANTHINE (1) IN AQUEOUS SOLUTION[a]

Expt	pH	Time, min	Xanthine (10), %	Hypoxanthine (8), %	6,8-Dihydroxypurine (7), %	1, %	Recovery, %
1	3.0[b]	15	2	20	0	24	46
2	3.0[b]	120	0	6	0	0	6
3	0	30	<1	14	3	76	93[c]
4	0	120	<1	35	4	26	67[d]
5	3.0	5	4	16	0	77	97
6	3.0	10	6	24	<1	43	73
7	3.0	15	7	40	<1	16	63
8	3.0	30	9	38	1	2	50
9	3.0	60	9	42	1	0	51
10	3.0	120	9	40	1	0	50
11	8.5	30	17	7	0	6	30[e]
12	8.5	60	18	6	0	0	24[e]
13	13	30	24	9	0	24	57[e]
14	13	60	19	6	0	2	27[e]

[a] Corex filter. [b] Without N_2 flushing. [c] Trace of 8-trifluoromethylhypoxanthine. [d] 2% 8-trifluoromethylhypoxanthine. [e] Trace of a third, unidentified product.

SCHEME I

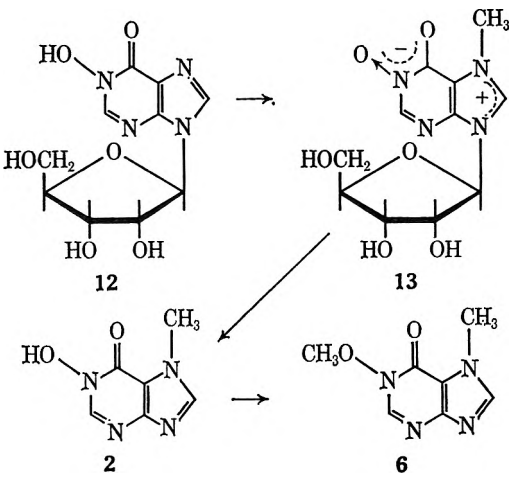


acted more slowly than the neutral species. Hypoxanthine was again the major product (35%), while the yield of 6,8-dihydroxypurine increased to 4%, and less than 1% of xanthine was found. In addition, 8-trifluoromethylhypoxanthine (2% after 120 min) was produced. It was identified from its uv spectral properties by comparison with an authentic sample.[10]

Irradiation of the monoanion **3** at pH 8.5 (pK_a = 5.65 and 10.10[9]) gave much less photoreduction to hypoxanthine (~6%), increased rearrangement to xanthine (17–18%), and no 6,8-dihydroxypurine (expt 11–12). A trace of a third product, not yet identified, was noted which showed uv absorption, λ_{max} (pH) 248, 286 (0), 276 nm (12). Irradiation of the dianion of **1** (5) in 28% NH_4OH, pH ~13, gave results similar to those from the monoanion **3** (expt 13–14).

Selectively Alkylated Derivatives of 1.—Methylation of 12, an improved preparation of which is reported, can be achieved at N-7 by reaction of the neutral species with CH_3I in CH_3SOCH_3 (Scheme II).[11] Hydrolysis of

SCHEME II



1-hydroxy-7-methylinosine (**13**) yielded 1-hydroxy-7-methylhypoxanthine (**2**). Alkylation of the anion of **2** with CH_3I and K_2CO_3 in dimethylacetamide produced 1-methoxy-7-methylhypoxanthine (**6**). The uv spectra and nmr data confirm the assigned structures for **2** and **6**.

Irradiation of Methyl Derivatives of 1.—The single pK_a of 1-hydroxy-7-methylhypoxanthine (**2**), 5.63 ± 0.02, is comparable to the first pK_a of **1**, and each is associated with increased absorption near 230 nm. Thus, both ionizations occur from the 1-hydroxyl group. The protonation pK of **2** is 1.6 ± 0.1. The neutral species of **2**, irradiated at pH 3 (expt 16–17, Table II), gave primarily deoxygenation to 7-methyl-

TABLE II

PHOTOLYSIS OF 1-HYDROXY-7-METHYLHYPOXANTHINE (2)

Expt	Solvent	pH	Time, min	7-Methylxanthine (11), %	7-Methylhypoxanthine (9), %	2, %	Recovery, %
15	H_2O[a]	0	30	2	13	63	78%[b]
16	H_2O[a]	3.0	15	9	14	39	62[c]
17	H_2O[a]	3.0	30	7	42	10	59[c]
18	H_2O[a]	9.0	15	6	3	66	>75[d]
19	H_2O[a]	9.0	30	10	5	17	>32[d]
20	CH_3OH[a]		15	0	27	54	81[c]
21	CH_3OH[a]		30	0	42	26	68[c]
22	EtOH[a]		15	0	42	32	74[c,d]
23	CH_3CN[a]		30	2	74	0	76[c]
24	Dioxane[a]		45	0	70	0	70
25	H_2O[e]	9.0	30	<1	<1	97	97
26	H_2O[e]	9.0	300	2	<1	68	70
27	H_2O[e,f]	9.0	30	<1	11	84	95
28	H_2O[e,f]	9.0	300	2	82	0	84

[a] Corex filter. [b] Product with properties similar to 6,8-dihydroxypurine, ~2%. [c] Small amount of product (<1%) thought to be 6,8-dihydroxy-7-methylpurine. [d] One additional unidentified product. [e] Pyrex filter. [f] 10% acetone as sensitizer.

(10) A. Giner-Sorolla and A. Bendich, *J. Amer. Chem. Soc.*, **80**, 5744 (1958).

(11) The anion of 1-hydroxyinosine (**12**) can be alkylated at the 1 position to produce 1-alkoxyinosines [private communications, A. A. Watson, this laboratory, and J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 1334 (1972), prior to publication]. These positions of alkylation of **12** parallel those observed for the anion and the neutral species of inosine.[12]

(12) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **85**, 193 (1963).

hypoxanthine (9), a small amount of 7-methylxanthine (11), and a trace of another material which resembled 6,8-dihydroxypurine, both in retention volume on a Dowex-50 [H+] column and in uv spectrum. It is presumably 6,8-dihydroxy-7-methylpurine (7, R = CH_3). Irradiation of the cation of 2 at pH 0 (expt 15) gave primarily deoxygenation, less 7-methylxanthine, and more product presumed to be 6,8-dihydroxy-7-methylpurine.

The anion of 2 (4), irradiated at pH 9.0, gave yields of deoxygenation (9) and rearrangement (11) products comparable to those obtained from monoanion 3 (expt 18–19). An unidentified product, similar to that obtained from 3 in trace amounts, was also obtained.[13]

1-Hydroxy-7-methylhypoxanthine (2) is sufficiently soluble to permit irradiation studies in nonaqueous media (expt 20–24, Table II). In methanol or ethanol solution, up to 40% or more of 2 was photoreduced to 9; traces of 6,8-dihydroxy-7-methylpurine (7, R = CH_3) were noted, but no rearrangement to 11 was obtained. In CH_3CN solution photolysis of 2 gave 9 (74%), 11 (2%), and a trace of 7 (R = CH_3). The irradiation of 2 in dioxane solution gave 9 (70%) and no other products.

1-Methoxy-7-methylhypoxanthine (6) was irradiated under N_2 through a Corex filter in several solvents (expt 29–32, Table III). Only photoreduction to 7-methylhypoxanthine (9) resulted, in a 50% or greater yield. Traces of two other products were detected in water.

TABLE III
PHOTOLYSIS OF 1-METHOXY-7-METHYLHYPOXANTHINE[a]

Expt	Time, min	Solvent	7-Methylhypoxanthine (9), %	6, %
29	15	H_2O	52[b]	0
30	10	CH_3OH	67	0
31	10	CH_3CN	60	0
32	20	Dioxane	52	0

[a] Corex filter. [b] Two additional minor peaks also noted.

Sensitizer Studies.—The solubility of 2 and 6 in acetonitrile and dioxane permitted studies with triplet sensitizers (Table IV).[16,17] A Pyrex filter (280-nm cutoff) eliminated the majority of the main absorption band at 256 nm, but not the small absorption that extends slightly beyond 280 nm. Direct irradiation of 2 or 6 for 30 min or more in each solvent, through Pyrex without a sensitizer, gave a low yield (1–6%) of the reduction product, 9, but no rearrangement to 7-methylxanthine (11) (expt 33 and 39, Table IV). This production of 9 was much lower than that obtained from irradiations through Corex (Tables II and III) and can be attributed to reaction following excitation of the small absorption beyond 280 nm. With sensitizers in each solvent, both 1-hydroxy- and 1-methoxy-7-methylhypoxanthine, 2 and 6, gave 9, and in most cases as the only photoproduct. In the presence of acetophenone, a small quantity of a second product was noted from 6.

Sensitized irradiation of anion 4 was limited, by solubility, to an aqueous medium. Irradiation of it at pH 9, through Pyrex in the presence of 10% acetone, gave a greater yield of photoreduction than did similar irradiation without acetone (expt 25–28, Table II).

Discussion

In most studies on the photochemistry of heterocyclic aromatic N-oxides,[18] little or no possibility existed for the presence of an alternative tautomeric species, as in the N-oxides of pyridine, quinoline, and isoquinoline. In purine N-oxides the presence of a carbonyl group in the same ring with the N-oxide favors existence of the neutral species as the N-hydroxy tautomer in preference to the hydroxy N-oxide form.[9,19] The enhanced formation of the N-hydroxy tautomer, in essence a cyclic hydroxamic acid, can occur when the two groups are either "ortho"[9] or "para"[19] to each other.

It has been repeatedly observed that the N-oxide group, regardless of its tautomeric form, decreases all ionization pK_a's relative to those of the parent purine.[19,20] Where the N-hydroxy tautomer predominates, the N-hydroxyl proton is usually the first to ionize. Its ionization is always accompanied by the appearance of an intense uv absorption band near 230 nm[9,19,21–23] that has been attributed to the formation of an enolate anion, as in 3, in which the resonance form of the N–O bond is equivalent to an N-oxide or nitrone group.[19] We have examined the effect of different pH's on the photochemistry of a simple N-hydroxypurine and correlated them with changes in ionic and tautomeric forms.

The first ionization of 1-hydroxyhypoxanthine (1) has been assigned to the proton of the 1-hydroxyl.[9] The neutral species of 1 shows a single absorption band at 250 nm similar to that of the neutral species of hypoxanthine (8) (λ_{max} 249 nm)[24] and 1-methylhypoxanthine (251 nm).[24] The neutral species of 1-hydroxy-7-methylhypoxanthine (2) also shows a single band at

(13) This product was well separated and followed 9 when eluted with 1 N HCl from a Dowex-50 [H+] column. A sample isolated from a Dowex-50 [H+] column and applied to a paper chromatogram had R_f 0.46 in CH_3CN–H_2O–(28%) NH_4OH (7:2:1, v/v) and gave a negative Pauly test.[14] It showed uv absorption, λ_{max} (pH 0) 248, 287 nm. In acid solution this product was slowly converted to 7-methylhypoxanthine (9), which was identified by paper and column (A-6) chromatography and its uv absorption properties.

On a Bio-Rex A-6[15] (formate) column eluted with 0.34 M ammonium formate buffer (pH 4.7), a third photolysis product was also eluted well after 11, 9, and 2. A paper chromatogram of the crude photolysis mixture developed in CH_3CN–H_2O–NH_4OH (7:2:1) showed one uv-absorbing spot at R_f 0.65 in addition to those of 11, 9, and 2, which were all near R_f 0.4. The component at R_f 0.65 gave a blue Pauly test on the chromatogram and had the same uv spectrum as the unknown product eluted from an A-6 (formate) column, λ_{max} (pH) 237 (0), 246 (6), 252 nm (11). This product was stable to acid hydrolysis, but was not stable to prolonged irradiation. In expt 5–10 (Table I) it gradually diminished after 30 min. The positions of elution on the two columns indicate that the unknowns are fairly basic and that the one that gave a positive Pauly test is an imidazole.

(14) H. Pauly, *Hoppe-Seyler's Z. Physiol. Chem.*, **42**, 508 (1904).

(15) M. Uziel, C. K. Koh, and W. E. Cohn, *Anal. Biochem.*, **25**, 77 (1968).

(16) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, p 298.

(17) (a) N. C. Yang, D. S. McClure, S. L. Murov, J. J. Houser, and R. Dusenberg, *J. Amer. Chem. Soc.*, **89**, 5466 (1967). (b) For examples see B. M. Monroe and C. C. Wamser, *Mol. Photochem.*, **2**, 213 (1970), and references therein.

(18) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

(19) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).

(20) M. A. Stevens and G. B. Brown, *J. Amer. Chem. Soc.*, **80**, 2759 (1958).

(21) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **32**, 1151 (1967).

(22) A. A. Watson and G. B. Brown, *ibid.*, **37**, 1867 (1972).

(23) G. Zvilichovsky and G. B. Brown, *ibid.*, **37**, 1871 (1972).

(24) G. B. Elion, *ibid.*, **27**, 2478 (1962).

TABLE IV

SENSITIZATION STUDIES[a]

Expt	Solvent Sensitizer[b]	1-Hydroxy-7-methylhypoxanthine (2) Time, min	9, %	2, %	Recovery, %	1-Methoxy-7-methylhypoxanthine (6) Time, min	9, %	6, %	Recovery, %
33	Acetonitrile	30	5	92	97	30	4	95	99
34	+ Acetophenone (73.6)[d]	30	65	0	65	30	75	0	>75[c]
35	+ *m*-CH_3O-acetophenone (72.4)[e]	30	53	47	100	30	6	92	98
36	+ Benzophenone (68.5)[d]	40	87	4	91	30	33	67	100
37	+ Benzophenone					120	63	12	75
38	+ Fluorene (67.6)[d]	30	8	92	100	30	9	91	100
39	Dioxane	30	6	92	98	30	1	99	100
		240	26	35	61				
40	+ Acetophenone	30	48	30	78	30	68	0	>68[c]
41	+ *m*-CH_3O-acetophenone	30	49	32	81	30	17	72	89
42	+ Benzophenone	30	9	88	97	30	4	96	100
43	+ Fluorene	30	3	80	83	30	4	96	100
44	Acetone (neat)	30	78	0	78	30	65	0	65

[a] Pyrex filter. [b] 0.2 *M* in sensitizer; values in parentheses are triplet energy levels in kcal/mol. [c] One additional unknown noted, λ_{max} (pH 0 and 11) 247 nm. [d] Reference 16. [e] Reference 17a.

256 nm, which is close to that of 7-methylhypoxanthine (255.5 nm)[24] and to that of 1-methoxy-7-methylhypoxanthine (256 nm), a derivative of **2** constrained in the *N*-alkoxy-6-oxo form. From these data it is deduced that the neutral species of both **1** and **2** exist as the *N*-hydroxy-6-oxo tautomer.

The photochemical reactivity of the neutral species of **1** and **2** was studied and in both cases the major product (~40%), from the direct irradiation in aqueous solution through a Corex filter, was the deoxygenated purine **8** or **9** (Tables I and II). The xanthine derivatives **10** and **11** were also produced from the irradiations of **1** and **2**, but in yields of only 9–10%. These two types of reactions, deoxygenation and rearrangement, are analogous to those observed earlier for the direct irradiation of adenine and adenosine 1-oxides,[2-5] both of which are thought to exist primarily in the *N*-oxide form.[20] The predominance of the deoxygenation path for the neutral species of **1** and **2** contrasts with the ratio of reduction to rearrangement observed for adenine *N*-oxide, from which almost equal amounts of reduction and rearrangement products were obtained.[3,5]

A third product from the irradiation of **1** at pH's 0 and 3 was identified as 6,8-dihydroxypurine (**7**), and a similar product, presumed to be the 7-methyl derivative of **7**, was also obtained from **2**; in each instance it represented 4% or less of the starting material. This production of an 8-hydroxypurine is reminiscent of the photochemical hydroxylation of naphthalene that is induced by irradiation of it with pyridine *N*-oxide in CH_2Cl solution,[25] and of the photochemical epoxidation of olefins in the presence of *N*-oxides.[26]

In 1-methoxy-7-methylhypoxanthine (**6**), the absence of any ionizable or tautomerizable proton unequivocally defines the tautomeric form. Thus, **6** should provide a model for the photochemical products that would be expected from the 1-hydroxy-6-oxo tautomer in the total absence of other species. In aqueous solution **6** was rapidly reduced photochemically to one product, 7-methylhypoxanthine (**9**), in 52% yield (expt 29, Table III). This yield correlates well with the ~40% of **8** or **9** produced from the neutral species of **1** and **2**.

The ionization of the *N*-hydroxyl proton of **1** or **2** to the anionic species, **3** or **4**, modifies the predominant form of the N–O bond from *N*-hydroxy to an enolate *N*-oxide, and this is accompanied by an alteration in the ratio of the photochemical products. Irradiation of the monoanion **3** (expt 11–12) produced a greater extent of rearrangement to **10** (17–18%) than that obtained from the neutral species **1**. In turn, the yield of the deoxygenated purine **8** from **3** was reduced to about 6%. Further ionization of the imidazole hydrogen of **3** to the dianion **5** had no influence on the course of photochemical reactions (expt 13–14).

Irradiation of the anion of the 7-methyl derivative, **4** (expt 18–19, Table II), resulted in a similar decrease in the reduction to **9**, relative to that (expt 16–17) of its neutral species, **2**. However, the yields of the rearrangement product, **11**, from either **2** or its anion **4** were virtually unchanged, in contrast to the effect of ionization of **1** to **3** that was accompanied by an increase in photoisomerization to xanthine from 9 to 17% (expt 8–9 and 11–12).

From the results of the irradiations of **1**, **2**, and **6**, it may be deduced that (a) the primary photochemical reaction of the *N*-hydroxy tautomer is deoxygenation and that (b) rearrangement proceeds *via* the enolate anion. Several results require consideration in relation to these deductions. These include the observation of some rearrangement from the neutral species **1** and **2** at pH 3, some deoxygenation from the anions **3**, **4**, and **5**, and the less than quantitative recoveries even from **6**.

The photolysis products, hypoxanthine (**8**), xanthine (**10**), and 6,8-dihydroxypurine (**7**), are stable under the irradiation conditions; continued irradiation after the disappearance of **1** did not reduce the recoveries of **7**, **8**, and **10** and overall recoveries remained near 50%. A time study irradiation of **1** at pH 3 (expt 5–10) showed that the decrease in the total recovery of material was associated with direct destruction of the chromophore, which suggests that **1** undergoes additional reactions.

Upon irradiations of the enolate anions **3** or **4**, there was a smaller overall recovery, ~25% (expt 11–12 and 18–19). Only a trace of one uv-absorbing product

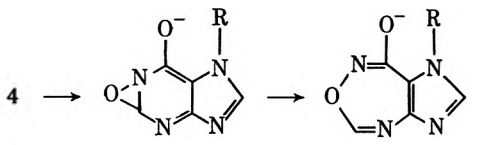
(25) D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 457 (1970).

(26) T. Tsuchiya, H. Arai, and H. Igeta, *ibid.*, 2747 (1969).

other than those in Table I was detected from the irradiation of **3**, but larger amounts of a similar product were noted from the irradiation of **4**.

Since the N–O group in these enolate anions may be considered as a nitrone or *N*-oxide, it is reasonable to assume that the photochemical rearrangement to xanthine proceeds *via* an oxazirane intermediate (**14**) (Scheme III). Oxaziranes have been proposed as inter-

SCHEME III



14 **15**

mediates in the N to C rearrangement of oxygen both for nitrones and for aromatic *N*-oxides.[18] They have been shown to yield not only the expected rearrangement product,[18,27] but also oxadiazepines, which result from isomerization of the oxazirane intermediates, and hydrolysis products of the oxadiazepines.

If an oxazirane intermediate is assumed, then the lower recoveries from the irradiations of **3** and **4** and the additional products from **4** could well be derived from secondary reactions, including photochemical, of the oxazirane **14** and the imidazolo oxadiazepine **15**. Chromatograms of the photolysis mixtures showed the presence of a product that gave a positive Pauly test for imidazoles.[13] This supports the proposal that **14** or, more likely, **15** undergoes ring opening to an imidazole. The alkaline pH's necessary for anions **3** and **4** should facilitate decomposition of such intermediates. The comparison of the photochemistry of the enolate anions, **3**, **4**, and **5**, to that of heterocyclic *N*-oxides can also be extended to the photoreduction noted for these anions, since photochemical deoxygenation is frequently observed for *N*-oxides of aromatic amines.[18]

Some photorearrangement of oxygen to the adjacent carbon occurred from **1** and **2** even at pH 3, where less than 1% of the corresponding anionic species **3** or **4** should be present. For the rearrangement to proceed through the enolate anions at pH 3, either the quantum efficiency of the rearrangement reaction must be considerably higher than that of the reduction reaction, or the pK_a of the excited singlet of **1** and **2** must be lower than that of the ground state. The amount of starting material photochemically modified in a given time was similar for the neutral species and for the monoanions (Tables I and II), which would argue against a significantly higher quantum efficiency for the rearrangement reaction than for photoreduction.

Direct measurement of excited state pK_a's was not possible because of the weak fluorescence of **1** and **2**, but these were calculated[28] from uv absorption data to be 2.73 and 1.26 for the first ionizations of **1** and **2**. These pK_a's for the excited singlets of **1** and **2** are, thus, sufficiently lower than those of the ground states to explain the extent of rearrangement observed at pH 3. They also permit an explanation of the differing amounts of rearrangement observed from the neutral species of **1** and **2**, in comparison to that observed from their respective monoanions, **3** and **4**. The yield of xanthine from **3** was twice that from **1** (expt 11–12 and 8–9), while the yield of 7-methylxanthine (**11**) was the same for both **2** and **4** (expt 16–19). From the calculated pK_a* of 2.7 for the excited singlet of **1**, a medium at pH 3 would allow this singlet to be only about half dissociated and an increase in pH will permit further ionization. This, in turn, will lead to a larger amount of rearrangement from the excited state of anion **3**. By comparison, from the calculated pK_a* of 1.2 for the excited singlet of **2**, a medium at pH 3 would permit almost complete ionization, and an increase in pH should cause no change in the yield of product from **4**.

At pH 0, well below the pK_a's of the excited singlets of **1** and **2**, photoreduction was not affected, but the amount of rearrangement to **10** or **11** was significantly decreased. The greater yield of **11** (2%) than **10** (<1%) is also in agreement with the calculated values for the excited state pK_a's, since **1** (pK_a* = 2.7) should be essentially un-ionized at pH 0, while a medium of pH 0 should permit **2** (pK_a* = 1.2) to ionize slightly (~6%). These interpretations of the results in terms of the pK's of the excited states are in accord with the proposal that rearrangement occurs *via* the enolate anion. It also follows that the recoveries of only 50% from **1** and **2** at pH 3 may, in part, be attributed to greater production of the labile imidazolo oxadiazepine **15**, as suggested above for the anions **3** and **4**.

However, when neither tautomerism nor ionization was possible and no rearrangement was observed, as in the case of **6** (Table III), recoveries still did not exceed 70%. This indicates that reactions which destroy the purine ring system occur even from the 1-methoxy compound, and that similar reactions should be expected for the 1-hydroxy derivatives. In agreement with this, there was still some loss of uv-absorbing components at pH 0, where reactions from the *N*-hydroxy species are favored and those from the enolate anions should be minimal. Oxidation of the 4–5 double bond is common in purines,[29,30] and the isolation of 6,8-dihydroxypurine demonstrates that reaction can occur at the imidazole ring. In fact, the amount of 8 substitution increased under conditions that favored reaction from the *N*-hydroxy species.[31] Loss of the purine chromophore may occur from reactions of the oxygen lost from N-1, which might react either as a hydroxyl radical or as singlet oxygen.

Irradiation studies of **2** in organic solvents (expt 20–24) showed that photoreduction predominated under these conditions. The absence of photorearrangement in nonaqueous solvents, except the more polar CH_3CN (expt 23), suggests that the less polar organic solvents do not support ionization of **2**. Therefore, a decreased proportion of the reaction products originate from the anion **4**, and the photolysis of **2** approaches that for the *N*-hydroxy species alone and more closely resembles the irradiation of the nonionizable **6**.

Sensitizer Studies.—The photoreduction of **2** and **6**

(27) J. Streith, C. Leibovici, and P. Martz, *Bull. Soc. Chim. Fr.*, 4152 (1971).

(28) H. H. Jaffe, D. L. Beveridge, and H. L. Jones, *J. Amer. Chem. Soc.*, **86**, 2932 (1964). pK*'s were calculated from the expression pK* − pK = (ν_B − ν_{BH^+})Nhc/2.303 RT using 300°K for T and for ν_B and ν_{BH^+} 259 and 250 nm for **1**[9] and 271 and 256 nm for **2**.

(29) P. H. Stahl, *Biochemistry*, **8**, 733 (1969).

(30) N. J. M. Birdsall, T.-C. Lee, T. J. Delia, and J. C. Parham, *J. Org. Chem.*, **36**, 2635 (1971).

(31) See expt 3–10 (Table I) and expt 15–17 (Table II), footnotes *b* and *c*.

was promoted by acetophenone in CH_3CN (expt 34, Table IV). In dioxane it promoted reduction of **6**, but was less effective with **2** (expt 40). Benzophenone gave less consistent results as a sensitizer. In CH_3CN it promoted photoreduction of **2** but was less efficient with **6** (expt 36); in dioxane it was not an active sensitizer for either **2** or **6** (expt 42).

To determine whether the photoreduction could be proceeding through chemical sensitization, that is, by reduction by ketyl radicals rather than by triplet energy transfer, *m*-methoxyacetophenone was also studied (expt 35 and 41). *m*-Methoxyacetophenone is a high energy sensitizer (E_T 72.4 kcal) with a lower π–π^* than n–π^* triplet energy level.[17a] Thus, it is a poor hydrogen abstractor and has a low efficiency as a chemical sensitizer.[17b] In CH_3CN it did not sensitize the photoreduction of **6** (expt 35) and in dioxane it was only marginally effective for **6** (expt 41), even though the triplet energy is above 72 kcal/mol.[17] These results indicate that for 1-methoxy-7-methylhypoxanthine chemical sensitization plays a predominant role in photoreduction sensitized by ketones. Since *m*-methoxyacetophenone fails to sensitize the photoreduction of **6** by triplet energy transfer, the loss of the methoxy group from **6** must occur from the excited singlet.

In contrast, the *m*-methoxyacetophenone-sensitized photoreduction of 1-hydroxy-7-methylhypoxanthine (**2**) in CH_3CN must take place by a combination of chemical sensitization and triplet-energy transfer. While half the starting material was photoreduced in 30 min in the presence of *m*-methoxyacetophenone (expt 35), much more was photoreduced with acetophenone or benzophenone (expt 34 and 36). In dioxane the similarity of the results with acetophenone and *m*-methoxyacetophenone (expt 40 and 41) demonstrates that deoxygenation from **2**, and therefore probably also from **1**, occurs from the triplet state and that sensitization takes place only through a triplet energy transfer mechanism in this solvent. Fluorene did not sensitize the photoreduction of **2** or **6** in either solvent (expt 38 and 43). Acetone promoted the photoreduction of both **2** and **6**, presumably by mechanisms similar to those for acetophenone (expt 44).

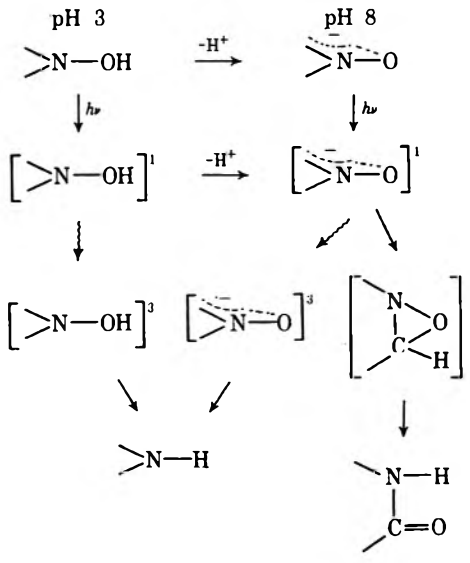
In a triplet quenching experiment irradiation of 1-hydroxy-7-methylhypoxanthine (**2**) for 30 min in CH_3CN (Corex) in the presence of piperylene (1.0 *M*) gave 7-methylxanthine (1.4%), 7-methylhypoxanthine (47%), and unreacted **2** (15%). Under similar conditions but in the absence of piperylene (expt 23, Table II), no starting material remained and the yield of 7-methylhypoxanthine was notably higher (74%). These results complement those in Table IV and are compatible with a triplet intermediate for photoreduction.

The differing results obtained with the triplet sensitizers in CH_3CN and in dioxane (Table IV) indicate some influence of the solvent, of a type not previously noted in chemical sensitizations. In CH_3CN both acetophenone and benzophenone reduced **2** and **6**, while dioxane did not permit chemical sensitization by benzophenone for either. Dioxane eliminated such sensitization by acetophenone for **2**, but did not prevent the reduction of **6** by acetophenone. This suggests that acetonitrile, usually considered to be an unreactive solvent for photochemistry, may have sufficiently labile hydrogens to support chemical sensitization while dioxane does not.[32]

Ten per cent of acetone at pH 9 was used for the sensitization of the monoanion **4** (expt 25–28, Table II). Since the Pyrex filter did not completely eliminate absorption by **4**, some rearrangement as well as photoreduction was detected without a sensitizer. The much greater extent of photoreduction in the presence of acetone suggests that deoxygenation proceeds from the triplet state of **4**, although the possibility of chemical sensitization, in whole or in part, cannot be excluded. These results imply that rearrangement may occur from the excited singlet of the enolate anions, paralleling the conclusions of a recent study of pyridine *N*-oxide which proposed that photoisomerization occurs from the singlet state while photoreduction is a triplet process.[35]

The results and proposals discussed are summarized in Scheme IV. Excitation of the neutral *N*-hydroxy

SCHEME IV



species at pH 3 or below would produce the excited singlet >NOH^1. Intersystem crossing would yield the *N*-hydroxy triplet >NOH^3, which leads ultimately to the photoreduced purine. Alternatively, ionization of the >NOH^1 singlet, which is more acidic than the ground state, would produce the excited singlet of the

(32) The influence of solvent polarity should be considered as a possible contributor to the differing results obtained in dioxane and in CH_3CN. Excited-state energy inversion can result from a difference in solvent polarity.[33,34] As the polarity of the medium is increased, the π–π^* state drops in energy and the n–π^* state rises. Both acetophenone and benzophenone have n–π^* lowest excited triplets. In CH_3CN, the π–π^* state of these ketones should be lower and the n–π^* state higher than in dioxane. It is evident that in CH_3CN $^3\pi$–π^* is not lowered below ^{3}n–π^* for either ketone, since their ability to act as sensitizers is opposite to that of *m*-methoxyacetophenone which is known to have ^{3}n–$\pi^* > {}^3\pi$–π^*.[17] In dioxane the lower polarity would increase the difference in energy between these states, making π–$\pi^* \gg$ n–π^*. Thus, the results in Table IV do not agree with those expected from an inversion of energy levels owing to a different solvent polarity. This supports the proposal of chemical sensitization.

In the case of benzophenone it is possible that solvent polarity may play some role. This would require that ^{3}n–π^* energy in CH_3CN is just sufficient for triplet energy transfer, but that in dioxane its energy level is below the requisite levels for transfer to **2** or **6**.

(33) L. A. Singer, *Tetrahedron Lett.*, 923 (1969).

(34) A. A. Lamola, *J. Chem. Phys.*, **47**, 4810 (1967).

(35) F. Bellamy, L. G. R. Barragan, and J. Streith, *J. Chem. Soc. D*, 456 (1971).

enolate anion $=NO^{-1}$. This excited anion may also be obtained by direct excitation of the ionized ground state. The excited anion singlet may photoisomerize to xanthine or decay to the triplet anion $=NO^{-3}$, which, in turn, also yields the photoreduction product.

Experimental Section

General Procedure for Direct Irradiation.—Samples were irradiated in 1.4×10^{-4} *M* solutions of the solvents specified. CF_3CO_2H (3 *M*), 10^{-3} *M* HCl, and dilute NH_4OH were used for pH 0, 3, and 8.5, respectively. Nitrogen was bubbled through the solutions for 2 hr prior to irradiation, and they were irradiated in an immersion type apparatus equipped with a 450-W Hanovia high-pressure mercury lamp, with the use of either a Corex or a Pyrex filter. The disappearance of starting material was followed by changes in the uv absorption or by paper chromatography of aliquots withdrawn at various intervals during the irradiations. When the reactions were complete, the solutions were concentrated under vacuum to a small volume, and the products were separated and isolated by chromatography over a BioRad AG-50, X8 [H^+], 200–400 mesh column (9 × 400 mm). The products were eluted with 1 *N* HCl from the column in the sequence 10 (or 11), 1 (or 2), 8 (or 9), 6, unknowns (from anions). Yields of the reaction products were calculated from their respective ϵ_{max} values.[9,24,36] For 8-trifluoromethylhypoxanthine[10] λ_{max} (ϵ_{max}) at pH 0 is 253.5 nm (11,100). The results, expressed as per cent yields based on starting material, are in Tables I–IV. Values were reproducible within ±5%.

General Procedure for Sensitized Irradiation.—A solution 1.4×10^{-4} *M* in sample and 0.2 *M* in sensitizer in either *p*-dioxane or CH_3CN was flushed with N_2 for 2 hr in an immersion apparatus and was irradiated with a high-pressure mercury lamp through a Pyrex filter. The solvent was evaporated under vacuum; the solid residue was washed with 200 ml of ether. The flask was rinsed again with a small amount of ether, then with 100 ml of water. The combined ethereal extractions were washed with 100 ml of water. The aqueous layers were combined and evaporated to a small volume under vacuum, and the products were separated and quantitated as described previously.

Materials.—Spectroquality *p*-dioxane and CH_3CN (Matheson Coleman and Bell) and analytical grade acetone and anhydrous methanol (Mallinckrodt) were used as received. Benzophenone, *m*-methoxyacetophenone (Aldrich), and acetophenone and fluorene (J. T. Baker) were used without purification. Melting points are uncorrected. Paper and tlc chromatograms were developed, ascending, with Whatman No. 1 paper or Chromagram silica gel sheet with fluorescent indicator (Eastman). Nmr spectra were measured with a Varian A-60 spectrometer and fluorescence spectra with a Ferrand spectrofluorometer. An ISCO uv analyzer was used to monitor column eluates. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. pK_a's were determined at 27 ± 1° by methods described[37] titrimetrically in 0.001 *M* solutions or spectrophotometrically in 0.01 *M* buffers.[38]

1-Hydroxyhypoxanthine.—This was prepared as described.[9,39]

1-Hydroxyinosine (12).—A solution of adenosine 1-oxide[40] (28.3 g, 0.1 mol) and $NaNO_2$ (69 g, 1.0 mol) dissolved in 1 l. of 29% (v/v) acetic acid was allowed to stand at room temperature for 24 hr. It was then extracted with ether and the aqueous layer was evaporated to dryness under vacuum. The residue was extracted three times with 300-ml aliquots of hot CH_3OH. The extracts were combined and the CH_3OH was evaporated under reduced pressure. Pure 1-hydroxyinosine[9,41] was isolated from the residue by chramatography over Dowex-50, X8, 200–400 mesh [H^+] by elution with H_2O, yield 15.5 g (54%). It was identical in all respects with an authentic sample.[9]

1-Hydroxy-7-methylhypoxanthine (2).—A suspension of 1-hydroxyinosine (7.0 g, 25 mmol) in 40 ml of DMSO was stirred with excess CH_3I (10 ml) at 25° for 5 hr. As reaction proceeded, unreacted 2 gradually dissolved. The solution was then diluted with 300 ml of acetone and filtered through Celite, and the reddish filtrate was diluted with 300 ml of MeOH saturated with NH_3 and adjusted to an apparent pH of 8–9 by bubbling with NH_3. The white precipitate was collected and hydrolyzed with 50 ml of 1 *N* HCl on a steam bath for 30 min. 1-Hydroxy-7-methylhypoxanthine was isolated by chromatography over Dowex-50 [H^+], eluting with water: yield 1.7 g (41%); mp >290° dec; nmr (DMSO-d_6) δ 4.05 (s, 3, NCH_3), 8.18 (s, 1), 8.40 (s, 1).

A sample for analysis was obtained by dissolving a sample in aqueous NH_4OH, treating it with charcoal, filtering, and then acidifying with HOAc and chilling. Colorless crystals were collected and dried at 80° under vacuum over P_2O_5.

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.09; H, 3.60; N, 33.66.

pH	Charge	λ_{max}, nm ($\epsilon \times 10^{-3}$)	Apparent pK_a
0	+	251 (8.4)	
			1.6 ± 0.1
3.6	0	256 (7.9)	
			5.63[a] ± 0.02
9	−	230.5 (35.3), 272 (6.4)	

[a] Titrimetrically.

1-Methoxy-7-methylhypoxanthine (6).—To a solution of 333 mg (2.0 mmol) of 1-hydroxy-7-methylhypoxanthine and 276 mg (2.0 mmol) of finely powdered anhydrous K_2CO_3 in 50 ml of *N*,*N*-dimethylacetamide was added an excess, over 300 mg, of CH_3I, and the mixture was stirred overnight. Tlc ($CHCl_3$–CH_3OH, 9:1 v/v) showed the disappearance of starting material, R_f 0.0, and the appearance of a new spot with R_f 0.8. The yellow mixture was filtered and the filtrate was treated with charcoal and evaporated to dryness under vacuum. The 1-methoxy-7-methylhypoxanthine was chromatographed over a silica gel column, 100–200 mesh, with $CHCl_3$–CH_3OH, (9:1) v/v, yield 240 mg (66%), mp 190–191°. The column eluate was monitored (ISCO) until all 6 had been eluted. The analytical sample was obtained after recrystallization from MeOH and it was dried at 80° over P_2O_5 under vacuum: nmr (D_2O) δ 4.02 (s, 3, NCH_3), 4.12 (s, 3, OCH_3), 8.13 (s, 1), and 8.50 (s, 1); λ_{max} (pH 9) 213 nm (ϵ 24,900), 256 (7500); (pH 0) 250 (8200).

Anal. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.09. Found: C, 46.69; H, 4.46; N, 31.15.

Registry No.—**1**, 5193-34-0; **2**, 40387-36-8; **6**, 40387-37-9; **12**, 5383-06-2; adenosine 1-oxide, 146-92-9; CH_3I, 74-88-4.

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(36) R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).

(37) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

(38) D. D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).

(39) H. Kawashima, T. Meguro, and I. Kumashiro, *Bull. Chem. Soc. Jap.*, **39**, 633 (1966).

(40) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Amer. Chem. Soc.*, **80**, 2755 (1958).

(41) H. Sigel and H. Brintzinger, *Helv. Chim. Acta*, **48**, 433 (1965).

The Structure of Daphmacropodine, a New Alkaloid from *Daphniphyllum macropodum* Miquel, and Its Chemical Conversion into Daphmacrine

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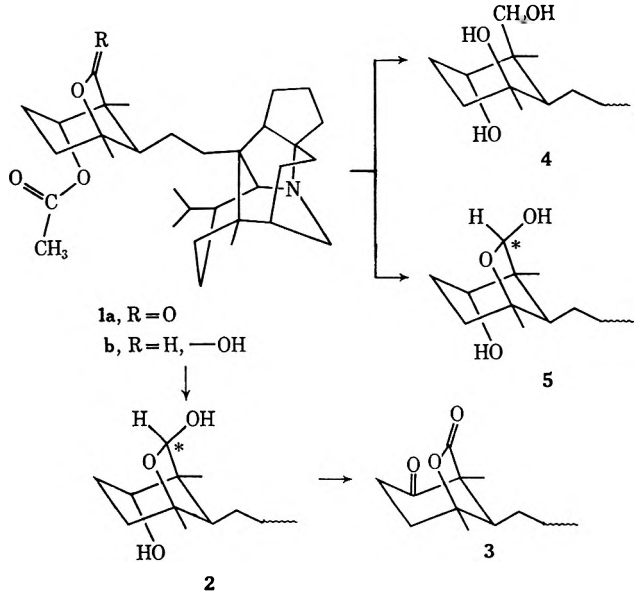
In previous publications,[1a-d] we have reported the isolation from the bark of *Daphniphyllum macropodum* Miquel (Euphorbiaceae) of eight new alkaloids, *viz.*, daphnimacropine,[1a] macrodaphnidine (yuzurimine),[1b,2] daphniphyllamine (daphniphylline),[1b,2] daphmacrine,[1b,d,3] macrodaphniphyllidine,[1b] macrodaphnine,[1b,c] macrodaphniphyllamine,[1b] and daphmacropodine,[1b] and have elucidated the structures of all of them, except for daphmacropodine. These alkaloids possess unusual structures and apparently belong to a new group of alkaloids.

Chart I



The present paper describes the structure of the remaining alkaloid, daphmacropodine,[4] from this same plant, and its chemical interrelation with daphmacrine (**1a**).[1b,d,3]

Daphmacropodine (**1b**), $C_{32}H_{51}O_4N$, crystallized from acetone to show mp 214°, $[\alpha]D$ +4.9° (*c* 1.11, $CHCl_3$), hydrobromide mp 215–218° (from acetone). It showed an ester carbonyl band at 1740 cm^{-1} in the infrared spectrum. The mass spectrum gave peaks at *m/e* 513 (M^+), 498 ($M^+ - CH_3$), 470 [$M^+ - (CH_3)_2CH$], 453 ($M^+ - CH_3COOH$), 430, 412, 407, 392, 364, 300, 286, 272, and 230. The fragment peaks at *m/e* 286, 272, and 230 are typical of daphniphyllamine and related alkaloids.[1b] The nmr spectrum ($CDCl_3$, 100 Hz) displayed signals at τ 9.10 (3 H) and 8.99 (3 H) (doublets, J = 6.5 Hz, one isopropyl), 9.02 (3 H), 8.96 (3 H), and 8.68 (3 H) (singlets, three quaternary methyls), 7.92 (3 H, singlet, one acetoxyl), and 5.26 (1 H, triplet, J_{AX+BX} = 8 Hz, equatorial proton adjacent to the acetoxyl group). A one-proton singlet at τ 5.22 suggested the presence of a hemiacetal grouping [HO(H)C(OC)R].[5]

Mild alkaline hydrolysis of daphmacropodine (**1b**) and subsequent chromatography afforded a deacetyl derivative (**2**), $C_{30}H_{49}O_3N$. The hemiacetal structure shown in **1b** was confirmed by oxidation of this derivative with Jones reagent[6] at 0°. The crude product obtained was converted into the hydrochloride and chromatography furnished a pure keto lactone (**3**) as the hydrochloride, ir (KBr) 1766 (γ-lactone) and 1716 cm^{-1} (six-membered ketone). Reduction of daphmacropodine (**1b**) with lithium aluminum hydride in ether–dioxane yielded a triol (**4**), $C_{30}H_{51}O_3N$, mp 238.5–239° (from ethanol–acetone). Chromatography of the mother liquors of this triol[7] yielded a second alcohol (**5**), $C_{30}H_{49}O_3N$, mp 204–205° (from acetone). The infrared spectrum of this alcohol proved to be different from that of the deacetyl derivative **2** obtained by alkaline hydrolysis of daphmacropodine (**1b**), and it is assumed that they are anomers which differ in the configuration at the asterisked carbon.[8] On reduction with lithium aluminum hydride, daphmacropodine (**1b**) yielded the same two alcohols, **4** and **5**.

The above experimental results revealed the hemiacetal nature and also the close relation of daphmacropodine (**1b**) to daphmacrine (**1a**), whose lactonic structure and absolute configuration have been established by X-ray crystallographic analysis.[1d,3]

The crude product from Jones oxidation[6] of daphmacropodine (**1b**) was converted into a lactone hydrobromide, mp >300° (*ca.* 315°) (from acetone–ether), which was identical with daphmacrine (**1a**) hydrobromide.

Experimental Section

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer

(1) (a) N. Kamijo, T. Nakano, S. Terao, and K. Osaki, *Tetrahedron Lett.*, 2889 (1966); (b) T. Nakano and Y. Saeki, *ibid.*, 4791 (1967); (c) T. Nakano and B. Nilsson, *ibid.*, 2883 (1969); (d) T. Nakano, Y. Saeki, C. S. Gibbons, and J. Trotter, *Chem. Commun.*, 600 (1968).

(2) N. Sakabe, H. Irikawa, H. Sakurai, and Y. Hirata, *Tetrahedron Lett.*, 963, 965, 5363, 6309 (1966); *ibid.*, 553 (1967).

(3) Note that the absolute configuration of this alkaloid has also been established: C. S. Gibbons and J. Trotter, *J. Chem. Soc. B*, 840 (1969).

(4) A brief description of this alkaloid has been presented at the 5th International Symposium on the Chemistry of Natural Products, London, July 1968. Also see ref 1b.

(5) D. Lavie, M. K. Jain, and I. Kirson, *J. Chem. Soc. C*, 1347 (1967).

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(7) T. Nakano and S. Terao, *J. Chem. Soc.*, 1417 (1966).

(8) The relative configurations at this carbon of these two anomers and daphmacropodine (**1b**) itself have not been studied because of the small amounts available.

337 spectrometer for potassium bromide disks. Rotations were measured at 26° with a Kreis polarimeter 0.01 for solutions in chloroform. Nmr spectra were obtained for solutions in deuteriochloroform with a Varian HA-100 spectrometer, with tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU 6E at 70 eV using a direct inlet system. Thin layer chromatograms were prepared on silica gel G and developed with chloroform–ethylamine (usually 100:2–5, v/v); the spots were observed either by spraying with Dragendorff's reagent or by exposure to iodine vapor. All extracts were dried over anhydrous sodium sulfate or magnesium sulfate before evaporation. Microanalyses were carried out by A. Bernhardt, Microanalytical Laboratory, 5251 Elbach über Engelskirchen, West Germany.

Alkaline Hydrolysis of Daphmacropodine (1b).—The alkaloid (100 mg) was heated under reflux with 1 *N* methanolic sodium hydroxide (10 ml) for 1.5 hr. After addition of water, the product was extracted with chloroform and the chloroform extract was washed with water, dried, and evaporated. The crude product (92 mg) thus obtained was chromatographed over Merck standardized alumina (activity II–III). Elution with 2–5% methanol in chloroform yielded the deacetyl derivative **2** (35 mg). After recrystallization from acetone, it showed mp 130–135°.

Anal. Calcd for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.15; H, 10.26; N, 3.10.

Oxidation of the Deacetyl Derivative 2 with Jones Reagent.[6]—The deacetyl derivative **2** (50 mg) in acetone (3 ml) was oxidized with stirring at 0° with Jones reagent (0.08 ml). After 10 min, methanol was added to destroy the excess reagent. The solution was diluted with water and basified with aqueous ammonia, and the product was extracted with chloroform. Washing of the chloroform extract with water, drying, and evaporation yielded a crude product (49 mg). This was converted into the hydrochloride and purified by chromatography over Mallinckrodt silicic acid (3 g). Elution with 10% methanol in chloroform yielded a keto lactone (**3**) (25 mg) as the hydrochloride, mp 179–180° (from acetone–ether), mass spectrum *m/e* 467 (M^+ − HCl), 452, 424, 369, 302, 290, 286, 272, and 230.

Anal. Calcd for $C_{30}H_{45}O_3N \cdot HCl$: C, 71.40; H, 9.19; N, 2.77. Found: C, 71.25; H, 8.89; N, 2.51.

Reduction of Daphmacropodine (1b) with Lithium Aluminum Hydride.—A solution of the alkaloid (300 mg) in anhydrous dioxane (6 ml) was added dropwise at room temperature to a stirred suspension of lithium aluminum hydride (150 mg) in anhydrous ether (80 ml). After 4 hr, a mixture of ethyl acetate (5 ml) and chloroform (15 ml) was added and the solution was stirred for 40 min. Then ethyl acetate (5 ml) saturated with water (1 ml) was added and stirring was continued for a further 20 min. The solution was filtered and the filtrate was concentrated *in vacuo* and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to yield crystals (290 mg) which gave two spots on tlc. Purification by recrystallization from ethanol–acetone yielded a triol (**4**) (139 mg), mp 238–239°, mass spectrum *m/e* 473 (M^+), 455 ($M^+ - H_2O$), 440 [$M^+ - (H_2O + CH_3)$], 424 [$M^+ - (H_2O + CH_2OH)$], 412 {$M^+ - [H_2O + (CH_3)_2CH]$}, 372, 300, 286, 272, and 230.

Anal. Calcd for $C_{30}H_{51}O_3N$: C, 76.06; H, 10.85; N, 2.96. Found: C, 75.89; H, 10.66; N, 2.79.

The mother liquor of the above triol was chromatographed on neutralized Mallinckrodt silicic acid[7] (10 g). Elution with 1–2% ethanol in chloroform yielded a second alcohol (70 mg) (**5**), mp 204–205° (from acetone), mass spectrum *m/e* 471 (M^+), 456 ($M^+ - CH_3$), 453 ($M^+ - H_2O$), 438 [$M^+ - (H_2O + CH_3)$], 428 [$M^+ - (CH_3)_2CH$], 412, 388, 306, 300, 294, 286, 272, and 230.

Anal. Calcd for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.27; H, 10.28; N, 2.69.

The ir spectrum of this alcohol was found to be different from that of the deacetyl derivative **2**.

Reduction of Daphmacrine (1a) with Lithium Aluminum Hydride.—To a stirred suspension of lithium aluminum hydride (100 mg) in anhydrous ether (10 ml) was added dropwise at room temperature a solution of the alkaloid (98 mg) in anhydrous ether (10 ml). After 1 hr, anhydrous ether (30 ml) was added and the mixture was stirred at room temperature overnight. The excess reagent was decomposed by addition of a saturated aqueous solution of sodium sulfate. After basification with aqueous ammonia, the product was extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to yield a crude product (95 mg) which gave two spots on tlc. After recrystallization from acetone, a triol (**4**) (44 mg), mp 238–239°, was separated. The mother liquor of this triol was chromatographed on neutralized silicic acid[7] and elution with 1% methanol in chloroform afforded a second alcohol (**5**) (12 mg), mp 202–203° (from acetone). These two alcohols were also obtained by the lithium aluminum hydride reduction of daphmacropodine (**1b**) (see above).

Oxidation of Daphmacropodine (1b) with Jones Reagent.[6]—The alkaloid (80 mg) in acetone (8 ml) was treated with Jones reagent (0.2 ml) at 0° for 10 min. Methanol was added to decompose the excess reagent. The solution was then basified with aqueous ammonia and the product (80 mg) was isolated in the usual way. The product was converted into the hydrobromide and purified by chromatography on Mallinckrodt silicic acid (1.0 g). Elution with 1% methanol in chloroform furnished a lactone (**1a**) as the hydrobromide (50 mg), mp >300°.

Anal. Calcd for $C_{32}H_{49}O_4N \cdot HBr$: C, 64.84; H, 8.50; N, 2.36. Found: C, 64.56; H, 8.32; N, 2.17.

Its ir spectrum was identical with that of daphmacrine hydrobromide.

Registry No.—**1a**, 19775-48-5; **1a** HBr, 39729-20-9; **1b**, 39729-21-0; **1b** HBr, 39729-22-1; **2**, 39729-23-2; **3** HCl, 39729-24-3; **4**, 39729-25-4; **5**, 39729-26-5; lithium aluminum hydride, 16853-85-3.

An Improved Synthesis of Aminoethanethiols

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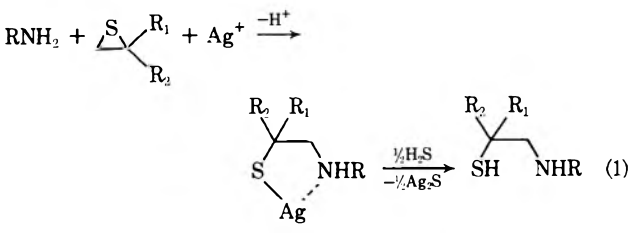
Of the variety of synthetic routes used to prepare aminoethanethiols, one of the most direct involves the addition of amines to episulfides or episulfide precursors.[1] Although this reaction is general, applying to both aromatic and aliphatic amines, it suffers from the fact that it often requires elevated temperatures in sealed tubes and that the yields are dependent on solvent polarity.[1,2a,d] A further disadvantage of this reaction is that the product aminoethanethiols are further mercaptoethylated on sulfur or nitrogen to give bismercaptoethylated products or polymers resulting from polymercaptoethylation.[2] The addition of excess amine has been successfully used to obviate these side reactions,[1,2a] but has also necessitated separating the excess amine from the product.

We have found that the mercaptoethylation of primary aliphatic amines can be carried out near room temperature with equimolar amounts of episulfide and amine in aqueous media containing amine–silver ion complex. Although only little effort has been spent



(1)

(1) D. D. Reynolds and D. L. Johnson, *Mech. React. Sulfur Compounds*, **5**, 103 (1970).

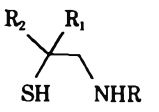
(2) (a) R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962); (b) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947); (c) N. S. Isaacs, *Can. J. Chem.*, **44**, 395 (1966); (d) E. Tobler, *Ind. Eng. Chem., Prod. Res. Develop.*, **8**, 415 (1969).

optimizing reaction conditions, aminoethanethiols have been obtained in yields of 40–90%.

The procedure involves the addition of episulfide to an aqueous mixture of silver nitrate and amine. In reactions employing equimolar concentrations of amine, episulfide, and silver ion, excess triethylamine is added to prevent precipitation of Ag_2O. The addition of episulfide to silver–amine complex is accompanied by the evolution of heat and in the absence of external cooling the temperature of the reaction mixture can rise to 50°. However, the yields of the reaction do not appear to be a function of temperature within the range of 20–50°, as shown by comparing yields for compounds **1** and **3**, which were prepared without external cooling, with **2**, **4**, and **5**, which were synthesized at 20–35°.

The advantages afforded by this method are the mild reaction conditions involved, its general application to various primary aliphatic amines, and the ease with which the product can be separated from unreacted starting material *via* its silver complex. Moreover, as seen from Table I, the method is equally applicable to mono- and disubstituted episulfides as well as ethylene sulfide.

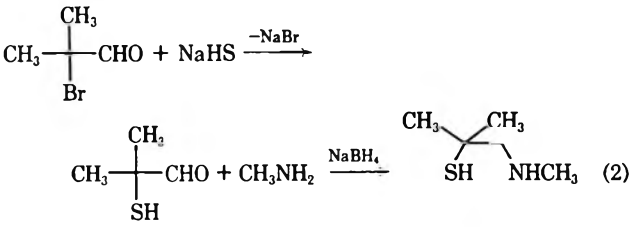
TABLE I



Compd	R	R_1	R_2	Yield, %
1	$C_{10}H_{21}$	H	H	90
2	$(CH_2)_3OCH_3$	CH_3	H	40
3	$(CH_2)_3N(n\text{-}C_4H_9)_2$	CH_3	CH_3	40
4	$C_{16}H_{33}$	CH_3	CH_3	61
5	CH_3	CH_3	CH_3	79

With these unsymmetrically substituted episulfides the question of regiospecificity arises. It is known that unsymmetrically substituted episulfides suffer nucleophilic attack at the least substituted carbon atom,[3] and there are numerous examples of this in the addition of amines to episulfides.[2b-d,4] However, electrophilic reagents lead to appreciable ring opening at both carbon centers of such compounds.[3] Moreover, sulfenyl chloride additions to olefins which are presumed to go through similar episulfonium ion intermediates also lead to products derived from attack of chloride at both carbon centers.[5] It was therefore of interest to see if the incorporation of an electrophile such as silver ion resulted in a reversal of the usual mode of episulfide ring opening by amines.

The direction of ring opening was established by comparing the product obtained from the reaction in eq 1 using isobutylene sulfide and methylamine with 1,1-dimethyl-2-methylaminoethanethiol prepared as shown in eq 2. The hydrochloride salts of both aminoethanethiols had the same ir and nmr spectra, and both disulfide dihydrochloride salts melted with decomposition at 268–270°. The mercaptoamines were converted into thiazolidines by reaction with *p*-dimethylaminobenzaldehyde and the dihydrochloride salts of these two derivatives were shown to be identical by ir, nmr, and melting point. Thus the product from the silver nitrate mediated reaction of isobutylene sulfide and methylamine was assigned structure **5**, *i.e.*, the isomer derived from amine attack at the least substituted carbon atom.[6] By analogy mercaptoethylamines **2**, **3**, and **4** were assigned structures shown in Table I.



Apparently the activation provided by silver ion in the mercaptoethylation of amines resulted in a predominance of the same isomer as obtained without silver present. Possible roles attributed to silver ion in this reaction are that it acts as an electrophile for sulfur resulting in C–S bond weakening, it coordinates to the reagents to form a kinetically active ternary complex, or it provides a more favorable free energy for the reaction by forming a stable complex with the product.[7]

Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 421 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Melting points are uncorrected and were taken in sealed capillaries on a Mel-Temp. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Isobutylene sulfide was prepared from the epoxide,[8] which in turn was purchased from Research Organic/Inorganic Corp. All other episulfides and amines were purchased from Aldrich or Eastman and used as received. *Caution!* Although aminoethanethiols prepared by this method have been distilled without incident several times, a mild explosion occurred on two occasions of continued heating of the pot residue. Incomplete removal of nitrate ion prior to distillation was presumed to be the cause. In this light it is noteworthy to mention that AgOAc has been successfully used in replacement of $AgNO_3$ for the preparation of **5**.

2-Decylaminoethanethiol (1).—To a stirring solution of 15.5 g (0.153 mol) of triethylamine in 75 ml of distilled water was slowly added a solution of 12 g (0.071 mol) of $AgNO_3$ in 20 ml of water. A small amount of black Ag_2O formed. The temperature was adjusted to 25° and 14.5 g (0.092 mol) of decylamine was added. Dropwise addition of 5 g (0.084 mol) of ethylene sulfide was accompanied by evolution of heat and formation of an insoluble yellow silver complex. After stirring for 1.5 hr the silver complex was filtered off, washed with distilled water, and suspended in 100 ml of distilled water. Hydrogen sulfide was bubbled through the vigorously stirred mixture to liberate the free mercaptoethylamine. The mixture was filtered and the Ag_2S precipitate was washed with hot ethanol. The washings were combined with the original filtrate and evaporated *in vacuo*. The residue was treated with 100 ml of water and extracted with ether. Solvent evaporation led to 16.5 g (90% yield) of product, $n^{25}D$ 1.4702 (lit.[9] $n^{25}D$ 1.4674). *Anal.* Calcd for $C_{12}H_{27}NS$: C, 66.29; H, 12.52; N, 6.44; S, 14.75. Found: C, 66.09; H, 12.38; N, 6.18; S, 14.66.

(3) N. V. Schwartz, *J. Org. Chem.*, **33**, 2895 (1968).

(4) (a) J. M. Stewart, *J. Org. Chem.*, **28**, 596 (1963); (b) R. Daniels, B. D. Martin, and B. K. Lee, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Washington, D. C., March 1962, p 33N; (c) J. B. Wright, *J. Amer. Chem. Soc.*, **79**, 1694 (1957); (d) S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **29**, 974 (1964).

(5) W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969).

(6) Private communication from Dr. J. W. Foley confirmed that Raney nickel desulfurization of the mercaptoethylation product gave methyl isobutylamine.

(7) (a) D. Hopgood and D. L. Leussing, *J. Amer. Chem. Soc.*, **91**, 3740 (1969); (b) R. Breslow and M. Schmir, *ibid.*, **93**, 4960 (1971).

(8) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947).

(9) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5126 (1961).

1-Methyl-2-(3-methoxypropylamino)ethanethiol (2).—An aqueous (260 ml) mixture of 50 g (0.29 mol) of $AgNO_3$ and 63.5 g (0.71 mol) of methoxypropylamine was made up as described above and 19 g (0.26 mol) of propylene sulfide was slowly added. An oily semisolid separated out. After stirring for 2 hr, 70% $HClO_4$ was slowly added until no further precipitation occurred. The supernatant was decanted off and the residue was washed with water until the washings were at pH 7. The free mercaptoethylamine was liberated from its silver complex as described above. Claisen distillation led to 1 g of forerun, 17 g (40% yield) of clear liquid distilling at 56° (0.95 mm), $n^{25}D$ 1.4705, and 9 g of residue. *Anal.* Calcd for $C_7H_{17}NOS$: C, 51.48; H, 10.49; N, 8.58; S, 19.64. Found: C, 51.65; H, 10.37; N, 8.58; S, 19.67.

1,1-Dimethyl-2-(3-di-*n*-butylaminopropylamino)ethanethiol (3).—An aqueous (160 ml) mixture of 34 g (0.20 mol) of $AgNO_3$, 53 g (0.53 mol) of triethylamine, and 35.3 g (0.19 mol) of di-*n*-butylaminopropylamine was made up in the usual way, and 16.5 g (0.18 mol) of isobutylene sulfide was slowly added to it. During the episulfide addition the reaction mixture became more viscous. After stirring overnight, H_2S was bubbled through the reaction mixture and the Ag_2S precipitate was filtered off. Further work-up as described above led to an oil residue. Claisen distillation of the oil residue led to 4 g of forerun distilling at 114–123° (0.45 mm), $n^{27}D$ 1.4644, 10 g distilling at 123–128° (0.5 mm), $n^{27}D$ 1.4666, and 10.5 g distilling at 128° (0.45 mm), $n^{27}D$ 1.4666. The yield based on the last two cuts was 40%. *Anal.* Calcd for $C_{15}H_{34}N_2S$: C, 65.63; H, 12.48; N, 10.20; S, 11.68. Found: C, 65.64; H, 12.22; N, 10.34; S, 11.46.

1,1-Dimethyl-2-hexadecylammoniumethanethiol Perchlorate (4).—An aqueous (300 ml) mixture of 65 g (0.38 mol) of $AgNO_3$, 105 g (1.04 mol) of triethylamine, and 77 g (0.32 mol) of hexadecylamine was made up and 31.5 g (0.36 mol) of isobutylene sulfide was slowly added. After stirring for 3.5 hr, 110 g (0.78 mol) of 70% $HClO_4$ was added. Within 10 min the mixture agglomerated. The supernatant was decanted off and 600 ml of 50% aqueous ethanol was added. The mercaptoethylamine was liberated from its silver complex with H_2S, and $HClO_4$ (about 30 g) was added until the mixture was below pH 2. After heating on the steam bath to help dissolve the product, the mixture was filtered. The Ag_2S precipitate was treated with ethanol, heated, and again filtered. Upon addition of water to the combined filtrates a white solid came out of solution which was dried over P_2O_5. The yield of crude product was 84 g (61% yield). Recrystallization from hexane–methanol and twice from ethanol gave the disulfide salt,[10] mp 224–228° dec. *Anal.* Calcd for $C_{40}H_{86}N_2S_2Cl_2O_8$: C, 55.98; H, 10.10; N, 3.27; S, 7.47; Cl, 8.26. Found: C, 56.38; H, 10.26; N, 3.59; S, 7.61; Cl, 8.02.

1,1-Dimethyl-2-methylaminoethanethiol Hydrochloride (5).—An aqueous (120 ml) mixture of 88.5 g (0.52 mol) of $AgNO_3$ and 163 g (2.10 mol) of 40% methylamine was made up and 44.5 g (0.51 mol) of isobutylene sulfide was slowly added. Toward the end of the episulfide addition a yellow solid precipitated out which congealed after 45 min of stirring. The supernatant was decanted off and the residue was washed repeatedly with water to remove excess methylamine. Aqueous HCl was added and the mercaptoethylamine was liberated from its silver complex with H_2S. The Ag_2S was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with hot $CHCl_3$, leaving behind CH_3NH_3Cl. The dried solvent was removed under reduced pressure. The resulting residue was triturated with ether to yield 62 g (79% yield) of white solid which was crystallized from dioxane–methanol:[10] mp 222–224° dec; ir (KBr) 2950, 1457 (CH), 2645, 2490, 2400, 1585 (NH_2^+), 1415 (CH_2N^+), 1390, 1365, 1175, 1162 cm^{-1} [$(CH_3)_2C$]; nmr (D_2O) δ 1.43 [6, s, $C(CH_3)_2$], 2.77 (3, s, NCH_3), 3.16 (2, s, CH_2). *Anal.* Calcd for $C_5H_{14}NSCl$: C, 38.57; H, 9.06; N, 9.00; S, 20.60. Found: C, 38.73; H, 9.35; N, 8.84; S, 20.97.

2-(*p*-Dimethylaminophenyl)-3,5,5-trimethylthiazolidine Dihydrochloride.—A mixture of 2 g (0.013 mol) of 5, 1.1 g (0.013 mol) of $NaHCO_3$, and 2 g (0.013 mol) of *p*-dimethylaminobenzaldehyde in 100 ml of 95% ethanol was refluxed through a Soxhlet extractor containing CaC_2 for an overnight period. The NaCl was filtered off and the filtrate was evaporated to dryness. The resulting oil was dissolved in absolute ethanol and the solution was made acidic with gaseous HCl. Upon cooling a yellow solid came out of solution which was recrystallized from ethanol–ether to give 2.2 g (48% yield) of white product: mp 216–217° dec; ir (KBr) 3000, 2940, 2900, 1460, 1137, 827 (CH), 2670–2300 (NH^+), 1610, 1510 cm^{-1} (aromatic); nmr (D_2O) δ 1.77, 1.80 [6, $C(CH_3)_2$], 2.93 (3, s, NCH_3), 3.40 [6, s, $N(CH_3)_2$], 3.67 (1, A of AB q, J = 12 Hz, CH_2), 4.03 (1, B of AB q, J = 12 Hz, CH_2), 5.96 (1, s, CH), and an AA'BB' pattern centered at 7.84 (4, m, C_6H_4). *Anal.* Calcd for $C_{14}H_{24}N_2SCl_2$: C, 52.00; H, 7.48; N, 8.66; S, 9.92. Found: C, 51.93; H, 7.51; N, 8.65; S, 9.78.

1,1-Dimethyl-2-methylaminoethanethiol Hydrochloride (5) by Reduction of Mercaptoisobutyraldehyde Schiff Base.—A solution of 2.5 g of $NaSH \cdot xH_2O$ in 10 ml of methanol was added to 4 g (0.026 mol) of bromoisobutyraldehyde[11] in 20 ml of methanol. After standing for 1.5 hr, 2.5 g (0.032 mol) of 40% methylamine and 20 ml of acetic acid were added and the mixture was stirred for 5 min. While cooling, 10 ml of acetic acid and 8.5 g (0.22 mol) of $NaBH_4$ were alternately added in small portions.[12] The mixture was stirred for 1.5 hr and water was added to destroy the excess $NaBH_4$. Methanol and HCl were added and the mixture was distilled until the distillate no longer showed a green flame test for boron. The remainder of the solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ was removed under vacuum and the residue was triturated with ether to give 1 g (25% yield) of crude product which was recrystallized from dioxane–methanol.

Registry No.—**1**, 5891-06-5; **2**, 39981-44-7; **3**, 39981-45-8; **4** disulfide perchlorate salt, 39981-46-9; **5** HCl, 39981-47-0; decylamine, 2016-57-1; ethylene sulfide, 420-12-2; 3-methoxypropylamine, 5332-73-0; propylene sulfide, 1072-43-1; di-*n*-butylaminopropylamine, 102-83-0; isobutylene sulfide, 3772-13-2; hexadecylamine, 143-27-1; methylamine, 74-89-5; 2-(*p*-dimethylaminophenyl)-3,5,5-trimethylthiazolidine dihydrochloride, 39981-49-2; *p*-dimethylaminobenzaldehyde, 100-10-7; bromoisobutyraldehyde, 13206-46-7.

Acknowledgment.—The authors wish to thank Mr. J. D. Gondolfe for his help in the synthesis of compound **5**.

(10) A % SH test using 2,2'-dithiodipyridine as described by D. R. Grassetti and J. F. Murray, Jr., *Arch. Biochem. Biophys.*, **119**, 41 (1967), showed that repeated recrystallization of the aminoethanethiol salt led to the disulfide salt, presumably *via* aerial oxidation.

(11) T. A. Favorskaya and D. A. Shkurgina, *J. Gen. Chem. USSR*, **25**, 713 (1955); *Chem. Abstr.*, **50**, 2427 (1956).

(12) V. J. Hruby and V. du Vigneaud, *J. Amer. Chem. Soc.*, **91**, 3624 (1969).

The Mechanism of the Robinson–Gabriel Synthesis of Oxazoles

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Received March 7, 1973

One of the most commonly used methods for the preparation of oxazoles is the Robinson–Gabriel synthesis, in which an α-acylamino ketone undergoes cyclization and dehydration on treatment with PCl_5 or a strong mineral acid.[2,3] This synthesis is especially applicable to the formation of 2,5-diaryloxazoles, compounds of current interest in our studies on the reactions of heterocyclic systems with singlet oxygen.

As pointed out by Cornforth,[4] there are two reason-

(1) NSF Predoctoral Fellow, 1970–1973.

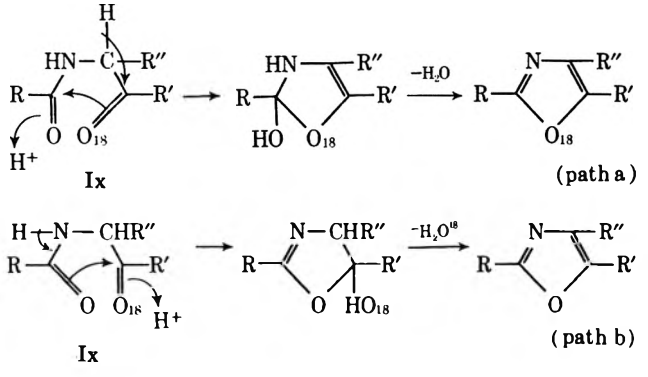
(2) R. Robinson, *J. Chem. Soc.*, **95**, 2167 (1909).

(3) S. Gabriel, *Ber.*, **43**, 1283 (1910).

(4) R. C. Elderfield, Ed., "Heterocyclic Compounds," Vol. V, Wiley, New York, N. Y., 1957, p 302.

able pathways which may be considered in viewing the mechanism of this reaction. These alternative routes, summarized in Scheme I, differ in the nature of the oxygen atom incorporated into the oxazole, *i.e.*, ketone oxygen (path a) *vs.* amide oxygen (path b). We sought to differentiate between these two possibilities using oxygen-18 tracer methods in conjunction with high-resolution mass spectrometry.

SCHEME I



For these studies, we prepared α-benzamidopropiophenone[5,6] (Ix) with an oxygen-18 label in the keto portion of the molecule, and, in a second case (Iy),

with an oxygen-18 label in the amide carbonyl group.

To incorporate the labeled oxygen into Ix, the keto amide was allowed to equilibrate with 30% $H_2{}^{18}O$ in anhydrous THF with no catalyst present.[7] It is well known that under these conditions the ketone oxygen undergoes rapid exchange with the labeled water while the amide oxygen undergoes no exchange.[8] Mass spectrometric analysis indicated 26.7 ± 0.5% label in the keto oxygen. Cyclization with concentrated sulfuric acid afforded 2,5-diphenyl-4-methyloxazole,[6] the mass spectrum of which showed 0.2 ± 0.5% label present, thereby indicating that the amide oxygen is incorporated, and the ketone oxygen expelled in the formation of the oxazole, in accord with path b.

In an independent proof of mechanism, α-aminopropiophenone[5] was allowed to react with O-18 enriched benzoyl chloride[9] (from *ca.* 9.5% doubly labeled benzoic acid), yielding Iy with 9.6 ± 0.5% ^{18}O in the amide oxygen. Cyclization as above gave 2,5-diphenyl-4-methyloxazole containing 9.7 ± 0.5% oxygen-18 as shown by mass spectrometric analysis. These results clearly show that in this case the amide oxygen is retained in the product, again in accord with pathway b.[10]

(5) L. Behr-Bregowski, *Ber.*, **30**, 1521 (1897).
(6) J. Lister and R. Robinson, *J. Chem. Soc.*, **101**, 1297 (1912).
(7) A. Murray and D. Williams, "Organic Syntheses with Isotopes," part III, Interscience, New York, N. Y., 1958, p 1887.
(8) W. H. Mears and H. Sobotka, *J. Amer. Chem. Soc.*, **61**, 880 (1939).
(9) Reference 7, pp 1870–1871.
(10) This is the pathway favored by Paquette in picturing the mechanism of oxazole formation by the cyclization of α-acylamino ketones. See L. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968, p 191.

Experimental Section

Ketone-^{18}O-Labeled α-Benzamidopropiophenone (Ix).—α-Benzamidopropiophenone[6,8] (1.00 g, 3.96 mmol), 30% $H_2{}^{18}O$ (0.10 ml), and 5 ml of tetrahydrofuran (distilled from lithium aluminum hydride) were refluxed for 1.5 hr. The solvent was removed *in vacuo* and the labeled keto amide was recrystallized from diethyl ether, mp 103–104° (lit. mp 104–105°[6]). The high-resolution mass spectrum shows the parent peak (*m/e* 253) with a P + 2 peak indicating an ^{18}O enrichment of 26.7 ± 0.5%.

Amide-^{18}O-Labeled α-Benzamidopropiophenone (Iy).—Aminopropiophenone stannic chloride[5] (1.82 g, 2.89 mmol of amino ketone) was suspended in 18 ml of water with stirring and ice-bath cooling. Benzoyl-^{18}O chloride[9] (1.21 g, 8.65 mmol) of *ca.* 9.5% enrichment and aqueous potassium hydroxide (5.50 g in 8 ml) were added successively, and the mixture was stirred for 0.5 hr. Ether extraction followed by drying over anhydrous magnesium sulfate, filtration, and removal of solvent yielded 0.60 g (82%) of Iy, mp 104–105°, tlc behavior identical with Ix. The high-resolution mass spectrum shows the parent peak (*m/e* 253) with a P + 2 peak having 9.6 ± 0.5% enrichment in ^{18}O.

2,5-Diphenyl-4-methyloxazole. A.—A 0.3-g portion of ketone-labeled α-benzamidopropiophenone (Ix) was added to 3 ml of concentrated sulfuric acid with stirring. After 10 min, copious quantities of water were added to the reaction mixture until the milky white product was completely precipitated. The 2,5-diphenyl-4-methyloxazole was collected by filtration and recrystallized from petroleum ether (bp 30–60°) to yield 0.20 g (72%), mp 80–81° (lit. mp 82°[6]). The high-resolution mass spectrum shows the parent peak (*m/e* 235) with a P + 2 peak having 0.2 ± 0.5% ^{18}O enrichment.

B.—A 0.5-g portion of amide-labeled α-benzamidopropiophenone (Iy) was cyclized as described previously for Ix. The oxazole obtained (81%, mp 81–82°) was analyzed by high-resolution mass spectroscopy. The parent peak (*m/e* 235) had a P + 2 peak showing an ^{18}O enrichment of 9.7 ± 0.5%.

Registry No.—Ix, 39982-24-6; Iy, 39982-25-7; 2,5-diphenyl-4-methyloxazole, 2549-31-7.

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The Reaction of Trityloxyamine with Lead Tetraacetate

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Considerable interest continues to be expressed in the generation of *O*-nitrene intermediates, although rarely has their existence been substantiated by the weight of experimental evidence.[1] A notable exception may be cited in the work of Brois,[2] who successfully trapped methoxynitrene with tetramethylethylene during the lead tetraacetate (LTA) oxidation of methoxyamine. Recently the oxidation of several *O*-arylalkylhydroxylamines with LTA has been studied by Carey[3] and Partch.[4] The suggestion by the latter author that such oxidations may involve the intermediate unstable hyponitrite esters as well as the actual isolation

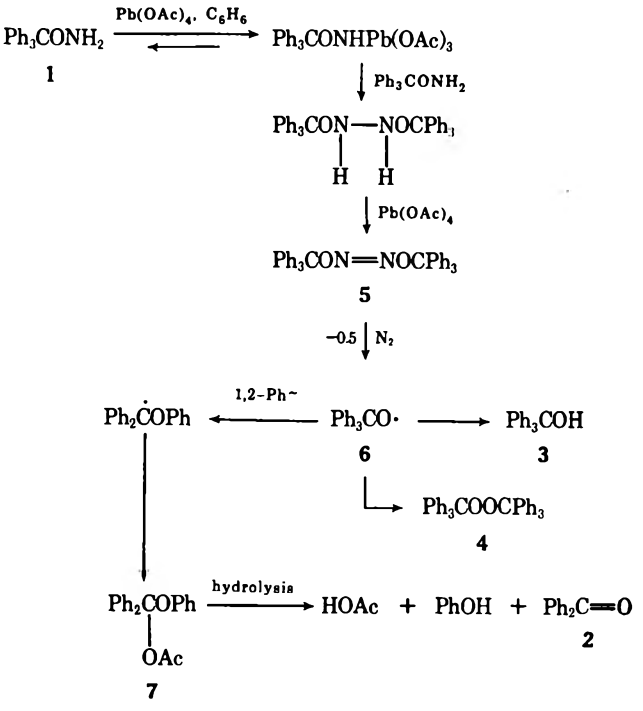
(1) J. Boyer and J. Woodyard, *J. Org. Chem.*, **33**, 3329 (1968); A. Hassner, R. Wiederkehr, and A. Kascheres, *ibid.*, **35**, 1962 (1970).
(2) S. Brois, *J. Amer. Chem. Soc.*, **92**, 1079 (1970).
(3) F. Carey and L. Hayes, *J. Amer. Chem. Soc.*, **92**, 7613 (1970).
(4) R. Partch, B. Stokes, D. Bergman, and M. Budnik, *Chem. Commun.*, 1504 (1971).

of such a hyponitrite ester in the oxidative bromination of ethoxyamine[5] prompts the report herein of the results regarding the LTA oxidation of the recently[6] prepared trityloxyamine (1).

When a mixture of 1 and LTA was stirred in anhydrous benzene for 1 hr at room temperature followed by the usual work-up, vpc analysis revealed the presence of benzophenone (12%) and triphenylcarbinol (75%). That the benzophenone (2) did not derive from the decomposition of triphenylcarbinol (3) under vpc conditions was indicated by the appearance of the absorption band at 1667 cm^{-1} in the infrared spectrum of the crude reaction mixture prior to work-up. In a related experiment, the crude reaction mixture was simply filtered from the precipitated inorganic salts and after removal of the solvent the residue was chromatographed without any prior aqueous work-up. Initial elution yielded a mixture of 2 (12%) and triphenylmethyl peroxide (4) (8%) while further elution yielded 3 (71%). Triphenylmethyl peroxide (4) was identified by a comparison of its melting point and infrared spectrum with those of an authentic sample.[7] That 3 is not derived *via* a concerted fragmentation–recombination pathway from hydrolysis of trityl acetate was substantiated by two experimental observations. First, control experiments demonstrated the stability of an authentic sample of trityl acetate[8] under the work-up conditions; second, the attempt to trap the possible trityl carbonium ion intermediate when the reaction was conducted in the presence of excess added sodium azide was unsuccessful.[9]

A final and mechanistically significant experiment was conducted at Dry Ice–acetone temperature in the presence of 2,3-dimethylbutadiene in an attempt to trap the oxynitrene intermediate from 1. The latter was completely unsuccessful; however, triphenylmethyl peroxide (4) (85%) was successfully isolated. The mechanistic significance of the isolation of 4 in high yield at −78° is that it offers the first reported experimental evidence that the postulated[3,4] precursor to the formation of alcohols from LTA and O-substituted hydroxylamines is an oxy radical (RO·) 6. It is therefore suggested that the observed products arise from the homolytic decomposition of the presumably very unstable[10] hyponitrite ester[7] 5 to yield the trityloxy radical 6 [it is worth mentioning that the reaction of trityl chloride and silver hyponitrite in benzene was demonstrated by Spielman[7] to produce nitrogen and triphenylmethyl peroxide (4), the latter arising from the decomposition of the unstable intermediate hyponitrite ester 5]. The trityloxy radical 6 may either couple to produce 4, abstract hydrogen to give 3, or suffer carbon-to-oxygen phenyl migration[11] to yield the labile ketal acetate (7) known to hydrolyze to 3, phenol, and acetic acid (Scheme I).

SCHEME I



Experimental Section

All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Spectracord infrared spectrophotometer. The nmr spectra were determined with a Varian A-60 instrument. Gas chromatographic analyses were performed on an F & M Scientific Model 720 dual column temperature programmed gas chromatograph.

Trityloxyamine (1) was prepared according to the procedure of Lutz:[6] mp 80–82° (lit.[6] mp 83–85°); ir (CCl_4) 3320 and 3240 cm^{-1}; nmr (CCl_4) τ 2.6–3.2 (m, 15 H), 5.4 (s, 2 H).

Reaction of LTA with Trityloxyamine (1).—Into a 300-ml three-necked round-bottom flask equipped with a dropping funnel, reflux condenser, and magnetic stirrer was placed 4.90 g (0.01 mol) of LTA. The system was evacuated for 2 hr on a vacuum pump, after which 100 ml of sodium-dried benzene was introduced. The entire reaction was conducted under a nitrogen atmosphere. After the dropwise addition of a solution of 1 (2.75 g, 0.01 mol) in benzene (100 ml), the reaction mixture was stirred at room temperature[12] for 1 hr. The mixture was filtered and the benzene solution was washed with ethylene glycol, water, aqueous sodium carbonate, and water and dried ($MgSO_4$). Removal of the benzene under vacuum followed by treatment of the residue with CCl_4 yielded 1.95 g (0.0075 mol, 75%) of 3, mp 158–160°, undepressed by admixture with an authentic sample, ir (KBr) 3480 and 3610 cm^{-1}.

In a second run, the benzene solution was concentrated to 10 ml and aliquots were subjected to vpc analysis (2 ft × 0.25 in. UC-W 98 silicone gum rubber column at 230°). Two peaks were observed; the first corresponded to 2 (12%) and the second to 3 (75%). The assignments were confirmed by selective peak enhancement upon coinjection with authentic samples. In addition the first peak 2 was collected, ir (CCl_4) 1667 cm^{-1}.

In another experiment, 1 (350 mg, 1.25 mmol) was treated with LTA in the presence of a 100-fold molar excess of sodium azide. The reaction mixture was not subjected to any work-up, but was filtered, the benzene was removed, and the residue was dissolved in benzene (5 ml) and chromatographed on 50 g of neutral alumina. Elution with 50% (v/v) hexane–benzene yielded a solid mixture of 2 and 4. The solid mixture was washed with cold ether and the insoluble portion was filtered, yielding 50 mg (0.096

(5) L. Seed, British Patent 795,824 (1959); *Chem Abstr.*, **53**, 219*f* (1959).
(6) W. B. Lutz, *J. Org. Chem.*, **36**, 3835 (1971).
(7) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1955, p 81; M. A. Spielman, *J. Amer. Chem. Soc.*, **57**, 1117 (1935).
(8) M. Gomberg, *Chem. Ber.*, **35**, 1835 (1902).
(9) I. Necsoiu and C. D. Nenitzescu, *Chem. Ind. (London)*, 377 (1960).
(10) For general references to hyponitrite chemistry see M. Hughes, *Quart. Rev.*, **22**, 1 (1968); J. Boyer and J. Woodyard, *J. Org. Chem.*, **33**, 3329 (1968); J. Cooley, M. Mosher, and M. Khan, *J. Amer. Chem. Soc.*, **90**, 1867 (1968).
(11) W. H. Starnes Jr., *J. Amer. Chem. Soc.*, **90**, 1807 (1968); P. D. Bartlett and J. D. Cotman Jr., *ibid.*, **72**, 3095 (1950); R. O. C. Norman and R. A. Watson, *J. Chem. Soc.*, 184 (1968); M. S. Kharasch, A. C. Poshkus, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 1485 (1951); M. S. Kharasch, A. Fono, and W. Nudenberg, *ibid.*, **15**, 763 (1950).

(12) When 1 and LTA were refluxed together in benzene for 1 hr followed by the usual work-up a 30% yield of 3 resulted, and the remaining oil was nondistillable; however, a crude ir spectrum indicated a small amount of 2.

mmol, 8%) of 4, mp 179–181°, ir (KBr) 1155 and 874 cm^{-1}. Removal of the ether yielded approximately 27 mg (0.15 mmol, 12%) of 2, ir (CCl_4) 1667 cm^{-1}. Finally, elution with benzene gave 247 mg (0.95 mmol, 71%) of 3, mp 158–160°.

In a final experiment a magnetically stirred mixture consisting of 13.1 g (0.16 mol) of freshly distilled 2,3-dimethylbutadiene,[13] 4.87 g (0.01 mol + 10% excess) of LTA from which the acetic acid had previously been removed *in vacuo*, and 36 ml of methylene chloride was immersed in a Dry Ice–acetone bath and maintained under a nitrogen atmosphere. A solution of 2.75 g (0.01 mol) of 1 in 25 ml of methylene chloride was then admitted dropwise during a period of 30 min. The brown reaction mixture was stirred for 1 hr, at the end of which time the color had entirely discharged. Work-up of the reaction mixture in the usual aqueous fashion, followed by the removal of the solvent and excess 2,3-dimethylbutadiene *via* rotary evaporator, yielded as the major product 2.20 g (0.0043 mol, 85%) of a crystalline white solid, mp 179–183°. The white solid exhibited the same melting point behavior noted with authentic trityl peroxide,[7] and, analogously, was also insoluble in either cold benzene or cold ether but readily soluble in cold concentrated sulfuric acid. In the latter solvent, an orange-red solution resulted. The spectral (ir, nmr) properties of the product were identical with those of authentic trityl peroxide.[7] Recrystallization of the solid from benzene–chloroform gave the analytical sample.

Anal. Calcd for $C_{38}H_{30}O_2$: C, 88.00; H, 5.79. Found: C, 87.51; H, 6.02.

Registry No.—1, 31938-11-1; 2, 119-61-9; 3, 76-84-6; 4, 596-30-5; LTA, 546-67-8.

(13) C. F. H. Allen and A. Bell, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 312.

Amine–Hydroperoxide Adducts. Use in Synthesis of Silyl Alkyl Peroxides

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Silyl alkyl peroxides (compounds containing one or more Si–O–O–C bonds) were first reported by Buncel and Davies in 1956.[1] Subsequently, a number of publications were released concerning the preparation and characterization.[2–5]

The general method for the preparation of silyl alkyl peroxides involves reaction of an alkyl, aryl, or aralkyl hydroperoxide with a chlorosilane.

$$R_{4-n}SiX_n + nR'OOH \longrightarrow R_{4-n}Si(OOR')_n + nHX$$

n = 1, 2, 3, 4
R, R′ = alkyl, aralkyl, aryl
X = Cl, Br, F

Such reactions are usually carried out in an inert solvent in the presence of an acid acceptor, pyridine for instance. Much lower yields result in the absence of acid acceptors.[2]

A less frequently used method involves the condensation of trimethylsilyl alkyl amines with *tert*-butyl hydroperoxide. A 20% yield of trimethyl(*tert*-butylperoxy)-silane has been reported.[5]

Generally speaking, there are two drawbacks to these methods: (1) the yields are fairly low, especially for silyl alkyl peroxides containing more than one peroxy group; (2) the silyl alkyl peroxides made must be purified by distillation or other suitable means subsequent to the preparation step.

Results and Discussion

Synthesis by the Amine–Hydroperoxide Adduct Method.—The amine–hydroperoxide adduct synthesis of silyl peroxides requires two steps: (1) preparation of the amine–hydroperoxide adduct; (2) reaction of the adduct with chlorosilane in an inert solvent. Preparation of the adduct is carried out by mixing stoichiometric amounts of a suitable amine and the hydroperoxide in an inert solvent.[6] Assuming that the proper solvent has been selected, the crystalline adduct separates and can be collected by filtration.

Not all amines form adducts with hydroperoxides. For the majority of our work we have used 1,4-diazabicyclooctane (Dabco). The selection of Dabco resulted when other amines examined failed one or more of the following criteria: (1) the adduct must be a solid at the reaction temperature; (2) the solid adduct should be fairly insoluble in the solvent of choice; (3) the amine should not be oxidized by any of the reactants or products.

Primary and secondary amines were largely ruled out by 3. The convenience of operating at ambient temperatures, or slightly above, eliminated those amines which gave insoluble adducts only at lower temperatures.

No compromises were required when Dabco was used as the adduct amine. Both nitrogens of Dabco are involved and the resulting adduct contains 2 mol of hydroperoxide/mol of Dabco. The same solvent used for adduct preparation may be used for the halosilane reaction. The reaction is exothermic and usually complete within minutes. Once the Dabco hydrochloride is removed by filtration, solvent evaporation produces very pure silyl alkyl peroxide.

Hexamethylenetetramine (Hexa) also formed solid *tert*-butyl or cumyl hydroperoxide adducts. Unlike Dabco, only one nitrogen was involved in the Hexa adduct. When treated with halosilanes, poor yields, typically below 50%, of silyl alkyl peroxides were obtained. Reasoning that the remaining nitrogens were involved, calcium chloride was introduced into the reaction medium prior to the addition of halosilane to complex and nitrogens not involved in adduct formation. Under these conditions, high yields of product were obtained. Other metal salts (Ba^{2+}, Mg^{2+}) capable of complexing nitrogen were used successfully. Metals which did not complex had no effect.

Tables I–IV list the silyl alkyl peroxides prepared using the amine–hydroperoxide adduct technique. For convenience they are grouped according to the number of alkylperoxy substituents on silicon. References are given, where available, to those compounds appearing in the literature previously along with their reported yields.[7–9]

(1) E. Buncel and A. G. Davies, *Chem. Ind. (London)*, 1052 (1956).
(2) A. G. Davies and E. Buncel, British Patent 827,366 (Feb 3, 1960).
(3) H. Jenkner, U. S. Patent 2,997,497 (Aug 22, 1961).
(4) G. Sosnovsky and J. H. Brown, *Chem. Rev.*, **66**, 529 (1966).
(5) R. A. Pike and L. H. Shaffer, *Chem. Ind. (London)*, 1294 (1957).
(6) A. A. Oswald, U. S. Patent 3,236,850 (Feb 22, 1966).
(7) A. K. Litkovets and T. I. Yurzhenko, *Dokl. Akad. Nauk SSSR*, **142**, 1316 (1962).
(8) T. I. Yurzhenko and A. K. Litkovets, *ibid.*, **136**, 1361 (1961).
(9) E. Buncel and A. G. Davies, *J. Chem. Soc.*, 1550 (1958).

TABLE I

MONOPEROXYSILANE

Registry no.	Compd	Yield, % (lit.)	Dec temp, °C	Physical characteristics, lit.	O–O frequency in the ir, cm^{-1}	Characteristic nmr signals,[f] δ
3965-63-7	Trimethyl(*tert*-butylperoxy)silane[a]	91 (54–59)	114 (boiling)	Colorless liquid, bp 41° (41 mm)[g]	906 (m)	0.1 (s, 9, trimethylsilyl), 1.15 (s, 9, *tert*-butyl)
18057-16-4	Trimethyl(α,α-dimethylbenzylperoxy)silane[b]	75 (53)	176	Colorless liquid, bp 43° (0.05 mm)[g]	905 (m)	0.13 (s, 9, trimethylsilyl), 1.55 (s, 6, isopropyl)
2097-21-4	Triethyl(*tert*-butylperoxy)silane	74	175	Colorless liquid, bp 39° (0.05 mm)[h]	903 (w)	0.92 (t, 9, methyl), 1.18 (s, 9, *tert*-butyl)
39809-93-3	Triethyl(α,α-dimethylbenzylperoxy)silane	80	167	Colorless liquid	909 (m)	0.88 (t, 9, methyl), 1.54 (s, 6, isopropyl)
39809-94-4	Tri-*n*-butyl(*tert*-butylperoxy)silane	95	170	Colorless liquid	903 (w)	0.90 (t, 9, methyl), 1.21 (s, 9, *tert*-butyl)
39809-95-5	Tri-*n*-butyl(α,α-dimethylbenzylperoxy)silane	95	157	Colorless liquid	902 (vw)	0.90 (t, 9, methyl), 1.56 (s, 6, isopropyl)
25836-01-5	Allyldimethyl(*tert*-butylperoxy)-silane[c]	95	178	Colorless liquid	927 (w)	0.13 (s, 6, dimethylsilyl), 1.16 (s, 9, *tert*-butyl)
39809-97-7	Vinyldiphenyl(α,α-dimethylbenzylperoxy)silane	92	155	Colorless liquid	900 (w)	1.52 (s, 6, isopropyl), 6.2 (m, 3, vinyl), 7.36 (m, 5, phenyl), 7.65 (m, 10, phenylsilyl)
39809-98-8	Chloromethyldimethyl(α,α-dimethylbenzylperoxy)silane	95	172	Slightly yellowish liquid	903 (m)	0.27 (s, 6, dimethylsilyl), 1.56 (s, 6, isopropyl), 2.82 (s, 2, methylene)
39809-99-9	Dimethylphenyl(α,α-dimethylbenzylperoxy)silane[d]	93	215	Colorless liquid	902 (w)	0.42 (s, 6, dimethylsilyl), 1.47 (s, 6, isopropyl)
39810-00-9	Methyldiphenyl(α,α-dimethylbenzylperoxy)silane	93	177	Colorless liquid	902 (w)	0.70 (s, 3, methylsilyl), 1.50 (s, 6, isopropyl)
18751-58-1	Triphenyl(*tert*-butylperoxy)silane[e]	95 (80)	205	White crystal of mp 62°, 50°[g]	902–920 (vw)	1.13 (s, 9, *tert*-butyl), 7.45 (m, 15, triphenylsilyl)
31731-51-8	Triphenyl(α,α-dimethylbenzylperoxy)silane	70	220	White crystal of mp 72°	904 (vw)	1.51 (s, 6, isopropyl), 7.45 (m, 15, triphenylsilyl), 7.75 (m, 5, phenyl)

[a] Calcd for $C_7H_{18}O_2Si$: C, 51.8; H, 11.2 Found: C, 52.03; H, 11.27. [b] Calcd for $C_{12}H_{20}O_2Si$: C, 64.25; H, 8.92. Found: C, 63.95; H, 8.88. [c] Calcd for $C_9H_{20}O_2Si$: C, 57.44; H, 10.64. Found: C, 57.16; H, 10.57. [d] Calcd for $C_{17}H_{22}O_2Si$: C, 69.23; H, 7.69. Found: C, 68.92; H, 7.87. [e] Calcd for $C_{22}H_{24}O_2Si$: C, 73.07; H, 7.69. Found: C, 72.79; H, 7.82. [f] m = multiple signals. [g] Reference 9. [h] Reference 4.

TABLE II

BISPEROXYSILANE

Registry no.	Compd	Yield, % (lit.)	Dec temp, °C	Physical characteristics, lit.	O–O frequency in the ir, cm^{-1}	Characteristic nmr signals, δ
10196-44-8	Dimethylbis(*tert*-butylperoxy)silane[a]	76	185	Colorless liquid	910 (m)	0.24 (s, 6, dimethylsilyl), 1.22 (s, 18, *tert*-butyl)
31602-49-0	Dimethylbis(α,α-dimethylbenzylperoxy)silane	85	142	Colorless liquid	913 (m)	0.23 (s, 6, dimethylsilyl), 1.58 (s, 12, isopropyl)
18027-26-4	Allylmethylbis(*tert*-butylperoxy)silane	90 (40)[d]	170	Colorless liquid, bp 31° (0.1 mm)[e]	900–930 (m)	0.26 (s, 3, methylsilyl), 1.25 (s, 18, *tert*-butyl), 1.81 (d, 2, methylenesilyl)
18002-70-5	Vinylmethylbis(*tert*-butylperoxy)silane[b]	92 (57)[f]	170	Colorless liquid, bp 90° (20 mm)[g]	910 (m)	0.24 (s, 3, methylsilyl), 1.25 (s, 18, *tert*-butyl)
39810-07-6	Vinylphenylbis(*tert*-butylperoxy)silane	95	137	Colorless liquid	905–925 (m)	1.25 (s, 18, *tert*-butyl), 6.23 (m, 3, vinyl), 7.57 (m, 5, phenyl)
15188-08-6	Diphenylbis(*tert*-butylperoxy)silane[c]	89	165	Colorless liquid, bp 110° (0.001 mm)[d]	905	1.21 (s, 18, t-butyl), 7.50 (m, 10, phenyl)

[a] Calcd for $C_{10}H_{24}O_4Si$: C, 50.85; H, 10.17. Found: C, 51.09; H, 10.46. [b] Calcd for $C_{11}H_{24}O_4Si$: C, 53.23; H, 9.68. Found: C, 51.71; H, 9.39. [c] Calcd for $C_{20}H_{28}O_4Si$: C, 66.67; H, 7.78. Found: C, 64.97; H, 7.49. [d] Reference 9. [e] Reference 7. [f] Reference 10. [g] Reference 8.

Most of the silyl alkyl peroxides exhibit characteristic O–O absorption bands in the infrared.[10] Monoperoxysilanes usually show a weak band near 905 cm^{-1}. With increasing alkylperoxy substitution on silicon, both frequency and intensity are increased. Furthermore, two overlapping bands located between 900 and 940 cm^{-1} have been observed for most of the multiply substituted alkylperoxy silanes. Along with the infrared data, nmr data are included in Tables I–IV.

As might be expected, increasing the number of alkylperoxy substituents decreases the thermal stability of the silyl alkyl peroxides. Using a qualitative test in which peroxides are examined for the temperature at which the onset of rapid gas evolution occurs, compounds of general formula $(CH_3)_nSi(OO\text{–}cumyl)_{4-n}$ gave decomposition points of 176, 142, 100, <100° as n increased from 1 to 4. A similar trend was measured when *tert*-butyl was substituted for cumyl.

(10) A. Simon and H. Arnold, *J. Prakt. Chem.*, (4) **8** (5–6), 241 (1959).

Experimental Section

Dabco-*tert*-Butyl Hydroperoxide Adduct.—Syntheses of both the titled adduct and the Dabco–cumyl hydroperoxide adduct were carried out according to the literature procedures[6] without modification.

Hexa-*tert*-Butyl Hydroperoxide Adduct.—To a solution containing 60 parts of *tert*-butyl hydroperoxide in 500 parts of hexane was added 43.5 parts of Hexa (Union Carbide Hexa, purity 99%). The slurry was stirred for 1 hr at room temperature. The white crystals were removed by filtration. Upon evaporating the filtrate an additional quantity was obtained. The total yield was 78 parts, corresponding to 100% theoretical. The salt decomposed without melting at 73° (lit. mp 74° dec).[6] Spectroscopic data showed the product to be a Hexa-*tert*-butyl hydroperoxide (1:1) adduct rather than the 1:2 adduct reported previously:[6] ir (KBr) 847 cm^{-1} (weak, peroxide); nmr ($CDCl_3$) δ 1.25 (t, 9, *tert*-butyl), 4.70 (t, 12, methylene).

Anal. Calcd for $C_{10}H_{22}O_2N_4$: C, 52.17, H, 9.56. Found: C, 52.51; H, 9.72.

Silyl Alkyl Peroxide *via* the Dabco–Hydroperoxide Adduct Method. General.—To a slurry of Dabco–hydroperoxide adduct and an inert medium was added with vigorous stirring a stoichiometric amount of a halosilane. A rapid, exothermic reac-

TABLE III

TRISPEROXYSILANE

Registry no.	Compd	Yield, % (lit.)	Dec temp, °C	Physical characteristics, lit.	O–O frequency in the ir, cm⁻¹	Characteristic nmr signals, δ
5797-01-3	Tris(*tert*-butylperoxy)silane	55	120	Colorless liquid	940 (s), 940 (s)	1.28 (s, 27, *tert*-butyl), *ca.* 1.35 (s, 1, silane)
10196-45-9	Methyltris(*tert*-butylperoxy)silane[c]	78 (49)[g]	150	Colorless liquid, bp 50° (0.1 mm)[h]	913 (s), 927 (s)	0.45 (s, 3, methyl), 1.28 (s, 27, *tert*-butyl)
31602-50-3	Methyltris(α,α-dimethylbenzylperoxy)-silane	57	100	Colorless liquid	923 (s)	0.45 (s, 3, methyl), 1.57 (s, 18, isopropyl), 7.35 (m, 15, phenyl)
31218-59-4	*n*-Hexyltris(*tert*-butylperoxy)silane	76	164	Colorless liquid	912 (s), 927 (m)	0.91 (t, 3, methyl), 1.27 (s, 27, *tert*-butyl)
39810-12-3	*n*-Hexyltris(α,α-dimethylbenzylperoxy)-silane	95	154	Colorless liquid	912 (s)	0.91 (t, 3, methyl), 1.57 (s, 18, isopropyl), 7.35 (m, 15, phenyl)
31218-60-7	*n*-Dodecyltris(*tert*-butylperoxy)silane	90	155	Colorless liquid	912 (m), 927 (w)	*Ca.* 0.95 (t, 3, methyl), 1.27 (s, 27, *tert*-butyl)
39810-14-5	*n*-Dodecyltris(α,α-dimethylbenzylperoxy)-silane	95	152	Colorless liquid	905 (m), 917 (m)	*Ca.* 0.95 (t, 3, methyl), 1.57 (s, 18, isopropyl), 7.30 (m, 15, phenyl)
15188-09-7	Vinyltris(*tert*-butylperoxy)silane[b]	86 (40)[i]	154	Colorless liquid, bp 78° (1 mm)[j]	913 (s), 930 (m)	1.27 (s, 27, *tert*-butyl), *ca.* 6.22 (m, 3, vinyl)
24685-79-8	Vinyltris(α,α-dimethylbenzylperoxy)silane	93	140	Slightly yellowish liquid	917 (s)	1.57 (s, 18, isopropyl), *ca.* 6.18 (m, 3, vinyl), 7.30 (m, 15, phenyl)
27612-79-9	Allyltris(*tert*-butylperoxy)silane[c]	80	174	Colorless liquid	917 (s), 927 (s)	1.27 (s, 27, *tert*-butyl), 2.05 (m, 2, methylenesilyl)
39810-18-9	Phenyltris(α,α-dimethylbenzylperoxy)silane	61	*f*	Colorless liquid	910–920 (m)	1.57 (s, 18, isopropyl)
39810-19-0	3,3,3-Trifluoropropyltris(*tert*-butylperoxy)-silane	80	177	Colorless liquid	913–926 (s)	1.25 (s, 27, *tert*-butyl)
27714-68-7	γ-Methacryloxypropyltris(*tert*-butylperoxy)-silane[d]	70	193	Colorless liquid	910 (m), 930 (m)	1.29 (s, 27, *tert*-butyl), 1.95 (s, 3, methyl), 4.17 (t, 2, ether methylene)
27612-88-0	Isocyanatopropyltris(*tert*-butylperoxy)-silane[e]	88	140	Colorless liquid	908–920 (s)	

[a] Calcd for $C_{13}H_{30}O_6Si$: C, 50.32; H, 9.68. Found: C, 50.00; H, 9.29. [b] Calcd for $C_{14}H_{30}O_6Si$: C, 52.46; H, 9.43. Found: C, 50.15; H, 9.22. [c] Calcd for $C_{15}H_{32}O_6Si$: C, 53.53; H, 9.58. Found: C, 51.20; H, 9.25. [d] Calcd for $C_{19}H_{36}O_8Si$: C, 54.02; H, 9.00. Found: C, 53.79; H, 8.78. [e] Calcd for $C_{16}H_{33}NO_7Si$: C, 50.66; H, 8.71. Found: C, 50.01; H, 8.41. [f] Decomposed gradually upon standing at room temperature. [g] Reference 11. [h] Reference 9. [i] Reference 10. [j] Reference 8.

TABLE IV

TETRAKISPEROXYSILANE

Registry no.	Compd	Yield, %	Dec temp, °C	Physical characteristics, lit.	O–O frequency in the ir, cm⁻¹	Characteristic nmr signals, δ
10196-46-0	Tetrakis(*tert*-butylperoxy)silane[a]	64	135	White crystal of mp 53°, 35–40°[c]	922 (m), 940 (s)	1.28 (s, 36, *tert*-butyl)
39810-23-6	Tetrakis(α,α-dimethylbenzylperoxy)silane[b]	64	<100	Viscous liquid	920–940 (s)	1.55 (s, 24, isopropyl), 7.35 (m, 20, phenyl)

[a] Calcd for $C_{16}H_{36}O_8Si$: C, 50.00; H, 9.37. Found: C, 49.69; H, 9.06. [b] Calcd for $C_{36}H_{44}O_8Si$: C, 68.35; H, 6.96. Found: C, 67.15; H, 6.59. [c] Reference 9.

tion usually occurred and the reaction temperature was kept below 35°, preferably below 15°, by adjusting the addition rate of halosilane and by using an outside cooling bath. The reaction was practically completed upon finishing addition of halosilane, although an additional 30 min of stirring was normally employed. The insoluble Dabco–HX salt was removed by filtration and used for regenerating the Dabco. The silyl alkyl peroxide was collected from the filtrate by evaporating the solvent under vacuum. The yield was usually greater than 70%. Occasionally, the product may be slightly colored. The color can be removed by a treatment with charcoal.

Silyl Alkyl Peroxides *via* the Hexa–Hydroperoxide Adduct Method. General.—To a slurry of Hexa–hydroperoxide adduct, anhydrous calcium chloride (excess amount) and an inert medium was added, while, under cooling, a stoichiometric amount of halosilane. The reaction was usually rapid and exothermic. Upon completion of reaction, the insoluble Hexa–HX and calcium chloride salts were removed by filtration and discarded. The silyl alkyl peroxide was recovered from the filtrate by evaporating the solvent. The yield and product purity are usually comparable but not quite as good as those of the Dabco–hydroperoxide salt method.

Instrumental.—The Varian Model A-60 and HA-100 instruments were used for the nmr measurements. Tetramethylsilane and $CDCl_3$ were employed as the internal standard and solvent, respectively. For infrared spectra, a Perkin-Elmer Model 221 was used with either KBr pellets or liquid film on NaCl plates. Thermal decomposition temperatures were taken with a Thomas-Hoover capillary apparatus.

Registry No.—Hexa-*tert*-butyl hydroperoxide adduct, 39810-24-7; Dabco–hydroperoxide adduct, 39810-25-8.

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Reactions of *N*-Nitrosamines with Grignard and Lithium Reagents

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In the course of studies on nitrogen-centered radicals we had the occasion to examine the reaction of *N*-nitrosamines with organometallic reagents. It is the purpose of this note to report the results of this study.

The early work in this area was carried out by Wieland and his coworkers. Thus Wieland and Fressel[1] found that the principal product in the reaction of *N*-nitrosodiethylamine and ethylmagnesium iodide was the diethylhydrazone of acetaldehyde, while the products with phenylmagnesium bromide were 1-phenyl-2,2-diethylhydrazine and a small amount of 1-ethyl-1-α-phenylethyl-2-phenylhydrazine. Reactions of *N*-nitrosodiarylamines with arylmagnesium halides were reported to give triarylhydrazines,[2,3] although *N,N,N'*-triphenyl-*o*-phenylenediamine (or an isomer) was reported to be the important product in a study of the reaction carried out by Gilman and Heck.[4]

We examined the reactions of diethylnitrosamine (**1**), diisopropylnitrosamine (**2**), diphenylnitrosamine (**3**), and dimethylnitrosamine (**4**) with methylmagnesium bromide, phenylmagnesium bromide, and methyllithium. The results are presented in Table I.

TABLE I
PRODUCTS OF REACTIONS OF *N*-NITROSAMINES WITH ORGANOMETALLIC REAGENTS

Reaction (temp, °C)	Products (yield, %)
Et_2NNO + 3MeMgBr	$H_2C{=}NNEt_2$ (4), Et_2NNMe_2 (4), $CH_3CH{=}NNEt_2$ (4), Et_2NNHEt (20)
Et_2NNO + MeLi (35)	Et_2NNHEt (41), $Et_2NN{=}CHCH_3$ (<2)
Et_2NNO + MeLi (−40)	$Et_2NN{=}CH_2$ (80)
Et_2NNO + PhMgBr	$Et_2NNHC_6H_5$ (50)
$(Me_2CH)_2NNO$ + MeLi	$(Me_2CH)_2NN{=}CH_2$ (30)
$(Me_2CH)_2NNO$ + MeMgBr or PhMgBr	No reaction
Ph_2NNO + MeMgBr	$Ph_2NN{=}CH_2$ (30)
Ph_2NNO + MeLi	Tar, trace Ph_2NH
Ph_2NNO + 2PhMgBr	Ph_2N-*o*-C_6H_4NHPh (5) (5) plus tar
Ph_2NNO + 5 PhMgBr	5 (9), Ph_2NNHPh (3)
Me_2NNO + MeLi (room temperature or −70)	Complex mixture (at least 8 products)

It is reasonable to assume that the initial reaction of *N*-nitrosamines with organometallic reagents should be the addition to the N=O double bond (eq 1). In

$$R_2NN{=}O + MR' \longrightarrow \underset{\mathbf{6}}{R_2NN(O^-M^+)R'} \qquad (1)$$

the case of the Grignard reagents this reaction may be preceded by the formation of a loose complex between the organometallic and the substrate. This was dramatically demonstrated in the reaction of diisopropylnitrosamine (**2**) with methylmagnesium bromide in ether solution. When the reactants were mixed the reaction mixture separated into two phases, the upper layer being primarily ether with a little **2** while the lower layer was a brownish, viscous oil which decomposed exothermally when exposed to the atmosphere. When the oil was hydrolyzed with water, better than 90% of the nitrosamine was recovered. The complex was apparently soluble in tetrahydrofuran but again the reaction did not proceed further. The formation of a similar complex was noted in the reaction of nitrosobenzene and phenylmagnesium bromide.[5] In that case, however, the complex dissolved when excess Grignard reagent was added. The complex is probably not compound **6** because attempts to trap it with methyl iodide or benzoyl chloride were unsuccessful.

Compound **6** is apparently very labile. In cases where elimination was possible **6** lost the elements of HO^-M^+. It is interesting to note that initial protonation of **6** does not seem to be necessary for the elimination to proceed. Thus, the formation of formaldehyde *N,N*-diethylhydrazone proceeded rapidly when diethylnitrosamine was mixed with methyllithium at −40° with rigorous exclusion of moisture.

The hydrazones of formaldehyde were easily transformed by addition of a second molecule of the organometallic to the carbon–nitrogen double bond After hydrolysis, the product of this addition was found to be the triethylhydrazine (predominant product) and a smaller amount of the hydrazone derived from acetaldehyde. The latter was formed by the loss of the elements of the metal hydride from the intermediate addition product. The addition of organometallics to C=N bonds has been known for many years and the addition of alkyllithiums to hydrazones is a useful preparative method for substituted hydrazines.[6] Formaldehyde diisopropylhydrazone was hindered enough so that the second addition did not occur under our conditions. The steric effect was also reflected in the relatively low yield of the hydrazone (30%). Diisopropylnitrosamine did not react with Grignard reagents to give stable products (*vide supra*); presumably the greater steric demands of the Grignard reagents, as opposed to the lithium reagents, prevented the addition from occurring.

The reaction of diphenylnitrosamine with phenylmagnesium bromide gives primarily intractable materials except for a small yield of *N,N,N'*-triphenyl-*o*-phenylenediamine and, in the case where a large excess of the Grignard reagent is used, triphenylhydrazine. It is tempting to speculate that the phenylenediamine is a product of the combination of two diphenylamino radicals. Wieland[7] also observed this product along with *N,N'*-diphenyldihydrophenazine in the thermal decomposition of tetraphenylhydrazine. The latter product was not found under our conditions. The triphenylhydrazine was probably formed by the reduction of the initial addition product **6**, probably by another molecule of the Grignard reagent. No isolatable products were obtained when diphenylnitrosamine was treated with methyllithium. The reaction proceeded rapidly but only intractable tars were obtained.

The reaction of dimethylnitrosamine with methyllithium gave a complex mixture of products, even when the reaction was carried out at low temperatures (−70°).

In conclusion, the reaction of dialkylnitrosamines with organometallic reagents, particularly alkyllithium, may provide a relatively simple route for the preparation of trialkylhydrazines, either by a direct reaction or by further reactions of the initially formed alde-

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(6) A. Marxer and M. Horvath, *Helv. Chim. Acta*, **47**, 1101 (1964).
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hyde hydrazones. The reaction is sensitive to steric effects, particularly in the case of the Grignard reagents. In general, the lithium reagents gave a cleaner reaction mixture. The yields, as quoted in Table I, probably can be improved by further optimizing the reaction conditions.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237 instrument; nmr spectra were recorded on a Varian Model A-60 spectrometer. Mass spectra were obtained with a Perkin-Elmer Hitachi RMU-6D spectrometer. The glpc separations were carried out on a Varian Aerograph Model 1520 dual column instrument. The columns used for the separations were made of Pyrex (aluminum columns are generally unsatisfactory) and packed with acid-washed Chromosorb W coated with 5% Apiezon N. Microanalyses were performed by A. Bernhardt, Engelskirchen, West Germany.

Materials.—Methylmagnesium bromide was obtained as a 3 *M* ethereal solution and methyllithium as a 2*M* ethereal solution from Alfa Inorganics. Diphenylamine was Aldrich reagent grade and was recrystallized from methanol. Diisopropylamine was Matheson reagent grade. Reagent grade ether (Mallinckrodt) was distilled from sodium or from lithium aluminium hydride and was stored over sodium ribbon.

Preparation of Nitrosamines.—All the nitrosamines were prepared in a similar manner and hence only the preparation of diisopropylnitrosamine will be described. To diisopropylamine hydrochloride [prepared from 50 g (0.5 mol) of diisopropylamine] in acidic aqueous solution was added, dropwise with stirring, 34.5 g (0.5 mol) of sodium nitrite. The reaction was kept at 70° for 2 hr. The reaction mixture separated into two phases and the organic phase was extracted with ether. Evaporation of the ether *in vacuo* yielded the crystalline product, which was recrystallized from methanol, yield 33 g (51%), mp 46–47° (lit.[8] mp 48°).

Reactions with Methyllithium.—All these reactions again were carried out in a similar manner. A detailed procedure will be given for the reaction with diisopropylnitrosamine, followed by a description of the products from the other reactions.

An ethereal solution of methyllithium (0.12 mol) was transferred with a syringe into a flask equipped with a dropping funnel and a condenser and swept with a dry nitrogen stream. The flask was cooled in an ice bath. An ethereal solution of 13 g (0.1 mol) of diisopropylnitrosamine was added dropwise to the methyllithium. After the addition was completed the reaction solution was allowed to warm to room temperature and was then heated at reflux for 2 hr. The flask was cooled in an ice bath and sufficient water was added to dissolve the inorganic precipitates. The ether layer was separated and the aqueous layer was extracted several times with ether. The combined ether extracts were dried and the ether was removed by distillation. The residue was distilled at atmospheric pressure. The product distilled over the range of 138–144°. The residue in the pot contained unreacted nitrosamine and tarry materials. The yield of formaldehyde diisopropylhydrazone was 3.9 g (30%), bp 140–142°. The analytical sample was purified by glpc.

Anal. Calcd for $C_7H_{16}N_2$: C, 65.59; H, 12.57; N, 21.85. Found: C, 65.80; H, 12.32; N, 22.17.

The nmr spectrum (CCl_4) indicated two isopropyl groups (d, 12 H, 1.10 ppm; septet, 2 H, 3.68 ppm, J = 6.8 Hz) and an AB quartet (2 H, 5.91 ppm, J = 12 Hz).

Reaction of Diethylnitrosamine with Methyllithium.—The reaction carried out at −40° produced exclusively formaldehyde diethylhydrazone in approximately 80% yield.

Anal. Calcd for $C_5H_{12}N_2$: C, 59.93; H, 12.08; N, 27.95. Found: C, 59.87; H, 12.05; N, 27.89.

The nmr spectrum (CCl_4) indicated two ethyl groups (triplet, 6 H, J = 7.0 Hz at 1.04 ppm and quartet, 4 H, J = 7.0 Hz at 3.11 ppm) and an AB quartet (2 H, J = 12 Hz at 5.93 ppm).

The reaction in refluxing ether produced primarily triethylhydrazine. From 10.2 g (0.1 mol) of diethylnitrosamine there was obtained 4.8 g (41%) of triethylhydrazine, bp 115° [lit.[9] bp 43–44° (30 mm)].

Anal. Calcd for $C_6H_{16}N_2$: C, 62.01; H, 13.88; N, 24.10. Found: C, 61.92; H, 14.23; N, 23.83.

The nmr spectrum (CCl_4) indicated two different kinds of ethyl groups. The spectrum consisted of two overlapping methyl triplets at 0.96 and 1.00 ppm in a 1:2 ratio accounting for nine protons and a complex absorption between 2.25 and 3.06 ppm accounting for methylene protons and 1 NH proton.

Reactions with Grignard Reagents.—These reactions were all carried out in a similar manner and so only the reaction of diethylnitrosamine with methylmagnesium bromide will be described. Into a 500-ml flask fitted with a condenser, a dropping funnel, a gas inlet, and a stirrer and cooled in an ice bath was placed 0.6 mol of methylmagnesium bromide. Diethyl-*N*-nitrosamine (20.4 g, 0.2 mol) in 50 ml of dry ether was added dropwise with stirring. A nitrogen atmosphere was maintained throughout. After the addition was complete the mixture was allowed to warm to room temperature and was then heated at reflux for 2 hr. The excess Grignard reagent was decomposed by careful addition of water. After the removal of ether by distillation the reaction mixture was steam distilled. The distillate was saturated with sodium hydroxide and extracted several times with ether. The combined ether extracts were concentrated and the concentrate was subjected to glpc analysis. It was found to contain four products in a 1:5:1:1 ratio. These products were separated by glpc and were found to be 1,1-diethyl-2,2-dimethylhydrazine (4% yield), nmr spectrum (CCl_4) 0.99 (triplet, 6 H, J = 7.0 Hz), 2.33 (singlet, 6 H), 2.35 ppm (quartet, 4 H, J = 7.0 Hz) (*Anal.* Calcd for $C_6H_{16}N_2$: C, 62.01; H, 13.90; N, 24.10. Found: C, 61.93; H, 14.36; N, 23.94.); triethylhydrazine (20% yield), *vide supra;* formaldehyde diethylhydrazone (4% yield), *vide supra;* and acetaldehyde diethylhydrazone (4% yield), nmr spectrum (CCl_4) 1.00 (triplet, 6 H, J = 7.0 Hz), 1.82 (doublet, 3 H, J = 5.2 Hz), 2.95 (quartet, 4 H, J = 7.0 Hz), 6.65 ppm (quartet, 1 H, J = 5.2 Hz).

Anal. Calcd for $C_6H_{14}N_2$: C, 63.10; H, 12.35; N, 24.53. Found: C, 63.05; H, 12.20; N, 24.57.

Reaction of Diethyl-*N*-nitrosamine with Phenylmagnesium Bromide.—From a Grignard reagent generated from 7.2 g (0.3 g-atom) of magnesium turnings and 50 g (0.31 mol) of bromobenzene plus 10.2 g (0.1 mol) of diethyl-*N*-nitrosamine there was collected 8.2 g (50%) of 1-phenyl-2,2-diethylhydrazine: bp 107–108° (14 mm) [lit.[1] bp 107–110° (12 mm)]; nmr spectrum (CCl_4) 1.07 (triplet, 6 H, J = 7.0 Hz), 2.62 (quartet, 4 H, J = 7.0 Hz), 3.95 (broad singlet, 1 H), 6.36–7.10 ppm (multiplet, 5 H, aromatic); mol wt 164 (mass spectrum).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.08; H, 9.82; N, 17.06. Found: C, 72.95; H, 9.92; N, 17.93.

No other product, except some biphenyl, was isolated from this reaction.

Reaction of Diphenyl-*N*-nitrosamine with Methylmagnesium Bromide.—From a reaction of 0.2 mol of methylmagnesium bromide with 19.8 g (0.1 mol) of diphenyl-*N*-nitrosamine at −40° there was obtained a dark, tarry residue. This residue was extracted thoroughly with *n*-hexane. Evaporation of the resulting solution yielded 5.3 g (27%) of formaldehyde diphenylhydrazone, mp 33–34° (lit.[10] mp 34.5°), nmr spectrum (CCl_4) 5.92 (singlet, 2 H), 6.73–7.30 ppm (aromatic multiplet, 10 H).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.17; N, 14.07. Found: C, 79.80; H, 6.14; N, 13.98.

Reaction of Diphenyl-*N*-nitrosamine with Phenylmagnesium Bromide.—The procedure followed was essentially that of Wieland and Roseau[11] except that a nitrogen atmosphere was maintained over the reaction. The resulting tarry product was extracted with cold hexane. The hexane was evaporated to yield 1.7 g (5%) of *N,N,N'*-triphenyl-*o*-phenylenediamine, mp 89–90° (lit.[12] mp 94.5°), nmr spectrum (CCl_4) 5.62 (broad singlet, 1 H), 6.55–7.27 ppm (aromatic multiplet, 19 H).

Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.67; H, 5.99; N, 8.60. Found: C, 85.66; H, 6.10; N, 8.60.

When a fivefold excess of Grignard reagent was used there was obtained a small amount (~3%) of triphenylhydrazine, mp 138–139° (crystals turn brown at 135°) (lit.[13] mp 142°, turned brown at 139°), nmr spectrum (CCl_4) 5.90 (broad singlet, 1 H), 6.65–7.20 (aromatic multiplet, 15 H). The yield of *N,N,N'*-tri-

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phenyl-*o*-phenylenediamine in this reaction was a somewhat higher 9%.

Reaction of Diisopropyl-*N*-nitrosamine with Phenyl- and Methylmagnesium Bromide.—Many attempts were made to get these reactions to proceed. The following results were typical. A mixture of 0.1 mol of methylmagnesium bromide and 13 g (0.1 mol) of diisopropyl-*N*-nitrosamine was heated at reflux for 6 hr. Upon treatment of the reaction mixture with water and extraction with ether, followed by distillation, there was obtained 11.5 g (90%) of the starting nitrosamine.

Cautionary Note.—While nitrosamines are easy to prepare and to work with, it should be remembered that many of them are potent carcinogens. Proper precautions against inhalation of the vapors and contact with skin should be maintained always. Preparative glpc should be carried out with caution. Unreacted nitrosamines should not be vented into the atmosphere. In our case any unreacted nitrosamine which came through the glpc column was trapped in a collection tube chilled in a Dry Ice–acetone bath.

Registry No.—Methyllithium, 917-54-4; diisopropylnitrosamine, 601-77-4; formaldehyde diisopropylhydrazone, 39837-46-2; diethyl-*N*-nitrosamine, 55-18-5; formaldehyde diethylhydrazone, 28236-89-7; triethylhydrazine, 39837-47-3; methylmagnesium bromide, 75-16-1; 1,1-diethyl-2,2-dimethylhydrazine, 21849-74-1; acetaldehyde diethylhydrazone, 7422-91-5; phenylmagnesium bromide, 100-58-3; 1-phenyl-2,2-diethylhydrazine, 39837-50-8; diphenyl-*N*-nitrosamine, 86-30-6; formaldehyde diphenylhydrazone, 38392-47-1; *N,N,N'*-triphenyl-*o*-phenylenediamine, 29325-54-0; triphenylhydrazine, 606-88-2.

Deuterium Isotope Effects in the Palladium(II) and Thallium(III) Oxidation of Ethylene[1]

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Palladium(II) salts in aqueous solution oxidize ethylene to acetaldehyde[3] while thallium(III) salts

$$Pd(II) + C_2H_4 + H_2O \longrightarrow Pd(0) + CH_3CHO + 2H^+ \quad (1)$$

oxidize ethylene to a mixture of acetaldehyde and ethylene glycol.[4] Kinetic studies[5-7] indicate that in

$$Tl(III) + C_2H_4 \xrightarrow{H_2O} Tl(I) + CH_3CHO + HOCH_2CH_2OH \quad (2)$$

chloride containing aqueous solution, the slow step of the Pd(II) oxidation is rearrangement of a hydroxy olefin π complex to a β-hydroxyethylpalladium(II) alkyl, **1** (or hydroxypalladation adduct in analogy with the well-known hydroxymercuration adduct[8]). This intermediate rapidly decomposes to acetaldehyde and Pd(0). Equation 3 was assigned as the slow step on

$$PdCl_3(OH)(C_2H_4) \xrightarrow[\text{slow}]{H_2O} \underset{\mathbf{1}}{Cl_2(H_2O)Pd\text{–}CH_2CH_2OH} \quad (3)$$

$$\mathbf{1} \xrightarrow{\text{fast}} Pd(0) + HCl + Cl^- + CH_3CHO \quad (4)$$

the basis of isotope effects. When the reaction is carried out in D_2O the acetaldehyde is undeuterated.[3] Thus the decomposition of **1** must involve a transfer of proton from one carbon to the other. This transfer of proton would be expected to involve a positive isotope effect if deuterated ethylene is oxidized. However, it was found that the rate of C_2D_4 oxidation was the same as that of C_2H_4 oxidation within experimental error,[7] suggesting that the decomposition of **1** occurs after the slow step of the reaction. This conclusion is subject to some uncertainty, since isotope effects in decomposition of adducts such as **1** have not been studied.

Kinetic studies[9,10] as well as other evidence[11] of the Tl(III) oxidation in aqueous perchloric acid indicate that it proceeds *via* a hydroxythallation adduct, **2**, analogous to **1**. The formation of the adduct was

$$Tl^{3+} + C_2H_4 + H_2O \xrightarrow[\text{slow}]{} \underset{\mathbf{2}}{HOCH_2CH_2Tl^{2+}} + H^+ \quad (5)$$

$$\mathbf{2} \xrightarrow{\text{fast}} \text{products} \quad (6)$$

again assigned as the slow step on the basis of the kinetics. Thus the reaction displayed no proton inhibition, which would have been expected if eq 5 were an equilibrium.

This note will describe further studies of the isotope effects in these two oxidations for the purpose of testing earlier conclusions concerning the rate-determining steps. First, C_2D_4 was oxidized by both reagents and the acetaldehyde product was analyzed for deuterium content. In both cases the product was over 95% CD_3CDO, indicating that both **1** and **2** decompose by hydride shifts. In the case of Pd(II), this result confirms the earlier work using C_2H_4 in D_2O.[3]

Next the kinetic isotope effect for C_2D_4 as compared with C_2H_4 was measured for Tl(III) in aqueous $HClO_4$. The value of k_H/k_D was found to be 0.8. The isotope effect of less than one must result from the fact that hydrogen is a better electron withdrawer than deuterium,[15] and the Tl(III) oxidation is very sensitive to electronic effects. In any case the isotope effect is about one, the value expected if eq 5 is the rate-determining step.

In order to substantiate this conclusion concerning the rate-determining steps of these oxidations, it is necessary to have some knowledge of the actual deuterium isotope effects in the decomposition of **1** and **2**. Since they cannot be measured by kinetic measurements, they were determined by a competitive method using *cis*- and *trans*-1,2 dideuterioethylene.

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(11) In several cases stable oxythallation adducts have been prepared and characterized.[12-14]

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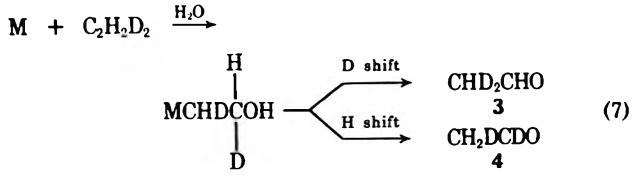
Thus, as shown in eq 7 [M = Pd(II) or Tl(III)], either mode of hydroxymetalation will give a choice of



(7)

an H or a D transfer. The ratio of the tendencies for H to transfer as opposed to D is a measure of the isotope effect. Thus the 4/3 ratio measures the isotope effect. The value found for Pd(II) was 1.70 and that for Tl(III) was 1.92. These isotope effects, in conjunction with the kinetic isotope effects, support the earlier conclusion[7,9] that hydroxymetalation is the rate-determining step in both oxidations.

The magnitude of the isotope effects is not large in either oxidation, suggesting that both bond breaking and bond making are important in the transition state.

Experimental Section

Reagents.—The preparation and analysis of the $Tl(ClO_4)_3$[9] and palladium(II) chloride[7] stock solutions have been described. The C_2D_4 was purchased from Volk Radiochemical Co., and the D_2O from Bio-Rad Laboratories.

Preparation of *cis*- and *trans*-Ethylene-d_2.—The procedures were essentially the same as that used previously for preparing *cis*- and *trans*-ethylene-d_2 from acetylene-d_2.[16] However, in the present work undeuterated acetylene was reduced in D_2O. The reactions were carried out in a 750-ml soft-drink bottle capped with a metal cap having holes sealed by a rubber liner. The bottle could be evacuated or pressured with gas by means of syringe needles inserted through the rubber liner. An excess of the reducing solution (chromous chloride for the trans isomer and copper activated zinc for the cis[16]) in about 150 ml of D_2O was prepared in the bottle and the bottle was evacuated. The bottle was then pressured to about 5 psig with acetylene and agitated on a mechanical shaker for several hours. Samples were removed by means of a syringe equipped with needle and analyzed by infrared and mass spectrometry. All the acetylene had reacted and each isomer could be shown to be uncontaminated by the other isomer by means of the infrared spectra.[16]

Oxidation Rates.—These reactions were carried out in tubes which were capped in the same fashion as the pop bottles. The volume of the tube is about 17 ml. Five milliliters of a Pd(II) or Tl(III) solution which was about 0.1 *M* in the metal ion and 0.5 *M* in $HClO_4$ was put in the tube, the tube was capped and evacuated, and the ethylene-d_4 or ethylene-d_2 was admitted to the tube. The tubes were agitated for periods from 1 to 10 min and then a gas sample was removed by means of a syringe for infrared. The tube was then opened, zinc dust was added to reduce any unreacted metal ion, and the perchloric acid was neutralized with sodium acetate. About 1 ml of solution was then injected into a gas chromotograph and the acetaldehyde peak was collected in a 100% collection tube and analyzed by mass spectrometry. This technique has been described.[17] A 6-ft Carbowax 20M on ABS (70–80 mesh) column at 80° was used for the collection.

In the case of the ethylene-d_4 the deuterium content was obtained by the relative intensities of the parent ions.[18] It was found that the quantities of lower deuterated acetaldehydes, such as acetaldehyde-d_3, increased with time; so the runs were carried to small conversions. Reaction times were 2 min or less. For both Tl(III) and Pd(II) the acetaldehyde-d_4 content was between 95 and 98% for triplicate runs with the remainder being mainly acetaldehyde-d_3.

The ethylene-d_2 runs were carried out in the same fashion. The deuterium distributions were determined by the ratio of the m/e 30 (CDO) and 29 (CHO) peaks. Previous work indicates[18] that this should be a good measure of CD_2HCHO and CH_2DCDO contents.

Preliminary work indicated that *cis*- and *trans*-dideuteroethylenes both gave the same ratios of 3 and 4. Because of ease of preparation the trans isomer was used for the final quantitative work. The $C_2H_2D_2O$ originally formed exchanged with solvent to give lower deuterated acetaldehydes. For that reason short reaction times were employed. Two runs with 0.28 *M* $Tl(ClO_4)_3$ in 2 *M* $HClO_4$ at reaction times of less than 10 min gave identical 4/3 ratios of 1.92. The formation of lower deuterated acetaldehydes which obscured the mass spectra results was particularly serious with $PdCl_2$. Apparently the Pd(0) precipitated in the course of reaction and caused the formation of monodeuterated ethylene as well as catalyzed cis–trans isomerization. The infrared spectra of the unreacted gases in runs with *trans*-$C_2H_2D_2$ indicated the presence of *cis*-$C_2H_2D_2$ and C_2H_3D. One run at a reaction time of 2 min gave a 4/3 ratio of 1.70. At times of 1 hr the ratio fell to 1.33.

In the Tl(III) runs no such isomerization or exchange of *trans*-$C_2H_2D_2$ was observed.

Kinetic Runs.—A constant-volume reactor was used for these studies. The apparatus and procedure have been described.[7] As reported previously, the kinetics of undeuterated ethylene followed the expected second-order kinetics [first order in Tl(III) and first order in C_2H_4)]. The value of k_2 at 25° and 0.5 *M* $HClO_4$ was found to be 0.63 M^{-1} sec^{-1}, a value consistent with results at atmospheric ethylene pressure.[9] In the present study the value of k_2 was determined using ethylene-d_4. The initial ethylene pressure was about 70 mm. The value of k_2 for duplicate runs were 0.76 and 0.82 M^{-1} sec^{-1}.

Registry No.—Palladium, 7440-05-3; thallium, 7440-28-0; ethylene, 74-85-1; *cis*-ethylene-d_2, 2813-62-9; *trans*-ethylene-d_2, 1517-53-9; acetylene, 74-86-2; ethylene-d_4, 683-73-8; D_2O, 7789-20-0.

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(16) P. P. Nicholas and R. T. Carroll, *J. Org. Chem.*, **33**, 2345 (1968).
(17) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 3853 (1971).
(18) R. K. Brinton and F. E. Blacet, *J. Chem. Phys.*, **17**, 797 (1949).

Vapor-Phase Catalytic Dienol Dehydration. Influence of Various Metal Oxides on Product Distribution[1]

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trans-1,5-Heptadien-4-ol was dehydrated over Al_2O_3, WO_3, and ZrO_2 at 250°, yielding 3-*trans*,5-*trans*-, and 3-*cis*,5-*trans*-1,3,5-heptatriene as primary dehydration products and methyl-1,3-cyclohexadienes resulting from thermal cyclization of the cis,trans isomer. 1,3,6-Heptatriene, arising from 1,4 dehydration, was also obtained in significant amounts from both WO_3 and ZrO_2. Tungsten oxide is much more reactive than either Al_2O_3 or ZrO_2 both as a dehydration catalyst and subsequently in causing isomerization of the dehydration products. Both ZrO_2 and WO_3 yield significantly higher 3-cis/3-trans isomer ratios, in the product trienes, than has previously been reported for alumina.

Recent investigations[2-4] of various aspects of the

(1) Supported in part by a National Science Foundation Student Science Training Program Grant, GW-6564. The author acknowledges the assistance of two students, Kevin Bennet and Patricia Maier.
(2) C. Spangler, *J. Org. Chem.*, **31**, 346 (1966).
(3) C. Spangler and N. Johnson, *ibid.*, **34**, 1444 (1969).
(4) C. Spangler and R. Hennis, *ibid.*, **36**, 917 (1971).

TABLE I

DEHYDRATION OF *trans*-1,5-HEPTADIEN-4-OL (1)

Catalyst[a,b] (column length, cm)	% recovery	Products, % of total[c]										
		trans,-*trans*-2	*cis*,-*trans*-2	*trans*,-*cis*-2	cis/trans[d]	cis/trans[e]	3	4	5	6	7	8[f]	1
A (25)	70[g]	36.5	23.7	3.3	0.6	1.3	2.3		24.6			8.0	
B (25)	74	46.0	10.3	3.1	0.2	1.0	0.9	0.5	36.0	1.0	1.1	1.0	
C (25)	76	23.5	23.9	3.2	0.9	1.8	1.2	1.4	19.1	0.9		24.6	
D (25)	60	13.3	8.4	1.8	0.6	2.9	11.6	11.5	11.7	2.0	4.3	13.8	
A (15)	79	21.4	12.9		0.6	0.9			6.5				58.8
C (15)	86	9.1	21.5		2.4	2.4						19.4	49.2
D (15)	70	31.2	35.4		1.1	1.3	3.2		1.3			25.2	1.2
D (15), 200°	72	30.6	36.0		1.2	1.2	0.7		1.3			27.4	3.0

[a] Catalyst A is Houdry HA-100S (γ-Al_2O_3, Houdry Process and Chemical Co.); B is KA-101 alumina (Kaiser Chemicals); C is zirconium oxide (98% ZrO_2, Strem Chemicals); D is tungsten oxide (95% WO_3, Strem Chemicals). [b] All dehydrations were carried out at 250° except as indicated. [c] For totals less than 100%, the balance is composed of unidentified low-boiling products. [d] Ratio of 3,4-cis configuration to 3,4-trans configuration, produced by dehydration. [e] [3,4-cis + cyclization products] to 3,4-trans ratio. [f] 1,3,-Heptatriene produced by dehydration. [g] Percentage yield based on complete dehydration, corrected for any residual alcohol and dehydrogenation in the product distribution (*e.g.*, toluene).

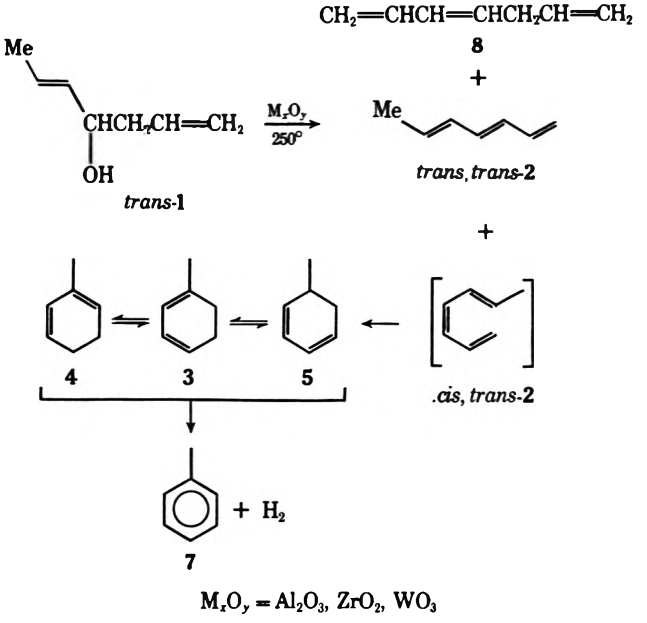
catalytic dehydration of substituted hexadienols have concentrated on the mechanism of alumina-catalyzed dehydration at elevated (200–400°) temperature. Alumina dehydration of *trans*-1,5-heptadien4-ol (**1**) yields 1,3,5-heptatriene (**2**), 1-, 2-, and 5-methyl-1,3-cyclohexadiene (**3**, **4**, and **5**), methylenecyclohexene (**6**), and toluene (**7**). The latter two products are usually produced only in small quantities. The product distribution is consistent with simple elimination to yield a mixture of cis and trans isomers about the incipient 3,4 double bond of 1,3,5-heptatriene, followed by electrocyclic ring closure of the central cis isomers and alumina-catalyzed isomerization of the resultant 5-methyl-1,3-cyclohexadiene. It has also been shown[4] that thermal isomerization of the methyl-1,3-cyclohexadienes *via* [1,5] sigmatropic hydrogen migration is not important under nonequilibrium fast-flow conditions, even though alumina-catalyzed isomerization is extensive.

Several metal oxides other than alumina have been utilized in catalytic dehydration of alcohols; however, none have been utilized for dienol dehydration. In the light of the apparent complexity of the alumina process, we investigated two other common metal oxides, zirconium oxide (ZrO_2) and tungsten oxide (WO_3), as potentially useful catalysts in dienol dehydration studies. In particular we were interested in the cis–trans isomer distribution in the newly introduced double bond, and the overall product distribution.

In the present study, *trans*-1,5-heptadien-4-ol (**1**) was dehydrated over alumina (two different types), zirconium oxide, and tungsten oxide at 250°. Two different alumina catalysts were utilized to explore the presence or absence of specific catalytic effect on the product distribution. Conversions of **1** to products varied from 50% to complete dehydration, thus allowing an estimation as to whether product distributions varied significantly with percentage conversion. Product distributions for the four catalysts are shown in Table I. The results indicate that all four catalysts follow the same general reaction scheme (Scheme I), except that a nonconjugated triene, 1,3,6-heptatriene (**8**), is a major dehydration product when either WO_3 or ZrO_2 is utilized. It is also significant that WO_3 appears to exhibit much greater reactivity than either Al_2O_3 or ZrO_2, yielding essentially complete dehydration

SCHEME I

METAL OXIDE CATALYZED DEHYDRATION OF *trans*-1,5-HEPTADIEN-4-OL



M_xO_y = Al_2O_3, ZrO_2, WO_3

under conditions which yield only 50% conversion with the other catalysts.

The relative yields of cis and trans configurations about the incipient 3,4 double bond were of particular interest. As previously shown,[3] alumina-catalyzed dehydration shows little cis–trans preference. In confirmation of this, both alumina catalysts employed in the present study show ratios close to unity, once corrections are made for the amount of cyclization product obtained. However, both zirconium oxide and tungsten oxide preferentially yield a cis configuration under conditions of complete dehydration. Although the two trienes formed as primary dehydration products have *trans,trans*-2 and *cis,trans*-2 configurations under conditions of complete dehydration a third isomer, *trans,cis*-2, also appears, probably as a result of isomerization of the trans,trans isomer. In order to determine if the observed 3,4-cis/3,4-trans product ratio was a measure of the nature of the dehydration transition state, or the result of catalyst-induced on-column isomerization after dehydration,

TABLE II
THERMOLYSIS OF 1,3,5-HEPTATRIENE[a]

Catalyst/ support[b]	Recovery, %	Products, % of total: trans,-trans-2	cis,-trans-2	trans,-cis-2	cis/trans[d]	cis/trans[e]	3	4	5	6	7	8[f]
A	77	53.3	36.2	6.0	0.61	0.69			4.5			
B	75	52.9	26.3	7.4	0.44	0.66	0.9		12.5			
C	77	51.3	33.1	6.7	0.58	0.69	0.2		6.7			
D[c]	70	30.7	22.7	5.7	0.78	1.16	4.9	4.9	5.4	1.5	4.1	8.9
Pyrex helices	85	54.0	32.4	7.3	0.53	0.63	0.3		6.0			

[a] All thermolyses carried out with 3.0-g samples at 250° and a starting composition of 54.8% *trans,trans*-2, 37.2% *cis,trans*-2, and 8.0% *trans,cis*-2 (cis/trans = 0.60). [b] All columns packed to a depth of 15 cm. [c] In addition, 8.7% of monoolefinic and 2.5% of a mixture of six low-boiling components were also present. [d] Ratio of 3,4-cis configuration produced by thermal and/or catalytic isomerization. [e] [3,4-cis + cyclization products] to 3,4-trans ratio. [f] 1,3,6-Heptatriene produced by catalytic isomerization.

TABLE III
THERMOLYSIS OF 1,3,6-HEPTATRIENE (8)[a]

Catalyst[a] (temp, °C)	Recovery, %	Products, % of total: trans,-trans-2	cis,-trans-2	trans,-cis-2	3	4	5	8
A (250)	75[b]	33.0	12.0	2.1			Trace	51.5
C (250)	72[b]	7.8	3.5	Trace	1.5		Trace	87.0
D (200)	70[c]	7.5	8.5	Trace	1.3		1.5	76.5
D (250)	60[c,d]	7.2	4.2	1.2	6.9	6.4	7.1	26.9

[a] All columns packed to a depth of 15 cm. [b] Thermolyses carried out with 1.0-g samples at 250° and a starting trans-sample purity of 99% (glpc). [c] Thermolyses carried out with 5.0 g-samples at 250°. [d] Toluene (12%) and several unidentified low-boiling products were also obtained. [e] Chemical Samples Co.

pure 1,3,5-heptatriene (2) was thermolyzed under dehydration conditions, and the results are shown in Table II. Alumina and zirconium oxide show little difference in their behavior and the cis–trans ratio does not change significantly upon thermolysis. Tungsten oxide again demonstrates its increased reactivity in that the ratio increases to 1.16 from a starting value of 0.60. It could be argued that the lack of change in the 1,3,5-heptatriene cis/trans ratio upon thermolysis over catalysts A, B, and C (Table II) would prove little if the isomers had already achieved thermal equilibrium. Recently, James and Egger[5] and coworkers have shown that the equilibrium lies in the range 0.2–0.4 in the temperature range 171–254°. Thus it would appear that little isomerization occurs at 250° over Al_2O_3 or ZrO_2, and that the cis/trans products ratio is indicative of the nature of the transition state. Appreciable isomerization occurs over WO_3, yielding a product distribution that parallels the dehydration distribution in both identity and complexity.

An interesting difference between the compositions obtained from alumina, zirconium oxide, and tungsten oxide is the presence of large quantities of the unconjugated triene, 1,3,6-heptatriene (8). This product is most probably obtained *via* 1,4 dehydration of 1, although isomerization of the conjugated isomer cannot be precluded. We favor the former interpretation not only from the thermolytic behavior of 2 on the various catalysts (Table II), but also on the observation that 8 is formed in large quantity for both partial and complete dehydration. Thus 8 appears to be a primary dehydration product of 1. Nazarov and Mavrov[6] have observed similar behavior in the dehydration of various allyl and vinyl carbinols over ZrO_2/pumice, where they obtained nonconjugated products in quantities ranging from 18 to 21%. In an attempt to estimate whether the quantities of 8 obtained were an accurate measure of primary 1,4 dehydration, 8 was thermolyzed at 250° over Al_2O_3, ZrO_2, and WO_3 under conditions identical with those employed during dehydration (Table III). Tungsten oxide again demonstrated the greatest catalytic activity (73% isomerization) at 250° and the lowest percentage recovery of volatile products. Even at 200° WO_3 demonstrates a greater reactivity than ZrO_2 (24% isomerization). Isomerization to 2, the conjugated triene, was extensive (47%) for Al_2O_3, and less so for ZrO_2 (11%). This may well explain why recovery percentages are, in general, considerably lower for WO_3 than for the other two catalysts. Thus it is probable that 1,4 dehydration is actually more important for all the catalysts employed in this study than the product distribution alone would indicate.

Several general conclusions can be drawn from the above studies. We find the action of both Al_2O_3 and ZrO_2, with the exception of 1,4 dehydration, to be quite similar, as are their reactivities. Tungsten oxide appears to be much more reactive and prone to secondary catalytic reactions with the primary dehydration products. Both ZrO_2 and WO_3 yield substantially higher cis/trans product ratios than for Al_2O_3, which indicates different steric requirements in the transition state. In this respect, both ZrO_2 and WO_3 are more closely related to ThO_2, for which a concerted cis elimination *via* a cyclic transition state has been proposed.[7] Such transition states are usually formed to preferentially minimize steric interactions and bring a larger portion of the molecule closer to the catalyst surface. Thus dehydration of 2-butanol or 2-octanol over ThO_2 at 350–450° yields predominantly 1 olefins[7] by eliminating a terminal methyl proton in preference to an interior secondary methylene proton. This may indeed explain the relatively large quantities of 1,4-dehydration products that are observed for both ZrO_2 and WO_3.

(5) T. James and K. Egger, *J. Chem. Soc. B*. 348 (1971).

(6) I. N. Nazarov and M. U. Mavrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 365 (1958); *Chem. Abstr.*, **52**, 12746*d* (1958).

(7) A. J. Lundeen and R. Van Hoozer, *J. Amer. Chem. Soc.*, **85**, 2180 (1963).

Experimental Section[8]

Nature of Catalysts.—Catalyst A[9] (Houdry HA-100s) is a γ-alumina catalyst which has been described as essentially nonacidic, and has been utilized as a dehydration catalyst in a large number of published examples[10] by several different workers. Catalyst A has a sodium content of 0.1–0.2% and was utilized in the form of 0.125-in. pellets.

Catalyst B[11] (Kaiser Chemicals, KA-101) is a quasiamorphous alumina, as determined by X-ray diffraction,[12] which can be referred to as χ,ρ-alumina. The X-ray pattern is diffuse and intermediate between amorphous ρ and the more crystalline χ, but distinct from each. A minor phase (*ca.* 20–30%) which coexists with the above dominant phase resembles γ-alumina, but is more diffuse. The catalyst is supplied as pellets, 8–14 mesh, with a surface area of 360 m^2/g. Sodium content is 0.40%, expressed as Na_2O.

Catalyst C[13] is catalytic zirconium oxide, containing 98% ZrO_2 and 2% alumina with a surface area of 50 m^2/g and a pore volume of 0.21 cc/g, supplied as 0.125-in. pellets.

Catalyst D[13] is catalytic tungsten oxide, containing approximately 95% WO_3 with a surface area of 17 m^2/g and a pore volume of 0.19 cc/g.

Catalysts were prepared by heating at the dehydration temperature for a period of 1 hr under reduced pressure (20–25 mm) in a nitrogen atmosphere. Fresh samples of catalyst were used in each run. After this pretreatment they were used directly as described below.

Dehydration of *trans*-1,5-Heptadien-4-ol (1).—*trans*-1,5-Heptadien-4-ol[14] (10 g, 0.09 mol) was added dropwise at a rate of 0.25 ml/min through a 22-mm Pyrex tube packed to a depth of either 15 or 25 cm with catalyst and externally heated with a Lindberg Hevi-Duty split-tube furnace. A pressure of 20–25 mm was maintained in the system to facilitate rapid removal of the product from the column. The product was trapped in a flask immersed in a Dry Ice–acetone bath, and subsequently warmed to room temperature, washed with water, filtered through anhydrous magnesium sulfate, and analyzed immediately by glpc (see Table I for product analyses). No attempt was made to maximize the yields.

The dehydration products were identified by collecting each peak emanating from the chromatograph in glass V tubes immersed in cooling baths: (a) in isooctane for uv analysis, and (b) in $CDCl_3$ for nmr analysis. In each case, the product was identified by comparison of the uv, nmr, and glpc retention times to those of authentic samples in our laboratories.

Registry No.—**1**, 24581-03-1; **8**, 1002-27-3; 1,3,5-heptatriene, 2196-23-8; Al_2O_3, 1344-28-1; ZrO_2, 1314-23-4; WO_3, 1314-35-8.

(8) Gas–liquid partition chromatography was performed with an Aerograph Model 202-1B dual column instrument equipped with a Hewlett-Packard Model 3370-A electronic integrator for peak area measurement; dual 15-ft 15% TCEP on 60/80 mesh Chromosorb W columns were utilized for analysis. Ultraviolet spectra were obtained with a Perkin-Elmer Model 202, nmr spectra with a Varian A60-A using TMS as an internal standard ($CDCl_3$ solvent). All compounds were identified by both uv and nmr spectra and glpc retention times and comparison to authentic samples.

(9) Houdry Process and Chemical Co.

(10) See, for example, L. Klemm, J. Shabtai, and D. Taylor, *J. Org. Chem.*, **33**, 1480 (1968), and references cited therein.

(11) Kaiser Chemicals, Division of Kaiser Aluminum and Chemical Corp.

(12) Private communication, Dr. Robert B. Emerson, Staff Research Associate, Chemical Aluminas, Kaiser Chemicals, Box 1031, Baton Rouge, La.

(13) Strem Chemicals, Inc.

(14) C. Spangler and G. F. Woods, *J. Org. Chem.*, **30**, 2218 (1965).

Photochemical Deoxygenation of Aryl Sulfoxides

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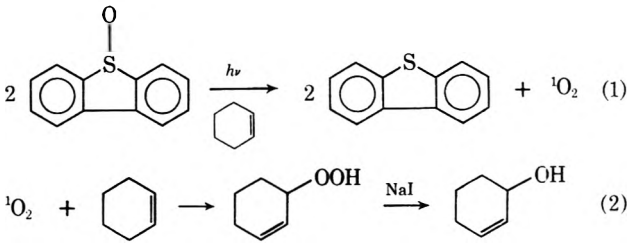
Several selective and mild chemical methods have recently been reported for reduction of sulfoxides to the corresponding sulfides.[2] To supplement these reports, we wish to communicate the photodeoxygenation of some aryl sulfoxides in good yields.

Kharasch and Khodair[3] found that diphenyl sulfoxide on direct photolysis in benzene gave biphenyl (53%), diphenyl sulfide (7%), and a small amount of diphenyl disulfide and that dibenzothiophene and dibenzothiophene dioxide were inert under these conditions. We find that in nonaromatic solvents direct photolysis of the aryl sulfoxides in Table I gives good to excellent yields of the corresponding sulfides. Diphenyl and *p*-tolyl phenyl sulfides, however, are photolabile, giving several products,[3,4] so that the yields of sulfide are diminished. Nevertheless, sensitized photolysis of diphenyl and *p*-tolyl phenyl sulfoxides with triplet sensitizer benzophenone or acridine[5] gives only the corresponding sulfides as products[6] and indicates that the photoreduction probably proceeds *via* the triplet excited state.[5] In further support of this conclusion, it was found that piperylene[7] could effectively prevent the deoxygenation of diphenyl sulfoxide, for example.

To determine the fate of the oxygen lost, dibenzothiophene oxide was photolyzed in the presence of cyclohexene as a trap for singlet oxygen.[8] From the amount of 2-cyclohexen-1-ol obtained (glc yield), we find a minimum of 41% of the available oxygen in the sulfoxide reacting as $^1O_2$ (eq 1, 2).[9]



Photolysis of *dialkyl* sulfoxides[10] has been found to give mixtures of products, notably aldehydes and disulfides, but not dialkyl sulfides. Pyrolysis of dialkyl sulfoxides with available β hydrogens is known to give largely olefinic products and sulfenic acids.[11] If only α hydrogens are available a rearrangement of the sulfoxide and formation of aldehydic and sulfhydryl prod-

(1) NSF Predoctoral Fellow, 1970–1972.

(2) J. P. A. Castrillón and H. H. Szmant, *J. Org. Chem.* **30**, 1338 (1965); I. Granoth, A. Kalir, and Z. Pelak, *J. Chem. Soc. C*, 2424 (1969); D. W. Chasar, *J. Org. Chem.*, **36**, 613 (1971); T-L. Ho and C. M. Wong, *Syn. Commun.*, **3**, 37 (1973); H. C. Brown and M. Ravindran, *Synthesis*, 42 (1973).

(3) N. Kharasch and A. I. A. Khodair, *Chem. Commun.*, 98 (1967).

(4) W. Carruthers, *Nature (London)*, **209**, 908 (1966).

(5) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, pp 131, 132.

(6) Sulfide products can be easily purified from sensitizers and sulfoxides by tlc or column chromatography with silica gel.

(7) N. C. Yang, *J. Amer. Chem. Soc.*, **90**, 504 (1968); G. S. Hammond, P. A. Leermakers, and N. J. Turro, *ibid.*, **83**, 2396 (1961).

(8) K. Gollnick, *Advan. Photochem.*, **6**, 1 (1968).

(9) A referee has pointed out that formation of oxygen atoms seems more likely than direct formation of singlet molecular oxygen, and that sensitization by dibenzothiophene of $^3O_2$ formed in the reaction to singlet oxygen may account for the peroxide detected. Although our data do not permit unambiguous distinction between direct and indirect formation of singlet oxygen, the relatively good yield of peroxide formed and the absence of any products expected from cyclohexene and atomic oxygen [*e.g.*, epoxycyclohexane and cyclohexanone: T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 2747 (1969)] give some support to direct formation of singlet oxygen.

(10) R. G. Petrova and R. Kh. Freidlina, *Izv. Akad. Nauk SSSR, Ser. Khim.* (10), 1857 (1966); T. Sato, Y. Goto, T. Tohyama, S. Hayashi, and K. Kata, *Bull. Chem. Soc. Jap.*, **40**, 2975 (1967).

(11) C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960).

TABLE I
PHOTOLYSIS OF ARYL SULFOXIDES

Registry no.	Sulfoxide	Solvent	Time, hr	Filter[a]	% conversion[b]	Yield of sulfide, %[b]
1013-23-6	Dibenzothiophene oxide	C_6H_6	23	R	~100	>95
		50% aq AcOH	10	C	~80	>90
		50% aq AcOH[c]	4.25	U	50	90–95
945-51-7	$(C_6H_5)_2SO$	C_6H_{12}	21	R	100	40
		50% aq AcOH	7	N	40–50	~70
948-56-1	p-$CH_3C_6H_4S(O)C_6H_5$	50% aq AcOH	10	N	~30	~85
		C_6H_6[d]	6	P	40–50	90–95
1193-82-4	$C_6H_5S(O)CH_3$	C_6H_{12}	7	N	~80	~95
		50% aq AcOH	7	N	0	

[a] R = Rayonet reactor with low-pressure Hg arc lamps; others using Hanovia H-450W medium-pressure immersion lamp with N, no filters; C, Corex filter; P, Pyrex filter; and U, uranium glass filter (cut off about 320 nm). [b] Yields and conversions were determined by tlc, vpc, and nmr analysis. Identifications were confirmed by mass spectrometry. [c] With acridine or chrysene as triplet sensitizer; under the same conditions with no sensitizer, about 10% conversion to sulfide was observed. [d] With acridine or benzophenone as triplet sensitizers; under the same conditions with no sensitizer there was no reaction.

ucts may occur.[12] With this in mind, we attempted the pyrolysis[13] of aryl sulfoxides. While diphenyl sulfoxide was stable to heat (250°), dibenzothiophene oxide readily (250°, several minutes) lost oxygen by an undetermined mechanism to give near-quantitative yields of dibenzothiophene as determined by tlc and nmr. Methyl phenyl sulfoxide under the same conditions gave thioanisole (80–90% conversion, 60–70% yield by nmr) plus other products. Aryl sulfides were found to be thermally stable.

Experimental Section

p-Tolyl phenyl sulfide was made from commercially available thiophenol and p-iodotoluene by the method of Fournier, *et al.*[14] Sulfoxides were either obtained commercially (Aldrich or Eastman) or prepared from the corresponding available sulfides by m-chloroperbenzoic acid oxidation according to the method of Johnson and McCants.[15] Solvents and sensitizers were commercially available and purified before use. Thin layer chromatography was done on commercial silica gel plates (Eastman) with no activation, and vapor phase chromatography was performed on a Varian Aerograph Model 1200 with SE-30 columns.

General Procedure for Photolysis.—Substrates, sensitizers, and solvents were added to dry quartz test tubes and degassing was effected by freeze–pump–thaw cycles or nitrogen purging. Solutions were irradiated while suspended vertically around a Hanovia immersion lamp or in a Srinivasan-Griffin photochemical reactor and analyzed. Acid solutions were made alkaline and extracted with methylene chloride before analysis.

Thus, 45 mg (0.22 mol) of dibenzothiophene oxide was dissolved in 10 ml of benzene in a quartz test tube and degassed by three freeze–pump–thaw cycles. The stoppered solution was irradiated (Rayonet reactor) for 23 hr at 40–50°. The reaction mixture was filtered through a short column of silica gel and the solvent was removed under vacuum, giving 39 mg (96%) of chromatographically pure dibenzothiophene (tlc, nmr).

Trapping of Singlet Oxygen.[16]—To a quartz test tube were added 30 mg (0.15 mmol) of dibenzothiophene oxide, 10 ml of cyclohexene, and 1 ml of acetic acid. The solution was purged with nitrogen and photolyzed (Hanovia lamp with Pyrex filter) until tlc showed that no sulfoxide remained. The reaction mixture gave positive spot tests[17] for peroxide and was treated with sodium iodide for 4 hr, after which the spot tests were negative. Work-up was by the method of Nickon and Bagli[16] and analysis of the final solution by vapor phase chromatography showed approximately 4 mg (±1 mg, 0.031–0.051 mmol) of 2-cyclohexen-1-ol (comparison with known sample). This corresponds to a lower limit yield of 41% overall from the available oxygen (0.075 mmol of O_2) in dibenzothiophene oxide.

Acknowledgment.—We thank the Research Corporation for partial financial support and Professor D. O. Cowan for several helpful discussions.

(12) W. Carruthers, I. D. Entwistle, R. A. W. Johnstone, and B. J. Millard, *Chem. Ind. (London)*, 342 (1966).

(13) Pyrolyses were done neat, condensed phase, in stoppered nmr tubes. Atmosphere had no effect.

(14) E. Fournier, L. Petit, J. Pichon, and M. Dursin, *Bull. Soc. Chim. Fr.* (5), 1754 (1966).

(15) C. R. Johnson and D. M. McCants, *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(16) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961).

(17) F. Feigl, "Spot Tests in Organic Analysis," 6th ed, Elsevier, Amsterdam, 1960, pp 534, 535.

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

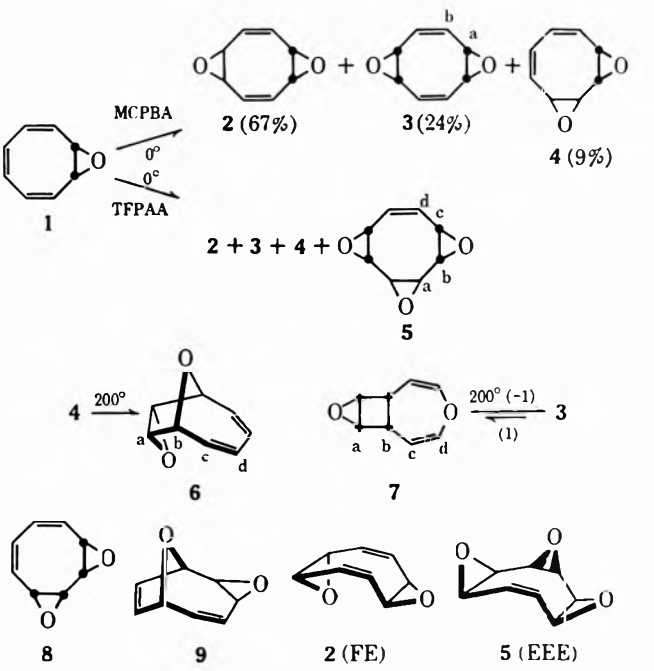
Dioxa and Trioxa Derivatives of C_8H_8

Summary: Peracid oxidation of cyclooctatetraene oxide yields dioxiranes **2**, **3**, and **4** and trioxirane **5**, while thermal treatment of **3** and **4** affords isomers **7** and **6**, respectively.

Sir: In an extension of our work with the heteronins[1] and their bicyclic tautomers[2-4] we have synthesized compounds containing additional heteroatoms within the basic C_8H_8 constituent and we now report on one trioxa and five dioxa members of the family.[5]

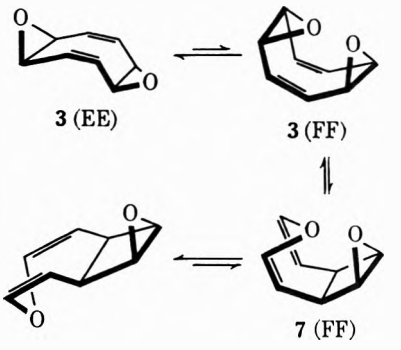
Treatment of cyclooctatetraene oxide (**1**)[6] with *m*-chloroperbenzoic acid produces, in 75% yield, a three-component mixture consisting of[7] ~67% **2** [mp 40.5–41°; nmr (60 MHz, $CDCl_3$) τ 3.93 (2 H, d, J = 11 Hz), 4.42 (2 H, br d, J = 11 Hz), 6.19 (2 H, d, J = 2 Hz), 6.40 (2 H, s); uv $\lambda_{max}^{C_6H_{14}}$ 198 nm (ϵ ~4300); *m/e* 136 (P^+, 42%)], 24% **3** [mp 165.5–166.5°; nmr (60 MHz, $CDCl_3$) τ 4.20 (4 H, s), 6.33 (4 H, s); uv $\lambda_{max}^{C_6H_{14}}$ 196 nm (ϵ ~2100); *m/e* 136 (P^+, 6.3%)], and 9% **4** [mp 41–42°; nmr (60 MHz, $CDCl_3$) τ 3.93 (2 H, d, J = 11 Hz), 4.25 (2 H, d, J = 11 Hz), 6.36 (2 H, d, J = 4 Hz), 6.83 (2 H, d, J = 4 Hz); $\lambda_{max}^{C_6H_{14}}$ 222 nm (ϵ 2500); *m/e* 136 (P^+, 35%)]. Exposure of **1** to trifluoroperacetic acid instead of *m*-chloroperbenzoic acid yields in 70% yield a mixture[7] of **2** (30%), **3** (50%), **4** (5%), and the trioxa homolog, **5** [15%, mp 145–146°; nmr (60 MHz, $CDCl_3$) τ 4.02 (2 H, s), 6.43 (2 H, d, J = 3.5 Hz), 6.63 (2 H, d, J = 3.5 Hz), 6.90 (2 H, s); uv $\lambda_{max}^{C_6H_{14}}$ 200 nm (ϵ ~1100); *m/e* 152 (P^+, 1.3%)] (Scheme I).

Scheme I



The structural and stereochemical details of **2** follow from its nmr spectrum which implicates the presence of two magnetically distinct nonadjacent oxirane functions within a rigid frame,[8] *e.g.*, **2** (FE).[9] By contrast, the nmr spectrum of **3** requires a structure with only two magnetically distinct sets of protons. In addition, the absence of coupling between "olefinic" and "oxirane" protons in **3** is consistent with its existence in the diextended form **3** (EE) (Scheme II), in which the H_a–H_b dihedral angle is measured (from Dreiding molecular models) to be ~90° as opposed to the sterically more demanding difolded arrangement **3** (FF), where H_a–H_b is estimated at ~40°.[10] The formulation of **4** as a 1,3-dioxirane also follows from the nmr spectrum which is best accommodated by the presence of two symmetrically disposed, vicinally positioned oxirane groups. The trans disposition of the groups in **4** is also indicated by the nmr characteristics of this substance[11] and is further confirmed by its conversion to **5** on oxidation and to **6** on thermolysis (*vide infra*).

Scheme II



(1) A. G. Anastassiou, *Accounts Chem. Res.*, **5**, 281 (1972).

(2) A. G. Anastassiou and R. P. Cellura, *J. Org. Chem.*, **37**, 3126 (1972).

(3) A. G. Anastassiou, R. L. Elliott, and A. Lichtenfeld, *Tetrahedron Lett.*, 4569 (1972), and references cited therein.

(4) A. G. Anastassiou and B. Chao, *Chem. Commun.*, 979 (1971); *ibid.*, 277 (1972).

(5) All new substances yielded correct combustion analyses.

(6) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Justus Liebigs Ann. Chem.*, **560**, 93 (1948); A. C. Cope and B. D. Tiffany, *J. Amer. Chem. Soc.*, **73**, 4158 (1951).

(7) Experimental details will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-2421. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(8) Meaningfully, the nmr resonances of **2** remain temperature invariant on cooling to −85° but undergo the expected coalescence or heating. The observed coalescence temperature, T_c (diphenyl ether) ~135°, corresponds to a $\Delta G^{\ddagger}$ term of ~20.5 kcal/mol for the ring inversion process which alters the effective shape of the molecule from static C_s to dynamic C_{2h}.

(9) The notations F and E stand for folded and extended, respectively, and are employed as a conformational label of each C_8H_8O unit present in the molecule.

(10) The nmr spectrum of **3** remains invariant in the temperature range of −60° to 161°. This finding might be interpreted in one of two ways: (i) **3** is conformationally rigid and (ii) **3** (EE) is the predominant component in a rapidly interconverting system of **3** (EE) and **3** (FF). In light of the nmr demonstration that **2** is conformationally rigid, we strongly favor the first interpretation, *i.e.*, that **3** is rigidly held as shown in **3** (EE).

(11) Inspection of Dreiding molecular models reveals that of the two stereoisomers **4** and **8** only the former possesses such static symmetry (C_2) and dihedral angles as are consistent with the nmr characteristics of the 1,3-dioxirane.

The nmr spectrum of **5** requires that the molecule possess C_s symmetry and, further, that it exist in the sterically favorable conformation shown in **5** (EEE), where both dihedral angles, H_a–H_b and H_c–H_b, are estimated at ~90°.[12]

Prolonged exposure of **4** at 198°, in benzene, leads cleanly and irreversibly (k = 1.36 ± 0.15 × 10^{-5} sec^{-1}; $\Delta G^{\ddagger}$ = 38.5 kcal/mol)[13] to **6** [mp 97–97.5°; nmr (60 MHz, C_6D_6) τ 3.8–4.5 (4 H, H_d + H_c), 5.82 (2, H dd, H_b, J_{bc} = 4.5 Hz, J_{ba} = 2 Hz), 6.52 (2 H, d, H_a, J_{ab} = 2 Hz); uv $\lambda_{max}^{C_6H_{14}}$ 237 nm (sh, ϵ 680), 245 (sh, 950), 253 (1200), 262 (1240), 272 (720); m/e 136 (P^+, 59%)] by what appears to be an unprecedented $[1,5]_s$ thermal shift of an oxa bridge. The assignment of an anti dioxa structure to **6** follows from the magnitude of J_{ab} (2 Hz)[14] and confirms the trans disposition of the oxirane groups in **4**.

In sharp contrast to the **4** → **6** conversion thermolysis of **3** at 202°, in benzene, produces an equilibrium mixture consisting (nmr) of ~60% **3** and 40% **7** [mp 33–34°; nmr (60 MHz, $CDCl_3$) τ 3.72 (2 H, d, H_d, J_{dc} = 8 Hz), 5.50 (2 H, dd, H_c, J_{cd} = 8 Hz, J_{cb} = 2.5 Hz), 6.60 (2 H, s, H_a), 7.25 (2 H, br s, H_b); uv $\lambda_{max}^{C_6H_{14}}$ 206 nm (ϵ ~3700), 218 (3400); m/e 136 (P^+, 33%)] and materializing with k_1 = 5.0 × 10^{-5} sec^{-1}, $\Delta G^{\ddagger}$ = 37.6 kcal/mol, and k_{-1} = 7.87 ± 0.23 × 10^{-5} sec^{-1}, $\Delta G^{\ddagger}$ = 37.2 kcal/mol. With regard to mechanism, we note that the obvious requirement of coiled forms **3** (FF) and **7** (FF) for bond relocation (Scheme II) coupled with the undoubted natural tendency of these substances to favor sterically less demanding conformations, *e.g.*, **3** (EE), introduces at this stage some uncertainty as to whether the measured activation reflects the EE to FF ring inversion,[10] the productive **3** (FF) ⇆ **7** (FF) "Cope" process, or possibly a combination of both.

Compared to dioxides **3** and **4**, trioxirane **5** displays striking thermal stability, remaining unchanged (nmr) on heating at 255° for ~20 hr.

Despite their requirement for high thermal activation, the bond relocations of **3** and **4** proceed entirely along symmetry-allowed pathways, the failure of either substrate to rearrange to the symmetry-disallowed isomer **9** being especially notable in this connection. Orbital symmetry control must also be responsible for the resistance of these substances to thermolyze into monocyclic structures, which sharply contrasts the tendency of their $C_6H_6O_2$ and $C_6H_6O_3$ counterparts to do so readily.[15] Specifically, cross-link disrotation of **2**, **3**, **4**, and **5** to all-cis monocyclic frames is predicted to be possible in the electronically excited state but not in the ground state. Preliminary experimentation designed to test this prediction has, to date, been frustrated by the lack of effective chromophores in these substances.

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(16) Eastman Kodak Graduate Fellow, 1973.

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(12) The conformational rigidity of **5** is perhaps best understood in light of the fact that ring inversion would necessarily convert the arrangement shown in **5** (EEE) into the sterically less accessible FFF form.

(13) The rate of rearrangement in C_6D_6 was monitored by nmr spectroscopy.

(14) Examination of Dreiding molecular models reveals the H_a–H_b dihedral angle to be ~20° for **6** and ~80° for the alternate (exo) stereochemical arrangement. The association of J = 2 Hz with the 20° dihedral angle of the endo stereochemical variant (**6**) follows from a well-documented correlation of J *vs.* dihedral angle among cyclic epoxides: K. Tori, T. Komeno and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964); see also ref 15a.

(15) (a) H. J. Alterbach and E. Vogel, *Angew. Chem.*, **84**, 985 (1972); (b) E. Vogel, H.-J. Altenbach, and D. Cremer, *ibid.*, **84**, 983 (1972); (c) E. Vogel, H.-J. Altenbach, and C.-D. Sommerfeld, *ibid.*, **84**, 986 (1972); (d) R. Schwesinger and H. Prinzbach, *ibid.*, **84**, 990 (1972).

The Fast Base-Induced Reaction of α,α-Dichloromethyl Methyl Ether with Organoboranes. A New General Route from Organoboranes to the Corresponding Carbon Structures

Summary: The base-induced reaction of α,α-dichloromethyl ether with a representative series of organoboranes provides a new convenient low temperature route to tertiary carbinols in high yield.

Sir: The reaction of organoboranes with α,α-dichloromethyl methyl ether (DCME) induced by lithium triethylcarboxide provides a convenient route to the corresponding tertiary carbinols in excellent yield (eq 1). The initial transfer reaction is very rapid, being

$$R_3B + CHCl_2OCH_3 + LiOCEt_3 \xrightarrow[25°]{THF} \xrightarrow{NaOH,\ H_2O_2} R_3COH \quad (1)$$

complete within 15 min at 25 or 0°, and the boron intermediates are oxidized readily to the corresponding carbinols. Consequently, this reaction provides a valuable means of converting organoboranes into the corresponding carbon structures under relatively mild conditions of time and temperature.

This procedure (eq 2) provides a simple alternative

$$(n\text{-}Bu)_3B + CHCl_2OCH_3 + LiOCEt_3 \xrightarrow[15\ min]{THF,\ 25°} [\ ] \xrightarrow{[O]} \underset{94\%}{(n\text{-}Bu)_3COH} \quad (2)$$

to the reaction of organoboranes with carbon monoxide[1-3] (eq 3) or with sodium cyanide and trifluoroacetic

$$(n\text{-}Bu)_3B + CO \xrightarrow[8\ hr]{diglyme,\ 125°} [\ ] \xrightarrow{[O]} \underset{90\%}{(n\text{-}Bu)_3COH} \quad (3)$$

anhydride[4] (eq 4) as synthetic routes for the replace-

$$[(n\text{-}Bu)_3BCN]^-Na^+ \xrightarrow[-78°,\ then\ 45°\ for\ 12\ hr]{(CF_3CO)_2O} [\ ] \xrightarrow{[O]} \underset{73\%}{(n\text{-}Bu)_3COH} \quad (4)$$

ment of boron in organoboranes by carbon. Treatment of a representative series of organoboranes, many of which are readily prepared by the hydroboration of

(1) M. E. Hillman, *J. Amer. Chem. Soc.*, **84**, 4715 (1962).

(2) H. C. Brown and M. W. Rathke, *J. Amer. Chem. Soc.*, **89**, 2737 (1967).

(3) For a review of the carbonylation reaction of organoboranes with pertinent literature references, see H. C. Brown, *Accounts Chem. Res.*, **2**, 65 (1969).

(4) A. Pelter, M. G. Hutchings, and K. Smith, *Chem. Commun.*, 1048 (1971).

olefins,[5,6] with DCME and lithium triethylcarboxide provides yields of tertiary carbinols comparable to or greater than those obtained by the previous two procedures. The results are presented in Table I.

TABLE I

SYNTHESIS OF TERTIARY CARBINOLS *via* THE REACTION OF REPRESENTATIVE ORGANOBORANES WITH DCME AND LITHIUM TRIETHYLCARBOXIDE

Organoborane	Tertiary carbinol obtained on oxidation	Yield of carbinol, %[a]
Tri-*n*-butylborane	Tri-*n*-butylcarbinol	94[b]
Tri-*sec*-butylborane	Tri-*sec*-butylcarbinol	95 (85)[c]
Triisobutylborane	Triisobutylcarbinol	99
Tricyclopentylborane	Tricyclopentylcarbinol	97 (91)[c]
Tricyclohexylborane	Tricyclohexylcarbinol	92
Tri-*exo*-norbornylborane	Tri-2-norbornylcarbinol	84[d]
B-Cyclohexylborinane[e]	1-Cyclohexylcyclohexanol	71[f]
Triphenylborane	Triphenylcarbinol	95[g]

[a] Glpc analysis. [b] 30% excess base and DCME are required. Stoichiometric amounts result in only an 85% yield of tri-*n*-butylcarbinol. [c] Isolated yields by distillation of the product under reduced pressure. Products were compared with authentic samples obtained from carbonylation of the trialkylboranes.[2] [d] 50% excess base and DCME are required. Stoichiometric amounts result in only a 69% yield of tri-2-norbornylcarbinol. [e] H. C. Brown and E. Negishi, *J. Organometal. Chem.*, **26**, C67 (1971). [f] Use of 100% excess base increased the yield of 1-cyclohexylcyclohexanol to 79%. [g] Use of 100% excess base is required. Stoichiometric amount results in only a 54% yield of triphenyl transfer products. Oxidation using sodium acetate–hydrogen peroxide is necessary to avoid protonolysis of the benzylic organoboron intermediate. Oxidation with sodium hydroxide–hydrogen peroxide gives triphenylmethane (59%) and triphenylcarbinol (33%).

We previously reported that chlorodifluoromethane reacts with tri-*n*-butylborane and lithium triethylcarboxide to produce tri-*n*-butylcarbinol on oxidation in essentially quantitative yields.[7] This reaction appeared very promising. However, extension to tri-*sec*-butylborane and other secondary and hindered organoboranes gave poor results which were traced to the intermediate formation of highly hindered triethylcarbinol esters of *tert*-alkylfluoroboronic acids[8] (eq 5)

$$(sec\text{-Bu})_3B + CHClF_2 + 2LiOCEt_3 \xrightarrow[1\ hr]{THF,\ 65^\circ} (sec\text{-Bu})_3C{-}B(F)(OCEt_3) + HOCEt_3 + LiCl + LiF \quad (5)$$

in essentially quantitative yield, but remarkably resistant to oxidation to the trialkylcarbinols.

This difficulty led us to seek a more favorable route for the conversion of organoboranes to the corresponding carbinols. We had noted that the reaction of organoboranes with chlorodifluoromethane and other trisubstituted methanes required 2 equiv of lithium triethylcarboxide, whereas DCME required only 1.[7] This suggested that the reaction with DCME might not involve the formation of such a hindered boronic ester of triethylcarbinol. This proved to be the case. Treatment of tri-*sec*-butylborane with 1 equiv each of lithium triethylcarboxide and DCME revealed the presence in the reaction mixture of 1 equiv of free triethylcarbinol. Nmr revealed the intermediate to be the methyl *tert*-alkylchloroboronic ester[9] (eq 6). This intermediate is

$$(sec\text{-Bu})_3B + CHCl_2OCH_3 + LiOCEt_3 \xrightarrow[25^\circ]{THF} (sec\text{-Bu})_3C{-}B(Cl)(OCH_3) + HOCEt_3 + LiCl \quad (6)$$

readily oxidized with alkaline hydrogen peroxide in a manner similar to that previously noted for the ethylene glycol esters of the *tert*-alkylboronic acids formed in the carbonylation of organoboranes in diglyme[2] (eq 7).

$$(sec\text{-Bu})_3B + CO \xrightarrow[(CH_2OH)_2]{125^\circ} (sec\text{-Bu})_3C{-}B(O{-}CH_2)(O{-}CH_2) \xrightarrow[H_2O_2]{NaOH} (sec\text{-Bu})_3COH \quad (7)$$

Thus, treatment of the reaction product from DCME and lithium triethylcarboxide with alkaline hydrogen peroxide provided a 95% yield of tri-*sec*-butylcarbinol. Equally satisfactory results were realized with other organoboranes (Table I). Consequently, the DCME–lithium triethylcarboxide treatment of organoboranes provides the desired general route for replacement of the boron atom by carbon. As was pointed out, this transformation has major possibilities for the synthesis of carbon structures.

As indicated previously, the reaction of organoboranes with DCME and lithium triethylcarboxide is very rapid at room temperature or even 0°. In fact, the reaction is complete shortly after the addition of the alkoxide. Addition of 1 molar equiv of lithium triethylcarboxide to a solution of tri-*sec*-butylborane and DCME at 0° followed by warming to room temperature for merely 10 min results in a 95% yield of tri-*sec*-butylcarbinol on oxidation. Stirring at 0° for 15 min gives a 90% yield of the tertiary carbinol. The simplicity of the reaction, the moderate temperature, and the speed with which it occurs offer major advantages over the procedures previously availabe for converting organoboranes to the corresponding carbon structures (eq 3 and 4). It clearly possesses very wide generality, as indicated by its use to synthesize 1-cyclohexylcyclohexanol and triphenylcarbinol (Table I).

Because of the marked facility of the reaction, we thought that less hindered alkoxides than lithium triethylcarboxide might be effective. However, the less hindered trialkylboranes proved to be highly sensitive to the steric requirements of the alkoxide, whereas the more hindered trialkylboranes can tolerate less hindered alkoxides than lithium triethylcarboxide. The results realized with three lithium alkoxides of increasing steric bulk with a series of trialkylboranes of varying steric requirements and DCME are presented in Table II. Lithium alkoxides are superior to sodium or potas-

(5) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(6) H. C. Brown, "Boranes in Organic Synthesis," Cornell University Press, Ithaca, N. Y., 1972.

(7) H. C. Brown, B. A. Carlson, and R. H. Prager, *J. Amer. Chem. Soc.*, **93**, 2070 (1971).

(8) H. C. Brown and B. A. Carlson, *J. Organometal. Chem.*, in press.

(9) Nmr shifts of the methoxy protons were correlated with those of the corresponding dimethyl-*tert*-alkylboronic ester and other methylalkylchloroboronic esters and dimethylalkylboronic esters reported by H. Vahrenkamp and V. Noth, *J. Organometal. Chem.*, **13**, 23 (1968).

TABLE II

REACTION[a] OF TRIALKYLBORANES WITH DCME UNDER THE INFLUENCE OF A SERIES OF LITHIUM ALKOXIDES OF INCREASING STERIC BULK

Lithium alkoxide	Yield of trialkylcarbinol oxidation product, %[b] (n-Bu)3B	(sec-Bu)3B	(c-Hex)3B
Lithium *tert*-butoxide	33	86	77
Lithium *tert*-amyloxide	55	88	79
Lithium triethylcarboxide	84	95	92

[a] Carried out under standard conditions of addition of 1 molar equiv of lithium alkoxide to a stirred solution of 1 molar equiv of trialkylborane plus 1.1 molar equiv of DCME in THF at 0° followed by warming to room temperature for 30 min and oxidation with alkaline hydrogen peroxide. [b] Analysis by glpc.

sium alkoxides, as previously observed for the reaction of tri-*n*-butylborane with chlorodifluoromethane.[7]

The following procedure describing the preparation of tricyclopentylcarbinol from tricyclopentylborane is representative. In an oven-dried 300-ml flask, maintained under a nitrogen atmosphere and fitted with a septum inlet, magnetic stirrer, and reflux condenser, are placed 50 ml of a 1 *M* solution of tricyclopentylborane in THF prepared by the hydroboration of cyclopentene.[5,6] The solution is cooled to 0° and 55 mmol (5.33 g) DCME are added followed by the addition of 50 mmol of lithium triethylcarboxide (27 ml of a 1.84 *M* solution in hexane) over 5 min. The reaction is then allowed to warm to room temperature for 30 min during which time a heavy white precipitate of lithium salt forms. Then, 50 ml of 95% ethanol is added followed by 12 g of sodium hydroxide. Oxidation is accomplished by the slow, careful addition of 40 ml of 30% hydrogen peroxide at 0° followed by warming to 50–60° for 1 hr. The aqueous phase is salted out with anhydrous potassium carbonate and the organic phase is separated. The solvents are removed on a rotary evaporator and the residue is fractionally distilled under reduced pressure giving 10.8 g (91%) of tricyclopentylcarbinol, bp 152–153° (2 mm). Nmr, ir, and glpc were checked against those of an authentic sample of tricyclopentylcarbinol obtained from the carbonylation of tricyclopentylborane.[2]

It is of great interest why the reaction of DCME ($HCCl_2OCH_3$) is so much faster than the corresponding reaction of chloroform ($HCCl_3$).[7] Hine has suggested that DCME, in contrast to chloroform, may react with bases by a concerted mechanism to go directly to methoxychlorocarbene.[10,11] However, discussion of this possibility will be deferred until we can complete an investigation now underway.

(10) J. Hine, R. J. Rosscup, and D. C. Duffey, *J. Amer. Chem. Soc.*, **82**, 6120 (1960).

(11) Methoxycarbene, presumably formed from lithium alkyls and DCME, does not give the clean reaction with organoboranes observed here: A. Suzuki, S. Nozawa, N. Miyaura, M. Itoh, and H. C. Brown, *Tetrahedron Lett.*, 2955 (1969).

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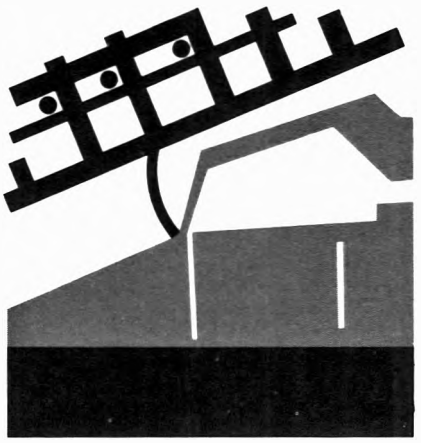
Electrodeposition of Coatings



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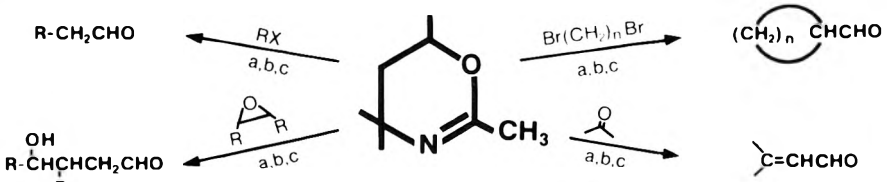
OF ALDEHYDES AND ESTERS

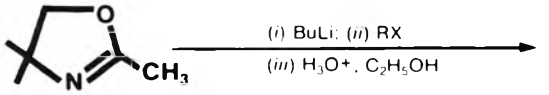
Meyers and coworkers have recently demonstrated a reaction sequence for the two-carbon homologation of electrophiles to aldehydes using **5,6-dihydro-2,4,4,6-tetramethyl-4*H*-1,3-oxazine**.[1]



Reagents: a = BuLi; b $NaBH_4$; c H_3O^+

The sequence involves (*i*) the generation of a carbanion with butyllithium, (*ii*) the reaction of the carbanion with electrophiles to give C-alkylated products, (*iii*) the reduction of the alkylated oxazines with $NaBH_4$ and (*iv*) the hydrolysis of the tetrahydrooxazines to aldehydes. In this manner alkyl halides afford good overall yields of the *homologous aldehydes*. Dihaloalkanes, also, are converted to *cyclic aldehydes*, while epoxides react to form *γ-hydroxyaldehydes*. Ketones give good yields of *α,β-unsaturated aldehydes*. Cleavage of the alkylated oxazines without reduction by $NaBH_4$ provides substituted acetic esters.

In contrast, oxazolines formed by reacting the carbanion of **2,4,4-trimethyl-2-oxazoline** with alkyl halides cannot be reduced with $NaBH_4$ but are readily hydrolyzed to *substituted acetic esters*.[2]



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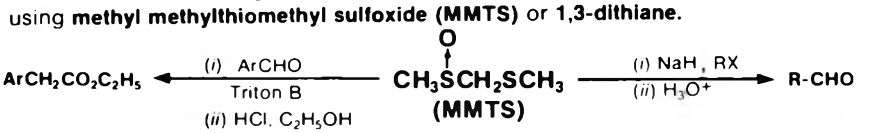
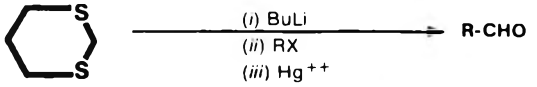
1. A.I. Meyers *et al.*, *J. Org. Chem.*, **38**, 36 (1973).
2. A.I. Meyers and D.L. Temple, Jr., *J. Amer. Chem. Soc.*, **92**, 6644 (1970).

17,963-9	5,6-Dihydro-2,4,4,6-tetramethyl-4*H*-1,3-oxazine	10g	6.00	50g	19.00
17,874-8	2,4,4-Trimethyl-2-oxazoline	25g	7.20	100g	19.25

A one-carbon homologation of alkyl halides to aldehydes may be effected by using **methyl methylthiomethyl sulfoxide (MMTS)** or **1,3-dithiane.**



The carbanion derived from MMTS reacts with alkyl halides to give aldehyde dimethyl mercaptal S-oxides which are readily hydrolyzed with a catalytic amount of sulfuric acid to the corresponding *aldehydes*.[1] The reaction of MMTS and an aromatic aldehyde with Triton B followed by cleavage in an alcohol containing acid yields *phenylacetic esters*.[2]



2-Lithio-1,3-dithiane, formed from 1,3-dithiane and butyllithium, reacts with alkyl halides to give good yields of aldehydes after oxidative hydrolysis with mercuric salts.[3]

References
1. K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, 3151 (1971).
2. K. Ogura and G. Tsuchihashi, *ibid.*, 1383 (1972).
3. D. Seebach, *Synthesis*, 17 (1969).

17,795-4	Methyl methylthiomethyl sulfoxide (MMTS)	12.4g†	13.00	50g	38.00
15,787-2	1,3-Dithiane	12g	8.50	25g	14.15	100g 44.00

† Designates molar unit