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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 6

MARCH 23, 1973

Organic Fluoronitrogens. XI.[1] Hydroxy Addition Compounds of Fluorimines

J. L. ZOLLINGER,* C. D. WRIGHT, J. J. MCBRADY, D. H. DYBVIG, F. A. FLEMING, G. A. KURHAJEC, R. A. MITSCH, AND E. W. NEUVAR

Contribution No. 670 from the Central Research Laboratories, 3M Company, St. Paul, Minnesota 55133

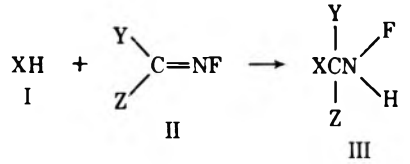
Received September 27, 1972

The reaction of *N*-fluorimines with hydroxy compounds yields saturated adducts possessing the NFH function. The adducts undergo a number of reactions depending on structure. These include loss of HF or HNF_2 to give new fluorimines, and fluorination to yield NF_2 derivatives. The addition of alcohols to pentafluoroguanidine (**1**) followed by fluorination of the resulting adduct affords a high-yield route to $C(NF_2)_3$ compounds.

Recent brief publications[2-4] on addition reactions of *N*-fluorimino (>C=NF) compounds prompted us to describe our rather extensive work in this area. This paper will deal with the addition of OH compounds to *N*-fluorimines and some of the reactions of the adducts; an accompanying paper[5] will consider the addition of NH compounds to *N*-fluorimines.

The *N*-fluorimines to be considered are listed in Table I.[6-9] Most of the reactions and discussion will concern compounds **1** and **4**.

Adducts are formed according to the following general equation.

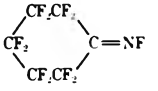


X = RO, R_2C=NO, RCOO, etc.

The ease of addition is a function of the nucleophilicity of the addend I and the structure of the fluorimine II. Methyl alcohol reacts at room temperature with **1**, **2**, and **3**, while heat or a basic catalyst is required to prepare the methyl alcohol adduct of **4** or **5**. Negatively substituted alcohols (*e.g.*, CF_3CH_2OH) and carboxylic acids require a basic catalyst for addition to **1**.

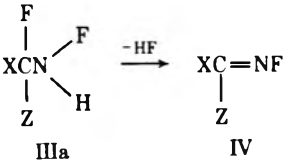
TABLE I

N-FLUORIMINO COMPOUNDS

Compd	Structure	No.	Bp, °C	Ref
Pentafluoroguanidine	$(F_2N)_2C$=NF	1	−2	*a*
Tetrafluoroformamidine	F_2NCF=NF	2	−29	*a*
N-Fluorotetrafluoroethylidine imine	CF_3CF=NF	3	−32	*b*
N-Fluorohexafluoroisopropylidine imine	$(CF_3)_2C$=NF	4	−12	*c*
N-Fluorodecafluorocyclohexylidine imine		5	60	*d*

[a] Reference 6. [b] Reference 7. [c] Reference 8. [d] Reference 9.

The adduct III is stable when Y and Z are perfluoroalkyl groups. For example, $C_2H_5OC(CF_3)_2NFH$ distills at 93–94°.[2] However, if Y (or Z) is F, the adduct III is not isolated; instead, a new fluorimine IV is the product resulting from the elimination of HF from the unstable intermediate IIIa.



To illustrate, when CH_3OH reacts with CF_3CF=NF (**3**) at room temperature, the intermediate adduct is not observed and conversion to $CH_3OC(CF_3)$=NF (**6**) is obtained within 5 min.

If Y (or Z) of III is the NF_2 group, the adducts are more stable than the IIIa type, but loss of HNF_2 may

(1) Previous publication in this series: R. A. Mitsch, *J. Org. Chem.*, **33**, 1847 (1968).

(2) K. N. Makarov, B. L. Dyatkin, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (8), 1924 (1968), describe the addition of alcohols and amines to $(CF_3)_2C$=NF.

(3) D. L. Ross, C. L. Coon, and M. E. Hill, *J. Org. Chem.*, **35**, 3093 (1970), discuss the addition of methanol to $C_2F_7C(NF_2)$=NF and fluorination of the adduct.

(4) A. V. Fokin, *et al.*, *Izv. Akad. Nauk SSSR, Ser. Khim.* (1), 199 (1970), describe the addition of methanol to $(F_2N)_2C$=NF and fluorination of the adduct.

(5) C. D. Wright and J. L. Zollinger, *J. Org. Chem.*, **38**, 1075 (1973).

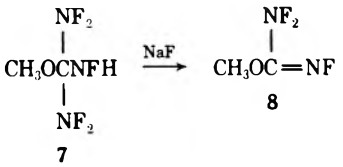
(6) R. J. Koshar, D. R. Husted, and C. D. Wright, *ibid.*, **32**, 3859 (1967).

(7) B. C. Bishop, J. B. Hynes, and L. A. Bigelow, *J. Amer. Chem. Soc.*, **86**, 1827 (1964).

(8) R. D. Dresdner, F. N. Tlumac, and J. A. Young, *ibid.*, **82**, 5831 (1960).

(9) R. A. Mitsch, *ibid.*, **87**, 328 (1965).

also occur. The loss is spontaneous in some cases, but heating or treatment with basic reagents is usually required. For example, $(CH_3)_2CHOH$ and **1** yield a mixture of $(CH_3)_2CHOC(NF_2)_2NFH$ (**13**) and $(CH_3)_2CHOC(NF_2)=NF$ (**14**) in 1 day at room temperature. The adduct **7** (from CH_3OH and **1**) is stable for weeks



7 **8**

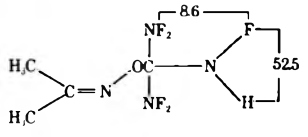
in glass at room temperature, but passage over NaF pellets in a stream of N_2 at about 25° results in complete conversion to methoxytrifluoroformamidine (**8**).

Fluorine and proton nmr spectroscopy were the most useful analytical tools for following the course of reactions and assigning product structures.[10] This is illustrated in Table II for the acetone oxime adduct of **1**.

TABLE II

NMR SPECTRUM OF $(CH_3)_2C{=}NOC(NF_2)_2NFH$ (**30**)

	Peak	Type	Assignment	Area ratio
Fluorine, ϕ	−20.5	Doublet	NF_2	4
	133.1	Double quintet	NFH	1
Proton, τ	0.90	Doublet	NFH	1
	7.94	Singlet	CH_3	3
	8.02	Singlet	CH_3	3
J values, Hz				



The NFH group is a doublet in both the ^{19}F and ^1H spectra. The wide splitting (52.5 Hz) present in this doublet in both spectra is characteristic of F and H attached to the same atom. The fivefold structure of each of these doublet peaks in the ^{19}F nmr spectrum arises from interaction with the F of the NFH group by the four F atoms of the NF_2 groups. The rather narrow splitting (8.6 Hz) observed is of the expected order of magnitude for F atoms separated by three atoms. The presence of two methyl group peaks in the ^1H nmr spectrum of **30** is expected from the geometry of the molecule.

Table III lists some representative adducts of **1** along with yields and ^{19}F nmr absorptions. Additional reaction details and analytical data are reported in the Experimental Section for selected derivatives listed in Table III. Chemical shifts and spin–spin couplings of most adducts are similar to the values found for **30** discussed above. In many adducts of **1**, however, the NF_2 and NFH absorptions are collapsed into broad singlet peaks and do not show the splittings observed in **30**. It should also be noted that the position of the NFH peak in alcohol adducts of **1** is sensitive to the solvent system. For example, the NFH peak of **7** is at ϕ 144.6 when excess CH_3OH is present and at 138.9 when free of CH_3OH.

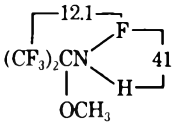
(10) J. P. Freeman in "Advances in Fluorine Chemistry," Vol. 6, J. C. Tatlow, R. D. Peacock, and H. H. Hyman, Ed., Butterworths, London, 1970, p 313.

In addition to the alcohols listed in Table III, C_2H_5OH, n-C_3H_7OH, c-$C_6H_{11}OH$, $OCH_2CH_2CH_2CH$-CH_2OH, $HO(CH_2)_{11}NH_2 \cdot HClO_4$, and $HO(CH_2)_9COOH$ also formed adducts with **1** in high yields. Reaction of **1** with $(CH_3)_3COH$ gave no reaction at room temperature and mainly decomposition products on heating or catalysis. The reaction of *m*-cresol and **1** resulted in an explosion. Negatively substituted phenols gave adducts (**20** and **21**).

Besides the base-catalyzed reaction of CH_3COOH and **1**, HCOOH and C_6H_5COOH also formed addition products. However, CF_3COOH failed to react under similar conditions. Degradation products and by-products in the reaction of CH_3COOH with **1** included CH_3COF, HNF_2, and $FC(NF_2)_2NFH$ (**38**). The latter compound appears to arise from the addition of HF to **1**. ^{19}F nmr absorptions at ϕ −21.8 (s, 4, NF_2), 133.8 (t, 1, CF), and 136.4 (d, J = 53 Hz, 1, NFH) are consistent with the assigned structure. **38** was observed frequently in reactions involving pentafluoroguanidine (**1**).

The fluorimine **4** did not react with alcohols unless heated or catalyzed. In the presence of trimethylamine, several alcohols and acetone oxime formed saturated addition products in high conversions.

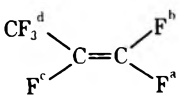
These are listed in Table IV along with yields and ^{19}F nmr data. As in the case with adducts of **1**, the NFH absorption is a complex doublet at high field. The broad doublet splitting is due to the H and the multiplet to the CF_3 groups. The CF_3 groups are split into a doublet by NF. The spin–spin coupling constants (hertz) are shown for **39**.



39

Reaction of lower aliphatic alcohols with **2** or **3** are rapid at room temperature, yielding mainly new fluorimines by loss of HF from the unstable adducts, as discussed earlier. Both syn and anti isomers are obtained in the reaction of **3** with CH_3OH or n-C_4H_9OH. The pure isomers isolated from the CH_3OH reaction by glpc were carefully analyzed. Structure, nmr absorption (ϕ, τ), and splitting (hertz) are shown along with other physical property data in Table V.

The absolute structure assignments for **6a** and **6b** are based on the analogous structure

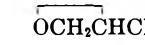
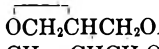
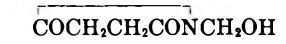
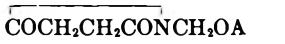


where J_{ad} = 8.3 and J_{bd} = 21.7 Hz.[11] The corresponding spin–spin coupling constants for **6a** and **6b** are 8.8 and 24.6 Hz, respectively (Table V).

The reaction of CF_3CH_2OH and **3** required pyridine catalysis at room temperature. The major product (67%) was $CF_3CH_2OCF(CF_3)NFH$ (**45**), as evidenced by the characteristic complex multiplet in the ^{19}F nmr at ϕ 138.2 due to NFH and the sharp peak at 130.3 for the CF group. About 33% of the product was CF_3CH_2-$OC(CF_3)=NF$ (**46**) (isomer a, probably syn) with ^{19}F

(11) H. M. McConnell, *et al.*, *J. Chem. Phys.*, **24**, 479 (1956).

TABLE III
HYDROXY ADDUCTS OF $(F_2N)_2C{=}NF$ (1)[a]

Registry no.	Reactant	Product[b]	No.	Yield,[c] %	Fluorine nmr absorptions, ϕ[d] NF_2	NFH	=NF
67-56-1	CH_3OH	$CH_3OC(NF_2)_2NFH$	7	90	−20.6	138.9	
71-36-3	n-C_4H_9OH	n-C_4H_9OA[b]	9	88	−21.1	138.1	
		n-$C_4H_9OC(NF_2){=}NF$	10	~10	−42.8		44.3
112-53-8	n-$C_{12}H_{25}OH$	n-$C_{12}H_{25}OA$	11	90	−20.8	137.2	
		n-$C_{12}H_{25}OC(NF_2){=}NF$	12	~10	−42.7		44.0
67-63-0	$(CH_3)_2CHOH$	$(CH_3)_2CHOA$	13	61	−21.0	137.4	
		$(CH_3)_2CHOC(NF_2){=}NF$	14	18	−42.6		43.0
100-51-6	$C_6H_5CH_2OH$	$C_6H_5CH_2OA$	15	70	−21.3	137.3	
		$C_6H_5CH_2OC(NF_2){=}NF$	16	10	−42.8		40.6
107-21-1	$HOCH_2CH_2OH$	$HOCH_2CH_2OA$	17	90	−20	142	
	$HOCH_2CH_2OH$[e]	$AOCH_2CH_2OA$	18	80	−21.7	142.2	
75-89-8	CF_3CH_2OH[f]	CF_3CH_2OA	19	60	−21.7	138.5	
120-47-8	p-$C_2H_5OOCC_6H_4OH$[f]	p-$C_2H_5OOCC_6H_4OA$	20	90	−22.0	138.9	
100-02-7	p-$NO_2C_6H_4OH$	p-$NO_2C_6H_4OA$	21	80	−23.2	138.6	
107-07-3	$ClCH_2CH_2OH$	$ClCH_2CH_2OA$	22	70	−21.2	138.9	
556-52-5			23	90	−20.9	142.3	
107-18-6	$CH_2{=}CHCH_2OH$	$CH_2{=}CHCH_2OA$	24	80	−21	141.7	
107-19-7	$CH{\equiv}CCH_2OH$	$CH{\equiv}CCH_2OA$	25	70	−21.3	142	
46-35-5	CH_3OOCCH_2OH	CH_3OOCCH_2OA	26	80	−21.6	140.7	
1679-53-4	$HOOC(CH_2)_9OH$	$HOOC(CH_2)_9OA$	27	80	−21	143.6	
38092-76-1	$HClO_4 \cdot H_2NCH_2CH_2OH$[e,f]	$HClO_4 \cdot H_2NCH_2CH_2OA$	28	80	−22	141.4	
15588-62-2	$HClO_4 \cdot H_2NOH$[e,f]	$HClO_4 \cdot H_2NOA$	29	30	−31	113	
127-06-0	$(CH_3)_2C{=}NOH$	$(CH_3)_2C{=}NOA$	30	90	−20.5[g]	133.1[g]	
2580-79-2	$+C(NH_2){=}NOH]_2$	$+C(NH_2){=}NOA]_2$	31	80	−22.3	138.3	
1794-86-1	$Cl_2C{=}NOH$[f]	$Cl_2C{=}NOA$	32	80	−23.4	137.5	
31767-13-2	$CH_3OOCCH{=}NOH$	$CH_3OOCCH{=}NOA$	33	70	−22.6	137.6	
5146-68-9			34	90	−22.0	139.6	
64-19-7	CH_3COOH[h]	CH_3COOA	35	70	−23	132	
7722-84-1	HOOH (98%)	HOOA	36	70	−22.5	139.5	
75-91-2	$(CH_3)_3COOH$[f]	$(CH_3)_3COOA$[i]	37	80	−22.9	140.3	

[a] In a typical reaction, the anhydrous OH reagent was treated with a 10-30% excess of 1 for 1 day at room temperature in a sealed nmr tube, with internal $CFCl_3$ reference, and, if needed, a solvent (usually CH_3CN) and catalyst. [b] The products are nonvolatile liquids or solids. By-products such as HNF_2, $FC(NF_2)_2NFH$ (38), and small amounts of $ROC(NF_2){=}NF$ are not reported. A = $C(NF_2)_2NFH$. [c] Based on ^{19}F nmr analysis of reaction mixture. [d] Chemical shifts are in parts per million relative to $CFCl_3$ as internal reference.[16] Position of NFH peak is sensitive to the solvent system. [e] Large excess of 1. [f] Urea catalyst. [g] See text for detailed nmr analysis. [h] CH_3COOK catalyst, reaction 5 min at 0°. [i] Stable at −78°, unstable at 25°.

nmr peaks at ϕ 38.3 (=NF), 71.3 (CCF_3), and 76 (CH_2CF_3) in appropriate ratios. A weak absorption at ϕ 67.8 (CCF_3) may be due to a small amount of isomer b.

The reaction of CH_3OH and 2 gave a rapid room-temperature conversion to the same isomer of the fluorimine 8 as obtained from the reaction of the adduct 7 and NaF (above), by elimination of HF from the unstable intermediate adduct.

$$\underset{2}{F_2NCF{=}NF} + CH_3OH \longrightarrow [CH_3OCF(NF_2)NFH] \xrightarrow[66\%]{-HF} \underset{8}{CH_3OC(NF_2){=}NF}$$

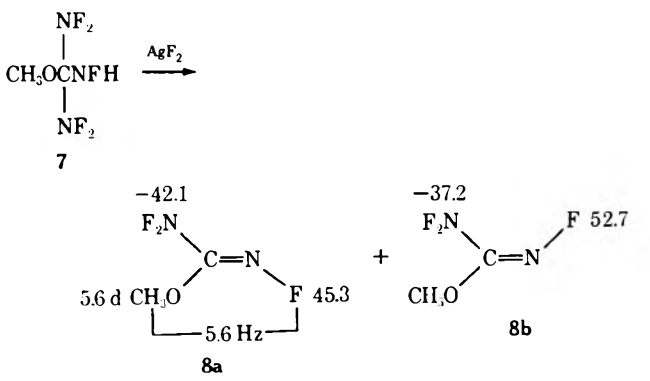
Other products isolated in this reaction include CH_3OCONF_2 (7%) and $(CH_3O)_2C{=}O$ (15%). These products are apparently derived from 8 *via* successive hydrolysis and methanolysis steps.

$$\underset{8}{CH_3OC(NF_2){=}NF} \xrightarrow{H_2O} CH_3O\overset{O}{\overset{\|}{C}}NF_2 \xrightarrow{CH_3OH} CH_3O\overset{O}{\overset{\|}{C}}OCH_3$$

The reaction of isopropyl difluorocarbamate with isopropyl alcohol to yield diisopropyl carbonate has been reported.[12a]

(12) (a) V. Grakauskas and K. Baum, *J. Amer. Chem. Soc.*, **91**, 1679 (1969); (b) R. A. Mitsch, E. W. Neuvar, R. J. Koshar, and D. H. Dybvig, *J. Heterocycl. Chem.*, **2**, 371 (1965).

Reactions of Adducts. Conversion to Fluorimines.—The most characteristic reaction of fluorimine adducts derived from 1, 2, or 3 is loss of HF or HNF_2 to yield new fluorimines, *e.g.*, 6, 8, and 14. As noted in the earlier discussion, these derivatives may form spontaneously, by heating or by treatment with basic reagents. As described earlier, only one geometric isomer of 8 (8a) was formed when 7 was passed over a

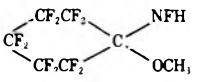


bed of NaF pellets or 2 was treated with CH_3OH. However, when 7 was treated with AgF_2 at 0°, both syn and anti isomers were obtained.

Isomer a, compound 8a, has been assigned the syn ($CH_3O/{=}NF$) configuration shown on the basis of a com-

TABLE IV

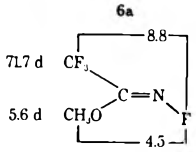
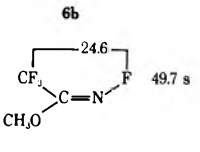
ADDUCTS OF 4[a] AND 5[b]

Fluorimine	Reactant	Product	No.	Yield, %	^{19}F Nmr spectra, ϕ[c] CF$_3$	NFH
4	CH_3OH	$(CF_3)_2C(OCH_3)NFH$	39	80	73.6	143.4
4	$(CH_3)_2CHOH$	$(CF_3)_2C[OCH(CH_3)_2]NFH$	40	70	73.8	142.8
4	n-C_4H_9OH	$(CF_3)_2C(OC_4H_9)NFH$	41	100	73.7	144.6
4	$(CH_3)_2C{=}NOH$	$(CF_3)_2C[ON{=}C(CH_3)_2]NFH$	42	100	72.8	140.6
4	CF_3CH_2OH[d]	$(CF_3)_2C(OCH_2CF_3)NFH$	43	80	76.5 82.2 (CF_3CH_2)	138
5	CH_3OH[b]		44	60	110–145 (ring)	150[e]

[a] Reactions were run overnight at room temperature in sealed glass nmr tubes with excess of OH reagent, plus $(CH_3)_3N$ catalyst and $CFCl_3$ solvent (except as noted in *d*). [b] Run as in *a*, except no catalyst and reaction heated for 16 hr at 53°. [c] NFH absorption may be a few parts per million high because of excess OH compound; see text. [d] CH_3CN solvent. No adduct with $CFCl_3$ solvent. [e] ^{1}H nmr peaks: τ 1.5 (NH), 6.2 (CH_3).

TABLE V

PROPERTIES OF THE ISOMERS OF 6

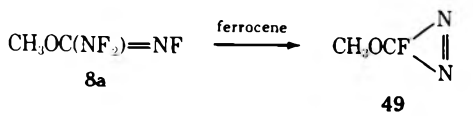
No.	6a	6b
Structure and nmr (ϕ, τ)		
Isomer	a	b
Config	syn	anti
Ratio	1	3
T_R[a]	336	370
Bp, °C[b]	47	50
Mp, °C	−96	−90
Ir, μ (C=N)	6.09	6.01
Mol wt[c]	150	152

[a] Relative to $CFCl_3$ = 100 on column C (Experimental Section) at 50°. [b] Extrapolated to 760 mm from vapor pressure data. [c] From mass spectral effusion rates on m/e 76. Formula weight = 145. (See Experimental Section for elemental analysis and mass spectral data.)

parison of the nmr spectral data (ϕ, τ) with that given for the syn (CH_3O/=NF) isomer of $CF_3C(OCH_3)$=NF (**6**) (Table V). The ^{1}H nmr peaks for CH_3 in **6a** and **8a** are both doublets (split by F in C=NF) and are identical in chemical shift (τ 5.6) and nearly identical in coupling constants (4.5 *vs.* 6 Hz). ^{19}F nmr absorptions for F in the C=NF group also give support for the assigned structures. The syn isomers **6a** and **8a** have peaks at ϕ 46.7 and 45.3, respectively, while both the anti isomers **6b** and **8b** have absorptions at a slightly higher field, ϕ 49.7 and 52.7, respectively. Additional data on these isomers are reported in the Experimental Section.

A partial conversion to the two geometric isomers of $CF_3CO_2CH_2CH_2OC(NF_2)$=NF (**47**) formed during gas chromatography of $CF_3CO_2CH_2CH_2OC(NF_2)_2NFH$ (**48**) (from **17** and trifluoroacetic anhydride) at 100°. Most of **48** survived this separation procedure.

The alkoxy trifluoroformamidine compounds undergo the reductive defluorination cyclization reaction described by Mitsch.[1] This is illustrated by the conversion of **8a** to fluoromethoxydiazirine (**49**) in 90% yield.



The characterization of **49** has been reported,[12b] but the synthetic route has not been described before.

Fluorination. Preparation of Tris(difluoroamino)-methyl Compounds.—A very general reaction of fluorimine adducts containing the NFH group is fluorination with elemental fluorine to convert this function to the NF_2 group. Under suitable conditions (dilute F_2, low temperature, solvents) good conversion to the corresponding NF_2 compound is obtained with no replacement of other H atoms in the molecule by F. Adducts of **1** are converted by this process to compounds containing the highly fluorinated tris(difluoramino)methyl, $C(NF_2)_3$, group. For example see below.

$$\underset{\mathbf{7}}{CH_3OC(NF_2)_2NFH} \xrightarrow[-35°]{F_2} \underset{\mathbf{50}}{CH_3OC(NF_2)_3}$$

The ^{19}F nmr spectrum of **50** shows only a single broad peak at ϕ −22.2. More concentrated F_2 and higher temperatures yield, in addition to **50**, the more highly fluorinated compounds $FCH_2OC(NF_2)_3$ (**51**) and $F_2CHOC(NF_2)_3$ (**52**). The presence of F atoms in the methyl group shifts the ^{19}F nmr peaks (NF_2) to lower field: ϕ −23.5 for **51** and −24.5 for **52**.

The preparation of several $C(NF_2)_3$ compounds is summarized in Table VI. Fluorination conditions, yields, and ^{19}F nmr chemical shifts are given. Purification was effected by glpc or column chromatography (solids). Additional data and analytical results are reported in the Experimental Section.

Fluorination of **39** gave the NF_2 derivative **64**, a liquid, bp 63°.

$$\underset{\mathbf{39}}{CH_3OC(CF_3)_2NFH} \xrightarrow{F_2} \underset{\mathbf{64}}{CH_3OC(CF_3)_2NF_2}$$

In contrast with the relatively unstable alcohol adducts of **1**, the $C(NF_2)_3$ derivatives have remarkably good stability if protected from reducing agents. For example, thermal stability is indicated by the isolation of $(F_2N)_3COCH_2CH_2OC(NF_2)_3$ (**54**) by chromatography at 100°. Chemical stability is illustrated by the sealed-tube reactions of mixtures of **50**, **51**, and **52** shown below.

$$\underset{\mathbf{51}}{FCH_2OC(NF_2)_3},\ \underset{\mathbf{52}}{F_2CHOC(NF_2)_3} + CH_3COONa \xrightarrow[150°,\ 3\ hr]{CH_3COOH}$$

slight reaction

$$\underset{\mathbf{50}}{CH_3OC(NF_2)_3},\ \underset{\mathbf{51}}{FCH_2OC(NF_2)_3} + CH_3COBr \xrightarrow[50°,\ 16\ hr]{BF_3}$$

no reaction

TABLE VI

TRIS(DIFLUORAMINO)METHYL COMPOUNDS FROM THE FLUORINATION OF PENTAFLUOROGUANIDINE (1) ADDUCTS[a]

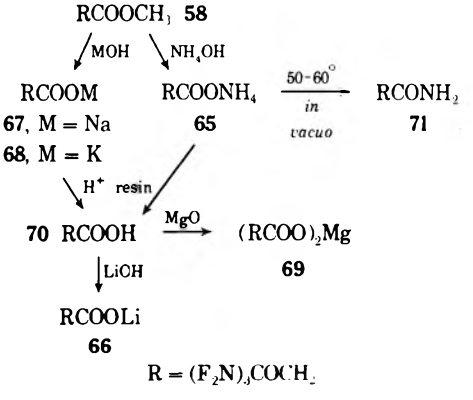
Fluorination			Product			
Adduct[b]	% F_2[c]	Temp range, °C	Formula[d]	No.	Yield, %	^{19}F nmr, ϕ, NF_2
7	2.7	−35	$CH_3OC(NF_2)_3$	50	30	−22.2
7	4.3	−20	CH_3OT[d]	50	10	−22.2
			FCH_2OT	51	30	−23.5
			F_2CHOT	52	25	−24.5
17	6	−20 to −10	$HOCH_2CH_2OT$	53	70	−23.6
18	5	−23 to 25	$TOCH_2CH_2OT$	54	80	−23
23	8	−20	OCH_2CHCH_2OT	55	70	−23.1
22	3	−45	$ClCH_2CH_2OT$	56	70	−23.1
34	5	−23 to 25	$COCH_2CH_2CONCH_2OT$	57	80	−24.3
26	5	0	CH_3OOCCH_2OT	58	80	−23.1
28	4	−23 to 0	$HClO_4 \cdot H_2NCH_2CH_2OT$	59	80	−24.0
33	3	−23 to 25	$CH_3OOCCH{=}NOT$	60	70	−24.0
30	3	−35	$(CH_3)_2C{=}NOT$	61	70	−24.4
			$FCH_2C(CH_3){=}NOT$	62	Small	−26.2
32	10	−30	$Cl_2C{=}NOT$	63	35	−25.2

[a] Fluorinations were conducted in CH_3CN or CF_3CH_2OH solvent in most cases. Adducts 7 and 30 were fluorinated without solvent [b] From Table III. [c] Diluted with N_2. [d] T = $C(NF_2)_3$.

Heating a mixture of **50** and **51** with $AlCl_3$ at 150° for 16 hr caused the decomposition of **50**, but **51** survived, apparently owing to its lower electron density at the ether oxygen when compared with **50**. *Caution.* Although moderate thermal and chemical stability is indicated by the above information, these $C(NF_2)_3$ compounds are still powerful oxidizing agents and are also sensitive to impact. (See Experimental Section.)

Tris(difluoramino)methyl compounds possessing other reactive functional groups have been subjected to a number of chemical reactions with high retention of the $C(NF_2)_3$ structure. Methyl [tris(difluoramino)-methoxy]acetate (**58**) has been transformed to the free acid and several of its salts. Heating the ammonium salt afforded the corresponding amide. These reactions are shown in Scheme I. Except for amide

SCHEME I



formation all reactions were run at room temperature, usually in alcohol or water. Further data are reported in Table IX.

Reaction of $(F_2N)_3COCH_2CH_2OH$ (**53**) with $(CF_3CO)_2O$ gave a good conversion to the trifluoroacetyl derivative **72**.

The perchlorate salt **59** (Table VI) was readily converted to the free amine $(F_2N)_3COCH_2CH_2NH_2$ (**73**) by reaction with base. Other salts were prepared by neutralization of **73** with the appropriate acid. In this manner, salts containing the following anions were prepared: Cl^-, Br^-, NO_3^-, HF_2^-, SO_4^{2-}, and $C_2O_4^{2-}$. In addition to these, a salt, mp 83–88°, bearing the $C(NF_2)_3$ group in both cation and anion was prepared. (See Table X).

$$\mathbf{59} + \mathbf{68} \xrightarrow{CH_3OH} (F_2N)_3COCH_2CH_2NH_3^+ {}^-OOCCH_2OC(NF_2)_3 + KClO_4$$
79

The Cl atoms in $(F_2N)_3CON{=}CCl_2$ (**63**) were easily displaced by nucleophilic reagents. Thus, reaction with $(CH_3)_2NH$ at 25° gave the corresponding bis(dimethylamino) compound (nmr and ir), and treatment with $NaOCH_3$ afforded the expected methoxy derivative **80**.

$$\mathbf{63} + NaOCH_3 \xrightarrow[6\text{ hr, }25°]{CFCl_3} (F_2N)_3CON{=}C(OCH_3)_2$$
80

Other Adduct Reactions.—Heating the adduct **39** with acetic anhydride at 80–90° gave no evidence for formation of the *N*-acetyl derivative. Instead, a gradual conversion to the starting imine **4** and methyl acetate took place, indicating that an equilibrium exists between **39** and the starting materials which is shifted to the left as CH_3OH forms the acetate.

$$(CF_3)_2C{=}NF + CH_3OH \rightleftharpoons CH_3OC(CF_3)_2NFH$$
4 **39**

Reaction of **7** with acetyl chloride or Cl_2 in a sealed tube at room temperature gave a partial conversion to a chloro compound **81**. Methyl acetate was a by-product in the first reaction. Cleavage of ethers by acid chlorides to yield esters and alkyl chlorides is

$$CH_3OC(NF_2)_2NFH + CH_3COCl \longrightarrow ClC(NF_2)_2NFH + CH_3COOCH_3$$
7 **81**

known;[13] however, zinc chloride was required as catalyst. ^{19}F nmr absorptions for **81** are at ϕ − 31.2 (NF_2) and 107.4 (NFH), the latter a double quintet, in

(13) R. C. Fuson, "Advanced Organic Chemistry," Wiley, New York, N. Y., 1950, p 178.

an area ratio of 4:1. The presence of Cl shifts the F peaks to lower field. The related compound $ClCF(NF_2)_2$, prepared from **38** and NO_2Cl, has NF_2 absorptions in the same region as **81**, ϕ − 30.9.[14] The adduct **7** reacts with gaseous formaldehyde in acetonitrile to give an 80% conversion to a mixture of the methylol and methylene derivatives in a ratio of about 2:1.

$$7 + CH_2O \xrightarrow[CH_3CN]{25^\circ} CH_3OC(NF_2)_2NFCH_2OH + [CH_3OC(NF_2)_2NF]_2CH_2$$
82 **83**

A broad singlet peak in the ^{19}F nmr at ϕ − 23 was assigned to NF_2 of **82** and **83**, and absorptions at 85 and 79, both triplets ($J \cong 40$ Hz) with finer splittings ($J \cong 12$ Hz), were attributed to NF of **82** and **83**, respectively. Analogous reactions have been reported[12] for the *N*-fluorourethane, $C_2H_5OCONFH$. The resulting methylol derivative $C_2H_5OCONFCH_2OH$ has a ^{19}F nmr chemical shift for the NF group of ϕ 75, a triplet with J = 32 Hz, position and splittings in reasonable agreement with the values found for NF of **82**.

Reaction of **7** with NOF, CF_3COONO, or NO_2Cl resulted in the replacement of the NFH group with F to yield $CH_3OCF(NF_2)_2$ (**84**), with ^{19}F nmr peaks at ϕ

$$CH_3OC(NF_2)_2NFH \xrightarrow[-78^\circ]{NOF}$$
7

$$CH_3OC(NF_2)_2N(NO)F \xrightarrow{25^\circ} CH_3OCF(NF_2)_2$$
84

$$7 \xrightarrow[25^\circ]{NO_2Cl} CH_3OC(NF_2)_2N(NO_2)F \longrightarrow \mathbf{84} + CH_3OC(NF_2)_2NFCl$$
85

− 18.9 (NF_2) and 120 (CF). The suspected unstable intermediates in these reactions are the NNO and NNO_2 compounds shown.

In the reactions of NOF with **7**, a stable blue color (due to the NNO intermediate) formed immediately at −78°, but, on warming to room temperature, the reaction mixture became irreversibly colorless and **84** was present. A second product in the NO_2Cl reaction was tentatively identified as $CH_3OC(NF_2)_2NFCl$ (**85**), ^{19}F nmr ϕ − 24.8 (NF_2) and 9.7 (NFCl). A similar chemical shift, ϕ 7.9, has been reported[15] for NFCl in the compound CF_3NFCl.

Experimental Section

Precautions.—Some of the fluoronitrogen compounds described in this paper are shatteringly explosive under certain conditions. All adducts and fluorinated adducts of **1** should be considered explosive, while derivatives of **3**, **4**, and **5** are less sensitive. Suitable protective equipment should be used during all phases of work with **1** and its derivatives. In regard to these latter compounds, we have operated within a quantity limit of 1 g in borosilicate glass vessels using poly(methylmethacrylate) shielding panels, face shields, ear plugs, and heavy leather gloves and jackets. For quantities greater than 1 g, remote handling is recommended. Some liquid products have exploded during phase changes (freezing, thawing, distillation) and impact. Besides exploding on impact, solids derived from **1** are also sensitive to abrasion or grinding. Although liquid nitrogen and liquid oxygen have been used as coolants for the transfer of small quantities of volatile fluoronitrogen compounds under vacuum, the use of nonflammable slush baths ($CFCl_3$, CCl_4, etc.) with temperatures above the melting point of the compound or mixture are preferred. A previous paper[6] in this series should be consulted for further precautions.

General.—The fluorimines **1** and **2** were prepared by the procedures reported.[6] The other fluorimines (**3**, **4**, and **5**) were synthesized by the reductive defluorination[9] of the appropriate difluoramino precursors or, in the case of **4**, the dehydrofluorination of a new compound, $(CF_3)_2CFNFH$ (**86**). Liquid alcohols were either distilled or predried over anhydrous $CaSO_4$ or molecular sieves. Other hydroxy compounds were commercial reagent chemicals or were synthesized and purified as required and noted in the appropriate experiment. Fluorine was obtained from the General Chemical Division of Allied Chemical Corp.

Nmr spectra were measured on a Varian V-4300-2 instrument operating at 40.0 MHz. Values for ^1H chemical shifts are given in τ units with respect to $(CH_3)_4Si$ as an internal reference, and values for the ^{19}F chemical shifts, employing $CFCl_3$ as internal reference, are given in ϕ units.[16] Infrared spectra were recorded by means of a Perkin-Elmer double-beam spectrophotometer, Model 21. A Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer was used to obtain the mass spectra and molecular weights by effusion rate measurements. An ionization potential of 70 eV and an ionization chamber temperature of 250° were employed. Gas–liquid partition chromatographic (glpc) analyses and separations were carried out on a Perkin-Elmer vapor fractometer, Model 154-D, equipped with a thermistor detector and modified gas sampling and back flush valves. Dry helium was used as the carrier gas. The various nitrogen–fluorine compounds eluting from the columns were collected in flame-dried borosilicate glass traps cooled with liquid nitrogen or appropriate nonflammable slush baths. Columns used for glpc are listed in Table VII.

TABLE VII
GAS CHROMATOGRAPHY COLUMNS

Column	Liquid phase	%	Support	Length, ft	Diameter, in.
A	LSX-30295[a]	20	Celite[b]	10	0.5
B	FS-1265[a]	20	Fluoropak 80[c]	3.3	0.5
C	FS-1265	33	Chromosorb P[b]	24	0.25
D	FS-1265	20	Chromosorb P	15	0.5
E	FS-1265	30	Anakrom ABS[d]	6	0.375
F	KF-8126[e]	33	Chromosorb P	6.5	0.5
G	KF-8126	33	Chromosorb P	18	0.5
H	SE-30[f]	20	Celite	10	0.25
I	SF-96[f]	25	Anakrom ABS	6.5	0.5
J	FC-45[e]	25	Celite	6.5	0.5

[a] Dow Corning. [b] Johns-Manville. [c] The Fluorocarbon Co. [d] Analab Co. [e] 3M Co. [f] General Electric Co.

Relative retention times (T_R) for compounds isolated by glpc were calculated according to the following equation.

$$T_R = (T_{compound} - T_{air})/(T_{ref} - T_{air}) \times 100$$

Elemental analyses were carried out using published procedures.[17] Analysis of some compounds proved difficult because of explosions and problems encountered in purifying unstable materials. In these cases, structure determinations were based upon nmr, ir, and mass spectral data.

Adducts of Pentafluoroguanidine (1) and Other Fluorimines.—Approximate yields and some ^{19}F nmr absorptions are presented in Table III for derivatives of **1** and in Table IV for derivatives of **4** and **5**.

Apparatus and Procedure.—On a small scale (0.05–0.2 g), the addition compounds were prepared in the borosilicate glass tubes (~1.5 ml capacity) used for nmr spectroscopy. In a typical reaction, the dry reactant, catalyst (if needed), solvent (if used), and $CFCl_3$ containing $Si(CH_3)_4$ (nmr internal reference compounds)

(14) D. H. Dybvig (3M Co.), U. S. Patent 3,358,028 (1967).
(15) J. B. Hynes, B. C. Bishop, and L. A. Bigelow, *Inorg. Chem.*, **6**, 417 (1967).
(16) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959); G. V. D. Tiers, *ibid.*, **62**, 1151 (1958).
(17) P. B. Olson and R. E. Kolb, *Michrochem. J.*, **12**, 117 (1967); P. B. Olson and R. T. Knafla, *ibid.*, **13**, 362 (1968); J. G. Gagnon and P. B. Olson, *Anal. Chem.*, **40**, 1856 (1968).

were placed in the nmr tube. Then 1, or other fluorimine, was added by vacuum transfer employing a liquid nitrogen bath (−196°) or a $CFCl_3$ slush bath (−110°). The latter bath is recommended for quantities of 1 over 0.2 g, since this fluorimine (mp −148°) frequently explodes during phase changes, as mentioned above. The tube was sealed off with a flame and the reaction mixture was allowed to warm over a period of several minutes to the desired reaction temperature (usually room temperature, ~25°) and maintained for the appropriate length of time. Heating was sometimes required. The course and extent of reaction was conveniently followed by fluorine nmr spectroscopy.

On a larger scale (0.5–1.0 g), a 2.5-cm diameter glass reactor of approximately 10 ml capacity, fitted with a poly(tetrafluoroethylene) needle valve was employed. A small poly(tetrafluoroethylene) coated magnetic stirring bar was often used in this reactor.

Reactions of adducts and their derivatives were also carried out in the glass reaction tubes described above.

Fluorination Apparatus and Procedure.—Method A: The adduct, essentially free of solvent, was placed in a shallow copper vessel in a 0.4-l. copper reactor. The reactor was purged with dry nitrogen and cooled to the desired temperature, and fluorine, diluted with nitrogen, was passed over the adduct. The effluent gas stream was conducted through copper tubing and (generally) a tube containing NaF pellets to remove HF, and then into a glass trap cooled with liquid air or oxygen where products were collected.

Method B: The apparatus consisted of a glass nmr tube having a 2.5-cm diameter glass bulb approximately 12.5 cm from the bottom, the latter connected to a poly(tetrafluoroethylene) needle valve through the center of which was inserted a poly(chlorotrifluoroethylene) capillary extending down into the nmr tube portion of the reactor. The fluorimine adduct (in trifluoroethanol or acetonitrile solvent) in the reactor was usually cooled to −24° with a CCl_4 slush bath; then fluorine gas (25–100% in excess of theoretical), diluted with nitrogen, was continuously recirculated through the solution at atmospheric pressure by means of a diaphragm-activated pump. The cooling bath was allowed to warm slowly to room temperature during the fluorination.

Method C: The reactor was either borosilicate glass or poly(chlorotrifluoroethylene) of 10 to 30 ml capacity in which a solution (acetonitrile) of the adduct was placed. The dilute (nitrogen) fluorine stream was passed into the cooled reaction mixture and the effluent gases were collected as in method A.

Methoxybis(difluoramino)fluoraminomethane (7).—Anhydrous methyl alcohol (0.057 g, 1.8 mmol) and 1 (0.48 g, 0.33 mmol) were condensed in a glass nmr tube (as described above). The sealed tube was allowed to stand at room temperature for 20 hr. Fluorine and proton nmr analyses revealed complete reaction of 1 with methyl alcohol to give the adduct 7, a liquid with vapor pressure of 11 mm at 22°. The ^{19}F nmr spectrum has only a singlet peak (area 4) at ϕ − 20.6 (NF_2) and a double quintet (area 1) centered at 138.9 (NFH), J_{FF} = 8.4, J_{HF} = 54.2 Hz. The proton nmr spectrum shows a singlet at τ 6.0 (CH_3O). The infrared spectrum of the adduct possesses the following peaks: 3.04 (m) NH, 3.38 (w) CH, 6.84 (m), 7.06 (m), 7.70 (s), 8.00 (m), 8.82 (m), 9.65–11.36 μ (vs) NF.

A sample was purified by glpc on column B at 25° (T_R = 3750, CH_2Cl_2 = 100). Some CH_3OH was present as an impurity (ir).

Anal. Calcd for 87% $C_2H_4F_5N_3O$·13% CH_3OH: C, 16.6; F, 45.7. Found: C, 16.5; F, 45.6.

Reaction of 7 with Metal Fluorides. Methoxytrifluoroformamidine (8).—The above adduct 7, prepared from 88 mg (2.74 mmol) of methyl alcohol and 0.45 g (3.0 mmol) of 1, pumped free of excess 1, was cooled to −110° under vacuum and then allowed to warm slowly to room temperature while the vapors were conducted through an evacuated U tube containing about 25 g of powdered anhydrous sodium fluoride. The resulting product gases were conducted into two evacuated traps connected in series, cooled to −78 and −110°, respectively. The −78° trap on warming was found to contain 1.9 mmol of 8 (isomer a) and the −110° trap contained an equivalent amount of difluoramine.

This same isomer was obtained in 66% yield by the reaction of the fluorimine 2 with CH_3OH (0.5 hr, 25°). Other reaction products isolated by glpc in this latter reaction were CH_3OCONF_2[18] (7%) and $(CH_3O)_2C{=}O$ (15%).

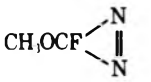
Both geometric isomers of 8 were obtained when 0.09 g (0.5 mmol) of 7 was charged to a 20-ml glass tube cooled to −78° containing 0.16 g of AgF_2. The tube was closed and allowed to warm gradually to 0° and kept there for 1.5 hr. The volatile reaction products were HNF_2, N_2F_4, and the syn and anti isomers of 8. The isomers were separated by glpc on column D at 60°. Properties are reported in Table VIII.

TABLE VIII
PROPERTIES OF $CH_3OC(NF_2){=}NF$ (8)

	Compd		
No.	8a	8b	Assignment
Isomer	a	b	
Configuration[a]	syn	anti	
Vapor pressure, 25°	72 mm		
Mol wt[b]	125		
^{19}F nmr, ϕ	−42.1	−37.2	$-NF_2$
	45.3	52.7	$=NF$
^1H nmr, τ	5.95 d		CH_3
	(J = 3.5 Hz)		
Infrared spectra, μ	3.37	3.38	CH
	5.94	6.05	C=N
	7.93	7.51	COC
	10.97, 11.36	10.17, 11.27	NF and NF_2
T_R ($CFCl_3$ = 100)	804	686	
Analysis	c		

[a] $CH_3O/{=}NF$. [b] By mass spectral effusion rates. Theory, 128. [c] Calcd for $C_2H_3F_3N_2O$: C, 18.8; F, 44.5. Found: C, 19.2; F, 45.7.

Reaction of 8 with Ferrocene. Fluoromethoxydiazirine (49).—A mixture of 64 mg (0.05 mmol) of 8 (syn), 93 mg (0.50 mmol) of $C_{10}H_{10}Fe$, and 1.0 ml of xylene hexafluoride was stirred for 1 hr at 25°. The reaction mixture was fractionated under vacuum through traps at −35 and −196° connected in series. The −196° traps contained 0.47 mmol (92%) of almost pure 49. The compound was purified by glpc at room temperature on column F.



49

Elemental and spectral analyses, along with some chemical properties, have been reported.[7]

Reaction of 7 with NOF and CF_3COONO. Methoxybis(difluoramino)fluoromethane (84).—In a glass nmr tube containing 54 mg (0.30 mmol) of 7 and 0.08 ml of $CFCl_3$ was added 0.4 mmol of nitrosyl fluoride (from reaction of N_2F_4 and N_2O_4 at 25°) and the tube was sealed. A pale purple solution formed at once on mixing the reactants at −78°. The solution became colorless on warming to room temperature. The ^{19}F nmr spectrum, run within 1 hr, showed, besides a small amount of unreacted 7, absorptions at ϕ − 18.9 and 120.0 (ratio 4:1) assigned to NF_2 and F of $CH_3OCF(NF_2)_2$ (84), respectively. The ^1H nmr spectrum had one peak at τ 6.06 due to CH_3. This compound was also formed by the reaction (1 day at 0°) of 7 with excess trifluoroacetyl nitrite and as one of the products in the reaction (1.5 hr at 25°) of nitryl chloride and 7. The other nonvolatile product of the latter reaction may be $CH_3OC(NF_2)_2NFCl$ (85). ^{19}F nmr peaks are at ϕ − 24.8 (NF_2) and 9.7 (NF) in 4:1 ratio, ^1H nmr τ 5.93 (OCH_3).

A sample of 84 was purified by glpc using column A at 25° (T_R = 402, $CFCl_3$ = 100).

Anal. Calcd for $C_2H_3F_5N_2O$: C, 14.5; F, 57.2; mol wt, 166. Found: C, 14.2; F, 53.2; mol wt, 149 (by mass spectrometer effusion studies.) Some principal ions from mass spectral analysis include, m/e, ion (rel intensity), 15, CH_3^+ (150); 31, CH_3O^+ and/or CF^+ (76); 52, NF_2^+ (5); 62, $C_2H_3FO^+$ (10); 81, $C_2H_3F_2O^+$ (17); and 114, $C_2H_3F_3NO^+$ (9.8).

Heating 84 for 4.5 hr at 115° in anhydrous HBr (38% in acetic acid) caused only slight decomposition (nmr).

Reaction of 7 with Cl_2 or CH_3COCl. Chlorobis(difluoramino)fluoraminomethane (81).—Reaction of 54 mg (0.3 mmol) of 7 with 0.40 mmol of Cl_2 gas in a sealed nmr tube with 0.08 ml of $CFCl_3$ for 16 hr at 25° gave a partial conversion to a product identified as $ClC(NF_2)_2NFH$ (81): nmr ϕ − 31.2 (s, 4, NF_2), 107.4 (d, J_{FH} = 51 Hz, quintet, J_{FF} = 5.3 Hz, 1, NFH); τ 0.35 (d, J_{FH} = 50 Hz, NFH).

(18) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).

A similar reaction with acetyl chloride (2 hr, 25°) also gave a partial conversion to **81** plus methyl acetate.

Reaction of 7 with Formaldehyde. Methoxybis(difluoramino)hydroxymethylfluoraminomethane (82). Bis[methoxybis(difluoramino)methylfluoramino]methane (83).—Excess gaseous formaldehyde, produced by heating paraformaldehyde in mineral oil, was swept with a N_2 stream into a reactor containing a stirred solution of the adduct **7** (0.45 g, 2.5 mmol) in 1 ml of CH_3CN at 25°. After 0.5 hr, a liquid–solid mixture was present. The solid was paraformaldehyde (ir). ^{19}F nmr analysis of the liquid phase indicated an 80% conversion to a mixture of the methylol derivative **82**, $CH_3OC(NF_2)_2NFCH_2OH$, and the methylene compound **83**, $[CH_3OC(NF_2)_2NF]_2CH_2$, in a 2:1 ratio. ^{19}F nmr peaks were at ϕ − 23.0 (s, 8, NF_2 of **82** and **83**), 79.0 (t, $J \cong 40$ Hz, m, $J \cong 12$ Hz, 1, $NFCH_2NF$), 85.0 (t, $J \cong 39$ Hz, m, $J \cong 12$ Hz, 1, $NFCH_2OH$).

Fluorination of 7. Methoxytris(difluoramino)methane (50).—Employing method A, 0.8 g (4.4 mmol) of **7** was fluorinated with 80 mmol of F_2 (2.7% in N_2) at −35° over a period of 3 hr. The product, isolated from the −183° trap, was mainly $CH_3OC(NF_2)_3$ (**50**). This compound is a colorless, mobile liquid with a vapor pressure of about 70 mm at 25° [extrapolated bp ~75° (lit.[4] bp 70–71°)], mol wt calcd 199, found (mass spectral effusion rate) 193. The ^{19}F nmr spectrum has a single peak at ϕ − 22.2 (lit.[4] −24.2, external CF_3COOH reference), ^1H nmr τ 5.87 (CH_3). The infrared spectrum has absorptions at 3.35 (w), CH, 6.82 (m), 7.83 (s), 9.6–11.2 μ (s) NF.

This ether (**50**) did not react with $AlCl_3$ or 100% H_2SO_4 at room temperature, but decomposed slowly on warming (50–70°) with these reagents.

Fluoromethoxytris(difluoramino)methane (51) and Difluoromethoxytris(difluoramino)methane (52).—Again employing method A, 1.0 g (0.55 mmol) of **7** was fluorinated at −20° with 60 mmol of F_2 (4.3% in N_2) to yield the following distribution of products: 10% **50**, 30% $FCH_2OC(NF_2)_3$ (**51**), and 25% $F_2CHOC(NF_2)_3$ (**52**). The compounds were isolated by glpc on column A at 25°. T_R ($CFCl_3$ = 100) values: **50**, 637; **51**, 676; **52**, 310. Nmr: **51**, ϕ − 23.5 (s, 6, NF_2), 149.3 (t, J = 49.2 Hz, 1, FCH_2–), τ 4.16 (d, J = 49.2 Hz, FCH_2); **52**, ϕ −24.5 (s, 3, NF_2), 80.6 (d, J = 68.3 Hz, 1, F_2CH–), τ 3.04 (t, J = 68.3 Hz, F_2CH–). The mass spectrum of **52** includes these fragments, m/e, ion (rel intensity): 31, CF^+ (5.8); 33, NF^+ (5.0); 51, CHF_2^+ (100); 52, NF_2^+ (4.9); 80, CNF_2O^+ (3.6); 112, $C_2HF_3NO^+$ (0.7); 168, $CF_6N_3^+$ (0.9); 184, $CF_6N_3O^+$ (0.1).

2-(Hydroxy)ethoxybis(difluoramino)fluoraminomethane (17).—Ethylene glycol (0.32 g, 5.1 mmol), 3 ml of CH_3CN, and 0.76 g (5.1 mmol) of **1** were stirred overnight at room temperature. Most of **1** was consumed. The reaction mixture was analyzed by nmr: ϕ − 20 (s, 4, NF_2), 142 (d, 1, J = ~50 Hz, NFH); τ − 0.5 (d, 1, J = ~53 Hz, NFH), 5.6 (t, 2, CH_2OC), 6.25 (d, 2, CH_2OH), all consistent for $HOCH_2CH_2C(NF_2)_2NFH$ (**17**).

Reaction of 17 with Trifluoroacetic Anhydride. 2-(Trifluoroacetoxy)ethoxybis(difluoramino)fluoraminomethane (48) and 2-(Trifluoroacetoxy)ethoxytrifluoroformamidine (47).—Reaction of excess $(CF_3CO)_2O$ with an acetonitrile solution of **17** for 9 days at 25° followed by glpc on column E at 100° gave two main liquid fractions. The less volatile (T_R = 3290, CH_3CN = 100), major component was identified as $CF_3COOCH_2CH_2OC(NF_2)_2NFH$ (**48**): nmr ϕ − 21.3 (s, 4, NF_2), 39.1 (d, 1, NFH), 76 (s, 3, CF_3); τ 1.25 (NFH), 5.4 (CH_2); ir 3.08 (w) NH, 5.58 (s) C=O, 10.75–11.26 μ (s) NF. The other fraction (T_R = 1960, CH_3CN = 100) was identified as the two isomers of $CF_3COOCH_2CH_2OC(NF_2)$=NF (**47**) (see discussion of isomers of **6** and **8** in text): nmr ϕ − 43 (NF_2, syn RO/=NF), 40.8 (=NF, syn), −37.7 (NF_2, anti), 49.0 (=NF, anti), 75.7 (CF_3); τ 5.5 (CH_2); ir 3.37 (w) CH, 5.56 (s) C=O, 5.94 (m) C=N, 6.07 (m) C=N, 8.18 (s), 8.60 (vs) CO, 10.26–11.5 μ (m) NF.

Fluorination of 17. 2-(Hydroxy)ethoxytris(difluoramino)methane (53).—Employing fluorination method C, the adduct **17** prepared from 0.97 g (6.5 mmol) of **1** and 0.40 g (6.5 mmol) of $HOCH_2CH_2OH$ in 2 ml of CH_3CN was fluorinated at −30° using 30 mmol of F_2 (5% in N_2). The main reaction product isolated by glpc on column E at 100° (T_R = 550, CH_3CN = 100) was a colorless liquid, identified as $HOCH_2CH_2OC(NF_2)_3$ (**53**): nmr ϕ − 23.3 (s, NF_2), τ 5.49 (t, CH_2OC), 6.10 (t, $HOCH_2$), 5.97 (HO–); ir 3.00 (w) OH, 3.45 (w) CH, 7.93 (s), CO, 8.50 (m), 9.75–11.25 μ (s) NF.

Reaction of 53 with Trifluoroacetic Anhydride. 2-(Trifluoroacetoxy)ethoxytris(difluoramino)methane (72).—The CH_3CN solution of **53** from the previous reaction was mixed with 2.4 g (11.4 mmol) of $(CF_3CO)_2O$ and allowed to stir at room temperature overnight. The reaction mixture was fractionated by glpc on column E at 80° to yield, in addition to $CF_3COOCH_2CH_2OOCCF_3$ and $CF_3COOCH_2CH_2OH$, $CF_3COOCH_2CH_2OC(NF_2)_3$ (**72**) (T_R = 1380, CH_3CN = 100) as the principal product: nmr ϕ − 23.0 (s, 2, NF_2), 75.8 (s, 1, CF_3); τ 5.37 (s, CH_2); ir 3.37 (w) CH, 5.56 (s) C=O, 8.60 (vs), 10.33–11.22 μ (s) NF.

1,2-Bis[tris(difluoramino)methoxy]ethane (54).—The diadduct **18** was prepared by reaction of a tenfold molar excess of **1** with $HOCH_2CH_2OH$ in CH_3CN at room temperature for 10 days. Concentration of the reaction mixture gave **18** as an impact sensitive, viscous pale yellow oil: nmr ϕ − 21.7 (d, J = 52 Hz, 4, NF_2), 142.2 (d, J = 50 Hz, quintet, J = 10 Hz, 1, NFH); τ − 0.35 (d, J = 51 Hz, NFH), 5.4 (s, CH_2).

A sample of **18** dissolved in 0.5 ml of CF_3CH_2OH was fluorinated at −23 to 25° using method B and a 20% excess of F_2 (5% in N_2). Evaporation of the solvent gave $(F_2N)_3COCH_2CH_2OC(NF_2)_3$ (**54**) as a pale yellow, viscous oil, vapor pressure <1 mm at 25°. Purification by glpc at 100° on column H afforded a pure sample (T_R = 342, C_2Cl_4 = 100); nmr ϕ − 23.0 (s, NF_2), τ 5.3 (s, CH_2); ir 3.36 (m) CH, 6.85 (w), 7.20 (w), 8.11 (s) CO, 9.73 (s), 10.28–11.24 μ (s) NF.

Anal. Calcd for $C_4H_4F_{12}N_6O_2$: C, 12.1; F, 57.6; N, 21.2. Found: C, 13.3; F, 55.9; N, 22.0.

2-Chloroethoxytris(difluoramino)methane (56).—The adduct $ClCH_2CH_2OC(NF_2)_2NFH$ (**22**) prepared from 0.24 g (3 mmol) of $ClCH_2CH_2OH$ and 0.52 g (3.5 mmol) of **1** (1 ml of CH_3CN solvent, 18 mg of urea catalyst, stirred overnight at 25°) was fluorinated at −45° using method C and 15 mmol of F_2 (3% in N_2). The reaction mixture was fractionated by glpc on column I at 80° to give $ClCH_2CH_2OC(NF_2)_3$ (**56**) as a colorless liquid (T_R = 352, CCl_4 = 100), vapor pressure about 4 mm at 23°: nmr ϕ − 23.1 (s, NF_2), τ 5.40 (t, J = 5.5 Hz, CH_2O), 6.29 (t, J = 5.5 Hz, $ClCH_2$), 8.0 (CH_3CN impurity); ir 3.36 (w) CH, 6.82 (w), 6.96 (w), 7.12 (w), 8.00 (s) CO, 9.35 (w), 9.9–11.3 (s) NF, 14.70 μ (m).

Anal. Calcd for 96% $C_3H_4ClF_6N_3O$·4% CH_3CN: F, 43.8; N, 17.9; mol wt, 247.5. Found: F, 43.8; N, 17.9; mol wt, 248 (by mass spectral effusion rate on mass 65 peak).

Methyl[tris(difluoramino)methoxy]acetate (58).—The adduct $CH_3OOCCH_2OC(NF_2)_2NFH$ (**26**), prepared from 0.52 ml (7.4 mmol) of methyl glycolate and 1.2 g (7.9 mmol) of **1** (3 ml of CH_3CN, 20 mg of urea catalyst, reacted overnight at 25°), was fluorinated at 0° using method C and 46 mmol of F_2 (5% in N_2) over a 5.5-hr period. Volatile components were removed under vacuum. The residual liquid, vapor pressure <1 mm at 25°, was purified by glpc on column H at 80° to yield pure $CH_3OOCCH_2OC(NF_2)_3$ (**58**) (T_R = 218, C_2Cl_4 = 100); nmr ϕ −23.1 (NF_2), τ 5.14 (CH_2), 6.22 (CH_3); ir 3.36 (w) CH, 5.63 (s) C=O, 6.92 (m), 7.17 (m), 7.74 (m), 8.20 (s) CO, 9.50 (m), 10.66–11.23 μ (m) NF. *Anal.* Calcd for $C_4H_5F_6N_3O_3$: C, 18.7; F, 44.3. Found: C, 18.6; F, 44.0. Derivatives of **58** are listed in Table IX.

Tris(difluoramino)methoxyethylammonium Perchlorate (59) and Tris(difluoramino)methoxyethylamine (73).—The adduct $HClO_4$·$H_2NCH_2CH_2OC(NF_2)_2NFH$ (**28**), prepared by the reaction of 0.32 g (2 mmol) of ethanolammonium perchlorate and 0.6 g (4 mmol) of **1** (3 ml of CH_3CN solvent, 15 mg of urea catalyst, stirred for 2 days, 25°), was fluorinated (method C) with about 30 mmol of F_2 (5% in N_2) at −10°. The crude $HClO_4$·$H_2NCH_2CH_2OC(NF_2)_3$ (**59**) contained a carbonyl impurity by ir analysis. A 0.2-g sample of solid crude **59** dissolved in 10 ml of ice water was shaken with 100 ml of FC-75 fluorocarbon solvent (3M Co.) and 4 ml of saturated $NaHCO_3$ (aqueous). The FC-75 extract, containing the high-boiling liquid amine $H_2NCH_2CH_2OC(NF_2)_3$ (**73**), was titrated with 0.10 *N* $HClO_4$ (methyl red indicator). The isolated **59** product (60 mg), mp 208–210° dec, was free of carbonyl impurity: ir 3.15 (s) NH_2^+, 6.19 (m), 6.64 (m), 8.02 (s), 9.18 (vs) ClO_4^-, 9.9–11.3 μ (s) NF_2. ^{19}F nmr analysis showed a broad single peak at ϕ − 24.0. A sample for elemental analysis was prepared by first dissolving 1 g of the above product in 10 ml of ice water. This solution was extracted with 20 ml of ethyl acetate, and the extract was washed with 10 ml of ice water and concentrated to a volume of about 2 ml. This solution was added to about 60 ml of chloroform. The white crystals of **59** obtained after filtering and drying under vacuum weighed 0.40 g and melted at 218–220° dec. (The ir spectrum was essentially unchanged.) *Anal.* Calcd for $C_3H_7ClF_6N_4O_5$ (328.5): C, 10.97; F, 34.69; N, 17.06. Found: C,

TABLE IX
DERIVATIVES OF $(F_2N)_3COCH_2COOCH_3$ (58)

No.	Compd[a]	Synthesis[b]	Appearance	^{19}F Nmr, ϕ, NF_2	Ir, μ C=O
65	$RCOONH_4$	c	Solid, mp 85–88° dec	−23.9	6.14
66	RCOOLi	d	Hygroscopic solid		6.12
67	RCOONa	e	Solid		6.17
68	RCOOK	f	Needles		6.08
69	$(RCOO)_2Mg$	g	Solid, mp 220° dec		6.09
70	RCOOH	h	Liquid	−23.4	5.73
71	$RCONH_2$	i	Crystals, mp 90–92°		5.95

[a] R = $(F_2N)_3COCH_2$. [b] All reactions run on 15–30 mg of NF compound. [c] **58** in C_2H_5OH, excess 3% NH_4OH, 12 hr, 25°. [d] **70**, neutralize with methanolic LiOH. [e] **58**, saponify (3 days, 25°) with stoichiometric amount of 0.10 *N* NaOH (aqueous). [f] **58**, saponify (18 hr, 25°) with stoichiometric amount of 0.024 *N* KOH (C_2H_5OH). [g] **70** in CH_3OH plus stoichiometric amount of MgO, 25°. *Anal.* Calcd for $C_6H_4F_{12}MgN_6O_6$: C, 14.2; H, 0.8; Mg, 4.8. Found: C, 15.0; H, 1.2; Mg, 4.5. [h] **65** in CH_3OH percolated through acid ion exchange resin (Biorad AG 50). [i] **65** heated 50–60° at 0.1 mm. *Anal.* Calcd for $C_3H_4F_6N_4O_2$: C, 14.9; H, 1.67; F, 47.1; N, 23.1. Found: C, 16.1; H, 2.0; F, 46.5; N, 22.8.

11.14; F, 34.5; N, 17.4; equiv wt, 326. Salts of **73** are listed in Table X.

***O*-Tris(difluoramino)methylacetoxime (61).**—The adduct **30**, prepared by reaction of 0.154 g (2.1 mmol) of acetoxime and 0.42 g (2.8 mmol) of **1** for 0.5 hr at −78° and 0.5 hr at 25°, was fluorinated (method A) with 60 mmol of F_2 (2.7% in N_2) at −20° for 2 hr. The fluorinated products were volatilized from the fluorination chamber into the −183° trap with a stream of N_2 at room temperature. The products were then fractionated under vacuum through −35, −119, and −196° traps in series. The −35° trap contained $(CH_3)_2C{=}NOC(NF_2)_3$ (**61**) and a small amount of $FCH_2C(CH_3)C{=}NOC(NF_2)_3$ (**62**): nmr of **61** ϕ − 24.4 (NF_2), τ 7.92, 7.98 (syn and anti CH_3); nmr of **62** ϕ − 26.2 (NF_2), τ 7.81 (CH_3), 5.10 (d, CH_2F).

***O,O'*-Bis[bis(difluoramino)fluoraminomethyl]diaminoglyoxime (31).**—A mixture of 0.181 g (1.54 mmol) of diaminoglyoxime, 2.2 g of dioxane, and 0.95 g (6.4 mmol) of **1** was stirred at room temperature for 1 hr. Excess **1** and solvent were removed under reduced pressure (0.1 mm, 25°). The residual white solid was crystallized from benzene, mp 90° dec. Nmr and elemental analyses indicated the structure to be $+C(NH_2){=}NOC(NF_2)_2NFH]_2$ (**31**) with 0.5 mol of dioxane of crystallization: nmr ϕ − 21.2 (d, J = 8.6 Hz, 4, NF_2), 138.3 (d, J = 49.3 Hz, quintet, J = 8.4 Hz, 1, NFH); τ −1.13 (NFH), 3.38 (NH_2), 6.33 (CH_2 of dioxane). *Anal.* Calcd for $C_6H_{10}F_{10}N_{10}O_3$: C, 18.8; F, 38.0. Found: C, 19.6; F, 37.4, 38.6.

Conducting the synthesis in acetonitrile yields **31** free of complexing solvent. Recrystallization from CCl_4 affords a white solid, mp 69–71°, which is very sensitive to impact and slowly decomposes at 25°.

Anal. Calcd for $C_4H_6F_{10}N_{10}O_2$: C, 11.5; F, 45.7; N, 33.6. Found: C, 11.2; F, 43.2; N, 35.1.

***O*-Tris(difluoramino)methyldichloroformoxime (63).**—The adduct $Cl_2C{=}NOC(NF_2)_2NFH$ (**32**), prepared by treating 0.52 g (4.6 mmol) of $Cl_2C{=}NOH$,[19] 0.75 g (5.1 mmol) of **1**, and 25 mg of urea in 5 ml of CH_3CN at room temperature for 2 hr, was fluorinated (method C) with 37 mmol of F_2 (10% in N_2) at −30°. Separation of the reaction mixture by glpc on column E at 50° afforded a 40% yield of pure $(F_2N)_3CON{=}CCl_2$ (**63**) (T_R = 310, CH_3CN = 100) as a colorless liquid, vapor pressure about 5 mm at 25°. ^{19}F nmr showed a single peak for NF_2 at ϕ − 25.2; ir 6.29 μ (m) C=N; mass spectrum *m/e* (ions) 42 (CON^+), 52 (NF_2^+), 82 (CCl_2^+), 96 ($NCCl_2^+$).

Anal. Calcd for $C_2Cl_2F_6N_4O$: C, 8.6; N, 19.9; Cl, 25.2; F, 40.6; mol wt, 281. Found: C, 9.6; N, 19.9; Cl, 24.9; F, 41.4; mol wt, 270 (by mass spectral effusion rates).

(19) E. Gryzskiewicz-Trochimowski, K. Dymowski, and E. Schmidt, *Bull. Soc. Chim. Fr.*, 597 (1948).

Reaction of 63 with Sodium Methoxide. Dimethyl *N*-[Tris(difluoramino)methoxy]iminocarbonate (80).—To a solution of 0.282 g (1.0 mmol) of **63** in 15 ml of $CFCl_3$ was added 0.140 g (2.6 mmol) of $NaOCH_3$. The reaction mixture was stirred for 6 hr at room temperature and filtered through glass wool, and the filtrate was concentrated under vacuum at −30° to yield the product $(F_2N)_3CON{=}C(OCH_3)_2$ (**80**) as a pale yellow liquid, vapor pressure <1 mm at 25°: nmr ϕ − 24.0 (NF_2), τ 6.12 and 6.6 (syn and anti CH_3 groups); ir 6.18 μ (C=N). The mass spectrum was consistent with the assigned structure, including a parent peak at *m/e* 272.

Anal. Calcd for $C_4H_6F_6N_4O_3$: C, 17.6; F, 41.9; mol wt, 272. Found: C, 18.4; F, 40.6; mol wt, 277 (by mass spectral effusion rates).

Bis(difluoramino)fluoraminomethyl Hydroperoxide (36).—A mixture of 93 mg (2.8 mmol) of H_2O_2 (98% purity, FMC Corp.), 20 mg of urea catalyst, 2.0 ml of $CH_3COOC_2H_5$ solvent, and 0.95 g (6 mmol) of **1** was stirred at room temperature for 2 hr. Volatiles and part of solvent were removed from the pale yellow solution. ^{19}F nmr analysis of the residual liquid showed only peaks due to the adduct $HOOC(NF_2)_2NFH$ (**36**), ϕ − 22.5 (s, 4, NF_2), 139.5 (d, 1, NFH). (The same nmr absorptions were obtained when equimolar quantities of **1** and H_2O_2 were used, although yields were lower, indicating that the structure of **36** is a 1:1 adduct as shown.)

Acetoxybis(difluoramino)fluoraminomethane (35) and Bis(difluoramino)fluoraminofluoromethane (38).—A mixture of 0.08 ml (1.33 mmol) of glacial acetic acid (containing 5 mol % CH_3COOK catalyst), 45 mg (0.3 mmol) of **1**, and about 0.1 ml of CH_3OCH_3 was allowed to warm from −196° and the temperature was held at 0° for 5 min. ^{19}F nmr analysis run at − 28° showed about a 70% conversion to the adduct $CH_3COOC(NF_2)_2NFH$ (**35**): ϕ − 23 (s, 4, NF_2) and 132 (d, 1, NFH). Some CH_3COF and HNF_2 were also present. Longer reaction times or higher temperature caused decomposition of **35** and gave more of these by-products and also $F^aC(NF_2{}^b)_2NF^cH^d$ (**38**) (HF adduct of **1**): ^{19}F nmr ($CFCl_3$) ϕ −21.8 (s, 4, NF_2), 133.8 (t, J_{a-cd} = 16 Hz, 1, FC), 136.4 (d, $J_{c-d} \cong$ 57 Hz, m, J_{b-c} = small, 1, NFH). **38** was isolated by glpc on column J at 25° (T_R 280, $CFCl_3$ = 100): ir 3.02 (m) NH, 6.99 (m), 7.57 (m), 8.08 (m), 8.32 (m), 8.64 (w), 9.7–11.1 (s), NF, 11.8 μ (m); mol wt calcd 169, found (by mass spectral effusion rates) 170.

***N*-Fluorohexafluoroisopropylidine Imine (4).**—Using method C, without solvent, 12 mmol of $(CF_3)_2C{=}NH$[20] was fluorinated at −78° with 30 mmol of F_2 (5% in N_2). The −183° trap contained 3.9 mmol of a mixture of $(CF_3)_2C{=}NF$ (**4**), bp −12° (lit.[8] bp −13 to 11.7°), and $(CF_3)_2CFNF_2$ (**87**), bp 0° (lit.[8] bp −2 to 1°), which were separated by glpc on column G at 25° (T_R of **4** = 81, **87** = 102, CF_2Cl_2 = 100). The reactor contained 9.5 mmol of a liquid, bp about 45°, assigned the structure $(CF_3{}^a)_2CF^bNF^cH^d$ (**86**) [*Anal.* Calcd mol wt: 203. Found: 203 (by mass spectral effusion rates).]: nmr ϕ 75.9 (d, J_{a-c} = 11.9 Hz; d, J_{a-b} = 3.6 Hz; 6, CF_3), 134.7 (d, J_{c-d} = 57 Hz; d, J_{c-b} = 20.8 Hz; septet, J_{c-a} = 12.2 Hz; 1, NFH), 151.4 (d, J_{b-c} = 20.8 Hz; d, J_{b-d} = 14.2 Hz; septet, J_{a-b} = 3.1 Hz; 1, CF); ir 3.00 (w) NH, 7.63 (s), 7.95 (vs), 8.20 (s), 8.46 (s), 9.00 (m), 9.78 (m), 10.42 (m), 11.58 (m), 13.5–14.0 μ (s). Vaporizing **86** slowly through a bed of NaF pellets at 25° eliminated HF and gave a quantitative conversion to **4** [treatment of **87** with $(C_6H_5)_3P$ also yielded **4**].

Methoxybis(trifluoromethyl)difluoraminomethane (64).—The reaction mixture containing the adduct $(CF_3)_2C(OCH_3)NFH$ (**39**), prepared from 0.55 g (3 mmol) of **4** and 80 mg (2.5 mmol) of CH_3OH [1 ml of CH_3CN, 15 mg of $(CH_3)_3N$ catalyst, overnight, 25°], was fluorinated using method C at −20° with 15 mmol of F_2 (3% in N_2). The contents of the −183° trap (2.2 mmol) were separated by glpc on column F at 22.5°. The peak eluting at 15 min (air = 0.7 min) was trapped (about 1 mmol) and identified as $(CF_3)_2C(OCH_3)NF_2$ (**64**): bp (from vapor pressure data) 68°; mp *ca.* −82°; nmr ϕ − 19.2 (s, 1, NF_2), 70.7 (t, J = 12.6 Hz, 3, CF_3).

Anal. Calcd for $C_4H_3F_8NO$: F, 65.2; N, 6.0. Found: F, 64.6; N, 6.0.

***N*-Fluoromethoxytrifluoroethylidine Imine (6).**—A mixture of 0.33 g (2.5 mmol) of **3** ($CF_3CF{=}NF$) and 64 mg (2.0 mmol) of CH_3OH was allowed to stand at room temperature for 3 days. (The reaction was nearly complete after 5 min.) The products were separated by glpc on column C at 50°. Both geometric

(20) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

TABLE X
SALTS OF $(F_2N)_3COCH_2CH_2NH_2$ (73)[a]

No.	Salt[b]	Mp, °C[c]	Equiv wt Theory	Equiv wt Found	Anal., % Calcd C	Calcd F	Found C	Found F
59	$RCH_2NH_3^+ClO_4^-$	218–220	328.5	326	11.0	34.7	11.1	34.5
74	$RCH_2NH_3^+Cl^-$	120	264.5	258	13.6	43.1	13.5	42.4
75	$RCH_2NH_3^+Br^-$	96	309		12.7		11.6	
76	$RCH_2NH_3^+HF_2^-$[d]	118	268					
77	$[RCH_2NH_3^+]_2SO_4^{2-}$	138	277	259	13.0		13.0	
78	$[RCH_2NH_3^+]_2C_2O_4^{2-}$[e]	144	273	263	17.6		18.2	
79	$RCH_2NH_3^+{}^-OOCR'$	83–88	471 [ir 6.0 μ (C=O)]					

[a] Preparation of 73 described in the preceding example, except that pure 59 starting material was employed. [b] R = $(F_2N)_3COCH_2$. Salts, except where noted, were made by neutralization of FC-75 solutions of the free amine 73 (about 0.2 g) with the appropriate dilute (about 0.1 *N*), aqueous acid, concentration of the aqueous phase, and drying the solid in a vacuum desiccator. [c] The temperature at which most of the melting took place. [d] Titrated 73 with HF, but ir analysis supported the HF_2^- rather than the F^- salt. Hygroscopic solid which sublimed near the melting point. [e] Recrystallized from CH_3OH. [f] 0.1 mmol of $(F_2N)_3COCH_2COOK$ in 4 ml of CH_3OH plus 0.1 mmol of 59 in 1 ml of CH_3OH; $KClO_4$ was filtered off and the solution was evaporated.

isomers of $CH_3OC(CF_3)$=NF were isolated: isomer a (syn, CH_3O/=NF) (6a) and isomer b (anti) (6b) in a ratio of 1:3. Table V in the text lists many of the properties of these compounds. The mass spectra of 6a and 6b contain these ions (abundance).

m/e	15	28	31	69	76	126	145
6a	100	15	65.9	72.5	4.5	0	7.2
6b	100	12.9	68.0	54.6	4.2	3.0	2.6
Ion	CH_3^+	CO^+	CH_3O^+	CF_3^+	$C_2F_2N^+$	$C_3H_3F_3NO^+$	$C_3H_2F_4NO^+$

Anal. Calcd for $C_3H_3F_4NO$ (6b) (145.06): C, 24.8; F, 52.4. Found: C, 23.8; F, 52.4.

N-**Fluoro-*n*-butoxytrifluoroethylidine Imine** (88).—A mixture of 40 mg (0.3 mmol) of 3, 37 mg (0.5 mmol) of dry n-C_4H_9OH, and about 0.2 ml of $CFCl_3$ was allowed to react overnight at room temperature. ^{19}F nmr analysis indicated the presence of the anti (8a) and syn (8b) isomers of n-$C_4H_9OC(CF_3)$=NF in a ratio of about 1:4, ϕ: (8a) 49.2 (=NF), 68.8 (CF_3); (8b) 44.1 (=NF), 71.5 (CF_3).

Registry No.—1, 10051-06-6; 2, 14362-70-0; 3, 758-35-0; 4, 2802-70-2; 5, 839-09-8; *syn*-6, 38088-66-3; *anti*-6, 38088-67-4; 7, 38087-75-1; *syn*-8, 38088-68-5; *anti*-8, 38088-69-6; 9, 38087-76-2; 10, 38087-77-3; 11, 38087-78-4; 12, 38087-79-5; 13, 38087-80-8; 14, 38087-81-9; 15, 38087-82-0; 16, 38087-83-1; 17, 38087-84-2; 18, 38165-82-1; 19, 38087-85-3; 20, 38087-86-4; 21, 38087-87-5; 22, 38087-88-6; 23, 38087-89-7; 24, 38087-90-0; 25, 38087-91-1; 26, 38165-83-2; 27, 38088-04-9; 28, 38088-05-0; 29, 38088-06-1; 30, 38088-07-2; 31, 38165-86-5; 32, 35431-00-6; 33, 38088-09-4; 34, 38088-10-7; 35, 38088-11-8; 36, 38088-12-9; 37, 38088-13-0; 38, 38088-14-1; 39, 38088-15-2; 40, 38088-16-3; 41, 38088-17-4; 42, 38092-35-2; 43, 38146-44-0; 44, 38092-36-3; 47, 38092-37-4; 48, 38092-38-5; 50, 26901-93-9; 51, 38092-40-9; 52, 38092-41-0; 53, 38092-42-1; 54, 38092,43-2; 55, 38092-44-3; 56, 38092-45-4; 57, 38092-46-5; 58, 38092-47-6; 59, 25448-61-7; 60, 38092-49-8; 61, 38092-50-1; 62, 38092-51-2; 63, 35431-01-7; 64, 38092-53-4; 65, 38165-87-6; 66, 38165-88-7; 67, 38092-54-5; 68, 38092-55-6; 69, 38092-56-7; 70, 38092-57-8; 71, 38092-58-9; 72, 38092-59-0; 73, 38165-85-4; 74, 38092-60-3; 75, 38092-61-4; 76, 38092-62-5; 77, 38092-63-6; 78, 38092-64-7; 79, 38092-65-8; 80, 35431-02-8; 81, 38092-67-0; 82, 38092-68-1; 83, 38092-69-2; 84, 38092-70-5; 85, 38092-71-6; 86, 22341-37-3; 87, 662-23-7; 88, 38092-74-9.

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Organic Fluoronitrogens. XII.[1] Amino Addition Compounds of Fluorimines. Tetrakis(difluoramino)methane

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The addition of amino compounds to *N*-fluorimines to yield saturated and unsaturated products is described. Pentafluoroguanidine (1) and ammonia react at −110° to form the adduct $H_2NC(NF_2)_2NFH$ (2). On warming to 25°, 2 loses HNF_2 to yield $H_2NC(NF_2)=NF$ (3). Fluorination of 2 at low temperature affords the completely fluorinated derivative, $C(NF_2)_4$ (4), an explosive, oxidizing liquid.

A previous paper[1] described the addition of hydroxy compounds to *N*-fluorimines and the chemistry of the products. In this paper, NH adducts of fluorimines, especially pentafluoroguanidine (1),[2] will be considered. Many of the NF compounds discussed in this paper are explosive and all work was conducted on a small scale with appropriate shielding.

The principal reactions which occur when amino compounds are treated with 1 are shown below.

$$R_1R_2NH + \underset{1}{(F_2N)_2C{=}NF} \longrightarrow \underset{A}{R_1R_2NC(NF_2)NFH} \xrightarrow{-HNF_2} \underset{B}{R_1R_2NC(NF_2){=}NF}$$

The double bond in 1 is very electron deficient and a large variety of amino compounds may be added. The rate of addition and the types of products formed (A and/or B) depend upon the nucleophilicity of the amino compound and the reaction conditions, as summarized in Table II. Amines such as ammonia, *p*-cyanoaniline, and *p*-trifluoromethylaniline add to 1 at low temperature to form saturated products of type A. Warming these adducts to room temperature causes loss of HNF_2 to yield the unsaturated derivatives of type B. More basic amines such as *n*-butylamine and dimethylamine react rapidly at low temperature, *e.g.*, −78°, to yield exclusively the unsaturated (B) derivatives. For example, ^{19}F nmr analysis of the reaction mixture from dimethylamine and 1 at −78° showed no evidence for the intermediate saturated adduct (A). Amino compounds of very low nucleophilicity, such as succinimide, require a basic catalyst for the addition reaction to take place. Polar solvents with low melting points such as acetonitrile, dimethyl ether, diethyl ether, and tetrahydrofuran were found useful to facilitate reaction and to prevent explosions initiated by exotherms.

The addition of anhydrous NH_3 to 1 takes place rapidly in CH_3OCH_3 solution at −110° to afford a high yield of the saturated adduct 2, as determined by ^{19}F nmr and ir analyses.

$$NH_3 + \underset{1}{(F_2N)_2C{=}NF} \xrightarrow{-110°} \underset{2}{H_2NC(NF_2)NFH}$$

If 2 is allowed to warm to room temperature, HNF_2 is eliminated and 1,1,2-trifluoroguanidine (3) is formed in high yield.

$$\underset{2}{H_2NC(NF_2)NFH} \xrightarrow{25°} \underset{3}{H_2NC(NF_2){=}NF} + HNF_2$$

Tetrakis(difluoramino)methane.—Fluorination of 2 with a large excess of dilute F_2 at about −30° (neat) gave a mixture of products shown in the equation below, which were separated by glpc (peak area per cents observed were 20, 16, 14, <5, <5, and <5, respectively).

$$\underset{2}{H_2NC(NF_2)NFH} \xrightarrow{F_2} \underset{4}{C(NF_2)_4} + \underset{5}{FC(NF_2)_3} + \underset{1}{(F_2N)_2C{=}NF} + \underset{6}{CF_2(NF_2)_2} + \underset{7}{CF(NF_2){=}NF} + \underset{9}{(F_2N)_3CNFH}$$

The most interesting product is the new compound[3] tetrakis(difluoramino)methane (4) in which all H atoms of 2 have been replaced by F. A small amount of the NFH compound 9, an intermediate to 4, was also isolated. The other products arise from cleavage of C–N bonds during fluorination, or, in the case of 1, the fluorination of 3 (which forms easily from 2 as mentioned above). The compounds 5,[2] 6,[4] and 7[2] have been reported. 4 was isolated by glpc and many of its properties were determined (Table I). It is an explosive (impact sensitive), oxidizing, volatile liquid, but, when manipulated with care, exhibited surprising stability (up to 175°). The presence of the strongly electronegative F atoms attached to N appears to stabilize the molecule much as do the O atoms in the analogous tetranitromethane, $C(NO_2)_4$.

The fluorination of 2 was observed to take place by a stepwise replacement of H atoms by F. The

$$\underset{2}{H_2NC(NF_2)NFH} \xrightarrow{F_2} \underset{8}{HFNC(NF_2)NFH} \xrightarrow{F_2} \underset{9}{(F_2N)_3CNFH} \xrightarrow{F_2} \underset{4}{C(NF_2)_4}$$

$$\underset{2}{H_2NC(NF_2)NFH} \searrow \underset{10}{H_2NC(NF_2)_3}$$

(1) Previous publication in this series: J. L. Zollinger, *et al.*, *J. Org. Chem.*, **38**, 1065 (1973).

(2) R. J. Koshar, D. R. Husted, and C. D. Wright, *ibid.* **32**, 3859 (1967).

(3) Preparation of 4 is also disclosed by W. C. Firth, Jr., S. Frank, and M. D. Meyers, *ibid.*, **38**, 1088 (1973), by the fluorination of $(F_2N)_2C(NFH)$-NCO.

(4) R. J. Koshar, D. R. Husted, and R. A. Meiklejohn, *ibid.*, **31**, 4232 (1966).

TABLE I

TETRAKIS(DIFLUORAMINO)METHANE (4)

Structural formula: $C(NF_2)_4$

Anal. Calcd for CF_8N_4: C, 5.45; F, 69.1; N, 25.45; mol wt, 220. Found: C, 5.8; F, 68.2; N, 26.0; mol wt,[a] 223.

Appearance: colorless liquid

Boiling point:[b] 40°

Melting point: −13.5 to −12.5°

Heat of vaporization: 6.5 kcal/mol

Trouton's constant: 21.1

T_R: 111[c]

^{19}F nmr (ϕ): −29.3, broad singlet (NF_2)

Density (25°):[d] 1.68 g/cc

Critical temperature:[e] 175°

Solubility: miscible with $CFCl_3$, CF_2Cl_2, CF_3CH_2OH, and N_2F_4

Impact sensitivity:[f] less than 33 kg-cm

DTA: 210° smooth exotherm starts; 250° maximum rate of exotherm.

Thermal stability: solutions of **4** in $CFCl_3$ in glass were unchanged after 12 hr at 125°; complete decomposition occurred after 12 hr at 165°.

[a] By mass spectral effusion rates. [b] Log P (mm) = 7.498 − 1449/T (−12 to 60°). [c] Relative retention time ($CFCl_3$ = 100) on a 0.5 in. × 20 ft glpc column of 20% FS-1265 (Dow-Corning) on firebrick at 25°. [d] Orthobaric liquid density: $d_t = 1.744 - 2.505 \times 10^{-3}t - 2.372 \times 10^{-6}t^2 - 2.338 \times 10^{-8}t^3$. [e] Meniscus disappearance in glass. Some decomposition. [f] As determined by dropping a 2-kg steel block on a sealed glass ampoule of **4**.

progress of the reaction in CH_3CN solution at −35° was monitored by glpc and ^{19}F nmr analysis of liquid samples withdrawn from the reactor during fluorination.

The intermediate products **8** and **9** were isolated by glpc and identified by ^{19}F nmr and ir analyses. **8** was also characterized by its mass spectrum and a molecular weight determination. The concentration of **8** reached a maximum after about 1 molar equiv of F_2 had been added. Compound **10**, a possible intermediate in the synthesis, was not observed.[5] The ^{19}F nmr spectrum expected for **10** would be a single broad absorption in the ϕ −25 region. The initial fluorination product, however, exhibited peaks at ϕ −23.6 (s) and 135.0 (d) in an area ratio of 2:1, consistent for structure **8**. These results indicate that the NH_2 group in **2** is more reactive toward F_2 than the NFH group. The monohydride **9** exhibits ^{19}F nmr absorptions at ϕ −26.4 (s) and 136.1 (complex) in a ratio of 6:1.

As H is replaced by F in the compound series **2**, **8**, **9**, **4**, the ^{19}F nmr absorption for the NF_2 group is observed to shift in increments of about 3 ppm to progressively lower field: −20.5, −23.6, −26.4, and −29.3.

Thermal stability increases as one progresses through the above series of compounds. Whereas **2** was converted to **3** on warming to room temperature, **8** and **9** were isolated by glpc at 50°. **8** was unchanged in $CFCl_3$ solution in glass on standing for 18 days at room temperature. Treatment of **9** with NaF or heating yields **1** by loss of HNF_2.

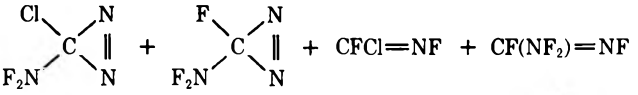
The acetone hydrazone adduct **20** in Table II was stable only at low temperatures. However, warming to room temperature did not yield the unsaturated product (type B) observed for other adducts, *e.g.*, **2**, but gave a mixture of products, including **23** and **24**,[6] resulting from apparent cleavage and rearrangement reactions.

$$\underset{\mathbf{20}}{(CH_3)_2C{=}NNHC(NF_2)_2NFH} \xrightarrow{25^\circ} \underset{\mathbf{23}}{FC(NF_2)_2NH_2} + \underset{\mathbf{24}}{F_2NCF_2NFH}$$

Other products identified in the reaction were HNF_2, N_2O, and acetone. **23** and **24** were isolated by glpc and characterized (see Experimental Section).

Unexpected products were also obtained in the reaction of semicarbazide hydrochloride and **1**.

$$\underset{\mathbf{1}}{H_2NCONHNH_2{\cdot}HCl} + (F_2N)_2C{=}NF \xrightarrow{25^\circ}$$



25 **26** **27** **7**

When the reaction was monitored by glpc, the concentration of **25** in the gas phase was observed to increase with time to a maximum at 6 hr, then decrease. After 18 hr, no **25** was present. The properties of **25** have been published,[7] but the synthetic route was not given. The diazirine **26** has been reported.[8] The syn and anti isomers of both **27**[9] and **7**[2] were detected among the products of the reaction.

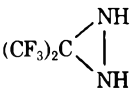
1,1,2-Trifluoroguanidine (**3**), originally isolated from the decomposition of **2**, was also formed when **7** and

$$\underset{\mathbf{7}}{CF(NF_2){=}NF} + NH_3 \xrightarrow{25^\circ} \left[H_2NC(NF_2)NHF \right] \xrightarrow{-HF} \underset{\mathbf{3}}{H_2NC(NF_2){=}NF}$$

NH_3 were allowed to react. The presumed intermediate adduct was not isolated but lost HF to yield **3**.

Additions of NH compounds to other *N*-fluorimines are summarized in Table III. No saturated adducts were observed in reactions of $CF_3CF{=}NF$[1] (**28**) with amines; instead, loss of HF occurred to yield $H_2NC(CF_3){=}NF$ (**30**) and $(CH_3)_2NC(CF_3){=}NF$ (**31**) in high yields from NH_3 and $(CH_3)_2NH$, respectively.

The addition of NH_3 to $(CF_3)_2C{=}NF$[1] (**29**) is mildly exothermic in ethyl ether solution and the product was a solid characterized as the diaziridine **32**, which



32

was recently reported.[10] **32** is formed in quantitative yield, apparently from a 1,3 elimination of HF from an intermediate adduct not isolated.

(5) Compound **10** has been prepared by the hydrolysis of $(F_2N)_3CNCO$: W. C. Firth, Jr., and S. Frank, *ibid.*, **38**, 1083 (1973).

(6) Compound **24** was isolated and characterized by R. J. Koshar. Another route to **24** has been reported, but no properties were given (U. S. Patent 3,410,853).

(7) R. A. Mitsch, E. W. Neuvar, R. J. Koshar, and D. H. Dybvig, *J. Heterocycl. Chem.*, **2**, 371 (1965).

(8) R. A. Mitsch, *J. Org. Chem.*, **33**, 1847 (1968).

(9) D. H. Dybvig, *Inorg. Chem.*, **5**, 1795 (1966).

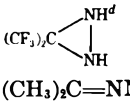
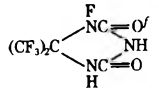
(10) (a) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965), synthesized **32** from $(CF_3)_2C{=}NH + HN_3$. (b) K. N. Makarov, B. L. Dyatkin, and I. L. Knunyants [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1924 (1968); *Chem. Abstr.*, **70**, 3878y (1969)] prepared **32** from **29** and NH_3.

TABLE II
ADDITION OF NH COMPOUNDS TO $(F_2N)_2C{=}NF$ (1)[a]

Reactant	Product[b]	No.	Conditions: Temp, °C	Conditions: Time, hr	Yield,[c] %	^{19}F Nmr absorptions, φ[d]: NF_2	NFH	=NF
NH_3	$H_2NC(NF_2)_2NFH$	2	−110	0.25	90	−20.5	135.1	
NH_3	$H_2NC(NF_2){=}NF$	3	25	24	80	−47.2		50.7
p-$CF_3C_6H_4NH_2$	*p*-$CF_3C_6H_4NH$-A[e]	11	25	0.25	60	−24	137	62 (CF_3)
	p-$CF_3C_6H_4NH$-T[f]	12			20	−45		38
p-$NCC_6H_4NH_2$	*p*-NCC_6H_4NH-A	13	25	0.25	60	−24d[g]	136 m[h]	
	p-NCC_6H_4NH-T	14			20	−45		34
n-$C_4H_9NH_2$	*n*-C_4H_9NH-T	15	0	0.1	50	−44		62.4
$(CH_3)_2NH$	$(CH_3)_2N$-T	16	−80	0.5	90	−40.8		61.7
$(CH_3)_3CNH_2$	*syn*-$(CH_3)_3CNH$-T[i]	17	25	0.5	50	−45.9		54.7
	anti-$(CH_3)_3CNH$-T	18			25	−41.6		61.2
$HClO_4 \cdot H_2NNH_2$	$HClO_4 \cdot H_2NNH$-A	19	25	20	60	−24.6	139.5	
$(CH_3)_2C{=}NNH_2$	$(CH_3)_2C{=}NNH$-A	20	−90	0.5	80	−20.4	138.2	
$CF_3CONHNH_2$	$CF_3CONHNH$-A	21	0	0.25	60	−22.4	141.2	75 (CF_3)
$COCH_2CH_2CONH$[j]	$COCH_2CH_2CON$-A	22	25	72	20	−25.1	121.5	

[a] In a typical reaction, the anhydrous amino compound is treated with 10–20 mol % excess of pentafluoroguanidine (1) in a sealed nmr tube with internal $CFCl_3$ reference and CH_3CN solvent at the temperature and time indicated. [b] The products are nonvolatile explosive solids or liquids. See Experimental Section for further properties of compounds **2** and **3**. [c] Yields were estimated from nmr data. [d] Chemical shifts are in parts per million relative to $CFCl_3$ as internal reference. [e] A is the $C(NF_2)_2NFH$ group. [f] T is the $C(NF_2){=}NF$ group. [g] Doublet, J_{FH} = 51.4 Hz. [h] Quintet, J_{FF} = 11.2 Hz. [i] Assignment of syn configuration [with respect to $(CH_3)_3CNH$ and =NF groups] is based on analogy with the isomers of $CH_3OC(NF_2){=}NF$ described in our previous paper.[1] [j] Triethylamine catalyst.

TABLE III
ADDITION OF NH COMPOUNDS TO OTHER FLUORIMINES[a]

Fluorimine	No.	Reactant	Temp, °C	Products	No.	Yield, %	^{19}F nmr, φ	Ir, μ
$CF(NF_2){=}NF$	7	NH_3	−78	$H_2NC(NF_2){=}NF$[b]	3	80	−47.2 (NF_2) 50.7 (NF)	5.85 (C=N)
$CF_3CF{=}NF$	28	NH_3	−78	$H_2NC(CF_3){=}NF$	30	95	70.5 (CF_3) 49.4 (NF)	3.02 (NH) 5.99 (C=N)
$CF_3CF{=}NF$	28	$(CH_3)_2NH$	−78	$(CH_3)_2NC(CF_3){=}NF$	31	90	65.5 (CF_3)[c] 45.9 (NF)	6.09 (C=N)
$(CF_3)_2C{=}NF$	29	NH_3	25		32	95	75.2 (CF_3)	3.05 (NH)
$(CF_3)_2C{=}NF$	29	$(CH_3)_2NH$	25	$(CH_3)_2C{=}NN(CH_3)_2$[b]	33	95	63.7, 52.0 (CF_3)	6.25 (C=N)
$(CF_3)_2C{=}NF$	29	HNCO[e]	25		35	50	74.1 (d, CF_3) 87.5 (m, NF)	5.75 (C=O)

[a] Reactions carried out in sealed tubes using excess fluorimine, and $CFCl_3$ as solvent and internal nmr reference. [b] See Experimental Section. [c] Doublet, J = 8.6 Hz. [d] Known compound[10] (see text). [e] $(CH_3)_3N$ catalyst. [f] Analogous compound, where NF is NH, reported[10a] from $(CF_3)_2C{=}NH$ plus 2HNCO. The multiplet for NF appears to be a sevenfold peak in the ^{19}F nmr spectrum of **35**, as would be expected from coupling with the six F atoms of the CF_3 groups, mp 109–110°.

The reaction of **29** and $(CH_3)_2NH$ afforded quantitative yields of $(CF_3)_2C{=}NN(CH_3)_2$ (**33**) formed by addition inverse to that seen in all other reactions in our studies.[11] **33** was thoroughly characterized and was synthesized independently as follows.

$$(CF_3)_2C{=}O + H_2NN(CH_3)_2 \longrightarrow (CF_3)_2C(OH)NHN(CH_3)_2 \xrightarrow{POCl_3} \mathbf{33}$$

Dimerization of **33** to the diazetidine **34** occurred either "spontaneously" in glassware or by catalysis with concentrated sulfuric acid. The nmr spectra

$$2(CF_3)_2C{=}NN(CH_3)_2 \xrightarrow{H_2SO_4} (CF_3)_2C(NN(CH_3)_2)\text{—}(NN(CH_3)_2)C(CF_3)_2$$

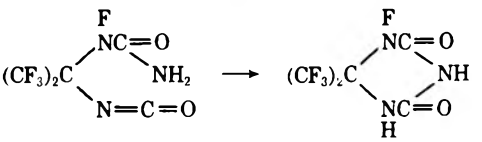
33 **34**

of **34** contained only single peaks for H and F. The structure was further confirmed by mass spectral and elemental analyses.

Two moles of HNCO react with **29** to yield what is believed to be the cyclic product, **35**. Similar cyclic

$$(CF_3)_2C{=}NF + HNCO \longrightarrow (CF_3)_2C(NFH)(NCO) \xrightarrow{HNCO}$$

29



35

compounds have been prepared by reaction of HNCO with **1**[12] and with $(CF_3)_2C{=}NH$.[10a] A possible path to **35** is shown.

(11) (a) Reference 10b reported the closely related reaction of **29** and $HN(C_2H_5)_2$ to yield $(CF_3)_2C{=}NN(C_2H_5)_2$, also involving an inverse addition. (b) **33** was recently reported by F. J. Weight, *J. Org. Chem.*, **37**, 1314 (1972).

(12) W. C. Firth, Jr., S. Frank, and E. J. Schriffert, *J. Org. Chem.* **38**, 1080 (1973).

Experimental Section

Precautions.—Many of the fluoronitrogen compounds described in this paper are shatteringly explosive under certain conditions. See the previous paper[1] for details concerning safety, starting materials, reaction procedures, equipment, compound purification, and analytical methods. Manufacturers of liquid phases and solid supports for glpc are listed in Table VII in ref 1.

Only the principal and structurally significant ions from mass spectral analyses are presented.

Derivatives of Pentafluoroguanidine (1) and Other Fluorimines.—Approximate yields and ^{19}F nmr absorptions are presented in Table II for NH derivatives of 1 and in Table III for derivatives of 28 and 29. Many of the properties of $C(NF_2)_4$ (4) are given in Table I.

Preparation of Bis(difluoramino)fluoraminomethylamine (2) and 1,1,2-Trifluoroguanidine (3).—Pentafluoroguanidine (1, 0.46 g, 3.1 mmol) was added by vacuum transfer over a 1-min period to a stirred solution of anhydrous ammonia (0.05 g, 2.9 mmol) in 5 ml of dimethyl ether at −110° ($CFCl_3$ slush bath) in an approximately 10-ml capacity borosilicate glass reactor fitted with a polytetrafluoroethylene (ptfe) needle valve and a ptfe-coated magnetic stirring bar. The mixture was warmed to −63° ($CHCl_3$ slush bath) while solvent and unreacted 1 were removed under pump vacuum. After 0.5 hr the yellow liquid residue had a vapor pressure of less than 1 mm at −63° and was identified (nmr) as $H_2NC(NF_2)_2NFH$ (2), complexed with about three molecules of CH_3OCH_3. Nmr analysis was run quickly (to avoid decomposition) at 25° in CH_3CN solution with $CFCl_3$ and $Si(CH_3)_4$ as internal references. ^{19}F nmr peaks were found at ϕ −20.5 (singlet, area ~4) due to NF_2 and at 135.1 (double quintet, J_{FH} = 50.5, J_{FF} = 9.8 Hz, area 1) due to NFH. ^1H nmr analysis gave peaks at τ 1 assigned to NFH and 5.8 due to CH_3OCH_3. Absorptions assigned to 2 constituted over 90% of the peaks in the fluorine nmr spectrum.

Other products, which increased in amount slowly as the sample remained at room temperature (it was stable at −78°), were HNF_2 (ϕ 7), $CF(NF_2)_2NFH$ (HF adduct of 1, reported[1] in previous work), and the major decomposition product, $H_2NC(NF_2)$=NF (3), from loss of HNF_2 by 2. Compound 3 was purified by glpc on a 0.25 in. × 9 ft column (30% SF-96 on Anakrom ABS) at 75°, T_R = 121 ($CHCl$=CCl_2 = 100), vapor pressure approximately 2 mm at 25°: nmr (CH_3CN, $CFCl_3$) ϕ −47.2 (s, 2, NF_2), 50.7 (s, 1, =NF); τ 4.07 (broad singlet, NH_2); ir (liquid) 2.88 (s), 2.95 (s), 3.02 (s) and 3.17 (m) all due to NH_2, 5.85 (s) C=N, 6.28 (m), 7.34 (m), 9.65 (w), 9.95 (w), 10.90 (m), 11.65 (vs) NF, 14.25 μ (w); mass spectrum *m/e*, ion (rel intensity), 27, CHN^+ (42); 28, CH_2N^+ (81), 41, CHN_2^+ (16); 42, $CH_2N_2^+$ (72); 46, $CHFN^+$ (40), 56, $CH_2N_3^+$ (1.7); 61, $CH_2FN_2^+$ (100); 75, $CH_2FN_3^+$ (1); 113, $CH_2F_3N_3^+$ (16.5), parent peak (no peaks at higher mass). *Anal.* Calcd for $CH_2F_3N_3$ (113.05): C, 10.6; F, 50.4; N, 37.2. Found: C, 10.9; F, 50.0; N, 35.9.

Treatment of 3 with aqueous NaOH liberates 1 mol of N_2 per mol of compound, as observed in the reaction of 1 and base.[13] Fluorination of 3 yields 1.

Fluorination of 2. Preparation of Tetrakis(difluoramino)methane (4) without Solvent.—The adduct 2 (approximately 2.9 mmol), prepared as above and free of most of the solvent, was fluorinated in the glass reactor with approximately sixfold molar excess of 3% F_2 (97% N_2) at −30° over a period of about 5 hr. The effluent gases were passed through a tube filled with NaF at 25° and into two borosilicate glass traps (containing glass beads) connected in series and cooled with liquid oxygen. The products were separated by glpc (Table IV) on a 0.5 in. × 18 ft column (33% KF-8126 on Celite) at 25°. The products isolated (area %) included $C(NF_2)_4$ 4 (20), 5 (16), 1 (14), 7 (<5), 6(<5), and $(F_2N)_3CNFH$ 9 (<5), isolated in the backflush (see below for analysis of 9). All except 4[2] and 9 are known compounds.[2,4]

TABLE IV

GAS CHROMATOGRAPHY DATA (AT 25°) FOR $C(NF_2)_4$

Column	Dimensions, in. × ft	T_R[a]
33% KF-8126 on Celite	0.5 × 5	153
33% KF-8126 on Celite	0.5 × 18	160
20% FS-1265 on firebrick	0.5 × 20	111
33% FC-45 on Celite	0.5 × 24	468

[a] Relative to $CFCl_3$ = 100; $T_R = (T_{compound} - T_{air})/(T_{ref} - T_{air}) \times 100$

(13) R. L. Rebertus and B. W. Nippoldt, *J. Org. Chem.* **32**, 4044 (1967).

In Trifluoroethanol.—The adduct 2 described above was dissolved in dry trifluoroethanol and fluorinated with 2 to 20% F_2 (N_2 diluent) at about −30°. The gaseous products were again separated by glpc to afford about a 20% yield of 4 (based on NH_3 used to prepare 2).

Most of the properties of $C(NF_2)_4$ are presented in Table I. Additional data (glpc, ir, and mass spectrum) are given below.

The infrared spectrum (gas) of 4 contains the following absorptions: 8.94 (m), 9.47 (w), 10.19 (vs) NF, 10.51 (vs) NF, 10.96 (vs) NF, 14.76 μ (w).

The mass spectrum of 4, reported in Table V, was run on a Consolidated Electrodynamics Corp. Model 21-1030 mass spectrometer. An ionization potential of 70 eV and an ionization temperature of 250° were employed.

TABLE V

MASS SPECTRUM OF $C(NF_2)_4$

m/e[a]	Ion	Rel intensity	*m/e*[a]	Ion	Rel intensity
14	N	5.33	40	CN_2	7.78
19	F	1.92	45	CNF	5.51
26	CN	7.52	47	N_2F	2.33
28	N_2	3.77	50	CF_2	16.91
31	CF	56.94	52	NF_2	64.15
33	NF	41.05	54	CN_3	1.00
59	CN_2F	7.94	97	CN_2F_3	100.0
64	CNF_2	79.77	98	Isotope	1.82
65	Isotope	1.16	116	CN_2F_4	0.81
78	CN_3F_2	11.99	168	CN_2F_6	38.27
83	CNF_3	1.11			

[a] I_m = 0.258 A and 0.538 (*m/e* 64, 168).

Fluorination of 2, Bis(difluoramino)bis(fluoramino)methane (8), and Tris(difluoramino)fluoraminomethane (9).—In a 20-ml capacity poly(chlorotrifluoroethylene) reactor containing a ptfe-coated magnetic stirring bar were condensed 3 ml of CH_3OCH_3 and 1.2 g (8 mmol) of 1 at −110°. To this stirred solution was transferred over several minutes under vacuum a gaseous mixture of NH_3 (5 mmol) and CH_3OCH_3 (from 2 ml of liquid). After stirring for 10 min at −110°, the reactor was warmed to −63° and most of the CH_3OCH_3 was removed under vacuum to a vapor pressure of 25 mm. CH_3CN (2 ml) was added and the reaction mixture was fluorinated at −37° by means of a tube placed beneath the liquid through which a stream of 3% F_2 (97% N_2) was introduced at a rate of 50–100 cc/min. The reaction mixture was monitored by glpc (approximately 0.01-ml samples) on a 0.25 in. × 6 ft SF-96 column on Anakrom ABS at 50°. The principal peaks are shown in Table VI.

TABLE VI

FLUORINATION OF $H_2NC(NF_2)_2NFH$ (2)

			Glpc peaks and areas			
		Time, min	1.58	3.50	9.50	11.25
Time, hr	F_2, mmol	T_R Identity	100 CH_3CN	258 9	758 8	904 8[a]
1.5	3.2		31	*b*	2.5	4.9
2.0	5.3		22	*b*	2.3	2.6
2.75	8.5		32	0.3	5.7	1.6
3.75	12.7		35	7.3	5.3	1.8
4.5	16		66	10.1	3.8	0.5

[a] Represents adduct 2, since 2 converts to 3 on heating. [b] Trace.

Compounds 8 and 9 were isolated by glpc using the same column described above except that the dimensions were 0.375 in. × 14 ft. Compound 8, $(F_2N)_2C(NFH)_2$, is a colorless liquid with vapor pressure about 20 mm at 22°: ^{19}F nmr ($CFCl_3$) ϕ −23.6 (s, 2, NF_2), 135.0 (d, 1, NFH); ir 3.01 (m) NH, 7.01 (m), 9.84 (m), 10.66–11.79 μ (s) NF; mass spectrum *m/e* (ion) 28

(N_2^+, largest peak), 45 (CFN^+), 46 ($CHFN^+$), 59 (CFN_2^+), 61 ($CH_2FN_2^+$), 64 (CF_2N^+), 79 ($CHF_2N_2^+$), 80 ($CH_2F_2N_2^+$), 113 ($CH_2F_3N_3^+$), 132 ($CH_2F_4N_3^+$, parent minus NF_2 group); mol wt (theory), 184; found (by mass spectral effusion rates on *m/e* 64 peak), 192.

Compound **9** [$(F_2N)_3CNFH$] is a colorless liquid: ^{19}F nmr ϕ −26.4 (s, 6, NF_2), 136.1 (d, J = 5 Hz, 1, NFH); ir 3.03 (w) NH, 10.07 (s) NF, 10.48 (s) NF, 11.07 (vs) NF, 11.89 μ (s) NF; mass spectrum *m/e*, ion (rel intensity), 31, CF^+ (100); 34, NHF^+ (51); 52, NF_2^+ (41); 64, CF_2N^+ (27); 79, $CHF_2N_2^+$ (35); 97, $CF_3N_2^+$ (23); 150, $CHF_5N_3^+$ (16); the latter peak is the parent minus NF_2.

Treatment of **9** with NaF caused loss of HNF_2 and formation of **1**.

Preparation of *N*-Bis(difluoramino)fluoraminomethyl-*N'*-isopropylidine Hydrazine (20), Bis(difluoramino)fluoromethylamine (23), and Difluoraminofluoraminodifluoromethane (24).—In a 1.5-ml capacity glass nmr tube was placed 18.7 mg (0.26 mmol) of acetone hydrazone; then 0.1 ml of dimethyl ether, 0.03 ml of $CFCl_3$, and 0.45 g (0.30 mmol) of **1** were transferred in under vacuum using a −110° bath. The tube was sealed with a flame and the reagents were mixed at −110° to give a yellow solution. The ^{19}F nmr was run at −95 to −85°. The principal peaks were at ϕ −20.4 (s, 4, NF_2) and 138.2 (d m, 1, NFH), consistent for the adduct **20** [$(CH_3)_2C{=}NNHC(NF_2)_2$-NFH]. **20** decomposed on warming to room temperature.

The reaction was repeated on a 20 times larger scale, and the reaction mixture was allowed to warm to room temperature while it was pumped through 0, −78, and −196° traps connected in series. A dark, oxidizing oil remained in the reactor; the 0° trap was empty, the −78° trap contained a pale yellow liquid, and the −196° trap contained only dimethyl ether. The contents of the −78° trap were separated by glpc on a 0.5 in. × 14 ft column (25% SF-96 on Anakrom ABS) at 25°. The main components were dimethyl ether and HNF_2 (74 total area %) eluting at 1.8–2.5 min. The peak eluting at 5.9 min (T_R = 85, $CFCl_3$ = 100), 4.7%, was identified as a mixture of F_2NCF_2-NFH (**24**) and N_2O. The 23.4-min peak (3.9%) was found to be $FC(NF_2)_2NH_2$ (**23**).

Properties of 23 follow: bp 68° (extrapolated from vapor pressure data); ^{19}F nmr ($CFCl_3$) ϕ −21.4 (s, 4, NF_2), 113.6 (s, 1, CF); ir (gas) 2.86 and 2.93 (w), NH_2, 6.20 (m), 7.63 (m), 8.84 (w), 9.21 (w), 9.84 (w), 10.60 (s), and 11.26 μ (m), NF_2; mass spectrum *m/e*, ion (rel intensity), 16, NH_2^+ (7.7); 28, CH_2N^+ (24.6); 31, CF^+ (37); 33 NF^+ (27); 41, CHN_2^+ (39); 46, $CHFN^+$ (100); 47, CH_2FN^+ (22); 60, $CHFN_2^+$ (51); 66, $CH_2F_2N^-$ (17); 99, $CH_2F_3N_2^+$ (22). *Anal.* Calcd for $CH_2F_3N_3$ (151): C, 8.0; F, 62.9. Found: C, 8.1; F, 61.0.

Properties of 24 (further purified by glpc)[6] follow: bp 17.7° (from vapor pressure data); nmr ($CFCl_3$) ϕ −17.0 (s, 2, NF_2), 104.4 (d, $J_{CF_2/NF}$ = 12.7 Hz, d, $J_{CF_2/NF}$ = 27.5 Hz, 2, CF_2), 132.3 (d, J_{FH} = 56 Hz, t, J_{F/CF_2} = 27.5 Hz, 1, NFH); $\tau \sim 0$ (d, J = 56 Hz, NFH); ir (gas) 3.0 (w) NH, 7.0 (m), 7.6 (s), 8.1 (s), 8.4 (m), 8.7 (m), 9.7 (m), 10.1 (m), 10.75 (vs), and 11.7 μ (s) NF_2; mass spectrum *m/e*, ion (rel intensity), 31, CF^+ (18); 46, $CHFN^+$ (30); 50, CF_2^+ (13); 52, NF_2^+ (10); 64, CF_2N^+ (100); 65, CHF_2N^+ (30); 69, CF_3^+ (50); 84, CHF_3N^+ (99); 98, $CHF_3N_2^+$ (7); 116, CF_4N_2 (2); mol wt, theory for CHF_5N_2, 136; found (from mass spectral effusion rates), 133. **24** slowly loses HF to yield **7**.

Preparation of Chlorodifluoraminodiazirine (25).[14]—Semicarbazide hydrochloride (0.10 g, 1 mmol) was treated with 0.15 g (1 mmol) of **1** by condensing the latter into a glass reactor at −110° and allowing the mixture to warm slowly to room temperature while stirring by means of a ptfe-coated magnetic stirring bar. The gas phase was sampled periodically and studied by glpc on a 0.25 in. × 24 ft column (Kel-F tetramer on Celite) at 25°. A peak with a T_R of 46 ($CFCl_3$ = 100) was observed to reach maximum concentration after 6 hr. This product was trapped out and fully characterized as chlorodifluoraminodiazirine (**25**). Properties and analytical data have been reported.[7] Other products identified (glpc, nmr, ir) in this reaction include **26**,[8] **27**,[9] and **7**.[2]

Preparation of 1,1-Dimethyl-2,3,3-trifluoroguanidine (31).[14]—A glass nmr tube was charged with 0.135 g (0.30 mmol) of $(CH_3)_2NH$, 0.060 g (0.40 mmol) of **1**, 0.1 g of CH_3OCH_3, and 0.035 g of $CFCl_3$. The tube was sealed and allowed to warm to −78° and the ^{19}F nmr spectrum was obtained at this temperature. Complete conversion to $(CH_3)_2NC(NF_2){=}NF$ (**31**) had taken place with no evidence for the intermediate adduct $(CH_3)_2$-$NC(NF_2)_2NFH$. ^{19}F nmr peaks for **31** were at ϕ −40.8 (s, 2, NF_2) and 61.7 (s, 1, =NF). **31** was purified by glpc on a 0.375 in. × 15 ft column (SF-96 on Anakrom ABS) at 80°. The peak eluting at about 12 min was trapped for analysis: mass spectrum *m/e*, ion (rel intensity), 15, CH_3^+ (100); 28, CH_2N^+ (92); 33, NF^+ (24); 42, $C_2H_4N^+$ (72); 69, $C_3H_5N_2^+$ (82); 70, $C_3H_6N_2^+$ (86); 89, $C_3H_6FN_2^+$ (59); 141, $C_3H_6F_3N_3^+$ (26, parent ion). *Anal.* Calcd for $C_3H_6F_3N_3$ (141.1): C, 25.5; F, 40.4. Found: C, 25.5; F, 40.4.

The nonbasicity of **31** was demonstrated by the absence of a shift in the ^{19}F nmr peaks after addition of anhydrous HCl.

Preparation of *N*,*N*-Dimethyl-*N'*-hexafluorisopropylidine Hydrazine (33).[11b]—A mixture of 0.35 g (3 mmol) of **29**, $(CF_3)_2$-C=NF, 0.11 g (2.5 mmol) of $HN(CH_3)_2$, and 0.4 g of $CFCl_3$ was allowed to react at room temperature in a sealed tube for 18 hr. ^{19}F nmr revealed no **29** remaining. Separation of the reaction mixture by glpc on a 0.375 in. × 12 ft column (FS-1265, 25%, on Chromosorb P) at 100° afforded a colorless liquid, T_R 638 (CCl_4 = 100), having a vapor pressure of about 2 mm at 25°, and identified as $(CF_3)_2C{=}NN(CH_3)_2$ (**33**): nmr ϕ 63.7 (quartet, J_{F-F} = 8.5 Hz, anti CF_3), 52.0 (quartet, J_{F-F} = 8.5 Hz, septet, J_{F-H} = 2.7 Hz, syn CF_3); τ 6.75 (multiplet, CH_3); ir 6.25 μ (C=N); mass spectral analysis gave a large parent peak at *m/e* 208, and lower molecular weight fragments. *Anal.* Calcd for $C_5H_6F_6N_2$ (208.1): C, 28.85; H, 2.9; F, 54.8; N, 13.5. Found: C, 29.7; H, 3.3; F, 54.0; N, 13.6. Compound **33** was also synthesized by the reaction of hexafluoroacetone and *N*,*N*-dimethylhydrazine followed by dehydration of the intermediate adduct (see equation in text). This was the method used to prepare an analogous compound, $(CF_3)_2C{=}NNH_2$.[10a]

Dimerization of 33. Preparation of 1,1,3,3-Tetramethyl-2,2-4,4-tetrakis(trifluoromethyl)-1,3-diazetidine (34).—In the initial preparation of **33** (from **29** and dimethylamine), some of the chromatographed product was allowed to remain in the borosilicate glass trap for several days, during which time it appeared to partially crystallize. Vaporizing the liquid portion (**33**) under vacuum and analysis of the solid residue, mp 112–113°, revealed that a cyclization–dimerization had apparently occurred to yield the diazetidine **34**. Treatment of **33** with concentrated H_2SO_4 also induced cyclization to **34**, but uv irradiation was without effect. The dimer **34** was analyzed by nmr, ir, and mass spectrum: nmr ($CFCl_3$) ϕ 69.6 (s, CF_3), τ 7.29 (s, CH_3); ir showed no peaks due to unsaturation between 3.5 and 6.8 μ; mass spectrum *m/e*, ion (rel intensity), 15, CH_3^+ (30.4); 28, N_2^+ or CH_2N^+ (17.4); 42, $CH_2N_2^+$ or $C_2H_4N^+$ (53.5); 43, $CH_3N_2^+$ or $C_2H_5N^+$ (100); 69, CF_3^+ (8.6); 139, $C_4H_6N_2F_4$ (42.3); 189, $C_5H_6F_5N_2^+$ (8.7); 207, $C_5H_5F_6N_2^+$ (2.8); 208, $C_5H_6F_6N_2^+$ (2.7, 50% parent peak); 265, $C_7H_{11}F_6N_4^+$ (1.6); 416, $C_{10}H_{12}F_{12}N_4^+$ (11.6, parent peak). *Anal.* Calcd for $C_{10}H_{12}F_{12}N_4$ (416.24): C, 28.85; H, 2.9; F, 54.8; N, 13.5. Found: C, 29.5; H, 2.9; F, 55.0; N, 14.0.

Registry No.—**1**, 10051-06-6; **2**, 35404-98-9; **3**, 37950-72-4; **4**, 17125-65-4; **7**, 14362-70-0; **8**, 37931-22-9; **9**, 37931-23-0; **11**, 37931-24-1; **12**, 37931-25-2; **13**, 37931-26-3; **14**, 37931-27-4; **15**, 37931-28-5; **16**, 37931-29-6; **17**, 37931-30-9; **18**, 37931-31-0; **19**, 37931-32-1; **20**, 37931-33-2; **21**, 37931-34-3; **22**, 37931-35-4; **23**, 37931-36-5; **24**, 37931-37-6; **28**, 758-35-0; **29**, 2802-70-2; **30**, 37931-40-1; **31**, 37931-11-6; **32**, 1619-94-9; **33**, 34224-15-2; **34**, 37931-14-9; **35**, 37931-15-0; NH_3, 7664-41-7; *p*-$CF_3C_6H_4NH_2$, 455-14-1; *p*-$NCC_6H_4NH_2$, 873-74-5; *n*-$C_4H_9NH_2$, 109-73-9; $(CH_3)_2NH$, 124-40-3; $(CH_3)_3CNH_2$, 75-64-9; $HClO_4 \cdot H_2NNH_2$, 27978-54-7; $(CH_3)_2C{=}NNH_2$, 5281-20-9; $CF_3CONHNH_2$, 1538-08-5; $COCH_2CH_2CONH$, 123-56-8.

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The Addition of Isocyanic Acid to Pentafluoroguanidine. Bis(difluoramino)fluoraminomethyl Isocyanate and Tris(difluoramino)methyl Isocyanate

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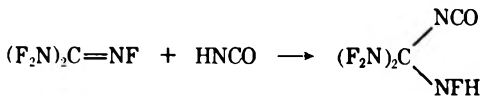
Isocyanic acid and pentafluoroguanidine reacted in the presence of a catalyst to form a 1:1 adduct, bis(difluoramino)fluoraminomethyl isocyanate (**1**), and a 2:1 adduct (**2**). The products obtained from the reactions of **1** with ethyl alchol, water, isocyanic acid, and 100% sulfuric acid are described. Fluorination of **1** gave tris(difluoramino)methyl isocyanate (**3**) and tetrakis(difluoramino)methane.

In connection with a program on the synthesis of compounds with a high content of N–F bonds, the addition of isocyanic acid to pentafluoroguanidine[2,3] was invcstigated. The addition was successful,[4,5]



1

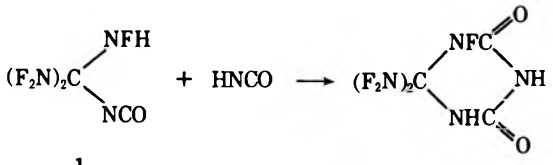
and the adduct proved to be a useful intermediate for the synthesis of a variety of new N–F compounds.

The low nucleophilicity of isocyanic acid and its rapid polymerization at room temperature operate against the desired addition to pentafluoroguanidine. Because of the low nucleophilicity of isocyanic acid, a basic catalyst, in this case urea, was added. When the catalyst was not used, erratic results were obtained. In order to minimize the polymerization reaction, a temperature of about −30° was used during the initial phase of the reaction. At this temperature isocyanic acid is quite stable, while at 0° it polymerizes readily.

The liquid 1:1 adduct (**1**) was separated from unchanged pentafluoroguanidine, isocyanic acid, and solid by-products by fractionation in a vacuum line.

The 1:1 adduct was assigned structure **1** on the basis of its infrared spectrum, proton and fluorine nmr spectra, and chemical reactions. Infrared absorptions at 3340 and 1410 cm^{-1} caused by the NH group in conjunction with a doublet of multiplets in the ^{19}F nmr spectrum at 125.0 ppm (J = 53 Hz) and a doublet at τ 1.59 (J = 53 Hz) in the ^{1}H nmr spectrum[6] establish the presence of an –NFH group. A broad, strong peak at −26.8 ppm was assigned to the difluoramino groups. Characteristic infrared absorptions at 2300 and 1480 cm^{-1} showed the presence of an isocyanate group.[8] The infrared spectrum is shown in Figure 1. Several reactions of **1** have established the presence of a carbon tetranitrogen skeleton and thus eliminated the possibility of a cyanate structure.

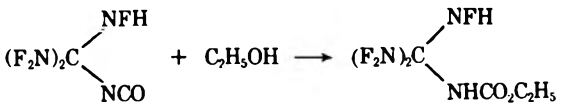
A 2:1 adduct (**2**) was extracted from the solid by-products formed during the preparation of **1**. It can also be prepared by the reaction of **1** with isocyanic



1 **2**

acid. The formulation of **2** as a cyclic compound is based upon the facts that the infrared and nmr spectra, respectively, show that the isocyanic acid has reacted with both the isocyanate and fluoramino groups, while its volatility (sufficient to allow vacuum sublimation at 50°) indicates that the compound is not a polymer. The question of whether the reaction occurs by initial reaction of the isocyanate or fluoramino group with isocyanic acid is not resolved.

The expected carbamate formed when **1** was treated with anhydrous ethyl alcohol.



The reaction of **1** with water was followed using fluorine nmr analysis. The results indicated that the amine which formed initially was unstable and lost difluoramine to form 1,1,2-trifluoroguanidine. Tri-

(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, with monitoring by the Bureau of Naval Weapons, RMMP, under Contract NOrd 18728, and by the Bureau of Naval Weapons under Contract NOw 65-0277-c.

(2) R. A. Davis, J. L. Kroon, and D. A. Rausch, *J. Org. Chem.*, **32**, 1662 (1967); R. J. Koshar, D. R. Husted, and C. D. Wright, *ibid.*, **32**, 3859 (1967); R. J. Koshar and D. R. Husted, U. S. Patent 3,461,162 (1969).

(3) The pentafluoroguanidine was prepared by S. Frank, M. D. Meyers, and A. J. Fanelli, of these laboratories. An aqueous fluorination of guanidine hydrofluoride was used.

(4) A related addition of isocyanic acid to hexafluoroisopropylidenimine has been reported: W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

(5) Other adducts of pentafluoroguanidine have also been prepared: J. L. Zollinger, C. D. Wright, J. J. McBrady, D. H. Dybvig, F. A. Fleming, G. A. Kurhajec, R. A. Mitsch, and E. W. Neuvar, *ibid.*, **38**, 1065 (1973); C. D. Wright and J. L. Zollinger, *ibid.*, **38**, 1075 (1973).

(6) Fluorine and proton nmr spectra are reported in parts per million from trichlorofluoromethane and in τ values,[7] respectively.

(7) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(8) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 3428 (1956).

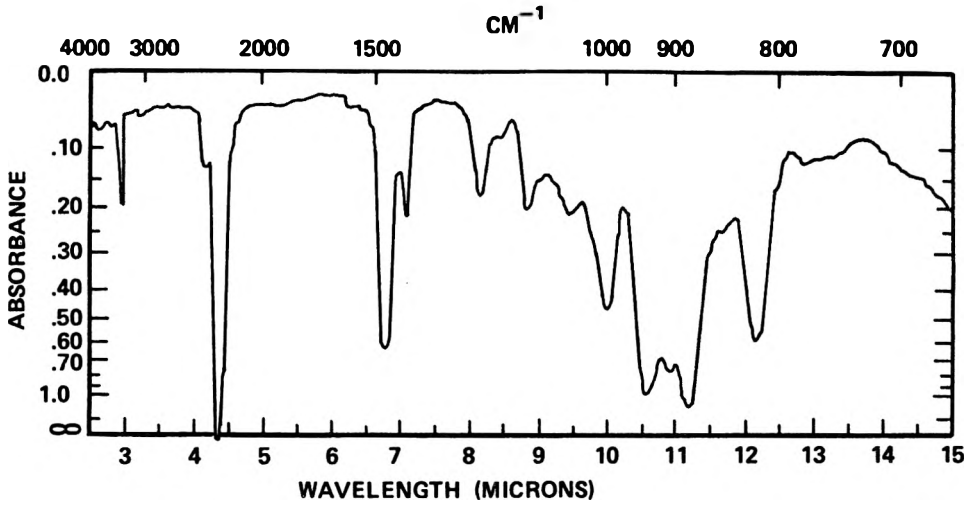


Figure 1.—Infrared spectrum of bis(difluoramino)fluoraminomethyl isocyanate (9 Torr in a 100-mm cell).

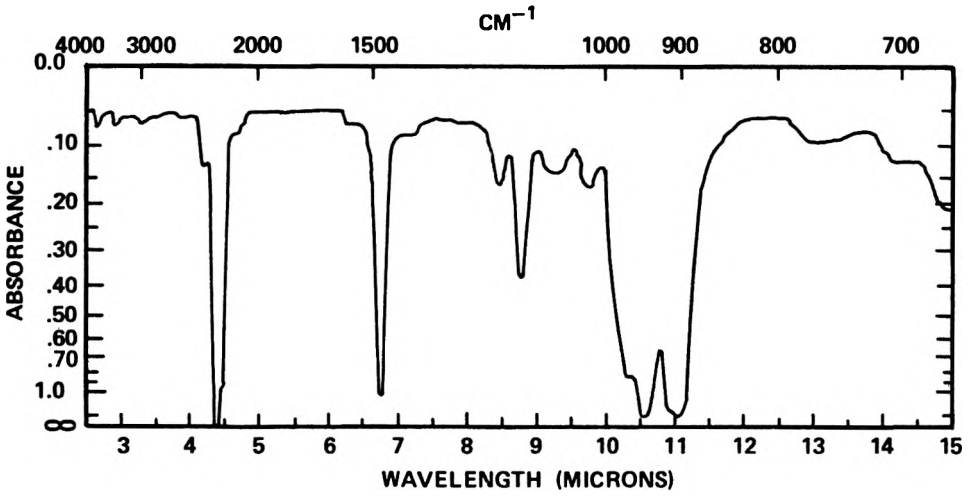
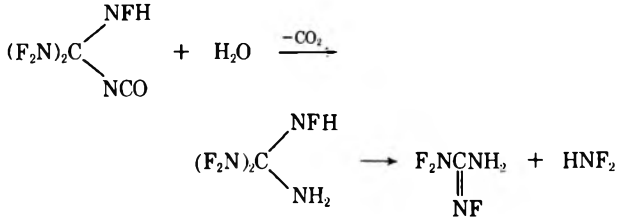
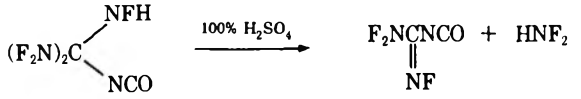


Figure 2.—Infrared spectrum of tris(difluoramino)methyl isocyanate (11 Torr in a 100-mm cell).

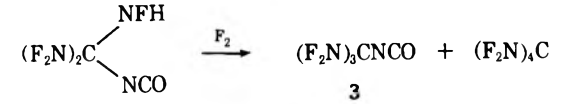
fluoroguanidine was isolated and identified on the basis of its infrared spectrum.



Trifluoramidino isocyanate[9] and difluoramine were formed when **1** was treated with 100% sulfuric acid.



Mild fluorination of **1** gave a mixture of tris(difluoramino)methyl isocyanate (**3**) and tetrakis(difluoramino)methane. Sodium fluoride was present in the fluorination system as a hydrogen fluoride scavenger. It was later discovered that the sodium fluoride was necessary for formation of tetrakis(difluoramino)methane.[10] The conditions which have been developed for the preparation of either product in high yield will be described, together with the properties of tetrakis(difluoramino)methane, in another publication.[10] A scaled-up version of the process for the preparation of **3** was used to prepare samples for physical and chemical studies.[11] The isocyanate, a colorless liquid, bp 63°, was purified by fractional codistillation[12] or by treatment with sulfuric acid followed by fractionation in a vacuum line. The molecular weight, elemental analysis, infrared spectrum, and fluorine nmr spectrum were in good agreement with the proposed structure. The infrared spectrum is shown in Figure 2; band positions are given in the Experimental Section.



(9) Trifluoramidino isocyanate was first prepared by T. H. Brownlee of these laboratories by the reaction of isocyanic acid with pentafluoroguanidine in sulfolane solution. We are grateful for permission to mention these results.

(10) S. Frank, W. C. Firth, Jr., and M. D. Meyers, *J. Org. Chem.*, **38**, 1088 (1973).

(11) We wish to thank the people of the Engineering Section of our department, under the direction of R. B. Wainright and R. C. Bell, for providing this material.

(12) G. H. Cady and D. P. Siegwarth, *Anal. Chem.*, **31**, 618 (1959).

Experimental Section

Caution.—The compounds discussed in this paper which contain NF groups are very powerful explosives and extremely sensitive to impact, friction, and perhaps temperature changes! They are also strong oxidizing agents. Even quantities as small as 100 mg are regarded as dangerous. Therefore all work should be carried out with adequate protective clothing, equipment for remote manipulation of apparatus, and suitable barricades.[13]

Volatile reagents and products were manipulated in a Pyrex glass vaccum line. Joints and stopcocks were lubricated with Kel-F No. 90 grease. The reactions were carried out in Pyrex glass reactors made from Lab-Crest valves (Fisher and Porter Co.). Apparatus was routinely dried.

Fluorine and proton nmr spectra were obtained with a Varian DP-60 high-resolution spectrometer operating at 56.4 MHz. Chemical shifts are in parts per million from trichlorofluoromethane (internal standard or solvent), and a negative chemical shift means a deshielded ^{19}F nucleus compared to the standard. Proton spectra are given in τ values.[7]

Unless specified, infrared spectra were obtained with a Perkin-Elmer Model 137B instrument. The melting point data on solid compounds were obtained on a Fisher-Johns apparatus and are uncorrected.

Isocyanic acid was prepared by the procedure described in the literature,[14,15] with a few exceptions. Cyanuric acid (Eastman Kodak Co., Eastman Grade) was used without purification, but was dried at 200° *in vacuo*.[16] The isocyanic acid was dried with phosphorus pentoxide and distilled in a vacuum line. Treatment with silver oxide to remove hydrogen cyanide was unnecessary for our purposes and was omitted. The isocyanic acid could be stored indefinitely in a Dry Ice bath, and was handled as a gas at pressures of about 100 mm in a vacuum line. Above 140 mm polymerization may occur.[16]

Bis(difluoramino)fluoraminomethyl Isocyanate (1).—Equimolar amounts (1.5 mmol each) of pentafluoroguanidine and isocyanic acid were condensed into a dry reactor, which contained powdered urea (9.0 mg, 0.15 mmol) as a catalyst. The reaction was allowed to proceed at −30° for 3 hr and then for 1 hr at room temperature. The volatile products were fractionated in a vacuum line. A −45° trap retained 1 in generally 30–50% yield based on pentafluoroguanidine charged. Nmr spectra were determined on a dilute solution of 1 in trichlorofluoromethane, with tetramethylsilane as an internal proton standard.

The adduct 1 formed small amounts of difluoramine and a yellow syrup upon standing for 1 week in the liquid phase at room temperature, but was recovered essentially quantitatively after being heated as a liquid for 4 hr at 70°.

The −45° volatiles from the reaction consisted of unchanged isocyanic acid and pentafluoroguanidine. The reactor contained a white solid from which the 2:1 adduct 2 could be extracted with either anhydrous methanol or anhydrous ethyl ether. Either recrystallization or vacuum sublimation was used for purification. Another preparation is described below.

6,6-Bis(difluoramino)-5-fluorodihydro-*s*-triazine-2,4(1*H*,3*H*)-dione (2).—Equimolar quantities (1.0 mmol each) of 1 and isocyanic acid were vacuum transferred into a small, dry sublimation apparatus, which contained 0.1 mmol of urea. The same time–temperature program that was used for the preparation of 1 produced a 90–100% conversion to 2. In a similar reaction in which no urea was added, only a trace amount of a solid product was produced.

The solid product was vacuum sublimed at 50°: mp 143–145° dec; $\nu_{max}^{mineral\ oil}$ 3230 (NH), 1780 and 1748 (C=O), and complex NF absorptions. The fluorine nmr spectrum in methanol solution showed broad peaks at −22.5 (NF_2) and 90.2 ppm (NF) from trichlorofluoromethane (internal). The compound was soluble in methanol, ethyl ether, and sulfur dioxide and insoluble in trichlorofluoromethane and benzene.

Anal. Calcd for $C_3H_2F_5N_5O_2$: F, 40.41; N, 29.79. Found: F, 39.69; N, 29.01.

Ethyl Bis(difluoramino)fluoraminomethylcarbamate.—Reagent grade ethanol (0.6 mmol), predried over Drierite, and 1 (0.6 mmol) were condensed into a 1.3-ml reactor at −196°. After 1 hr at room temperature, small amounts of difluoramine and ethanol were removed from the solid carbamate: mp 62–64°; $\nu_{max}^{mineral\ oil}$ 3410 (NH), 3220 (NH), 1740 (C=O),[8] and 1500 cm^{-1} (NH deformation),[8] and broad bands in the NF region; ^1H nmr (in trichlorofluoromethane) τ −0.45 (doublet, broad lines, NFH, J = 48.5 Hz), 3.67 (broad, NH), 5.76 (quadruplet, CH_2), 8.69 (triplet, CH_3); ^{19}F nmr (in trichlorofluoromethane) showed two broad peaks at −22.8 and −22.2 ppm caused by some nonequivalence in the NF_2 groups and a doublet (broad lines, J = 45 ± 5 Hz) at 131.8 ppm (NFH).

The carbamate was stable at room temperature for at least 16 hr and in trichlorofluoromethane solution for at least 57 days.

Reaction of 1 with Water (Preparation of 1,1,2-Trifluoroguanidine).—A 1.3-ml reactor was charged with 0.5 mmol of water and anhydrous ethyl ether (solvent). Then 1 (0.38 mmol) and trichlorofluoromethane (0.5 mmol) were added by vacuum transfer to the reactor at −196°. The reaction mixture was allowed to stand for 1 hr at 0° and, finally, allowed to warm to room temperature. Effervescence occurred intermittently.

After 1 hr at room temperature, the ^{19}F nmr spectrum showed peaks for 1,1,2-trifluoroguanidine (−47.4, NF_2; 50.7, =NF), aminobis(difluoramino)fluoraminomethane (−20.6, NF_2; 135.8 doublet, broad lines, NHF), and difluoramine (6.95). After 6 hr at room temperature, the sample showed strong signals due to the trifluoroguanidine and difluoramine, and much weaker signals at −36.9 and −35.2 ppm.

In another experiment, whose object was the preparation of the urea, 1 (0.48 mmol) and water (0.24 mmol) were combined at −196° and allowed to warm to room temperature. After 1 hr the volatile fraction at room temperature was removed, leaving a trace of unidentified yellow syrup. Infrared analysis of the volatiles showed difluoramine, silicon tetrafluoride, some recovered 1, and the trifluoroguanidine. 1,1,2-Trifluoroguanidine was isolated by vacuum line fractionation using a −2° trap and identified by its major infrared absorptions: ν_{max}^{gas} 3584 and 3472 (NH_2), 1704 (C=N), 1570 (NH deformation), 870 cm^{-1} (broad, NF).

Reaction of 1 with 100% Sulfuric Acid.—The 100% sulfuric acid was prepared by adding 97% sulfuric acid to 20% fuming sulfuric acid until no fumes were observed when moist air was passed over the liquid (fair and foggy method).[17] The sulfuric acid was added to a 5-mm o.d. reactor to a height of 15 mm, and 1 (0.38 mmol) was added by vacuum transfer. After 0.5 hr of reaction infrared analysis of the volatile fraction showed recovered 1, trifluoramidino isocyanate, and difluoramine. The reaction was allowed to resume. After 2 hr of reaction, infrared analysis showed only trifluoramidino isocyanate and difluoramine.

Tris(difluoramino)methyl Isocyanate (3).—The adduct 1 was fluorinated[10] and the resulting 3 was purified by fractional codistillation.[12] The fluorine nmr spectrum showed a broad, strong peak at −30.1 ppm in trichlorofluoromethane solution. This sample was stored for over 3 years without change in the nmr spectrum.

Anal. Calcd for $C_2F_6N_4O$: C, 11.4; N, 26.7; F, 54.3. Found: C, 11.7; N, 25.5; F, 52.7.

Additional samples were purified by treatment with 96% sulfuric acid. In a typical procedure, the crude isocyanate (1.4 mmol), which appeared to be contaminated with tris(difluoramino)methylamine and trifluoramidino isocyanate according to its infrared spectrum, was condensed at −196° into an evacuated reactor (volume *ca.* 4 ml) containing 1.0 ml of 96% sulfuric acid. The reaction mixture was allowed to thaw and was then stirred for 1 hr at room temperature. The product was fractionated in a vacuum line with traps at −45 and −78°. No gaseous material was retained by the −45° trap. The purified isocyanate (1.2 mmol) condensed at −78°. Analysis by fractional codistillation found 99.0% tris(difluoramino)methyl isocyanate, 0.6% (probably) tris(difluoramino)methylamine, and 0.4% (probably) carbon dioxide.

The following properties were determined on isocyanate which had been purified by treatment with sulfuric acid [mol wt 210 (calcd 210)]. The infrared spectrum was obtained by Mr. N. B.

(13) The various types of shielding to be used with such compounds have been described by C. L. Knapp, *Ind. Eng. Chem.*, **55**, No. 2, 25 (1963), and D. R. Smith, *J. Chem. Educ.*, **41**, A520 (1964).

(14) G. Brauer, "Handbuch der Praparativen Anorganischen Chemie," Vol. I, Ferdinand Enke, Stuttgart, Germany, 1960, p 592.

(15) We wish to thank Dr. Robert Church, formerly of these laboratories, for an initial gift of isocyanic acid.

(16) G. Herzberg and C. Reid, *Discuss. Faraday Soc.*, **9**, 92 (1950).

(17) W. J. Jolly, "Synthetic Inorganic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1960, pp 122–123.

Colthup using a Perkin-Elmer Model 521 grating infrared spectrophotometer. Sample pressures of 11, 4, and 2 mm in a 100-mm cell were used: ν_{max}^{film} (w, m, s, v, sh = weak, medium, strong, very, shoulder) 3770 (vw), 3430 (vw), 3055 (vw), 2395 (w), 2292 (vs, NCO asymmetric stretching), 2247 (s), 2150 (vw, sh), 1587 (vw), 1488 (s, NCO symmetric stretching), 1400 (vw), 1180 (w), 1140 (m, N–C–N asymmetric stretching), 1080 (w), 1022 (w), 968 (s, sh, NF_2 stretching), 947 (s, NF_2 stretching), 907 (s, NF_2 stretching), 760 (vw), 700 (vw). The gas at pressures of 55 and 118 mm in a 5-cm quartz cell showed continuous absorption in the ultraviolet region beginning at *ca.* 270 mμ, with an extremely weak, anomalous peak at 253 mμ superimposed on the general absorption.

The vapor pressure curve was measured in a grease-free system constructed from Lab-Crest valves (Fisher and Porter Co.). Pressures were measured with a 10-mm o.d. mercury manometer and a meter stick. Temperatures were measured with a calibrated copper–constantan thermocouple, made from Leeds and Northrup No. 24-55-1-A wire, and a Leeds and Northrup temperature potentiometer, Cat. No. 8692. The sample was cooled to −78° and pumped on immediately before it was introduced into the vapor pressure apparatus. After the data were obtained the sample was analyzed by fractional codistillation [found: isocyanate, 99.4%, probably tris(difluoramino)-methylamine, 0.6%]. The vapor pressure data were described by the equation $\log P$ (mm) $= -1728/T + 8.0208$; extrapolated bp 63 ± 1°; ΔH_v 7.91 kcal/mol; Trouton's constant 23.5.

Registry No.—**1**, 37950-68-8; **2**, 37950-69-9; **3**, 37950-70-2; pentafluoroguanidine, 10051-06-6; isocyanic acid, 75-13-8; ethyl bis(difluoramino)fluoraminomethylcarbamate, 37950-71-3; trichlorofluoromethane, 75-69-4; 1,1,2-trifluoroguanidine, 37950-72-4.

Acknowledgment.—We wish to thank Dr. J. E. Lancaster and Mrs. M. Neglia for obtaining the nmr spectra and Mr. J. H. Deonarine and staff of the Research Service Department of these laboratories for the elemental analyses. We also wish to thank Dr. V. P. Wystrach for encouragement and guidance.

The Chemistry of Tris(difluoramino)methyl Isocyanate

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Tris(difluoramino)methyl isocyanate (**1**) reacted with a variety of reagents to form compounds containing a tris(difluoramino)methyl group attached to a nitrogen substituent. Carbamates were prepared from methanol, ethylene glycol, allyl alcohol, poly(allyl alcohol), glycidol, and polyglycidol. Ammonia gave the urea **2**, which was converted to the biuret **3** by additional isocyanate. The biurea **4** was formed with hydrazine. Results obtained when the isocyanate was treated with nitramide are also described. The isocyanate reacted with water to form the amine **6**, which reacted under special conditions with additional isocyanate to form the 1,3-disubstituted urea **7**. The isocyanate formed a 1:1 adduct with pyridine and a formamidine (**8**) with dimethylformamide. Isobutylene and butadiene did not react appreciably with the isocyanate, and acids did not give the expected reactions. Nmr spectra of the products are discussed.

The preparation of tris(difluoramino)methyl isocyanate (**1**)[2] made possible the relatively facile synthesis of a variety of interesting compounds containing a tris(difluoramino)methyl group attached to a nitrogen substituent, compounds containing the rare carbon tetranitrogen skeleton. The preparation and characterization of these derivatives are described in this paper.

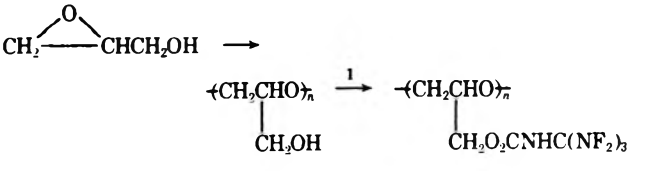
Reactions with Alcohols.—Alcohols reacted as expected with the isocyanate to form carbamates. No catalyst was necessary to obtain products from methanol, ethylene glycol, allyl alcohol, glycidol, polyglycidol, and poly(allyl alcohol). Di- and polycarbamates formed without difficulty from ethylene glycol and polyhydroxylic alcohols. However, satisfactory conditions for reaction with poly(vinyl alcohol) were not found, because of the lack of a suitable solvent. The carbamates were thermally quite stable. Thus, the methyl carbamate was recovered unchanged after 4 hr at 71–76° in a sealed tube, and the polyglycidol adduct was heated to 150° on a Koefler hot-stage microscope without sign of decomposition.

$$(F_2N)_3CNCO + ROH \longrightarrow (F_2N)_3CNHCO_2R$$

Attempted polymerization of allyl tris(difluoramino)-methylcarbamate gave a viscous liquid from which an amorphous solid could be isolated.

The carbamate from glycidol and **1** gave a complex product when treated with boron trifluoride. Thus, two main peaks were observed in the fluorine nmr spectrum, and there was a strong unexpected infrared absorbtion at 1689 cm^{-1} in addition to the expected carbonyl absorption at 1764 cm^{-1}. A similar product was obtained when the glycidol adduct was heated in an attempt to effect the rearrangement reported[3] for N-substituted glycidyl carbamates. These materials were not characterized further.

The carbamate of polyglycidol was made by an alternate route involving polymerization of glycidol[4] followed by reaction with **1**. Similarly, an adduct of



poly(allyl alcohol) and **1** was prepared. Both of these adducts contained some unchanged hydroxyl groups.

Reactions with NH Compounds.—Ammonia reacted rapidly with the isocyanate to form the urea **2**, which

(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, with monitoring by the Bureau of Naval Weapons, RMMP, under Contract NOrd 18728, and by the Bureau of Naval Weapons under Contracts NOw 65-0277-c and NOw 66-0397-c.

(2) W. C. Firth, Jr., S. Frank, and E. J. Schriffert, *J. Org. Chem.*, **38**, 1080 (1973).

(3) Y. Inakura and Y. Taneda, *ibid.*, **24**, 1992 (1959).

(4) S. R. Sandler and F. R. Berg, *J. Polym. Sci., Part A-1*, **4**, 1253 (1966).

$$(F_2N)_3CNCO + NH_3 \longrightarrow \underset{\mathbf{2}}{(F_2N)_3CNHCONH_2} \xrightarrow{\mathbf{1}} \underset{\mathbf{3}}{[(F_2N)_3CNHCO]_2NH}$$

reacted slowly with additional isocyanate to form the biuret **3**. The urea and perchloric acid formed a perchlorate salt.

$$(F_2N)_3CNHCONH_2 + HClO_4 \longrightarrow (F_2N)_3CNHCONH_3{}^+ClO_4{}^-$$

Hydrazine reacted with 2 mol of isocyanate to form the biurea **4**. These products from ammonia and

$$2(F_2N)_3CNCO + N_2H_4 \longrightarrow \underset{\mathbf{4}}{[(F_2N)_3CNHCONH]_2}$$

hydrazine are white solids, which explode violently upon mild impact. They decomposed, without melting, below 200° on a melting point block.

Nitramide and **1** formed an unstable adduct which decomposed into the carbamic acid **5** and nitrous oxide. The carbamic acid is also unstable and, in turn, forms the amine **6** and carbon dioxide.

$$(F_2N)_3CNCO \xrightarrow{NH_2NO_2} [(F_2N)_3CNHCONHNO_2] \xrightarrow{-N_2O} \underset{\mathbf{5}}{(F_2N)_3CNHCO_2H}$$

$$(F_2N)_3CNHCO_2H \longrightarrow \underset{\mathbf{6}}{(F_2N)_3CNH_2} + CO_2$$

Reaction with Water.—Usually water and isocyanates react to form ureas. However, isocyanates which bear strong electron-withdrawing substituents will give the amine instead.[5] As might be expected, therefore, **1** reacts with water to form the amine **6** rather

$$(F_2N)_3CNCO + H_2O \longrightarrow \underset{\mathbf{6}}{(F_2N)_3CNHCO_2H} \longrightarrow (F_2N)_3CNH_2 + CO_2$$

than the urea under ordinary conditions. A basic catalyst can be used, but is not necessary for reaction. The formation of the intermediate carbamic acid has been observed by nmr spectroscopy in an uncatalyzed reaction, and a small amount was isolated and characterized by its infrared spectrum.

Preparation of the urea **7** by reaction of the amine and

$$(F_2N)_3CNH_2 + (F_2N)_3CNCO \longrightarrow \underset{\mathbf{7}}{(F_2N)_3CNHCONHC(NF_2)_3}$$

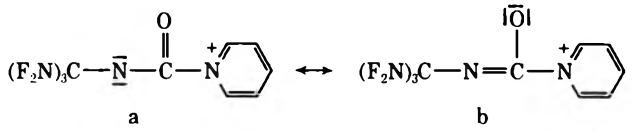
isocyanate was attempted. However, the amine was very unreactive. For example, there was no reaction after 19 days at room temperature in ethyl ether–trichlorofluoromethane solution. Even after 64 days only a small amount of reaction had occurred.

However, it was then discovered that triphenylphosphine oxide caused the amine and isocyanate to form a complex of the desired urea and triphenylphosphine oxide relatively rapidly.[6] The urea was displaced from the complex by trifluoroacetic acid and other acids. Complexes of tertiary phosphine oxides

$$(F_2N)_3CNH_2 + (F_2N)_3CNCO + (C_6H_5)_3PO \longrightarrow [(F_2N)_3CNH]_2C{=}O\cdot(C_6H_5)_3PO \xrightarrow{CF_3CO_2H} [(F_2N)_3CNH]_2C{=}O + (C_6H_5)_3PO\cdot CF_3CO_2H$$

and various acids are known, and the infrared spectra of some of the complexes have been described.[7] Comparison of the infrared spectra of the urea, triphenylphosphine oxide, and the crude complex indicated that the urea and phosphine oxide formed a complex in which the phosphine oxide is hydrogen bonded to the NH groups. This conclusion is based upon a shift to longer wavelength of the P=O absorption in the complex compared to the free phosphine oxide. The carbonyl group of the complexed urea is less hydrogen bonded than that of the free urea and absorbs at a shorter wavelength.

Adduct Formation with Pyridine.—When pyridine was treated with a 100% molar excess of the isocyanate in acetonitrile solution, or without a solvent, a high yield of a 1:1 adduct was obtained.[8] The isocyanate was liberated from the adduct by hydrogen chloride and boron trifluoride. The infrared spectrum of the adduct shows a strong carbonyl absorption at 1770 cm^{-1}. This wavelength is consistent with a structure in which there is little contribution from resonance hybrid b, probably because of enhanced stabilization



a b

of the negative charge on nitrogen by the tris(difluoramino)methyl group.

Several reaction products from the isocyanate and pyridine, in which the amount of pyridine was varied up to a maximum of 100 mol %, were examined by ^{19}F nmr. As the pyridine content of the mixture increased, the chemical shift of the tris(difluoramino)-methyl peak became progressively more positive. However, only one peak was observed even though the amount of pyridine was insufficient to combine with all of the isocyanate. These data indicate that the pyridine–isocyanate complex rapidly exchanges with uncomplexed isocyanate.

The data seem more consistent with simple complex formation than with a dimerization induced by the pyridine. If pyridine does induce the formation of a dimer, the dimer must rapidly exchange with isocyanate and must also dissociate back to isocyanate when the pyridine is neutralized with acids.

Reaction with Dimethylformamide.—In harmony with the chemistry of other isocyanates,[9a,b] dimethylformamide and **1** condensed with the elimination of carbon dioxide to form the formamidine, a liquid of low volatility. The reaction took place easily at room temperature.

$$(F_2N)_3CNCO + HCON(CH_3)_2 \longrightarrow \underset{\mathbf{8}}{(F_2N)_3CN{=}CHN(CH_3)_2} + CO_2$$

Attempted Reactions with Olefins.—Because **1** reacted easily with dimethylformamide at room temperature, as does *p*-toluenesulfonyl isocyanate,[9a] the

(5) J. H. Saunders and K. C. Frisch, "Polyurethanes: Chemistry and Technology," Part I, Chemistry, Interscience, New York, N. Y., 1962, pp 76–78.

(6) Catalysis of isocyanate reactions by pyridine *N*-oxide has been reported: J. Burkus, *J. Org. Chem.*, **27**, 474 (1962). To our knowledge, phosphine oxides have not been used before.

(7) J. R. Van Wazer, "Phosphorus and Its Compounds," Vol. I, Interscience, New York, N. Y., 1958, p 287; D. Hadzi, *J. Chem. Soc.*, 5128 (1962).

(8) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965), has reviewed comparable adducts of sulfonyl isocyanates.

(9) (a) C. King, *J. Org. Chem.*, **25**, 353 (1960); (b) M. L. Weiner, *ibid.*, **25**, 2245 (1960).

possibility that it would show reactivity with olefins comparable to chlorosulfonyl isocyanate[10] was investigated. While chlorosulfonyl isocyanate reacts readily with isobutylene and butadiene, **1** failed to react appreciably with isobutylene in the liquid phase at room temperature during 23 days. The mixture (96% recovery) was unchanged according to analysis by infrared spectroscopy. Similarly, 97% of a mixture of **1** and 1,3-butadiene was recovered after 8 days.

Attempted Reactions with Acids.—While a number of attempts were made to add acids to **1**, the usual result was little or no reaction. Formic acid and isocyanic acid failed to react in the absence of a catalyst. The isocyanic acid polymerized, but essentially all of **1** was recovered. Hydrogen chloride failed to react with **1** in trichlorofluoromethane solution with pyridine as the catalyst.

Nmr Spectra.—The ^{19}F nmr spectra for a number of compounds containing a tris(difluoramino)methyl group attached to a nitrogen substituent are listed in Table I

TABLE I

^{19}F NMR SPECTRA OF TRIS(DIFLUORAMINO)METHYL GROUPS ATTACHED TO VARIOUS NITROGEN SUBSTITUENTS

Compd (X = NF_2)	Solvent	δ_F[a]
$X_3CN{=}CHN(CH_3)_2$	$CFCl_3$	−24.2[b]
X_3CNH_2	$CFCl_3$	−24.5
X_3CNHCO_2H	$(C_2H_5)_2O$	−26.8
$X_3CNHCO_2CH_3$	$CFCl_3$	−26.8
	$CFCl_3$	−26.9[c]
$X_3CNHCO_2CH_2CH{=}CH_2$	$CFCl_3$	−27.2
$X_3CNHCONH_2$	$(C_2H_5)_2O$	−27.3
$(X_3CNHCONH)_2$	CH_3CN	−28.0
$(X_3CNHCONHCX_3)(Ph_3PO)$	CH_2Cl_2	−28.0
$(X_3CNHCO)_2NH$	$(C_2H_5)_2O$	−28.1[d]
$(X_3CNH)_2CO$	$(C_2H_5)_2O$	−28.2
X_3CN_3[e]	$CFCl_3$	−28.7
$X_3CNHCONH_3{}^+ClO_4{}^-$	CH_3NO_2	−28.9
X_4C[f]	$CFCl_3$	−29.5
X_3CNCO[f]	$CFCl_3$	−30.1

[a] Parts per million from trichlorofluoromethane (internal). [b] Weak additional peak at −27.6. [c] Weak additional peak at −25.9. [d] Very weak additional peak at −27.3. [e] M. D. Meyers, unpublished results. [f] Reference 2.

in order of chemical shift. They occur within a relatively small range (−24.2 to −30.1 ppm). The chemical shifts of structurally similar compounds are further clustered within this range. Thus, the chemical shifts of compounds in which the tris(difluoramino)methyl group is attached to N_3, NF_2, or NCO are at the deshielded end, all of the compounds of the $(F_2N)_3CNHCON<$ type occur in approximately the middle of the range, and compounds in which tris(difluoraminomethyl) groups are attached to NH_2 and $N{=}CN(CH_3)_2$ groups are found at the shielded end of the range. It appears to be possible to use these empirical correlations to draw tentative conclusions about the possibility of a tris(difluoramino)methyl compound in an unknown mixture and even the type of compound present.

The adducts of tris(difluoramino)methyl isocyanate and active hydrogen compounds showed surprisingly sharp ^{19}F nmr peaks compared to tris(difluoramino)methyl isocyanate itself and many other NF compounds.

The proton nmr spectra of compounds with the $(F_2N)_3CNHCOY$ structure were observed as broad lines, a common shape for protons attached to nitrogen, in the range of τ 0.49–2.1. τ values of this magnitude indicate that the protons are more acidic than those of ordinary *N*-alkylamides,[11] an effect no doubt caused by the electron-withdrawing effect of the tris(difluoramino)methyl group. When the substituent Y also contained NH groups, the latter were observed as separate peaks, and so the proton environments of the NH groups are not rapidly averaged by exchange.

Experimental Section

Caution.—The compounds described in this paper which contain NF groups are very powerful explosives and extremely sensitive to impact, friction, and perhaps temperature changes! They are also strong oxidizing agents. Even quantities as small as 100 mg are regarded as dangerous. Therefore all work should be carried out with adequate protective clothing, equipment for remote manipulation of apparatus, and suitable barricades.[12]

Volatile reagents and products were manipulated in a Pyrex glass vacuum line. Joints and stopcocks were lubricated with Kel-F No. 90 grease. The reactions were carried out in Pyrex glass reactors, in many cases made from Lab-Crest valves (Fisher and Porter Co.). Apparatus was routinely dried.

^{19}F nmr spectra (Table I) were obtained with a Varian DP-60 high-resolution spectrometer operating at 56.4 MHz. Chemical shifts are in parts per million from trichlorofluoromethane (internal standard or solvent) and a negative chemical shift means a deshielded ^{19}F nucleus compared to the standard. ^1H nmr spectra were determined with either a Varian DP-60 or Varian A-60 spectrometer and calibrated with tetramethylsilane (internal). The results are reported in τ values.[13]

Unless specified, infrared spectra were obtained with a Perkin-Elmer Model 137B Infracord. The melting point data were obtained on a Fisher-Johns apparatus and are uncorrected.

Methyl Tris(difluoramino)methylcarbamate.—Less than 1 mmol of isocyanate was condensed at −196° into a reactor containing anhydrous reagent-grade methanol in 30–50 mol % excess. The reaction was allowed to take place at room temperature. The excess methanol was removed by vacuum transfer, and the residual carbamate was purified by vacuum sublimation: mp 43–44°; $\nu_{max}^{mineral\ oil}$ 3280 (NH), 1740 (C=O),[14] 1515 cm^{-1} (NH deformation)[14] and broad, strong NF absorptions.

Anal. Calcd for $C_3H_4F_6N_4O_2$: F, 47.09. Found: F, 47.70.

Ethylene *N,N'*-Bis[tris(difluoramino)methyl]dicarbamate.—Ethylene glycol (0.11 mmol) and the isocyanate (0.3 mmol) were allowed to react at room temperature for 25 hr. The volatile fraction was removed under vacuum to give a solid residue (49 mg, 96% yield of dicarbamate based on ethylene glycol): mp 136–137°; $\nu_{max}^{mineral\ oil}$ 3236 (NH), 1748 (C=O), 1534 cm^{-1} (NH deformation), strong bands in the NF region.

Anal. Calcd for $C_6H_6F_{12}N_8O_4$: F, 47.29. Found: F, 46.70.

Allyl Tris(difluoramino)methylcarbamate.—Redistilled allyl alcohol (68 μl, 1.0 mmol) and the isocyanate (1.10 mmol) were allowed to react for 17 hr at room temperature. The reactor was then cooled to 0°, and the volatile fraction (0.11 mmol) was removed by vacuum transfer until the residue, a colorless liquid, showed no vapor pressure at room temperature. The yield was 269.8 mg (100% based on allyl alcohol).

The preparation was also carried out in trichlorofluoromethane and in ethyl ether. Center cuts of the carbamate were obtained by bulb-to-bulb distillation at room temperature: mp 11.6–12.6°; ν_{max}^{liquid} 3436 (sh) and 3268 (NH), 2985 (CH), 1754 (C=O), 1520 (NH deformation), and 990–885 cm^{-1} (three broad bands,

(10) R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963); H. Hoffmann and H. J. Diehr, *Tetrahedron Lett.*, **No. 27**, 1875 (1963).

(11) M. W. Dietrich and R. E. Keller, *Anal. Chem.*, **36**, 258 (1964).

(12) The various types of shielding to be used with such compounds have been described by C. L. Knapp, *Ind. Eng. Chem.*, **55**, No. 2, 25 (1963), and D. R. Smith, *J. Chem. Educ.*, **41**, A520 (1964).

(13) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(14) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 3428 (1956).

NF); proton nmr in carbon tetrachloride at τ 3.13 (broad, 1.0 H, NH), 5.31 (1.9 H, CH_2), *ca.* 4.67 (2.0 H, CH_2=), and *ca.* 4.10 (1.1 H, =CH-).[15]

Polymerization of the Allyl Tris(difluoramino)methylcarbamate.—The carbamate was converted to a viscous liquid by heat, either alone or with benzoyl peroxide as catalyst. A hard, amorphous, light amber solid could be isolated by removal of most of the volatile material under vacuum at 25–50° and then the extraction of the residue with carbon tetrachloride. The lack of absorption at 1420 cm^{-1} in Halocarbon oil indicated the absence of monomer.

2,3-Epoxypropyl Tris(difluoramino)methylcarbamate.—Eastman grade glycidol was freshly distilled bulb-to-bulb at *ca.* 60° under vacuum. The glycidol (0.99 mmol) and isocyanate (1.10 mmol) were combined at −196° and allowed to react at room temperature for 18 hr. The volatile fraction was removed at room temperature until the colorless, viscous liquid residue showed essentially no vapor pressure at room temperature. The yield was essentially quantitative: ν_{max}^{liquid} 3205 (NH), 1765 (C=O), 1522 cm^{-1} (NH deformation); ^1H nmr (in trichlorofluoromethane) τ 2.36 (1 H, broad, NH), *ca.* 5.4 and *ca.* 6.1 (2 H, $-OCH_2-$), *ca.* 6.75 (1 H, ring CH), *ca.* 7.2 (2 H, ring CH_2).

Anal. Calcd for $C_5H_6F_6N_4O_3$: F, 40.12. Found: F, 40.67.

Some infrared spectra of this carbamate showed weak bands which were characteristic of products obtained when this carbamate was treated with boron trifluoride (see below) or heated for several hours at 55–85°.

Reaction of 2,3-Epoxypropyl Tris(difluoramino)methylcarbamate Catalyzed by Boron Trifluoride.—A solution of the carbamate in trichlorofluoromethane was treated with a catalytic amount of boron trifluoride at −196° and then allowed to react at 0° overnight and at room temperature for *ca.* 27 hr. The product was washed with trichlorofluoromethane and dried under vacuum. Essentially the same product was formed when the carbamate was treated with boron trifluoride under comparable conditions, but without a solvent.

The product varied from an amorphous solid to a syrup and showed ν_{max}^{neat} 3425, 3226 (NH), 1764 (C=O), 1689, and 1522 cm^{-1} (NH deformation); ^{19}F nmr at −27.3 (strong, sharp), −26.4 (medium, sharp), and −24.5 ppm (very weak) in acetone-d_6.

Adduct of Polyglycidol and 1.—Polyglycidol was prepared as described in the literature[4] from 1 g of glycidol and 9 mg of pyridine. The polyglycidol (70 mg, 0.94 mmol) and 1 (1.1 mmol) were allowed to react for 21 hr at room temperature and for 24 hr at 59–60°. The volatile fraction was removed at room temperature and at 60–64° under vacuum. The yield of adduct was 228 mg, corresponding to the addition of 0.748 mmol of isocyanate and a fluorine content of 37.6% (found, 36.5%). The product was an amorphous white powder at 90 × magnification. $\nu_{max}^{mineral\ oil}$ 3425, 3268, 1767 (C=O), and 1531 cm^{-1} (NH deformation). The sample appeared to soften and melt from less than 60° to *ca.* 100° to give a clear viscous liquid. There was no sign of decomposition when heating was continued up to 150°.

Adduct of Poly(allyl alcohol) and 1.[16]—Poly(allyl alcohol) was prepared as described in the patent literature[17] by heating allyl alcohol at 100° for 144 hr with 2.1% of a 90% aqueous solution of hydrogen peroxide (1.9% hydrogen peroxide). The product was pumped on for 2 hr at 105°.

The poly(allyl alcohol) (0.88 mmol) and isocyanate (0.98 mmol) were allowed to react in acetonitrile for 18 hr at room temperature. The polymer dissolved as the reaction proceeded. A volatile fraction was removed by vacuum transfer at room temperature, and the residue was dissolved in anhydrous ethyl ether (0.5 ml). The ether solution was added dropwise to 12 ml of *n*-heptane, and the precipitated polymer was dried under vacuum, $\nu_{max}^{mineral\ oil}$ 3546, 3448, 3300, 1751 (C=O), and 1524 cm^{-1} (NH deformation). The polymer obtained was 86% of that calculated for complete reaction. The fluorine content indicated that some unchanged hydroxyl groups remained.

Anal. Calcd for $(C_5H_6F_6N_4O_2)_n$: F, 42.53. Found: F, 36.89.

Tris(difluoramino)methylurea.—The isocyanate (0.90 mmol) and anhydrous ethyl ether (7.8 mmol) were added by vacuum transfer to a reactor (*ca.* 4 ml) and stirred. The reactor was cooled to −196° and 0.86 mmol of anhydrous ammonia was added by vacuum transfer. The bath was then removed and, as soon as the reaction mixture liquefied, stirring was started. Stirring was continued for 1.25 hr. The volatile fraction was then removed under vacuum. The residue was dissolved in *ca.* 2 ml of dry ethyl ether, and the solution was transferred to two dry centrifuge tubes. Each solution was concentrated to *ca.* 0.4 ml using a stream of prepurified nitrogen. Anhydrous redistilled petroleum ether (bp 30–60°) was added to bring the total volume of solution in each tube to 3.5 ml. The white solid which precipitated was separated and dried at room temperature. The yield was 150 mg (0.66 mmol, 77% based on ammonia), $\nu_{max}^{mineral\ oil}$ 3559, 3390, 3205, 1733 (C=O), 1695 (C=O), and 1546 cm^{-1} (NH deformation). The ^1H nmr spectrum of an acetone-d_6 solution of the urea showed broad peaks at τ 1.52 (1 H, -NH-) and 3.62 (2 H, $-NH_2$); at −39 and −61° the two protons of the NH_2 group became nonequivalent.

Anal. Calcd for $C_2H_3F_6N_3O$: F, 50.20. Found: F, 50.33.

Tris(difluoramino)methylurea Perchlorate.[18]—Reaction of the urea (0.3 mmol) and perchloric acid (0.3 mmol) in chloroform at −60° for 1 hr followed by warming to room temperature produced a white, hygroscopic solid, which decomposed below 55°: $\nu_{max}^{mineral\ oil}$ in a polyethylene cell[19] 3356, 3226, 2505, 1689 (C=O), and 1105 cm^{-1} (ClO_4^-); ^1H nmr τ 0.05 (3 H, broad, $-NH_3^+$) and 1.12 (1 H, broad, -NH-).

Anal. Calcd for $C_2H_4ClF_6N_3O_3$: F, 34.80; N, 21.38. Found: F, 34.74; N, 20.91.

1,5-Bis[tris(difluoramino)methyl]biuret (3).—Approximately 1.0 ml of anhydrous ethyl ether and 1.54 mmol of 1 were vacuum transferred into a reactor (*ca.* 4 ml). The mixture was stirred at room temperature and recooled to −196°, and 0.54 mmol of ammonia was then added by vacuum transfer. The bath was removed. As soon as the reaction mixture liquefied, it was stirred for 15 min. After 1 week, the volatile fraction was removed by vacuum transfer. A solution of the solid residue in 2.2 ml of anhydrous ethyl ether was centrifuged to remove a trace amount of yellow solid and divided into two equal parts. The ether was removed under vacuum and the solid residues were dried for 1 hr at 59°. The yield of solid was 168 mg (0.384 mmol, 71% yield based on ammonia). The biuret appeared to decompose without melting below 200°.

Anal. Calcd for $C_4H_3F_{12}N_9O_2$: F, 52.16; N, 28.84. Found: F, 50.35; N, 28.59.

The ^1H nmr spectrum consisted of either two broad overlapping peaks at τ 0.49 and 0.72 (respective area ratio 2:1) or a single, very broad peak at τ 0.58 in which the overlapping peaks had merged (probably by NH exchange). The biuret is apparently capable of existing in two solid modifications with different infrared spectra. Thus, the modification initially obtained had $\nu_{max}^{mineral\ oil}$ 3344, 1770 (sh), 1754, 1724, 1709 (sh), 1538 cm^{-1}. Exposure of this material to atmospheric moisture did not affect its infrared spectrum. However, when samples of the biuret with this spectrum were allowed to stand at room temperature, the spectrum in the 3600–1700-cm^{-1} range slowly changed to $\nu_{max}^{mineral\ oil}$ 3597, 3521, 3226, 1754, and 1730 cm^{-1}. When this latter modification was recovered from ether solution or was heated at 80° it converted to the original form.[20]

1,6-Bis[tris(difluoramino)methyl]biurea (4).—A solution of 16.3 μl of technical anhydrous 98.5% hydrazine (0.50 mmol of hydrazine) in 1.5 ml of acetonitrile (reagent grade, dried over P_2O_5 and distilled) was prepared under a nitrogen atmosphere and transferred to a reactor (*ca.* 4 ml). The reactor was then cooled in a liquid nitrogen bath and evacuated, and 1.1 mmol of isocyanate was added by vacuum transfer. The liquid nitrogen bath was replaced with an ice bath. As soon as the reaction mixture liquefied, stirring was started. After 15 min the ice bath was removed. After a total reaction time of 1 hr, the clear yellow solution and 0.7 ml of an acetonitrile rinse were transferred under nitrogen to a centrifuge tube. The solution was treated with portions of decolorizing charcoal until the yellow

(15) The spin–spin coupling patterns were indicative of the allyl group by comparison with Varian Associates, "NMR Spectra Catalog," 1962 Spectrum 34.

(16) We wish to thank Mr. E. J. Schriffert, of these laboratories, for this experiment.

(17) N. V. de Bataafsche Petroleum Maatschappij, Dutch Patent 66,784 (1950); *Chem. Abstr.*, **45**, 5451 (1951).

(18) We wish to thank Mr. E. J. Schriffert, of these laboratories, for this experiment.

(19) I. Cohen, *J. Chem. Educ.*, **39**, 262 (1962); T. Robinson, *Nature (London)*, **184**, 448 (1959).

(20) We wish to thank Dr. J. J. Keavney and J. Habermann, of these laboratories, for the latter experiment.

color had been removed. The supernatant liquid was decanted into two tared centrifuge tubes. Each tube was heated in an oil bath (55°) and the solvent was removed in a stream of nitrogen until the volume of solution was 0.3 ml. The warm solutions were then diluted to 1.0 ml with reagent grade methylene chloride. Crystals immediately separated. After approximately 0.75 hr at room temperature, the crystals, which were initially almost invisible in the solvent, had become white. The crystals were separated (centrifuge) and each portion was washed with 0.8 ml of methylene chloride and dried at room temperature. The yield of white solid was 125 mg (0.28 mmol of the biurea, 55% yield), $\nu_{max}^{mineral\ oil}$ 3344, 3247, 3067, 1715, and 1555 cm^{-1}. ^1H nmr in acetonitrile showed two broad peaks with an area ratio of 1:1 at τ 2.09 and 2.44.

Anal. Calcd for $C_4H_4F_{12}N_{10}O_2$: F, 50.43; N, 30.98. Found: F, 50.71; N, 30.06, 31.41.

Reaction of Nitramide with 1.—Nitramide[21] (34.3 mg, 0.554 mmol) was dissolved in anhydrous ethyl ether (*ca.* 0.3 ml). The solution was added to a reactor which was made by sealing a 5-mm o.d. nmr tube to a Lab-Crest valve. Isocyanate (0.58 mmol) and tetramethylsilane (0.1 mmol) were added by vacuum transfer, and the reaction was allowed to proceed at room temperature. After *ca.* 2.5 hr, a ^1H nmr spectrum showed a broad, strong peak at τ 0.18 assigned to the adduct and broad, weak peaks at −1.4 and 1.2, which are assigned to the carbamic acid **5**.[22] After about 30 hr, peaks caused by the carbamic acid were present and, as well, a broad peak at τ 5.5, probably caused by tris(difluoramino)methylamine.

A gas, which amounted to 0.69 mmol, was separated after 2 additional days. Analysis by mass spectrometry found 75.2% nitrous oxide (0.52 mmol), 22.8% carbon dioxide (0.16 mmol), and 1.7% tetramethylsilane.

Hydrolysis of Tris(difluoramino)methyl Isocyanate.—A reactor was made by sealing a 5-mm o.d. nmr tube to a Lab-Crest valve and charged with 8.0 μl (0.44 mmol) of water. Ethyl ether (*ca.* 0.2 ml), isocyanate (0.46 mmol), and trichlorofluoromethane (0.3 mmol) were added to the reactor by vacuum transfer. The reaction was allowed to proceed at room temperature. A ^{19}F nmr spectrum of the reaction mixture after *ca.* 7 hr showed strong peaks at −24.3, −26.8, and −29.9 ppm assigned to the amine **6**, carbamic acid **5**, and isocyanate, respectively. After 4 days a ^1H nmr spectrum showed a broad peak assigned to the amine at τ 5.50 and two broad peaks assigned to the carbamic acid at *ca.* 1.2 and *ca.* −1.2.

A small amount of a white solid, which appears to be the carbamic acid, was isolated from a reaction of **1** with water: ν_{max} 3344 (NH), 3125–2500 (CO_2H), 1715 (C=O), and 1536 cm^{-1} (NH deformation).

Tris(difluoramino)methylamine (6).—A reactor (*ca.* 1.3 ml) was charged with 13 μl (0.72 mmol) of water and 0.71 mmol of the isocyanate, containing small amounts of **6** and silicon tetrafluoride. After 19 hr of reaction at room temperature the product was fractionated using a −78° trap to retain the amine (0.5 mmol) and pass carbon dioxide. Samples of the amine were purified by fractional codistillation[23] or dried by passage of the vapors through magnesium perchlorate ("Dehydrite") or phosphorus pentoxide. Extended contact results in decomposition. Properties of the amine were determined: ν_{max}^{gas} NH_2 at 3571, 3472, and 1613 cm^{-1}; ^1H nmr τ 6.80 (weak unassigned peak at 8.50), in trichlorofluoromethane; estimated (by extrapolation of vapor pressure data) bp 95°;[24] mol wt, 184 (gas density) (calcd 184).[24]

Attempted Reactions of Tris(difluoramino)methylamine and Tris(difluoramino)methyl Isocyanate in the Absence of Triphenylphosphine Oxide.—The amine (0.3 mmol) and isocyanate (0.3 mmol) were heated in a small reactor (volume *ca.* 1.3 ml) at 62° (1 hr), 64–92° (1 hr), and 92° (4⅓ hr). A liquid phase was present throughout the treatment. Most of the mixture of starting materials was recovered unchanged.

Reaction of Tris(difluoramino)methylamine and Tris(difluoramino)methyl Isocyanate in the Presence of Triphenylphosphine Oxide.—Two reaction mixtures were prepared which were comparable with the exception that only one contained triphenylphosphine oxide. The compositions of the reaction mixtures were as in Table II. After 8 days at room temperature,

TABLE II

Component	Reaction A, mmol	Reaction B, mmol
$(F_2N)_3CNCO$	0.33	0.33
$(F_2N)_3CNH_2$	0.31	0.31
$(C_6H_5)_3PO$	0.09	None
Benzene	1.0	1.0
$CFCl_3$ (internal nmr standard)	0.54	0.54

the ^{19}F nmr spectra were determined. Reaction A, which contained triphenylphosphine oxide, showed a strong signal at −28.0 ppm due to the complex of **7** and triphenylphosphine oxide, as well as the two signals of the isocyanate and amine. Reaction B showed only the two signals of the starting materials.

1,3-Bis[tris(difluoramino)methyl]urea (7).—An approximately 4-ml Pyrex glass reactor, made from a Lab-Crest quick-opening needle valve with a Teflon stem, was equipped with a stirring bar, flamed under vacuum, and filled with nitrogen. The reactor was then charged with 139 mg (0.50 mmol) of triphenylphosphine oxide (Aldrich Chemical Co., mp 156–157°), 9.0 μl (0.50 mmol) of water, and 1.0 ml of benzene (reagent grade, further dried over "Baker Analyzed" sodium–lead alloy, 9.7% active sodium). The reactor was cooled to −196°, evacuated, thawed, again cooled to −196°, and briefly pumped on. The isocyanate (1.0 mmol) was condensed into the reactor at −196°. The −196° bath was removed, and (after 10 min) the reaction mixture was stirred for 2 hr. Bubbles, probably of carbon dioxide, were observed. After 7 days at room temperature, the volatile fraction was removed and fractionated in the vacuum line using a trap at −132°. The fraction which passed through the trap amounted to 0.57 mmol. An infrared spectrum showed characteristic carbon dioxide absorptions and only weak NF absorptions. Analysis by mass spectrometry indicated >90% carbon dioxide. The solid residue was pumped on through a −196° trap until no more volatiles were retained by the trap.

The solid residue[25] was washed out of the reactor with trifluoroacetic acid. The resulting 3.0 ml of solution was divided into three parts. Each part was concentrated to 0.5 ml. The small amount of solid present was dissolved by warming the mixture in a water bath. Then each solution was diluted to 4.0 ml with reagent grade carbon tetrachloride, mixed, and placed in an ice–water bath for 45 min. The solid **7** was separated from the cold solution (centrifuge), washed twice with 0.5-ml portions of carbon tetrachloride, and dried. The yield of **7** was 38% based on the isocyanate charged. ^1H nmr indicated 2.4% by weight of triphenylphosphine oxide, although an infrared spectrum of a mull in mineral oil did not detect any of this impurity. Triphenylphosphine oxide, when present in **7** in sufficient amounts, was detected through peaks at 1149, 1120, and 746 cm^{-1}.

In a preferred alternative procedure, the crude complex was dissolved in methylene chloride to give 3.0 ml of solution. Any insoluble material was removed (centrifuge). Aliquots (1 ml) of the solution were diluted to 3.5 ml with methylene chloride and treated with 0.5 ml of trifluoroacetic acid.[26] As previously described, the mixture was cooled, and **7** was separated, washed with methylene chloride, and dried.

The analytical sample was washed twice with methylene chloride and a third time with hot methylene chloride.

Anal. Calcd for $C_3H_2F_{12}N_8O$: F, 57.85; N, 28.43. Found: F, 58.04; N, 28.63.

The sample showed $\nu_{max}^{mineral\ oil}$ 3311 (NH) and 1704 cm^{-1} (C=O), ^1H nmr τ 1.39 (broad); the material sublimed when a melting point determination with a Fisher-Johns apparatus was attempted and turned somewhat yellow and partially sublimed when heated up to 200° in a sealed tube under nitrogen.

Microscopy[27] has shown the presence of liquid inclusions in

(21) C. A. Marlies, V. K. LaMer, and J. Greenspan, *Inorg. Syn.*, **1**, 68 (1939). Prepared by R. F. Phillips of these laboratories.

(22) The ^1H nmr spectrum of nitramide has been reported by J. D. Ray and R. A. Ogg, Jr., *J. Chem. Phys.*, **26**, 1452 (1957).

(23) G. H. Cady and D. P. Siegwarth, *Anal. Chem.*, **31**, 618 (1959).

(24) We wish to thank J. J. Keavney, R. S. Kolat, and J. P. Habermann for the boiling point, and M. D. Meyers and E. J. Schriffert for the molecular weight.

(25) The solid residue from a similar reaction mixture showed $\nu_{max}^{mineral\ oil}$ 1779 (C=O) and 1149 cm^{-1} (≡P=O···NH=).

(26) The solid which precipitates is very difficult to see in the mixture of methylene chloride and trifluoroacetic acid.

(27) Microscopical work by F. Farwell of these laboratories.

many samples of the urea. Vacuum sublimation at *ca.* 60° can be used to reduce these inclusions.[28]

Reaction of Tris(difluoramino)methyl Isocyanate with Pyridine.—The 18-ml reactor had two arms, one of which was attached by means of a special ring joint and a Viton-A O ring.[29] Pyridine (0.31 mmol) was dissolved in *ca.* 0.5 ml of anhydrous acetonitrile, which was added by vacuum transfer. The isocyanate (0.64 mmol) was then condensed in at −196°, and the mixture was stirred for 1.5 hr at 0°. The excess isocyanate and acetonitrile were removed under vacuum at −23°, and the residue was sublimed at room temperature into the detachable arm in 94% yield, calculated for a 1:1 adduct, $\nu_{max}^{mineral\ oil}$ 1770 cm^{-1} (C=O). The product was stored at −80° and handled in a dry atmosphere, since it is very hygroscopic and discolors at room temperature.

Anal. Calcd for $C_7H_5F_6N_5O$: F, 39.43. Found: F, 37.95.

Another reaction between pyridine and a 100% excess of isocyanate was run without solvent at −23°. Intermittent mixing was effected by transfers of the reaction mixture back and forth between the two arms of the above reactor and by periodic condensation of the unchanged isocyanate onto the solid product. The infrared spectrum of the solid product was the same as that of the product prepared in acetonitrile solution.

^{19}F nmr spectra of the following samples in acetonitrile solution were obtained: the isocyanate (−30.6 ppm); various mixtures of the isocyanate and pyridine after reaction for 2.25 hr at −23° without solvent (0.11 mol pyridine per mol isocyanate) (−29.7 ppm), 0.20 (−29.6 ppm), 0.49 (−28.5 ppm); the 1:1 adduct (−26.7 ppm) prepared in acetonitrile from 0.6 mmol of isocyanate and 0.5 mmol of pyridine followed by removal of the excess isocyanate and solvent under vacuum at −23°. Acetonitrile and nmr standards were added by vacuum transfer to the above samples.

***N,N*-Dimethyl-*N'*-tris(difluoramino)methylformamidine (8).**—A 6-ml reactor was charged in a glove bag under a nitrogen atmosphere with 73 μl (0.94 mmol) of dimethylformamide. The dimethylformamide had been distilled twice in a dry apparatus from phosphorus pentoxide at atmospheric pressure. The reactor was then cooled to −196° and evacuated, and 0.94 mmol of tris(difluoramino)methyl isocyanate was added by vacuum transfer. The liquid nitrogen bath was removed and, as soon as the frost on the outside of the reactor had melted, magnetic stirring was started. The reaction mixture was stirred for 2.5 hr and allowed to stand at room temperature for an additional 21 hr.

A fraction which was volatile at room temperature was removed from the reactor by vacuum transfer. It amounted to 0.88 mmol and was 95% carbon dioxide (0.84 mmol, 89% of theory) according to mass spectrometric analysis.

The residue remaining in the reactor consisted of a liquid and a small amount of white solid. A solution of the liquid in 1.5 ml of reagent grade carbon tetrachloride was washed three times with 0.5-ml portions of deionized water. Centrifugation helped separate the liquid layers, and the bottom (carbon tetrachloride) layer was withdrawn by pipette. The carbon tetrachloride solution was dried with anhydrous sodium sulfate, and the sodium sulfate was rinsed with 0.2 ml of carbon tetrachloride. The formamidine was obtained as a colorless liquid residue by removal of the more volatile carbon tetrachloride, ν_{max} 1639 cm^{-1} (C=N),[9a] ^1H nmr 2.04 (1 H, somewhat broadened, –N=CH–), 6.91 and 6.97 (6 H, overlapping, nonequivalent methyl groups).

Anal. Calcd for $C_4H_7F_6N_5$: F, 47.67. Found: F, 47.62.

Registry No.—**3**, 37950-73-5; **4**, 37950-74-6; **6**, 37950-75-7; **7**, 37950-76-8; **8**, 37950-77-9; methyl tris(difluoramino)methylcarbamate, 37950-78-0; ethylene *N,N'*-bis[tris(difluoramino)methyl]dicarbamate, 37950-79-1; allyl tris(difluoramino)methylcarbamate, 37950-80-4; 2,3-epoxypropyl tris(difluoramino)methylcarbamate, 37950-81-5; tris(difluoramino)methylurea, 37950-82-6; tris(difluoramino)methylurea perchlorate, 37950-83-7; adduct of pyridine and tris(difluoramino)-methyl isocyanate, 37950-84-8; **1**, 37950-70-2.

Acknowledgment.—It is a pleasure to acknowledge the contributions of the following persons: Dr. J. E. Lancaster and Mrs. M. Neglia determined the nmr spectra; Mr. J. H. Deonarine and staff carried out the elemental analyses; Mr. R. C. Bell and staff prepared the isocyanate; Dr. V. P. Wystrach provided helpful consultations.

(28) Work done by A. J. Fanelli, R. F. Phillips, and E. J. Schriffert of these laboratories.

(29) Delmar Scientific Laboratories, Inc., Maywood, Ill.

Fluorinations in the Presence of Sodium Fluoride. Preparation of Tetrakis(difluoramino)methane

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Fluorination of bis(difluoramino)fluoraminomethyl isocyanate, $(F_2N)_2C(NFH)NCO$, with elemental fluorine in the presence of sodium fluoride gave tetrakis(difluoramino)methane. In the absence of sodium fluoride the product was tris(difluoramino)methyl isocyanate. Sodium fluoride similarly induced fluorinations of isocyanic acid and pentafluoroguanidine. Tetrakis(difluoramino)methane is a liquid, bp 40.2°, mp −13°. The ir spectrum, mass spectrum, vapor pressure, heat of fusion, and density are also reported.

As part of a program on the synthesis of CNF_2 oxidizers, we wished to synthesize tetrakis(difluoramino)methane, $(F_2N)_4C$, because of its extraordinarily high content of NF_2 oxidizing groups and unusual carbon tetranitrogen skeleton. Our synthetic approach was to add isocyanic acid to pentafluoroguanidine and then fluorinate the adduct.[2]

In the fluorination, liquid pentafluoroguanidine–isocyanic acid adduct at 0° was entrained by a stream of fluorine diluted with helium and passed in the vapor phase through sodium fluoride pellets to remove the expected hydrogen fluoride. The products were condensed at −196°, separated by fractional codistillation,[3] and analyzed by infrared spectroscopy. Both

$$(F_2N)_2C{=}NF + HNCO \longrightarrow (F_2N)_2C\begin{matrix}\diagup NFH\\ \diagdown NCO\end{matrix}$$

$$(F_2N)_2C\begin{matrix}\diagup NFH\\ \diagdown NCO\end{matrix} + F_2 \longrightarrow$$

$$(F_2N)_3CNCO\ (+HF) \xrightarrow{F_2} (F_2N)_4C + COF_2$$

(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, with monitoring by the Bureau of Naval Weapons, RMMP, under Contract NOrd 18728.

(2) W. C. Firth, Jr., S. Frank, and E. J. Schriffert, *J. Org. Chem.*, **38**, 1080 (1973). Tetrakis(difluoramino)methane has also been synthesized by addition of ammonia to pentafluoroguanidine followed by fluorination: C. D. Wright and J. L. Zollinger, *J. Org. Chem.*, **38**, 1075 (1973).

(3) G. H. Cady and D. P. Siegwarth, *Anal. Chem.*, **31**, 618 (1959).

tetrakis(difluoramino)methane and tris(difluoramino)-methyl isocyanate were formed in this reaction.

Subsequently it was discovered that formation of tetrakis(difluoramino)methane depended upon the presence in the fluorination apparatus of sodium fluoride. If sodium fluoride was omitted, fluorination stopped with formation of tris(difluoramino)methyl isocyanate. This effect of sodium fluoride can be used to control the fluorination to give either the isocyanate or tetrakis(difluoramino)methane to the essential exclusion of the undesired product, as shown in Table I.

TABLE I
FLUORINATIONS

Compd, mmol	NaF	Time, min	Yield, % $(F_2N)_4NCO$	Yield, % $(F_2N)_4C$
$(F_2N)_2C(NFH)NCO$, 2.4–2.9	No	45–50	75–88	0
$(F_2N)_2C(NFH)NCO$, 1.4	Yes	30	0	92
$(F_2N)_3CNCO$, 0.5	Yes	17		80

The effect of NaF on the course of this fluorination suggested the idea of fluorinating isocyanic acid by the new technique. Surprisingly, no reaction occurred in the absence of NaF pellets. However, when fluorine gas (14% in He) was passed over liquid HNCO (at −78°) and then through NaF pellets at 25°, smooth fluorination gave the expected end products.

$$HN{=}C{=}O \xrightarrow{F_2\text{–He}} [N.R.] \xrightarrow[25°]{NaF} NF_3 + F_2C{=}O + HF \text{ (as } SiF_4)$$

Another example of this catalytic effect of NaF in these vapor-phase fluorinations was the successful fluorination of pentafluoroguanidine, otherwise not reactive to fluorine, to give an 82% yield of tris(difluoramino)fluoromethane.[4]

$$(F_2N)_2C{=}NF \xrightarrow[24°]{27\%\ F_2/N_2} (F_2N)_3CF + \text{small amounts of } CF_4, NF_3$$

Tetrakis(difluoramino)methane, the perfluoro analog of tetranitromethane, is a colorless liquid, stable to storage in glass, and unreactive at room temperature with mercury, water, anhydrous calcium sulfate, or mineral oil. The compound was unchanged after 4 hr at 70° in the liquid phase in a glass capillary. Its physical properties are summarized in Table II.

The fluorine nmr signal at ϕ^*[5] −29.5 is in the expected region.[6]

The mass spectrum does not show the parent m/e 220 peak. Instead the largest mass corresponds to the parent peak after loss of NF_2, a common situation with CNF_2 compounds.

(4) R. J. Kosher, D. R. Husted, and C. D. Wright, *J. Org. Chem.*, **32**, 3859 (1967).
(5) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).
(6) W. C. Firth, Jr., and S. Frank, *J. Org. Chem.*, **38**, 1083 (1973).

TABLE II
PHYSICAL PROPERTIES OF TETRAKIS(DIFLUORAMINO)METHANE

^{19}F nmr: single, broad peak at ϕ^* −29.5
Ir spectrum: 1120 (m), 1060 (w), 980 (s), 950 (s), and 910 cm^{-1} (s)
Mass spectrum (most abundant m/e's): 168, 97, 64, 52
Vapor pressure: $\log P$ (mm) = 6.8640 − 1096.1/(234.7 + T, °C) (0–70°)
Boiling point: 40.2°
$\Delta H°_{vap}$: 6.61 kcal/mol at 25°
$\Delta S°_{vap}$: 18.68 cal/mol deg at 25°
Melting point: −13°
ΔH_{fusion}: 850 cal/mol
Density: $\rho = 1.8053 - 1.9815 \times 10^{-3} T - 13.9275 \times 10^{-6} T^2 + 6.623 \times 10^{-8} T^3$ (T in °C over the range 0–60°); 1.748 g/ml at 25°

The five main infrared absorptions are reasonable for a compound of this type. Probable assignments based upon comparison with difluorocyanamide[7] are NF_2 out-of-phase stretching at 910 cm^{-1}; NF_2 in-phase stretching plus CN stretching at 950, 980, and 1060 cm^{-1}; and NCN out-of-phase stretching at 1120 cm^{-1}.

Experimental Section

Caution.—The NF compounds are extremely sensitive explosives and strong oxidizing agents. Further details on the handling of these compounds and the general experimental techniques used have been described elsewhere.[2]

Fluorination of Bis(difluoramino)fluoraminomethyl Isocyanate.—The fluorinations were conveniently carried out by passing a stream of F_2 (16 cc/min) diluted with He (50 cc/min) into a simple glass reaction train consisting of three 70-ml U tubes and a cold trap connected in series. The first U tube contained liquid bis(difluoramino)fluoraminomethyl isocyanate and was cooled in a 0° bath. The second U tube was left empty or filled with NaF pellets, depending on whether tris(difluoramino)-methyl isocyanate or tetrakis(difluoramino)methane, respectively, was desired. The product was trapped out in the third U tube at −196°.

After a simple vacuum line fractionation to remove by-products such as SiF_4 and COF_2, which can be volatilized at −78°, the products were purified by fractional codistillation.[3] The purification and properties of the isocyanate are described elsewhere.[2,6]

Anal. Calcd for CN_4F_8: C, 5.46; N, 25.46; F, 69.08. Found: C, 5.4; N, 25.0; F, 68.6.

Registry No.—Tetrakis(difluoramino)methane, 17125-65-4.

Acknowledgment.—We wish to thank Dr. J. E. Lancaster and Mrs. M. Neglia for the nmr spectrum, Mr. J. H. Deonarine and staff of our Research Service Department for the elemental analyses, Dr. R. S. Kolat and Dr. J. J. Keavney for determinations of physical properties, and Mr. N. B. Colthup for assistance in the interpretation of the ir spectrum. The encouragement of Dr. V. P. Wystrach is appreciated.

(7) N. B. Colthup, *Spectrochim. Acta, Part A*, **23**, 2167 (1967).

Photochemical Reactivity of Conjugated Imino Ethers. II. 6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine

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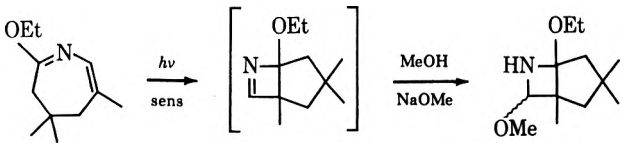
The sensitized photochemical reactivity of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III) is described. In benzene solvent with acetophenone sensitization, III dimerizes to form a linear dimer V, and in methanol solvent with xanthone sensitization, III undergoes ionic solvent addition. Both reactions are rationalized in terms of a highly strained trans intermediate.

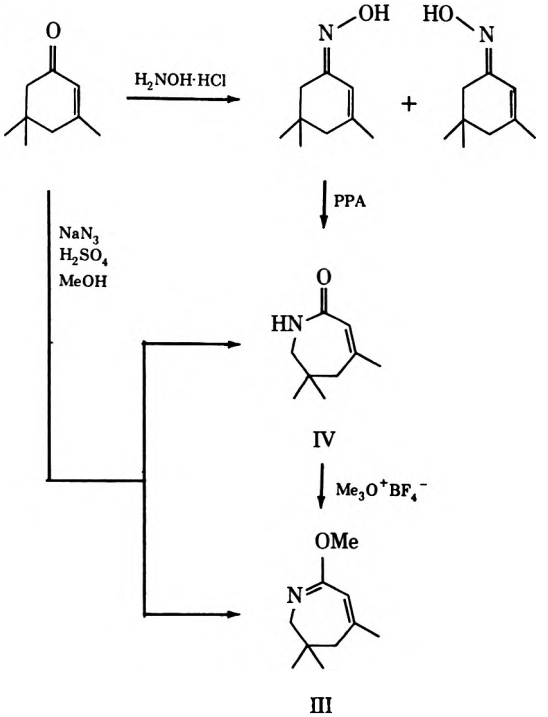
Recently we reported the photochemical valence isomerization of a cyclic conjugated imino ether (I) to an unstable 1-azetine derivative (II).[1] We now wish to report on the photochemical reactivity of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III), a



I II

system structurally related to I which contains a permutation of the imino ether functional group.

Azepine III was prepared by the Schmidt rearrangement of isophorone in absolute methanol. From the Schmidt reaction both the azepine and the corresponding lactam, 6,7-dihydro-4,6,6-trimethyl-5*H*-azepin-2-one (IV), were isolated. Treatment of lactam IV, which could also be prepared by Beckmann rearrangement of isophorone syn oxime,[2] with trimethyloxonium fluoroborate likewise yielded the desired conjugated imino ether. The structure of III is unambiguously established by the spectroscopic data. In the infrared III shows strong absorption at 1670 and 1640



III

cm^{-1} for carbon–nitrogen and carbon–carbon double bond stretching bands, respectively. The nmr spectrum, shown in Table I, has a characteristic methoxyl singlet at δ 3.57 ppm. A mass spectral parent ion occurs at *m/e* 167 (16% of base), and a strong π–π^* band appears at 212 nm (ϵ 8700) in the ultraviolet.

Irradiation of the unsaturated imino ether in *n*-heptane solvent with a 450-W mercury lamp through a Vycor filter for 2 hr resulted in about 60% destruction of starting material. Gas chromatographic analysis of the reaction mixture showed 19 products, each in less than 5% yield. Because of the complexity, no attempt was made to isolate and identify the photoproducts from the direct irradiation.

When acetophenone was employed as a photosensitizer in the irradiation of III in benzene solvent with a Pyrex filter, a single photoproduct was observed in the gas chromatogram. Mass spectral analysis of the isolated product indicated that it was dimeric, with a parent ion at *m/e* 334 (57% of base) and not the expected valence isomer, 7-methoxy-3,3,5-trimethylazabicyclo[3.2.0]hept-6-ene.[3] The photoproduct was assigned the linear dimeric structure V based upon the molecular weight and the following evidence. In the infrared spectrum strong carbon–nitrogen double bond stretching bands, characteristic of imino ether functional groups, appear at 1650 and 1675 cm^{-1}. A band of medium intensity appears at 1640 cm^{-1} and is assigned as a carbon–carbon double bond stretching band. The carbon–carbon double bond is further characterized as geminally disubstituted by the appearance of a strong C–H bending vibration at 1130 cm^{-1}. The absence of conjugated functional groups is established by the observation of only end absorption in the uv spectrum.

The 100-MHz nmr spectrum of V is reported in Table I in two different solvents, carbon tetrachloride and benzonitrile, and in benzonitrile at two different temperatures, 40 and 180°. At 40° in both solvents four methyl singlets, one methyl doublet, and two methoxyl singlets are distinct. The methoxyl chemical shifts are consistent with imino ether type methoxyls (see nmr spectrum of VIa for a comparison of methoxyl chemical shifts). The chemical shifts of the olefinic protons suggest an exocyclic methylene, in agreement with the ir evidence. The protons at positions 3 and 3′ appear as the AB portion of an ABX type pattern. The X proton at position 4′ is further split by the methyl protons at 4′ and the methylene protons at 5′ and appears as a complex multiplet.

(1) T. H. Koch and D. A. Brown, *J. Org. Chem.*, **36**, 1934 (1971).
(2) R. H. Mazur, *ibid.*, **26**, 1289 (1961).
(3) Photochemical valence isomerization has been reported for structurally similar molecules: J.-L. Derocque, W. J. Theuer, and J. A. Moore, *J. Org. Chem.*, **33**, 4381 (1968).

TABLE I
NMR DATA[a]

Compd	Solvent	Temp, °C	Ring positions 2,2′	3,3′	4,4′	5,5′	6,6′	7,7′
III	CCl_4	Ambient	3.57 s (3 H)	5.5–5.7 m (1 H)	1.88 d (3 H) J = 1 Hz	1.95 s (2 H)	0.95 s (6 H)	3.08 s (2 H)
VIa	CCl_4	Ambient	3.52 s (3 H)	2.43 d (1 H) 2.52 d (1 H) J = 14 Hz	1.10 s (3 H) 3.15 s (3 H)	1.15 d (1 H) 1.87 d (1 H) J = 15 Hz	0.87 s (3 H) 0.97 s (3 H)	3.12 s (2 H)
V	CCl_4	40	3.42 s (3 H) 3.48 s (3 H)	3.3–3.7 (2 H)[b]	4.70 s (1 H) 4.75 s (1 H) 0.74 d (3 H) J = 7 Hz 1.8–2.1 m (1 H)	2.05 s (2 H)[c] 1.1–1.4 m (2 H)	0.75 s (3 H) 0.87 s (3 H) 0.89 s (3 H) 0.93 s (3 H)	3.22 s (2 H) 3.22 d (1 H) 3.40 d (1 H) J = 13 Hz
V	PhCN	40	3.57 s (3 H) 3.67 s (3 H)	3.76 c (1 H)[b] 3.94 c (1 H)	4.90 s (1 H) 4.97 s (1 H) 0.88 d (3 H) J = 8 Hz 1.9–2.3 m (1 H)	2.22 s (2 H)[c] 1.2–1.6 m (2 H)	0.89 s (3 H) 0.95 s (3 H) 0.98 s (3 H) 1.03 s (3 H)	3.47 s (2 H) 3.43 d (1 H) 3.63 d (1 H) J = 14 Hz
V	PhCN	180	3.60 s (3 H) 3.67 s (3 H)	3.76 c (1 H)[b] 3.94 c (1 H)	4.96 s (2 H) 0.89 d (3 H) J = 8 Hz 1.9–2.3 m (1 H)	2.20 d (1 H)[c] 2.33 d (1 H) J = 14 Hz 1.39 d (2 H) J = 7 Hz	0.90 s (3 H) 0.94 s (6 H) 1.02 s (3 H)	3.46 s (2 H) 3.55 s (2 H)

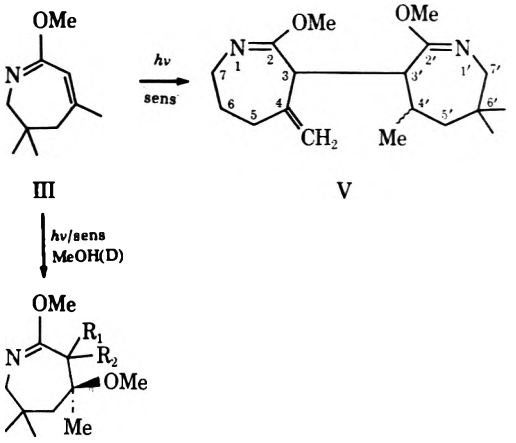
[a] The nmr spectrum of III was measured at 60 MHz and the nmr spectra of VIa and V at 100 MHz. Chemical shifts are given in parts per million relative to TMS on the δ scale and coupling constants are given in hertz. The following abbreviations are used: s, singlet; d, doublet; m, multiplet; c, complex. [b] These protons appear as the AB portion of an ABX pattern. The X portion of the pattern is complicated by further coupling to adjacent protons at positions 4′ and 5′. In CCl_4 an insufficient portion of the pattern is visible for the calculation of chemical shifts and coupling constants. In PhCN J_{AB} = 12.2, J_{AX} = 3.9, and J_{BX} = 0.1 Hz and J_{AX} and J_{BX} are of opposite sign. [c] The protons at position 5 appear as a slightly broadened singlet in CCl_4 and PhCN at ambient temperature but appear as an AB pattern at 180° in PhCN.

Several patterns in the spectrum in benzonitrile simplify upon heating; the changes were reversible on cooling. The absorptions assigned to the methylene protons at positions 7 and 7′ appear as singlets at 180°; the absorption assigned to the methylene protons at position 5 changes from a broad singlet at 40° to an AB pattern at 180°; and the pattern assigned to the methylene protons at position 5′ collapses from a multiplet to a doublet. Some of the simplifications observed upon heating are more dramatic than expected. More complex patterns might be anticipated for the three methylene groups at positions 7, 7′, and 5′. A similar simplicity, however, is observed for the methylene protons at position 7 of VIa (*vide infra*).

The 70-eV mass spectral fragmentation provides further evidence for the assigned structure. The base peak appears at m/e 167, corresponding to a reverse ene reaction. Fragments are also observed at m/e 168 (46%) and 166 (22%) corresponding to a simple fragmentation of the 3–3′ bond with charge retention alternately in both fragments. Fragment ions at m/e 167 (67%) and 168 (10%) are still observed at 15 eV. At this ionization potential the base peak is the parent ion. The assigned structure is consistent with a single-crystal X-ray analysis.[4]

The quantum yields of dimerization have been determined with acetophenone, triphenylamine, and triphenylene sensitization and are reported in Table II.

When the sensitized irradiation of III is conducted in absolute methanol as solvent, the photodimerization is no longer observed. Under these conditions a methanol solvent adduct is formed and assigned structure VIa, 2,4-dimethoxy-4,5,6,7-tetrahydro-4,6,6-trimethyl-3*H*-azepine, based upon the spectroscopic



VIa, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = D$
c, $R_1 = D$; $R_2 = H$

TABLE II[a]
QUANTUM YIELD DATA

Sensitizer	E_T[b]	ϕ_{isc}[c]	[Sens]	[Azepine]	ϕ Dimer	ϕ Destruction
Acetophenone	74	1.0	0.20	0.021	0.032	0.06
Triphenylamine	70	0.88	0.0013	0.022	0.011	0.03
Triphenylene	67	0.96	0.0038	0.022	0.012	0.03

[a] Quantum yields were measured at 3000 A with potassium ferrioxalate actinometry at 30°: C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc., Ser. A*, **235**, 518 (1956). [b] W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 4537 (1964). [c] A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

evidence. The 100-MHz nmr spectrum shown in Table I is the most definitive, with two characteristic singlets at δ 3.15 and 3.52 ppm. The mass spectrum

(4) T. H. Koch and C. Tsai, unpublished work.

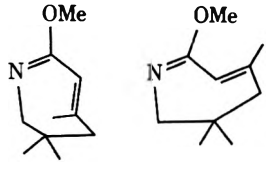
shows a weak parent ion at m/e 199 (2% of base), and in the infrared only a carbon–nitrogen double bond stretching band is observed (1680 cm^{-1}).

With methanol-*O*-*d* solvent and xanthone sensitization, deuterium is incorporated in the photoproduct at position 3, giving a mixture of VIb and VIc. The nonstereospecific addition of methanol is shown by the nmr pattern for the proton at position 3, which appears as a complex multiplet. For stereospecific addition the pattern would have appeared as a 1:1:1 triplet resulting from coupling to deuterium.

When the irradiation of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine is carried out in two parts benzene and one part methanol, both solvent addition and dimerization are observed in the ratio of approximately 12:1. In this medium solvent addition and dimerization appear to be in competition, occurring from a common intermediate. A possible intermediate that is consistent with the experimental results and with evidence in hydrocarbon systems is a trans isomer of III.

Cyclohexenes and cycloheptenes commonly add methanol in an ionic fashion under photosensitized conditions.[5] Twisted or trans isomers have been proposed as probable intermediates. Upon direct irradiation, 2-cycloheptenone also adds alcohols in an ionic fasion to the carbon–carbon double bond,[6] most likely *via* a trans isomer.[7,8] With cyclic olefins smaller than six carbons for which twisted or trans isomers are highly improbable, free-radical addition of alcohol is observed.[5]

There are two possible trans isomers of III, one in which the unsaturated functional groups are cisoid (VII) and one in which they are transoid (VIII). The cisoid isomer would be expected to undergo conrotatory ring closure to yield the valence isomer, 7-methoxy-3,3,5-trimethylazabicyclo[3.2.0]hept-6-ene.[9] Since this is not an observed reaction of III, we favor the transoid intermediate VIII. Reaction of VIII with methanol



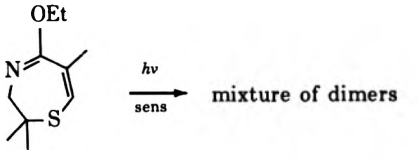
VII VIII

could occur by initial protonation at position 3, relieving the ring strain and generating a tertiary carbonium ion subsequently trapped by methoxide. Consistent with observation, this mechanism would give a nonstereospecific addition of methanol-*O*-*d*. The dimerization could occur from VIII by a symmetry-allowed $_{\pi}2_s + {}_{\pi}2_s + {}_{\sigma}2_s$[10] ene reaction. The low quantum efficiency observed for dimerization (Table II) could result in part from a triplet decay ratio favoring III as well as from competitive thermal relaxation of VIII.

An alternative mechanism for dimerization, although not applicable to solvent addition, would involve initial hydrogen atom abstraction from the allylic methyl group of III by the sensitizer followed by radical addition or radical–radical combination. This mechanism is rendered unlikely because of the stereospecificity observed for the dimerization. Moreover, π,π^* sensitizers such as triphenylamine and triphenylene would not be expected to abstract hydrogen atoms from azepine.

Attempts to observe or trap (except by irradiation in methanol) a transient such as VIII have been unsuccessful. In trapping experiments, if dienes such as furan are added directly to the irradiation solution, they serve as efficient quenchers of the photosensitizer. Addition of furan to a cold (−78°) solution of III and acetophenone after irradiation did not yield an adduct but only photodimer. Low-temperature irradiation at −75° in *n*-heptane with triphenylamine sensitization and at −190° as a glass with acetophenone sensitization, both followed by ir analysis,[11] revealed only the presence of starting material, photodimer, and sensitizer. It is not surprising that an intermediate such as VIII with four sp^2 atoms in a seven-membered ring would not be observed even at −190°. *trans*-2-Cycloheptenone, which has only three sp^2 atoms in a seven membered ring, is unstable at −120°.[8]

The photochemical reactivity of 5-ethoxy-2,3-dihydro-2,2,6-trimethyl-1,4-thiazepine (IX), a molecule structurally related to III, has recently been reported.[12] Irradiation of IX in aprotic solvents with thioxanthone sensitization gave a mixture of dimers of unspecified structures. In methanol solvent again with thioxanthone sensitization no solvent addition occurred and only dimers were isolated. The difference in triplet state reactivity between III and IX may result from



IX

the electronic effects of the sulfur and/or the position of the allylic methyl group. Certainly for III the allylic methyl group is ideally located for an ene reaction from an intermediate such as VIII.

Experimental Section

Melting points and boiling points are uncorrected. Melting points were measured with a Thomas-Hoover Unimelt apparatus. Perkin-Elmer Model 337 and Cary 14 spectrophotometers were used to determine ir and uv spectra, respectively. Nmr spectra were recorded with Varian A-60A and HA-100 and JEOL PS-100 spectrometers and chemical shifts are reported in δ units from internal tetramethylsilane. The mass spectra were obtained with Varian Mat CH-5 and CH-7 spectrometers. Glpc analyses and isolations were performed with a Varian Aerograph (Model 200) gas chromatograph equipped with a thermal conductivity detector, and peak areas were measured by Disc integration. Microanalyses were performed by Spang Microanalytical

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syn-**Isophorone Oxime.**—Freshly distilled isophorone (138 g, 1 mol), bp 80–82° (9 mm), was added to a solution of 68 g (1 mol) of hydroxylamine hydrochloride, 275 ml (1.38 mol) of 20% sodium hydroxide, and 413 ml of water. Enough ethanol (126 ml) was added to make a homogeneous solution which was refluxed for 3 hr and allowed to stand overnight. The ethanol was evaporated and the oxime was collected by vacuum filtration, yielding 130 g (84%), mp 98–100°. The nmr spectrum indicated that the oxime was a mixture of 90% syn and 10% anti oxime. Recrystallization of the mixture from petroleum ether (bp 30–60°) yielded 115 g (75%) of syn oxime, mp 101–102°. The observed melting point is in disagreement with the literature melting point, 77–78.5.[2] The material isolated by Mazur was shown by nmr to be a mixture of isophorone oximes. Nmr (CCl_4) showed δ 1.00 (s, 6 H), 1.85 (broad s, 3 H), 1.94 (broad s, 2 H), 2.08 (s, 3 H, syn oxime), 2.35 (s, 3 H, anti oxime), 5.90 (broad s, 1 H, anti oxime), 6.65 (broad s, 1 H, syn oxime), 9.65 ppm (s, 1 H).

6,7-Dihydro-4,6,6-trimethyl-5*H*-azepin-2-one (IV).—6,7-Dihydro-4,6,6-trimethyl-5*H*-azepin-2-one (IV) was prepared by the Beckman rearrangement of the syn oxime of isophorone with polyphosphoric acid according to the procedure reported by Mazur.[2] The yield of azepinone (mp 112–113°) was a good deal higher (64%) since pure syn oxime was used. Nmr (CCl_4) showed δ 0.98 (s, 6 H), 1.94 (d, J = 1 Hz, 3 H), 2.02 (s, 2 H), 2.83 (d, J = 5 Hz, 2 H), 5.58–5.78 (m, 1 H), 8.16 (broad absorption, 1 H); ir (KBr) 3180, 3020, 1660, and 1620 cm^{-1}.

6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III). Schmidt Reaction.—Distilled isophorone (55.2 g, 0.40 mol), sodium azide (39.0 g, 0.60 mol), and 500 ml of absolute methanol were placed in a three-neck reaction flask equipped with mechanical stirrer, addition funnel, and thermometer. Concentrated sulfuric acid (120 ml) was added dropwise at a rate to maintain the temperature at less than 35°. The solution became very viscous and an additional 200 ml of absolute methanol was added. The solution was stirred overnight and then brought to pH 10 with 10% aqueous sodium hydroxide solution (350 ml). The precipitate was removed by filtration and the filtrate was extracted with 3 × 100 ml of ether. The combined ether extracts were dried with magnesium sulfate and the ether was removed by rotary evaporation. 6,7-Dihydro-4,6,6-trimethyl-5*H*-azepin-2-one (IV) (9.6 g, 16% yield) precipitated from the residual oil (34 g, 51% yield). The physical and spectroscopic properties of the azepinone were identical with those of the authentic sample prepared by the Beckman rearrangement of the syn oxime of isophorone. Distillation of the residual oil, bp 55–57° (2 mm), yielded 25.8 g (39%) of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III). The azepine was separated from residual lactam by chromatography on a 0.5 in. × 2 ft column of thin layer grade Woelm neutral alumina at 50 psi, eluting with 80 ml of benzene. To remove a 5% impurity of similar boiling point the azepine was then distilled at 10.5 mm pressure through a Nester-Faust Teflon annular spinning band column which had been rinsed with 3% ammonium hydroxide, distilled water, and acetone. The column was allowed to equilibrate with a pot temperature of 120° for 2 hr after reflux had begun. About 2-g fractions were then collected at a 1:1 reflux ratio. The per cent of the impurity in each fraction was analyzed by glpc with Disc integration on a 0.25 in. × 7 ft column of 5% SE-30 on 60/80 mesh Chromosorb W at 140° (He flow 60 cc/min). The first fraction contained 20% of the impurity; the second, 2%; and the remainder, less than 0.5%. A sample of the impurity (80% pure) was collected by glpc with the 0.25-in. SE-30 column at 90° (He flow 60 cc/min). Spectroscopic analysis indicated that the impurity was 6,7-dihydro-2-methoxy-4,6,6-trimethyl-3*H*-azepine. Nmr (CCl_4) showed δ 0.93 (s, 6 H), 1.65 (d, J = 1 Hz, 3 H), 2.87 (s, 2 H), 3.25 (d, J = 1 Hz, 2 H), 3.55 (s, 3 H), 4.85–5.07 (m, 1 H); ir (neat) 2960, 1690, 1645 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 167 (16), 166 (16), 154 (16), 153 (23), 152 (62), 124 (32), 110 (24), 96 (28), 95 (30), 56 (49), 55 (53), 53 (58), 42 (30), 41 (base). An analytical sample of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine was collected by glpc under the same conditions. Nmr (CCl_4) showed δ 0.95 (s, 6 H), 1.88 (d, J = 1 Hz, 3 H), 1.95 (s, 2 H), 3.08 (s, 2 H), 3.57 (s, 3 H), 5.54–5.67 (m, 1 H); ir (neat) 2940, 1670, and 1640 cm^{-1}; uv λ_{max} (EtOH) 212 nm (ε 8700); mass spectrum (70 eV) m/e (rel intensity) 167 (21), 152 (base), 137 (9), 134 (14), 110 (11), 96 (29), 81 (16), 67 (18), 42 (21).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.59; H, 10.07; N, 8.27.

Trimethyloxonium Fluoroborate.—Trimethyloxonium fluoroborate was prepared by the procedure described by Meerwein.[13] To a solution of 10 g of trimethyloxonium fluoroborate in 500 ml of dry methylene chloride was added a solution of 10 g of 6,7-dihydro-4,6,6-trimethyl-5*H*-azepin-2-one in 50 ml of dry methylene chloride. The reaction mixture was refluxed for 12 hr and then hydrolyzed by slowly adding 18 g of 50% aqueous potassium carbonate solution. The precipitate was removed by filtration and the filtrate was dried over magnesium sulfate, filtered, and rotary evaporated. Nmr analysis of the crude oil showed 65% unreacted azepinone and 35% 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III). An analytical sample of the azepine was collected by glpc (0.37 in. × 10 ft column of 5% FS-1265 on 60/80 mesh Chromosorb W at 110°, He flow 60 cc/min) and was identical by nmr and ir analyses with that prepared by the Schmidt reaction.

Irradiation of 6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III) in the Absence of Sensitizer.—6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (0.3 g) in 190 ml of *n*-heptane was irradiated with a 450-W mercury lamp through a Vycor filter for 2 hr. Gas chromatographic analysis of the crude reaction mixture with a 5% SE-30 on 60/80 mesh Chromosorb W column temperature programmed from 100 to 250° showed about 60% destruction of starting material and formation of 19 products each in less than 5% yield.

Photosensitized Dimerization of 6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III).—6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (10 g) and 0.72 g of acetophenone in 450 ml of reagent grade benzene were irradiated with a 450-W mercury lamp in a Pyrex immersion well for 8 hr. After rotary evaporation of the solvent, crude dimer (10 g) was recrystallized successively from *n*-heptane and absolute ethanol and sublimed at 70° (0.05 mm), yielding 3.0 g (30%) of 3-(2′-methoxy-4′,5′,6′,7′-tetrahydro-4′,6′,6′-trimethyl-3′(3′*H*)azepinyl)-6,6-dimethyl-2-methoxy-4-methylene-4,5,6,7-tetrahydro-3*H*-azepine (V): mp 120–121°; nmr (100 MHz, CCl_4) δ 0.75 (s, 3 H), 0.74 (d, J = 7 Hz, 3 H), 0.87 (s, 3 H), 0.89 (s, 3 H), 0.93 (s, 3 H), 1.1–1.4 (m, 2 H), 2.05 (broad s, 2 H), 1.8–2.1 (m, 1 H), 3.22 (s, 2 H), 3.22 (d, J = 13 Hz, 1 H), 3.40 (d, J = 13 Hz, 1 H), 3.42 (s, 3 H), 3.48 (s, 3 H), 3.3–3.7 (m, 2 H), 4.70 (s, 1 H), 4.75 ppm (s, 1 H); nmr (PhCN, 40°) δ 0.89 (s, 3 H), 0.88 (d, J = 8 Hz, 3 H), 0.95 (s, 3 H), 0.98 (s, 3 H), 1.03 (s, 3 H), 1.2–1.6 (m, 2 H), 1.9–2.3 (m, 1 H), 2.22 (broad s, 2 H), 3.47 (s, 2 H), 3.43 (d, J = 14 Hz, 1 H), 3.63 (d, J = 14 Hz, 1 H), 3.57 (s, 3 H), 3.67 (s, 3 H), 3.76 and 3.94 (AB portion of an ABX pattern, J_{AX} = 3.9, J_{BX} = 0.1, J_{AB} = 12.2 Hz, J_{AX} and J_{BX} are of opposite sign), 4.90 (s, 1 H), 4.97 (s, 1 H); nmr (PhCN, 180°) δ 0.90 (s, 3 H), 0.89 (d, J = 8 Hz, 3 H), 0.94 (s, 6 H), 1.02 (s, 3 H), 1.39 (d, J = 7 Hz, 2 H), 1.9–2.3 (m, 1 H), 2.20 (d, J = 14 Hz, 1 H), 2.33 (d, J = 14 Hz, 1 H), 3.46 (s, 2 H), 3.55 (s, 2 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 3.76 and 3.94 (AB portion of an ABX pattern as described), 4.96 ppm (s, 2 H); ir (KBr) 2950, 2775, 1675, 1650, 1640 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 335 (13), 334 (57), 320 (11), 319 (48), 225 (13), 224 (83), 169 (31), 168 (46), 167 (base), 166 (22), 152 (96), 124 (22), 112 (48), 82 (31), 55 (35); mass spectrum (15 ev) m/e (rel intensity) 335 (28), 334 (base), 319 (13), 224 (65), 169 (28), 168 (10), 167 (65); metastables at m/e 303 and 138 relate fragment 319 to the parent ion and fragment ion 152 to 167, respectively.

Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.34. Found: C, 71.86; H, 10.06; N, 8.39.

Photosensitized Irradiation of 6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III) in Methanol.—6,7-Dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (0.289 g) and xanthone (0.103 g) in 120 ml of absolute methanol (freshly distilled from magnesium methoxide) were degassed with nitrogen and irradiated in a Pyrex immersion well with a 450-W mercury lamp for 40 min. Gas chromatographic analysis of the irradiated solution with a column of 5% SE-30 on 60/80 mesh Chromosorb W temperature programmed from 100 to 200° at 4 deg/min indicated the absence of photodimer, the presence of a small quantity of starting azepine, and a new photoproduct as well as xanthone. The solvent was rotary evaporated and the residual oil was molecularly distilled at 60° (2 mm), yielding 0.105 g of a colorless oil. Gas chromatographic analysis of the oil with the SE-30 column at 125° showed that it consisted of 22% starting azepine

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and 65% product, identified as 2,4-dimethoxy-4,5,6,7-tetrahydro-4,6,6-trimethyl-3*H*-azepine (VIa, 21% yield). An analytical sample of the solvent addition product was collected by glpc with a 0.37 in. × 10 ft column of 5% SE-30 on 60/80 mesh Chromosorb W at 155°, helium 60 cc/min. Nmr (100 MHz, CCl_4) showed δ 0.87 (s, 3 H), 0.97 (s, 3 H), 1.10 (s, 3 H), 1.15 (d, J = 15 Hz, 1 H), 1.87 (d, J = 15 Hz, 1 H), 2.43 (d, J = 14 Hz, 1 H), 2.52 (d, J = 14 Hz, 1 H), 3.12 (s, 2 H), 3.15 (s, 3 H), 3.52 ppm (s, 3 H); ir (neat) 2950 and 1680 cm^{-1}; mass spectrum m/e (rel intensity) 199 (2), 184 (13), 169 (14), 168 (30), 152 (15), 128 (17), 113 (13), 112 (24), 111 (base), 110 (12), 99 (41), 86 (14), 55 (18), 43 (15), 41 (19).

Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.33; H, 10.66; N, 7.04.

The irradiation was also performed on a 10-ml scale in 99.5% methanol-*O*-*d*. The nmr spectrum of the solvent adduct (VIb and VIc) isolated by preparative glpc was identical with that of the methanol adduct (VIa) except in the region δ 2.40–2.60 ppm. Here the absorption appears as a 1 H multiplet.

Formation of Methanol Addition Product and Dimer in Methanol–Benzene Solvent Mixture.—To each of two 13-mm test tubes was added 2.0 ml of a benzene solution 0.02 *M* in 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III) and 0.007 *M* in xanthone. To each tube was then added 1.0 ml of anhydrous methanol. The tubes were degassed by four freeze (liquid nitrogen), pump (2 × 10^{-5} mm), thaw cycles and sealed. One of the tubes was irradiated for 24 hr at 3500 A in a Rayonet reactor. The second tube was kept in the dark for the same length of time. Destruction of azepine and formation of methanol addition product were analyzed relative to external phenyl acetate by glpc with a column of 5% SE-30 on 60/80 mesh Chromosorb W at 100°, helium 70 cc/min. Formation of dimer and destruction of xanthone were analyzed relative to external anthracene with the same column at 195°. Reaction mixture compositions are corrected for differences in thermal conductivity and are as follows.

Solution	% Destruction of azepine	% Methanol adduct VIa	% Dimer V	% Destruction of xanthone
MeOH/PhH, dark	0	0	0	0
MeOH/PhH, $h\nu$	89	37	3	66

Attempted Trapping of an Intermediate with Furan.—A Pyrex test tube was charged with 0.25 g of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III) and 0.060 g of acetophenone in 15 ml of heptane. After degassing with nitrogen, the test tube was placed in a quartz dewar cooled with Dry Ice–ethanol. The reaction mixture was irradiated for 4 hr with a 450-W mercury lamp through a window in the Dewar. After the irradiation 1.0 g of furan was immediately added and the reaction mixture was allowed to warm to room temperature. The solvent was removed by rotary evaporation. Nmr and glpc analysis of the residual oil indicated that only starting materials and photodimer were present.

Attempted Infrared Observation of an Intermediate.—An infrared solution cell with a 0.20-mm path length was filled with a *n*-heptane solution of 6,7-dihydro-2-methoxy-4,6,6-trimethyl-5*H*-azepine (III) and triphenylamine of appropriate concentration for ir spectroscopy. The ratio of the carbon–carbon double bond stretch of the azepine (1640 cm^{-1}) to the stretching band of the phenyl groups of triphenylamine (1590 cm^{-1}) was approximately 9:1. The solution cell was attached to the base of a stainless steel dewar, enclosed in a shroud (Air Products), and cooled to −75° by charging the dewar with Dry Ice–acetone. After a low-temperature ir spectrum was obtained, the solution was irradiated for 2000 sec with an external 200-W super pressure mercury lamp (Bausch and Lomb) through a Corning CS-054 filter. While still at −75° a terminal ir spectrum was obtained. Comparison of the 12 peaks between 2000 and 1200 cm^{-1} in the terminal spectrum with peaks in the initial spectrum and with peaks in an ir spectrum of photodimer in *n*-heptane indicated that only starting materials and photodimers were present to any observable extent in the cold irradiated solution. During the irradiation approximately 75% of the azepine was destroyed.

A thin film of approximately five parts azepine (III) and one part acetophenone was cooled to −190° with liquid nitrogen in an Air Products cell and similarly irradiated for 1200 sec. Infrared analysis of the irradiated film (at −190°) showed that at least 50% of the azepine had been destroyed. Warming the cell to room temperature resulted in no distinguishable changes. The terminal infrared spectrum was consistent with a mixture of azepine, dimer, and acetophenone.

Reagents Used for Quantum Yield.—Acetophenone from Matheson Coleman and Bell was distilled at 81–81.5° (11 mm) prior to use. Triphenylamine (194–196°) was used without further purification. Spectrograde benzene was used as the solvent without further purification.

Quantum Yield Measurements.—Quantum yield experiments were performed in a Rayonet photochemical reactor Model RPR-100 using RPR-3000A lamps equipped with a rotating wheel. The wheel was constructed from an aluminum drum, 7 in. in diameter and 2.25 in. thick, mounted on a central shaft of 0.75 in. aluminum rod. On the perimeter of the drum were located 30 cylindrical compartments 13 mm in diameter. Each compartment was exposed to the lamps through a 0.25 × 0.75 in. slit. At the base and top of the shaft are ball bearings which are rigidly attached to the Rayonet reactor. The wheel was rotated at 48 rpm. The quantum yield apparatus was cooled with air which had passed through a water-cooled heat exchanger. The apparatus equilibrated at 30°. Calibration of the compartments of the wheel with potassium ferrioxalate actinometer[14] demonstrated that each compartment received identical quantities of light (±1%).

Samples (3.0 ml) of the appropriate concentration (Table I) of sensitizer and azepine (III) were placed in 13-mm Pyrex test tubes and degassed by four freeze (liquid nitrogen), pump (2 × 10^{-5} mm), thaw cycles and sealed. Sensitizer concentrations were selected such that greater than 99% of the incident light below 4000 A was absorbed. During the irradiation the lamp intensity was monitored with potassium ferrioxalate actinometry and averaged 2.5 × 10^{15} quanta/sec (uncorrected for the low intensity at wavelengths greater than 4000 A). Analyses were performed with a 0.25 in. × 7 ft gas chromatographic column of 5% SE-30 on nonacid-washed, 60/80 mesh Chromosorb W with helium flow at 60 cc/min. Destruction of starting material was analyzed at 100° relative to external triglyme and formation of dimer, at 190° relative to external anthracene. Areas of azepine (III) and dimer (V) were corrected for differences in thermal conductivity.

Registry No.—III, 37991-60-9; IV, 23137-74-8; V, 37991-62-1; VIa, 37991-63-2; isophorone, 78-59-1; *syn*-isophorone oxime, 28052-11-1; *anti*-isophorone oxime, 26358-61-2; 6,7-dihydro-2-methoxy-4,6,6-trimethyl-3*H*-azepine, 37991-64-3; trimethyloxonium fluoroborate, 420-37-1.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the General Medical Institute (GM-18349) for support of this research. The authors acknowledge the technical assistance of Mr. William Utton in the preparation of *syn*-isophorone oxime.

(14) See Table II, footnote c.

The Preparation and Properties of Isomeric Diamino-*v*-triazolopyridines. 1- and 3-Deaza-2,6-diamino-8-azapurines[1]

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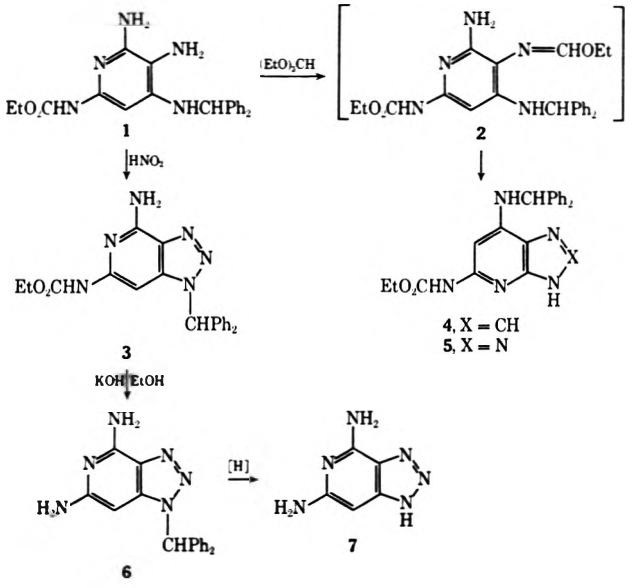
Received November 21, 1972

The nitrosation of ethyl 5,6-diamino-4-[(diphenylmethyl)amino]pyridine-2-carbamate (**1**) resulted in ring closure between the 5-amino- and 4-(diphenylmethyl)amino groups to give ethyl 4-amino-1-[(diphenylmethyl)-amino]-1*H*-*v*-triazolo[4,5-*c*]pyridine-6-carbamate (**3**). Removal of the blocking groups of **3** gave 4,6-diamino-1*H*-*v*-triazolo[4,5-*c*]pyridine (**7**). The isomeric 5,7-diamino-3*H*-*v*-triazolo[4,5-*b*]pyridine (**14**) was prepared from 5-amino-7-chloro-3*H*-*v*-triazolo[4,5-*b*]pyridine (**10**) by reduction of the corresponding 7-azido derivative **12**. Two other routes for the preparation of **14** are discussed. The Dimroth rearrangement between **7** and **14** was investigated.

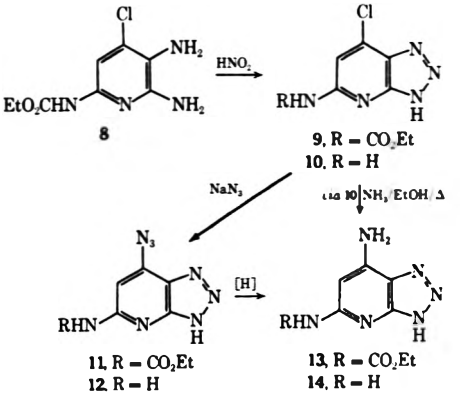
The isomeric 4,6-diamino-1*H*-*v*-triazolo[4,5-*c*]pyridine (8-aza-3-deaza-2,6-diaminopurine) (**7**) and 5,7-diamino-3*H*-*v*-triazolo[4,5-*b*]pyridine (8-aza-1-deaza-2,6-diaminopurine) (**14**) compounds are of theoretical and biological interest as purine ring analogs. Although the nitrosation of the known 2,3,4,6-tetraaminopyridine[2] might provide either one or both of **7** and **14**, this method might lead to ambiguous structural assignments. The present paper describes the effect of the (diphenylmethyl)amino group on the mode of cyclization in tetraaminopyridines, the nucleophilic displacement of the chloro group in the 5-amino-7-chlorotriazolopyridine **10**, and the Dimroth rearrangement between **7** and **14**.[3]

Treatment of **1** with ethyl orthoformate was shown to result in cyclization between the 5,6-diamino groups to give ethyl 7-[(diphenylmethyl)amino]-3*H*-imidazo-[4,5-*b*]pyridine-5-carbamate (**4**).[4] This mode of cyclization was attributed to steric interaction between the 4-[(diphenylmethyl)amino] and 5-[(ethoxymethylene)amino] groups of the presumed intermediate **2**. In contrast, nitrosation of **1** gave a homogeneous product (tlc), which was assigned structure **3** rather than **5**. Initially the assignment of structure was based on the greater nucleophilicity of the (diphenylmethyl)-amino group over that of the 6-amino group in the presumed 5-diazopyridine intermediate (see **21** and **22**), and this surmise was confirmed by the results described below.



Cleavage of the urethane group of **3** was effected with refluxing ethanolic KOH to give **6**. Support for this structure (**6**) was provided by its pmr spectrum, which showed the CH of the Ph_2CHN group as a singlet. This CH in the isomeric compound obtained from **5** might appear as a doublet as a result of spin–spin coupling between the CH and NH of the Ph_2CHNH group. This type of splitting is observed in the spectrum of the related imidazopyridine **4**.[4] Removal of the diphenylmethyl blocking group of **6** to give **7** was more difficult. Treatment of **6** with concentrated HCl[4] at room temperature gave mainly recovered **6** and unidentified decomposition products, but none of **7**. Similarly, hydrogenation of **6** in the presence of Raney nickel gave none of **7**. In contrast, hydrogenation of **6** in the presence of palladium at 60° resulted in overreduction (1.8 molar equiv of H_2), but the resulting mixture gave a 45% yield of **7**. Additional proof for the structure of **7** (and **3**) was provided by the synthesis of the isomeric compound **14**.

Nitrosation of **8**[4] gave a good yield of **9**. Treatment of **9** with sodium azide resulted in azidodechlorination to give **11**, which was readily hydrogenated in the presence of palladium to give **13**. The azide reaction demonstrated that the reactivity of the chloro group in the triazolopyridine **9** was greater than that of the chloro group in the corresponding imidazopyridine series.[4] Simultaneously, a similar sequence of reactions was used to prepare the 5,7-diamino compound **14**.



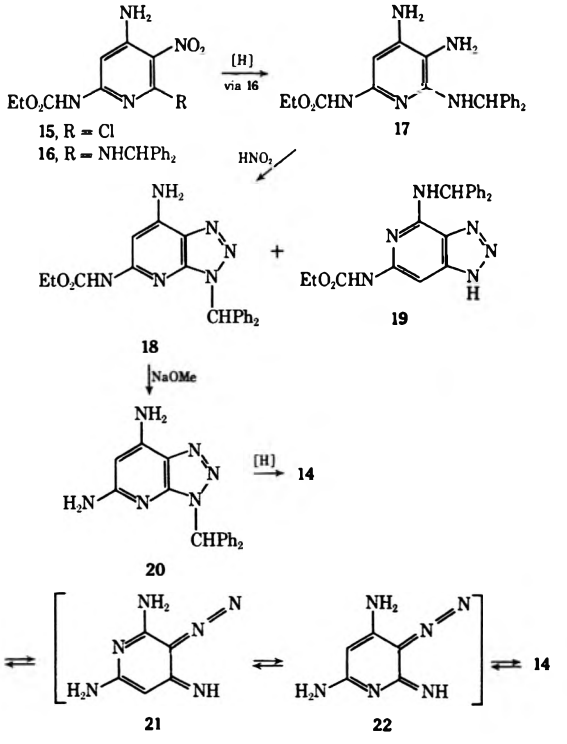
(1) This investigation was supported by Contract NIH-71-2021 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

(2) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **33**, 2393 (1968).

(3) C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *ibid.*, **37**, 3601 (1972); *Chem. Commun.*, 52 (1972).

(4) C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.*, in press.

Treatment of **9** with NaOMe in refluxing ethanol for 26 hr gave **10**, which was treated with sodium azide to give **12**. Unexpectedly, hydrogenation of **12** with either Raney nickel or palladium resulted in only partial conversion to **14**. Apparently the formation of **14** poisoned the catalysts. However, treatment of **12** with sodium hydrosulfite gave a pure sample of the desired product **14**. Also, treatment of **10** with 12% ethanolic ammonia in the presence of NH_4Cl in a bomb at 150° for 19 hr resulted in a 16% yield of **14** contaminated with a trace amount of **10** (tlc). In another approach, reaction of **15**[5] with diphenylmethylamine gave **16**, which was hydrogenated in the presence of Raney nickel to give **17**. Nitrosation of **17** gave a



mixture from which pure **18** was separated. This reaction gave another product that was homogeneous (tlc) and analyzed correctly for **19**. However, this sample was insoluble in dilute NaOH, and on storage was converted to a mixture containing **18** (tlc). These results suggested that the sample initially isolated was an unstable polymeric material rather than **19**. Cleavage of the urethane group of **18** was effected with $NaOCH_3$ in PrOH to give **20**. Hydrogenation of the latter in the presence of a palladium catalyst was difficult and gave only partial conversion to **14**.

The results of previous studies suggested that rearrangement of **7** to **14** might occur readily.[3] Although the chemical shifts of the ring CH's of **7** and **14** are quite similar in deuterated DMSO, the signals from these protons are readily distinguished in the spectrum of the mixture, so that pmr spectroscopy could be used to monitor the rearrangement. Treatment of **7** with 12% ethanolic ammonia in a bomb at 150° gave about a 50% conversion to **14** in 17 hr and about an 85% conversion in 120 hr (7 half-lives). Presumably, this conversion involves the diazopyridine intermediates **21** and **22**. These results show that the thermodynamic stability of **14** is greater than that of **7** in the presence of ammonia, which was confirmed by treatment of **14** with ethanolic ammonia. No rearrangement of **14** to **7** either at 150° or 175° was detected by tlc.

(5) R. D. Elliott, C. Temple, Jr., J. L. Frye, and J. A. Montgomery, *J. Org. Chem.*, **36**, 2818 (1971).

Experimental Section[6]

Ethyl 4-Amino-1-(diphenylmethyl)-1*H*-*v*-triazolo[4,5-*c*]pyridine-6-carbamate (3).—Solid sodium nitrite (1.5 g) was added to a solution of 1 (7.9 g)[4] in DMF (100 ml) containing 1 *N* HCl (21 ml) at 5°. After the addition was complete the reaction mixture was stirred at room temperature for 5 hr and diluted with H_2O (1000 ml). The resulting suspension was adjusted to pH 8 (paper) with $NaHCO_3$, and the crude product was collected by filtration and washed with H_2O, yield 7.0 g (86%). The analytical sample, recrystallized from EtOH, decomposed from about 120°.

Anal. Calcd for $C_{21}H_{20}N_6O_2$: C, 64.93; H, 5.19; N, 21.64. Found: C, 64.66; H, 5.24; N, 21.37.

4,6-Diamino-1-(diphenylmethyl)-1*H*-*v*-triazolo[4,5-*c*]pyridine (6).—A mixture of **3** (1.0 g) and KOH (1.4 g) in EtOH (50 ml) was refluxed for 10 hr, cooled, and filtered. The resulting residue was suspended in H_2O (20 ml), and the mixture was acidified to pH 5 (paper) with HOAc. The solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.31 g (38%), mp 245–246°.

Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.33; H, 5.10; N, 26.57. Found: C, 68.11; H, 5.07; N, 26.40.

The reaction filtrate from above was worked up in a similar manner to give an additional 0.37 g of crude **6**. The total yield was 0.68 g (83%).

4,6-Diamino-1*H*-*v*-triazolo[4,5-*c*]pyridine (7).—A suspension of **6** (2.0 g) in a mixture of EtOH (200 ml) and DMF (2 ml) was hydrogenated in the presence of 5% palladium on charcoal (2 g) at atmospheric pressure and room temperature. The uptake of hydrogen was very slow. After 2 hr additional 5% palladium (2 g) was added, and the mixture was hydrogenated at 60° for 72 hr. The uptake ceased after about 1.8 molar proportions of H_2 was absorbed. The catalyst was removed by filtration (Celite), and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was washed with Et_2O and recrystallized from H_2O (dried 78°), yield 0.43 g (45%), mp 228–229° dec.

Anal. Calcd for $C_5H_6N_6$: C, 40.00; H, 4.03; N, 55.97. Found: C, 39.88; H, 3.99; N, 55.77.

Ethyl 7-Chloro-3*H*-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (9).—Solid sodium nitrite (3.3 g) was added slowly with stirring to a suspension of **8** (10 g)[4] in 5% aqueous HOAc (200 ml), which was cooled in an ice bath. After the addition was complete the reaction mixture was stirred at room temperature for 20 hr. The solid was collected by filtration and reprecipitated from hot EtOH (Norit) by the addition of H_2O, yield 9.0 g (86%), mp 211° dec.

Anal. Calcd for $C_8H_8ClN_5O_2$: C, 39.77; H, 3.34; Cl, 14.67; N, 28.98. Found: C, 39.62; H, 3.62; Cl, 14.50; N, 28.65.

5-Amino-7-chloro-3*H*-*v*-triazolo[4,5-*b*]pyridine (10).—A mixture of **9** (5.0 g) and MeONa (5.6 g) in EtOH (250 ml) was refluxed for 26 hr. The reaction mixture was evaporated to dryness, and the residue was dissolved in 1 *N* HCl (155 ml). The resulting solution was adjusted first to pH 8 (paper) with dilute NH_4OH and then to pH 5 with dilute HCl. After chilling, the product was collected by filtration and dried *in vacuo* over P_2O_5 at 78°, yield 3.0 g (86%), mp >350°.

Anal. Calcd for $C_5H_4ClN_5$: C, 35.41; H, 2.38; Cl, 20.91; N, 41.30. Found: C, 35.20; H, 2.49; Cl, 20.93; N, 41.16.

Ethyl 7-Azido-3*H*-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (11).—A solution of **9** (1.0 g) in a mixture of 1:1 EtOH–H_2O (50 ml) containing sodium azide (6.0 g) was refluxed for 48 hr. The reaction mixture was evaporated to dryness, the residue was dissolved in H_2O, and the resulting solution was acidified to pH 5 (paper) with HOAc. The solid that deposited was collected by filtration, recrystallized from aqueous EtOH, and dried *in vacuo* over P_2O_5 at 56°, yield 0.62 g (60%). This sample decomposed from ~160°.

Anal. Calcd for $C_8H_8N_8O_2$: C, 38.71; H, 3.25; N, 45.15. Found: C, 38.96; H, 3.50; N, 45.22.

(6) Melting points, unless otherwise noted, were determined on a Mel-Temp apparatus, and thin layer chromatograms (silica gel H) were developed with mixtures of $CHCl_3$ and MeOH.

TABLE I

SPECTRAL PROPERTIES OF SOME *v*-TRIAZOLOPYRIDINES

Compd	Uv absorption[a] spectra at pH 7, λ_{max}, nm ($\epsilon \times 10^{-3}$)	Ir absorption[b] spectra in KBr, selected bands, cm^{-1}	Pmr spectral assignments,[c] chemical shifts, δ (rel area)
3	233 (28.3), 290 (11.4), 303 sh (10.8)	1730, 1630, 1605	1.21 t (3, CH_3), 4.10 q (2, CH_2), 7.01,[d] 7.10, 7.37 m [14, NH_2, CH (C_6H_5, CH)], 9.43 (1, NH)[d]
6	228 sh (24.9), 285 (6.33), 322 (7.12)	1645, 1600, 1590	5.42,[e] 5.55[d] (3, 7 H, NH_2), 6.73 (2, NH_2),[d] 7.21, 7.37 (11, HCPh, C_6H_5)
7	225 (27.1), 275 (4.75), 314 (5.37)	1660, 1620, 1595	5.43 br, 5.68 (3, NH_2, 7 H), 6.60 br (2, NH_2), ~14 br (1, NH)
9	222 (22.9), 302 (14.9)	1750, 1725, 1595	
10	265 sh (5.10), 293 (7.41)[f]	1615, 1535	6.72 (6 H), 6.85 (NH_2), ~14 br (NH)
11	222 (21.5), 300 (17.5)	2115, 1700, 1615	
12	284 (12.6), 307 sh (9.55)[f]	2120, 1625, 1580	1.08, 3.48 (CH_3CH_2OH), 6.17 (1, 6 H), 6.64 (2, NH_2),[d] ~12 (1, NH)[d]
13	281 (16.9), 302 (22.2)[g]	1715, 1700, 1645	
14	280 sh (15.6), 293 (18.2)[f]	1640, 1600, 1535	5.71 (1, 6 H), 7.43 br (2, NH_2), ~9.6 br (4, NH_2, NH, NH^+)
17	222 (34.8), 296 (8.10)	1725, 1660, 1610	
18	232 (22.7), 283 (16.4), 297 sh (14.1)	1720, 1650, 1630	1.23 t (CH_3), 4.13 q (2, CH_2), 7.17, 7.24,[h] 7.35 [14, CH (CH, NH_2), C_6H_5], 9.81 (1, NH)
20	292 (16.0)	1625, 1600, 1515	3.33 br (4, NH_2 + H_2O), 5.61 (1, 6 H), 6.32 br (2, NH_2), 7.07 (1, HCPh), 7.32 (10, C_6H_5)

[a] Cary Model 17 spectrophotometer. Unless otherwise noted, solvent contains 10% MeOH and 90% pH 7 phosphate buffer. [b] Perkin-Elmer Model 521 and 621 spectrophotometers. [c] Pmr spectra of samples were determined in DMSO-d_6 solutions (5–10% w/v) with Varian A-60A and XL-100-15 spectrometers with TMS as an internal reference; peak positions quoted in the case of multiples are measured from the approximate center, and the relative peak areas are given to the nearest whole number. [d] Undergoes deuterium exchange on addition of D_2O. [e] Undergoes deuterium exchange in the presence of D_2O within 96 hr. [f] Solvent contains 0.8% DMSO, 9.2% MeOH, and 90% pH 7 phosphate buffer. [g] Determined in 0.1 *N* HCl as solvent. [h] Undergoes partial deuterium exchange on addition of D_2O.

5-Amino-7-azido-3*H*-*v*-triazolo[4,5-*b*]pyridine (12).—A mixture of **10** (0.50 g) and sodium azide (4.3 g) in 1:1 PrOH–H_2O (30 ml) was refluxed for 68 hr. The reaction mixture was evaporated to dryness, and the residue was treated with H_2O (35 ml). After filtration the filtrate was acidified with HOAc to pH 5 (paper) to deposit the product, yield 0.32 g (62%). A sample (0.13 g) of this material was recrystallized from EtOH, yield 0.10 g (77% recovery), mp 245° dec. The presence of EtOH in the sample was confirmed by the pmr spectrum (Table I).

Anal. Calcd for $C_5H_4N_8 \cdot {}^1/_4C_2H_6O$: C, 35.20; H, 2.96; N, 59.71. Found: C, 35.32; H, 2.72; N, 59.74.

Ethyl 7-Amino-3*H*-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (13).—A suspension of **11** (0.50 g) in EtOH (125 ml) was hydrogenated in the presence of 5% palladium on charcoal at atmospheric pressure and room temperature for 4 hr. After the reaction mixture was warmed, the catalyst was removed by filtration (Celite) and washed with EtOH. The combined filtrate and wash was evaporated to dryness *in vacuo;* the resulting solid was recrystallized from 30% aqueous EtOH and dried *in vacuo* over P_2O_5 at 100° for 18 hr, yield 0.34 g (74%), mp >300°.

Anal. Calcd for $C_8H_{10}N_6O_2 \cdot {}^1/_3H_2O$: C, 42.11; H, 4.71; N, 36.84. Found: C, 42.06; H, 4.53; N, 36.51.

A sample of this product was dried *in vacuo* over P_2O_5 at 110°.

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.54; N, 37.82. Found: C, 42.80; H, 4.68; N, 37.75.

5,7-Diamino-3*H*-*v*-triazolo[4,5-*b*]pyridine (14).—A mixture of **12** (0.18 g) in MeOH (45 ml) and H_2O (20 ml) containing sodium hydrosulfite (1.0 g) was refluxed for 4.5 hr, acidified to pH 1 (paper) with dilute H_2SO_4, and filtered. The filtrate was adjusted to about pH 5 with dilute NaOH and chilled to deposit the hemisulfate salt. The product was collected by filtration, washed with water and hot PrOH, and dried *in vacuo* over P_2O_5 at 78°, yield 0.10 g (49%), mp 305° dec.

Anal. Calcd for $C_5H_6N_6 \cdot {}^1/_2H_2SO_4$: C, 30.15; H, 3.55; N, 42.19. Found: C, 30.25; H, 3.46; N, 41.96.

B.—A solution of **20** (100 mg) in 5% ethanolic DMAC (10 ml) was hydrogenated in the presence of 5% palladium on charcoal for 6 hr at atmospheric pressure and room temperature. After filtration the catalyst was washed with hot DMAC, the combined filtrate and wash were evaporated to dryness, and the resulting residue was washed with hexane to remove Ph_2CH_2, yield 59 mg. Tlc indicated that this product was a mixture of **14** and **20**. A portion of this sample (30 mg) was washed with Et_2O to give **14** (7 mg). The uv spectrum of the latter was identical with that described above.

C.—A mixture of **7** (50 mg) in 12% ethanolic ammonia was heated in a bomb at 150° for 17 hr and evaporated to dryness *in vacuo*, yield 50 mg (100%). Tlc indicated that the product was a mixture of **7** and **14**, and the pmr spectrum in deuterated DMSO showed that the ratio of **7**:**14** was 1:1. In a similar experiment at 150° for 120 hr (7 half-lives), the ratio of **7**:**14** was 3:17.

Ethyl 4-Amino-6-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (16).—A mixture of **15** (4.00 g),[5] diphenylmethylamine (4.00 g), and Et_3N (3.12 g) in MeOH (60 ml) was heated at 75° for 36 hr. The resulting solution was cooled to deposit a yellow solid, which was collected by filtration. The product was washed with H_2O and MeOH and dried *in vacuo* over P_2O_5 at 78°, yield 4.55 g (73%), mp 159–160°.

Anal. Calcd for $C_{21}H_{21}N_5O_4$: C, 61.90; H, 5.20; N, 17.19. Found: C, 61.67; H, 5.14; N, 16.94.

An additional 0.9 g of crude product was obtained from the reaction filtrate. The total yield was 5.45 g (87%).

Ethyl 4,5-Diamino-6-[(diphenylmethyl)amino]-2-pyridinecarbamate (17).—A suspension of **16** (2.00 g) in EtOH (280 ml) was hydrogenated in the presence of Raney nickel (2.0 g wet, washed with H_2O and EtOH) at room temperature and atmospheric pressure. The resulting reaction mixture was filtered (Celite) into a flask containing concentrated HCl (1.0 ml). The dark filtrate was treated with Norit (0.5 g) and evaporated to dryness *in vacuo;* the pale pink solid was dried *in vacuo* over P_2O_5 at 78°, yield 1.45 g (66%). This material does not melt, but undergoes decomposition from 210°.

Anal. Calcd for $C_{21}H_{23}N_5O_2 \cdot 2HCl$: C, 56.00; H, 5.60; Cl, 15.74; N, 15.55. Found: C, 55.84; H, 5.49; Cl, 15.55; N, 15.40.

Ethyl 7-Amino-3-(diphenylmethyl)-3*H*-*v*-triazolo[4,5-*b*]pyridine-2-carbamate (18).—Solid sodium nitrite (1.1 g) was added with stirring to a solution of **17**·2HCl (6.4 g) in DMF (80 ml), which was precooled in an ice bath to 5°. After 30 min the ice bath was removed, and the solution was stirred at room temperature for 5 hr. After filtration the reaction mixture was poured into ice water (1500 ml), and the resulting solution was neutralized with $NaHCO_3$. The precipitate was collected by filtration,

dried *in vacuo* over P_2O_5, and extracted with boiling petroleum ether (3000 ml) (bp 80–110°). The product that crystallized from the cooled extract was collected by filtration, and the filtrate was used to again extract the insoluble material from the first extract. This procedure was repeated four times. The recrystallized crops were combined and dried *in vacuo* over P_2O_5, yield 2.6 g (47%). The pmr spectrum and tlc data indicated that this material was homogeneous; however, the melting point was indefinite. This sample solidified after melting at 208° on the Kofler Heizbank apparatus and melted at >350° on the Mel-Temp apparatus. In another experiment the homogeneous material (tlc) melted in these apparatus at 132 and 145–147°, respectively.

Anal. Calcd for $C_{21}H_{20}N_6O_2$: C, 64.93; H, 5.19; N, 21.64. Found: C, 65.14; H, 5.33; N, 21.50.

The petroleum ether insoluble material was homogeneous on tlc and analyzed correctly for ethyl 4-[(diphenylmethyl)amino]-1*H*-*v*-triazolo[4,5-*c*]pyridine-6-carbamate (**19**), yield 1.5 g (27%), mp ~315° dec. The insolubility of this product in deuterated DMSO precluded the determination of its pmr spectrum. However, after 3 years tlc indicated that this product was a mixture containing **18**, suggesting that the original material was an unstable polymeric product and not **19**.

Anal. Calcd for $C_{21}H_{20}N_6O_2$: C, 64.93; H, 5.19; N, 21.64. Found: C, 64.76; H, 4.99; N, 21.84.

5,7-Diamino-3-(diphenylmethyl)-3*H*-*v*-triazolo[4,5-*b*]pyridine (20).—A mixture of **18** (0.50 g) and $NaOCH_3$ (0.35 g) in PrOH (20 ml) was refluxed for 20 hr and evaporated to dryness *in vacuo*. The residue was heated in 0.1 *N* HCl at 50° for 15 min, cooled, and adjusted to pH 8 (paper) with dilute NaOH. The precipitate was collected by filtration, recrystallized from C_6H_6, and dried *in vacuo* over P_2O_5 at 56°, yield 0.28 g (69%), mp 115° (Kofler Heizbank).

Anal. Calcd for $C_{18}H_6N_6$: C, 68.34; H, 5.10; N, 26.57. Found: C, 68.38; H, 5.16; N, 26.37.

Registry No.—**1**, 38359-68-1; **3**, 38359-69-2; **6**, 38359-70-5; **7**, 38359-71-6; **8**, 37437-06-2; **9**, 38359-73-8; **10**, 38359-74-9; **11**, 38359-75-0; **12**, 38359-76-1; **13**, 38359-77-2; **14**, 38359-78-3; **15**, 6502-04-1; **16**, 38359-79-4; **17** 2HCl, 38359-80-7; **18**, 38359-81-8; **20**, 38359-82-9.

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Synthesis and Properties of Pyrido- and Azapyridocyanines

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A summary of the synthesis of 2,2′-, 2,4′-, and 4,4′-pyrido- and -azapyridocyanines, including the *N*,*N*′-(1,ω-alkylene)-2,2′-cyanines is given. Several new dyes of those classes are described, and it is shown that some previous results reported in the literature must be corrected.

Pyridocyanines have been proposed recently for coupling to the conjugated backbone in a proposed model for superconducting polymers.[2] This renewed interest in this dye class promoted us to report on a comprehensive study of the syntheses of pyridocyanines and the related class of azapyridocyanines, which were prepared for an investigation of their stereoisomerism and molecular spectra.[3,4]

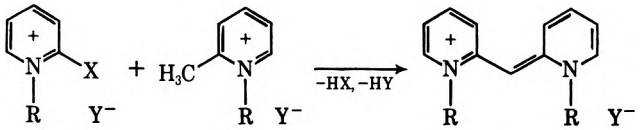
Although the syntheses of these dyes often *appear* to be straightforward, it became apparent during this work that syntheses and structures of several previously reported dyes needed revision. In addition, syntheses and properties of many new dyes of these classes will be reported. An earlier compilation of the syntheses and properties of cyanine dyes has been given by Hamer.[5]

Discussion

A. Pyridocyanines.—To synthesize pyridocyanines one can either quaternize the corresponding dipyridylmethanes or use condensation procedures. The first procedure is often useful for structure determination and the latter one is advantageous for the synthesis of large quantities of the dyes, because the starting materials can be obtained with less effort.

1. 2,2′-Pyridocyanines. a. *N*,*N*′-Dialkyl-2,2′-pyridocyanines (I).—The principle of synthesis of pyridocyanine dyes is well demonstrated by the various syntheses of the *N*,*N*′-dialkyl-2,2′-pyridocyanines (I).

Most commonly these dyes are synthesized by condensation from *N*-alkyl-2-X-pyridinium (**1**) [X = -I,[6] -Cl,[7,8] $-SR^9$ (R = CH_3, C_2H_5)] and *N*-alkyl-2-methylpyridinium salts (**2**) in the presence of suitable organic bases, *e.g.*, triethylamine.



1 **2** **I**

An alternative synthesis is from di(2-pyridyl)methane[10] (**3**) and alkyl iodide, which may proceed *via* two different routes.[11–13] With methyl iodide the reaction proceeds *via* the intermediate **6**,

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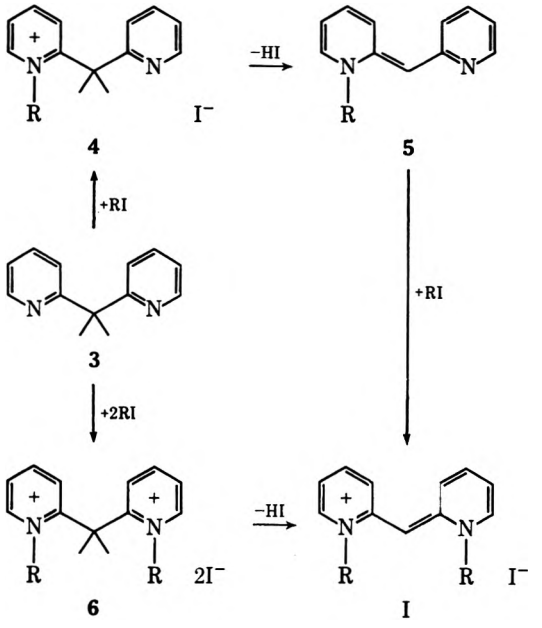
TABLE I

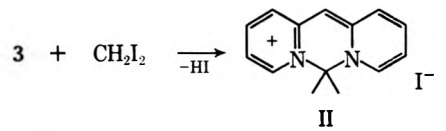
Dye	Anion	γ, cm^{-1}	$\epsilon_0 \times 10^{-3}$	Mp, °C[a]	Crystal form and color	Reference
I (R = C_2H_5)	I	20,700	31.0	235–237[b]	Brown needles	6, 7, 11
I (R = CH_3)	I	20,900	31.0	315–317[c]	Brown and green dichroic platelets	6, 11, 12
II	I	20,100	15.0	228–230		
IIa	I	19,800	12.0	195	Dark red crystals	11, 12, 14
IIb	I	19,600	9.0	257–259		
III	Br	20,600	28.0	200	Orange crystals	
	I			223–224	Yellowish brown crystals	
IV	I	20,800	53.0	218–219[d]	Violet shining crystals	6
V	I	20,700	125.5	174–176	Reddish brown crystals	12
VI	2I	19,800	55.5	320–322	Dark red and green dichroic crystals	16
VII (R = C_2H_5)	I	25,550	28.4	243–244	Nearly colorless platelets	3b, 18, 19
VII (R = CH_3)	I	25,750	28.4	290–292[e]	Nearly colorless needles	18, 19
VIII	I	24,200	15.8	258–260	Yellow needles	
IXa,b (R = C_2H_5)	I	31,000	30.0	148	Colorless needles	
IXa,b (R = CH_3)	I	31,000	30.6	242–243	Colorless, sturdy crystals	
X	I	25,900–26,600	36.2	213	Nearly colorless needles	
XI	I	25,500	66.6	204	Light yellow needles	

[a] All dyes decomposed on melting. [b] Lit.[11] mp 223–224°; lit.[6] mp 237–239°. [c] Lit.[11] mp 314–315°; lit.[6] mp 315–317°. [d] Lit.[6] mp 214–217°. [e] Lit.[18] mp 288–291°; lit.[19] mp 290°. [f] γ = long wavelength absorption in ethanol, 20°.

and with ethyl iodide *via* the intermediates **4** and **5**. The reaction path cannot be predicted but may be influenced by steric factors.



b. Di Cis Forms of the 2,2′-Pyridocyanine. i. *N,N′*-Methylene-2,2′-pyridocyanine Iodide (II).—The synthesis of dye II was accomplished by refluxing di(2-pyridyl)methane (**3**) with diiodomethane corresponding to the synthesis of *N,N′*-methylene-2,2′-cyanine.[8,11–14]



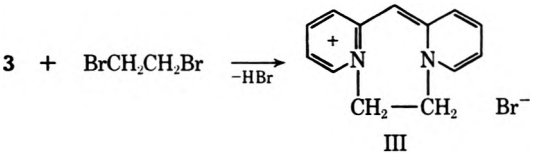
II

Although this reaction appears straightforward, three different products (II,[2] IIa,[11,12] IIb[13,14]) were reported as having structure II. All three have similar absorption spectra in the region up to 35,000 cm^{-1} so that one can assume that they have the same chromophore II.

These dyes differ slightly in the position of their long wavelength absorption maxima (γ) and significantly in their molar extinction coefficient ϵ_0 (referred to structure II), melting point, and nmr spectra.[4] Their properties are reported in Table I.

Dye IIa was reported to contain 2 mol of methanol per molecule in the crystal;[11,12] however, we were unable to repeat these results. Neither dye II nor dye IIb could be purified further by recrystallization and column chromatography. It was not possible to convert the dyes into each other. The dye which by its nmr spectrum[4,8] and analysis has structure II is listed in Table I as II. The structure of IIb could not be elucidated; however, additional bands in the short-wave region of the absorption spectrum, extinction coefficient, analysis, and additional signals in the nmr spectrum indicate that it probably has structure II with additional substituents (pyridyl?).

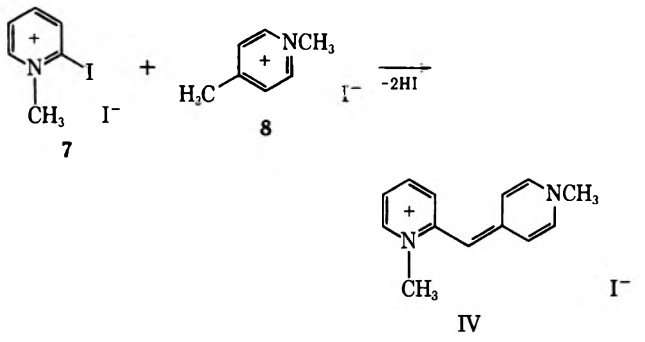
ii. *N,N′*-Ethylene-2,2′-pyridocyanine Bromide (III).—This dye was obtained by refluxing di(2-pyridyl)-methane (**3**) and 1,2-dibromoethane. No complications, such as those arising in the synthesis of dye II, were encountered. This dye shows intense green fluorescence in ethanol solution at room temperature.



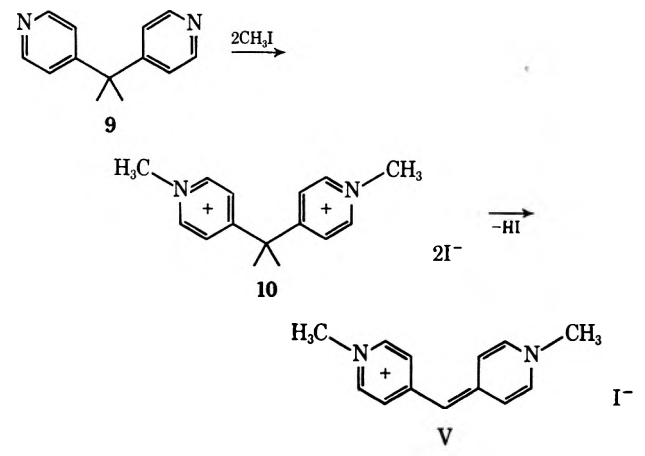
III

2. 2,4′-Pyridocyanines. *N,N′*-Dimethyl-2,4′-pyridocyanine Iodide (IV).—According to Brooker and Keyes,[6] this dye was obtained by condensation of *N*-methyl-2-iodopyridinium iodide (**7**) and 1,4-dimethylpyridinium iodide (**8**) in the presence of triethylamine. At present there is no synthesis known for 2,4′-dipyridylmethane and thus this dye could not be synthesized by quaternization of this base. Dye IV is yellow in solution but crystallizes from ethanol as deep violet platelets.

(14) E. Daltrozzo, G. Scheibe, and J. Smits, *Chimia*, **19**, 325 (1965).



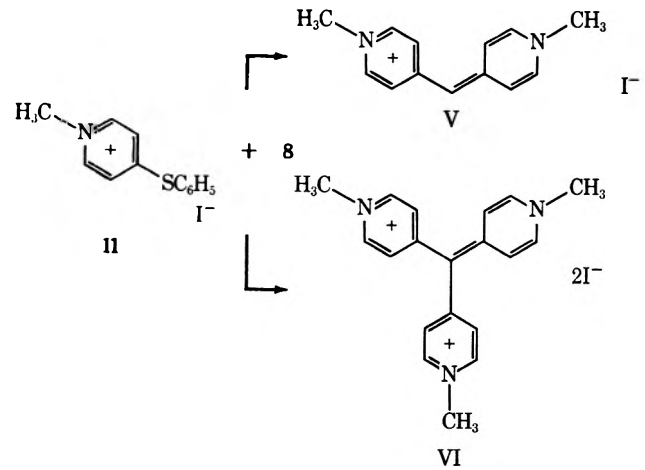
3. **4,4′-Pyridocyanines. a. *N,N′*-Dimethyl-4,4′-pyridocyanine Iodide (V).**—This dye (V) has been obtained by quaternization of di(4-pyridyl)methane (**9**) with methyl iodide.[12]



Proof of structure for V is provided by the synthesis itself and analysis. The base (**9**) was obtained from cyanodi(4-pyridyl)methane,[11,12] which was synthesized by the method of Sperber[15] from 4-chloropyridine and acetonitrile.

The properties of this dye are distinctly different from those of the dye to which Sprague and Brooker[16] attributed this structure.

b. *N,N′,N″*-Trimethyl-4,4′,4″-tripyridocyanine Iodide (VI).—To synthesize dye V, Sprague and Brooker[16] condensed *N*-methyl-4-phenylmercaptopyridinium iodide (**11**) and 1,4-dimethylpyridinium iodide (**8**) with triethylamine.



(15) N. Sperber, D. Papa, E. Schenk, and M. Sherlock, *J. Amer. Chem. Soc.*, **73**, 3856 (1951).

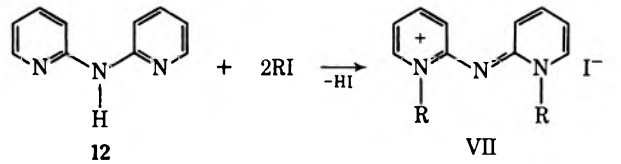
(16) R. H. Sprague and L. G. S. Brooker, *ibid.*, **59**, 2697 (1937).

Our experiments showed, however, that they had isolated dye VI instead of dye V. Dye VI is considerably less soluble in ethanol than dye V and can thus be purified easily by recrystallization in this solvent. A small amount of dye V was obtained from the mother liquors by column chromatography. The structures of V and VI have been confirmed by their analysis, nmr,[4,8] and electronic spectra.[2,8]

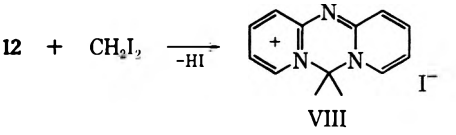
In their work on the absorption spectra of pyridocyanines, Levinson, *et al.*,[17] used dye VI; however, they based their discussion erroneously on structure V. The implications have been discussed previously.[2]

B. Azapyridocyanines.—For the synthesis of the azapyridocyanines no condensation procedures are known at present. Thus the corresponding dipyridylamines were quaternized with suitable agents. Dipyridylamines can generally be obtained in better yields and with less effort than the corresponding dipyridylmethanes.

1. 2,2′-Azopyridocyanines. a. *N,N′*-Dialkyl-2,2′-azapyridocyanine Iodide (VII).—Dyes of structure VII are obtained by reaction of di(2-pyridyl)amine (**12**) with alkyl iodide (alkyl = CH_3, C_2H_5) at elevated temperatures.[18,19] The doubly quaternized dye is formed immediately for both methyl and ethyl substitution (compare 2,2′-pyridocyanines above). Synthesis and properties of dye VII (R = C_2H_5) have not been reported previously.



b. *N,N′*-Methylene-2,2′-azapyridocyanine Iodide (VIII).—This di cis isomer of dye VII was obtained by reaction of di(2-pyridyl)amine (**12**) with diiodomethane without the complications encountered for the homolog dye II. Dye VII was separated from the



slightly soluble by-products by column chromatography on alumina. Its structure is supported by its analysis, model calculations, and electronic spectra.[3]

The aza analog of dye III, *N,N′*-ethylene-2,2′-azapyridocyanine, could not be obtained by reaction of di(2-pyridyl)amine (**12**) with 1,2-dibromo-, -dichloro-, or -diiodoethane.

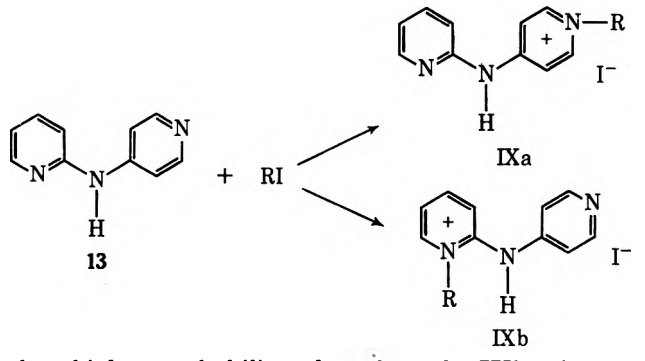
2. 2,4′-Azapyridocyanines. a. Monoalkylation Product of 2,4′-Dipyridylamine (IX).—Reaction of 2,4′-dipyridylamine (**13**) with alkyl iodide (alkyl = CH_3, C_2H_5) at elevated temperatures yielded only a monoalkylated product IX, which can have either structure IXa or IXb. Its molecular composition is supported by its analysis.

A distinction between structures IXa and IXb was not possible. However, structure IXa has a some-

(17) G. S. Levinson, W. T. Simpson, and W. Curtis, *ibid.*, **79**, 4314 (1957).

(18) E. Diepolder, *J. Prakt. Chem.*, **106**, 41 (1923).

(19) H. H. Credner, H. J. Friedrich, and G. Scheibe, *Chem. Ber.*, **95**, 1881 (1962).

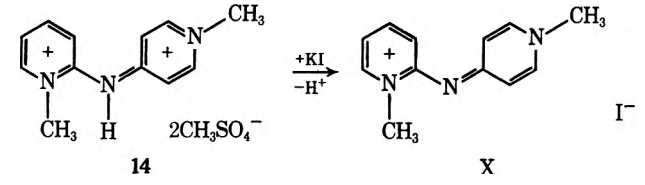


what higher probability than formula IXb, since 4-substituted pyridines are generally more easily quaternized than 2-substituted pyridines.

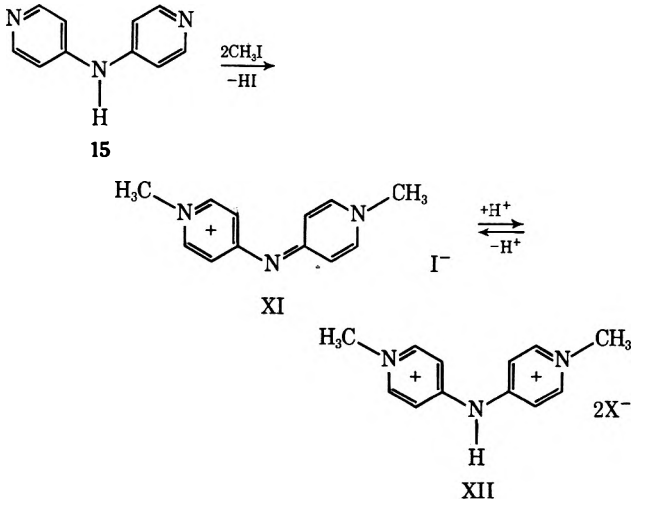
Compound IX reacted with alkyl iodide in the presence of barium oxide in methanol to yield a small amount of *N,N'*-dialkyl-2,4'-azapyridocyanine (X).

The 2,4'-dipyridylamine (**13**)[20,21] was synthesized according to Zwart and Wibaut[20] from 2-aminopyridine and 4-hydroxypyridine.

b. *N,N'*-Dimethyl-2,4'-azapyridocyanine Iodide (X).—Reaction of 2,4'-dipyridylamine (**13**) with dimethyl sulfate leads at once to the doubly quaternized intermediate **14**, which was not isolated, and further to the dye X. Its structure is supported by its absorption spectrum[3] and analysis.



3. *N,N'*-Dimethyl-4,4'-azapyridocyanine Iodide (XI).—This dye was synthesized from di(4-pyridyl)-amine (**15**) and methyl iodide.



A striking property of XI is its high basicity, so that a mixture of XI and XII is always obtained from the synthesis. Both compounds can be readily distinguished by their absorption spectra, because XII has its absorption peak at a wavelength (30,500 cm^{-1}) where XI has an absorption minimum (absorption peak 25,500 cm^{-1}). Dye XI can be obtained pure if the reaction mixture is dissolved in little aqueous ammonia and then chromatographed with acetonitrile on alumina. The equilibrium between XI and XII can be influenced arbitrarily by addition of acid or base. However, XII is unstable and decomposes in solution.

For the synthesis of di(4-pyridyl)amine (**15**)[22-24] the method of Koenigs and Jung[22] was preferred.

Experimental Section

The dyes are characterized by color, crystal form, melting point, absorption maxima (cm^{-1}), and molar extinction coefficient (ϵ_0) at room temperature (Table I). For all newly synthesized compounds the structures are supported by their analysis. The absorption, emission, and polarization spectra of these dyes were published previously and were found to be in excellent agreement with molecular orbital calculations (pyridocyanines,[3a] azapyridocyanines[3b]). The structures of all dyes are supported by their nmr spectra, which will be published in a separate report.[4] Where melting points were reported previously in the literature they are listed in Table I.

The following dyes have been synthesized according to published procedures: *N,N'*-dimethyl-(diethyl-, respectively) 2,2'-pyridocyanine (I),[6,11-13] *N,N'*-methylene-2,2'-pyridocyanine (II),[8,11-13] *N,N'*-dimethyl-2,4'-pyridocyanine (IV),[6] and *N,N'*-dimethyl-2,2'-azapyridocyanine iodide (VII, R = CH_3).[18,19] The synthesis of *N,N'*-dimethyl-4,4'-pyridocyanine (V) *via* di(4-pyridyl)methane (**9**) was reported elsewhere.[11,12] Novel observations in these syntheses and discrepancies with previously reported results are discussed in the previous sections.

The starting materials for the synthesis of the dyes were either commercially available or were synthesized following the published procedures mentioned in the text.

***N,N'*-Methylene-2,2'-pyridocyanine Iodide (II).**—Di(2-pyridyl)methane (**3**) (3.0 g, 0.018 mol) and 4.8 g (0.018 mol) of diiodomethane were heated until reaction began. After the reaction subsided, the reaction mixture was dissolved in 10 ml ethanol and then precipitated with ether to remove unreacted starting material. The precipitate was dissolved in a little methanol and twice chromatographed on alumina with acetone–methanol (9:1). The orange-green fluorescing zone was collected and evaporated to dryness *in vacuo*. The dark red residue was treated with a little absolute ethanol, whereupon it crystallized, yield *ca.* 0.80 g of II or IIb (15% referred to structure II).

In 11 of 12 repeats of this synthesis product IIb was isolated; only once was II isolated. In no case were both compounds isolated from the same reaction nor was the previously reported compound IIa.

The following variations were tried, but led to IIb: use of acetonitrile or nitromethane as reaction solvent, and addition of pyridine.[11] The di(2-pyridyl)methane (**3**) was synthesized according to Leete and Marion[10,11] as well as by saponification of cyanodi(2-pyridyl)methane[15] with sulfuric acid.[11,12] The base **3** was purified by distillation and by precipitation as the $ZnCl_2$ complex from methanol.[11] It was checked routinely for its purity and identity by nmr. At present it cannot be predicted under which conditions II or IIb will be obtained by this route.

Anal. Calcd for $C_{12}H_{11}N_2I$: C, 46.45; H, 3.55; N, 9.03. Found for II: C, 46.66; H, 3.71; N, 8.75. Found for IIb: C, 57.40; H, 4.68; N, 10.39.

***N,N'*-Ethylene-2,2'-pyridocyanine Bromide and Iodide (III).**—Di(2-pyridyl)methane (**3**) (3.0 g, 0.018 mol) and 6.5 g (0.036 mol) of ethylene bromide were heated to reflux for 15 min. The reaction product was washed with ether to remove unreacted starting materials, dissolved in a little ethanol, and chromatographed on alumina with acetone–methanol (9:1). The yellow, intensely green fluorescing zone was collected, concentrated, and the product precipitated with ether. The chromatography was repeated once, yield 1.1 g (22%). In a similar experiment the crude reaction product was treated with ammoniacal potassium iodide solution and twice chromatographed on alumina with acetonitrile to yield the dye iodide.

(20) C. Zwart and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas*, **74**, 1081 (1955).

(21) D. Jerchel and L. Jakob, *Chem. Ber.*, **91**, 1266 (1958).

(22) E. Koenigs and G. Jung, *J. Prakt. Chem.*, **137**, 141 (1933).

(23) M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **80**, 1376 (1961).

(24) E. Koenigs, H. Friedrich, and H. Jurany, *Chem. Ber.*, **58**, 2571 (1925).

Anal. Calcd for $C_{13}H_{13}N_2I$: C, 48.20; H, 4.01; N, 8.65. Found: C, 48.12; H, 4.16; N, 8.52.

N,N'-Dimethyl-4,4'-pyridocyanine iodide (V) and N,N',N''-trimethyl-4,4',4''-tripyridocyanine (VI) were synthesized following the procedure of Sprague and Brooker.[16] After two recrystallizations from ethanol dye VI was obtained as dark red crystals which showed green dichroism, yield 41%. The mother liquors were concentrated and filtered from a second crop of VI. The filtrate was chromatographed with acetone–methanol (9:1) on alumina and dye V was eluted in a yellow zone. After concentration of the solution, V was precipitated with ether and recrystallized from a little ethanol, yield *ca.* 5%.

Anal. Calcd for $C_{13}H_{15}N_2I$ (V): C, 47.85; H, 4.60; N, 8.59. Found: C, 47.76; H, 4.99; N, 8.52. Calcd for $C_{19}H_{21}N_3I$ (VI): C, 41.83; H, 3.85; N, 7.71. Found: C, 41.75; H, 4.05; N, 7.62

N,N'-Diethyl-2,2'-azapyridocyanine Iodide (VII, R = C_2H_5).—Di(2-pyridyl)amine (12) (2.0 g, 0.012 mol) and 5.5 g (0.036 mol) of iodoethane were heated to 100° for 4 hr in a sealed glass tube. The product was washed with ether and twice recrystallized from ethanol, yield 2.9 g (70%).

Anal. Calcd for $C_{14}H_{18}N_3I$: C, 47.30; H, 5.07; N, 11.83. Found: C, 47.20; H, 5.10; N, 11.70.

N,N'-Methylene-2,2'-azapyridocyanine Iodide (VIII).—A mixture of 3.0 g (0.018 mol) of di(2-pyridyl)amine (12) and 7.0 g (0.026 mol) of diiodomethane was heated to 100° for 4 hr in a sealed glass tube. The reaction product was washed with ether, then extracted with methanol, and chromatographed on alumina, first with acetone–methanol (9:1). The blue fluorescing zone was collected, concentrated, precipitated with ether, and once more chromatographed with acetonitrile, yield 0.6 g (10%).

Anal. Calcd for $C_{11}H_{10}N_3I \cdot H_2O$: C, 40.12; H, 3.65; N, 12.80. Found: C, 40.45; H, 3.50; N, 12.89.

Monoalkylation Product of 2,4'-Dipyridylamine (IX, R = CH_3).—A mixture of 1.0 g (0.006 mol) of 2,4'-dipyridylamine (13) and 2.5 g (0.018 mol) of iodomethane was heated to 100° for 3 hr in a sealed glass tube. The reaction product was washed with ether and recrystallized from ethanol, yield 1.5 g (80%). A similar reaction using 2.8 g (0.018 mol) of iodoethane in place of iodomethane yielded 1.5 g (80%) of IX (R = C_2H_5).

Anal. Calcd for $C_{11}H_{12}N_3I$ (R = CH_3): C, 42.17; H, 3.83; N, 13.42. Found: C, 42.15; H, 3.95; N, 13.30.

N,N'-Dimethyl-2,4'-azapyridocyanine Iodide (X).—2,4'-Dipyridylamine (13) (1.0 g, 0.006 mol) and 2.2 g (0.018 mol) of dimethyl sulfate were heated until reaction began. After it had subsided, the reaction mixture was dissolved in a little ammonia containing potassium iodide and then chromatographed on alumina with acetone–methanol (1:1). The blue fluorescing zone was collected and concentrated, and the product was precipitated with ether. It was again chromatographed as above, and once more with acetonitrile, yield 0.6 g (30%).

Anal. Calcd for $C_{12}H_{14}N_3I$: C, 44.03; H, 4.28; N, 12.84. Found: C, 44.03; H, 4.44; N, 12.81.

N,N'-Dimethyl-4,4'-azapyridocyanine Iodide (XI).—A mixture containing 1.0 g (0.006 mol) of di(4-pyridyl)amine (15) and 2.5 g (0.018 mol) of iodomethane was heated to 100° for 2 hr in a sealed glass tube. The reaction product was washed with ether, dissolved in a little concentrated ammonia, and chromatographed on alumina with acetonitrile. The blue fluorescing zone was collected and concentrated, and the product precipitated with ether. It was then dried *in vacuo* for 12 hr at 100° where it lost acetonitrile that was enclosed in the crystals, yield 1.5 g (80%).

Anal. Calcd for $C_{12}H_{14}N_3I$: C, 44.03; H, 4.28; N, 12.84. Found: C, 43.99; H, 4.32; N, 12.81.

Registry No.—3, 1132-37-2; 12, 1202-34-2; 13, 33932-96-6; 15, 1915-42-0; II, 38222-62-7; III bromide, 16521-09-8; III iodide, 38222-64-9; V, 16521-11-2; VI, 16610-36-9; VII (R = Et), 22013-57-6; VIII, 22013-58-7; IXa (R = Me), 38222-69-4; IXa (R = Et), 38222-70-7; IXb (R = Me), 38222-71-8; IXb (R = Et), 38222-72-9; X, 38222-73-0; XI, 22013-60-1.

Acknowledgment.—Thanks are due to Professor G. Scheibe for helpful discussions and for his encouragement of this research, and to the Deutsche Forschungsgemeinschaft for financial support.

Synthesis and Structure of a Trimer of 4,5-Dihydropyridazine

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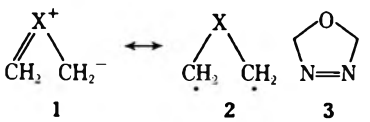
The synthesis and X-ray structure of the trimer of 4,5-dihydropyridazine (11), 4,4a,9,9a,14,14a-hexahydro-3*H*,8*H*,13*H*-tripyridazino[1,6-*a*:1',6'-c:1'',6''-*e*]-*s*-triazine (13), is described.

Dipolar structures or ylides (1) have been assigned to a number of "1,3-diradical" (2) systems. These intermediates have been examined theoretically,[1] observed spectroscopically,[2,3] trapped with dipolarophiles,[4,5] and studied kinetically.[4-6]

We were interested in preparing the oxadiazole ring system, (3), in an attempt to evaluate ylide character



1 2 3

(1, X = O) in the intermediate formed from thermolysis of 3.[7]

Results and Discussion

The most likely entry into the oxadiazole ring system appeared to be through the Diels–Alder addition of furan (4) and an azodicarboxylate (5). This reaction with diethyl azodicarboxylate has been reported, although the adduct 6a was only poorly characterized because of its instability.[8-12] Critical factors in its formation seem to be temperature, stoichiometry, and length of time allowed for formation of adduct. Apparently, once formed, the adduct undergoes additional

(1) E. F. Hayes and A. K. Q. Siu, *J. Amer. Chem. Soc.*, **93**, 2090 (1971).
(2) T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *ibid.*, **92**, 1402 (1970).
(3) D. R. Arnold and L. A. Karnischky, *ibid.*, **92**, 1404 (1970).
(4) R. Huisgen and H. Mäder, *ibid.*, **93**, 1777 (1971).
(5) H. Hermann, R. Huisgen, and H. Mäder, *ibid.*, **93**, 1779 (1971).
(6) R. M. Kellogg, S. Wassenaar, and J. Buter, *Tetrahedron Lett.*, 4689 (1970).
(7) Several examples of the thiadiazole (sulfur analog of 3) ring system are known; *cf.* ref 6; W. J. Middleton, *J. Org. Chem.*, **34**, 3201 (1969); D. H. R. Barton, E. H. Smith, and B. J. Willis, *Chem. Commun.*, 1226 (1970); R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1987 (1970); A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971).
(8) K. Alder and H. Niklas, *Justus Liebigs Ann. Chem.*, **585**, 81 (1954).
(9) P. Baranger and J. Kevisalles, *Bull. Soc. Chim. Fr.*, 704 (1957).
(10) J. G. Kuderna, J. W. Sims, J. F. Wikstrom, and S. B. Soloway, *J. Amer. Chem. Soc.*, **81**, 382 (1959).
(11) K. N. Zelenin and I. P. Bezhan, *Zh. Org. Khim.*, **2**, 1524 (1966).
(12) K. N. Zelenin and I. P. Bezhan, *Dokl. Akad. Nauk SSSR*, **191**, 295 (1970).

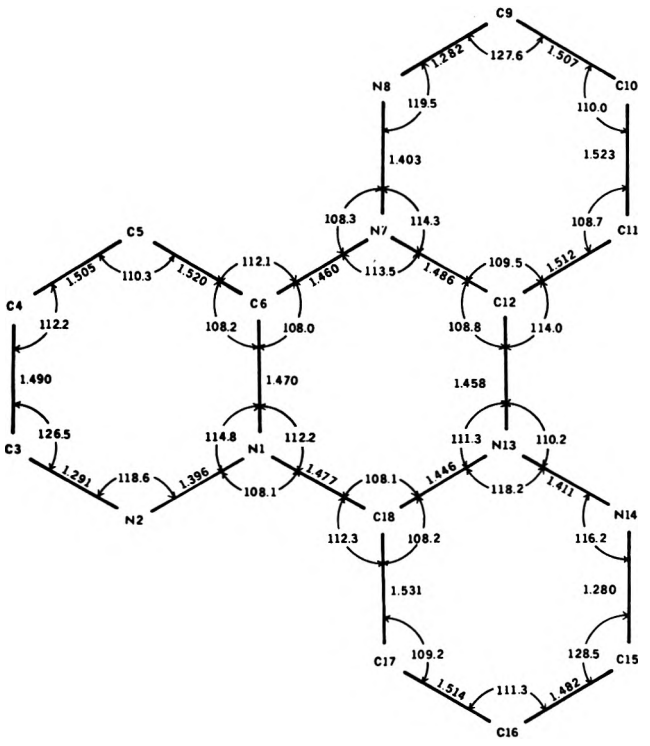
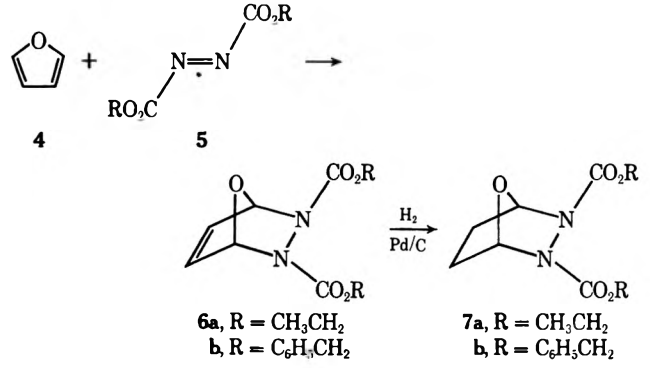
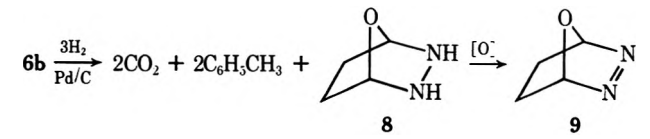


Figure 1.—Structural parameters for 4,4a,9,9a,14,14a-hexahydro-3*H*,8*H*,13*H*-tripyridazino[1,6-*a*:1′,6′-*c*:1″,6″-*e*]-*s*-triazine (**13**). The numbers shown are for crystallographic convenience and do not correspond to those used in the nomenclature.

reactions, giving polymeric products. Short time periods and near equal stoichiometry allowed us to isolate, after reduction, compound **7a** which could be readily characterized. However, hydrolysis of **7a** with



methanolic KOH proceeded rapidly at room temperature to yield considerable highly insoluble polymeric material. Repeated extraction of the product mass followed by chromatography yielded a small amount of material with mp 139.5–140.5° which was assigned the formula $C_{12}H_{18}N_6$ (**13**, *vide infra*) on the basis of its mass spectrum and elemental analysis. It was decided that nonaqueous conditions were necessary for isolation of the hydrazo product **8** which could then be oxidized to the desired oxadiazole derivative **9**. The benzyloxy



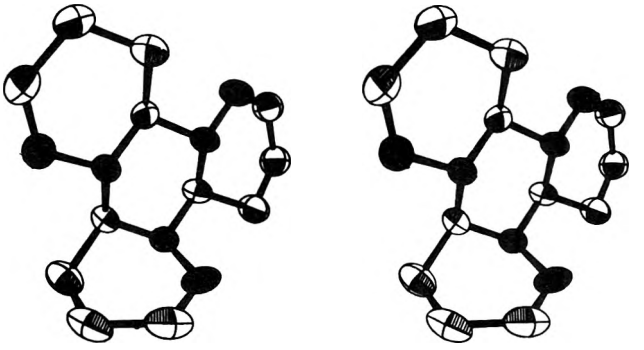
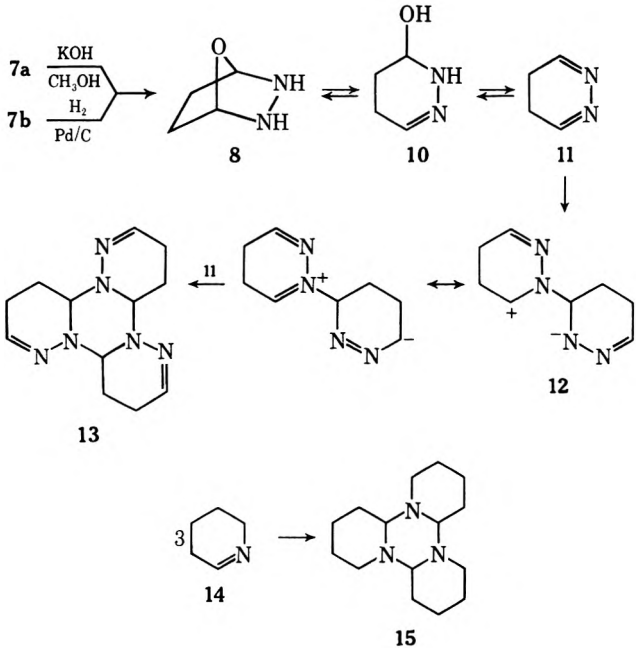


Figure 2.—Perspective view of **13**. The nitrogen atoms are completely shaded.

group, commonly used in peptide syntheses as a protecting group, seemed ideal for this purpose.[13] It was expected that reduction of **6b** would lead directly to **8**. However, it was found that the hydrogenation could be controlled so as to isolate **7b**, while more rigorous conditions gave the same compound isolated from the aqueous hydrolysis of **7a** ($C_{12}H_{18}N_6$). Analysis of spectral data including a 220-MHz nmr was not sufficient to assign a structure. An X-ray structure on a single crystal of the sample identified the compound as 4,4a,-9,9a,14,14a-hexahydro-3*H*,8*H*,13*H*-tripyridazino[1,6-*a*:1′,6′-*c*:1″,6″-*e*]-*s*-triazine (**13**) with the dimensions shown in Figure 1. Figure 2 shows the perspective view.

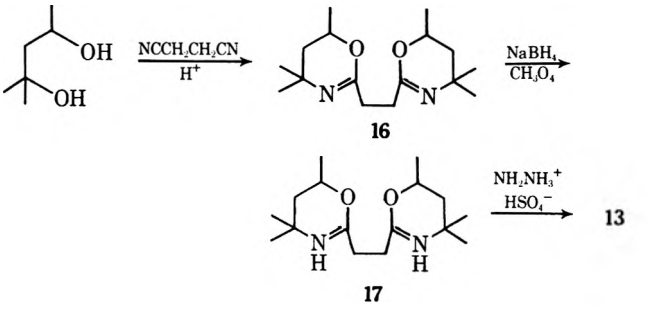
Since both **7a** and **7b** give rise to the same final product, it seems reasonable to assume a common intermediate. This intermediate (**8**) could tautomerize to **10** which, through loss of water, would give 4,5-dihydropyridazine (**11**). The trimerization of **11** can be imagined to involve formation of a "dimer," probably a resonance stabilized 1,4 dipole (**12**), which can add to another molecule of 4,5-dihydropyridazine. There are numerous examples of 1,4-dipolar cycloadditions involving products which resulted from combination of three fragments.[14] A similar trimerization, though



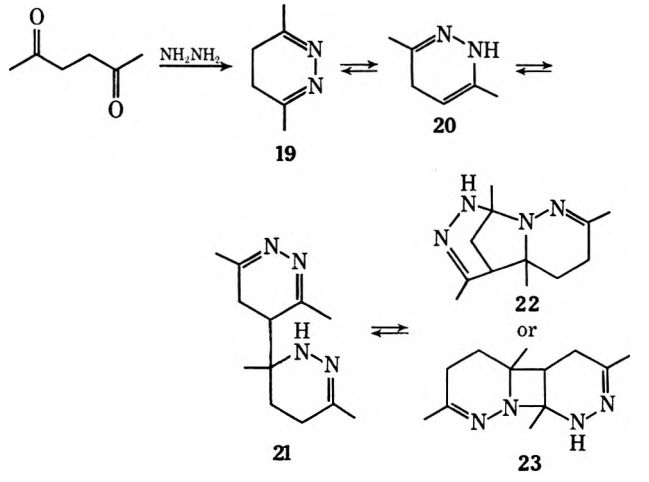
(13) L. F. Fieser and M. Feiser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 109.
(14) R. Huisgen, *Z. Chem.*, **8**, 290 (1968).

possibly not by the same mechanism, has been reported by Schöpf and coworkers[15] (**14** → **15**).

A natural approach in establishing the intermediacy of **11** is the independent synthesis of **11** from succinaldehyde and hydrazine. Because of the lability of succinaldehyde it was decided that good use could be made of the Meyers aldehyde reagent[16-18] which has been shown to be the procedure of choice for preparing a variety of carbonyl derivatives. The bis(oxazine) **16**[17] in reduced from **17**[18] is actually a protected form of succinaldehyde.[16] Treatment of **17** with hydrazine hydrogen sulfate afforded **13** presumably through **11**.



Part of the instability of dihydropyridazines can apparently be alleviated when bulky groups are incorporated into the ring. 3,6-Diphenyl-4,5-dihydropyridazine has been isolated and is reasonably stable.[19] In contrast, acetonylactetone (**18**) and hydrazine give a tricyclic dimer.[20,21] The authors[21] postulate **22** and **23** as possible structures for the dimer, preferring **22** on the basis of ^{13}C nmr data. It is thought to arise by a tautomerization of 3,6-dimethyl-4,5-dihydropyridazine (**19**)



followed by a series of addition reactions. Models of the trimer of 2,6-dimethyl-4,5-dihydropyridazine, with a structure corresponding to that of **13**, illustrate that the compound would be extremely strained as all three methyl groups would have to assume axial positions on the central rings' "chair-like" configuration (see Figure 2). This basically must account for the difference in reactivity between **13** and **19**.

(15) V. C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948).

(16) A. I. Meyers and N. Nazarenko, *J. Amer. Chem. Soc.*, **94**, 3243 (1972), and references listed therein.

(17) A. I. Meyers, *J. Org. Chem.*, **25**, 2231 (1960).

(18) A. I. Meyers, G. R. Malone, and H. W. Adickes, *Tetrahedron Lett.*, 3715 (1970).

(19) F. E. Henoch, K. G. Hampton, and C. R. Hauser, *J. Amer. Chem. Soc.*, **91**, 676 (1969).

(20) C. G. Overberger, N. P. Byrd, and R. B. Mesrobian, *ibid.*, **78**, 1961 (1956).

(21) P. De Mayo, J. B. Stothers, and M. C. Usselman, *Can. J. Chem.*, **50**, 613 (1972).

Experimental Section

Synthesis of Diethyl 7-Oxa-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (6a).—Diethyl azodicarboxylate (10 g) was stirred with furan (20 ml) for 3 hr. The reaction flask was protected from light. After 3 hr furan was removed under reduced pressure to give a colorless viscous liquid. This adduct was found to be unstable toward ethanol, light, acid, base, silica gel, alumina, and high temperature. The nmr of the product consisted of a triplet at 1.35 ppm (6 H, $-CH_2CH_3$), a quartet at 4.30 (4 H, $-CH_2CH_3$), a singlet at 6.50 (2 H), and a singlet at 6.75 ppm (2 H). The carbonyl absorption occurred at 1725 cm^{-1}.

Reduction of Diethyl 7-Oxa-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate.—Diethyl 7-oxa-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**6a**) obtained as above was hydrogenated over 10% Pd/C catalyst using 15 psi of hydrogen and ether as solvent. After 1 hr of shaking with hydrogen, the ethereal solution was filtered and concentrated to give a solid product which was recrystallized from methanol to give 7.5 g of diethyl 7-oxa-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (**7a**), mp 103–104°. The nmr spectrum consisted of a triplet at 1.37 (6 H, $-CH_2CH_2$), a singlet at 2.15 (4 H, $-CH_2CH_2-$), a quartet at 4.20 (4 H, $-CH_2-CH_3$), and a singlet at 6.00 ppm [2 H, $-C(N)H-O$]. *Anal.* Calcd for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.60; N, 11.46. Found: C, 49.20; H, 6.68; N, 11.46.

Synthesis of Dibenzyl 7-Oxa-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (6b).—Dibenzyl azodicarboxylate (5 g) was stirred with furan (20 ml) for 1 hr in a reaction flask protected from light. The excess furan was removed from the adduct under reduced pressure. The nmr consisted of a singlet at 5.25 (4 H, $-CH_2C_6H_5$), a multiplet at 6.65 (4 H, $-CH{=}CH-$, OCHN) and a singlet at 7.38 ppm (10 H, $-C_6H_5$). The carbonyl absorption occurred at 1725 cm^{-1}.

Reduction of Dibenzyl 7-Oxa-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate.—Dibenzyl 7-oxa-2,3-diazabicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylate (**6b**) obtained as above was hydrogenated over 10% Pd/C catalyst using 12 psi of hydrogen and ether as a solvent. After 1 hr the ethereal solution was filtered and concentrated to give 6.7 g of dibenzyl 7-oxa-2,3-diazabicyclo-[2.2.1]heptane-2,3-dicarboxylate (**7b**) as a viscous liquid.

The nmr consisted of a singlet at 1.93 (4 H, $-CH_2CH_3-$), a singlet at 5.14 (4 H, $-CH_2C_6H_5$), a singlet at 6.00 (2 H, $-NCHO$), and a singlet at 7.25 ppm (10 H, $-C_6H_5$). The carbonyl absorption occurred at 1725 cm^{-1}. *Anal.* Calcd for $C_{20}H_{20}O_5N_2$: C, 65.24; H, 5.47; N, 7.60. Found: C, 64.88; H, 5.57; N, 7.64.

Decomposition of Diethyl 7-Oxa-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (7a).—A solution of diethyl 7-oxa-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (**7a**, 6.0 g) in methanol (20 ml) was added to an aqueous methanolic solution of potassium hydroxide (6 g) under a nitrogen atmosphere. The reaction contents were then stirred for 4 hr and poured in 200 ml of water. After adjusting the pH to 7 the mixture was extracted with three 100-ml portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and concentrated to give a yellow solid which was chromatographed on a silica gel column using ether as an eluting solvent. The product so obtained was recrystallized from ether–petroleum ether to give 250 mg of compound **13**, mp 139.5–140.5°.

Hydrogenolysis of Dibenzyl 7-Oxa-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (7b).—A solution of dibenzyl 7-oxa-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (**7b**, 5.0 g) in ether (200 ml) was hydrogenated using 10% Pd/C (1.1 g) and 30 psi of hydrogen pressure for 24 hr. The catalyst was removed by filtration and the solution was concentrated under reduced pressure. The presence of toluene in the mixture of products was confirmed by nmr. Ether, 10 ml, was added to the residue and the insoluble part of the residue was separated by decantation. Removal of the ether gave 500 mg of viscous product which was chromatographed on silica gel column using benzene and then ether as eluting solvents. Compound **13** was recrystallized from ether petroleum ether to give 200 mg of product, mp 139.5–140.5°.

The nmr consisted of a complex multiplet at 1.70–2.70 (12 H, $-CH_2$), a complex multiplet from 3.50 to 3.75 (3 H, $-N-CH-N-$),

and a singlet at 6.82 ppm (3 H, -N=CH-). The ir indicated a prominent bond at 1620 cm^{-1} (-C=N-) and the mass spectrum showed a parent ion at 246. *Anal.* Calcd for $C_{12}H_{18}N_6$: C, 58.49; H, 7.33; N, 34.12. Found: C, 58.34; H, 7.29; N, 33.90.

Synthesis of 4,4a,9,9a,14,14a-Hexahydro-3*H*,8*H*,13*H*-tripyridazino[1,6-*a*:1′,6′-*c*:1″,6″-*e*]-*s*-triazine (13) from 1,2-Bis(tetrahydro-1,3-oxazin-2-yl)ethane (17).—1,2-Bis(tetrahydro-1,3-oxazin-2-yl)ethane[18] (17) was prepared by sodium borohydride reduction of 1,2-bis(dihydro-1,3-oxazin-2-yl)ethane[17] (16). A mixture of crude 17 (4.0 g, 3.5 mmol), hydrazine hydrogen sulfate (2.0 g, 15.9 mmol), and 400 ml of methanol was stirred under nitrogen at room temperature for 24 hr. The methanol was removed and after addition of water, the solution was extracted with several portions of ether. The dried ether extract upon concentrating yielded 300 mg of crude product which was washed with 2 ml of petroleum ether to remove the color. Recrystallization from ether gave 150 mg of pure product, mp 139–140°. The mixture melting point and the mass spectra of this sample and the one prepared from hydrogenation of 7b indicated, that the compounds were identical.

X-Ray Analysis of 13.—A crystal of dimensions 0.17 × 0.22 × 0.11 mm, mounted on a G.E. XRD-5 diffractometer, displayed *mmm* symmetry and axial extinctions for (*h*00) when *h* was odd; (0*k*0) when *k* was odd; (00*l*) when *l* was odd, uniquely identifying the space group as $P2_12_12_1$. Lattice constants were determined from a least-squares refinement of ten carefully measured 2θ values (1° take-off angle and a 0.05° slit) at $2\theta > 74°$ where the Cu $K\alpha_2$ doublet is resolvable. The resultant lattice constants and their estimated standard deviations are $a = 14.641 \pm 0.003$ Å, $b = 16.118 \pm 0.002$ Å, and $c = 5.228 \pm 0.001$ Å.

Data Collection and Refinement

Three dimensional intensity data were collected on a G.E. XRD-490 fully automated diffractometer by the stationary crystal–stationary counter method using balanced nickel and cobalt filters and Cu Kα radiation. A total of 1278 reflections were measured to a 2θ maximum of 130° (d = 0.85 Å), and of these 1017 (80%) were considered statistically acceptable by the criterion

$$[I_{N_i} - 2\sigma(I_{N_i})] - [I_{Co} + 2\sigma(I_{Co})] > 75 \text{ counts}$$

for 10-sec counting times. The data were corrected for α, $-\alpha_2$ splitting[22] as a function of 2θ and for absorption as a function of φ (linear μ = 7.0 cm^{-1} and a ratio of observed transmission factors of 1.38:1.00). Lorentz–polarization corrections were made and the intensities were reduced to structure amplitudes in the usual manner.

(22) A. Tulinsky, C. R. Worthington, and E. Pignatrao, *Acta Crystallogr.*, **12**, 623 (1959).

Normalized structure magnitudes were computed using a $K(s)$ curve[23] and two sets of tangent refinements were generated using $|E|$ greater than 1.3 in each. E maps were generated for each, one of which contained a random set of peaks and the other contained 18 peaks at chemically reasonable distances and angles. So as not to prejudice our approach, initially all atoms were assigned a carbon scattering factor curve.[24] Five cycles of block-diagonal least squares, using $1/\sigma^2$ weights, led to a value of R = 0.12. The assignment of the six nitrogen atoms was easily made at this stage on the basis of temperature factors, electron density peak heights, and such chemical evidence as bond distances and bond angles. With all of the atoms now properly assigned, additional cycles of isotropic least squares, conversion to anisotropic temperature factors, and further anisotropic refinement lowered the value of the reliability index to R = 0.11.

The 18 hydrogen atoms were readily located for a difference electron density map phased by the nonhydrogens. The absence of any peaks of height greater than 0.2 e/Å^3 about the six peaks earlier presumed to be nitrogens corroborates that assignment. Least-squares refinement was continued varying the coordinates of all atoms with the nonhydrogens having varying anisotropic temperature factors and the hydrogens having fixed isotropic temperature factors of 5.0 Å^2. The refinement converged at a value of R = 0.046 with all shifts less than one-tenth the estimated standard deviation of the respective parameter.[25]

Registry No.—**4**, 110-00-9; **5a**, 1972-28-7; **5b**, 2449-05-0; **6a**, 13925-26-3; **6b**, 37819-02-6; **7a**, 37819-03-7; **7b**, 37819-04-8; **13**, 37819-05-9; **16**, 37819-06-0; **17**, 37819-07-1.

Acknowledgment.—We appreciate substantive discussions with Professor A. I. Meyers regarding the oxazine ring system.

(23) J. Karle, H. Hauptman, and C. L. Christ, *ibid.*, **11**, 757 (1958).

(24) Scattering factors for nitrogen and carbon were taken from D. Cromer and J. Waber, *ibid.*, **18**, 104 (1965), whereas scattering factors for hydrogen were taken from "International Tables for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1968.

(25) Listings of structure factors, coordinates, and anisotropic temperature factors 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, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-1102. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Nonbenzenoid Aromatic Systems. VIII.[1a] Buffered Acetolysis of 2-(4- and 2-(6-Azulyl)ethyl Arenesulfonates and 3-(4-Azulyl)-1-propyl Nosylate. Examples of Ar_3-5 and Ar_3-6 Mechanisms

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Received December 1, 1972

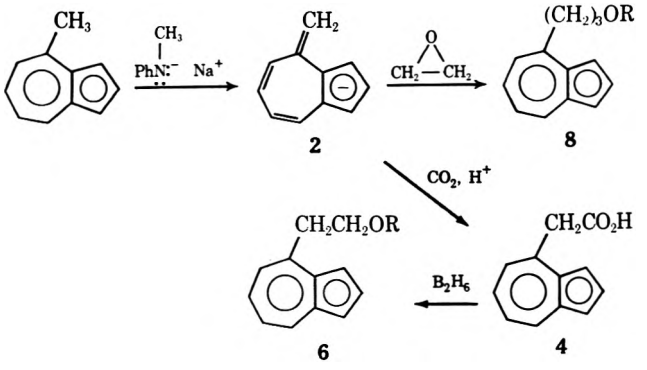
2-(4- (6) and 2-(6-Azulyl)ethyl (7) tosylates and nosylates were synthesized and subjected to buffered acetolyses. The k_{RONs}/k_{ROTs} ratio for these two systems was found to be 2.1–3.3 compared to 10–13.5 found for this ratio for 2-phenylethyl, 2-(*p*-anisyl)ethyl, and ethyl tosylates and nosylates. The reduced value for this ratio for the derivatives of 6 and 7 was caused by elimination to the corresponding vinylazulenes competing with solvolysis, $k_t = k_{solv} + k_{elim}$. Deuterium labeling in the 7-α,α-d_2-OTs after one solvolytic half-life showed no methylene scrambling in recovered 7-d_2-OTs or 7-d_2-OAc, whereas 7-α,α-d_2-ONs gave about 10% methylene scramble in both the nosylate and acetate. 6-α,α-d_2-ONs gave 0% label scramble under the same conditions. Azulene ring C_3 participation is argued for to explain this latter result for 6-ONs buffered acetolysis to form the tricyclic Ar_3-5 intermediate (15). To substantiate this proposal of producing 15, the buffered acetolysis of 2-(4-azulyl)propyl nosylate (8-ONs) was found to yield 4,5-dihydro-3*H*-benz[*cd*]azulene (18, 72%) and 8-OAc (27%). The kinetic data and activation parameters for these systems are discussed.

One of several interesting features in the use of the nonbenzenoid, nonalternate aromatic azulene nucleus in studying reactions potentially involving neighboring aromatic group participation is that the azulene ring has five structurally and chemically nonequivalent sites for attachment of the side chain containing the reaction center. We recently demonstrated that the 1-azulyl substituent in the buffered acetolysis of 2-(1-azulyl)ethyl OTs (1) is a *super power* in β-aryl participation in 2-arylethyl arenesulfonate solvolyses with exclusive reaction *via* the k_Δ pathway (the ionization step was rate determining) without the complicating factor of ion-pair return.[2,3]

The 1 and 3 positions of azulene are the sites of largest π-electron density[4] and have the smallest cation localization energy[4a] in the ground state. They are unique ring positions in that when bonded to an electrophile the intermediate is another "aromatic" system, the azulenium ion (a substituted vinyltropylium ion).[4a,5]

We now wish to report the results of buffered acetolyses of primary ω-azulylalkyl arenesulfonates with the alkyl side chain attached to the π-electron-poor azulene 4 and 6 positions.[4]

Substrate Syntheses.—The preparation of the ω-azulylalkanols took advantage of the relative acidities of the methyl group C–H bonds when attached to the azulene 4 and 6 positions.[6] Proton abstraction from 4- and 6-methylazulene with sodium *N*-methylanilide gave sodium 4- (2) and 6-methyleneazulenate (3),[6,7] respectively, which when carbonated produced 4- (4) and 6-azulylacetic acid (5), respectively.[6a] Reduction with diborane yielded the corresponding ethanols, 6-OH and 7-OH; deuteriodiborane reduction of 4 and 5 produced the α,α-dideuterioethanols, 6-OH-α,α-d_2 and 7-OH-α,α-d_2. 3-(4-Azulyl)-1-propanol (8-OH) was synthesized by allowing 2 to react with ethylene oxide.



The tosylate esters were prepared by the ether–powdered potassium hydroxide method.[8] The nosylate esters were prepared by allowing the alcohol to react with methyllithium in ether, producing the alkoxide, which was treated with *p*-nitrobenzenesulfonyl chloride.

Discussion of Kinetic and Product Results from 6 and 7 Arenesulfonates.—Potassium acetate buffered acetic acid (20% excess buffer) was the solvolytic medium used in these studies. The presence of the buffer is sessential owing to the basicity of azulene to strong acid producing azulenium ions. Potassium acetate has been shown to exert a special salt effect in the acetolysis of 2-(*p*-anisyl)ethyl OTs which may also be present in the buffered acetolysis of 1.[2] The kinetic buffered acetolysis data for arenesulfonates of 6-OH and 7-OH and their activation parameters are listed in Table I.

The initial studies involved the tosylates 6-OTs and 7-OTs to allow a direct comparison with 1. The rate constants for 6-OTs and 7-OTs were very similar and about 10^4 smaller than that of 1 at 110°. On the other hand, they were of the same order of magnitude

(1) (a) For paper VII see R. N. McDonald and H. E. Petty, *J. Org. Chem.*, **37**, 2957 (1972). (b) Phillips Petroleum Co. Fellowship, 1968–1969.

(2) R. N. McDonald and J. R. Curtis, *J. Amer. Chem. Soc.*, **93**, 2530 (1971).

(3) For a review on phenonium ions see C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer in "Carbonium Ions," Vol. 3, P. v. R. Schleyer and G. A. Olah, Ed., Interscience, New York, N. Y., 1972.

(4) For example see results of MO calculations in (a) E. Heilbronner in "Non-Benzenoid Aromatic Compounds," D. Ginsberg, Ed., Interscience, New York, N. Y., 1959; (b) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 456–457.

(5) 1-Azuloic acid has been shown to be a considerably weaker acid than benzoic acid, $\Delta pK_a = 1.2$: R. N. McDonald and R. R. Reitz, *J. Org. Chem.*, **37**, 2703 (1972).

(6) (a) K. Hafner, H. Pelster, and H. Patzett, *Justus Liebigs Ann. Chem.*, **650**, 80 (1961); (b) M. Scholz, L. Vien, G. Fischer, B. Tschapke, and M. Muhlstadt, *Chem. Ber.*, **100**, 375 (1967).

(7) The term azulenate refers to the general structure of the anion in the salts produced by such α-proton abstractions from 4- and 6-alkylazulenes[6a] and by nucleophilic additions to the azulene ring 4 and 6 positions.

(8) K. B. Wiberg and A. J. Ashe, *J. Amer. Chem. Soc.*, **90**, 63 (1968).

TABLE I

BUFFERED ACETOLYSIS KINETIC DATA FOR 2-(4- AND 2-(6-AZULYL)ETHYL TOSYLATES AND NOSYLATES

Compd	Temp, °C	10^5k,[a] sec^{-1}	Av 10^5k, sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu	k_{RONs}/k_{ROTs} (120°)
6-OTs[b]	140.0	22.5 ± 0.3	22.2			
		22.0 ± 0.5				
	120.0	5.60 ± 0.3	5.61	21.4 ± 0.5	−24.7 ± 1.0	
		5.62 ± 0.12				
6-ONs[b]	130.0	25.7 ± 0.8	26.0			
		26.3 ± 0.2				
	110.0	5.20 ± 0.01	5.18	24.0 ± 0.4	−16.1 ± 0.6	
		5.17 ± 0.06				
	120.0		(11.8)[c]			2.1
7-OTs[b]	140.0	25.4 ± 1.0	24.9			
		24.3 ± 0.5				
	120.0	5.67 ± 0.2	5.63	23.2 ± 0.5	−19.6 ± 1.3	
		5.58 ± 0.08				
7-ONs[b]	130.0	40.2 ± 0.2	40.0			
		39.8 ± 2.0				
	110.0	8.2 ± 0.4	8.3	23.4 ± 0.1	−16.5 ± 0.3	
		8.3 ± 0.4				
	120.0		(18.6)[c]			3.3

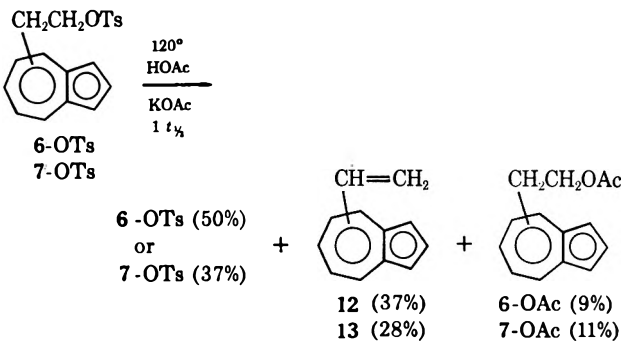
[a] Rate constants with standard deviations based on experimental infinity titers; using theoretical infinity titers, rate constants for derivatives of **6** and **7** increase by ~10%. [b] Sealed ampoule method, potentiometric titrations; 0.005 *M* ROX, 0.006 *M* KOAc. [c] Extrapolated.

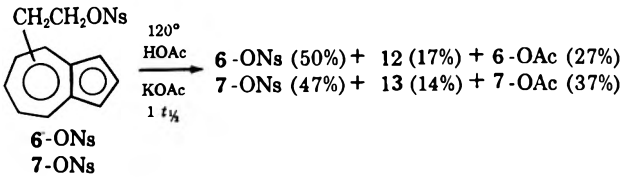
as the rate constant for unbuffered acetolysis of 2-phenylethyl OTs at 115° ($k_t = 1.27 \times 10^{-5}$ sec^{-1}).[9]

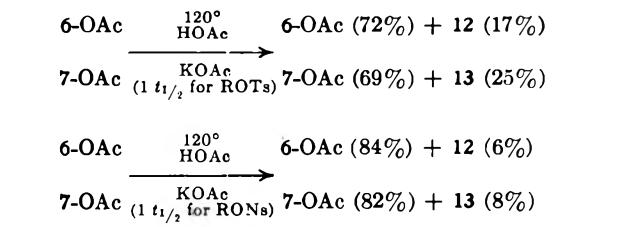
The relatively high temperatures required for reasonable rate measurements for **6**-OTs and **7**-OTs presented a special problem with these substrates and their products. After about one solvolytic half-life, ampoules of samples of each tosylate began to change color and after several half-lives a green (from **6**-OTs) or brown (from **7**-OTs) insoluble material formed a coating on the ampoule wall. Since *p*-nitrobenzenesulfonate (nosylate = Ns) esters contain a better leaving group, $^-$ONs, than tosylate esters, it was decided to change to the nosylate derivatives with the hope of significant temperature reduction required for their buffered acetolyses.

To acquaint ourselves with the preparation, handling, and solvolytic behavior of nosylate esters, we synthesized and subjected to buffered acetolyses 2-phenylethyl (**9**-ONs), 2-(*p*-anisyl)ethyl (**10**-ONs), and ethyl nosylate (**11**-ONs) along with the corresponding tosylate esters. The rate data and activation parameters for these three systems are listed in Table II. One point of immediate interest from the data in Table II is the reasonably constant value of k_{RONs}/k_{ROTs} = 10–13.5 for both nonparticipating and aryl participating buffered acetolyses. (The ratio for **10** may be somewhat high owing to the increased special salt effect in **10**-ONs with increased concentrations.) These ratios are in marked contrast to the k_{RONs}/k_{ROTs} = 2–3 found for the arenesulfonates of **6** and **7**.

To understand the reason for this reduced nosylate/tosylate rate ratio, we must examine the products derived from **6** and **7**. After one solvolytic half-life, the major products from **6**-OTs and **7**-OTs were 4-vinylazulene (**12**) and 6-vinylazulene (**13**), respectively, the product of elimination. The low recovery of **7**-OTs has been duplicated and is not understood, since the infinity titer is ~91% of theoretical and no deviation from linearity of the rate *vs.* time is observed. The nosylates, **6**-ONs and **7**-ONs, also underwent elimination to **12** and **13**, respectively, but to a smaller extent. A complicating feature of this reaction is that the acetates, **6**-OAc and **7**-OAc, also undergo elimination to **12** and **13**, respectively, under the buffered acetolysis conditions.







We can see from the results of these product studies that elimination to the vinylazulenes **12** and **13** is the major reaction pathway from the tosylate esters. With the nosylate esters, solvolysis to the corresponding acetates becomes competitive with elimination. The probable reason why elimination is so prevalent

(9) J. L. Coke, F. E. McFarlane, M. C. Mourning, and M. G. Jones, *J. Amer. Chem. Soc.*, **91**, 1154 (1969).

Table II

Buffered Acetolysis Data for 2-Phenylethyl, 2-(*p*-Anisyl)ethyl, and Ethyl Tosylates and Nosylates

Compd	Temp, °C	10^4k,[a] sec^{-1}	Avg 10^4k, sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu	k_{RONs}/k_{ROTs}
9-OTs[c]	130.0	4.93 ± 0.21	5.03			
		5.13 ± 0.08				
	110.0	0.980 ± 0.008	0.988	24.2 ± 0.2	−18.8 ± 0.4	
		0.995 ± 0.004				
9-ONs[c]	110.0	11.4 ± 0.1	11.3			11.4
		11.1 ± 0.1				
	90.0	1.85 ± 0.02	1.85	24.3 ± 0.2	−13.6 ± 0.4	
		1.85 ± 0.01				
10-OTs[b]	95.0	13.6 ± 0.3	14.1			
		14.6 ± 0.6				
	75.0	1.99 ± 0.04	2.01	24.1 ± 0.5	−11.2 ± 1.3	
		2.03 ± 0.05				
10-ONs[c]	75.0	27.0 ± 0.3	27.1			13.5
		27.1 ± 0.2				
	55.0	3.17 ± 0.04	3.18	23.6 ± 0.1	−7.3 ± 0.2	
		3.18 ± 0.02				
11-OTs[b]	140.0	22.1 ± 0.5	21.9			
		21.6 ± 0.4				
	120.0	4.82 ± 0.04	4.78	23.7 ± 0.3	−18.5 ± 0.7	
		4.73 ± 0.05				
11-ONs[b]	120.0	47.5 ± 0.2	46.8			9.8
		46.0 ± 0.3				
	100.0	9.59 ± 0.05	9.57	22.4 ± 0.3	−17.4 ± 0.8	
		9.55 ± 0.07				

[a] Rate constants with standard deviations based on experimental infinity titers. [b] Sealed ampoule technique, potentiometric titrations; 0.005 *M* ROX, 0.006 *M* KOAc. [c] As per *b* but 0.010 *M* ROX, 0.012 *M* KOAc.

with derivatives of **6** and **7** is the increased acidity of β-CH bonds of the ethyl side chains compared to other 2-arylethyl derivatives.[6]

While insufficient data are available to completely analyze the component process, k_{solv} and k_{elim}, in the buffered acetolyses of **6** and **7** arenesulfonates, it should be noted that the rate data from which the rate constants listed in Table I are derived show good linearity throughout the two half-lives followed from either plots of the data or examination of the calculated instantaneous first-order rate constants in the computer output. If we make three simplifying assumptions, (1) both k_{solv} and k_{elim} are first-order or pseudo-first-order reactions,[10] (2) **6**-OAc is stable to the reaction conditions except toward elimination to **12**, and (3) the amount of k_{solv} is represented by the quantity of **6**-OAc isolated after one half-life, we can estimate k_{solv} in these reactions. Since about 21% of the product from **6**-OTs is **6**-OAc formed by k_{solv}, this percentage of the k_t for **6**-OTs would be $\sim 1 \times 10^{-5}$ sec^{-1} at 120°, which is essentially the value expected for the solvent-assisted (k_s) process for **9**-OTs under these conditions.[11] This approach applied to k_t for **6**-ONs gives k_{solv} $\sim 7 \times 10^{-5}$ sec^{-1} at 120° and a k_{RONs}/k_{ROTs} of 7 for **6**, in reasonable agreement with those ratios listed in Table II. Similar analyses of the k_t's of the arenesulfonates of **7** lead to k_{solv} $\sim 1 \times 10^{-5}$ sec^{-1} (120°) for **7**-OTs and $\sim 1 \times 10^{-4}$ sec^{-1} (120°) for **7**-ONs; however, these estimates for **7** are further clouded by the low recovery of especially **7**-OTs for unknown reasons. Assuming that the above analysis is reasonable, it would appear that the major influence of the change in leaving group in going from **6**-OTs to **6**-ONs is felt in k_{solv} rather than k_{elim}.[12a]

In the activation parameters for tosylates and nosylates of **9**-OH, **10**-OH, and **11**-OH listed in Table II, while the $\Delta H^{\pm}$'s are reasonably constant, the $\Delta S^{\pm}$'s show what appears to be a trend toward more positive values for the two substrates which have been shown to involve at least partial β-aryl participation in their acetolyses.[9,11,12b] This same trend is seen with the derivatives of **7** and most particularly with the arenesulfonates of **6**, with the latter substrates showing an increase in $\Delta H^{\pm}$ also. However, since elimination to the vinylazulenes is a major pathway from the tosylates and remains important in the nosylates, it is impossible at present to ascertain the meaning of these changes in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ in the azulene substrates.[12b]

To determine if the azulene 4 and 6 positions were participating by the Ar_1-3 (k_Δ) pathway in the acetolyses of the arenesulfonates of **6** and **7**, respectively, the corresponding α,α-dideuterium derivatives were prepared and acetolyzed in the buffered acetic acid. The data are listed in Table III. As predicted from the analysis of the magnitude of k_{solv}, **7**-OTs contains only a negligible amount of the Ar_1-3 pathway after one solvolytic half-life. However, **7**-α,α-d_2-ONs showed about 10% scramble, which is strikingly similar to labeling results obtained in buffered acetolysis of **9**-OTs,[9] indicating the probable presence of Ar_1-3 participation by the azulene ring 6 position.[13] Considering the similar

(10) It would appear that this is a gross oversimplification in the case of k_{elim}.

(11) J. M. Harris, F. L. Schadt, P. v. R. Schleyer, and C. J. Lancelot, *J. Amer. Chem. Soc.*, **91**, 7508 (1969), list $k_s = 7.3 \times 10^{-6}$ sec^{-1} for **9**-OTs in unbuffered acetic acid at 115°, and have shown k_s to be reasonably independent of ring substituents.

(12) (a) A. K. Colter and R. D. Johnson, *ibid.*, **84**, 3289 (1962), reported k_{RONs}/k_{ROTs} = 20 for the second-order rate constants in the reaction of 2-pentyl arenesulfonates with sodium ethoxide in ethanol at 50°. (b) No attempt to build an argument for or against aryl participation based on such small absolute changes in these $\Delta S^{\pm}$'s is implied, since these calculated values are subject to several possible errors.

(13) The percentages of methylene scrambling in recovered **7**-d_2-ONs and product **7**-d_2-OAc show that ion-pair return from the ethylene-6-nzulenium nosylate ion pair is important with $F \approx 0.3$–0.4 (120°). For unbuffered acetolysis of **9**-OTs, F = 0.37 (115°) was reported.[9]

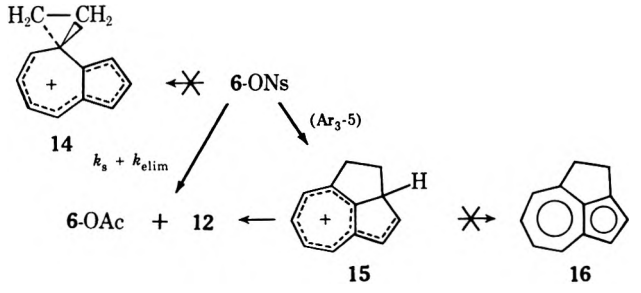
TABLE III
DEUTERIUM LABELING RESULTS FROM ARENESULFONATES AT 120° AFTER APPROXIMATELY ONE BUFFERED ACETOLYSIS HALF-LIFE[a]

Starting compd	% Scrambling[b,c] in ROAc	% Scrambling[b,c] in ROTs or RONs
7-α,α-d_2-OTs	1	>1
7-α,α-d_2-ONs	10	12
6-α,α-d_2-ONs	0	0

[a] Buffered acetic acid containing 20% molar excess KOAc. [b] Per cent scrambling determined by nmr integration of α- and β-methylenes *vs.* an internal standard and having a maximum of 50% ignoring any kinetic isotope effects. [c] Values considered to have error of ±1–2%.[13]

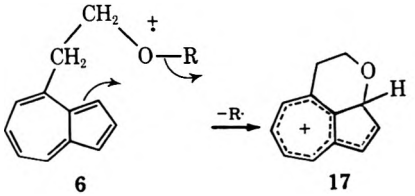
reactivities of the derivatives of **6** and **7**, we were surprised to find that 6-α,α-d_2-ONs showed no evidence of scrambling the α- and β-methylene groups by Ar_1-3 participation (**14**).

The total accumulated data, however, are consistent with at least partial ring participation for the buffered acetolysis of **6**-ONs. We suggest that this participation is of the Ar_3-5 type at the electron-rich ring C_3 position leading to tricyclic cation **15**. Reaction of **15** with the solvent must then occur at C_α of the former ethyl side chain to rearomatize with relief of strain to yield **6**-OAc rather than by proton abstraction to give **16**. It is also possible that proton abstraction



from C_β of the former ethyl side chain could occur to produce **12**. The potential presence of this latter pathway to **12** (presumably of the E1 type) would have the effect of increasing k_{solv} and reducing k_{elim} for **6**-ONs; a similar effect also cannot be ruled out for **6**-OTs.

The formation of tricyclic cation **15** had been proposed to explain the relative abundances of γ cleavage of $M\cdot^+ - TsO\cdot$, $M\cdot^+ - AcO\cdot$, and $M\cdot^+ - HO\cdot$ in the mass spectral fragmentations of **6**-OTs, **6**-OAc- and **6**-OH relative to the corresponding derivatives of **1**-OH and **7**-OH.[14] Of even greater significance was the $M\cdot^+ - Ts\cdot$, $M\cdot^+ - Ac\cdot$, and $Ac\cdot$, and, to a lesser extent, $M\cdot^+ - H\cdot$ fragmentations for the respective derivatives of **6**. These latter three fragmentation processes were characterized as being accompanied by bond formation with the ring C_3 position yielding tricyclic cation **17** and predicted ring C_3 participation



(14) R. G. Cooks, N. L. Wolfe, J. R. Curtis, H. E. Petty, and R. N. McDonald, *J. Org. Chem.*, **35**, 4048 (1970).

in the solvolysis of derivatives of 3-(4-azulyl)-1-propanol (**8**-OH).[14]

Buffered Acetolysis of 3-(4-Azulyl)-1-propyl Nosylate (8-ONs).—To substantiate the proposed intermediacy of **15** in the buffered acetolysis of **6**-ONs and the predictions from the mass spectral fragmentation data given above, we have examined the buffered acetolysis of **8**-ONs; the rate data are listed in Table IV.[15]

TABLE IV
BUFFERED ACETOLYSIS KINETIC DATA FOR 3-(4-AZULYL)-1-PROPYL NOSYLATE (8-ONs)

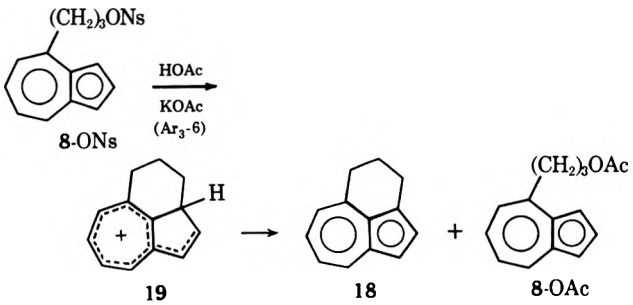
Temp, °C	10^5k,[a,b] sec^{-1}	Av 10^5k, sec^{-1}	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
120.0	127 ± 1 124 ± 6	126		
100.0	16.9 ± 0.7 17.3 ± 0.3	17.1	28.5 ± 0.5	−1.0 ± 1.3

[a] Rate constants with standard deviations based on experimental infinity points. [b] Conductometric method;[15] 0.0010 *M* ROX, 0.0012 *M* KOAc.

Compared to k_{solv} for **6**-ONs, **8**-ONs is characterized by an increase in rate by a factor of about 11 at 120°. The large, positive changes in both $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the buffered acetolysis of **8**-ONs compared to those for the tosylate and nosylate derivatives of **6**-OH, **7**-OH, **9**-OH, **10**-OH, and **11**-OH strongly indicate ring participation in the ionization of **8**-ONs.

The products from **8**-ONs isolated after 10 buffered acetolysis half-lives at 120° were 4,5-dihydro-3*H*-benz[*cd*]azulene (**18**) (51%), **8**-OAc (25%), and trace quantities of acylation products of **18** and **8**-OAc. Acetate **8**-OAc was shown *not* to arise from **18** under the acetolysis conditions; however, **18** was labile to the 10 $t_{1/2}$ acetolysis conditions at 120° with only 67% recovery. This corrects the yield of **18** produced from **8**-ONs to about 72%.[16] The isolation of **18** confirms participation by ring C_3 in the ionization of **8**-ONs.

Acetate **8**-OAc was also shown to be somewhat unstable to the acetolysis conditions at 120° with 91% recovery after 10 solvolytic half-lives. Using the previously mentioned approximations,[16] the amount of **8**-OAc produced from **8**-ONs was 27%. From the magnitude of $\Delta S^\ddagger$ (−1.0 ± 1.3), the formation of the entire amount of **8**-OAc by a k_s pathway seems unlikely. We suggest that both **18** and **8**-OAc are produced from **19** by proton abstraction and attack at C_1 of the former propyl side chain, respectively, by the solvent. This proposal is similar to the one sug-



(15) R. N. McDonald and G. E. Davis, *ibid.*, **38**, 138 (1973).

(16) The stability check of **18** is, of course, based on a full 10 solvolytic half-lives, while, from the acetolysis of **8**-ONs, a sizable concentration of **18** will only be present after ~1 solvolytic half-life. Assuming a linear rate of destruction of **18** with time and using 9 solvolytic half-lives as the basis for calculation, the amount of **18** produced in the buffered acetolysis of **8**-ONs was 72%.

gested for the destruction of intermediate **15** except that in the present case the tricyclic hydrocarbon **18** is more favorable in the product-forming reactions from the intermediate.[17]

Although a synthesis of **18** had been reported,[18] we felt that it was crucial to the present study to fully characterize the compound. The nmr spectrum of **18** [(CCl_4, internal TMS): τ 1.8–3.3 (azulyl H's, 6), 6.85 (t center, 4), and 7.87 (quintet center, 2)], while consistent with the tricyclic structure, was interesting in that both methylenes attached to the ring exhibited the same chemical shifts.[19] The visible λ_{max} for **18** and certain dimethylazulenes are listed in Table V and

TABLE V
VISIBLE λ_{max} OF CERTAIN ALKYL-SUBSTITUTED AZULENES

Compd	λ_{max}, nm
Azulene	580[a]
4,5-$(CH_3)_2$Az	578[a]
4,7-$(CH_3)_2$Az	579[a]
1,4-$(CH_3)_2$Az	595[a]
1,8-$(CH_3)_2$Az	599[a]
18	592

[a] Reference 4a.

establish that **18** is 1,8 disubstituted rather than 4,5 disubstituted.

Experimental Section[20]

1,4-Dimethylpyridinium Iodide.—To a solution of 93.0 g (1.00 mol) of 4-picoline in 500 ml of absolute ethanol was added 141.0 g (1.00 mol) of methyl iodide over a 15-min period. After stirring for 1 hr at room temperature and 1 hr heating under reflux, cooling the mixture gave 212 g (90%) of white needles of the product, which were filtered and washed with ether, mp 153.0–153.5° (lit.[21] mp 157–158°). The hygroscopic needles were stored in a desiccator until used.

6-Methylazulene.—This compound was prepared following the procedure similar to that given for the synthesis of 5,6-dimethylazulene.[22] To 100 ml of absolute ethanol[23] was added 5.1 g (0.22 g-atom) of sodium. After reaction and dissolution, the solution was cooled to ice-bath temperature and maintained under a nitrogen atmosphere while 14.5 g (0.22 mol) of freshly distilled cyclopentadiene was added. After 0.5 hr of stirring, 15.8 g (67.4 mmol) of 1,4-dimethylpyridinium iodide was added through Gooch tubing. The mixture was stirred for 1 hr at ice-bath temperature and 3.5 hr at room temperature. Heating to 60° resulted in formation of a hard, black mass which prevented adequate stirring. Distilled diethylene glycol (200 ml) was added and the product was removed by steam distillation with superheated steam (steam temperature, 300–325°; flask temperature, 130–140°, maintained by a heating mantle); steam distillation was continued until no further blue color appeared in the Eastman condensers with approximately 4 l. of distillate collected. The distillate was diluted with an equal volume of water and extracted with petroleum ether (bp 30–60°). The organic layer was washed with 200 ml of water, 200 ml of 10% hydrochloric acid, and two 200-ml portions of water. After drying ($MgSO_4$), concentration to about 25 ml volume, and standing overnight in a freezer, 1.30 (14%) of 6-methylazulene was obtained by filtration: mp 81.0–81.8° (lit.[24] mp 80°); nmr (CCl_4, internal TMS) τ 1.94 [d (J = 10.5 Hz), 2], 2.33 [t (J = 3.5 Hz), C_2 H, 1], 2.81 [d (J = 3.5 Hz), C_1 and C_3 H's, 2], 3.08 [d (J = 10.5 Hz), 2], and 7.60 (s, CH_3, 3).

A variety of modifications of the above method failed to improve the yield of 6-methylazulene; in fact, most attempts led to lower yields of product.

4-Methylazulene.—This hydrocarbon was prepared by the reported procedure of adding methyllithium to azulene (in tetrahydrofuran) followed by dehydrogenation of the dihydro product with chloranil[25] in 82% yield as a blue oil, nmr (CCl_4, internal TMS) τ 1.7–3.3 (m, ring H's, 7) and 7.10 (s, CH_3, 3).

4-Azulylacetic Acid (4).—To 1.06 g (7.5 mmol) of 4-methylazulene in 50 ml of dry ether under a dry nitrogen atmosphere was added 11.2 ml (7.5 mmol) of 0.66 M sodium N-methylanilide in ether[6a] at −15°. On standing, a golden precipitate was formed. Dry CO_2 was bubbled into the mixture and the color changed immediately to blue; CO_2 addition was continued for 20 min. Addition of water followed by extraction with ether gave 103 mg (10%) of recovered 4-methylazulene.

Acidification of the basic, aqueous layer followed by ether extraction gave 0.93 g (67%) of **4** after solvent evaporation, which was recrystallized from ether–petroleum ether to give blue crystals: mp 123–125° dec; ir (KBr) 5.9 μ (C=O); nmr (DMSO-d_6, internal TMS) τ −2 to 0 (broad s, OH, 1), 1.2–3.0 (m, Az H's, 7), and 5.74 (s, CH_2, 2); visible–uv (CH_2Cl_2) 677 nm (log ϵ 2.08), 617 (2.52), 575 (2.60), 356 (3.14), 343 (3.68), 329 (3.54), 286 (4.67), and 280 (4.68); mass spectrum (70 eV, direct) m/e (rel intensity) 186 (100) and 142 (19).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.15; H, 5.33.

Methyl 4-Azulyacetate.—Ethereal diazomethane was used to convert 50 mg (0.27 mmol) of 4-azulylacetic acid to its ester. Chromatography on basic alumina (CH_2Cl_2 eluent) gave 53 mg (98%) of the desired ester as a blue oil: ir (neat) 5.71 μ (C=O); nmr (CCl_4, internal TMS) τ 1.7–3.7 (m, Az H's, 7), 5.97 (s, CH_2, 2), and 6.43 (s, CH_3, 3); visible–uv (cyclohexane) 688 nm (OD 0.206), 650 (sh), 626 (0.529), 597 (0.592), 576 (0.598), 555 (sh), 356 (0.023), 344 (0.058), 302 (0.062), 286 (0.571), 280 (0.578), and 276 (sh); mass spectrum (70 eV, direct) m/e (rel intensity) 200 (100) and 141 (41).

This oil was converted to its 1,3,5-trinitrobenzene complex, which after recrystallization from ethyl acetate–petroleum ether gave brown needles, mp 134–135°.

Anal. Calcd for $C_{19}H_{15}N_3O_8$: C, 55.21; H, 3.66. Found: C, 55.27; H, 3.83.

4-Azulyethanol (6-OH).—To 145 mg (0.78 mmol) of acid **4** and 228 mg (6.0 mmol) of sodium borohydride in 25 ml of dry tetrahydrofuran was added dropwise 3 ml of boron trifluoride etherate dissolved in 20 ml of tetrahydrofuran and stirring was continued for an additional 45 min. This procedure and work-up was similar to that reported for the synthesis of 2-(1-azulyl)ethanol.[26] Chromatography of the product on basic alumina (CH_2Cl_2 eluent) gave 121 mg (92%) of **6-OH** initially as a blue oil which crystallized from carbon tetrachloride–petroluem ether: mp 58–59°; nmr (CCl_4, internal TMS) τ 1.6–3.3 (m, Az H's, 7), 6.18 [t (J = 7 Hz), α-CH_2, 2], 6.73 [t (J = 7 Hz), β-CH_2, 2], and 7.67 (s, OH, 1); visible–uv (CCl_4) 667 nm (log ϵ 2.14), 615 (2.55), 588 (2.59), 569 (2.61), 356 (3.50), 344 (3.79), 331 (3.69), and 281 (4.62); mass spectrum (70 eV, direct) m/e (rel intensity) 172 (100) and 143 (51).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.50; H, 6.90.

2-(4-Azulyl)ethyl Acetate (6-OAc).—A solution of 236 mg (1.37 mmol) of **6-OH** and 3 ml of acetic anhydride in 20 ml of dry pyridine was stirred at 0° for 12 hr. The cold solution was dissolved in 100 ml of methylene chloride, which was washed with two 20-ml portions of cold 10% hydrochloric acid and three 25-ml portions of cold water and dried ($MgSO_4$). Solvent evaporation and chromatography of the residue on basic, activity III–IV

(17) It is possible that hydrocarbon **16** was produced in the buffered acetolysis of **6-ONs** (possibly also from **6-OTs**) but decomposed during the product study.

(18) W. Triebs and H. Froitzheim, *Justus Liebigs Ann. Chem.*, **564**, 43 (1949).

(19) The methyl group resonances for 1-, 4-, 5-, and 6-methylazulene appear at τ 7.35, 7.10, 7.48, and 7.60, respectively, in carbon tetrachloride.

(20) All melting points were taken on a Kofler hot stage. Infrared, uv–visible, nmr, and mass spectra were recorded using P-E 137, Cary 11, Varian A-60 or T-60, and AEI MS-9 instruments, respectively. The alumina used was Alcoa F-20 basic alumina presumed to be activity I from the can. Microanalyses were determined by Galbraith Laboratories, Inc., or by M. M. Kim in this department using a Hewlett-Packard Model 185 C, H, N analyzer.

(21) E. D. Bergmann, F. E. Crane, and R. M. Fuoss, *J. Amer. Chem. Soc.*, **74**, 5979 (1952).

(22) C. W. Muth, M. L. DeMatte, A. R. Urbanik, and W. G. Isner, *J. Org. Chem.*, **31**, 3013 (1966).

(23) R. H. Manske, *J. Amer. Chem. Soc.*, **53**, 1106 (1931).

(24) P. A. Plattner and A. Studer, *Helv. Chim. Acta*, **29**, 1432 (1946).

(25) K. Hafner and H. Welds, *Justus Liebigs Ann. Chem.*, **606**, 90 (1957).

(26) A. G. Anderson, R. G. Anderson, and T. S. Fujita, *J. Org. Chem.*, **27**, 5435 (1962).

alumina[27] (CH_2Cl_2 eluent) yielded 282 mg (96%) of **6-OAc** as a blue oil: ir (neat) 5.74 μ (C=O); nmr (CCl_4, internal TMS) τ 1.7–3.3 (m, Az H's, 7), 5.64 [t (J = 7 Hz), α-CH_2, 2], 6.61 [t (J = 7 Hz), β-CH_2, 2], and 8.12 (s, CH_3, 3); visible-uv (cyclohexane) 684 nm (log ϵ 2.30), 622 (2.53), 594 (2.53), 573 (2.57), 555 (2.45), 350 (3.53), 342 (4.02), 330 (3.90), 284 (4.03), 279 (4.04), and 242 (3.76); mass spectrum (70 eV, direct) m/e (rel intensity) 214 (100), 171 (52), 154 (68), and 153 (74).

The oil was converted to its 1,3,5-trinitrobenzene complex, which was recrystallized from ethyl acetate–petroleum ether, mp 81–82°.

Anal. Calcd for $C_{20}H_{17}N_3O_8$: C, 56.21; H, 4.01; N, 9.83. Found: C, 56.26; H, 4.13; N, 9.63.

2-(4-Azulyl)ethyl Tosylate (6-OTs).—To a solution of 240 mg (1.40 mmol) of **6-OH** in 20 ml of dry ether at 0° was added 294 mg (1.54 mmol) of sublimed *p*-toluenesulfonyl chloride and 234 mg (4.2 mmol) of powdered potassium hydroxide in approximately three equal portions. After stirring for 3 hr at 0°, the ether layer was washed with three 20-ml portions of ice–water and dried ($MgSO_4$). Concentration and chromatography of the resultant blue oil on basic, activity III–IV alumina[27] (CH_2Cl_2 eluent) gave 340 mg (75%) of **6-OTs** initially as a blue oil which crystallized from ether–petroleum ether as blue crystals: mp 69.5–70.0°; ir (KBr) 7.4 and 9.3 μ; nmr ($CDCl_3$, internal TMS) τ 1.5–3.2 (m, ring H's, 11), 5.59 [t (J = 7 Hz), α-CH_2, 2], 6.53 [t (J = 7 Hz), β-CH_2, 2], and 7.74 (s, CH_3, 3); visible-uv (CH_2Cl_2) 674 nm (log ϵ 2.16), 615 (2.55), 572 (2.61), 355 (3.18), 342 (3.70), 286 (4.64), and 280 nm (4.68); mass spectrum (70 eV, direct) m/e (rel intensity) 326 (56) and 171 (100).

Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.90; H, 5.57. Found: C, 69.73; H, 5.56.

2-(4-Azulyl)ethyl Nosylate (6-ONs).—To a solution of 235 mg (1.36 mmol) of **6-OH** in 20 ml of dry ether at −20° was added 0.73 ml (1.22 mmol) of 1.67 M methyllithium in hexane (Foote). To the resultant cloudy solution was then added 314 mg (1.36 mmol) of sublimed *p*-nitrobenzenesulfonyl chloride. After 2 min the solution had clarified and was immediately poured onto a basic alumina column, where methylene chloride eluted 324 mg (67%) of **6-ONs**. Recrystallization from methylene chloride–petroleum ether gave brown needles: mp 108.5–109.5°; ir (KBr) 6.50, 7.30, 7.40, 8.43 μ; nmr ($CDCl_3$, internal TMS) τ 1.6–3.2 (m, ring H's, 11), 5.34 [t (J = 7 Hz), α-CH_2, 2] and 6.64 [t (J = 7 Hz), β-CH_2, 2]; visible-uv (CH_2Cl_2) 676 nm (log ϵ 2.08), 616 (2.46), 571 (2.56), 343 (3.62), 329 (3.48), 285 (4.63), and 280 (4.66).

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.49; H, 4.23. Found: C, 60.32; H, 4.35.

4-Vinylazulene–1,3,5-Trinitrobenzene Complex (12-TNB).—To 30 mg (0.092 mmol) of **6-OTs** in 10 ml of dry *tert*-butyl alcohol under a nitrogen atmosphere at 25° was added 2 ml (0.5 mmol) of 0.05 M potassium *tert*-butoxide in *tert*-butyl alcohol. After stirring for 15 min, 30 ml of ether was added, and the ether layer was separated, washed with three 10-ml portions of water, and dried ($MgSO_4$). Solvent concentration gave a blue oil which was chromatographed on basic alumina (petroleum ether eluent) to give 11 mg (77%) of 4-vinylazulene (**12**).

This compound was converted to its 1,3,5-trinitrobenzene complex and after recrystallization from ethyl acetate–petroleum ether was obtained as brown crystals: mp 142–143° (sublimation); ir (KBr) 6.13, 6.47, and 7.42 μ; nmr ($CDCl_3$, internal TMS) τ 0.70 (s, TNB H's, 3), 1.6–3.2 (m, Az H's and α-vinyl H, 8), and 3.7–4.5 (m, β-vinyl H's, 2); visible-uv (CH_2Cl_2) 713 nm (log ϵ 2.06), 644 (2.55), 5.92 (2.64), 347 (3.61), 292 (4.55), and 261 (4.53).

Anal. Calcd for $C_{18}H_{13}N_3O_6$: C, 58.86; H, 3.57. Found: C, 58.87; H, 3.51.

6-Azulylacetic Acid (5).—As in the preparation of acid **4**, 852 mg (6.0 mmol) of 6-methylazulene in 40 ml of ether was allowed to react with 10 ml of 0.680 M sodium N-methylanilide in ether at −20°. Warming to 5–10° caused the color of the solution to change to red. Carbonation at 0–10° and work-up gave 122 mg of 6-methylazulene and 958 mg (86%; 97% net yield) of **5**. A portion of **5** was chromatographed on deactivated (15% water) silica gel with ethyl acetate and the product was recrystallized from methylene chloride–hexane to give pure **5** as blue plates, mp 132–134° dec (lit.[6a] mp 126–127° dec).

Methyl 6-Azulylacetate.—**5** (50 mg, 0.28 mmol) was converted to the methyl ester with diazomethane in ether. Chromatography of the crude ester on basic alumina (CH_2Cl_2 eluent) gave 52 mg (97%) of the ester: mp 38–39°; ir (neat) 5.69 μ (C=O); nmr (CCl_4, internal TMS) τ 1.91 [d (J = 10 Hz), C_4 and C_8 H's, 2], 2.29 [t (J = 4 Hz), C_2 H, 1], 2.80 [d (J = 4 Hz), C_1 and C_3 H's, 2], 3.05 [d (J = 10 Hz), C_5 and C_7 H's, 2], 6.38 (s, CH_2, 2), and 6.42 (s, CH_3, 3); visible-uv (cyclohexane) 684 nm (log ϵ 1.98), 620 (2.42), 591 (2.45), 573 (2.49), 344 (3.80), 337 (3.62), 330 (3.65), 285 (4.86), and 279 mm (4.86); mass spectrum (70 eV, heated inlet) m/e (rel intensity) 201 (14), 200 (100), 141 (56), 139 (13), and 115 (27).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.14; H, 6.11.

2-(6-Azulyl)ethanol (7-OH). Method A.—Following the procedure used for **6-OH**, 147 mg (0.79 mmol) of **5** was reduced with diborane to give 123 mg (91%) of **7-OH**: mp 78–80°; nmr ($CDCl_3$, internal TMS) τ 1.80 [d (J = 10 Hz), C_4 and C_8 H's, 2], 2.16 [t (J = 4 Hz), C_2 H, 1], 2.55 [d (J = 4 Hz), C_1 and C_3 H's, 2], 2.86 [d (J = 10.5 Hz), C_5 and C_7 H's, 2], 6.13 [t (J = 6 Hz), α CH_2, 2], 7.05 [t (J = 6 Hz), β-CH_2, 2], and 8.20 (broad s, OH, 1); visible-uv (CH_2Cl_2) 672 nm (log ϵ 1.98), 610 (2.42), 565 (2.50), 344 (3.74), 336 (3.55), 329 (3.57), 286 (4.79), and 280 nm (4.80); mass spectrum (70 eV, heated inlet) m/e (rel intensity) 172 (100), 142 (22), 141 (68), and 115 (30).

Method B.—To a stirred solution of 1.00 g (7.05 mmol) of 6-methylazulene in 20 ml of dry ether under a nitrogen atmosphere at −20° was added 14.8 ml of 0.50 M sodium N-methylanilide in ether. A gold precipitate formed in the mixture, to which was added 212 mg (7.05 mmol) of paraformaldehyde through Gooch tubing. The mixture was allowed to warm to 25° and stirring was continued for 2 hr. The reaction mixture was diluted with water and ether, and the ether layer was separated, washed with four 100-ml portions of 5% hydrochloric acid, and dried ($MgSO_4$). Solvent concentration and chromatography of the blue residue on basic alumina gave two fractions; hexane eluted 900 mg of 6-methylazulene and chloroform eluted 110 mg (9%; 91% net yield) of **7-OH**, mp 78–79°, identical in all respects with the product from method A.

2-(6-Azulyl)ethyl Acetate (7-OAc).—Following the above method used for **6-OAc**, 147 mg (0.86 mmol) of **7-OH** yielded 135 mg (74%) of **7-OAc** as a blue oil: ir (neat) 5.86 μ (C=O); nmr (CCl_4, internal TMS): τ 1.95 [d (J = 10.5 Hz), C_4 and C_8 H's 2), 2.28 [t (J = 4 Hz), C_2 H, 1], 2.80 [d (J = 4 Hz), C_1 and C_3 H's, 2], 3.11 [d (J = 10.5 Hz), C_5 and C_7 H's, 2], 5.76 [t (J = 7.5 Hz), α-CH_2, 2], 7.05 [t (J = 7.5 Hz), β-CH_2, 2], and 8.08 (s, CH_3, 3); mass spectrum (70 eV, heated inlet) m/e (rel intensity) 214 (47), 154 (100), 153 (25), 141 (16), and 115 (16).

Acetate **7-OAc** was converted to its 1,3,5-trinitrobenzene complex in ethyl acetate which was recrystallized from ethyl acetate–hexane: mp 104.2–105.0°; visible-uv (CH_2Cl_2) 676 nm (log ϵ 1.99), 612 (2.42), 588 (2.47), 569 (2.50), 344 (3.74), 336 (3.56), 329 (3.59), 285 (4.79), and 279 (4.79).

Anal. Calcd for $C_{20}H_{17}N_3O_8$: C, 56.21; H, 4.01. Found: C, 56.36; H, 4.22.

2-(6-Azulyl)ethyl Tosylate (7-OTs).—Following the procedure used in the synthesis of **6-OTs**, 100 mg (0.58 mmol) of **7-OH** gave 168 mg (88%) of **7-OTs** as blue plates after recrystallization from methylene chloride–hexane: mp 107.5–108.5°; ir (KBr) 7.51 and 8.53 μ; nmr ($CDCl_3$, internal TMS) τ 1.86 [d (J = 10.5 Hz), C_4 and C_8 H's, 2], 2.12 [t (J = 4 Hz), C_2 H, 1], 2.45 [d (J = 8 Hz), tosyl H's, 2], 2.66 [d (J = 4 Hz), C_1 and C_3 H's, 2], 3.00 [d (J = 8 Hz), tosyl H's, 2], 3.12 [d (J = 10.5 Hz), C_5 and C_7 H's, 2], 5.67 [t (J = 6.5 Hz), α-CH_2, 2], 6.92 [t (J = 6.5 Hz), β-CH_2, 2], and 7.72 (s, CH_3, 3); visible-uv (CH_2Cl_2) 681 nm (log ϵ 2.00), 620 (2.42), 588 (2.47), 571 (2.49), 344 (3.73), 336 (3.56), 330 (3.58), 285 (4.77), and 279 (4.76); mass spectrum (70 eV, heated inlet) m/e (rel intensity) 326 (64), 154 (100), 141 (18), 115 (15), and 91 (15).

Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56. Found: C, 69.75; H, 5.37.

2-(6-Azulyl)ethyl Nosylate (7-ONs).—The procedure was that used in the preparation of **6-ONs** where 180 mg (1.05 mmol) of **7-OH** gave 220 mg (59%; 73% net yield) of **7-ONs** as black needles: mp 155° dec; ir (KBr) 7.41 and 8.49 μ; nmr (DMSO-d_6, internal TMS) τ 1.71–2.26 (m, 7), 2.70 [d (J = 4 Hz), 2], 2.98 [d (J = 11 Hz), 2], 5.46 [t (J = 6 Hz), α-CH_2, 2], and 6.86 [t (J = 6 Hz), β-CH_2, 2]; visible-uv (CH_2Cl_2) 684 nm (log ϵ 1.98), 622 (2.41), 5.90 (2.45), 573 (2.48), 344 (3.80), 337 (3.65), 330 (3.67), 285 (3.67), and 279 nm (4.85). An analytical sample was recrystallized from methylene chloride–hexane, mp 155° dec.

(27) Made by addition of 5% water to activity I alumina.[20]

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.49; H, 4.23. Found: C, 60.22; H, 4.30.

6-Vinylazulene (13).—This compound was isolated from several product study runs on 7-OTs and 7-ONs and was characterized as follows: mp 111–113°; ir (KBr) 6.38 (m), 6.69 (m), 11.79 (s), and 13.24 μ (s); nmr (CCl_4, internal TMS) τ 1.91 [d (J = 10.5 Hz), C_4 and C_8 H's, 2], 2.29 [t (J = 4 Hz), C_2 H, 1], 2.79 [d (J = 4 Hz), C_1 and C_3 H's, 2], 2.90 [d (J = 10.5 Hz), C_5 and C_7 H's, 2], and 3.15–4.80 (seven lines, vinyl H's, 3).

The 1,3,5-trinitrobenzene complex was prepared and recrystallized several times from ethanol: mp 118–119.5°; visible–uv (cyclohexane) 752 nm (log ϵ 1.96), 708 (2.10), 672 (2.40), 639 (2.45), 613 (2.51), 592 (2.46), 372 (3.88), 363 (3.64), 355 (3.75), 347 (3.67), and 291 (4.80).

Anal. Calcd for $C_{18}H_{13}N_3O_6$: C, 58.85; H, 3.57. Found: C, 58.66; H, 3.51.

2-(4-Azulyl)ethanol-α,α-d_2 (6-α,α-d_2-OH).—Analogous to the preparation of 6-OH, 147 mg (0.79 mmol) of acid 4 was reduced but using 147 mg (3.5 mmol) of sodium borodeuteride (Merck). This gave 132 mg (96%) of the labeled alcohol. Comparison of the integrated α- and β-methylene nmr signals showed 1.80 atoms of deuterium at C_α of the ethyl side chain.

2-(4-Azulyl)ethyl-α,α-d_2 Nosylate (6-α,α-d_2-ONs).—As in the synthesis of 6-ONs, 81 mg (0.47 mmol) of 6-α,α-d_2-OH was converted to 81 mg (48%, 68% net yield) of the labeled nosylate. Multiple integrations of the methylene nmr signals showed 1.80 atoms of deuterium at C_α of the ethyl side chain.

2-(6-Azulyl)ethanol-α,α-d_2 (7-α,α-d_2-OH).—This was prepared by the procedure given above for 6-α,α-d_2-OH with the labeled alcohol isolated in 94% yield. Multiple integrations of the α- and β-methylene nmr signals showed the presence of 1.85 atoms of deuterium at C_α of the ethyl side chain.

2-(6-Azulyl)ethyl-α,α-d_2 Tosylate (7-α,α-d_2-OTs).—Following the procedure given for the synthesis of 7-OTs, 177 mg (10 mmol) of the labeled alcohol produced 196 mg (59%, 93% net yield) of the labeled tosylate. Multiple integrations of the α- and β-methylene nmr signals showed the presence of 1.87 atoms of deuterium at C_α of the ethyl side chain.

2-(6-Azulyl)ethyl-α,α-d_2 Nosylate (7-α,α-d_2-ONs).—Following the above procedure for the synthesis of 7-ONs, 100 mg (0.58 mmol) of the labeled alcohol gave 105 mg (52%) of the labeled nosylate. Multiple integrations of the α- and β-methylene nmr signals showed the presence of 1.83 atoms of deuterium at C_α of the ethyl side chain.

3-(4-Azulyl)-1-propanol (8-OH).—To a solution of 294 mg (2.1 mmol) of 4-methylazulene in 20 ml of dry tetrahydrofuran at 0° under a nitrogen atmosphere was added 2.96 ml (2.1 mmol) of 0.71 M sodium N-methylanilide in ether followed by 2 ml (42 mmol) of ethylene oxide. The solution showed no immediate color change but after stirring for 4 hr had become blue-green. An additional 1 ml of ethylene oxide was added and stirring was continued for 1 hr. Water (20 ml) was added to the blue reaction mixture, which was then extracted with 50 ml of ether. The ether layer was washed with two 50-ml portions of cold 10% hydrochloric acid and three 50-ml portions of water, and dried ($MgSO_4$). Solvent evaporation and chromatography on basic activity II–III alumina[28] (1:1 CH_2Cl_2–$CHCl_3$ eluent) gave 130 mg (33%, 59% net yield) of 8-OH as a blue oil.

This was converted to its 1,3,5-trinitrobenzene complex, which after recrystallization from ethyl acetate–petroleum ether was brown needles: mp 108–109°; ir (KBr) 3.03 (OH), 6.45, 7.40, and 9.29 μ; nmr ($CDCl_3$, internal TMS) τ 0.86 (s, TNB H's, 3), 1.6–3.2 (m, Az H's, 7), 6.26 [t (J = 6 Hz), α CH_2, 2], 6.68 [t (J = 7 Hz), δ CH_2, 2], 7.88 (m, β CH_2, 2), and 8.42 (s, OH, 1); visible–uv (CH_2Cl_2) 657 nm (sh), 670 (sh), 566 (log ϵ 2.64), 355 (sh), 343 (3.75), 329 (3.63), 285 (4.73), and 280 (4.73); mass spectrum (70 eV, direct) m/e (rel intensity) 186 (19) and 142 (100).

Anal. Calcd. for $C_{19}H_{17}N_3O_7$: C, 57.15; H, 4.29; N, 10.52. Found: C, 57.50; H, 4.46; N, 10.28.

3-(4-Azulyl)-1-propyl Acetate (8-OAc).—A solution containing 200 mg (1.1 mmol) of 8-OH and 1 ml of acetic anhydride in 10 ml of dry pyridine was allowed to stand for 24 hr and worked up as given in the preparation of 6-OAc. Chromatography on basic, activity II–III alumina[28] (CH_2Cl_2 eluent) gave 225 mg (93%) of 8-OAc as a blue oil. The 1,3,5-trinitrobenzene complex was prepared and recrystallized from ethyl acetate–petroleum ether to give brown needles: mp 92–93°; ir (KBr) 5.71 μ (C=O); nmr ($CDCl_3$), internal TMS) τ 0.88 (s, TNB H's, 3), 1.7–3.2 (m, Az H's, 7), 5.84 [t (J = 6 Hz), α CH_2, 2], 6.72 [t (J = 7 Hz), δ CH_2, 2], and 7.5–8.1 (m, β CH_2 and CH_3 at τ 7.96, 5); visible–uv (CH_2Cl_2) 656 nm (sh), 605 (sh), 563 (log ϵ 2.56), 352 (3.46), 342 (3.92), 330 (3.82), 286 (4.89), and 280 (4.89).

Anal. Calcd for $C_{21}H_{19}N_3O_8$: C, 57.14; H, 4.34; N, 9.52. Found: C, 57.51; H, 4.53; N, 9.34.

3-(4-Azulyl)-1-propyl Nosylate (8-ONs).—Using the procedure described for the synthesis of 6-ONs, 117 mg (0.63 mmol) of 8-OH produced 156 mg (63%) of 8-ONs as a blue oil: ir (neat) 3.28, 6.49, and 8.48 μ; nmr ($CDCl_3$, internal TMS) τ 1.5–3.2 (m, ring H's, 11), 5.81 [t (J = 6 Hz), α CH_2, 2], 6.68 [t (J = 7 Hz), γ CH_2, 2], and 7.73 (m, β CH_2, 2).

The 1,3,5-trinitrobenzene complex was prepared and recrystallized from ethyl acetate–petroleum ether as brown needles: mp 101–103°; visible–uv (CH_2Cl_2) 605 nm (sh), 568 (log ϵ 2.63), 343 (3.72), 285 (4.67), and 280 (4.67).

Anal. Calcd for $C_{25}H_{20}N_4O_{11}S$: C, 51.37; H, 3.45; N, 9.59. Found: C, 51.70; H, 3.67; N, 9.32.

2-Phenylethyl Tosylate (9-OTs).—This compound was prepared by the usual method.[29] Recrystallization from methylene chloride–hexane gave white crystals, mp 38.5–39.0° (lit.[30] mp 37.5–38.2°).

2-Phenylethyl Nosylate (9-ONs).—Using the reaction conditions and work-up described for the synthesis of 6-ONs, 1.22 g (10 mmol) of 2-phenylethanol gave a white, crystalline residue after solvent evaporation which when recrystallized from methylene chloride–hexane gave 2.21 g (72%) of 9-ONs as white needles: mp 101.5–102°; nmr ($CDCl_3$, internal TMS) τ 1.71 [d (J = 9 Hz), nosyl H's, 2], 2.12 [d (J = 9 Hz), nosyl H's, 2], 2.80 (m, phenyl H's, 5), 5.67 [t (J = 6.5 Hz), α CH_2, 2], and 7.01 [t (J = 6.5 Hz), β CH_2, 2].

Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.71; H, 4.26. Found: C, 54.75; H, 4.18.

2-(p-Anisyl)ethyl Tosylate (10-OTs).—Large white needles of this compound were prepared by the usual method,[29] mp 57–58° (lit.[31] mp 57–58°).

2-(p-Anisyl)ethyl Nosylate (10-ONs).—Following the above procedure for synthesis of 9-ONs, 1.52 g (10 mmol) of 2-(p-anisyl)ethanol produced 2.48 g (74%) of 10-ONs as bright yellow needles: mp 97–97.5°; nmr ($CDCl_3$, internal TMS) τ 1.71 [d (J = 9.5 Hz), nosyl H's, 2], 2.08 [d (J = 9.5 Hz), nosyl H's, 2], 2.96 [d (J = 9 Hz), anisyl H's, 2], 3.24 [d (J = 9 Hz), anisyl H's, 2], 5.68 [t (J = 6.5 Hz), α CH_2, 2], 6.25 (s, OCH_3, 3), and 7.08 [t (J = 6.5 Hz), β CH_2, 2].

Anal. Calcd for $C_{15}H_{15}NO_6S$: C, 53.40; H, 4.48. Found: C, 53.45; H, 4.60.

Ethyl Tosylate (11-OTs).—Absolute ethanol was converted by the ether–powdered potassium hydroxide technique, as with 6-OTs, to 11-OTs and was trap-to-trap distilled (130°, 0.1 mm) as a colorless oil which crystallized on standing. Recrystallization from ether–petroleum ether gave 59% of crystalline 11-OTs: mp 33.0–33.5° (lit.[32] mp 32.2–32.3°); nmr (CCl_4, internal TMS) τ 2.52 (A_2B_2 m, tosyl H's, 4), 5.94 (q, α CH_2, 2), 7.61 (s, CH_3, 3), and 8.77 (t, CH_3, 3).

Anal. Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04. Found: C, 53.96; H, 5.97.

Ethyl Nosylate (11-ONs).—As in the preparation of 6-ONs, absolute ethanol was converted to 11-ONs and was chromatographed on basic alumina (CH_2Cl_2 eluent) to give a 60% yield of 11-ONs. Recrystallization from methylene chloride–petroleum ether produced white crystals: mp 91.5–92.0°; ir (KBr) 6.52, 7.35, 7.44, and 8.44 μ; nmr (DMSO-d_6, internal TMS) τ 1.95 (A_2B_2 m, nosyl H's, 4), 5.60 (q, CH_2, 2), and 8.67 (t, CH_3, 3).

Anal. Calcd for $C_8H_9NO_5$: C, 41.56; H, 3.92; N, 6.06. Found: C, 41.21; H, 4.00; N, 5.91.

Kinetic Methods.—Dissolved gases in purified acetic acid (distilled from acetic anhydride) containing 1% by volume of acetic anhydride were replaced by nitrogen by the freeze–thaw technique (4–6 cycles). All dilutions and manipulations of solvent were carried out in a glove box in a dry, nitrogen atmosphere.

(28) Made by addition of 3% water to activity I alumina.[20]

(29) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(30) W. H. Saunders, S. Asperger, and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958).

(31) S. Winstein, C. R. Lindgren, H. Marshall, and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

(32) H. R. McCleary and L. P. Hammett, *ibid.*, **63**, 2254 (1941).

Loaded 2-ml ampoules containing *ca.* 1.3 ml of solution were plugged, removed from the glove box, and sealed with a torch. About 1.1-ml samples were removed from the ampoules with a constant delivery pipette and diluted with a 9:1 mixture of acetic acid–acetic anhydride; for 0.01 *M* sulfonate ester, 10 ml of diluent was used while with 0.005 *M* substrate, 2 ml of diluent was added. Larger dilution volumes gave errant end-point readings during titrations. The titrant was perchloric acid in acetic acid containing 2% acetic anhydride.

All potentiometric titrations were carried out with a Metrohm Herisau E436D Potentiograph automatic titrator using an EA 147X micro, combination electrode. By comparison to the titrations for a standard buffer solution, the end points were taken at the same millivolt reading for all titrations for a particular solvolysis run (12–15 points over 2 half-lives). Two or more samples were titrated after 10 solvolytic half-lives and were taken as the extent of reaction at time infinity.

The buffer solutions were prepared by dissolving anhydrous potassium acetate in the acetic acid solvent. For the conductometric studies with 8-ONs, the solvent contained only 0.02% (v/v) of acetic anhydride. The conductivity method has been described[16] using the M-D Minicell;[33] the 3-ml working volume of this conductivity cell without significant loss of precision made these measurements with 8-ONs practical. The 120° temperature used with this method appears to be close to the maximum operating temperature for this solvent system in the conductivity method. Approximately 100 readings were taken on the bridge over about 2 half-lives for each run. It was interesting that the specific conductance of the runs with 8-ONs increased with time, whereas with tosylate esters in this solvent the specific conductance decreases (KOAc being replaced by KONs or KOTs).[15]

Rate constants were calculated using either a least-squares computer program (RATSOL2) developed by Professor K. Conrow or the LSKIN1 program[34] as modified for the IBM 360/50 system by Professor Conrow. Both programs gave essentially identical results.

Activation parameters and extrapolated rate data were calculated using a program developed by Professor Conrow. This program was written to calculate thermochemical data from rate data at two temperatures, giving a "best" value along with "maximum" and "minimum" values based on the errors associated with the rate data.

Preparative Buffered Acetolyses.—The general procedure employed for the preparative buffered acetolyses involved dissolving the arenesulfonate ester in potassium acetate buffered acetic acid of the same concentration as was employed in that ester's kinetic study. This solution was then loaded into a number of 10-ml ampoules in the glove box, which were plugged, removed, sealed, and placed in the constant-temperature bath for the appropriate time interval. The ampoules were then removed from the bath, quenched in ice–water, and opened, and the contents were combined and diluted with methylene chloride. After washing with several portions of water, saturated sodium bicarbonate solution, and water, the organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue could then be chromatographed and/or analyzed directly by nmr spectroscopy where multiple integrations of nmr absorptions were compared to those of an added standard compound, either 1,3,5-trinitrobenzene or dioxane. The results from such preparative runs are summarized in Table VI.

TABLE VI
SUMMARY OF PREPARATIVE BUFFERED ACETOLYSIS AT 120°

Starting material	Time ($t_{1/2}$)	Products (%)
6-OTs	1	6-OTs (50) + 12 (37) + 6-OAc (9)
6-ONs	1	6-ONs (50) + 12 (17) + 6-OAc (27)
7-OTs	1	7-OTs (37) + 13 (28) + 7-OAc (11)
7-ONs	1	7-ONs (47) + 13 (14) + 7-OAc (37)
8-ONs	10	18 (51) + 8-OAc (25)

TABLE VII
SUMMARY OF STABILITY TESTS FOR SOLVOLYTIC PRODUCTS AT 120°

Solvolytic product	Time ($t_{1/2}$)	Recovery (%)
6-OAc	1 (6-OTs)	6-OAc (72) + 12 (17)
	1 (6-ONs)	6-OAc (84) + 12 (6)
7-OAc	1 (7-OTs)	7-OAc (69) + 13 (25)
	1 (7-ONs)	7-OAc (82) + 13 (8)
13	1 (7-OTs)	13 (77)
	1 (7-ONs)	13 (84)
18	10 (8-ONs)	18 (67)
8-OAc	10 (8-ONs)	8-OAc (91)

Stability Tests for Solvolytic Products.—These product stability tests were carried out in the same manner as that described above for the preparative buffered acetolyses. The composition and amounts of the material(s) obtained from such tests were either from weights of isolated compounds or from multiple integrations of nmr spectral absorptions using an added standard. These results are summarized in Table VII.

Registry No.—**4**, 26157-13-1; **4** methyl ester, 26157-17-5; **4** methyl ester TNB, 38304-97-1; **5**, 26157-15-3; **5** methyl ester, 26156-73-0; **6**-OH, 13935-44-9; **6**-OAc, 26154-66-5; **6**-OAc TNB, 38305-02-1; **6**-OTs, 26154-63-2; **6**-ONs, 38305-04-3; **7**-OH, 26157-10-8; **7**-OAc, 26154-68-7; **7**-OAc TNB, 38305-07-6; **7**-OTs, 26211-00-7; **7**-ONs, 38305-09-8; **8**-OH, 38305-10-1; **8**-OH TNB, 38305-11-2; **8**-OAc, 38305-12-3; **8**-OAc TNB, 38305-13-4; **8**-ONs, 36740-21-3; **8**-ONs TNB, 38305-15-6; **9**-ONs, 24760-80-3; **10**-ONs, 24760-81-4; **11**-OTs, 80-40-0; **11**-ONs, 15481-55-7; **12**, 38305-18-9; **12** TNB, 38305-19-0; **13**, 38305-20-3; **13** TNB, 38305-21-4; 4-methylazulene, 17647-77-7.

Acknowledgment.—The authors wish to thank the National Science Foundation for support of this research (GP-7818, GP-10691) and instrument grants for the nmr (A-60 and T-60) and mass spectrometers used in this study, the Phillips Petroleum Co. for a fellowship to H. E. Petty (1968–1969), Professor Kenneth Conrow for untiring efforts in developing computer programs and other discussions, and Kansas State University for computer time.

(33) Available from R-M Research Products, Inc., 1820 Alabama, Manhattan, Kans. 66502.

(34) D. F. DeTar and C. E. DeTar in "Computer Programs for Chemistry," Vol. I, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1968.

Nonbenzenoid Aromatic Systems. IX. Aryl Participation in Mass Spectrometry. Mechanisms and Comparisons with Solvolytic Data for Some Azulene, Pyridine, and Benzene Derivatives[1]

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The nitrogen atom in 2-substituted pyridines participates in unique fragmentation reactions (formally simple δ- and ε-bond cleavages) which are analogous to those involving C_3 in 4-substituted azulenes. Free-radical character of the ring atom appears to be involved in these and other bond-forming reactions, none of which occur in benzene derivatives. 3-Pyridylpropanols, acetates, and tosylates apparently form pyridylethylenonium ions, but phenonium (phenylethylenonium) ions are of no more than minor importance in 2-phenylethanols and their acetates and tosylates. Close relationships between electron impact and solvolytic phenomena are demonstrated in all three ring systems and particularly in the azulenes.

While concepts borrowed from solution chemistry have aided enormously in the development of organic mass spectrometry, the reverse process is only now beginning to develop. Previously we compared and contrasted the solvolytic and electron impact induced behavior of azulylethanols and their esters and made predictions concerning the solvolysis of 3-(4-azulyl)-propyl tosylate based on mass-spectral results.[3] Here we report mass-spectral data for the 3-(azulyl)-1-propanol derivatives and compare it with solvolytic data for this system.[4] In addition, we have sought a better understanding of aryl participation in the mass spectrometer by studying (i) benzene derivatives and (ii) alkylpyridines, where the heteroatom might be involved, and by comparing these systems with the azulene compounds.

Pyridine Derivatives.—Important features of the mass spectra of the 3-(pyridyl)-1-propanols (**1**–**3**), -propyl acetates (**4**–**6**), and -propyl tosylates (**7**–**9**), as well as the 2-(pyridyl)ethanols (**10** and **11**), appear in Table I. Nomenclature for bond cleavage is standard, *i.e.*, for the propyl tosylates

$$\mathrm{Py}\overset{\alpha}{-}\mathrm{CH_2}\overset{\beta}{-}\mathrm{CH_2}\overset{\gamma}{-}\mathrm{CH_2}\overset{\delta}{-}\mathrm{O}\overset{\epsilon}{-}\mathrm{Ts}$$

where Py = pyridyl and Ts = *p*-toluenesulfonyl. Fragment ion abundances appear in Table I under the type of bond cleavage by which, formally, the ions arise. We are primarily concerned with processes which cannot be accounted for as simple bond cleavages and for which aryl-participation mechanisms are therefore possible.[3] These processes are γ, δ, and ε cleavage in the propanol series and γ and δ cleavage in the ethanols. While analogous fragmentations appear to occur in the alcohols, acetates, and tosylates, it is significant to note that H· loss from the alcohols (**1**–**3** and **10** and **11**) does not correspond, mechanistically, to Ac· and Ts· loss. This is shown by the observation that the O-deuterated analogs of both **1** and **10** lose predominantly H· rather than D·. The low efficiency of H· loss relative to loss of the more stable radicals, Ac· and Ts·, has been noted previously in connection with aryl-participation reactions in 4-substituted azulenes.[3]

TABLE I
PARTIAL MASS SPECTRA OF SOME PYRIDINE DERIVATIVES[a]

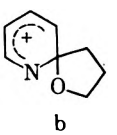
		Bond cleavage				
Compd	M^+	ε	δ	γ	β	β + H
1, 3-(2-Py)-1-PrOH	0.2	1.8[b]	8	20	6	100
2, 3-(3-Py)-1-PrOH	37	1[b]	0	17	44	22
3, 3-(4-Py)-1-PrOH	42	1[b]	0	23	33	98
4, 3-(2-Py)-1-PrOAc	≪0.1	18	24	18	6	100
5, 3-(3-Py)-1-PrOAc	15	3	0	42	32	13
6, 3-(4-Py)-1-PrOAc	0.5	6	2	25	30	15
7,[c] 3-(2-Py)-1-PrOTs	≪0.1	19	77	63	70	94
8,[c] 3-(3-Py)-1-PrOTs	20	4	9	67	52	21
9,[c] 3-(4-Py)-1-PrOTs	100	3	15	11	19	14
10, 2-(2-Py)EtOH	16		23[b]	67	14	99
11, 2-(4-Py)EtOH	41		1[b]	19[d]	14	99

[a] All data are corrected for ^{13}C contributions and expressed relative to the base peak in the uncorrected spectrum. [b] Hydrogen atom loss; see text. [c] The tosylates were difficult to purify (see Experimental Section) and some variation was observed in their spectra. [d] Shown by metastable analysis to arise from low abundance impurity ion (*m/e* 134) as well as the molecular ion.

The results of Table I indicate that the ionized 2-substituted pyridines **1**, **4**, and **7** are much more reactive than their isomers; their molecular ion abundances do not exceed 0.2% and they yield abundant ions due to γ, δ, and ε cleavages (with the qualification regarding H· loss from alcohols noted above). Of these processes only γ cleavage occurs with facility in the 3- and 4-substituted pyridines. The contrast between the 2- and the 3- and 4-substituted compounds is also evident in such normal fragmentations as loss of acetic acid from the acetates. The sequence $M\cdot^+ - AcOH - H\cdot$ gives the base peak in the 3- and 4-pyridyl acetates, **5** and **6**, but an ion of only 9% abundance in the 2-pyridyl compound **4**.

The mechanisms involved in the interesting δ- and ε-bond scissions can now be explored in more detail. These reactions are, to a high degree, specific to the 2-substituted pyridines. This is best seen by comparing daughter ion–molecular ion abundance ratios. For example, for *p*-toluenesulfonyl radical loss these ratios are >190 (**7**), 0.2 (**8**), and 0.03 (**9**). The specificity, which is generally rather more marked for δ than for ε cleavage, implies that the spiro type ions a and b (and

a



b

(1) For part VIII, see ref 4.

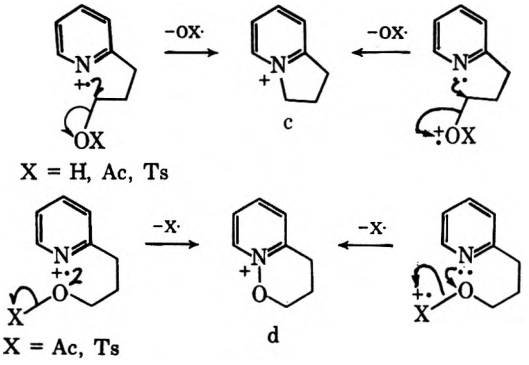
(2) Address correspondence to this author at Department of Chemistry, Purdue University, Lafayette, Indiana 47907.

(3) R. G. Cooks, N. L. Wolfe, J. R. Curtis, H. E. Petty, and R. N. McDonald, *J. Org. Chem.*, **35**, 4048 (1970).

(4) R. N. McDonald, N. L. Wolfe, and H. E. Petty, *ibid.*, **38**, 1006 (1973).

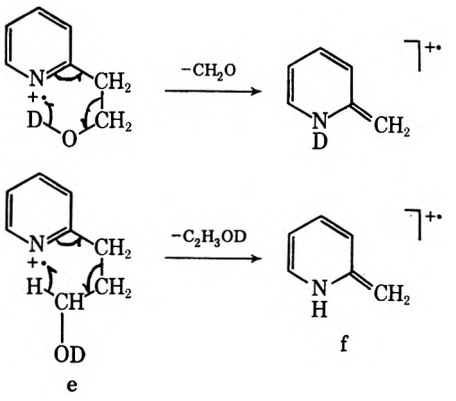
their meta and para isomers) are not formed as the major products of δ and ε cleavage, respectively.

It is, therefore, apparent that the nitrogen atom plays a direct role in these fragmentation mechanisms, just as was noted for the C_3 carbon atom in the fragmentation of 2-(4-azulyl)ethanol and its derivatives.[3] These results also demonstrate that, in the most general sense, the aryl group participates in the fragmentation of the substituents. If the analogy with the participation reactions observed in the azulenes[3] holds, δ cleavage in the propyl pyridine series will yield ion c and ε cleavage ion d. Note that, in illustrating the formation of ions c

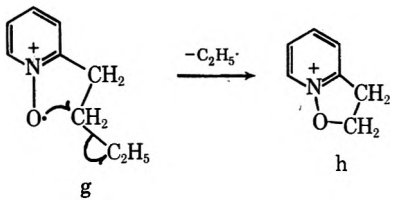


and d, reactants ionized on the pyridine ring, as well as those ionized in the substituent, have been considered. Analogous possibilities existed for the participation mechanism in the 2-(4-azulyl)ethanol derivatives and appearance potential data favored the substituent ionization mechanism.[3] More recently, Shapiro and coworkers[5] have interpreted their results on anchimeric assistance in the fragmentation of homoallylic systems in terms of participation with expulsion of the leaving group once it begins to bear charge. In spite of these precedents for substituent ionization in other systems, there is considerable evidence that the ring ionization mechanism may be involved in the pyridines.

First, the appearance potential of the δ-cleavage ion in 2-(2-pyridyl)ethyl tosylate (10.2 eV) is considerably larger than both the IP of ethyl tosylate (8.4 eV) and the IP expected for an alkylpyridine (approximately 9.0 eV[6]). The thermochemical data therefore do not correspond to those observed in the earlier studies, although they do not allow a definitive choice between ring and substituent ionization. Second, many other reactions of the pyridine derivatives appear to be initiated by an ionized nitrogen atom. For example, the alcohols **10** and **1** both undergo the specific six-membered hydrogen transfers shown below. It is also interesting that 3-phenylpropyl bromide shows reciprocal hydrogen transfer between the ortho and C_1 positions in the molecular ion.[7] This supports the suggested e → f sequence. Third, the observed loss of $C_2H_5\cdot$ from 2-*n*-butylpyridine *N*-oxide, but not from its isomers,[8] is also best explained as proceeding from a ring-ionized rather than a side-chain ionized form of the molecular ion.

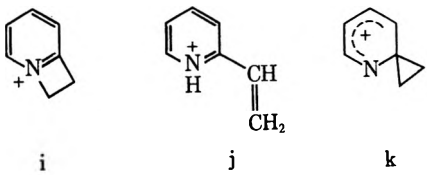


Representation of *N*-oxide molecular ions in the oxy-radical form (*e.g.*, g) helps explain many aspects of their spectra; for example the rearrangements of nitrones, and the relationship between their mass spectra and photochemistry, is rationalized.[9] The sequence g → h may be responsible for $C_2H_5\cdot$ loss.



In summary, the major bond-forming reactions in the pyridine derivatives **1**–**11** (δ and ε cleavage, and β cleavage with hydrogen migration) appear to involve a form of the molecular ion in which a nitrogen lone-pair electron has been removed.

The remaining reaction of interest, γ cleavage, does not show the specificity to the 2 isomer shown by δ and ε cleavage. Hence, while it will be readily accepted that the reaction does not merely involve simple cleavage, participation by the nitrogen atom is not demanded. Similar conclusions apply to the alkylpyridines whose spectra are given in Table II.[10,11] While it is true that 2-alkylpyridines do show more γ cleavage (measured in terms of fragment ion–molecular ion abundance ratios) than their isomers, the differences are not particularly large. Hence, γ-cleavage mechanisms which involve cyclization to nitrogen, to give ion i, or hydrogen abstraction by nitrogen, to give ion j, are not indicated. Rather, formation of a spiro phenonium type ion k is



probably involved, both in the alkylpyridines and in compounds **1**–**11**. It is interesting to note from Table II that δ cleavage in the butylpyridines is specific to 2-*n*-butylpyridine, suggesting the formation of ion c rather than the unstable spiro (5.4) system a.

(5) K. B. Tomer, J. Turk, and R. H. Shapiro, *Org. Mass Spectrom.*, **6**, 235 (1972).

(6) J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. T. Herron, K. Draxl, and F. H. Field, "Ionization Potentials, Appearance Potentials, and Heats of Formation of Gaseous Positive Ions," NSRDS-NBS 26, U. S. Government Printing Office, Washington, D. C., 1969, p 101.

(7) N. M. M. Nibbering and T. J. deBoer, *Tetrahedron*, **24**, 1427 (1968).

(8) D. A. Lightner, R. Nicoletti, G. B. Quistad, and E. Irwin, *Org. Mass Spectrom.*, **4**, 571 (1970).

(9) B. S. Larsen, G. Schroll, S. O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968); R. G. Cooks, *Org. Mass Spectrom.*, **2**, 481 (1969).

(10) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier, Amsterdam, 1960, p 403.

(11) S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

TABLE II

PARTIAL MASS SPECTRA OF SOME ALKYLPYRIDINES[a]

Compd	Ref	M+	Bond cleavage δ	γ	β	β + H
2-*n*-Butylpyridine	8	3	12	33	12	100
3-*n*-Butylpyridine	8	63	1.5	13	100	84
4-*n*-Butylpyridine	8	49	0	10	12	100
2-*n*-Propylpyridine	10	3	14	27	14	99
4-*n*-Propylpyridine	11	90	15	42	57	96

[a] See footnote *a*, Table I.

Benzene Derivatives.—The apparent formation of phenonium-ion analogs k from substituted pyridines reopens the question of mass spectral phenonium-ion formation in benzene derivatives. This question has previously been studied using ω-phenylalkyl bromides with disputed results.[12] In Table III some literature

TABLE III

PARTIAL MASS SPECTRA OF SOME BENZENE DERIVATIVES[a]

Compd	Ref	M+	Bond cleavage ε	δ	γ
$Ph(CH_2)_2Br$	13	33			46
$Ph(CH_2)_3Br$	7	19		2	2
$Ph(CH_2)_4Br$	12		5	2	11
$Ph(CH_2)_2OH$	14	16		0	2
$Ph(CH_2)_3OH$	15	15	0	0	14
$Ph(CH_2)_3ONO$	16	0	49	0	56
$Ph(CH_2)_3CO_2Me$	17	51	31	0	31

[a] See footnote *a*, Table I.

data[12-17] on other alkylbenzene derivatives are collected. Although differences in bond strengths and radical stabilities must be considered, these results clearly demonstrate the preference for γ *vs.* δ cleavage. This does not prove aryl participation but it is certainly consistent with the formation of spiro-fused product ions.[18]

We have examined 2-phenylethyl tosylate (**12**) and nosylate (**13**) and the corresponding *p*-methoxy (**14** and **15**) and *p*-nitro arenesulfonates (**16** and **17**). The unsubstituted and *p*-methoxy tosylates and the *p*-methoxy nosylate undergo γ cleavage, albeit to give ions of low abundance (2–4%).[20] The other compounds do not undergo γ cleavage, nor does the 2-(*p*-nitrophenyl)-ethanol (**18**), while the process gives an ion of 2% relative abundance from 2-phenylethanol.[14] The substituent effect evident in these results suggests that γ cleavage is accompanied by phenonium-ion formation but does not prove this,[21] and the multiple ion compositions contributing to a single mass peak make energy measurements impossible. Besides the question of $C_8H_9^+$ ion structure, it is interesting that the γ-cleavage ions in compounds **12–18** have such low abundances relative to their 3-(2-pyridyl)propanol counterparts. Some role for the lone pair ionized form of the pyridine molecular ion is indicated but substantial mechanistic questions remain. The complete absence of $M\cdot^+ - Ts\cdot$, $M\cdot^+ - Ns\cdot$, and $M\cdot^+ - H\cdot$ ions in compounds **12–18** is, on the other hand, completely in line with expectations based on the pyridine data.

Azulene Derivatives.—Major features of the mass spectra of 3-(4-azulyl)-1-propyl tosylate (**19**) and its 6-azulyl isomer (**20**) appear in Table IV. The former

TABLE IV

PARTIAL MASS SPECTRA OF SOME AZULENE DERIVATIVES[a]

Compd	M+	ε	δ	γ	β	β + H	M+ − XOH[c]
3-(4-Az)-1-PrOTs, **19**	2	33	10	17[b]	55	0	17
3-(6-Az)-1-PrOTs, **20**	100	2	1	15[b]	23	6	45
3-(4-Az)-1-PrOH, **21**	19	0.5	1.5	18	48	94	6
3-(6-Az)-1-PrOH, **22**	52	0.8	1	25	70	92	4
3-(1-Az)-1-PrOH, **23**	25	0	0	12	100	0	0.7

[a] See footnote *a*, Table I. [b] Includes contributions from Ts^+. [c] X = Ts (**19**, **20**); X = H (**21–23**).

compound undergoes δ- and ε-bond cleavages, in complete analogy with the γ- and δ-bond cleavages observed in its ethyl analog.[3] The absence of these unusual modes of fragmentation in compound **20**, the observation of a metastable peak linking the molecular ion of compound **19** and the ε-cleavage daughter ion, and the energetics of ε-bond cleavage (IP, 7.3 eV; AP, ε-cleavage, 10.2 eV) all emphasize the similarity between the aryl participation reactions occurring in **19** and 2-(4-azulyl)ethyl tosylate (IP, 7.3 eV; AP, δ cleavage, 10.5 eV).[3]

In discussing the 2-(4-azulyl)ethanol derivatives, we suggested[3] that the unique reactivity of C_3 was responsible for the unexpected mass spectrometric reactions. This reactivity could either be due to the high electron density at C_3 or to the fact that C_3 is the position of greatest spin density in the molecular ion.[23] The latter possibility, involving a form of the molecular ion ionized in the azulene system, was considered less likely than a side-chain ionization mechanism, partly because of the energetics involved. Either mechanism implies that the δ- and ε-cleavage products in the propyl tosylate (**19**) should have structures l and m, respectively. They are illustrated as being formed from side chain ionized forms of the molecular ion.

A metastable peak was observed for loss of water from the ε-cleavage product ion in compound **19**. This requires that the ring in ion l be opened in those ions having sufficient energy to undergo further frag-

(12) Compare R. H. Shapiro and T. F. Jenkins, *Org. Mass Spectrom.*, **2**, 771 (1969), with H. F. Grützmacher, *ibid.*, **3**, 131 (1970).

(13) N. M. M. Nibbering and T. J. deBoer, *ibid.*, **2**, 157 (1969).

(14) N. M. M. Nibbering and T. J. deBoer, *ibid.*, **1**, 365 (1968).

(15) N. M. M. Nibbering and T. J. deBoer, *Tetrahedron*, **24**, 1415 (1968).

(16) N. M. M. Nibbering and T. J. deBoer, *Org. Mass Spectrom.*, **3**, 487 (1970).

(17) I. Howe, D. H. Williams, D. G. I. Kingston, and H. P. Tannenbaum, *J. Chem. Soc. B*, 439 (1969). Compare D. H. Williams and I. Howe, *Arch. Mass Spectral Data*, **1**, 122 (1970).

(18) An exceptional case, where δ cleavage occurs with some facility, is provided by 4-phenylbutylamine.[19]

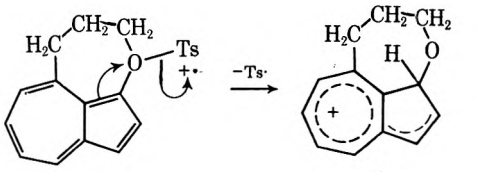
(19) D. A. Lightner, F. W. Sunderman, L. Hurtado, and E. Thommen, *Org. Mass Spectrom.*, **3**, 1325 (1970).

(20) These ions occur at the same nominal mass as the ^{13}C isotope peaks of the $M\cdot^+ - TsOH$ ($NsOH$) fragment ions. High resolution (30,000) was employed to establish the presence of the γ-cleavage ion in compound **14**: required for $C_9H_{11}O^+$, 135.0810; found, 135.0812.

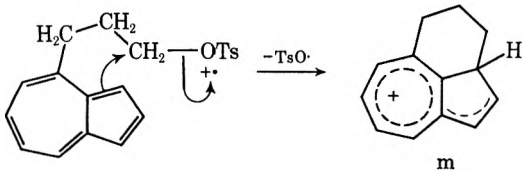
(21) Arguments based on substituent effects have appeared several times in discussions of phenonium-type ion formation in the mass spectrometer. Shapiro and Jenkins[12] employed this argument in their study on 2-arylethyl bromides, and a σ^0, but not a σ^+ or σ, correlation in the ethylenediamines $ArN(Me)CH_2CH_2N(Me)Ph$ has been suggested[22] as evidence against phenonium-type ion formation. The caution necessary in using such arguments is well illustrated by the behavior of methyl 4-arylbutyrates, where electron donation repressed the γ-cleavage process.[15]

(22) H. Giezendanner, M. Hesse, and H. Schmidt, *Org. Mass Spectrom.*, **4**, 405 (1970).

(23) I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, **43**, 2712 (1965).

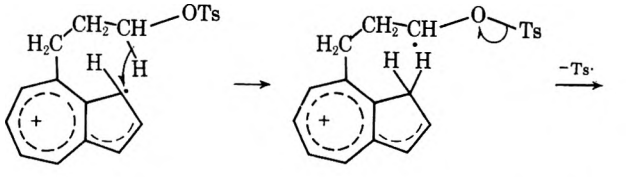


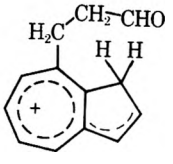
l



m

mentations or, alternatively, it suggests that ϵ cleavage occurs in these higher energy ions by an alternative mechanism which does not give a cyclized product. The formation of the protonated β-azulylalkanal (n)





n

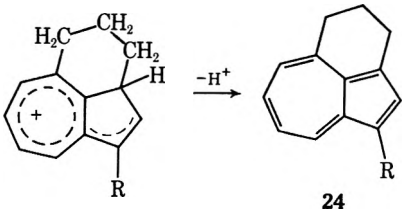
is possible, since it invokes the unique reactivity of C_3 in allowing fragmentation only in the 4-substituted azulene. (In 4-azulylacetic acids hydrogen transfer to a C_3 radical site was previously suggested.[3])

This type of mechanism involves participation by the aryl group, but only in the sense that the radical site on the ring abstracts a hydrogen atom from the substituent and so causes its fragmentation. It should also be noted that this general mechanism can be considered as an alternative to the direct participation mechanisms so far proposed for the pyridine as well as the azulene series.

There is no direct evidence on whether δ cleavage in compound **19** (*i.e.*, loss of TsO·) involves hydrogen transfer or direct aryl participation to give ion m, although solvolytic data (*vide infra*) support the latter view. It is also noteworthy that TsO· loss is relatively much more important in **19** than in its ethyl analog, a fact which can be simply explained as a result of aryl participation with formation of a six- rather than a five-membered cyclic product. The appearance potential for δ cleavage could not be determined, since the ^{13}C isotope of the low AP $M\cdot^+ - TsOH$ process interfered.

The 3-(4- and 3-(6-azulyl)-1-propanols (**21** and **22**) together with the 1-azulyl isomer (**23**)[24] have also been studied. This latter compound, **23**, shows the expected dominance of simple β cleavage, but γ cleavage also occurs. Aryl participation with formation of an ethyleneazulenium ion, so important in solution,[25] may be involved.[26] The spectra of alcohols **21** and **22** are surprisingly similar; both show very low abundance $M\cdot^+ - H\cdot$ and $M\cdot^+ - HO\cdot$ ions and rather more abundant $M\cdot^+ - \cdot CH_2OH$ ions. Radical stability differences account for the dissimilar behavior of **21** and its tosylate, **19**, while the similarity between **21** and **22** continues a trend noted and commented upon in the ethanols.[3]

Relationships to Solution Chemistry.—Buffered acetolysis of 3-(4-azulyl)-1-propyl nosylate (**19**) yields the 4,5-dihydro-3*H*-benz[*cd*]azulene (**24**, R = H) in 72%



R = H or Ac

24

yield, and $\Delta S^{\pm} = -1.0 \pm 1.3$ eu for this solvolysis.[4] These results indicate that solvolysis proceeds by participation of the 3 position of the azulene ring, in complete analogy to the δ-cleavage process in the mass spectrometer. This solvolysis behavior was previously predicted after a consideration of the mass spectra of the azulylethyl tosylates.[3] The mass spectrum of the 3-acetyl solvolysis product (**24**, R = $COCH_3$), obtained in ~1% yield, shows $M\cdot^+$ (30%), $M\cdot^+ - H\cdot$ (30%), $M\cdot^+ - Me\cdot$ (100%).

ω-Pyridylalkyl tosylates have not been solvolyzed, but the mass spectral results lead one to predict that in the propyl series the 2-substituted pyridyl tosylate will show an important k_Δ process. Significantly, this was by far the least stable of the three isomeric pyridyl-1-propyl tosylates, decomposing in 1–2 days in carbon tetrachloride solution at room temperature.

The contrast between β-(*p*-nitrophenyl)ethyl tosylate (**16**), which shows no aryl participation, and β-(*p*-anisyl)ethyl tosylate (**14**), which does undergo γ cleavage, presumably due to aryl participation, also has its parallels in solvolytic processes.[27] Thus the *p*-methoxy tosylate undergoes mainly a k_Δ process while the *p*-nitro tosylate reacts, almost exclusively, by the k_s route.

Conclusions.—The mechanistic threads common to the different aromatic systems studied here and the promise offered that there exist important relationships between neighboring group participation in the mass spectrometer and in solution constitute the most important results of this study. An extended investigation of aryl participation upon electron impact would appear to be warranted on the following grounds.

(1) Mass spectrometry might find use as a means of quickly surveying systems of potential interest for solvolytic studies.

(2) Fresh insights into solvent effects and a separation of k_Δ from k_s routes might be suggested by comparison of the results of the two methods.

(3) This type of comparative investigation seems to yield valuable information on gaseous ion structures and

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(26) γ cleavage was not observed at all in 1-azulylethanol.[3] This appears to be an instance of a quite general phenomenon (see Table III) associated with the reluctance to cleave a C–O bond and liberate HO·.

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it may serve as a probe of transition-state geometry in solution.

(4) Useful information on the relative importance of participating groups, preferred ring sizes, and relative radical stabilities can be obtained.

Experimental Section

Pyridyl-1-propanols 1–3 were commercial samples (Aldrich Chemical Co.) and were redistilled before use. The acetate 4 was prepared by acetylation of the alcohol with acetyl chloride in the presence of pyridine at −10 to 10°, and the product was fractionally distilled, bp 59–62° (0.08 mm). Acetates 5 and 6 were prepared by the same method, but in the absence of pyridine, to give products, bp 113–114° (2.5 mm) and 42° (0.75 mm), respectively. Tosylates 7–9 were prepared by Wiberg's method[28] using as reactant a suspension of powdered KOH in ether; products were extracted and chromatographed on alumina but could not be crystallized. Alcohols 10 and 11 were prepared from the corresponding picolines and paraformaldehyde;[29,30a] the products had bp 87–89° (2 mm) [lit.[29] bp 114–116° (9 mm)] and 121–122° (2 mm) [lit.[30a] 151–152° (13–14 mm)], respectively. 2-Phenethyl tosylate (12) and *p*-anisylethyl tosylate (14) were prepared by the method of Wiberg.[28] Nosylates 13, 15, and 17 were prepared by adding an ether solution of the corresponding alcohols to an ether solution of methyllithium (1 molar equiv) and adding an equivalent amount of *p*-nitrobenzenesulfonyl chloride.[4] Alcohol 18 was prepared by the sequence phenylacetonitrile → *p*-nitrophenylacetonitrile, mp 116° (lit.[30b] mp 116–117°), → *p*-nitrophenylacetic acid, mp 151–153° (lit.[31] mp 151–152°), → 2-(*p*-nitrophenyl)-ethanol. The corresponding tosylate (16) was prepared by Wiberg's method.[28] The preparation of the azulylpropanols and tosylates is detailed elsewhere[4,24] (the methylazulenes were converted to the carbanions and allowed to react with ethylene oxide to form the alcohols). 2-(2-Pyridyl)ethyl tosylate was a gift from Dr. G. Jones, University of Keele. The purity of all compounds was checked by nmr and in the few cases among the tosylates where impurities were present these did not contribute to the peaks of interest in the mass spectra.

Mass spectra were obtained by direct insertion for the tosylates and nosylates and by use of the heated introduction system in other cases. Spectra were obtained at 70 eV, 100 μA, and 8 kV on an AEI MS9 mass spectrometer. Ionization and appearance potentials were measured against benzene as internal standard using the semilog plot technique.

Registry No.—1, 2859-68-9; 2, 2859-67-8; 3, 2629-72-3; 4, 38456-23-4; 5, 38456-24-5; 6, 38456-25-6; 7, 38456-26-7; 8, 38456-27-8; 9, 38456-28-9; 10, 103-74-2; 11, 5344-27-4; 19, 38456-31-4; 20, 38456-32-5; 21, 38305-10-1; 22, 38456-34-7; 23, 35046-09-4.

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The Study and Characterization of Nucleosides by Mass Spectrometry. III. Comparison between the Mass Spectra of Trimethylsilyl Derivatives of Purine 2′- and 3′-Linked Anhydro, Thioanhydro, and Aminoanhydro Nucleosides

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The mass spectra of trimethylsilyl derivatives of several purine O, S, and NH linked anhydro nucleosides were studied in order to determine the positional effects of 8,2′ *vs.* 8,3′ linkage of base to sugar. Principal ions in the spectra were common to both series of anhydro nucleosides but variations in intensity could be used to distinguish between them. These variations could be related to the anticipated ease of formation of the basic ion type from the skeleton of the molecule.

Cyclonucleosides are important analogs of natural nucleosides. They are characterized by having, in addition to the *N*-glycoside linkage, a covalent linkage, either directly or *via* bridging atoms, between the 2′, 3′, or 5′ carbons of the sugar and a carbon or nitrogen atom (other than the nitrogen of the glycoside bond) of the purine or pyrimidine ring. Anhydro nucleosides are cyclonucleosides in which the extra covalent linkage is *via* bridging atoms. Acid or base hydrolysis of the anhydro linkage normally leads to ribo, arabino, or xylo nucleosides.[1] Nucleophilic displacement of the anhydro linkage leads to nucleosides modified on the sugar moiety[1–3] and sometimes on the base moiety.[1,4–6] Chemical conversion of anhydro nucleosides has led to the synthesis of modified nucleosides such as the antitumor drug arabinocytidine[7,8] and the antibiotic cordycepin.[6] They have been used as model substrates for studies of enzyme activity[9,10] and as intermediates in the chemical synthesis of nucleotides.[11–13] Recently, the synthesis and properties of the dinucleoside monophosphate A^spA^s and its conversion to dApdA have been described.[14] In conjunction with our synthetic objectives it was necessary to develop methods of identifying small quantities of specific anhydro nucleosides and to estimate their purity. We have found mass

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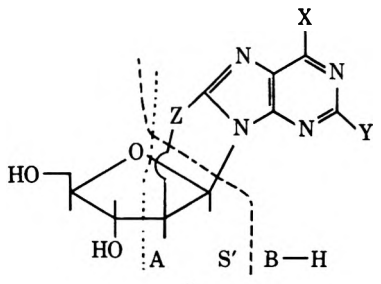
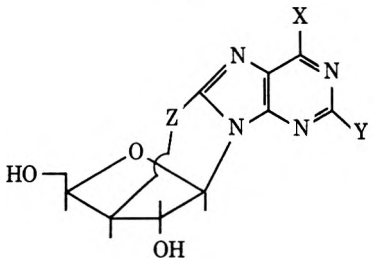
spectrometry to be an invaluable and powerful aid in these studies. For purine anhydro nucleosides a major difficulty lies in the distinction between the 8,2′- and 8,3′-linked isomers **1** and **2**.



1



2

The isomers do not separate by paper chromatography or electrophoresis. Since gas chromatography of trimethylsilyl (TMS) derivatives of natural purine nucleosides has been achieved,[15] a gc–mass spectral method appears to hold future promise for identifying anhydro nucleosides. In this paper we report mass spectra obtained for TMS derivatives of several purine anhydro nucleosides with the objective of identifying basic ion types, emphasizing trends in relative intensities, and providing data which can be used to identify isomers or for analytical purposes.

Results and Discussion

Table I lists the purine anhydro nucleosides (and an abbreviation for each) presently available to us, together with their melting points, and also sample temperatures required for mass spectral analysis of the free compounds (when attempted) and of the TMS derivatives. Partial mass spectra of some O, S, and NH bridged 8,2′-, 8,3′- and 8,5′-anhydroadenosines,[16,17] certain of their *N*-methyl analogs,[17,18] and 8,2′-thioanhydroinosines[19] have been reported, as well as a molecular ion for 8,2′-SAnG.[20] No systematic interpretation of the spectra has been given. The mass spectra of the 8,2′- and 8,3′-linked isomers are either very similar,[16] or they show unexpected fragmentations[18] which reduce the possibility of distinguishing structural differences between them by mass spectrometry. Additionally, it has been found that the spectra of 2,2′- and 2,3′-anhydrouridines are very similar.[21] These observations probably arise from the polar nature of the molecules and the consequent high temperatures necessary to cause vaporization of the samples. (See Table I for temperatures required in our instrument for the free anhydro nucleosides.) These differences should be reduced by the preparation of volatile derivatives. We have found trimethylsilylation to be a satisfactory derivatization procedure. The method is simple and the mass spectra of these derivatives show abundant molecular ions. In addition, the TMS-d_9 derivatives are valuable aids in spectral interpretation. The deuterium shifts, combined with the availability of the various bases, largely compensate for the nonavailability of a high-resolution mass spectrometer. Under mild conditions (see Exprimental Section), one hydrogen of each OH and NH_2 group of sugar and base moieties was replaced by TMS. For compounds 8,2′-NHAnA and 8,2′-NHAnG the hydrogen of the bridging NH group was replaced at room temperature, but for 8,2′-NHAnI warming of the reaction mixture was required. (Acetylation is sometimes used to produce volatile derivatives. We note that the trimethylsilyl derivatives are probably preferable for compounds described here. We have found[22] that the di-*O*-acetyl derivatives of 2′- and 3′-linked anhydrouridines have indistinguishable mass spectra, possibly because of a thermally or electron-impact induced molecular rearrangement. On the other hand, the corresponding di-*O*-TMS derivatives have readily distinguishable spectra.[21,22])

The mass spectra we obtained for the free anhydroadenosines 8,2′-OAnA, 8,2′-SAnA, and 8,2′-NHAnA agreed well with those reported in the literature and will not be further discussed. The relative intensities of structurally significant ions for the TMS derivatives are shown in Tables II and III for the 2′- and 3′-linked compounds, respectively.[23] In many cases *m/e* 73 (Me_3Si^+) was the biggest peak, but, since the derivatives have different numbers and types of TMS-derived groups, it seemed preferable to ignore this ion when assigning the base peak. Thus its relative intensity is usually greater than 100 in Tables II and III. When this is done, the molecular ion often becomes the base peak. These spectra show many of the basic ion types observed in the mass spectra of TMS derivatives of pyrimidine cyclonucleosides[21,24,25] and natural purine nucleosides,[26] and in addition two additional ion types labelled below as A^+ and $(A + 13)^+$. In contrast to the previous spectra, the present spectra show much less extensive fragmentation and though characteristic ions in the spectra are of lower abundance they are of sufficient intensity to provide structural information. Except for trivial processes, metastable ions were generally absent from the spectra. Individual ion types will be discussed separately.

M^+ and $(M - CH_3)^+$.—Both ions are of high abundance in all spectra. Thus it is to be expected that the molecular ion will be easily recognized for TMS derivatives of compounds of these structure types. In

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TABLE I.—COMPOUNDS STUDIED, MELTING POINTS, AND SAMPLE TEMPERATURES REQUIRED FOR MASS SPECTRAL ANALYSIS[d]

Compd	Abbreviation	Registry no.	X	Y	Z	Mp, °C	Sample temperature— Free compd	TMS deriv
8,2′-Anhydroadenosine	8,2′-OAnA	13089-44-6	NH_2	H	O	170 dec	170	47
8,2′-Thioanhydroadenosine	8,2′-SAnA	16667-76-8	NH_2	H	S	159–162	190	52
8,2′-Aminoanhydroadenosine	8,2′-NHAnA	33962-27-5	NH_2	H	NH	260 dec	215	80
8,2′-Anhydroinosine	8,2′-OAnI	38659-93-7	OH	H	O	232 dec		134
8,2′-Thioanhydroinosine	8,2′-SAnI	38659-94-8	OH	H	S	217 dec	dec[a]	115
8,2′-Aminoanhydroinosine	8,2′-NHAnI	38659-95-9	OH	H	NH	210 dec		44,[b] 134[c]
8,2′-Anhydroguanosine	8,2′-OAnG	38659-96-0	OH	NH_2	O	210 dec		109
8,2′-Thioanhydroguanosine	8,2′-SAnG	38659-97-1	OH	NH_2	S	256 dec	dec[a]	86
8,2′-Aminoanhydroguanosine	8,2′-NHAnG	38659-98-2	OH	NH_2	NH	203 dec		109
8,2′-Thioanhydroxanthosine	8,2′-SAnX	38659-99-3	OH	OH	S	173 dec	dec[a]	115
8,3′-Anhydroadenosine	8,3′-OAnA	28234-87-9	NH_2	H	O	266–267		40
8,3′-Thioanhydroadenosine	8,3′-SAnA	16667-78-0	NH_2	H	S	166–168		75
8,3′-Anhydroinosine	8,3′-OAnI	38660-01-4	OH	H	O	229 dec		62
8,3′-Thioanhydroinosine	8,3′-SAnI	38660-03-6	OH	H	S	218 dec		35
8,3′-Thioanhydroguanosine	8,3′-SAnG	38660-04-7	OH	NH_2	S	183 dec		131

[a] No spectrum could be obtained; upper temperature reached, 300°. [b] Tetrakis TMS derivative. [c] Tris TMS derivative. [d] Refer to structures 1 and 2 for locations of groups X, Y, and Z.

TABLE II.[b]—RELATIVE INTENSITIES OF SELECTED IONS IN THE MASS SPECTRA OF TMS DERIVATIVES OF PURINE 8,2′-ANHYDRO NUCLEOSIDES

Ion or *m/e*	OAnA(TMS)$_3$	SAnA(TMS)$_3$	NHAnA(TMS)$_4$	OAnI(TMS)$_3$	SAnI(TMS)$_3$	NHAnI(TMS)$_3$	NHAnI(TMS)$_4$	OAnG(TMS)$_4$	SAnG(TMS)$_4$	NHAnG(TMS)$_4$	SAnX(TMS)$_4$
M^+	481/100	497/100	552/100	482/35	498/47	481/46	553/66	569/100	585/100	640/100	586/100
$(M - CH_3)^+$	466/37	482/35	537/27	467/20	483/16	466/14	538/13	554/35	570/28	625/22	571/48
$(A + 30 + TMS)^+$	350/18	366/4	421	351/26	367/16	350	422	438/7	454/<1	509	455
$(A + TMS)^+$	320/3	336/3	391/1	321/10	337/18	320/8	392/4	408/3	424/2	479	425/6
$(A + 31)^+$	278/2	294	349	279/11	295	278	350	366	382/2	437	383
$(A + 13)^+$	260/29	276/6	331/4	261/16	277/11	260/10	332	348/7	364/1	419	365/4
$(A + H)^+$	248/8	264/15	319/13	249/20	265/43	248/28	320/28	336/7	352/5	407	353/23
A^+	247	263/3	318/9	248/19	264/10	247/16	319/16	335	351	406	352
$(B + HTMS)^+$	296/7	312/1	367	297/13	313/3	296/3	368	384/3	400	455	401/2
$(B + TMS)^+$	295/11	311/3	366	296/25	312/8	295/7	367	383/5	399	454	400/3
$(B + HTMS - CH_3)^+$	281/4	297	352	282/6	298	281	353/14	369/2	385	440	386/1
$(B + TMS - CH_3)^+$	280/15	296	351/1	281/13	297	280	352/7	368/4	384	439	385/2
$(B + 2H)^+$	224/5	240/5	295/3	225/13	241/8	224	296/11	312/3	328/1	383/27	329/8
$(B + H)^+$	223/10	239/16	294/8	224/9	240/17	223	295/26	311/7	327/3	382/82	328/22
B^+	222/8	238/19	293	223/16	239/18	222	294	310/5	326/2	381	327/9
$(B - H)^+$	221/5	237/19	292	222/10	238/48	221	293	309/4	325/3	380	326/22
$(S' - H)^+ \equiv 259$	14	13	7	69	53	16	51	9	1	6	13
$(S' - 2H)^+ \equiv 258$	5	2		13		5	7	4	<1	9	2
$(S' - 17)^+ \equiv 243$	7	3	3	14			11	8	1	16	3
$(S' - 43)^+ \equiv 217$	9	21	28	33	66	100[a]	100[a]	25	3	20	20
189	8	12	7	18	32	22	13	5	3		10
169	19	6	2	16	23	15	20	13	2	42	8
147	15	12	22	57	120	25	39	28	8	73	74
103	54	35	30	100[a]	100[a]	92	87	24	9	13	39
75	16	11	13	220	135	82	53	82	5	191	28
73	156	112	157	305	495	208	303	84	44	170	198
$\%\Sigma_{80}^{M}$	9.73	11.91	12.91	1.39	2.00	2.32	1.98	7.94	22.14	3.72	8.54

[a] Used as base peak when M^+ is not base peak. [b] The data presented are *m/e*/rel intensity (upper part of table); rel intensity (lower part of table).

TABLE III[a]

RELATIVE INTENSITIES OF SELECTED IONS IN THE MASS SPECTRA OF TMS DERIVATIVES OF PURINE 8,3′-ANHYDRO NUCLEOSIDES

Ion or *m/e*	OAnA(TMS)$_3$	OAnI(TMS)$_3$	SAnA(TMS)$_3$	SAnI(TMS)$_3$	SAnG(TMS)$_4$
M^-	481/100	482/100	497/100	498/100	585/100
$(M - CH_3)^+$	466/26	467/68	482/47	483/39	570/38
$(A + 30 + TMS)^+$	350/45	351/92	366/8	367/35	454/6
$(A + TMS)^+$	320/1	321/7	336	337/5	424
$(A + 31)^+$	278/3	279	294/9	295/5	382/8
$(A + 13)^+$	260/62	261/40	276/3	277/8	364
$(A + H)^+$	248/4	249/11	264	265	352/4
A^+	247/2	248/3	263	264	351/2
$(B + 2H)^+$	224/4	225/19	240/5	241/15	328/7
$(B + H)^+$	223/9	224/12	239/9	240/9	327/11
B^+	222/16	223/29	238/16	239/26	326/6
$(B - H)^+$	221/4	222/13	237/5	238/13	325
$(S' - H)^+ \equiv 259$	6	39	3	12	5
$(S' - 2H)^+ \equiv 258$	4	61	4	31	4
$(S' - 17)^+ \equiv 243$	6	28	9	30	15
$(S' - 43)^+ \equiv 217$	2	18		3	8
189	2	6			
169	13	47	5	17	9
147	10	22	6	14	32
103	19	46	22	23	16
75	21	37	15	55	105
73	156	254	89	181	131
$\%\Sigma^{M}_{50}$	10.52	4.52	11.89	4.94	5.29

[a] The data presented are *m/e*/rel intensity (upper part of table); rel intensity (lower part of table).

TABLE IV[a]

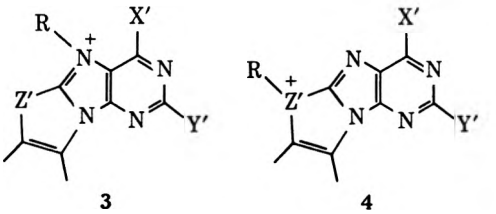
COMPARISON OF RELATIVE INTENSITIES OF SELECTED IONS IN THE MASS SPECTRA OF TMS DERIVATIVES OF PURINE 8,2′- AND 8,3′-ANHYDRO NUCLEOSIDES

Ion	Anticipated magnitude	OAnA(TMS)$_3$	OAnI(TMS)$_3$	SAnA(TMS)$_3$	SAnI(TMS)$_3$	SAnG(TMS)$_4$
$(A - H)^+$	2′ > 3′	8/4	20/11	15/—	43/—	5/4
$(A + TMS)^+$	2′ > 3′	3/1	10/7	3/—	18/5	2/—
A^+	2′ > 3′	—/2	19/3	3/—	10/—	—/2
$(A + 31)^+$	3′ > 2′	2/3	11/—	—/9	—/5	2/8
$(A + 30 + TMS)^+$	3′ > 2′	18/45	26/92	4/8	16/35	1/6
$(A + 13)^+$	3′ > 2′	29/62	16/40	6/3	11/8	1/—
$(S' - H)^+$	2′ > 3′	14/6	69/39	13/3	53/12	1/5
$(S' - 2H)^+$	3′ > 2′	5/4	13/61	2/4	—/31	1/4
$(S' - 17)^+$	3′ > 2′	7/6	14/28	3/9	—/30	1/15
$(S' - 43)^+$	2′ > 3′	9/2	33/18	21/—	66/3	3/8

[a] The data given are rel intensity for 2′-linked isomer/rel intensity for 3′-linked isomer.

doubtful cases, comparison of spectra with those of TMS-d_9 derivatives would remove possible ambiguities in determining whether the highest observed value of *m/e* is due to M^+ or $(M - CH_3)^+$. We note that the extent of fragmentation of the molecular ion, as emphasized by the percentage of the total ion current above *m/e* 50 carried by the molecular ion, *i.e.*, the $\%\Sigma^{M}_{50}$ values given in Tables II and III, is significantly greater for the anhydroinosines than for the other compounds.

$(A + H)^+$ and $(A + TMS)^+$.—These ions are characteristic of 2′-linked anhydro nucleosides of both pyrimidine and purine types. Structural analogs have been proposed previously[21,24,25] and invoke hydrogen or TMS transfer to the fused based plus anhydro-ring moiety to produce the well-stabilized ions **3** and **4**.



3 **4**

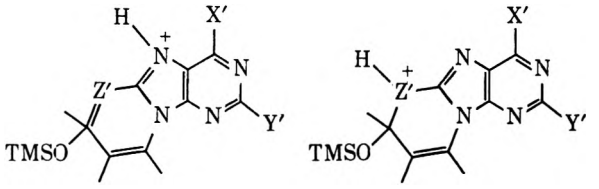
R = H or TMS
X′, Y′, Z′ = TMS derived function of X, Y, Z

The hydrogen transferred comes partially from the TMS groups and partially from the ribose skeleton, the ratio depending upon the nature of the base moiety and of the heteroatom of the anhydro linkage. Comparison of the spectra of the TMS and TMS-d_9 derivatives gives the following approximate values for the percentage of hydrogen transferred from the TMS groups under the instrumental conditions given in the Experimental Section: 8,2′-OAnA (50%), 8,2′-SAnA (50%), 8,2′-NHAnA (50%), 8,2′-SAnI (40%), 8,2′-NHAnI (50%), 8,2′-SAnG (20%).

Ions of the same mass as $(A + H)^+$ and $(A + TMS)^+$ are also present in the mass spectra of the 3′-linked isomers (Table III). Formation of these ions from the 3′-linked compounds presumably requires a ring

contraction and their formation should represent a less favorable fragmentation process. This expectation is supported by the data of Table IV, which directly compares the intensities of these ions for those nucleotides for which both isomers are available.

(A + 31)$^+$ and (A + 30 + TMS)$^+$.—Structural analogs of these ions have been observed in the mass spectra of pyrimidine[21,24,25] and purine[16,17,19] 2′- and 3′-anhydro nucleosides and TMS derivatives of pyrimidine[21,24,25] 2′- and 3′-anhydro nucleosides. For the 2′-linked compounds we have previously proposed[24] two requirements for the formation of these ions: (i) ring expansion to incorporate the $C_{3'}$ atom into a six-membered ring, and (ii) migration of hydrogen to the base moiety or heteroatom of the anhydro linkage to give the well-stabilized ions **5** and **6**.



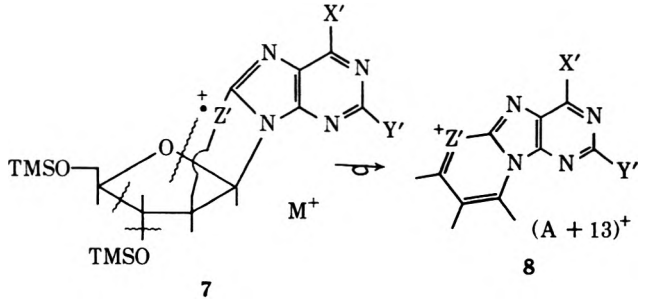
5 **6**

X′, Y′, Z′ = TMS derived function of X, Y, Z

For the 2′-linked compounds these ions are of generally low abundance (Table II) and have their highest intensities for the O-linked compounds. This implies that the proposed ring expansion required for these ions occurs more readily when O rather than S or NH is present in the anhydro linkage.

For the 3′-linked compounds the (A + 31)$^+$ and (A + 30 + TMS)$^+$ ions can be formed from the molecular ion without the necessity for ring expansion. We anticipate that their intensities should be higher for the 3′- than for the 2′-linked isomers. With one exception the data of Table IV support this view.

(A + 13)$^+$.—Comparison of the spectra of the TMS and TMS-d_9 derivatives of compounds containing the different bases identifies an ion which contains the base moiety with its TMS substituent(s) and the heteroatom of the anhydro linkage, and which can only be reasonably represented as (A + 13)$^-$. For the 2′-linked compounds the only logical route to its formation therefore involves fission of the $C_{3'}$–$C_{4'}$ bond and incorporation of the $C_{3'}$ and $H_{3'}$ atoms into the ion product.



7 **8**

A ring expansion is invoked which appears to occur more readily for the O-linked than for the NH- or S-linked compounds (Table II). This trend parallels that found for the formation of the (A + 31)$^+$ and (A + 30 + TMS)$^+$ ions. Because a ring expansion is not required we anticipated that this ion would have enhanced intensities for the 3′-linked compounds, but the data of Table IV are inconclusive, though in the expected sense for those ions of high intensity. Structural analogs of this ion have not been previously discussed, though examination of reported spectra reveals its presence at (M − 77)$^+$ for several free purine anhydro nucleosides.[16–19] In the case of 8,3′-anhydro-8-oxy-9β-D-xylofuranosyl-N^6-dimethyladenine this peak may have been misinterpreted.[18]

A$^+$.—This odd-electron ion is presumably stable because of the extended π system of the base. It has not been observed for pyrimidine anhydro nucleosides and is of generally low intensity here, except for some of the 2′-linked anhydroinosines. As anticipated, it is usually more abundant for the 2′- than for the 3′-linked isomers. Analogs of this ion can be found at (M − 90)$^+$ in reported spectra of purine anhydro nucleosides.[16–19]

(B − H)$^+$, B$^+$, (B + H)$^+$, (B + 2H)$^+$.—Comparison of the relative intensities of the ions in this group reveals that hydrogen transfer to the base moiety is not so extensive as for the pyrimidine analogs.[24,25] In particular, (B − H)$^+$ is sometimes prominent in this group, where it is usually insignificant for the pyrimidine compounds.

(B + TMS)$^+$, (B + HTMS)$^+$, (B + TMS − CH$_3$)$^+$, and (B + HTMS − CH$_3$)$^+$.—These low-intensity ions, whose compositions are supported by appropriate mass shifts in the spectra of the TMS-d_9 derivatives, have been observed in the spectra of TMS derivatives of purine nucleosides[26] and nucleotides,[27] but have not been previously reported for TMS derivatives of anhydro nucleosides.

(S′ − H)$^+$, (S′ − 2H)$^+$, and (S′ − 17)$^+$.—These ions, which are characteristic of the sugar moiety, occur at *m/e* 259, 258, and 243, respectively, and their mechanistic origins have been previously discussed.[21,24,25] Although the reason is not clear, the intensity of *m/e* 258 is greatly enhanced for 2,3′-anhydrouridine with respect to 2,2′-anhydrouridine,[21] as is the intensity of (S′ − 17)$^+$, which can be formed from (S′ − 2H)$^+$ by loss of a methyl group. Table IV shows that this observation generally holds for the purine anhydro nucleosides as well.

(S′ − 43)$^+$.—The structure of this ion, *m/e* 217, has been discussed previously.[21,24,27–29] In agreement with the requirement that it contain three skeletal carbon atoms its intensity is generally greater in the spectra of the 2′-linked than the 3′-lined anhydro nucleosides (Table IV) in spite of the known tendency for trimethylsilyl group migration.[21,24,26,28–33]

Other Ions.—The remaining prominent ions in most spectra, *i.e.*, *m/e* 189, 169, 147, 103, 75, and 73, are

(27) A. M. Lawson, R. N. Stillwell, M. M. Tacker, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **93**, 1014 (1971).
(28) D. C. DeJongh, T. Radford, J. D. Hribar, S. Hanessian, M. Bieber, G. Dawson, and C. C. Sweeley, *ibid.*, **91**, 1728 (1969).
(29) M. Zinbo and W. R. Sherman, *ibid.*, **92**, 2105 (1970).
(30) G. Peterson, *Tetrahedron*, **26**, 3413 (1970).
(31) S. Karady and S. H. Pines, *ibid.*, **26**, 4527 (1970).
(32) E. White, S. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **93**, 6340 (1971).
(33) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968).

either ribose- or TMS-derived fragments and have been discussed previously.[21,24,25]

Conclusion

In Table IV are listed for comparison the relative intensities of those ions expected to distinguish between 2′- and 3′-linked isomers. The general trends can be used to differentiate between the isomers, but, because of exceptions in the relative intensities in a few cases, caution must be exercised and all the ions listed in Table IV should be considered. The data can be used to identify isomers if a gas chromatographic separation can be achieved and to enable predictions to be made on the general form of the mass spectra of isomers not yet prepared. However, the positive identification of a single unknown isomer from the mass spectral data alone would remain uncertain.

Experimental Section

The mass spectra were recorded on a Hitachi RMU-6D single-focusing mass spectrometer using published procedures,[24] at an electron energy of 50 V and a nominal 900-V ion-accelerating energy. Trimethylsilyl derivatives were prepared[24] by treating 0.5 mg of a sample with 100 μl of BSTFA and 15 μl of TMCS (Pierce Chemical Co.). Complete trimethylsilylation (*i.e.*, one hydrogen of each OH, NH, or NH_2 group of sugar and base moieties was replaced by a TMS group[34]) was achieved overnight at room temperature in all cases except for 8,2′-NHAnI. Three TMS groups were incorporated at room temperature but four were incorporated by heating to 60° for 30 min. For the preparation of the TMS-d_9 derivatives BSA-d_{18} and TMCS-d_9 (Merck Sharpe and Dohme, Montreal) were used.

Syntheses of the compounds have been previously described: 8,2′-OAnA,[35,36] 8,2′-SAnA,[36-39] 8,2′-NHAnA,[17,39] 8,2′-OAnI,[40] 8,2′-SAnI,[19,20,38,39] 8,2′-NHAnI,[39] 8,2′-SAnG,[20,38,39,41] 8,2′-NHAnG,[39] 8,2′-SAnX,[20,40] 8,3′-OAnA,[35] 8,3′-OAnI,[40] 8,3′-SAnA,[37] 8,3′-SAnI,[19,40] 8,3′-SAnG.[42]

Acknowledgment.—We thank the National Research Council of Canada for financial support of this work.

(34) A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, Ill., 1968.
(35) M. Ikehara and M. Kaneko, *Chem. Pharm. Bull.*, **18**, 2401 (1970).
(36) M. Ikehara and S. Tezuka, *Tetrahedron Lett.*, 1169 (1972).
(37) M. Ikehara and M. Kaneko, *Tetrahedron*, **26**, 4251 (1970).
(38) K. K. Ogilvie, L. A. Slotin, J. B. Westmore, and D. C. K. Lin, *Can. J. Chem.*, **50**, 2249 (1972).
(39) K. K. Ogilvie, L. A. Slotin, J. B. Westmore, and D. C. K. Lin, *J. Heterocycl. Chem.*, **9**, 1179 (1972).
(40) M. Ikehara, *Chem. Pharm. Bull.*, **8**, 367 (1960).
(41) K. K. Ogilvie, L. A. Slotin, J. B. Westmore, and D. C. K. Lin, *Can. J. Chem.*, **50**, 1100 (1972).
(42) K. K. Ogilvie, L. A. Slotin, D. C. K. Lin, and J. B. Westmore, *ibid.*, **50**, 3276 (1972).

Noncoordinating Buffers. I. Synthesis and Characterization of Water-Soluble Derivatives of 2,6-Di-*tert*-butylpyridine

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Several derivatives of 2,6-di-*tert*-butylpyridine, containing alkyl, trimethylammonium [$-N(CH_3)_3^+$], or dimethylammonium [$-NH(CH_3)_2^+$] substituents, have been prepared and characterized. The mechanism of their synthesis, their water solubilities, pK_a's, and possible utilization as noncoordinating buffers and nonnucleophilic bases are briefly discussed.

Studies of reactions of metal ions in aqueous solution are limited by the fact that all common Lewis bases that may be used for buffering action will also coordinate to metals, making it impossible to investigate the behavior of uncomplexed metal ions in buffered media. In a search for water-soluble noncoordinating buffers, *i.e.*, weak bases that may donate their electron pair to a proton but not to a metal ion, several dimethylaminopyridines and quaternary ammonium pyridines with 2- and 6-*tert*-butyl substituents were prepared. The pyridine nitrogen of these compounds can coordinate to a proton, but is too sterically shielded to coordinate to Lewis acids even as small as CH_3^+ or BF_3.[1] This ensures that the title compounds will not coordinate to metal ions and that they will also have very low nucleophilic activity. It is now well known that the commonly used buffer 2,6-lutidine is not sufficiently shielded to prevent its coordination to metal ions.[2]

Results and Discussion

Synthesis.—The reaction of an alkyllithium compound with pyridine provides a direct method for the introduction of alkyl substituents ortho to the pyridine nitrogen. Since the original work of Ziegler and Zeiser[3] this reaction has been extensively utilized and studied, the intermediacy of a *N*-lithio 1,2-dihydropyridine derivative having been established.[4-6] In the presence of excess *tert*-butyllithium, pyridine is converted to 2,4,6-tri-*tert*-butylpyridine in one synthetic step.[7] Employing this one-step procedure, we have synthesized several *tert*-butylated pyridines (see Table I). Presumably these reactions proceed in a stepwise matter, there being enough *tert*-butyllithium present at the decomposition of the first dihydro derivative(s) so that subsequent reaction can occur.

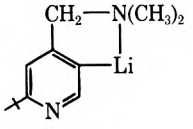
In addition to alkylating pyridine bases in the above manner, an alkyllithium may also metalate either the

(1) H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, **88**, 986 (1966).
(2) (a) J. R. Allen, D. H. Brown, R. H. Nuttal, and D. W. A. Sharp, *J. Inorg. Nucl. Chem.*, **26**, 1895 (1964); **27**, 1305 (1965). (b) 2,6-Lutidine coordinates to the pentaammineruthenium(II) center in dilute aqueous solution: Professor H. Taube, Stanford University, private communication (1972).
(3) K. Ziegler and H. Zeiser, *Ber.*, **63**, 1847 (1930).
(4) R. Foster and C. A. Fyfe, *Tetrahedron*, **25**, 1489 (1969).
(5) R. A. Abramovitch and G. A. Poulton, *Chem. Commun.*, 274 (1967).
(6) C. S. Giam and J. L. Stout, *ibid.*, 142 (1969).
(7) F. V. Scalzi and N. F. Golob, *J. Org. Chem.*, **36**, 2541 (1971).

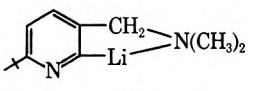
TABLE I
COMPOUNDS SYNTHESIZED

Compd[c]	Yield, %	Mp or bp, °C (mm)
(1) 2,4,6-Tri-*tert*-butylpyridine	33	70.1-70.3
(2) 2,6-Di-*tert*-butyl-4-methylpyridine	44	33.5-33.8
(3) 2,6-Di-*tert*-butyl-3-methylpyridine	40	48 (0.1)
(4) 4-Dimethylaminomethylpyridine	37	87 (10)
(5) 3-Dimethylaminomethylpyridine	80	90 (15)
(6) 2-*tert*-Butyl-4-dimethylaminomethylpyridine	20	60 (3)
(7) 2,6-Di-*tert*-butyl-4-dimethylaminomethylpyridine	<5	80 (2)
(8) 2-*tert*-Butyl-5-dimethylaminomethylpyridine	<10	97 (1)
(9) Trimethyl(2,6-di-*tert*-butyl-4-picolyl)ammonium perchlorate	50	246-247
(10) 2,6-Di-*tert*-butyl-4-dimethylaminopyridine	77	65-66
(11) Dimethyl(2,6-di-*tert*-butyl-4-pyridyl)ammonium salts		
(a) Perchlorate	>95	202.5-204.5
(b) Nitrate[a]	>95	151.2-152.0 dec
(c) Chloride[a]	>95	Sublimes *ca.* 240
(d) Bromide[a]	>95	Sublimes *ca.* 255[b]
(12) Trimethyl(2,6-di-*tert*-butyl-4-pyridyl)ammonium salts		
(a) Iodide	>95	171.2-171.8 dec
(b) Perchlorate	>95	290-291
(c) Nitrate	>95	226.5-227.0
(13) 2-*tert*-Butyl-6-dimethylaminopyridine	52	46-48 (0.07)
(14) Trimethyl(2-*tert*-butyl-6-pyridyl)ammonium salts		
(a) Iodide	92	192.2-192.9
(b) Perchlorate	>95	226.0-226.8
(c) Trifluoromethanesulfonate	>95	142.0-143.5
(15) 2,4-Di-*tert*-butyl-6-dimethylaminopyridine	50	97 (0.7)
(16) Trimethyl(2,4-di-*tert*-butyl-6-pyridyl)ammonium salts		
(a) Iodide	>95	197.9-198.4
(b) Perchlorate	>95	233.0-234.5

[a] Isolated both as pure salt and as chloroform adduct; melting point is that of pure salt. [b] With decomposition. [c] 1-16 (a-d).



II



III

pyridine ring or an activated substituent.[8,9] Brown and Kanner[1] pointed out that ring metalation could account for the yields of bipyridyl derivatives obtained in these reactions. Ring metalation proves to be a serious obstacle to the di-*tert*-butylation of 3- and 4-dimethylaminomethylpyridine, since in these compounds the side chain is capable of chelating the lithium and thus stabilizing the metalated product, a phenomenon previously observed with benzyldimethylamine[10] and related compounds.[11] The 3 compound does not add a second *tert*-butyl at all, presumably because the ring-metalated product III (i) has the 6 position blocked and (ii) is more stable than the analogous 5-metalated II because of the ortho-directing influence of the ring nitrogen.[9]

Quaternization of the several tertiary amines prepared in this work is easily accomplished with methyl iodide. Reaction at the hindered pyridine nitrogen is not observed to be a complication, even with 2-*tert*-butyl-6-dimethylaminopyridine. The iodide salts are easily converted to perchlorates, trifluoromethanesulfonates, nitrates, and chlorides by treatment with the appropriate silver salt. Because of the singular importance of perchlorate as a noncoordinating anion, a cheaper, more direct route to the preparation of perchlorate salts was sought. It was found that the methylating agent[12] trimethylsulfoxonium perchlorate (*vide infra*) readily quaternizes tertiary amines to their perchlorate salts in one step.

Properties.—Most of the sterically hindered pyridines prepared in this work have a measurable affinity for protons (see Table II) and are thus suitable for use in buffer systems. Brown and Kanner[1] first observed that the nitrogen of 2,6-di-*tert*-butylpyridine is so sterically shielded that it cannot comfortably coordinate to a fully solvated proton and thus the pK_a of this compound is 1.4 units lower than would be expected. Addition of an alkylammonium function to the pyridine nucleus further lowers the pK_a, since a formal positive charge repels the coordinated proton. The data in Table I show that this effect becomes larger as the positive charge is placed closer to the pyridine nitrogen, there being almost no effect in the trimethyl-(2,6-di-*tert*-butyl-4-picolyl)ammonium ion while the trimethyl(2-*tert*-butyl-6-pyridyl)ammonium ion is so acidic that it is only half protonated in 7 *F* HCl.

The water solubilities of some of the salts synthesized in this work are listed in Table III. For all cations tested, a perchlorate or trifluoromethanesulfonate counterion leads to a relatively insoluble salt. Likewise, for all anions tested, trimethylammonium salts have only limited solubility in water. However, the dimethylammonium derivatives are much more soluble

(8) (a) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966); (b) K. Schofield, "Hetero-aromatic Nitrogen Compounds: Pyrroles and Pyridines," Plenum Press, New York, N. Y., 1967, p 202; (c) L. E. Tenenbaum, "The Chemistry of Heterocyclic Compounds: Pyridine and Its Derivatives: Part II," E. Klingsberg, Ed., Interscience, New York, N. Y., 1961, p 155.

(9) H. Gilman, *Org. React.*, **8**, 258 (1954).

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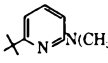
TABLE II
pK_a VALUES OF STERICALLY HINDERED PYRIDINES

Compd		pK_a[a]	Solvent
	2,6-Di-*tert*-butylpyridine	3.56[b]	50% EtOH
	2,4,6-Tri-*tert*-butylpyridine	4.02	50% EtOH
	2,6-Di-*tert*-butyl-4-methylpyridine	4.41	50% EtOH
	2,6-Di-*tert*-butyl-3-methylpyridine	4.25	50% EtOH
	Trimethyl(2,6-di-*tert*-butyl-4-picolyl)ammonium ion	3.51	Water
	Trimethyl(2,6-di-*tert*-butyl-4-pyridyl)ammonium ion	1.65	Water
	Dimethyl(2,6-di-*tert*-butyl-4-pyridyl)ammonium ion	1.6[c] 1.85 8.80	Water (pK_1) 50% EtOH (pK_1) 50% EtOH (pK_2)
	Trimethyl(2-*tert*-butyl-6-pyridyl)ammonium ion	<-1[d]	Water

[a] pK_a's determined at 27 ± 2°, μ = 0.1 *F*. [b] Lit.[1] 3.58. [c] ±0.1 pK_a units. [d] Approximately half protonated in 7 *F* HCl.

than the trimethylammonium analogs, presumably because of increased hydrogen bonding to the solvent. Thus, the nitrate, chloride, and bromide salts of the dimethyl(2,6-di-*tert*-butyl-4-pyridyl)ammonium cation can be used in aqueous systems as noncoordinating buffers,[13] or as bases of low nucleophilic activity, when the presence of these anions is not obnoxious.

Experimental Section

Melting points (Thomas-Hoover apparatus) were determined in open-end capillaries and are uncorrected. Pmr spectra were recorded on a Varian A-60A instrument using tetramethylsilane as a reference; all integrations gave relative peak areas within ±10% of those calculated for the proposed structure and are therefore not reported individually. Analyses were performed by the Schwarzkopf Microanalytical Laboratory and PCR Inc. Chloroaurate derivatives were prepared by a reported method.[1]

The detailed syntheses and characterization (derivatives, elemental analyses, pmr spectra, etc.) of all the compounds in Table I, except of 9 which is given below, are reported in the microfilm edition of this journal;[14] also included in this report are 4,4′,6,6′-tetra-*tert*-butyl-2,2′-bipyridyl and 4-(2-dimethylaminoethyl)pyridine. The multiple *tert*-butylation procedure used in these syntheses is similar to previously published procedures.[1,7,15]

Trimethylsulfoxonium Perchlorate.—Trimethylsulfoxonium iodide was prepared by the method of Kuhn and Trischmann[16] and converted to the perchlorate by three crystallizations from aqueous perchloric acid. The final product was washed with 95% ethanol and dried under vacuum (over P_2O_5). *Anal.* Calcd for $C_3H_9ClO_5S$: C, 18.71; H, 4.71; S, 16.65. Found: C, 18.60; H, 4.87; S, 16.81.

Trimethyl(2,6-di-*tert*-butyl-4-picolyl)ammonium Perchlorate.—2,6-Di-*tert*-butyl-4-dimethylaminomethylpyridine (1.2 g, 4.8 mmol) and trimethylsulfoxonium perchlorate (1.9 g, 10 mmol) were dissolved in 12 ml of sulfolane and heated under nitrogen at 140° for 5 hr to yield crystals (0.9 g, 50%): mp 246–247° (aqueous EtOH); pmr (DMSO-d_6) τ 8.60 [s, 2,6-C(CH_3)$_3$], 6.86 (s, NCH_3), 5.37 (s, CH_2), 2.53 (s, 3,5-H_{py}). *Anal.* Calcd for $C_{17}H_{31}N_2ClO_4$: C, 56.27; H, 8.61; N, 7.72. Found: C, 56.02; H, 8.99; N, 7.60.

pK_a and Solubility Measurements.—pK_a's were either determined spectrophotometrically *via* the method described by Brown and Kanner,[1] or were calculated directly from titration data. Spectra were recorded using a Cary 14 uv–visible spectrophotometer and pH readings were taken with a Beckman Research pH meter. Determinations were made at 27 ± 2°, ionic

TABLE III
SOLUBILITIES OF STERICALLY HINDERED PYRIDINES IN WATER AT 27 ± 2°

Compd	Solubility, *F*
Trimethyl(2,6-di-*tert*-butyl-4-picolyl)-ammonium perchlorate	0.00141
Trimethyl(2,6-di-*tert*-butyl-4-pyridyl)-ammonium perchlorate	0.00194
Trimethyl(2,6-di-*tert*-butyl-4-pyridyl)-ammonium nitrate	0.021
Dimethyl(2,6-di-*tert*-butyl-4-pyridyl)-ammonium perchlorate	0.016
Dimethyl(2,6-di-*tert*-butyl-4-pyridyl)-ammonium nitrate	1.5
Dimethyl(2,6-di-*tert*-butyl-4-pyridyl)-ammonium chloride	1.85
Dimethyl(2,6-di-*tert*-butyl-4-pyridyl)-ammonium bromide	1.0
Trimethyl(2-*tert*-butyl-6-pyridyl)-ammonium perchlorate	0.0205
Trimethyl(2-*tert*-butyl-6-pyridyl)-ammonium trifluoromethanesulfonate	0.0089

(13) The disparate pK_a's of the aniline and pyridine nitrogens (see Table II) ensure that in the pyridine buffer region the aniline nitrogen will be completely protonated and thus unable to coordinate to a metal ion.

(14) 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-73-1123. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(15) H. C. Van der Plas and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **81**, 841 (1962).

(16) R. Kuhn and H. Trischmann, *Justus Liebigs Ann. Chem.*, **611**, 117 (1958).

strength 0.1 F. The spectrophotometric pK_a values were obtained at two different wavelengths, agreement always being better than ±0.03 units. The error in reported pK_a values is estimated to be less than ±0.05 pK_a units. Solubilities were determined spectrophotometrically at 27 ± 2° and are estimated to be accurate to within ±5%.

Registry No.—**1**, 20336-15-6; **2**, 38222-83-2; **3**, 38222-84-3; **4**, 38222-85-4; **5**, 2055-21-2; **6**, 38222-86-5; **7**, 38222-87-6; **8**, 38222-88-7; **9**, 38222-89-8; **10**, 38222-90-1; **11a**, 38222-91-2; **11b**, 38222-92-3; **11c**, 38222-93-4; **11d**, 38222-94-5; **12a**, 38222-95-6; **12b**, 38222-96-7; **12c**, 38222-97-8; **13**, 38222-98-9; **14a**, 38222-99-0; **14b**, 38222-00-6; **14c**, 38222-01-7; **15**, 38223-02-8; **16a**, 38222-03-9; **16b**, 38223-04-0; pyridine, 110-86-1; 2,4,6-tri-*tert*-butylpyridine $HAuCl_4$ salt, 29930-36-7; 4,4′,6,6′-tetra-*tert*-butyl-2,2′-bipyridyl, 38223-05-1; 4-picoline, 108-894; 2,6-di-*tert*-butyl-4-methylpyridine $HAuCl_4$ salt, 38218-84-7; 3-picoline, 108-99-6; 2,6-di-*tert*-butyl-3-methylpyridine $HAuCl_4$ salt, 38295-40-8; 4-picolylamine, 3731-53-1; 3-picolylamine, 3731-52-0; 4-(2-dimethylaminoethyl)pyridine, 38223-06-2; 4-vinylpyridine, 100-43-6; 4-dimethylaminopyridine, 1122-58-3; 2-dimethylaminopyridine, 5683-33-0; 2-*tert*-butyl-6-dimethylaminopyridine $HAuCl_4$ salt, 38218-85-8; methyl iodide, 74-88-4; 2,6-di-*tert*-butylpyridine, 585-48-8; trimethylsulfoxonium iodide, 1774-47-6; trimethylsulfoxonium perchlorate, 38223-07-3.

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Amine Copper(I) Perchlorates. A Novel Class of Copper Species for Promoting Diazonium Ion Reactions

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Copper(I) perchlorates, complexed by heterocyclic amines, are effective at promoting homolytic cleavage of aryl diazonium salts in neutral medium. For 2-diazobenzophenone tetrafluoroborate the major products are 2,2′-dibenzoylbiphenyl (~70%) and 9-fluorenone (~30%). In the presence of cupric ion a high yield of 2-hydroxybenzophenone is obtained; with hydrogen atom donors, *e.g.*, ethanol, the major product is benzophenone.

The homolytic decomposition of aryl diazonium salts has been shown to be more effectively promoted by cuprous copper than by the metal itself.[2,3] In fact, the replacement of metallic copper by cuprous oxide in the decomposition of 2-diazobenzophenone tetrafluoroborate (**1**) at 45° has demonstrated that by accelerating homolytic carbon–nitrogen bond scission, competition by the heterolytic pathway is essentially eliminated. Not all cuprous salts are, however, suitable as catalysts. Owing to the greater solvation energy of copper(II) ion, as compared to that of copper(I) ion, in water,[4] all aquated copper(I) salts disproportionate to Cu(II) and Cu(0).[5] Cuprous oxide, which had been the catalyst of choice,[2,3] has the disadvantage of being effective in highly acidic medium only, owing to its insolubility in neutral water. Thus, diazonium ion decomposition requiring a neutral medium cannot be promoted by cuprous copper.

We have developed a series of relatively stable, soluble copper(I) salts, complexed by heterocyclic amines, which are effective in catalyzing homolytic diazonium ion decomposition in the pH range 2–6.

Results and Discussion

In the course of our investigations of aryl diazonium ion decompositions we have become interested in carrying out homolytic reactions in neutral water. The 2-diazobenzophenone system was selected for study because of the considerable amount of reliable data already available concerning both the thermal[3,6] and the copper-promoted[3] reactions.

Cuprous oxide, reported to be an effective catalyst in acid solution,[2,3] was found to promote homolytic decomposition of 2-diazobenzophenone tetrafluoroborate only at pH 1.25 or less. Other commercially available copper(I) salts (bromide, chloride, iodide, thiocyanate, and acetate) also failed to promote the reaction in neutral water. Copper(I) hydride,[7] prepared by the procedure of Whitesides, *et al.*,[8] was ineffective in catalyzing the decomposition.

Several known acetonitrile complexes of copper(I),[9] as well as bis(2,9-dimethyl-1,10-phenanthroline)copper(I) sulfate[10] and two pyridinecopper(I) salts, were prepared and examined for suitability in promoting the homolytic decomposition of **1** in neutral water. The results, summarized in Table I, indicated that although two of the acetonitrile complexes were effective within the desired pH range (entries 1, 2) they formed copper(II), either by oxidation or by disproportionation, too rapidly to serve as useful catalysts. In the very stable phenanthroline complex (entry 5), on the other hand, copper(I) was stabilized to the point where it was in-

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TABLE I

pH OF THE REACTION OF COPPER(I) SALTS WITH 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[a]

No.	Salt	pH[b]
1	Tetrakis(acetonitrile)copper(I) perchlorate[c]	5.1
2	Tetrakis(acetonitrile)copper(I) nitrate[c,d]	5.5
3	Tetrakis(acetonitrile)copper(I) tetrafluoroborate[c]	2.6
4	(Acetonitrile)$_x$copper(I) sulfate[e]	2.0
5	(2,9-Dimethyl-1,10-phenanthroline)$_x$copper(I) sulfate	*i*
6	(Pyridine)$_x$copper(I) nitrate[c,e,f]	
7	Tetrakis(pyridine)copper(I) perchlorate[g,h]	6.2

[a] The reaction consisted of adding 0.42 mmol of copper(I) salt to a stirred solution of 0.3 mmol of 2-diazobenzophenone tetrafluoroborate in 30 ml of water. Decomposition was monitored using the β-naphthol test: N. C. Cheronis and J. B. Entrokin, "Semimicro Qualitative Organic Analysis," Interscience, New York, N. Y., 1961. [b] The pH of the reaction was measured, using a pH meter, after the addition of the copper(I) complex to the diazonium salt. [c] The salt appeared as white crystals which turned blue on exposure to air. [d] This was the least stable of the acetonitrile complexes, turning blue rapidly on exposure to air. [e] The number of ligands (x) was presumed to be four, the most common coordination number of copper(I).[4] [f] (Pyridine)$_x$copper(I) nitrate was too unstable to react with the diazonium salt. [g] K. L. Chen and R. T. Twansato, *Inorg. Nucl. Chem. Lett.*, 4, 499 (1968). [h] A. H. Lewin, R. J. Michl, P. Ganis, U. Lepore, and G. Avitabile, *Chem. Commun.*, 1400 (1971). [i] No reaction.

capable of reducing the diazonium ion and was therefore ineffective as a catalyst. Tetrakis(pyridine)copper(I) perchlorate (entry 7) seemed to meet all the required specifications; other heterocyclic amine complexes of copper(I) perchlorate were therefore investigated. Surprisingly, although the coordination compounds of heterocyclic amines with many transition metals are well known, only little work has been done on such copper(I) complexes.[11,12] A series of perchlorate salts of copper(I) ligandated by pyridine, substituted pyridines, quinoline, and substituted quinolines was prepared by us, according to the procedure of Morgan.[13]

Effectiveness of these copper(I) perchlorate–amine complexes in promoting the homolytic decomposition of **1** was investigated and is examplified by the results obtained with tris(2-picoline)copper(I) perchlorate.[14] The effects of adding copper(II) species and hydrogen-donating solvents are shown in Tables II and III.

Basically, our results parallel those for the cuprous oxide promoted decomposition of **1** in acid solution.[3] Lewin and Cohen[3] have shown that the addition of cupric ions as cupric nitrate to the reaction mixture led to increased phenol production. In our work, copper(II) acetate hydrate was used, since it does not cause a large increase in acidity when dissolved in water as do most other copper(II) salts. Although cupric acetate was not so effective as cupric nitrate at low cupric ion concentration (entry 2, Table II) and the 200-fold increase in the ratio of 2-hydroxybenzophenone (**3**) to 9-fluorenone (**4**) previously reported[3] could not be achieved owing to the lesser solubility of cupric acetate,[15] the right trend was observed, with a 75-fold increase in the ratio of **3** and **4** upon addition of cupric species (entries 1 and 6, Table II).

TABLE II

THE EFFECT OF THE ADDITION OF COPPER(II) ACETATE HYDRATE IN THE DECOMPOSITION OF 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[a]

			Product yields, %[b-e]			
No.	Mmol of cupric ion [$Cu(OAc)_2 \cdot H_2O$]	pH	Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	Ratio of 3:4
1	0	6.2	1.0	1.0	28.0	0.04
2	3.5	6.0	1.0	*d*	24.0	
3	10.0		1.0	2.0	16.3	0.12
4	25.0		1.0	6.4	35.5	0.18
5	50.0		1.0	16.0	20.0	0.80
6	Saturated	5.2	2.0	39.0	12.6	3.10

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 1.22 mmol of tris(2-picoline)copper(I) perchlorate in 30 ml of water. [b] The yields were determined by vpc analysis *vs.* hexadecane as added internal standard. [c] The balance of the reaction was a fourth product, 2,2′-dibenzoylbiphenyl. [d] The product was present but as less than 1% of the overall reaction. [e] Overall yield was between 85 and 100%.

TABLE III

THE EFFECT OF HYDROGEN-DONATING SOLVENTS ON THE DECOMPOSITION OF 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[a]

		Product yields, %[b-d]		
No.	Composition of solution	Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)
1	3 ml acetone 27 ml water	13.3	4.5	13.1
2	15 ml acetone 15 ml water	10.5	7.2	1.5
3	3 ml ethanol 27 ml water	46.5	*d*	10.5
4	15 ml ethanol 15 ml water	77.0	*d*	2.0
5	30 ml water	1.0	1.0	28.0

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 1.0 mmol of tris(2-picoline)copper(I) perchlorate in 30 ml of solution. [b] The yields were determined by vpc analysis, *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was the fourth product 2,2′-dibenzoylbiphenyl. [d] The product was detected but as less than 1% of the overall reaction. [e] Dimers were found: for acetone, 2,5-hexadione; and for ethanol, 2,3-butanediol. [f] Overall yield was between 85 and 100%.

The presence of hydrogen donors in the reaction mixture had been shown to lead to reduction of the diazonium salt, *i.e.*, to benzophenone (**2**).[3] In our hands addition of acetone (entries 2, 3, Table III) and ethanol (entries 3, 4, Table III) to the reaction produced significant increases in the yield of benzophenone. Both 2,5-hexadione and 2,3-butanediol were observed as by-products, as expected from the coupling of the hydrogen donor radicals.

The most striking difference between the products of reactions promoted by cuprous oxide and by tris(2-picoline)copper(I) perchlorate lies in the fact that, whereas benzophenone (**2**), 2-hydroxybenzophenone

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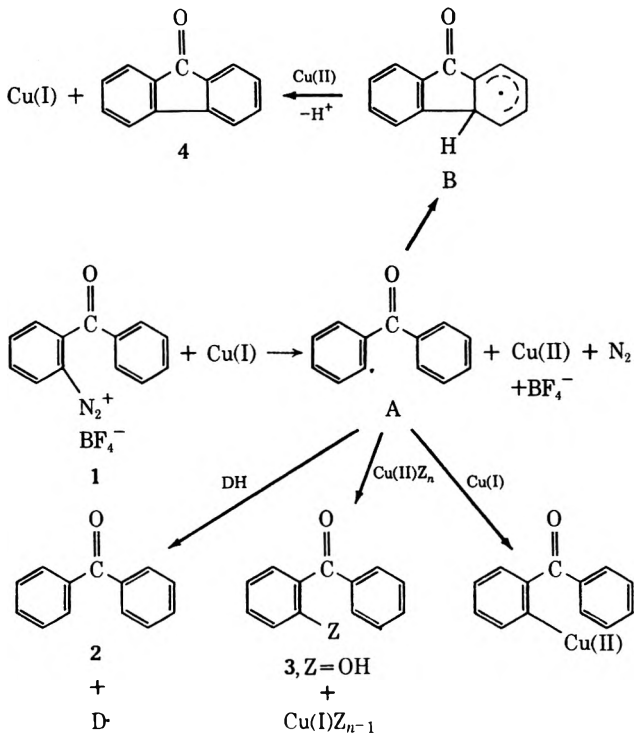
(15) "Handbook of Chemistry and Physics," 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1969.

(3), and 9-fluorenone (4) accounted for about 86% of the product in the copper(I) oxide promoted decomposition of 2-diazobenzophenone tetrafluoroborate (1),[3] (Scheme I) only 30% of the product could be accounted

SCHEME I

SUGGESTED REACTION COURSE FOR THE COPPER(I) CATALYZED DECOMPOSITION OF 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[3]



for in this way in the analogous decomposition by tris(2-picoline)copper(I) perchlorate. It was suspected that the balance of the product may be a dimer, and therefore the effect of dilution on the product composition was examined. It was found that the sum of the yields of benzophenone (2), 2-hydroxybenzophenone (3), and 9-fluorenone (4) increased from 30 to 50% at extreme dilution (Table IV), consistent with the fourth product being dimeric. Small concentration changes did not have any notable effect. In addition it may be noted that an increase in the sum of the yields of benzophenone (2), 2-hydroxybenzophenone (3), and 9-fluorenone (4) had been observed in the presence of large amounts of cupric species (Table II) as well as in the presence of hydrogen donors (Table III). It therefore appeared likely that the intermediate radical A was implicated, dimerizing to give 2,2′-dibenzoylbiphenyl (5) or reacting with radical B to give 5-(2-benzoylphenyl)hydrofluorenone (6) (Scheme II).

TABLE IV

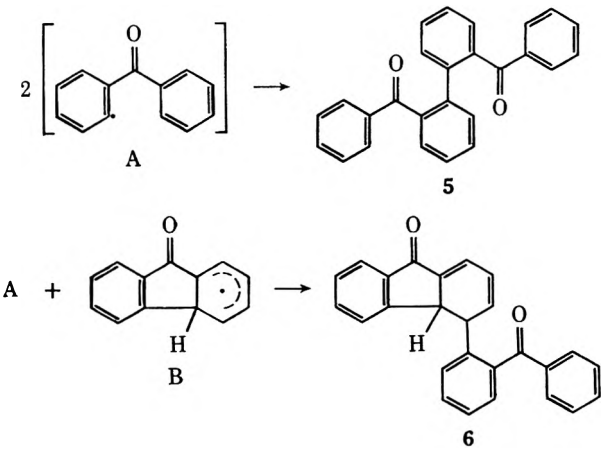
THE EFFECT OF DILUTION ON THE PRODUCT COMPOSITION IN THE DECOMPOSITION OF 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[a]

		Product yields, %[b-d]			
Water, ml	Dilution factor	Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	Sum of 2 + 3 + 4
30	1	1.0	1.0	28.0	30.0
60	2	1.0	1.0	29.6	31.6
90	3	1.0	2.2	32.8	36.0
150	5	1.0	4.7	44.2	49.9
300	10	1.0	3.4	42.7	48.1
800	27	1.0	3.8	44.4	49.2

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate with 1.0 mmol of tris(2-picoline)copper(I) perchlorate. [b] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was a fourth product, 2,2′-dibenzoylbiphenyl. [d] Overall yield was between 85 and 100%.

SCHEME II

POSSIBLE DIMERIC PRODUCTS INVOLVING RADICAL A



A high-boiling material was isolated from the product mixture which had neither azo stretch[16,17] nor bands typical for aliphatic or allylic hydrogens in the ir. The mass spectrum had major peaks at *m/e* 257, 105, and 77. An authentic sample of 2,2′-dibenzoylbiphenyl, prepared *via* the Ullmann biaryl synthesis of 2-iodobenzophenone,[18,19] had ir and mass spectra identical with those of the material isolated from the product mixture. The dimer was therefore assigned the structure 2,2′-dibenzoylbiphenyl (5).

The fact that dimer formation is extensive in reactions promoted by copper(I) perchlorate ligandated by heterocyclic amines, but is essentially negligible in cuprous oxide promoted decomposition, may be due to the difference in cuprous copper concentration. The concentration of cuprous ion from dissolution of cuprous oxide in 0.1 *N* H_2SO_4[3] is constant at 0.014 *M*,[20] whereas the initial concentration of cuprous copper in experiments with tris(2-picoline)copper(I) perchlorate is *ca.* 0.035 *M*. Since the rate of formation of radical A is a function of the concentration of cuprous copper, higher concentrations are A are more likely to be achieved with tris(2-picoline)copper(I) perchlorate[21] than with cuprous oxide, favoring dimerization of A. The effect of cuprous copper concentration on the extent of dimer (5) formation are consistent with the above explanation, as seen in Table V. At high copper(I) concentration (entry 1, Table V) the product is almost exclusively the dimer 5; a distinct trend toward diminished dimerization is observed with decreasing cuprous copper concentrations. At low copper(I) concentrations (entries

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(20) W. M. Latimer, "Oxidation Potentials," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1961, p 187.
(21) These may be localized by complexation with the metal species.

TABLE V

THE EFFECT OF CHANGING THE COPPER(I)/DIAZONIUM SALT RATIO IN THE DECOMPOSITION OF 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[a]

			Product yields, %[b-d]			
No.	Molarity of tris(2-picoline)-copper(I) perchlorate, *M*	Ratio of copper(I) diazonium salt	Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	Sum of 2 + 3 + 4
1	0.200	10.0	0	0	13.8	13.8
2	0.134	6.7	0	0	21.5	21.5
3	0.100	5.0	1.2	0.7	23.2	25.1
4	0.067	3.3	0	0	22.0	22.0
5	0.050	2.5	1.2	1.4	28.9	31.5
6	0.034	1.7	1.0	1.0	28.0	30.0
7	0.023	1.2	1.0	1.0	31.8	33.8
8	0.020	1.0	4.6	2.5	29.6	36.7
9	0.017	0.8	1.5	2.5	36.8	40.8
10	0.014	0.7	1.0	4.5	21.0	26.5
11	0.010	0.5	Incomplete reaction			

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate (1) in 30 ml of water. [b] The yields were determined by vpc analysis, *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was the fourth product, 2,2′-dibenzoylbiphenyl (5). [d] Overall yield was between 85 and 100%.

10, 11, Table V) the reaction becomes very sluggish and may no longer proceed by a homolytic pathway only, as suggested by the increased yield of phenol **3**.

It is noteworthy that the decomposition of 2-diazobenzophenone tetrafluoroborate (**1**) failed to go to completion when the ratio of copper(I) to diazonium salt dropped to 0.5 (entry 11, Table V). This observation is in accord with the proposed mechanism[3] (Scheme I), since, according to this mechanism, copper(I) is not a true catalyst because only the reactions to produce 2-hydroxybenzophenone (**3**) and possibly 9-fluorenone[22] (**4**) regenerate copper(I).

Since the aminecopper(I) perchlorates were effective in promoting diazonium ion decompositions in the pH range 2–6, whereas copper(I) oxide was effective at rather high acidity (pH 1) only, the effect of pH on the product composition was investigated. By use of appropriate buffers, the pH of the 2-diazobenzophenone tetrafluoroborate decomposition reaction catalyzed by tris(2-picoline)copper(I) perchlorate was varied between 6 and 2. Analysis of the product composition indicated a negligible pH effect (Table VI).

Conclusions

The aminecopper(I) perchlorates synthesized are effective in promoting homolytic decomposition of aryl diazonium salts in neutral solution. In dilute solution (*ca.* 0.002 *M*) in diazonium salt with a copper(I) to diazonium salt ratio of *ca.* 0.8, the results obtained are analogous to those obtained at pH 1 with cuprous oxide.[3] Thus, the copper(I)-promoted reaction of 2-diazobenzophenone tetrafluoroborate (**1**) yields primarily (a) 9-fluorenone (**4**) in pure water; (b) benzophenone (**2**) in the presence of hydrogen atom donors; and (c) ligand transfer product (*e.g.*, 2-hydroxybenzophenone, **3**) in the presence of cupric species with transferable ligands (*e.g.*, aquated cupric ions). The dimer, 2,2′-dibenzoylbiphenyl (**5**), is produced at high copper(I) concentrations. Copper(I) has been shown not to be a true catalyst, in agreement with the previously proposed mechanism,[2] since a nearly equimolar amount is required to complete the reaction.

(22) 9-Fluorenone may be produced from B *via* air oxidation.

TABLE VI

THE EFFECT OF ALTERING THE pH OF THE DECOMPOSITION OF 2-DIAZOBENZOPHENONE TETRAFLUOROBORATE (1)[a]

	Product yield, %[b-e]		
pH	Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)
6.0	1.0	1.0	28.0
5.0	1.2	*d*	28.3
4.0	1.0	*d*	34.4
2.0	1.0	2.0	31.1

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 1.22 mmol of tris(2-picoline)copper(I) perchlorate in 30 ml of buffered solution. [b] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was a fourth product, 2,2′-dibenzoylbiphenyl. [d] The product was present but as less than 1% of the overall reaction. [e] Overall yield was between 85 and 100%.

Experimental Section

Physical Measurements.—Infrared spectra in the wavenumber range 4000–600 cm^{-1} were obtained with a Perkin-Elmer Model 521 spectrophotometer using potassium bromide pellets.

pH Measurements were read with a Beckman Model 76 expanded-scale pH meter. The meter was standardized with buffer solutions purchased from Fisher Scientific.

Mass spectra were recorded on a Perkin-Elmer Hitachi RMU 6 mass spectrophotometer. The samples were normally run at 80 eV.

Gas chromatographic analysis was done on a Varian Aerograph Model A 90-P3 with a linear temperature programmer. The product mixture (benzophenone, 2-hydroxybenzophenone, and 9-fluorenone) was analyzed on a 6-ft 18% Apeizon L column (on 70/80 Anakrom ABS) at 210° with a helium flow rate of 50 ml/min. Analysis of 2,2′-dibenzoylbiphenyl was performed on a 6-ft 25% SE-30 column (on 70/80 Anakrom ABS) at various program rates from 50 to 320°, at a helium flow rate of 30 ml/min. Hexadecane (Metro Scientific) was used as the internal standard and the products were all calibrated *vs.* this standard.

Buffers.—The following buffers were obtained from Fisher Scientific and used directly: pH 6 monopotassium phosphate–sodium hydroxide, 0.05 *M*; pH 5 potassium biphthalate–sodium hydroxide, 0.05 *M*; pH 4 potassium biphthalate, 0.05 *M*; pH 2 potassium chloride–hydrochloric acid, 0.05 *M*.

2-Diazobenzophenone Tetrafluoroborate[23]—To a solution of 0.99 g (5 mmol) of 2-aminobenzophenone (Aldrich) in 30 ml of ethanol containing 2.65 g (15 mmol) of fluoroboric acid (Baker, 50% in H_2O) which was stirred and cooled to 0° was added 0.65 g (5.5 mmol) of isoamyl nitrite dropwise, keeping the temperature between 0 and 1°. The reaction mixture was stirred at 0° for 15 min, during which time precipitation took place. At the end of 15 min, 150 ml of ice-cold ether was added and the mixture was stirred at 0° for 30 min longer. The white precipitate (80% yield) was filtered and stored in a vial which was tightly capped and refrigerated.

Procedure for the Decomposition of the Diazonium Salt.—All the decomposition reactions were highly reproducible. When reactions were repeated and analyzed on the vpc, deviations of no more than 0.5% could be noted provided that the peaks were sufficiently large. For the small peaks (products of less than 5% of the reaction) large errors of 1–2% were apparent. All the products were stable under the reaction conditions. The internal standard, hexadecane, was always added in the same amount (0.088 ml, 0.3 mmol) to every reaction after it had been worked up.

The reactions were carried out as follows. The copper(I) catalyst was added to a solution of the diazonium salt in water, with stirring. If the reaction was to be performed in the presence of hydrogen donors, copper(II) ion, etc., they were added to

(23) J. Lipowitz and T. Cohen, *J. Org. Chem.*, **30**, 3891 (1965).

the water before addition of the diazonium salt and the copper(I) catalyst. A β-naphthol test was done on all the reactions to ascertain that all the diazonium salt had decomposed. When the reaction was complete, as indicated by a negative β-naphthol test, the reaction mixture was extracted three times with 150 ml of methylene chloride. If the reaction was performed in acidic solution, the combined organic extract was washed with saturated $NaHCO_3$ and water before drying. The combined organic extracts were then dried over anhydrous magnesium sulfate and concentrated at reduced pressure.

Copper(I) Hydride.[7,8]—Copper(I) hydride was prepared by the reaction of lithium aluminum hydride with copper(I) iodide in pyridine; however, the resulting CuH was impure and stable when exposed to air. In a procedure reported by Whitesides[8] using diisobutylaluminum hydride and copper(I) chloride in place of $LiAlH_4$ and CuI, a pure product of CuH was obtained. The material, which was light brown, decomposed in about 10 min after being dried from ether. This, however, was enough time for us to carry out experiments.

2-Iodobenzophenone.[18,19]—*o*-Iodobenzoyl chloride (Fisher, reagent grade) 50 g (0.188 mol), in 200 ml of dry benzene was gradually treated with 28 g (0.211 mol) of powdered anhydrous aluminum chloride, and the mixture was refluxed for 2 hr. After hydrolysis of the complex, *o*-iodobenzophenone along with other products was obtained as a nearly colorless liquid (34 g, 59%), bp 143° (0.3 mm), which solidified and gave needles, mp 32.5°, from hexane.

2,2′-Dibenzoylbiphenyl.—*o*-Iodobenzophenone, 20 g (0.065 mol), and 18 g (0.284 g-atom) of electrolytic copper (Fisher) in 40 ml of dimethylformamide were heated under reflux for 2 hr. The product was taken up in chloroform, the solvents were removed, and the solid residue was recrystallized from cyclohexane, yielding 9.0 g (76%) of 2,2′-dibenzoylbiphenyl as white needles, mp 167°.

Registry No.—**1**, 342-62-1; **2**, 119-61-9; **3**, 117-99-7; **4**, 486-25-9; **5**, 24018-00-6; salt 1, 14057-91-1; salt 2, 37847-53-3; salt 3, 15418-29-8; salt 4, 37821-06-0; salt 7, 37821-07-1; copper(II) acetate monohydrate, 6046-93-1; 2-iodobenzophenone, 25187-00-2.

Reaction of Acetaldehyde with Mono- and Binuclear Organoaluminum Compounds at Low Temperature

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Studies of the reaction of pentaalkyldialuminum alkali metal oxide and its nitrogen and sulfur analogs with acetaldehyde at −78, −20, and 0° are reported and compared with AlR_3 alone and with mononuclear complexes $AlR_3 \cdot Do$. AlR_3 gave addition and reduction products as the primary reaction and some secondary reaction products. The reactivity of $AlR_3 \cdot Do$ decreased with respect to both of the primary and secondary reactions with increase in the strength of the complex. Pentaalkyldialuminum complexes have high reactivity concerning the primary reaction, but have very low activity for the secondary reactions. The results can best be understood by a bimetallic cyclic transition state. With $[R_2AlZLi] \cdot [AlR'_3]$, R′ addition and R addition occurred simultaneously, indicating a slow alkyl exchange process through a bridging alkyl.

Our recent works on the polymerization catalyst revealed that the reaction products from trialkylaluminum with alkali metal hydroxide[1-4] and lithium amide[2,3,5] in a molar ratio of 2:1 gave highly isotactic polyacetaldehyde with desired properties.[4] Extensive studies on the syntheses in the pure state[6] and nmr spectroscopy[7] on the structures in solution have elucidated that the organoaluminum compound produced can be represented as a series of binuclear complexes of the formula $[R_2AlZM] \cdot [AlR_3]$ with high complex stability when Z = O or NR′, in which R_2AlZM serves as a donor and AlR_3 as an acceptor.

In order to study both the active species for initiation and the side reactions by the organoaluminum catalyst in the polymerization, detailed studies on the reaction with acetaldehyde were carried out at −78 (polymerization temperature), −20, and 0° (higher than the ceiling temperature of the polymerization). The binuclear organoaluminum compound was found to exhibit a characteristic reactivity of the AlR group as compared with trialkylaluminums and their mononuclear complexes. Our results may contribute also to fill the gaps in our knowledge of the reactions of organoaluminum reagents with carbonyl compounds,[8-10] in which reaction intermediates involving two metals have been presumed for a few cases.[11-13] On the basis of the reaction of acetaldehyde with $[R_2AlZM] \cdot [AlR'_3]$ new information on the intramolecular alkyl–alkyl and "alkyl–alkoxyl" exchange reactions is also obtained.

Results and Discussion

Trialkylaluminums.—On the basis of the results with $AlEt_3$, $AlMe_3$, and Al-*i*-Bu_3 (Table I), the reaction process of acetaldehyde can be summarized in Scheme I, which involves primary and secondary reactions.[14] In the primary reaction AlR_3 reacts with acetaldehyde in two ways; widely known Grignard addition (a) and reduction (b). The organoaluminum alkoxides derived from the primary reaction acts as the reagent for

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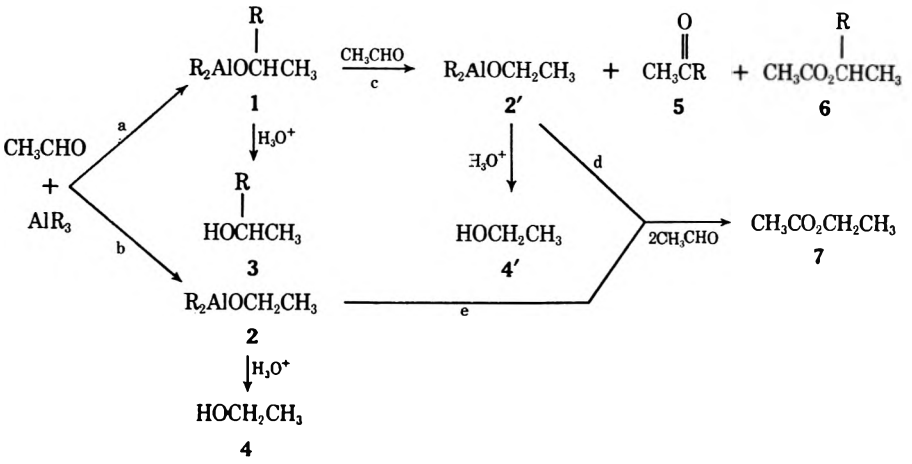
(2) H. Tani, T. Araki, N. Oguni, and T. Aoyagi, *ibid., Part B-4*, 97 (1966).
(3) H. Tani, T. Araki, N. Oguni, T. Aoyagi, K. Hayakawa, and M. Mikumo, Preprints of papers presented at International Symposium on Macromolecular Chemistry, Tokyo–Kyoto, Japan, 1966, Vol. I, p 193.
(4) T. Aoyagi, T. Araki, and H. Tani, *J. Polym. Sci., Part A-1*, **10**, 2325 (1972).
(5) H. Tani and N. Oguni, *ibid., Part B-3*, 123 (1965).
(6) T. Aoyagi, T. Araki, N. Oguni, M. Mikumo, and H. Tani, *Inorg. Chem.*, to be published.
(7) T. Aoyagi, T. Araki, N. Oguni, and H. Tani, *ibid.*, in press.
(8) (a) H. Gilman and K. E. Marple, *Rec. Trav. Chim. Pays-Bas*, **58**, 518 (1936); (b) H. Meerwein, G. Hinz, H. Majert, and H. Sönke, *J. Prakt. Chem.*, **147**, 226 (1936).
(9) (a) K. Ziegler in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, p 240; (b) H. Lehmkuhl and K. Ziegler in Hauben-Weyl's "Methoden der Organischen Chemie," Bd. 13/4, Metallorganische Verbindungen, Al, Ga, In, Tl. S.1, 1969.
(10) T. Eicher in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Wiley, New York, N. Y., 1966, p 677.
(11) E. C. Ashby, J. Laemmle, and H. M. Neaman, *J. Amer. Chem. Soc.*, **90**, 5179 (1968).
(12) E. A. Jeffery and T. Mole, *Aust. J. Chem.*, **23**, 715 (1970).
(13) S. Pasynkiewicz and E. Sliva, *J. Organometal. Chem.*, **3**, 121 (1965).
(14) Similar reaction products have been observed with substituted benzaldehyde recently: Y. Baba, *Yuki Gosei Kayaku Kyokai Shi*, **27**, 264 (1969).

SCHEME I



primary reaction secondary reaction

TABLE I

REACTION OF ACETALDEHYDE WITH AlR_3 AND Et_2AlOR[a]

Registry no.	Organoaluminum	Temp, °C	Time, hr	CH_3CHO concn[b]	Reaction product, mol/mol organoaluminum[c] 4	7	5	3	6	CH_3CHO recovered
97-93-8	$AlEt_3$	−78	2[d]	5	<0.1	0.10	0	0.91	0	4.2
	$AlEt_3$	−20	2[e]	5	0.5	0.83	<0.1	0.78	~0.2	2.7
	$AlEt_3$	0	24	5	0.72	1.6	0.43	0.13	0.35	
7062-93-3	Et_2AlO-*sec*-Bu	−78	20	3	0	<0.1	0	0[f]	0	3.2
	Et_2AlO-*sec*-Bu	−20	20	3	0.87	0.96	<0.1	−0.38[g]	0.23	1.4
	Et_2AlOEt	−20	20	3	0.1[f]	0.41	0	0	0	2.3
75-24-1	$AlMe_3$	−78	24	5	0	0	0	0.16	0	4.7
	$AlMe_3$	−20	5[h]	5	<0.1	0.63	<0.1	1.4	<0.1	2.7
	$AlMe_3$	0	5[i]	5	0.29	0.75	0.17	1.2	0.10	
100-99-2	Al-*i*-Bu_3	−78	1	5	0.51	<0.1	0	0.28	0	4.0
	Al-*i*-Bu_3	−20	20	5	0.70	2.1	~0.2	<0.1	~0.2	1.5

[a] Toluene (5 ml) and organoaluminum compound (4.7×10^{-4} mol) were used. [b] Mol/mol of organoaluminum compound. [c] Formation of paraldehyde did not exceed the amount yielded in the control experiment. [d] The results are almost identical at 1 hr, except for somewhat lower yield of **7**. [e] At 1 hr, yields of **4** and **7** were less than 50% of these values, and yield of **3** was *ca.* 15% higher than the value in this table. [f] 1.0 molar equiv of alcohols which was present originally in Et_2AlOR' was excluded. [g] Minus value means the consumption of *sec*-BuOAl group originally present in Et_2AlO-*sec*-Bu. [h] At 1 hr, yield of **7** was *ca.* 0.2 but yield of **3** was nearly the same as the value in this table. Compounds **4** and **5** were not observed at shorter reaction times. [i] At 1 hr, **4** (0.16), **7** (0.10), **3** (1.3), and **6** (<0.1) were observed.

the secondary reactions (Meerwein–Ponndorf–Verlay reduction, Oppenauer oxidation, and Tishchenko reaction) analogously to aluminum trialkoxides.[15]

At −78° the primary reactions occur preferentially with $AlEt_3$, $AlMe_3$, and Al-*i*-Bu_3. The addition reaction is highly predominant for $AlEt_3$[16] or $AlMe_3$. The pronounced difference in the reactivity between $AlEt_3$ and $AlMe_3$ can be related with the difference in their dimer stabilities.[17] Al-*i*-Bu_3, known as an effective reducing agent,[18] gives reduction product predominantly over addition product by a factor of 1.8. For the secondary reactions, not negligible amounts of **7** were solely detected for $AlEt_3$ and Al-*i*-Bu_3.

At −20°, the secondary reactions giving **4'**, **5**, **6**, and especially Tishchenko reaction product **7** become important. The results obtained with Et_2AlO-*sec*-Bu or Et_2AlOEt indicate that the complicated reaction products are derived from these alkoxide species. The secondary reactions are further promoted at 0°.

Mononuclear Complexes of AlR_3.—The complexes of AlR_3 (R = Et and Me) with organic donors were purified by distillation or sublimation and confirmed to be monomeric cryoscopically. The heats of formation of complexes $AlR_3 \cdot Do$ (Do: organic donor) have been determined by Bonitz[19] and Hendrickson, *et al.*[20] (see Table VI). The reactivity of each series of $AlR_3 \cdot Do$ with acetaldehyde is consistent with the complex stability of $AlR_3 \cdot Do$. Diethyl etherates react similarly to uncomplexed AlR_3. Tetrahydrofuranates are inactive for addition reactions at −78° but they give both of the primary and secondary reaction products at −20°, *e.g.*, **4** (<0.1 mol/mol $AlEt_3 \cdot THF$), **7** (0.61), and **3** (0.56). For aminates, the primary and subsequently

(15) (a) A. L. Wilds in "Organic Reactions," Vol. 2, R. Adams, Ed., Wiley, New York, N. Y., 1944, p 178; (b) O. H. Wheeler in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Wiley, New York, N. Y., 1966, p 532.

(16) H. Fujii, I. Tsukuma, T. Saegusa, and J. Furukawa, *Makromol. Chem.*, **82**, 32 (1965).

(17) A. W. Laubengayer and W. F. Gilliam, *J. Amer. Chem. Soc.*, **63**, 477 (1941).

(18) K. Ziegler, K. Schneider, and J. Schneider, *Angew. Chem.*, **67**, 425 (1955).

(19) E. Bonitz, *Ber.*, **88**, 742 (1955).

(20) C. H. Hendrickson, D. Duffy, and D. P. Eyman, *Inorg. Chem.*, **7**, 1047 (1968).

TABLE II
REACTION OF ACETALDEHYDE WITH $[R_2AlZM]\cdot[AlR_3]$[a]

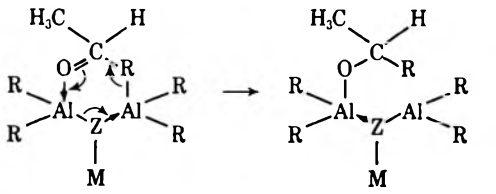
Registry no.	Organoaluminums	Temp, °C	Time, hr	CH_3CHO concn[b]	Reaction products, mol/mol of organoaluminum[c] 4	7	3	CH_3CHO recovered
37916-23-7	$[Et_2AlOLi]\cdot[AlEt_3]$	−78	24	5	0	0	1.28	3.7
	$[Et_2AlOLi]\cdot[AlEt_3]$	−20	24	5	0	0	1.59	3.3
	$[Et_2AlOLi]\cdot[AlEt_3]$	0	24	5	0	0	1.95	3.2 ± 0.2
	$[Et_2AlOLi]\cdot[AlEt_3]$	−20	24	100	<0.1	<0.1	1.26	
	$[Et_2AlOLi]\cdot[AlEt_3]$	0	1	100	<0.1	<0.1	1.32	
	$[Et_2AlOLi]\cdot[AlEt_3]$[d]	0	20	100	1.9	3.90	0.10	
37916-24-8	$[Et_2AlONa]\cdot[AlEt_3]$	−78	24	3	<0.1	0	0.50	2.4 ± 0.2
	$[Et_2AlONa]\cdot[AlEt_3]$	−20	24	3	<0.1	0	1.33	1.6 ± 0.2
	$[Et_2AlONa]\cdot[AlEt_3]$[e]	−20	24	100	0.73	<0.1	0.69	
37916-25-9	$[Me_2AlOLi]\cdot[AlMe_3]$	−78	24	5	0	0	0.78[f]	3.9
	$[Me_2AlOLi]\cdot[AlMe_3]$	−20	24	5	0	0	0.86	3.9
	$[Me_2AlOLi]\cdot[AlMe_3]$	0	24	5	0	0	1.07	
37916-26-0	$[i\text{-}Bu_2AlOLi]\cdot[Al\text{-}i\text{-}Bu_3]$[g]	−78	24	5	0.80	0	0.36	4.0
	$[i\text{-}Bu_2AlOLi]\cdot[Al\text{-}i\text{-}Bu_3]$[h]	−20	24	5	1.1	0	0.42	3.0
37916-27-1	$[Et_2AlNPhLi]\cdot[AlEt_3]$	−78	20	5	0	0	1.94	
	$[Et_2AlNPhLi]\cdot[AlEt_3]$	−20	20	5	0	0	2.27	
	$[Et_2AlNPhLi]\cdot[AlEt_3]$[i]	−20	20	100	~0.2	3.7	0.2	
37916-28-2	$[Et_2AlSNa]\cdot[AlEt_3]$	−78	24	5	<0.1	0	0.53	
	$[Et_2AlSNa]\cdot[AlEt_3]$	−78	24	10	0.55	<0.1	0.41	
	$[Et_2AlSNa]\cdot[AlEt_3]$	−20	24	5	0.27	<0.1	0.91	
	$[Et_2AlSNa]\cdot[AlEt_3]$[i]	−20	24	100	1.26	3.45	~0.2	

[a] Toluene (5 ml) and organoaluminum (4.7×10^{-4} mol) were used. [b] Mol/mol of organoaluminum. [c] Formation of paraldehyde did not exceed the amount obtained by the control experiment. The products **5** and **6** were not detected or otherwise noticed. [d] Formations of ethyl methyl ketone (~0.2) and *sec*-BuOAc (0.48 mol/mol of organoaluminum) were detected. [e] Formation of ethyl methyl ketone (<0.1) was observed. [f] Yield of **3**: 0.48 (12 min), 0.63 (1 hr), and 0.69 (2 hr). [g] Yield of **3** was almost unchanged from 12 min to 24 hr, but yield of **4** increased: 0.45 (12 min) and 0.72 (1 hr). [h] Almost the same results were obtained at 0°. [i] Formations of ethyl methyl ketone and *sec*-BuOAc (~0.2 each) were detected.

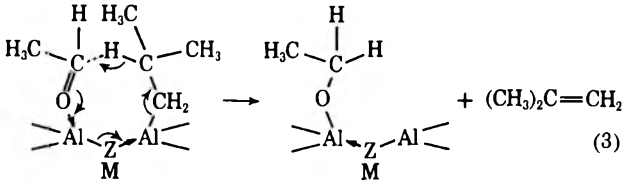
the secondary reactions are completely inhibited at the temperatures studied.[21,22] It is reasonable to assume that the reactions involve the following ligand exchange process, and a four-coordinated complex whose ligand cannot be substituted for acetaldehyde is inactive. The coordinating ability of acetaldehyde to AlR_3 can be estimated to be comparable with (or slightly lower than) tetrahydrofuran.

$$R_3Al\cdot Do \underset{-\,CH_3CHO}{\overset{+\,CH_3CHO}{\rightleftharpoons}} R_3Al\cdot OCHCH_3 + Do \qquad (1)$$

Pentaalkyl Dialuminum Compounds.—This series of compounds can best be represented as a complex of type $[R_2AlZM]\cdot[AlR_3]$.[6,7] In contrast to the organic donors, the Al-containing donors (R_2AlZM) suppress only the secondary reactions (Table II). $[R_2AlZM]\cdot[AlR_3]$ with R = Me, Et and Z = O, NPh was found to be a good reagent to give addition products, and the amount of the reaction products is almost saturated in 2 hr (Figure 1 and footnote of Table II). These results imply that the structure of the bimetallic complex is suitable for the primary reactions but not for the secondary reactions. Since we have already shown that $[R_2AlZM]\cdot[AlR_3]$ can exist as an unassociated state in nonpolar media,[6] and that an electron-donor molecule can coordinate preferentially with the Al atom in the R_2AlZM moiety,[7] the six-membered cyclic (eq 2) and eight-membered cyclic intermediates (eq 3) are highly



addition reaction (R = Me, Et, *i*-Bu) (2)



reduction (*i*-Bu derivatives) (3)

plausible for addition and reduction, respectively. Increase in the inhibiting effect of the organic donors added to $[Et_2AlOLi]\cdot[AlEt_3]$ (Table III) was in agreement with the order of increase in the strength of the base. This effect clearly indicates coordination of the aldehyde with the organoaluminum complex to be responsible for the reaction.

Further two factors can be considered to interpret the facts that the yield of the addition product by $[R_2AlZM]\cdot[AlR_3]$ at −78° is higher than that by the corresponding AlR_3, and that more than one of five AlR groups is readily consumed. Firstly, coordination of the R_2AlZM facilitates the Al^+-R^- localization in the AlR_3 moiety. Secondly, the monoalkoxide obtained by the primary reaction can be isomerized intramolecularly into a structure adequate for further addition or reduction. In this paper the latter is denoted as

(21) The reaction of $AlEt_3\cdot NEt_3$ with acetaldehyde depends upon the concentration of the system. At extremely high concentrations a complicated reaction including aldol condensation is observed (ref 23).

(22) The complexes $R_3Al\cdot OPPh_3$ show stability similar to the aminates for the reaction with acetaldehyde (ref 24).

(23) Y. Nakano, M. S. Thesis, Osaka University, 1967; H. Tani, T. Araki, and Y. Nakano, Abstract of Papers, 13th Annual Meeting of Polymer Science, Kobe, Japan, 1967, p 43.

(24) K. Lee, Ph.D. Thesis, Osaka University, 1970; H. Tani, T. Araki, and K. Lee, Abstract of Papers, 13th Annual Meeting of Polymer Science, Kobe, Japan, (1967), p 42.

TABLE III

REACTION OF ACETALDEHYDE WITH $[Et_2AlOLi]\cdot[AlEt_3]$ IN THE PRESENCE OF DONOR COMPOUNDS[a]

Donor	Donor/organoaluminum, mol/mol	Temp, °C	*sec*-BuOH formed,[b] mol/mol of organoaluminum
Et_2O	1[c]	−78	0.99
Et_2O	1	−20	1.51
THF	1[d]	−78	0.89
THF	1	−20	1.18
NEt_3	1[e]	−78	0.53
NEt_3	2	−78	0.05
NEt_3	5	−78	0
NEt_3	1	−20	0.57

[a] Toluene (5 ml) and $[Et_2AlOLi]\cdot[AlEt_3]$ (4.7×10^{-4} mol) were used. Concentration of acetaldehyde: 5 mol/mol $[Et_2AlOLi]\cdot[AlEt_3]$. Reaction time: 24 hr. [b] Any of other reaction products were not detected. [c] 1.1 molar equiv of *sec*-BuOH was formed at $Et_2O/[Et_2AlOLi]\cdot[AlEt_3]$ ratio = 5. [d] Yield of *sec*-BuOH was almost unchanged at 1 hr. [e] Yield of *sec*-BuOH was gradually increased from 0.22 (12 min) with increase of the time.

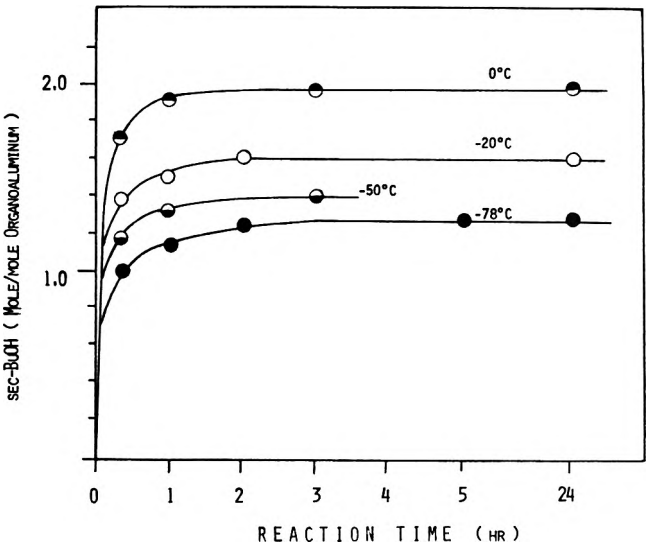


Figure 1.—Time dependence of the formation of *sec*-butyl alcohol by $[Et_2AlOLi]\cdot[AlEt_3]$ at various temperatures: toluene, 5 ml; $[Et_2AlOLi]\cdot[AlEt_3]$, 4.7×10^{-4} mol; CH_3CHO/organoaluminum, 5 mol/mol.

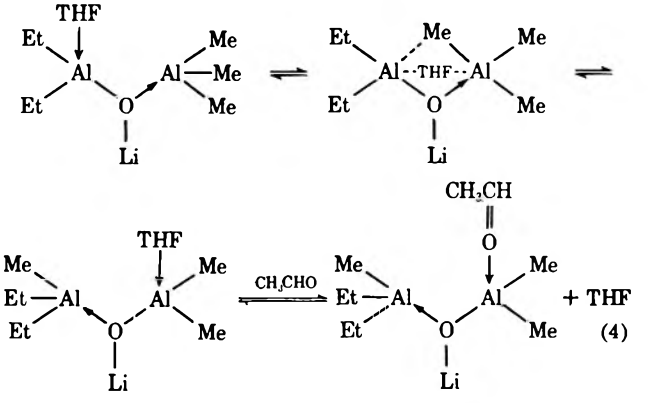
"alkyl/alkoxyl" exchange reaction. This process becomes prominent as the temperature increased or when the bond angle of Al–Z→Al becomes smaller (compare Al–O→Al with Al–N→Al).

The secondary reactions with $[R_2AlOM]\cdot[AlR_3]$ or $[R_2AlNPhM]\cdot[AlR_3]$ were detectable only at extremely high concentration of acetaldehyde at higher temperature. In contrast, $[Et_2AlSNa]\cdot[AlEt_3]$ gave the secondary reaction products more readily even under milder conditions. The facile occurrence of the products can be related with high tendency of the complex to dissociate into its moieties;[6] $[Et_2AlSNa]\cdot[AlEt_3] \rightleftarrows Et_2AlSNa + AlEt_3$ or $[Et_2AlSNa]\cdot[AlEt_3] + CH_3CHO \rightarrow [Et_2AlSNa]\cdot[Et_2AlO\text{-}sec\text{-}Bu] \rightleftarrows Et_2AlSNa + Et_2AlO\text{-}sec\text{-}Bu$. These results suggest that the secondary reactions are due to the dissociated moieties[25] of the complexes, especially AlR_3 or R_2AlOR' in the monometallic states. Further kinetic evidence will be necessary before more can be asserted about the monometallic process. The order of stability of the complex deduced is in the decreasing order of Z = O ≥ NPh ≫ S. The ionic property of M (by altering from Li to Na) does not affect the complex stability significantly. Et_2AlOLi or $Et_2AlNPhLi$ freed from $AlEt_3$ was confirmed not to form under various conditions any reaction products detectable by gas chromatography.

Intramolecular Alkyl/Alkyl and Alkyl/Alkoxyl Exchanges.—A previous nmr study[7] has indicated the existence of rapid alkyl/alkyl exchange processes in the binuclear complex containing a Li atom (at >60°). The reaction product of acetaldehyde with $[R_2AlZM]\cdot[AlR'_3]$, which was prepared[6] by complexation of R_2AlZM with AlR'_3, is a mixture of R- and R'-addition products (Table IV), indicating the existence of a slow alkyl/alkyl exchange process in addition. For *i*-Bu derivatives, the addition and reduction products are formed. The $\gamma_{R',R}$ values, defined as a ratio of AlR' to AlR groups reacted with acetaldehyde, vary with the reaction temperature, the complexation temperature, and aging period of the complex. Except for the complexes containing the *i*-Bu group which has decreased reactivity owing to its steric factor, the product of the AlR' group predominates as expected from the assumption made in eq 2. On the basis of the reaction data, the predominant species of the complex, prepared at −78° and aged for 1 hr, can be suggested as shown in Table V.

Since the number of alkyl groups consumed is higher than one per mole (at higher reaction temperature it reaches 2–3), an "alkyl/alkoxyl" exchange process must also be considered.[28] For the oxygen derivatives the exchange process appears not to be important at −78°[29] but it is observable at −20°. For the nitrogen derivative, the "alkyl/alkoxy" exchange occurs more rapidly at −78°, partly due to the decreased bond angle of Al–N→Al.

When an equimolar amount of THF (a donor with Lewis basicity comparable with acetaldehyde) is coor-



(25) Examination of Et_2AlSNa (freed from $AlEt_3$) revealed that it can give ethyl acetate at −20° at low acetaldehyde concentration without forming ethanol. The remarkably high yield of ethyl acetate by $[Et_2AlSNa]\cdot[AlEt_3]$ is probably due to this factor in addition to the species AlR_3 and/or R_2AlOR'. Ethyl acetate formation without Al alkoxide species seems to proceed by a mechanism other than Tishchenko reaction. Other examples have been observed with $Et_2AlOAlEt_2$ (ref 26) and with the hydrolysate of $AlEt_3$ by aqueous KOH solution (ref 27). For convenience we denote it "direct dimerization."

(26) T. Araki, T. Aoyagi, N. Ueyama, T. Aoyama, and H. Tani, *J. Polym. Sci., Part A-1*, in press.

(27) T. Aoyagi, T. Araki and H. Tani, *Makromol. Chem.*, in press.

(28) For convenience, the notation is used to distinguish from the alkyl/alkyl exchange process. In practice, a rotation around an Al–O→Al bond followed by exchange of alkyl groups also affords a similar result.

(29) Elimination of inert gas from the reaction system resulted in enhanced "alkyl/alkoxyl" exchange for some unclarified reason.

TABLE IV

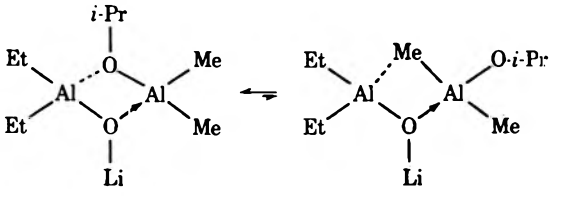
REACTION OF ACETALDEHYDE WITH $[R_2AlZLi]\cdot[AlR'_3]$[a]

Preparation and aging of organoaluminums		Reaction	Reaction products, mol/mol organoaluminum[b]				
Temp, °C	Time, hr	Temp, °C	CH_3CHOHR	CH_3CHOHR'	CH_3CH_2OH	Total	$\gamma_{R',R}$[c]
			$[Et_2AlOLi]\cdot[AlMe_3]$ (37916-29-3)[i]				
−78	1	−78	0.32	0.75	0	1.07	2.3[d]
−78	9	−78	0.44	0.86	0	1.30	2.0
−78	48	−78	0.43	0.79	0	1.22	1.9[e]
−78	1	−20	0.40	0.72	0	1.12	1.8
−78	1	0	0.47	0.88	0	1.35	1.7
0	1	−78	0.48	0.71	0	1.19	1.5
40	1	−78	0.53	0.71	0	1.24	1.3
40	9	−78	0.65	0.64	0	1.29	1.0
80	1	−78	0.53	0.71	0	1.24	1.3
			$[Me_2AlOLi]\cdot[AlEt_3]$ (37916-30-6)				
−78	1	−78	0.35	0.82	0	1.17	2.3[f]
−78	1	−20	0.50	1.04	0	1.54	2.1
−78	1	0	0.71	1.10	0	1.81	1.6
			$[Et_2AlOLi]\cdot[Al\text{-}i\text{-}Bu_3]$ (37916-31-7)				
−78	1	−78	0.58	0.13	0.25	0.96	0.7
−78	1	−20	0.68	0.18	0.43	1.29	0.9
			$[Et_2AlNPhLi]\cdot[AlMe_3]$ (37916-32-8)				
−78	1	−78	0.51	1.07	0	1.58	2.1
−78	1	−20	0.54	1.29	0	1.83	2.4
			$[Et_2AlNPhLi]\cdot[Al\text{-}i\text{-}Bu_3]$ (37916-33-9)				
−78	1	−78	1.20	0	0.44	1.64	0.4
−78	1	−20	1.20	0	1.50	2.70	1.3
			$[Et_2AlOLi\cdot THF]\cdot[AlMe_3]$ (37916-34-0)				
−78	1	−78	0.26	0.18	0	0.44	0.7
−78	1	−20	0.52	0.70	0	1.22	1.4
			$[Et_2AlOLi]\cdot[AlMe_3\cdot THF]$				
−78	1	−78	0.21	0.18	0	0.39	0.9[g]
−78	1	−20	0.43	0.53	0	0.96	1.2
			$[Et_2AlOLi]\cdot[AlMe_3]\cdot THF$				
−78	1	−78	0.18	0.35	0	0.53	1.9
−78	9	−78	0.16	0.17	0	0.33	1.1
−78	48	−78	0.21	0.05	0	0.26	0.2
			$[Me_2AlOLi]\cdot[AlEt_3\cdot THF]$ (37916-35-1)				
−78	1	−78	0.09	0.23	0	0.32	2.5
−78	1	−20	0.26	0.79	0	1.05	3.0
			$[Et_2AlOLi]\cdot[Me_2AlO\text{-}i\text{-}Pr]$[h] (37916-36-2)				
−78	48	−78	0	Trace	0	Trace	
−78	48	−20	Trace	Trace	0	Trace	
−78	48	0	Trace	Trace	0	Trace	

[a] Toluene (5 ml) and organoaluminum (4.7×10^{-4} mol) were used. Acetaldehyde concentration: 5 mol/mol of organoaluminum. Reaction time: 20 hr. [b] Any of other reaction products was not observed. [c] Ratio of R′ to R groups consumed in the reaction with acetaldehyde. [d] Time dependence of the reaction/time (hr), R addition, R′ addition, and $\gamma_{R',R}$ are given: 0.5, 0.28, 0.62, 2.2; 1, 0.35, 0.70, 2.0; 4, 0.36, 0.71, 2.0. [e] Time dependence of the reaction (see *d*): 0.5, 0.29, 0.61, 2.1; 1, 0.40, 0.80, 2.0; 5, 0.40, 0.79, 2.0. [f] Time dependence of the reaction (see *d*): 0.2, 0.28, 0.86, 3.1; 1, 0.36, 0.90, 2.5. [g] Time dependence of the reaction (see *d*): 0.2, 0.18, 0.15, 0.8; 0.5, 2.0, 0.17, 0.9; 5, 2.0, 0.18, 0.9. [h] The amount of *i*-PrOH corresponding to the *i*-PrO group which was present in the organoaluminum was not included. [i] Registry number.

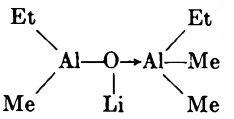
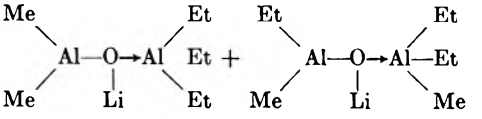
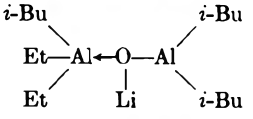
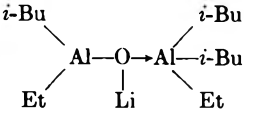
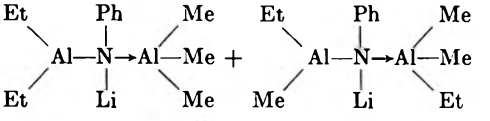
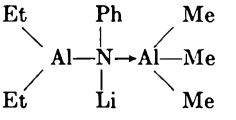
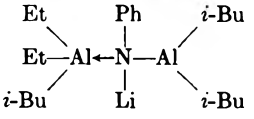
dinated with $[Et_2AlOLi]\cdot[AlMe_3]$ prior to addition of acetaldehyde, the $\gamma_{Me,Et}$ value decreases from 2 to 0.2 during a long aging period. This indicates that the rate of the alkyl/alkyl exchange process has been decreased by the addition of THF as observed in the nmr study.[7] Total consumption of the alkyl groups at −78° is lowered to less than one-half of the case without THF. In $[Et_2AlOLi]\cdot[AlMe_3\cdot THF]$, $[Et_2AlOLi\cdot THF]\cdot[AlMe_3]$, and $[Me_2AlOLi]\cdot[AlEt_3\cdot THF]$, methyl addition is considerably decreased as compared with ethyl addition, indicating that methyl bridging can compete with donation of THF more strongly than ethyl bridging.

It is interesting to note that, although the "alkyl/alkoxyl" exchange process can be seen when $[Et_2AlOLi]\cdot[AlMe_3]$ is directly reacted with acetaldehyde at higher temperature, the complex $[Et_2AlOLi]\cdot[Me_2AlOiPr]$ is virtually inactive to further addition reaction. This



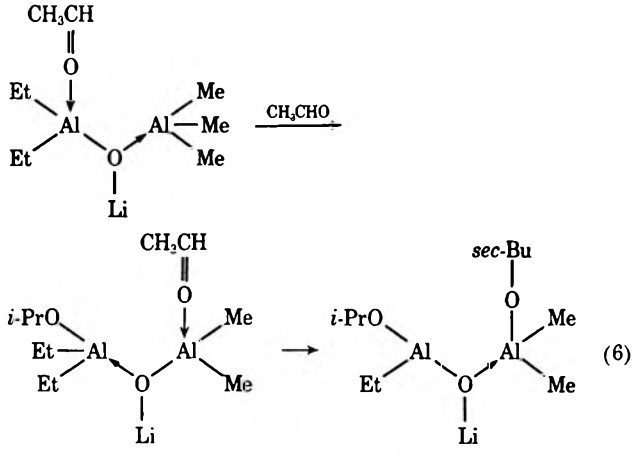
(5)

TABLE V
SUGGESTED SPECIES OF $[R_2AlZLi]\cdot[AlR'_3]$ PREDOMINANT AT THE TEMPERATURE OF REACTION WITH ACETALDEHYDE

Type of complex	Structure of predominant species: −78°	Higher temperature
$[Et_2AlOLi]\cdot[AlMe_3]$		Randomly distributed
$[Me_2AlOLi]\cdot[AlEt_3]$		Randomly distributed
$[Et_2AlOLi]\cdot[AliBu_3]$		
$[Et_2AlNPhLi]\cdot[AlMe_3]$		
$[Et_2AlNPhLi]\cdot[AliBu_3]$		Randomly distributed

observation implies the presence of a stable intermediate just like a stable dimer of R_2AlOR'[30] in the "alkyl/alkoxyl" exchange process.

With an excess mole of acetaldehyde, some of the organoaluminum molecules would be coordinated by the aldehyde simultaneously to the first formation of the alkoxyl group, and subsequently further addition would take place (eq 6).



(6)

The four-membered ring opens preferentially at the Al–OR side, not at the Al–OLi side. Thus, two kinds of solids $[Et_2AlOLi]\cdot[Et_2AlO\text{-}sec\text{-}Bu]$ could be obtained, one of which is less soluble and monomeric, regardless of its concentration in benzene solution. The other form is highly soluble and monomeric in dilute solution. The former has lower catalyst activity than the latter. The details of the study will be published elsewhere.

Experimental Section

Experiments were carried out under an argon atmosphere.

Materials.—Acetaldehyde was prepared from paraldehyde and purified as previously described.[27] Solvents were purified as described in another paper.[6]

(30) N. Davidson and H. C. Brown, *J. Amer. Chem. Soc.*, **64**, 316 (1942); E. G. Hoffmann, *Justus Liebigs Ann. Chem.*, **629**, 104 (1960).

Organoaluminums.—$AlMe_3$, $AlEt_3$, and Al-*i*-Bu_3 were obtained from a commercial source (Ethyl Corp.) and purified by single distillation under reduced pressure. Et_2AlO-*sec*-Bu, bp 52.5–53.0° (3×10^{-3} mm), and Et_2AlOEt, bp 40.5–45.0° (0.1×10^{-2} mm), were prepared from equimolar reactions of $AlEt_3$ with *sec*-BuOH and EtOH, respectively, and purified by distillation *in vacuo*. $AlR_3\cdot Do$ complexes were prepared from equimolar reactions of AlR_3 with corresponding organic Lewis bases, which are listed in Table VI. Preparation and purification of the binuclear organoaluminum complexes were carried out as described in another paper.[6] $[Et_2AlOLi]\cdot[AlMe_3\cdot THF]$, $[Et_2AlOLi\cdot THF]\cdot[AlMe_3]$, and $[Me_2AlOLi]\cdot[AlEt_3\cdot THF]$ were prepared by equimolar complexation of the corresponding moieties in toluene. The complexation temperature and aging periods are included in Table IV. $[Et_2AlOLi]\cdot[Me_2AlOiPr]$ was prepared by complexation of Et_2AlOLi with $Me_2AlOiPr$, prepared by equimolar reaction of $AlMe_3$ with *i*-PrOH and purified by distillation under a reduced pressure, bp 60° (1 mm), at 60° in toluene for 3 hr. Completion of the complexation was confirmed by nmr spectroscopy where disappearance of broad resonances due to Et_2AlOLi was observed.

Reaction of Acetaldehyde with Organoaluminum Compounds.—A cylindrical two-necked reactor attached to a vacuum line was filled by dry argon. Transfer of reagents was made by the aid of an argon-flushed hypodermic syringe. In a typical procedure, 0.13 ml of acetaldehyde chilled at −78° was added to a solution of 4.7×10^{-4} mol of $[Et_2AlOLi]\cdot[AlEt_3]$ in 5 ml of toluene which was kept at −20°, with stirring magnetically from the outside of the reactor. The reactor was sealed and stirring was continued at −20°. After 24 hr, the reactor was opened at −78° to add 1 ml of 2 *N* sulfuric acid. The aqueous portion froze immediately. The mixture was gradually (in 10 min) warmed up to room temperature, with stirring. The icy portion melted as the hydrolysis started. After cooling to −78° again, the mixture was neutralized with 2 *N* NaOH solution by gradual elevation of the temperature. The mixture was cooled to −78° with stirring to solidify the aqueous portion. Unsolidified toluene layer was subjected to glc analysis. (During the hydrolysis treatments, the neck of the reactor was chilled by Dry Ice to avoid elimination of volatile materials.)

Gas Chromatographic Analysis.—A Yanagimoto gas chromatograph GCG-220 apparatus was operated at 70° using a 2-m 15% tricresyl phosphate/Celite-545 (50–60 mesh) column, with eluting by hydrogen gas at a flow rate of 40 ml/min. Quantitative analysis was carried out by calibration with known amounts of corresponding authentic samples in 5 ml of toluene. Toluene was used as an internal standard. Accuracy of the analyses is ±5% except for ethanol (±10%, mainly due to high solubility in water) and acetaldehyde (±15%, due to solubility in water plus vaporization).

TABLE VI
$AlR_3 \cdot Do$ COMPOUNDS PREPARED

$AlR_3 \cdot Do$	Bp, °C (0.5 mm)	Calcd Al, %	Calcd Mol wt	Calcd R_3Al/Do	Found Al, %	Found Mol wt	Found R_3Al/Do[b]	Nmr[a] δ_{CH_3C}	Nmr[a] δ_{CH_2Al}	Nmr[a] $\Delta\delta_{CH_2CH_3}$	ΔH_f,[c] kcal/mol
$Et_3Al \cdot OEt_2$	63–64	14.33	188.3	1.00	14.32	180.5	1.00	1.41	0.17	−1.24	11.2[d]
$Et_3Al \cdot THF$	62–63	14.49	186.3	1.00	14.35	183.2	0.97	1.44	0.20	−1.24	14.0[d]
$Et_3Al \cdot NEt_3$	77–78	12.53	215.4	1.00	12.58	214.8	0.99	1.53	0.25	−1.28	
$Et_3Al \cdot Py$	92–93	13.96	193.3	1.00	13.89	191.1	0.91	1.46	0.37	−1.09	19.4[d]
$Me_3Al \cdot OEt_2$	22.5–23	18.45	146.2	1.00	17.45	146.6	1.00		−0.45[f]		20.2[e]
$Me_3Al \cdot THF$	31–32	18.71	144.2	1.00	17.56	148.0	1.00		−0.50[f]		22.9[e]
$Me_3Al \cdot NEt_3$	Mp 66	15.57	173.3	1.00	14.59	163.8	0.98		−0.41[f]		26.5[e]
$Me_3Al \cdot Py$	64–66	17.85	151.2	1.00	17.41	148.2	1.00		−0.29[f]		17.5[e]

[a] Chemical shift in benzene solution at 60 MHz. Values are internally standardized from benzene proton assumed as 7.37 ppm. [b] Determined from nmr spectra. [c] Heats of formation of complexes $AlR_3 \cdot Do$. [d] Reference 19. [e] Reference 20. [f] δ_{CH_3Al}.

Reaction of Acetaldehyde with R_2AlZM.—For Et_2AlOLi four runs were carried out with 3 molar equiv of acetaldehyde for 24 hr (at −78°, −20, and 0°) and with 100 molar equiv of acetaldehyde for 20 hr at 0°. Acetaldehyde was recovered almost unchanged. No detectable peaks were observed other than the solvent and the starting aldehyde. For Me_2AlOLi, three runs were made with 3 molar equiv of acetaldehyde for 20 hr at −78, −20, and 0°. The results were identical with the case of Et_2AlOLi. For $Et_2AlNPhLi$, two runs were made of reactions with 3 molar equiv of acetaldehyde for 20 hr at −78 and at −20°. The results were also identical with the case of Et_2AlOLi. For Et_2AlSNa, with 3 molar equiv of acetaldehyde, the reaction for 24 hr at −78° was identical with the case of Et_2AlOLi. At −20°, 0.14 molar equiv of ethyl acetate was observed as a sole reaction product. With 100 molar equiv of the aldehyde, 1.08 molar equiv of ethyl acetate accompanied by trace amounts of ethanol, methyl ethyl ketone, and *sec*-butyl acetate was detected after 24 hr at −20°.

Registry No.—Acetaldehyde, 75-07-0.

Acknowledgment.—We are grateful to Messrs. N. Oguni and M. Mikumo for preparation of some organoaluminum complexes.

A Mechanistic Study of the Reaction of Lithium Aluminum Hydride with *N*-Methylbenzanilides

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The relative rates of reduction *vs.* cleavage for various *N*-methylbenzanilides under the influence of lithium aluminum hydride are strongly dependent on the nature of substituents in the *N*-phenyl group. The effect of substituents in the *C*-phenyl moiety is small. The mechanistic implications of these observations are discussed. Investigations directed towards using *N*-methyl-*p*-chloranilides for the preparation of aldehydes and the use of $LiAlH_4$–$AlCl_3$ for the reduction of *N*-methylbenzanilide are also described.

The reduction of tertiary carboxamides with lithium aluminum hydride normally results in the formation of the corresponding amine.[1] In a significant number of cases, however, reductive cleavage (hereafter referred to simply as cleavage) of the peptide bond occurs to yield an aldehyde and/or an alcohol, as well as the amine derived from the cleavage process.[1-7] In spite of the great utility of both types of reactions in the synthesis of amines and aldehydes, no systematic study of electronic factors and their influence on the relative importance of reduction *vs.* cleavage has been conducted. Accordingly, we have conducted such a study in hopes of increasing the mechanistic understanding and synthetic utility of these reactions.

Both the reduction and cleavage of tertiary carboxamides are commonly believed to result from partitioning of an initially formed tetrahedral adduct (**1**).[1-4] Aldehyde has been proposed to result from hydrolysis of **1**, while the other products arise from nucleophilic attack by hydride on **1** (eq 1).[2] An alternate proposal[8] suggests that expulsion of amide ion from **1** yields aldehyde,[9] while formation and subsequent reduction of **3** is responsible for the "normal" reduction process to yield **2** (eq 2).

$$RCH_2OM + \ddot{N}R'R'' \leftarrow \underset{\underset{H}{|}}{\overset{OM}{\overset{|}{RCNR'R''}}} \rightarrow \underset{2}{RCH_2NR'R''} \quad (1)$$

1 (M = —Al(—)—)

$$RCHO + \ddot{N}R'R'' \leftarrow 1 \rightarrow \underset{3}{RCH{=}\overset{+}{N}R'R''} \rightarrow 2 \quad (2)$$

(1) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, Chapter 10.

(2) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **83**, 4549 (1961).

(3) W. Weygand, E. Eberhardt, H. Linden, F. Schofer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).

(4) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953). These authors suggest different intermediates for reduction and cleavage. They subsequently propose a single intermediate for both processes; see V. M. Micovic and M. L. Mihailovic, "Lithium Aluminum Hydride in Organic Synthesis," Izdavacko Preduzece, Belgrade, Yugoslavia, 1955, pp 58–60.

(5) F. Weygand and R. Mitgau, *Chem. Ber.*, **88**, 301 (1955).

(6) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **81**, 502 (1959).

(7) T. Axenrod, L. Loew, and P. S. Pregosin, *J. Org. Chem.*, **33**, 1274 (1968).

(8) Reference 1, p 545.

(9) Further reduction by $LiAlH_4$ would, of course, produce the corresponding alcohol.

The above mechanisms are based on experiments directed towards optimizing aldehyde yields. Accordingly, the main thrust of previous studies has been to delineate those structural features which enhance the rate of formation of **1** relative to subsequent steps.[10] In contrast, our experiments were designed to study the partitioning of **1** between the available reaction routes.

Experimental Design.—The *N*-methylbenzanilide system was selected for these studies since *N*-methylanilides had previously been shown to undergo cleavage,[3] substituents of varying electronic properties could be introduced while maintaining a constant steric environment about the reaction center, and finally certain desirable substituents were expected to be inert to $LiAlH_4$ under our reaction conditions.[11]

A 100% excess of standardized[12] $LiAlH_4$ solution (ether) was injected into a stirred amide solution contained in a bath thermostated at 25°. In spite of rigorous drying of reagents and equipment, small amounts of precipitate commonly separated at this stage. To minimize the significance of possible surface effects and for other reasons which are stated below, equimolar amounts of *N*-methylbenzanilide and the substituted *N*-methylbenzanilide were combined and simultaneously treated with $LiAlH_4$ in the same reaction vessel. After hydrolysis, analyses were conducted by quantitative glpc.

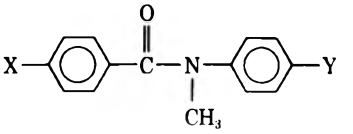
Each run thus produced benzyl alcohol, *N*-methylaniline, and *N*-methyl-*N*-benzylaniline. By comparing the yield of substituted benzyl alcohol or *N*-methylaniline with that of the unsubstituted material, a direct study of substituent effects on cleavage could be made under identical reaction conditions. Similarly, the effect of the substituents on reduction could be evaluated by comparing yields of the two tertiary amines. Any change in the nature of the reducing agent caused by traces of impurities such as water or by the interaction of reaction products with $LiAlH_4$, which could conceivably result in anomalous reduction *vs.* cleavage rates for the substituted compound, should be reflected in the reaction of *N*-methylbenzanilide as well.[13] The latter reaction thus served as a standard reaction for each run, and only the difference in reactivity between the standard and the substituted amide (Δ values given in Table I) need be considered for our purposes.

Results

The results of our studies are summarized in Table I. No products other than those expected from reduction and cleavage were observed in any of the reactions. Except where noted, each entry is the average of results for at least two different reactions. In at least one of the reactions for each entry the material balance exceeded 90%, and the percentages given are percentages of the reaction mixture. Product distributions for reactions yielding poorer material balances (generally >80%) did not vary significantly from reactions with good material balances. The per cent cleavage of *N*-methylbenzanilide (the standard reaction) for the 15 reactions yielding the data in Table I was 80 ± 5%.

TABLE I

SIMULTANEOUS REDUCTION OF *N*-METHYLBENZANILIDE AND SUBSTITUTED *N*-METHYLBENZANILIDE



Entry	Registry no.	Unsubstituted % cleavage	Substituted X	Substituted Y	Substituted % cleavage	Δ[d]
1[a]	1934-92-5	83				
2[b]	33672-81-0	84	OMe	H	72	12
3[b]	37950-87-1	80	F	H	86	−6
4[a]	1517-46-0	80	Cl	H	73	7
5[a]	33675-68-2	80	H	OMe	35	45
6[c]	2054-12-8	88	H	F	83	5
7[a]	10278-51-0	70	H	Cl	86	−16

[a] Average of two runs. [b] Average of three runs. [c] Single run; ratio of tertiary amines determined by nmr; see Table VI. [d] Δ = % cleavage for unsubstituted minus % cleavage for substituted.

Discussion

Reasonably constant values for the per cent cleavage of *N*-methylbenzanilide were obtained for all reactions except for those yielding data for entry 7 of Table I. Those values were reproducible (69%, 71%), and their large deviation from the mean (81 ± 3% excluding these data) may indicate some alteration in the nature of the reducing agent during the reaction progress.

Assuming that **1** is a common intermediate in the foregoing reactions, our data must be considered in terms of the effect of substituents on the competitive processes of reduction to tertiary amine and cleavage to a benzyl alcohol and an *N*-methylaniline. Hence, we discuss substituents in terms of their effect on the *relative* rates of reduction *vs.* cleavage for each amide.

Examination of Δ values in Table I for entries 5, 6, and 7 reveals that substituents in the *N*-phenyl group promote cleavage relative to reduction in the order *p*-Cl > *p*-H > *p*-F > *p*-OCH_3. This ordering conforms to the order of increasing σ^+ constants[14] and provides experimental support for the previously proposed mechanisms for cleavage (eq 1 and 2) both of which require enhancement in the rate of cleavage relative to reduction as the basicity of the departing nitrogen is decreased.[15]

The effects of substituents in the *C*-phenyl moiety on the relative rates of reduction and cleavage, as can be seen from entries 2, 3, and 4, were quite small. Moreover, decreased cleavage was observed for both *p*-methoxy (σ −0.27)[16] and *p*-chloro (σ 0.27).[16] We can provide two plausible explanations for this behavior.

(10) In the presence of a stoichiometric quantity of $LiAlH_4$, the maximum yield of aldehyde would be obtained if all the hydride were consumed in the formation of **1**. Aldehyde yields decrease to the extent that **1** or its reaction products react with hydride. Rapid formation of **1** is favored by decreased p–π interaction in the peptide bond and low steric requirements for groups bonded to nitrogen.

(11) G. J. Karabatsos and R. L. Shone, *J. Org. Chem.*, **33**, 619 (1968).

(12) H. Felkin, *Bull. Soc. Chim. Fr.*, **18**, 347 (1951).

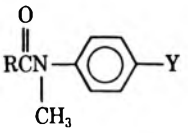
(13) Lithium alkoxyaluminum hydrides, for example, are known to be weaker reducing agents than $LiAlH_4$: H. C. Brown, *J. Chem. Educ.*, **38**, 173 (1961).

(14) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 90.

(15) (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 261; (b) reference 14, p 182.

(16) G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **20**, 75 (1966).

TABLE II
COMPARISON OF ALDEHYDE YIELDS FROM SUBSTITUTED N-METHYLBENZANILIDES



R	Y	Yield,[a] %	Lit. yield, %
C_6H_5	H	70	68[b]
C_6H_5	Cl	72	
p-$CH_3OC_6H_4$	H		51[c]
p-$CH_3OC_6H_4$	Cl	51	
o-$CH_3OC_6H_4$	H		30[b]
o-$CH_3OC_6H_4$	Cl	25	

[a] Yields were determined by the weight of unpurified 2,4-DNP derivatives, all of which had narrow melting ranges and agreed with literature values. [b] Reference 3. [c] Reference 5.

Assuming that the Brown mechanism (eq 1) is correct, the observed substituent effects are similar to those generally found for bimolecular nucleophilic substitution on benzyl halides.[17] Only if bond breakage in the transition state were equivalent for both C–N and C–O cleavage should no substituent effect be observed. The effect should be qualitatively the same for both processes, and hence one might anticipate only small substituent effects.

Alternatively the observed substituent effects may indicate a change in mechanism caused by the variation of substituents. If, for example, 1 were being partitioned simultaneously between the four processes outlined in eq 1 and 2, one would not necessarily anticipate a simple relationship between σ constants and the relative rates of reduction and cleavage. Substituents could clearly influence the rates of all four processes and thereby determine the predominant mechanism.

Studies with a "Mixed" Hydride Reagent.—Modifications in the reaction technique which would enhance reduction relative to cleavage would be of some synthetic utility. It has been reported[18] that use of $LiAlH_4$–$AlCl_3$ in place of $LiAlH_4$ alone significantly decreases the extent of cleavage of *N*-acetylpyrrole.

We accordingly investigated the use of $LiAlH_4/AlCl_3$ ratios of 1:1 and 1:2 in the reduction of *N*-methylbenzanilide. The product distributions observed for these reactions were virtually unchanged from that observed in previous reactions using $LiAlH_4$ alone.

Use of *N*-Methyl-*p*-chloroanilides for Aldehyde Preparation.—Successful aldehyde synthesis *via* partial reduction of tertiary carboxamides with $LiAlH_4$ should require rapid formation of 1 and relatively slower loss of amide ion. Since both of these processes should be enhanced by electron-withdrawing substituents in the *N*-phenyl group, the net result of such a substituent on the obtainable yield of aldehyde is uncertain. Accordingly, we conducted a series of experiments with the *N*-*p*-chlorophenyl group to evaluate its effect on aldehyde yield. The results summarized in Table II suggest that this group increases the rate of formation of 1 to about the same extent as subsequent steps and indicate a lack of synthetic advantage in using the *N*-*p*-chlorophenyl group in such reactions.

(17) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956); see also ref 14, p 172.
(18) R. F. Nystrom and C. Rainer Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

Experimental Section

Lithium Aluminum Hydride Stock Solution.—Lithium aluminum hydride (15.20 g, 0.40 mol) was extracted with 350 ml of anhydrous ether using a Soxhlet extractor. The resultant solution was standardized[12] before each use and was found to be 1.2–1.5 *M*.

Substituted Benzyl Chlorides.—To a refluxing solution of 8.00 g (0.063 mol) of 4-fluorobenzyl alcohol and 5 ml of pyridine in 50 ml of benzene was added dropwise with stirring 7.54 g (0.063 mol) of thionyl chloride. After refluxing for 4 hr, the reaction was cooled to room temperature and the pyridine hydrochloride removed by filtration. The filtrate was washed successively with 1 *M* hydrochloric acid, water, 5% sodium hydroxide, and water, and then dried over magnesium sulfate. Upon distillation 7.65 g (83%) of 4-fluorobenzyl chloride was obtained, bp 89° (35 mm), $n^{25}D$ 1.5095. The ir spectrum was identical with Sadtler spectrum no. 16978. Other substituted benzyl halides were synthesized in similar fashion and produced infrared spectra which were identical with those published by Sadtler.

Substituted *N*-methylanilines were prepared by lithium aluminum hydride reduction of the corresponding formanilides[19,20] (Table III).

Substituted *N*-methylbenzanilides were prepared from the appropriate acid chlorides and *N*-methylanilines (Table IV).

Substituted *N*-Methyl-*N*-benzylanilines.—To the appropriate *N*-methylaniline was added dropwise with stirring at 90° in a helium atmosphere an equimolar quantity of the appropriate benzyl chloride. After 2 hr, heating was ceased and the reaction allowed to stand overnight at room temperature. The residue was stirred for 1 hr with an equal volume of 25% sodium hydroxide, and the resultant solution was extracted twice with ether. After drying over anhydrous magnesium sulfate, the ethereal solution was concentrated and then vacuum distilled. The purity of the distillate was ascertained by glpc and, when necessary, residual secondary amine was removed by benzoylation. The foregoing method gave acceptable yields (30–73%) for all of the required compounds (Table V) with the exception of *N*-methyl-*N*-(4-methoxybenzyl)aniline.

Substituted Benzyl Alcohols.—All of the required benzyl alcohols were commercially available with the exception of *p*-fluorobenzyl alcohol, which was prepared by lithium aluminum hydride reduction of the acid chloride in ether.

Reduction, General Procedure.—All glassware was predried at 110° for 24 hr before use. All reductions were conducted in a 100-ml three-neck flask equipped with a condenser, drying tube, precision ground stirrer, and an adapter of our own design which was sealed with a rubber septum. A solution containing *N*-methylbenzanilide (2.4 mmol) and the substituted *N*-methylbenzanilide (2.4 mmol) in 25 ml of anhydrous ether was stirred in the foregoing apparatus for 15 min at 25° (water bath). Stock $LiAlH_4$ solution (5 mmol) was injected using a syringe, and stirring continued for 24 hr. The reaction was hydrolyzed with 2.0 ml of H_2O, and the precipitated aluminum salts were removed by filtration. The precipitate was washed with 5 ml of ether, refluxed briefly with an additional 10 ml of ether, and then discarded. The original filtrate and washings were combined for analysis.

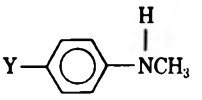
Analysis of Simultaneous Reductions.—Analyses were conducted by glpc under the conditions summarized in Table VI. Peak areas were determined using a planimeter or a Disc integrator. Each analysis consisted of determinations of a substituted and unsubstituted tertiary amine and of a substituted and unsubstituted cleavage product (either a benzyl alcohol or an *N*-methylaniline). Reactions which failed to produce >90% material balances for substituted and unsubstituted products alike were repeated until they did so.

Reductions with Mixed Hydride Reagents.—To a stirred mixture of 1.33 g (10 mmol) of aluminum chloride and 0.19 g (5 mmol) of lithium aluminum hydride in 10 ml of ether was added dropwise at 0° 1.05 g (5 mmol) of *N*-methylbenzanilide in 10 ml

(19) F. Benington, R. D. Moris, and L. C. Clark, *J. Org. Chem.*, **23**, 19 (1958).
(20) E. C. Horning, Ed., "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 590.

Table III

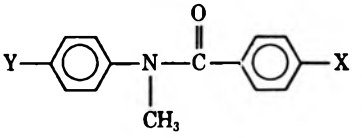
Properties of Substituted *N*-Methylanilides



Y	Registry no.	Bp, °C (mm)	$n^{25}D$	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
F	459-59-6	136 (120)	1.5314	67.18	6.44	11.19	66.93	6.43	11.32
OCH_3	5961-59-1	67 (0.15)	1.5640	70.09	8.03	10.22	69.84	7.81	10.30
Cl[a]		91-92 (4.2)	1.5820						

[a] F. D. Chattaway and K. J. P. Orton, *J. Chem. Soc.*, **79**, 461 (1901).

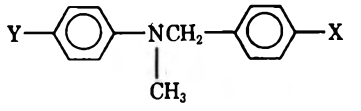
Table IV



X	Y	Mp, °C	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
OCH_3	H	74-75 (lit.[a] 74)						
F	H	90.5-91.5	73.33	5.29	6.11	73.10	5.23	6.10
Cl	H	51-52 (lit.[b] 51)						
H	OCH_3	73.5-76.5	74.66	6.27	5.81	74.62	6.22	5.88
H	F	84-88	73.33	5.29	6.11	73.19	5.26	6.03
H	Cl	67.5-70	68.43	4.92	5.70	68.60	5.06	5.57
OCH_3[c]	Cl	108.5-109.6	65.33	5.11	5.07	65.28	5.22	4.99
o-OCH_3[c]	Cl	86-86.5	65.33	5.11	5.07	65.43	5.25	5.02

[a] Reference 5. [b] J. S. Pizey and R. L. Wain, *J. Sci. Food Agr.*, **10**, 577 (1959). [c] These compounds were used only for aldehyde preparation (*vide infra*).

Table V

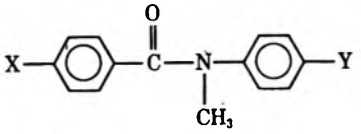


X	Y	Registry no.	Bp, °C (mm)	n_D (°C)	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
OCH_3	H	37931-52-5	122 (0.05)	1.5984 (27)	79.26	7.54	6.16	79.24	7.55	6.13
F	H		103 (0.15)[a]	1.5817 (26)[a]						
Cl	H		120 (0.10)[b]	1.6080 (25)[b]						
H	OCH_3	18606-61-6	115 (0.05)	1.5937 (26)	79.26	7.54	6.16	79.42	7.54	6.11
H	F	37931-54-7	95-96 (0.15)	1.5788 (26)	78.10	6.56	6.51	78.00	6.51	6.69
H	Cl	37931-55-8	110-120 (0.10)	1.6126 (23)	72.56	6.09	6.04	72.42	6.11	5.84

[a] Lit. bp 132–135° (1.0); $n^{25}D$ 1.5844 [V. Schoellkopf, V. Ludwig, M. Patsch, and W. Franken, *Justus Liebigs Ann. Chem.*, **703**, 77 (1967)]. [b] Lit. bp 144–146° (0.30); $n^{25}D$ 1.6097 (see ref in *a*).

Table VI

Analysis of Reaction Products from Substituted *N*-Methylbenzanilides



X	Y	Column[a]	Temp, °C[b]	Standard[b]
OCH_3	H	A	185 (220)	3-Bromoaniline (*N*-methylbenzanilide)
F	H	B	110 (150)	*N*,*N*-Dimethylaniline (4-methoxybenzyl alcohol)
Cl	H	C	215 (245)	3-Bromoaniline (*N*-methyl-4-fluorobenzanilide)
H	OCH_3	D (E)	205 (250)	2-Methoxyaniline (*o*-ethoxyacetanilide)
H	F[c]	D (A)	195 (195)	2-Methoxyaniline (*o*-ethoxyacetanilide)
H	Cl	C	215 (235)	3-Bromoaniline (*N*-methyl-4-fluorobenzanilide)

[a] Column A, 10 ft × 1/8 in., 10% Carbowax 20M on 70/80 Varaport 30; column B, 10 ft × 1/8 in., 5% XF1150 on 60/80 Chromosorb W; column C, 10 ft × 1/8 in., 10% (4:1) Carbowax 20M–KOH on 100/120 Varaport 30; column D, 10 ft × 1/8 in., 20% (4:1) Carbowax 20M–KOH on 60/80 Chromosorb W; column E, 6 ft × 1/8 in., 20% (4:1) Apiezon L–KOH on 60/80 Chromosorb W. [b] The tertiary amines required higher temperatures and therefore separate standards (in parentheses) for analysis. [c] Only the total weight of the two tertiary amines could be determined by glpc due to poor separation. Their ratio was determined by nmr using the ratio of areas under the two methylene peaks at τ 5.6 and 5.5.

of ether. After the addition was complete, the reaction was allowed to come to room temperature and was stirred for 22 hr. Hydrolysis and product isolation was conducted using the procedure of Micovic and Mihailovic.[4] Reductions in which the molar ratio of $AlCl_3/LiAlH_4$/amide was 1:1:1 were conducted in a similar fashion. Analyses were carried out by glpc on column A (Table VI) at 210°.

Partial Reduction of *N*-Methyl-*p*-chloroanilides.—Into 3 mmol of the anilide in 10 ml of tetrahydrofuran was injected with stirring at 0° 0.83 ml of 1.2 *M* lithium aluminum hydride in tetrahydrofuran. The reaction mixture was stirred at 0° for 10 hr and was then added to 100 ml of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *M* hydrochloric acid. The resultant solution was diluted with 100 ml of 2 *M* hydrochloric acid and allowed to stand for 5 hr; the resultant 2,4-DNP was isolated, dried, and weighed.

Acknowledgments.—The authors thank the Chemistry Department and the Research Council of the University of Dayton for financial support. Helpful discussions with Professor Paul G. Gassman of The Ohio State University during the preparation of this manuscript are gratefully acknowledged. The authors are also indebted to Mr. Kenneth Fey, who conducted the studies with the mixed hydride reagents as his senior research project.

Palladium(II)-Catalyzed Exchange and Isomerization Reactions. VIII. Isomerization of Vinylic Halides in Acetic Acid Catalyzed by Palladium(II) Chloride[1,2]

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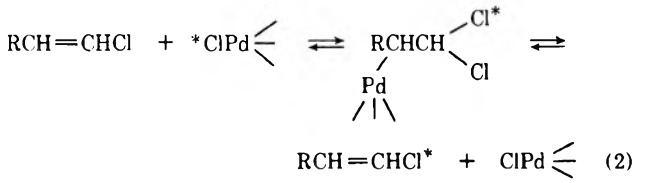
The palladium(II)-catalyzed isomerization of *cis*- and *trans*-1-chloropropene was found to obey the three-term rate expression rate = $(k_1[Li_2Pd_2Cl_6]/[LiCl] + k_2[Li_2Pd_2Cl_6] + k_3[Li_2Pd_2Cl_6]^{1/2})$[1-chloropropene]. 1-Bromopropene isomerization displayed mainly the k_2 and k_3 terms. The k_2 term most likely results from nonstereospecific chloropalladation–dechloropalladation in which the chloride adds to the carbon carrying the methyl and the palladium to the carbon carrying the halide. The k_1 and k_3 terms correspond to formation of monomer and dimeric π complexes, respectively. Isomerization is then accomplished through the π complexes without the intervention of an external reagent. A possible mechanism is rearrangement of the π complex to a Pd(II) σ-bonded carbonium ion which undergoes rotation before reverting to the π complex.

Paper IV[4] of this series describes a study of the radioactive chloride exchange of vinylic chlorides with radioactive lithium chloride. The rate expression for this exchange is given by eq 1.

$$\text{rate} = k[Li_2Pd_2Cl_6][\text{vinylic chloride}] \quad (1)$$

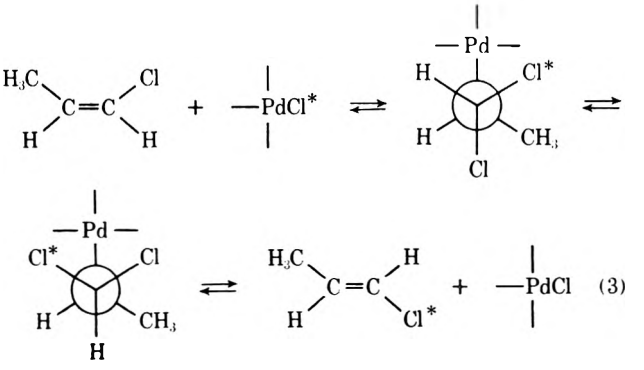
The mechanism which best fits all the experimental facts consists of chloropalladation followed by dechloropalladation to give exchange. Chloropalladation is not completely stereospecific but the main mode is apparently cis chloropalladation from the coordination sphere of Pd(II).



(2)

During the course of this work it was found that *cis*- or *trans*-1-chloropropene isomerized into the other isomer considerably faster than exchange with radioactive chloride. As shown in eq 3, this result would not have been predicted if isomerization occurred by mainly stereospecific cis chloropalladation–dechloropalladation. Thus some other route must be responsible for this isomerization.

This paper will describe a study of this reaction using vinylic chlorides and bromides as reactants.



(3)

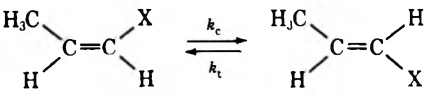
In paper VII of this series the study of a similar isomerization of enol propionates was described.[1] The rate expression for the isomerization is given by eq 4.

$$\text{rate} = \frac{k[Li_2Pd_2Cl_6][\text{enol propionate}]}{[LiCl]} \quad (4)$$

Effects of structure on rate as well as other mechanistic work showed that π-allylic or palladium hydride routes for this isomerization were very unlikely.[1,2]

Results

All runs were made at 25° in acetic acid solvent. The values of k_{obsd} for a given run are the sum of the pseudo-first-order rate constants, k_t and k_c for the reaction given by eq 5 (X = Cl or Br). The values of



(5)

k_c and k_t can readily be calculated from the composition of the equilibrium mixture, which was 74% cis when X is Cl and 70% cis when X is Br. For most

(1) Paper VII: P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 7316 (1972).

(2) For a preliminary account of this work, see P. M. Henry, *ibid.*, **93**, 3547 (1971).

(3) Address correspondence to author at Department of Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1.

(4) P. M. Henry, *J. Org. Chem.*, **37**, 2443 (1972).

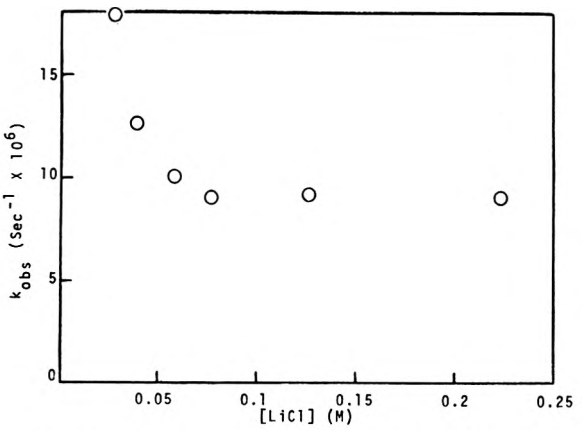


Figure 1.—Plot of k_{obsd} *vs.* [LiCl]; $[Li_2Pd_2Cl_6]$ = 0.015 ± 0.0004 *M*.

runs the vinylic chloride concentration was 0.2 *M*. Under the same reaction conditions runs starting with either *cis*- or *trans*-1-halopropene gave the values of k_{obsd}. For almost all runs the trans isomer was used, since it gave the biggest change in composition and therefore the most accurate values of k_{obsd}.

As in previous work the concentrations of the various Pd(II) and chloride species were determined from the total Pd(II) concentration, $[Pd(II)_t]$, and total chloride concentrations, $[Cl]_t$, making use of the previously determined[5] values of K_1 (0.1 M^{-1}) and K_D (2.6 M^{-1}) for the equilibria shown in eq 6 and 7.

$$Li_2Pd_2Cl_6 + 2LiCl \overset{K_1}{\rightleftharpoons} 2Li_2PdCl_4 \quad (6)$$

$$2LiCl \overset{K_D}{\rightleftharpoons} Li_2Cl_2 \quad (7)$$

Vinylic Chloride Isomerization.—The rate expression for isomerization was determined using *cis*- and *trans*-1-chloropropene. The dependence on 1-chloropropene concentration was determined under several reaction conditions. Typical results are given in Table I.

Table I
Dependence of k_{obsd} on 1-Chloropropene Concentration[a]

[*trans*-1-Chloropropene], *M*	k_{obsd}, sec^{-1} × 10^6
0.01	17.5
0.05	17.7
0.2	17.8
0.5	16.6

[a] $[Pd(II)]_t$ = 0.02052 *M*; $[Cl]_t$ = 0.0908 *M*.

Since the first-order rate constant, k_{obsd}, does not change with 1-chloropropene concentration, the reaction is first order in vinylic chloride.

The order in Pd(II) species and [LiCl] proved to be complicated. As shown in Figure 1, at low [LiCl] addition of more LiCl decreased the rate. However, above about 0.04 *M* LiCl, addition of LiCl did not affect the rate. Furthermore, if at the lowest [LiCl], a mole of $HgCl_2$ is added per mole of Pd(II) the rate is increased fivefold. That this acceleration resulted from further decrease in chloride resulting from formation of $HgCl_3^-$ species was demonstrated by running the isomerization in the presence of excess solid NaCl in the presence and absence of $HgCl_2$. In this case,

(5) P. M. Henry and O. Marks, *Inorg. Chem.*, **10**, 373 (1971).

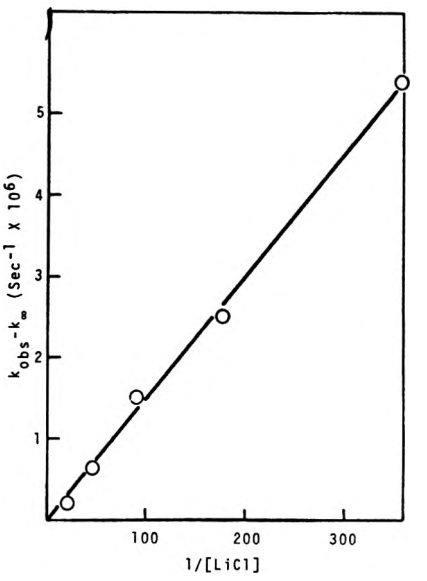


Figure 2.—Plot of $k_{obsd} - k_\infty$ *vs.* 1/[LiCl]; $[Li_2Pd_2Cl_6]$ = 0.0036 ± 0.0002 *M*.

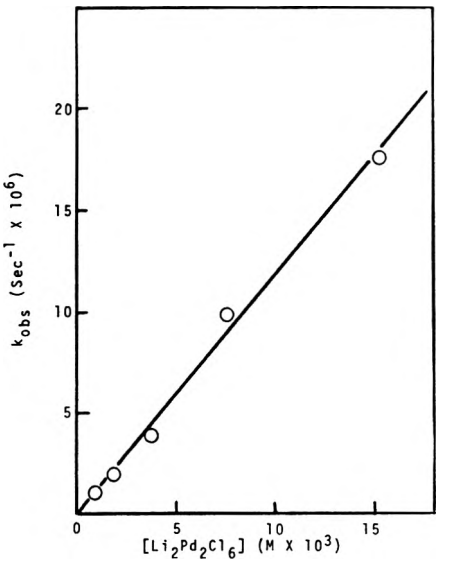


Figure 3.—Plot of $[Li_2Pd_2Cl_6]$ *vs.* k_{obsd} at low chlorides; [LiCl] = 0.011 ± 0.0003 *M*.

where the NaCl concentration was the saturation value[5] of 0.013 *M* for both runs, the rates were identical.

The nature of the chloride inhibition was determined in the following way. From the values of k_{obsd} at various [LiCl] was subtracted the value of k_{obsd} when the rate became unaffected by chloride (k_∞). These values were then plotted against 1/[LiCl]. As shown in Figure 2, the plot is linear and goes through the origin, indicating a first-order chloride inhibition. The order in $[Li_2Pd_2Cl_6]$ was then determined by plotting k_{obsd} *vs.* $[Li_2Pd_2Cl_6]$ at 0.011 *M* LiCl, a chloride concentration at which k_{obsd} consists almost exclusively of the chloride inhibited reaction; as shown in Figure 3, the plot is linear and goes through the origin. The rate expression for the reaction at low [LiCl] is thus given by eq 8.

$$\text{rate} = \frac{k[Li_2Pd_2Cl_6][\text{1-chloropropene}]}{[LiCl]} \quad (8)$$

The reaction was then studied at higher chloride, where the chloride-dependent reaction is negligible.

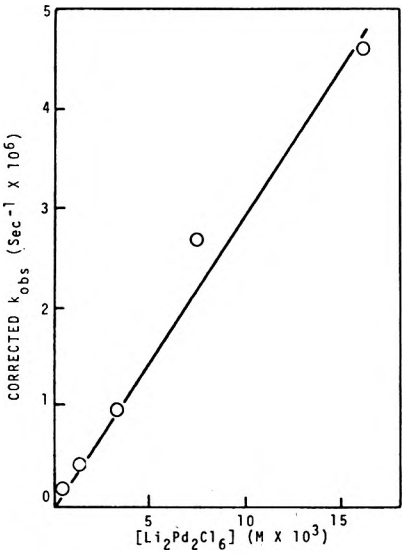


Figure 4.—Plot of corrected k_{obsd} *vs.* $[Li_2Pd_2Cl_6]$; [LiCl] = 0.207 ± 0.007 *M*.

An example of the dependence of rate on $[Li_2Pd_2Cl_6]$ is shown in Table II. The rate varies by a factor of

TABLE II
DEPENDENCE OF k_{obsd} ON $Li_2Pd_2Cl_6$ CONCENTRATION AT APPROXIMATELY 0.2 *M* LiCl[a]

$[Li_2Pd_2Cl_6]$, $M \times 10^3$	$[Li_2Pd_2Cl_6]^{1/2}$, $M^{1/2} \times 10^2$	k_{obsd}, sec^{-1} × 10^6	Contribution to k_{obsd}: 1st order, sec^{-1} × 10^6	Contribution to k_{obsd}: 1/2 order, sec^{-1} × 10^6
16.2	12.8	10.9	4.71	6.20
7.45	8.63	6.83	2.67	4.16
3.3	5.73	3.74	0.99	2.76
1.39	3.72	2.22	0.42	1.80
0.548	2.34	1.29	0.16	1.13

[a] [LiCl] = 0.207 ± 0.007 *M*.

a 8.5 while $[Li_2Pd_2Cl_6]$ varies by a factor of almost 30 and $[Li_2Pd_2Cl_6]^{1/2}$ varies by a factor of 5.5. Thus the dependence is not strictly first or 1/2 order in $[Li_2Pd_2Cl_6]$. Thus result suggests two terms, one first order and one 1/2 order. The contribution of each to k_{obsd} was calculated in the following fashion. The 1/2-order term should predominate at low $[Li_2Pd_2Cl_6]$ because the first-order term decreases more rapidly with decreasing $[Li_2Pd_2Cl_6]$. As a first approximation the k_{obsd} at lowest $[Li_2Pd_2Cl_6]$ was assumed to consist entirely of the 1/2-order term. The contribution of the 1/2 term at the other $[Li_2Pd_2Cl_6]$ could then be readily calculated and substrated from the values of k_{obsd} to give the first-order contributions. From the first approximation for the first-order contribution at the highest chloride the small contribution of the first-order term at the lowest $[Li_2Pd_2Cl_6]$ was calculated and substracted from k_{obsd} to give a second approximation for the 1/2-order contribution at lowest $[Li_2Pd_2Cl_6]$. The process was then repeated. After only three iterations the first- and 1/2-order contributions to k_{obsd} remained constant. They are given in the last two columns of Table II. A plot of the first-order contributions *vs.* $[Li_2Pd_2Cl_6]$, shown in Figure 4, is linear with zero intercept indicative of a first-order reaction.[6]

(6) Of course the values of the first-order contribution at the highest and lowest $[Li_2Pd_2Cl_6]$ are arranged to give a straight line through the origin. The important point is that the other three points fall on this straight line within experimental error.

The complex rate expression for $[Li_2Pd_2Cl_6]$ range of 0.00058 to 0.0162 *M* and a [LiCl] range of 0.0028 to 0.38 *M* is given by eq 9. Values of the rate constants are summarized in Table VI.

$$\text{rate} = \left(\frac{k_1[Li_2Pd_2Cl_6]}{[LiCl]} + k_2[Li_2Pd_2Cl_6] + k_3[Li_2PdCl_6]^{1/2}\right) \times [\text{vinylic halide}] \quad (9)$$

The effect of acetate and water on the rate exchange at two $[Cl]_t$ levels was determined. Data are given in Table III.

TABLE III
EFFECT OF LITHIUM ACETATE AND WATER ON RATE OF ISOMERIZATION[a]

$[Cl]_t$	[LiOAc]	$[H_2O]$	k_{obsd}, sec^{-1} × 10^6
0.0908	0	0	17.8
	0.1	0	13.5
	0.5	0	11.5
	0	2.5	14.8
0.4908	0	0	6.83
	0.5	0	6.42
	0	2.5	4.7

[a] $[Pd(II)]_t$ = 0.02052 for all runs. Rates measured using trans isomer.

The effect of acid on the rate of isomerization was tested. At $[Pd(II)]_t$ = 0.048 *M* and a $[Cl]_t$ of 0.37 *M*, the rate of isomerization is 8.9 × 10^{-6}. Under the same conditions except that the reaction mixture was now 1 *M* in CF_3COOH the value of k_{obsd} is 1.23 × 10^{-5} sec^{-1}.

cis-1-Chloropropene was isomerized to an equilibrium mixture in CH_3COOD which was 0.05 *M* in $[Pd(II)]_t$ and 0.3 *M* in $[Cl]_t$. The trans isomer was collected and analyzed by mass spectrometry. It was found to contain less than 0.2% deuterium.

1-Bromopropene Isomerization.—*cis*- and *trans*-1-bromopropene were isomerized to an equilibrium mixture of the two isomers without detectable quantities of 1-chloropropene being formed. Only upon long standing are materials with vpc retention times identical with those of *cis*- and *trans*-1-chloropropene found.

The effect of chloride concentration on rate is given in Table IV. The fact that the ratio in the last column

TABLE IV
VALUES OF k_{obsd} FOR ISOMERIZATION OF *trans*-1-BROMOPROPENE AT LOW CHLORIDE CONCENTRATIONS[a]

$[Cl]_t$, $M \times 10^2$	$[Li_2Pd_2Cl_6]$, $M \times 10^3$	[LiCl], $M \times 10^2$	k_{obsd}, sec^{-1} × 10^6	$k_{obsd}/[Li_2Pd_2Cl_6]$, M^{-1} sec^{-1} × 10^3
2.62	3.85	0.28	3.85	10.0
2.92	3.82	0.56	4.82	12.0
3.52	3.77	1.11	3.40	9.0
4.72	3.66	2.12	3.49	9.5
5.92	3.59	3.06	3.29	9.2

[a] Value of $[Pd(II)]_t$ for all runs was 0.00776 *M*; concentrations of Li_2PdCl_4 and Li_2Cl_2 can readily be calculated from concentrations of other species.

remains almost constant even at [LiCl] = 0.0028 *M* indicates no appreciable chloride inhibition.

Dependence of rate on $Li_2Pd_2Cl_6$ concentration is given in Table V. In this case the total rate variation

Table V
Dependence of k_{obsd} on $Li_2Pd_2Cl_6$ Concentration at Approximately 0.2 M LiCl[a]

$[Li_2Pd_2Cl_6]$, $M \times 10$	$[Li_2Pd_2Cl_6]^{1/2}$, $M \times 10^2$	k_{obsd}, $sec^{-1} \times 10^6$	Contributions to k_{obsd}: 1st order, $sec^{-1} \times 10^6$	Contributions to k_{obsd}: 1/2 order, $sec^{-1} \times 10^6$
10.1	10.05	6.91	5.65	1.26
4.55	6.74	3.03	2.19	0.84
1.95	4.46	1.36	0.80	0.56
0.78	2.8	0.78	0.44	0.35

[a] [LiCl] = 0.200 ± 0.002 M.

is about 9 while $[Li_2Pd_2Cl_6]$ varies by 13 and $[Li_2Pd_2Cl_6]^{1/2}$ varies by 3.6. Thus the first-order term is most important for 1-bromopropene. By procedures similar to those described earlier, the contribution of each term to k_{obsd} was calculated. They are listed in the last two columns of the table. The values of the rates constants are summarized in Table VI.

Table VI
Values of the Rate Constants for Isomerization and Exchange

	1-Chloropropene	1-Bromopropene
k_1	4.3×10^{-6} sec^{-1}	$<10^{-6}$ sec^{-1}
k_2	2.9×10^{-4} M^{-1} sec^{-1}	5.2×10^{-3} M^{-1} sec^{-1}
k_3	4.8×10^{-5} $M^{-1/2}$ sec^{-1}	1.25×10^{-4} $M^{-1/2}$ sec^{-1}
k_{ex}[a]	2.3×10^{-6} M^{-1} sec^{-1}	

[a] Rate of radioactive chloride exchange from ref 4. This value is for an equilibrium mixture of cis and trans isomers.

cis-1-Bromopropene was isomerized in CH_3COOD in the same fashion as *cis*-1-chloropropene. The *trans*-1-bromopropene formed contained less than 0.2% deuterium.

Discussion

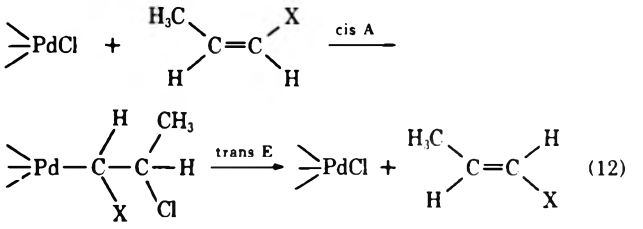
The general rate expression for isomerization of vinylic halides is given by eq 9 with rate constants listed in Table VI. The rate of radioactive chloride exchange for 1-chloropropene is included for purposes of comparison. In the case of isomerization of 1-chloropropene all three terms are detected, while, for 1-bromopropene, the k_2 term is by far the most important with the k_3 term barely detectable. This does not mean that k_1 and k_3 have lower values for 1-bromopropene than they do for 1-chloropropene. Rather, the value of k_2 for 1-bromopropene is about 20 times higher than that for 1-chloropropene. In fact k_3 for 1-bromopropene is approximately twice that for 1-chloropropene.

The various terms can readily be interpreted in terms of mechanism. The k_1 and k_3 terms correspond to the formation of π complexes without the intervention of any other external reagent to cause isomerization. The k_1 term results from π-complex formation *via* eq 10 and the k_3 term *via* eq 11 (VH = vinylic halide).

$$Li_2Pd_2Cl_6 + VH \underset{}{\overset{K_1}{\rightleftharpoons}} LiPd_2Cl_5(VH) + LiCl \quad (10)$$

$$Li_2Pd_2Cl_6 + 2VH \overset{K_3}{\rightleftharpoons} 2LiPdCl_3(VH) \quad (11)$$

The k_2 term is identical with that previously found for radioactive chloride exchange,[4] which apparently proceeds *via* a chloropalladation–dechloropalladation type mechanism as shown in eq 3. Thus, at least in the 1-chloropropene case, the k_2 term most likely results from nonstereospecific chloropalladation–dechloropalladation in the direction opposite from that shown in eq 3 (X = Cl or Br; A = addition, E = elimination).



(12)

It is necessary to postulate this mode of addition rather than the mode shown in eq 3 because the latter type of addition would predict rates of isomerization by this type of mechanism which would be close to the rate of exchange. In fact, as demonstrated by eq 3, since chloropalladation is mainly cis[4,7] the value of k_2 and rate of exchange should be very close. However, as shown in Table VI, the value of k_2 is much higher than k_{ex}. At a $Li_2Pd_2Cl_6$ concentration of about 0.0075 M, the rate of chloride exchange was only 5% of the rate of isomerization. According to the data in Table II, about 40% of the isomerization proceeds according to the k_2 term at this $Li_2Pd_2Cl_6$ concentration. Thus, most isomerization is proceeding according to eq 12 rather than eq 3.

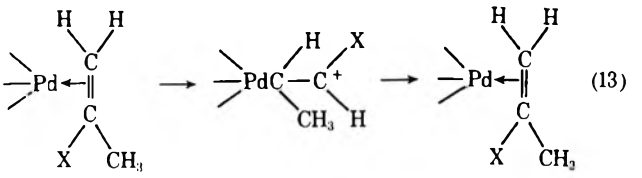
Ih the case of 1-bromopropene little is known about the mode of addition, since chloropalladation in the mode of eq 3 does not have to give exchange of chloride for bromide if chloride is eliminated much more readily than bromide. Certainly the reason that 1-bromopropene isomerizes more readily than 1-chloropropene is not immediately apparent. The differences in rate would not be expected to result from steric effects if isomerization occurred *via* eq 12, since the addition of bulkier groups to the double bond decreases the rate of chloropalladation.[4] It is difficult to predict the effect on rate of changing from a chloro to a bromo group if isomerization occurs by chloropalladation in the fashion opposite to eq 12.

As mentioned earlier, the k_1 and k_3 terms correspond to π-complex formation *via* eq 10 and 11, respectively. The π complex must then perform the isomerization without the intervention of any external reagent. The exact mechanism or mechanisms whereby the isomerization occurs is uncertain. One possibility is that chloropalladation can have rate expressions corresponding to k_1 and k_3 terms as well as the k_2 term. This seems very unlikely, since the earlier study of chloride exchange *via* chloropalladation no k_1 or k_3 terms were detected.[4]

As mentioned in the introduction, π-allylic or Pd(II) hydride mechanisms were eliminated by nonkinetic experiments.[1,2] Thus, a new mechanism must be operative. As discussed in a previous paper,[1] one possibility is rearrangement of the π complex to a σ-bonded diradical type intermediate analogous to those postulated for metal carbonyl catalyzed photoisomerization of olefins.[8]

(7) P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 7311 (1972).
(8) M. Wrighton, G. S. Hammond, and H. B. Grey, *ibid.*, **93**, 3285 (1971).

Another possibility is rearrangement of the π complex to a Pd(II) σ-bonded carbonium type intermediate which can reverse either to the cis or trans isomer (X = Cl or Br).



(13)

One prediction of the last mechanism is that it should display a large negative Hammet ρ. This prediction is being checked using systems in which steric factors can be separated from electronic factors. In any case more mechanistic work is required before a definite mechanism can be proposed.

Two points deserve comment. First, the isomerization of enol propionates displayed only the k_1 term while 1-chloropropene gave all three terms and 1-bromopropene gave mainly the k_2 term. Such wide differences in structure can cause considerable differences in reactivity.

Second, this is the first time the monomeric π complex (the k_3 term) has been found to be reactive, although the π complex was detected in previous exchange studies (papers III[9] and V[10]). The reason given for its lack of reactivity previously was the larger concentration of negative charge on the Pd(II) containing the olefin in this complex as compared with the dimeric π complex. This negative charge discouraged the approach of the nucleophiles necessary for exchange. In the present case no nucleophile is required for isomerization; so it is reasonable that the monomeric π complex is reactive.

Finally, the effect of acetate and H_2O on the isomerization rate shown in Table III is explicable on the basis of other studies. Thus, at the lower chloride, the replacement of chloride by acetate to give vinylic acetate occurs at a rate comparable to isomerization and the cis isomer reacts several times faster than the trans isomer.[7] Thus, the preferential reaction of the *cis*-1-chloropropene gives an apparent slower rate of isomerization of the trans isomer. At the higher chloride the effect of added acetate is much less, since the exchange reaction is strongly retarded by increasing chloride concentration.

In other studies[11] it was found that the addition of water shifts the equilibrium shown in eq 5 to the left; so for a given chloride concentration, addition of water will decrease the dimer concentration and thus decrease the rate of exchange. As expected, the retardation is important at both high and low chlorides.

(9) P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 5200 (1972).
(10) P. M. Henry, *Inorg. Chem.*, **11**, 1876 (1972).

Experimental Section

Materials.—The source of the *cis*- and *trans*-1-chloropropenes has been described previously,[4] as has the preparation and analysis of Pd(II) stock solutions.[5] The mixture of *cis*- and *trans*-1-bromopropenes was purchased from K & K Laboratories. Pure samples of the cis and trans isomers were obtained by preparative vpc using a 20 ft 20% Lac 446 on Chromosorb W (60–80 mesh). Temperature was 60° and helium flow rate was 100 ml/min.

Kinetic Runs.—The reaction mixtures were prepared by mixing known amounts of the Pd(II) and LiCl stock solutions and diluting to a known volume, usually 5 ml. The run was then started by adding the vinylic halide. The progress of the isomerization was followed by vpc analysis. For the 1-chloropropene run the Lac 446 column at 50° was used. For the 1-bromopropene runs the same column at 60° was used.

The data were treated in the usual fashion for runs approaching equilibrium.[12] The equilibrium mixture for 1-chloropropene contained 74% cis isomer while that for 1-bromopropene contained 74% cis isomer while that for 1-bromopropene contained 70% cis isomer.

Registry No.—Palladium, 7440-05-3; palladium(II) chloride, 7647-10-1; *cis*-1-chloropropene, 16136-84-8; *trans*-1-chloropropene, 16136-85-9; *cis*-1-bromopropene, 590-13-6; *trans*-1-bromopropene, 590-15-8; lithium acetate, 546-89-4; $Li_2Pd_2Cl_6$, 31183-05-8.

Acknowledgment.—The author gratefully acknowledges helpful discussions with Professor H. Taube and H. Goering. The author is also grateful to Mr. F. J. Kriss for his excellent technical assistance.

(11) P. M. Henry, submitted for publication.
(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," 2nd ed, Wiley, New York, N. Y., 1960, p 186.

Hydroperoxide Oxidations Catalyzed by Metals. IV. Molybdenum Hexacarbonyl Catalyzed Epoxidation of 1-Octene[1a]

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Additional kinetic data have been obtained on the epoxidation of 1-octene by cumene and *tert*-butyl hydroperoxide in the presence of molybdenum hexacarbonyl. In the temperature range 71–90°, the new data exhibit apparent first-order dependence on the hydroperoxide. The observed kinetic behavior is compatible with the previously proposed general mechanism for the epoxidation reaction. The kinetics for the molybdenum hexacarbonyl catalyzed epoxidation are consistent with a simple competitive inhibition step involving a coproduct alcohol–catalyst complex in which K_{eq}, the alcohol–catalyst complex equilibrium constant, approximately counterbalances K_p, the hydroperoxide–catalyst complex dissociation constant. In agreement with this interpretation, a plot of $1/k_{obsd}$ *vs.* the initial hydroperoxide concentration was linear. The slope and intercept of these plots were used to determine values of K_{eq} for cumenol of 3.1 and 6.5 M^{-1} at 84.6 and 72.6° and for *tert*-butyl alcohol 5.9 and 6.1 M^{-1} at 84.4 and 71.2°.

Initial kinetic data on the epoxidation of aliphatic olefins by *tert*-butyl hydroperoxide in the presence of molybdenum hexacarbonyl as catalyst indicated that the reaction was first order in olefin, hydroperoxide, and catalyst.[2] The kinetic and chemical data were satisfactorily explained by the mechanism proposed for this new method of epoxidizing olefins. The mechanism consisted of two steps. The initial step was a rapid equilibrium formation of a molybdenum carbonyl–hydroperoxide complex. The second step was the rate-determining reaction of the molybdenum carbonyl–hydroperoxide complex with the olefin to form the epoxide, coproduct alcohol, and the molybdenum catalyst. However, it was observed that the epoxidation reaction was retarded when alcohols were used as solvents. This observation might be expected from the proposed mechanism since an alcohol could compete with the hydroperoxide for the molybdenum catalyst and form a molybdenum–alcohol complex. If a molybdenum–alcohol complex did form, some retardation of the reaction rate and deviation from apparent first-order dependence on hydroperoxide would be expected as an epoxidation reaction proceeded and coproduct alcohol was produced. A kinetic study of the epoxidation of cyclohexene by *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate as catalyst showed that the coproduct *tert*-butyl alcohol very strongly inhibits the vanadium-catalyzed reaction and the rate dependence on hydroperoxide is analogous to the Michaelis–Menten equation for enzyme catalysis.[3] This paper suggested that the first-order dependence on hydroperoxide in the molybdenum-catalyzed reaction was a result of only partial activation of the molybdenum hexacarbonyl during the kinetic experiments.

Additional kinetic studies with 1-octene and molybdenum hexacarbonyl were made to determine the range of conditions for which the observation of first-order dependence on hydroperoxide was valid and to reconcile the experimental data with the proposed mechanism for the molybdenum-catalyzed epoxidation.

Results

Kinetic studies with molybdenum hexacarbonyl, as catalyst, were made over a temperature range of 71–91° using a large excess of 1-octene and both *tert*-butyl hydroperoxide and cumene hydroperoxide. The rate data were obtained by measurement of changes in hydroperoxide concentration. In addition, analysis of selected samples by gas chromatography demonstrated that the epoxidation proceeded in high yield. Hence, the 1:1 stoichiometry for epoxide formation was maintained while side reactions such as decomposition of the hydroperoxide were negligible. This has been demonstrated in previous reports on this reaction.[2-5]

In the kinetic experiments, the reaction flask was fitted with a continuously adjustable manostat attached to a vacuum pump which permitted the pressure and, because the solvent was under reflux, the temperature of the system to be controlled within narrow limits. Temperature variation was ±0.1°.

Since the reactions were carried out in a large excess of 1-octene, the data for the epoxidation reaction were plotted in the first-order form shown in Figures 1 and 2. For both *tert*-butyl hydroperoxide and cumene hydroperoxide, short induction periods were observed. These induction periods were related to the conversion of the molybdenum hexacarbonyl into the active catalyst.[2,5] Thus, the plots show a minor displacement of the straight line from the origin.

The kinetic data obtained for both *tert*-butyl and cumene hydroperoxide over the temperature range 71–91° at a high olefin concentration provided an excellent fit for pseudo-first-order dependence on the hydroperoxide. However, when the initial *tert*-butyl or cumene hydroperoxide concentration was varied at a specific temperature, the slopes of the psuedo-first-order plots, the observed pseudo-first-order rate constant (k_{obsd}), were found to be concentration dependent. This is shown in Figure 3 for cumene hydroperoxide. For both hydroperoxides, the observed pseudo-first-order rate constant (k_{obsd}) increased as the initial concentra-

(1) (a) Part of this paper was presented at the 159th National Meeting of the American Chemical Society, Division of Petroleum Chemistry, Symposium on New Olefin Chemistry, Houston, Texas, Feb 1970; (b) Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma.

(2) International Oxidation Symposium, San Francisco, Calif., Aug 1967; M. N. Sheng and J. G. Zajacek, *Advan. Chem. Ser.*, **76**, 418 (1968).

(3) E. S. Gould, R. R. Hiatt, and K. C. Irwin, *J. Amer. Chem. Soc.*, **90**, 4573 (1968).

(4) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970).

(5) G. R. Howe and R. R. Hiatt, *ibid.*, **36**, 2493 (1971).

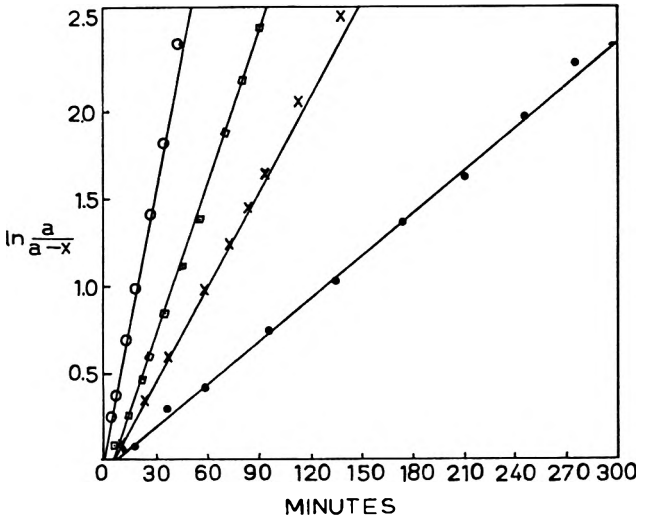

Figure 1.—First-order plot for the epoxidation of 1-octene by *tert*-butyl hydroperoxide with molybdenum hexacarbonyl catalyst. Molar concentration: 1-octene 6.27, *tert*-butyl hydroperoxide 0.212, molybdenum hexacarbonyl 4.48 × 10^{-4}. Reaction temperature (±0.1°): ⊙, 91.5°; ⊡, 84.3°; ×, 79.3°; ●, 71.2°.

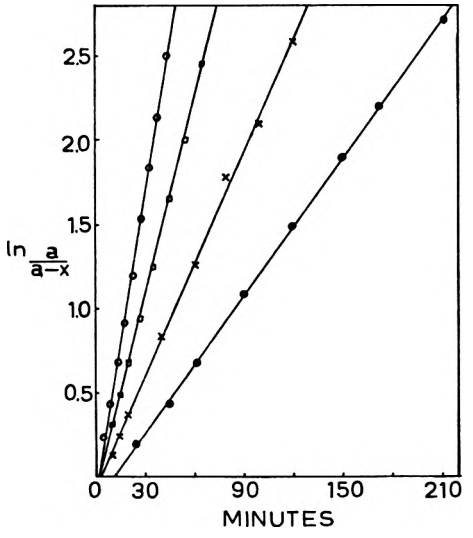

Figure 2.—First-order plot for the epoxidation of 1-octene by cumene hydroperoxide with molybdenum hexacarbonyl catalyst. Molar concentration: 1-octene 6.0, cumene hydroperoxide 0.18, molybdenum hexacarbonyl 4.4 × 10^{-4}. Reaction temperature (±0.1°): ⊙, 89.7°; ⊡, 84.6°; ×, 78.8°; ●, 72.6°.

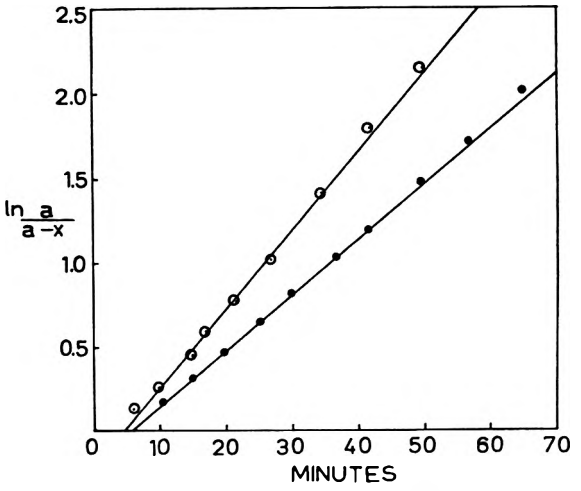

Figure 3.—First-order plot for the epoxidation of 1-octene by different concentrations of cumene hydroperoxide at 84.5°. Molar concentration: 1-octene 6.0, molybdenum hexacarbonyl 4.4 × 10^{-4}, cumene hydroperoxide 0.09 (⊙), 0.27 (●).

TABLE I
OBSERVED RATE CONSTANT FOR THE MOLYBDENUM HEXACARBONYL CATALYZED EPOXIDATION OF 1-OCTENE AT VARIOUS HYDROPEROXIDE CONCENTRATIONS

Hydroperoxide, *M*	k_{obsd} × 10^4, sec^{-1}	$1/k_{obsd}$ × 10^{-3}, sec
t-BuOOH[a] (71.2°)		
0.417	1.05 ± 0.03	9.52
0.208	1.49 ± 0.04	6.71
0.070	2.76 ± 0.15	3.62
t-BuOOH (84.4°)		
0.318	3.36 ± 0.16	2.98
0.212	4.84 ± 0.15	2.07
0.159	4.65 ± 0.15	2.15
0.106	5.80 ± 0.15	1.72
0.053	7.00 ± 0.30	1.27
CuOOH[b] (84.6°)		
0.270	5.69 ± 0.11	1.76
0.180	6.70 ± 0.25	1.49
0.135	7.30 ± 0.25	1.37
0.090	8.25 ± 0.20	1.21
CuOOH (72.6°)		
0.27	1.80 ± 0.09	5.56
0.18	2.32 ± 0.08	4.31
0.09	2.97 ± 0.12	3.37
0.045	4.04 ± 0.14	2.48

[a] 1-Octene, 6.27 *M*; $Mo(CO)_6$, 4.48 × 10^{-4} *M*. [b] 1-Octene, 6.0 *M*; $Mo(CO)_6$ 4.4 × 10^{-4} *M*.

tion of the hydroperoxide was decreased. These data are summarized in Table I. These experimental results confirm that the rate of epoxidation of 1-octene by either *tert*-butyl or cumene hydroperoxide in the presence of molybdenum hexacarbonyl is not *simple* first order in hydroperoxide as previously reported.[2]

Discussion

An understanding of the kinetic results was achieved by adding a third step to the proposed general mechanism for the epoxidation reaction catalyzed by molybdenum compounds. The additional step accounts for the observed retardation of the rate of the reaction by postulating the formation of a reversible complex between the catalyst and coproduct alcohol. There is ample evidence to support this postulate in prior studies.[2,3,5,6] The basic reaction mechanism then includes (1) a reversible complex formation between the active catalyst (Mo^{m+}) and the hydroperoxide, (2) a reversible inhibition by the coproduct alcohol, and (3) the reaction of the hydroperoxide–molybdenum complex with olefin to form the epoxide and by-product alcohol.

$$ROOH + Mo^{m+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ROOH\text{-}Mo^{m+} \quad (1)$$

$$ROH + Mo^{m+} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ROH\text{-}Mo^{m+} \quad (2)$$

$$C{=}C + ROOH\text{-}Mo^{m+} \xrightarrow{k_3} \underset{O}{C\text{—}C} + ROH + Mo^{m+} \quad (3)$$

(6) M. I. Farberov, G. A. Stozhkova, and A. V. Bondarenko, *Neftekhimiya*, **11**, 578 (1971).

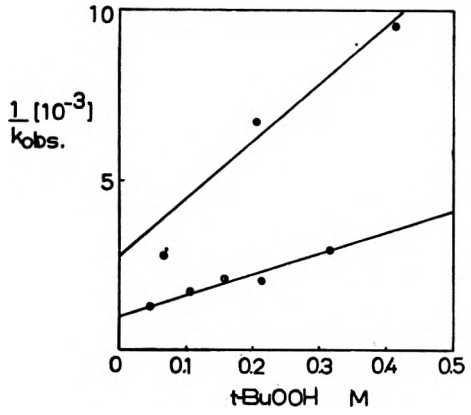

Figure 4.—Plot of the inverse of the observed rate constant for the epoxidation of 1-octene *vs.* the initial *tert*-butyl hydroperoxide concentration with molybdenum hexacarbonyl catalyst: ●, 71.2°, $K_{eq} = 6.1\ M^{-1}$; ⊙, 84.4°, $K_{eq} = 5.9\ M^{-1}$.

When the steady-state assumption is made for the active catalyst species Mo^{m+}, the general rate eq I is

$$\frac{-d(ROOH)}{dt} = \frac{d(\overset{O}{\diagup\diagdown}C\text{–}C)}{dt} = \frac{k_3(C{=}C)(ROOH)(Mo)_0}{K_p + K_pK_{eq}(ROH) + (ROOH)} \quad (I)$$

derivable, where K_p is the dissociation constant for the catalyst–hydroperoxide complex and K_{eq} is the equilibrium constant for the alcohol–catalyst complex. Since the concentration of alcohol is the difference between the initial and the unreacted hydroperoxide concentration, *i.e.*, $(ROH) = (ROOH)_0 - (ROOH)$, eq I can be rewritten as eq Ia

$$\frac{-d(ROOH)}{dt} = \frac{k_3(C{=}C)(Mo)_0}{[K_p/(ROOH)] + K_{eq}K_p[(ROOH)_0/(ROOH)] + (1 - K_pK_{eq})} \quad (Ia)$$

where

$$K_p = [k_{-1} + k_3(C{=}C)]/k_1$$

$$K_{eq} = (ROH\text{-}Mo^{m+})/(Mo^{m+})(ROH)$$

This equation is similar to the Michaelis–Menten equation for enzyme catalysis in the presence of a competitive inhibitor.[7] For the molybdenum-catalyzed epoxidation, the coproduct alcohol is the competitive inhibitor *via* a simple alcohol catalyst complex. The experimental observation of apparent first-order dependence of the rate on the hydroperoxide for the molybdenum carbonyl catalyzed epoxidation of 1-octene is shown in Figures 1 and 2. These experimental facts when applied to the rate eq Ia indicate that the term $(1 - K_pK_{eq})$ must be negligible relative to the remaining terms in the denominator. Elimination of this term from eq Ia transforms it into eq II. Equation II

$$\frac{-d(ROOH)}{dt} = \frac{k_3(C{=}C)(Mo)_0(ROOH)}{K_p + K_pK_{eq}(ROOH)_0} \quad (II)$$

explains the apparent first-order dependence on hydroperoxide. Also, eq II may be written in a form where either an observed rate constant (k_{obsd}) or the inverse

(7) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960.

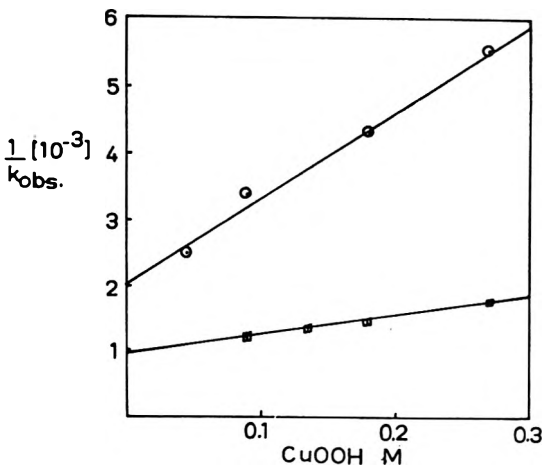

Figure 5.—Plot of the inverse of the observed rate constant for the epoxidation of 1-octene *vs.* the initial cumene hydroperoxide concentration with molybdenum hexacarbonyl catalyst: ⊙, 72.6°, $K_{eq} = 6.5\ M^{-1}$; ⊡, 84.6°, $K_{eq} = 3.1\ M^{-1}$.

of the observed rate constant ($1/k_{obsd}$) is obtained (eq III and IV).

$$k_{obsd} = \frac{-d(ROOH)/dt}{(ROOH)} = \frac{k_3(C{=}C)(Mo)_0}{K_p + K_pK_{eq}(ROOH)_0} \quad (III)$$

$$\frac{1}{k_{obsd}} = \frac{K_p}{k_3(C{=}C)(Mo)_0} + \frac{K_pK_{eq}(ROOH)_0}{k_3(C{=}C)(Mo)_0} \quad (IV)$$

Equation IV provides a way to test the validity of the assumption that term $(1 - K_pK_{eq})$ is small. According to this equation, a plot of the inverse of the observed rate constant *vs.* the initial hydroperoxide concentration must be linear. When the kinetic results listed in Table I for *tert*-butyl and cumene hydroperoxide are plotted in this manner, a good linear fit was obtained at both 71 and 84°. This is shown in Figures 4 and 5.

Equation IV also provides a way to calculate a value for K_{eq}, the equilibrium constant for the alcohol–catalyst complex. The slope of the lines in Figures 4 and 5 divided by the respective intercepts gives values for K_{eq}. The derived values are shown in Table II.

TABLE II
EQUILIBRIUM CONSTANT (K_{eq}) FOR THE MOLYBDENUM CARBONYL–ALCOHOL COMPLEX

	Temp, °C	Slope, sec M^{-1} × 10^{-3}	Intercept, sec × 10^{-3}	K_{eq}, M^{-1}
CuOOH	72.6	12.2 ± 1.0	2.00 ± 0.1	6.5 ± 0.5
	84.6	2.99 ± 0.1	0.95 ± 0.1	3.1 ± 0.3
t-BuOOH	71.2	16.7 ± 5.0	2.75 ± 1.0	6.1 ± 2.0
	84.4	6.01 ± 0.5	1.02 ± 0.1	5.9 ± 0.6

The low values for the equilibrium constant, K_{eq}, and the good fit of the plots support the view that with the molybdenum hexacarbonyl catalyst higher order alcohol–catalyst complexes are not important.

The kinetic data for the molybdenum hexacarbonyl catalyzed epoxidation of 1-octene are self-consistent with the assumption that the term $(1 - K_pK_{eq})$ is negligible compared to the other terms in the denominator of eq II. In terms of the proposed mechanism for the epoxidation reaction, this means the equilibrium constant (K_{eq}) for the formation of the alcohol–catalyst complex must be *approximately* the inverse of the dissociation constant (K_p) for the molybdenum–

hydroperoxide complex. Thus, the observed first-order dependence of the rate on the hydroperoxide requires during a reaction that the tendency to drift to a higher observed rate constant as a result of the hydroperoxide concentration term in the denominator is balanced by a shift toward a lower observed rate constant as a result of the coproduct alcohol produced.

It is also possible to make the further simplifying assumption that the term $(1 - K_pK_{eq})$ is equal to zero. If this is done, values for k_3 the rate of reaction between the olefin and the hydroperoxide–molybdenum carbonyl complex, and K_p, the dissociation constant for the molybdenum–hydroperoxide complex can be determined. Also, since data are available at two different temperatures, $\Delta H^{\circ\ddagger}$ and $\Delta S^{\circ\ddagger}$ for the k_3 reaction can be estimated. When this assumption is made for *tert*-butyl hydroperoxide, reasonable values are obtained for these parameters. The numbers are given in Table III. For cumene hydroperoxide, the

TABLE III
CALCULATED VALUES BASED ON THE ASSUMPTION $K_p = 1/K_{eq}$

Hydroperoxide	$\Delta H^{\circ\ddagger}$, kcal	$\Delta S^{\circ\ddagger}$, eu	Temp, °C	k_3, l. mol^{-1} sec^{-1}
tert-Butyl	19 ± 1.0	−14 ± 2.0	84.2	0.059 ± 0.002
			71.2	0.021 ± 0.002

values calculated for these parameters are unreasonable. This suggests the reaction with cumene hydroperoxide is more complicated then with *tert*-butyl hydroperoxide. The cumene hydroperoxide results are not understood, and calculations of this type are not emphasized because the errors involved in making the underlying assumptions are potentially very large.

Experimental Section

Materials.—The 1-octene (99 mol % purity) and *n*-octane (99 mol % purity) were obtained from Phillips Petroleum Co. Both were percolated through silica gel and distilled in a spinning band column. The olefin, bp 120–121°, was used without further treatment. *tert*-Butyl hydroperoxide (90% purity) was obtained from the Lucidol Division of Pennwalt Co., and cumene hydroperoxide (65% purity) was obtained from Matheson Chemical Co. The hydroperoxides were purified according to Davies[8] and distilled at reduced pressure in all-glass apparatus using a magnetically stirred oil bath and a magnetically stirred distilling flask. The colorless middle fraction, analyzing 100 ± 0.4% purity by iodometric titration,[9] were employed in the kinetic runs. Typical samples of *tert*-butyl hydroperoxide had bp 52° (39 mm); cumene hydroperoxide, bp 53° (0.23 mm). Molybdenum hexacarbonyl was obtained from Matheson Chemical Co.; it was purified by sublimation at reduced pressure and stored in the dark.

Kinetic Procedure.—Kinetic runs were made in a magnetically stirred glass flask fitted with a septum, reflux condenser, catalyst spoon, and calibrated thermometer. A vacuum system with an adjustable manostat controlled the temperature. The reaction was initiated by introduction of the molybdenum hexacarbonyl from the catalyst spoon. When molybdenyl acetylacetonate was the catalyst, a freshly prepared solution of the catalyst in dry benzene was introduced into the mixture with a syringe and needle through the septum. As the reaction proceeded, the temperature was controlled to ±0.1° by adjustment of the manostat. Samples were withdrawn from the system using a syringe. These aliquots were transferred to vials, cooled rapidly in ice, and analyzed for hydroperoxide using an iodometric method. Repeat analyses revealed a reproducibility better than 0.75%. A few samples from kinetic runs at low and high conversion of hydroperoxide were analyzed for epoxide using a Perkin-Elmer Model 226 gas chromatograph equipped with a 150 ft × 0.01 in. Carbowax 1540 capillary column. Sublimed triphenylphosphine was used to remove unreacted hydroperoxide before introducing the sample into the chromatograph. At the high olefin to hydroperoxide ratio used in these runs, the yield of epoxide based on the hydroperoxide converted was nearly quantitative (100 ± 5%) for both cumene and *tert*-butyl hydroperoxide.

In a typical experiment, a mixture of cumene hydroperoxide (0.27 *M*), molybdenum hexacarbonyl (4.4×10^{-4} *M*), 1-octene (6.0 *M*), and *n*-octane, sufficient to make the mixture to the standard volume, was allowed to react at 84.6° through greater than 90% conversion to give samples for which hydroperoxide *vs.* time data were generated. The amount of *n*-octane was varied from run to run to compensate for changes in hydroperoxide concentration. Typical data for this cumene hydroperoxide experiment are given below, where $k_{obsd} = 5.58 \pm 0.12 \times 10^{-4}$ sec^{-1}.

Wt % hydroperoxide	Time, sec
5.712	0
5.479	180
5.156	360
4.531	600
3.923	900
3.179	1260
2.636	1680
1.998	2160
1.414	2700
1.005	3300
0.743	3900
0.512	4500

Registry No.—Molybdenum hexacarbonyl, 13939-06-5; 1-octene, 111-66-0.

Acknowledgment.—The authors wish to thank George Kern for his valuable laboratory assistance.

(8) A. G. Davies, "Organic Peroxide," Butterworths, London, 1961, p 114.
(9) D. H. Weeler, *Oil Soap (Chicago)*, **9**, 89 (1932).

Epoxidation of Simple Allenes. Role of Cyclopropanones as Reactive Intermediates[1a]

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The peracid oxidation of tetramethylallene, 1,1-dimethylallene, and 1,2-cyclononadiene has been studied. The products of these reactions are rationalized in terms of initial formation of an allene oxide followed by competitive partitioning of this reactive species between valence isomerism to the related cyclopropanone and further oxidation to a dioxaspiropentane derivative. In addition to combining with the carboxylic acid generated during the oxidation to produce α-acyloxy ketones the cyclopropanones suffer further reaction with peracid to yield β-lactones or undergo "oxidative decarbonylation" to the corresponding olefins which are usually transformed into their epoxides under the reaction conditions. The dioxaspiropentanes also add carboxylic acid yielding α-acyloxy α'-hydroxy ketones. Thus, an excess of peracetic acid in buffered methanol gives **1**, **8**, and **12** as important products from tetramethylallene. A similar reaction under acidic conditions yields only **9**. 1,2-Cyclononadiene is transformed to **20**, **22**, **23**, and cyclooctene by peracid in methylene chloride. 1,1-Dimethylallene gives **30**, **31**, **32**, and **33** under these conditions, but only acetone and methyl acetate in methanol solvent.

We have previously reported on the peracetic acid oxidation of tetramethylallene in methylene chloride solution.[2] The formation of products **1**–**4** in this reaction was rationalized in terms of reactive intermediates **5** and **6** which are derived by straightforward mono- and di-epoxidation of the starting allene. Reasonable transformations of allene oxide **5** and dioxide **6** were postulated to lead to the observed products. This early study provided no information concerning the interesting possibility of valence isomerism of allene oxide **5** to cyclopropanone **7**. Subsequent work has resulted in the isolation and characterization of authentic allene oxide derivatives[3-5] and an example of a spiro dioxide.[6] Furthermore, the type of valence isomerism illustrated by the transformation of **5** to **7** has received experimental confirmation.[3,7] The present paper is concerned with further studies on epoxidation of simple allenes.

Merely changing the solvent from methylene chloride to methanol results in a striking modification of the product mixture derived from tetramethylallene. Thus, when 3 equiv of peracetic acid in methylene chloride was added to a methanol solution of the allene containing sodium carbonate, a minimum of nine products could be isolated and identified unambiguously. As in the earlier study the major product was acetoxy ketone **1** (47%). However, an important amount of tetramethylethylene oxide (**8**) (37%) was found, as were isolable quantities of the following materials: acetone, pinacolone (7%), methoxy ketone **9** (2%), methyl 2,2,3-trimethylbutanoate (**10**) (1%), methyl α-hydroxyisobutyrate (3%), hydroxy methoxy ketone **11** (2%), and 3-hydroxy-2,2,3-trimethylbutanoic acid β-lactone (**12**) (1%).

In methanol there is a sharp decrease in the products attributed to reactive intermediate **6**. For example, ketone **2** is not observed as a product in methanol, whereas it amounts to about 40% in a comparable methylene chloride experiment. Indeed, the only product directly attributable to **6** in the first reaction is ketone **11**. (The acetone and methyl α-hydroxyisobutyrate are probably secondary products of **11** derived by peracid oxidation and methanolysis of intermediate **13**.) The reaction is observably slower in methanol, probably a result of hydrogen-bonding interactions between the solvent and peracid.[8] Apparently, the intervention of competing processes prevent substantial conversion of **5** into **6** in methanol. In addition to retarding the epoxidation, the polar hydroxylic solvent may aid the competing reactions for the consumption of the allene oxide by the solvation of polar intermediates involved in these processes. Of course, methanol is also available as a nucleophile for reaction with reactive intermediates. Among the new epoxidation products are four which have suffered skeletal rearrangement, namely pinacolone, epoxide **8**, ester **10**, and lactone **12** (see Chart I). An attractive rationalization for these products invokes cyclopropanone **7** as an important intermediate.[9] In methanol **7** exists almost exclusively in the form of its hemiketal **14**, but reactions involving the small amount of the free ketone presumably present at equilibrium are known.[9] The base rearrangement of **7** to give ester **10** is amply documented.[9] Simple Baeyer–Villiger oxidation likewise presents a reasonable pathway to lactone **12**. This latter compound is, however, stable to the reaction conditions thereby ruling out a route to epoxide **8** by way of **12** (*e.g.*, decarboxylation[10] followed by epoxidation of the tetramethylethylene thus produced). Nonetheless when an authentic sample of **14** was subjected to the reaction conditions, a product mixture consisting of **8** (55%), methoxy ketone **9** (24%), acetoxy ketone **1** (11%), pinacolone (4%), and rearranged ester **10** (6%) was obtained. A trace of material with the appropriate glpc characteristics for tetramethylethylene was also detected, but this probably arises from decomposition of lactone **12**

(1) (a) Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. (b) Alfred P. Sloan Fellow 1968–1970; John Simon Guggenheim Fellow 1970–1971.

(2) J. K. Crandall and W. H. Machleder, *J. Amer. Chem. Soc.*, **90**, 7292 (1968).

(3) R. L. Camp and F. D. Greene, *ibid.*, **90**, 7349 (1968).

(4) J. K. Crandall and W. H. Machleder, *J. Heterocycl. Chem.*, **6**, 777 (1969).

(5) H. M. R. Hoffmann and R. H. Smithers, *Angew. Chem.*, **82**, 43 (1970).

(6) J. K. Crandall, W. H. Machleder, and M. J. Thomas, *J. Amer. Chem. Soc.*, **90**, 7346 (1968).

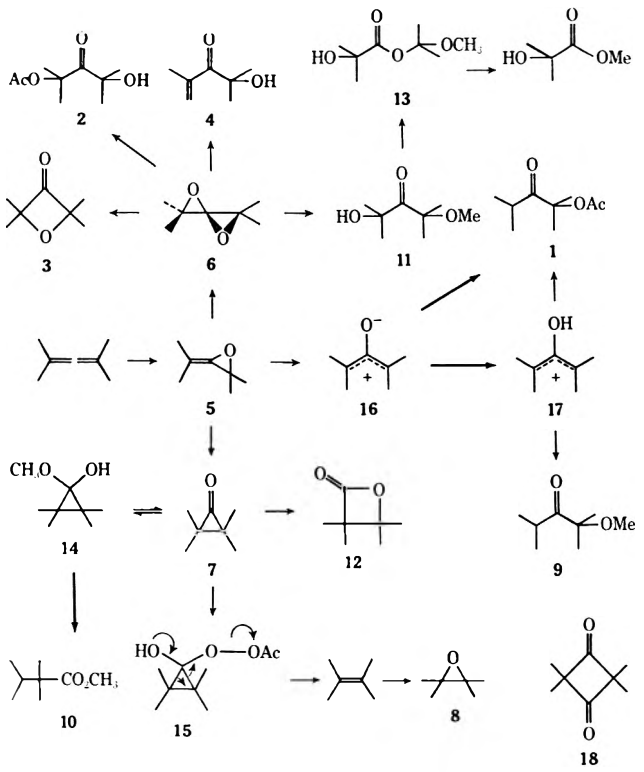
(7) J. K. Crandall and W. H. Machleder, *ibid.*, **90**, 7347 (1968).

(8) R. Curci, R. A. DiPrete, J. O. Edwards, and G. Modena, *J. Org. Chem.*, **35**, 740 (1970).

(9) For a review of cyclopropanone chemistry, see N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

(10) Y. Etienne and N. Fischer in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 2, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p 729.

CHART I



under the glpc conditions. A control experiment demonstrated that this olefin is rapidly transformed to epoxide **8** under the reaction conditions. These results suggest an "oxidative decarbonylation" pathway[11,12] for the conversion of **7** into the olefin precurser of epoxide **8**, most likely *via* fragmentation[13] of the intermediate peracid adduct **15**. It is noteworthy that this reaction does not go through the β-lactone **12**, a possibility that has not been excluded in other examples of "oxidative decarbonylation."

Accepting this evidence for the involvement of cyclopropanone **7** leads to the suggestion that **7** is formed by isomerization of the initially formed allene oxide. Subsequently performed studies have demonstrated clearly the operation of this type of transformation with other allenes,[3,7] thereby bolstering substantially this deduction. Evidently an important reaction of allene oxide **5** in methylene chloride is further epoxidation to dioxide **6**, whereas this process is not competitive with the isomerism of **5** to **7** in methanol. If this latter transformation involves the intermediacy of zwitterion **16** or some closely related species (*e.g.*, its protonated form **17**), the accelerating effect of a polar hydroxylic solvent can be readily appreciated.

An experiment performed by adding 1 equiv of peracid slowly to a methanol solution of the allene gave a product mixture containing **1** (72%), **9** (9%), **10** (9%), and **11** (9%), but no epoxide **8**. In the absence of excess oxidizing agent the cyclopropanone was evidently converted into alternate products in accord with expectations based on the mechanism elaborated above.

A dramatic variation in the reaction was again observed when the sodium carbonate buffer was omitted and a small amount of sulfuric acid was added to the reaction mixture. These conditions resulted in methoxy ketone **9** as the *only* oxidation product. Under acidic conditions methanol is the best available nucleophile and its addition occurs cleanly. This addition can conceivably operate on either allene oxide **5** or cyclopropanone **7**, although protonation and isomerization to stablized cation **17** probably precedes nucleophilic attack. Hemiketal **14** provides yet a third potential source of **17** in the presence of acid.

In order to better define the chemistry of **7**, this intermediate was generated under different conditions by the irradiation of **18**.[9] Production of the cyclopropanone in the presence of equivalent amounts of methanol and acetic acid in methylene chloride generated only acetoxy ketone **1**. A similar experiment to which a trace of strong acid had been added resulted in a 16:84 ratio of **1** to methoxy ketone **9**. Performing the photolysis in a methanol solution of sodium acetate yielded **1** (87%) in addition to small amounts of **9** and **10**. These results accord well with the proposed role of **7** as the product precursor in the peracid oxidations discussed above. However, the unavailability of allene oxide **5** for independent observation renders it difficult to explore the possibility that this species might be transformed to products without isomerization to **7**. Conversely, valence isomerization of **7** to **5** prior to product formation cannot be ruled out.[14]

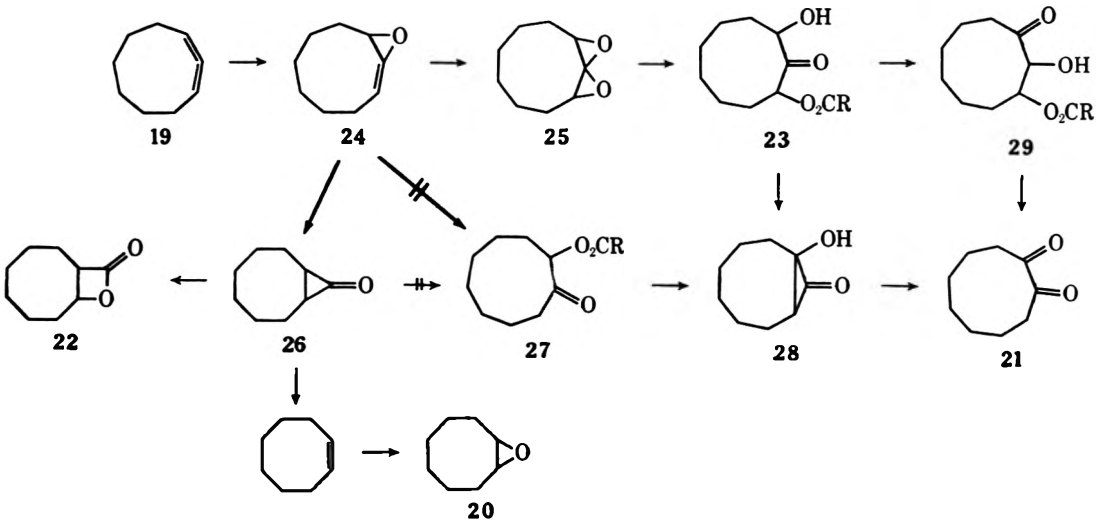
Rationalization of the variation in products in the photolysis experiments invokes the formation of an ion pair between **17** and acetate as the important step in the addition of acetic acid to **7** in the first experiment. Collapse to covalent product **1** follows logically. In the presence of strong acid, free **17** is generated and combines with the best available nucleophile, methanol. The preponderance of acetate product in methanolic sodium acetate solution is also explicable in terms of nucleophilic competition for the reactive electrophilic species which is probably zwitterion **16**.

The behavior of 1,2-cyclononadiene (**19**), a 1,3-disubstituted allene, towards peracid oxidation was also studied.[15] Reaction of **19** with 1 equiv of peracetic acid in methylene chloride solution, followed by glpc isolation yielded cyclooctene, unreacted **19**, cyclooctene oxide (**20**), and 1,2-cyclononadione (**21**) in an 11:16:29:44 ratio. Column chromatography of the crude product produced a small amount of an additional material which is tentatively identified as β-lactone **22** on the basis of its spectral characteristics, most notably a carbonyl band at 5.47 μ in the ir and loss of CO_2 as an important mass spectral fragmentation. Utilizing 3 equiv of peracid resulted in a 31:69 mixture of **20**/**21** as the only important products observed by glpc. However, examination of the crude reaction mixtures demonstrated that dione **21** was not present, but rather the data were consistent with the presence of an acetate ester, most probably **23a** (*vide infra*).

One equivalent of *m*-chloroperbenzoic acid (MCPBA) transformed **19** into a 12:4:84 mixture of **19**/**20**/**21** as viewed by glpc analysis. In this instance crystalline **23b** was isolated from the reaction mixture and

(11) J. E. Baldwin and J. H. I. Cardellia, *Chem. Commun.*, 558 (1968).
(12) J. K. Crandall and W. W. Conover, *Tetrahedron Lett.*, 583 (1971).
(13) A free-radical mechanism related to that found for cyclopropyl nitrites may operate here; see C. H. Depuy, H. L. Jones, and D. H. Gibson, *J. Amer. Chem. Soc.*, **94**, 3924 (1972).
(14) There is no concrete evidence for the presence of detectable amounts of the allene oxide isomer in equilibrium with **7**.[9]
(15) Subsequent to initiation of this work, a publication on the same subject appeared: W. P. Reeves and G. G. Stroebel, *Tetrahedron Lett.*, 2945 (1971).

CHART II



a, R = CH_3; b, R = *m*-ClC_6H_4; c, R = *p*-$NO_2C_6H_4$

shown to decompose cleanly to dione **21** upon injection onto the glpc column. An experiment performed with 3 equiv of *p*-nitroperbenzoic acid (PNPBA) gave a product mixture indicating an 18:72 ratio of **20**/**21** by glpc, but from which crystalline **23c** was isolated. This ester also yielded **21** cleanly by glpc decomposition.

These results can be accommodated within the general framework of allene epoxidation mechanisms as depicted in Chart II. Epoxidation of **19** leads to the reactive allene oxide intermediate **24**, which serves as a branching point for further reaction. On one hand, **24** is further epoxidized to a second reactive species, spiro dioxide **25**, which is the precursor of the major product **23** by addition of the appropriate acid. This pathway to **23** is supported by the isolation and characterization of an analogous compound in a different allene epoxidation.[6] Of course, dione **21** is a secondary decomposition product of **23** formed only upon injection into the gas chromatograph. It is noteworthy that **23** (analyzed as **21** by glpc) increases in relative quantity as the amount of peracid increases. The other mode of reaction for **24** involves valence isomerization to cyclopropanone **26**. This hypothesis is supported most strongly by the presence of lactone **22**, its further peracid oxidation product, in the crude product mixture. However, the major pathway for utilization of this reactive species is "oxidative decarbonylation" yielding cyclooctene and its epoxide **20** by yet another peracid oxidation. The isolation of cyclooctene itself in the reaction utilizing 1 equiv of peracetic acid is particularly significant since, in the reactions of tetramethylallene, the corresponding olefin was only postulated as an intermediate on the way to epoxide **8**. The relative efficiencies of the two product-forming routes from **24** as a function of available peracid is consistent with a balanced competition between valence isomerization and further epoxidation of **24**.

It was somewhat surprising to note that **24** does not give appreciable quantities of the simple carboxylic acid adduct **27**, normally the major product from allene epoxidations. An understanding of this observation is complicated by the ambiguity of the mechanistic pathway leading to this type product, which can conceivably be generated by addition of acid to either an allene oxide or cyclopropanone intermediate. The methylene chain of **24** is situated such as to retard SN2-type attack at the saturated epoxide center, a feature which could account for the predominance of other processes. Alternatively, reaction of cyclopropanone **26** with acid *via* a cationic intermediate analogous to **17** may be impeded by the paucity of stabilizing alkyl groups. It is not presently known what role is played by the strain inherent in these medium-ring derivatives.

Finally, it is now clear that dione **21** is not a primary product of the peracid oxidation as had been suggested earlier by Reeves and Stroebel.[15] The nature of this unanticipated transformation of **23** merits brief consideration. A most intriguing possibility involves pyrolytic 1,3 elimination of carboxylic acid to give hydroxycyclopropanone **28**, the anticipated tautomerism of which produces the dione. A related 1,3 elimination has been suggested to account for the pyrolytic conversion of 2-acetoxycycloalkanones into ring-contracted olefins, carbon monoxide, and acetic acid.[16] An alternate mechanism calls for tautomerization of **23** to isomeric ketol **29** prior to 1,2 elimination of acid and subsequent tautomerization to **21**. Experimental differentiation between these possibilities is not obvious.

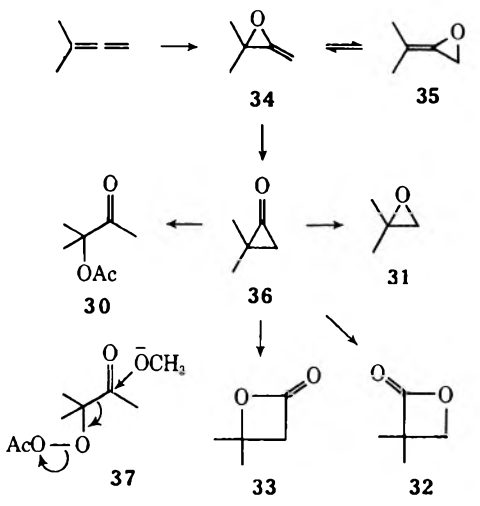
The geminally disubstituted compound, 1,1-dimethylallene, was also briefly examined. The addition of this allene to 3 equiv of peracetic acid in methylene chloride solution proceeded with the evolution of CO_2 and the formation of 3-acetoxy-3-methyl-2-butanone[17] (**30**) and isobutylene oxide (**31**) as major products. Appreciable quantities of acetone and 3-hydroxy-2,2-dimethylpropanoic acid β-lactone (**32**) were also isolated. The relative proportions of the latter four products were 50:25:17:8. In addition the presence of the isomeric β-lactone **33** was indicated by nmr examination of the crude product which displayed signals at the same chemical shifts as an authentic sample. Furthermore, **33** was shown to lose CO_2 under

(16) R. G. Carlson and J. H. Bateman, *J. Org. Chem.*, **32**, 1608 (1967).
(17) J. Boeseken, *Rec. Trav. Chim. Pays-Bas*, **54**, 657 (1935).

the reaction conditions. Lactone **32** was stable to similar treatment. Interestingly the use of methanol as solvent with an excess of peracetic acid gave only acetone and methyl acetate as products.

Chart III provides the familiar rationale for the observed results. As usual, epoxidation of the allene

CHART III



is the presumed initial step. In the case of this unsymmetrical allene, it is assumed that the normal accelerating effect of alkyl substituents will direct peracid attack to the more substituted double bond yielding **34**. It is possible that valence isomerism interconverts **34** and its isomer **35**, but transformation to cyclopropanone **36** is probably the prevailing process. Acetoxy ketone **30** arises by addition of acetic acid to the cyclopropanone and/or the allene oxide as discussed above. The lactones are Baeyer–Villiger products of the former and epoxide **31** is presumably derived from isobutylene also formed by peracid oxidation of **36**. The availability of a sample of **36** allowed confirmation of the **36** → **30** reaction with acetic acid.[18] Reaction of **36** with 40% peracetic acid in acetic acid at −78° resulted in rapid gas evolution (presumably CO_2) and the production of **30**.

The oxidation in methanol is puzzling. A conceivable route to the observed products involves nucleophilic addition of peracid to one of the intermediates leading to **37**, which could serve as a source of acetone and methyl acetate by the indicated fragmentation. The role of the solvent in directing reaction along this new pathway is not altogether clear, although several reasonable hypotheses can be put forth.

In conclusion, strong circumstantial evidence has been accrued for the involvement of cyclopropanones in the epoxidation reactions of representative allenes.

Experimental Section

General.—All nmr spectra were recorded on a Varian A-60 spectrometer using CCl_4 as solvent. Infrared spectra were obtained as liquid films with a Perkin-Elmer Infracord Model 137 spectrophotometer. Gas chromatography (glpc) was performed on Aerograph A600 (flame ionization detector) and A700 (preparative) instruments. The analytical columns were 5 ft × $^1/_8$ in. 15% Carbowax 20M on 60/80 Chromosorb W and 5 ft × $^1/_8$ in. 10% SE-30 on 80/100 Chromosorb W; preparative columns were 10 or 20 ft × $^3/_8$ in. 15% Carbowax on 60/80 Chromosorb W. Percentage composition data on product mixtures were estimated by peak areas and are uncorrected for compound response except where noted. Anhydrous magnesium sulfate was used as a drying agent.

Peracetic Acid Solutions.—Acetic acid was removed from commercially available 40% peracetic acid by adding the peracid dropwise to a cold mixture of excess anhydrous sodium carbonate suspended in methylene chloride. After the mixture was stirred for 45 min, the inorganic salts were removed by suction filtration through a layer of glass wool and anhydrous magnesium sulfate. The peracid solution was used immediately in the oxidation reaction. Nmr analysis indicated a 95:5 mixture of peracetic and acetic acids. When peracid is mentioned below, this implies that the given amount of 40% peracetic acid was treated according to the above procedure and used as the resulting acetic acid-free methylene chloride solution. Titration indicated that the total oxidizing activity of the peracid was undiminished.[19]

Epoxidation of Tetramethylallene with 3 Equiv of Peracetic Acid in Methanol.—To an ice-cold mixture of tetramethylallene (2.0 g) and sodium carbonate (20 g) in 80 ml of methanol was added 12 g of peracetic acid. After stirring for 3 hr, the excess peracetic acid was destroyed by the addition of 2-methyl-2-butene. The reaction mixture was then filtered and the solvent removed on the flash evaporator to give 2.4 g of crude material. Glpc analysis indicated nine reaction products in addition to a small amount of unreacted allene. All the components were isolated by preparative glpc. These were acetone, tetramethylethylene oxide, pinacolone, methyl 2,2,3-trimethylbutanoate, methoxy ketone **9**, methyl α-hydroxyisobutyrate, methoxy hydroxy ketone **11**, acetoxy ketone **1**, and 3-hydroxy-2,2,3-trimethylbutanoic acid β-lactone (**12**).

In one experiment the relative product percentages (excluding acetone) were determined by calibrated glpc analysis: **8** (37%), pinacolone (7%), **10** (1%), **9** (2%), methyl α-hydroxyisobutyrate (3%), **11** (2%), **1** (47%), and **12** (1%).

Epoxidation of Tetramethylallene with 1 Equiv of Peracetic Acid in Methanol.—Peracetic acid (2.0 g) was added very slowly to an ice-cold solution of allene (1.0 g) in 30 ml of methanol. After 4 hr a negative peracid test was obtained, and the reaction solution was poured into saturated sodium bicarbonate. The aqueous layer was extracted with methylene chloride and dried. A crude product of 1.4 g was obtained after solvent removal on the flash evaporator. Four products were isolated by preparative glpc and identified as acetone, **1**, **11**, and **10**. A fifth component was identified as **9** by glpc retention time. The ratio of **1**/**11**/**10**/**9** was 72:9:9:9.

3-Hydroxy-2,2,3-trimethylbutanoic Acid β-Lactone (12).—Tetramethylcyclobutane-1,3-dione (10 g) was pyrolyzed by passing through a vacuum flow system at 700° and 0.2 mm. The dimethyl ketene was trapped in a solution of 150 ml of acetone and 1.3 g of freshly distilled boron trifluoride etherate maintained at −75°. After 1 hr the reaction mixture was allowed to come to room temperature, and 2 g of dicyclohexylamine was added to destroy the boron trifluoride etherate. The solvent was removed on the flash evaporator to give crystalline material. Washing with cold hexane gave 4.3 g of a white crystalline material which was recrystallized from carbon tetrachloride to give pure **12**:[20] mp 127–128°; ir 5.49 μ; nmr δ 1.50 (s, 6) and 1.29 (s, 6).

Reaction of 12 with Peracetic Acid.—To an ice-cold mixture of 0.5 g of **12**, 2 g of sodium carbonate, and 0.1 g of benzene (internal standard) in 10 ml of methanol was added 0.8 g of peracetic acid. After 2.5 hr the reaction mixture was washed with saturated sodium bicarbonate and dried. The solvent was removed by distillation. Nmr and glpc analysis indicated that **12** had not been destroyed.

Epoxidation of Tetramethylallene in the Presence of Sulfuric Acid and Methanol.—A solution of 2.0 g of peracetic acid containing 10 drops of concentrated sulfuric acid was added at a moderate rate to an ice-cold solution of 1.0 g of allene in 30 ml of methanol. After 2.5 hr the reaction solution gave a negative peracid test. The solution was poured into saturated sodium carbonate, the aqueous layer was extracted with methylene chloride, and the extract was dried. A crude yield of 0.7 g was

(18) We thank Professor Turro for kindly providing us with this sample.

(19) F. P. Greenspan and D. G. Mackellar, *Anal. Chem.*, **20**, 1061 (1948).

(20) G. Natta, G. Mazzanti, G. Pregaglia, and M. Binaghi, *J. Amer. Chem. Soc.*, **82**, 5511 (1960).

obtained upon removal of the solvent. Glpc analysis indicated the presence of two components which were identified as **9** (43%) and 4-methoxy-2,4-dimethyl-2-pentene (57%). There was less than 1% of **1**.

Photolysis of 18 in the Presence of Acetic Acid and Methanol.—A methylene chloride solution (400 ml) containing 10.0 g of **18**, 4.3 g of acetic acid, and 2.3 g of methanol was irradiated for 1.25 hr using a 450-W Hanovia Type L medium-pressure quartz mercury vapor lamp fitted with a Pyrex filter. The resulting clear solution contained a single product identified as **1**. There was less than 1% of **9**.

Photolysis of 18 in the Presence of Methanol, Acetic Acid, and Sulfuric Acid.—A methylene chloride solution (400 ml) containing 10.0 g of **18**, 4.3 g of acetic acid, 2.3 g of methanol, and 12 drops of concentrated sulfuric acid was irradiated as described above for 1.25 hr at which point the reaction solution darkened. The solvent volume was reduced by flash evaporation, and the solution was washed with saturated sodium bicarbonate and dried. Glpc analysis indicated two reaction products which were identified as **1** and **9** in the ratio of 16:84.

Photolysis of 18 in the Presence of Sodium Acetate.—A solution of **18** (2 g) and sodium acetate (13 g) in 26 ml of methanol was photolyzed with 3000-Å light in a Rayonet photochemical reactor for 24 hr. The reaction solution was then poured into water, extracted with methylene chloride, and dried. After removing the solvent by flash evaporation, 2 g of crude product was obtained which glpc analysis indicated to be 87% of **1**. There was less than 5% of **9** or **10**.

1-Methoxy-1-hydroxy-2,2,3,3-tetramethylcyclopropane (14).[21]—A solution of 10 g of **18** in 400 ml of dry methanol was irradiated at 0° for 3.5 hr as described above. After the disappearance of starting material was indicated by glpc, the solvent was removed cautiously on the flash evaporator to give a clear, colorless liquid which was shown by nmr to contain 85% of **14**: ir 5.79, 8.21, 8.80, 9.03, and 9.11 μ; nmr δ 3.34 (s) and 1.05 (s). (Contaminants were **10** and methyl isobutyrate.) This material was stored at −20° and subsequent reactions were performed without further purification.

Reaction of 14 with Sodium Carbonate.—Approximately 1 g of **14** was added to a slurry of 4 g of sodium carbonate in 25 ml of methanol and 25 ml of methylene chloride at 0°. After stirring for 5 hr, the reaction mixture was filtered and washed with saturated sodium bicarbonate solution; the organic layer was dried. The solvent was removed cautiously to give unchanged starting material.

Reaction of 14 with Peracetic Acid.—To approximately 1 g of **14** and 4 g of sodium carbonate in 25 ml of methanol at 0° was added approximately 1.4 g of peracetic acid in 25 ml of methylene chloride. After 4 hr at 0° the reaction mixture was diluted with methylene chloride and filtered. The organic layer was washed with saturated sodium bicarbonate and dried. Analysis indicated 55% of **8**, 24% of **9**, 11% of **1**, 4% of pinacolone, and 6% of **10**.

Reaction of 14 with Peracetic Acid in the Presence of Tetramethylethylene.—To approximately 1 g of **14** and 5 g of sodium carbonate at 0° was added 1.4 g of peracetic acid in 25 ml of methylene chloride. Immediately after the peracetic acid solution was added, 60 mg of tetramethylethylene was introduced into the reaction flask. After stirring at 0° for 4 hr, the reaction mixture was processed as in the preceding experiment. Glpc analysis indicated that 60% of the product was **8** and no tetramethylethylene remained.

Reaction of 19 with Peracetic Acid.—To a slurry of 1 g of anhydrous Na_2CO_3 and 500 mg of **19** in 5 ml of CH_2Cl_2 at 0° was added 1 equiv of peracetic acid in 20 ml of cold CH_2Cl_2. The mixture was allowed to warm to room temperature and stirred for 8 hr at which time a negative starch–iodide test was obtained. The mixture was filtered and the solvent was removed from the filtrate to give 543 mg of a colorless oil: ir 2.8, 5.47, 5.60, 5.73, 5.80, and 8.0 μ; nmr δ 2.04 (s) and 3.6 (m). Analytical glpc showed four major peaks in a ratio of 11:16:29:44. The first two materials were identified as cyclooctene and unreacted starting material by glpc and mass spectral comparisons with authentic samples. The remaining peaks were isolated and identified as **20** and **21**: ir 5.87 μ; nmr δ 2.64 (t, 4, J = 6 Hz), 1.83 (m, 4), and 1.47 (m, 6).[22]

Column chromatography of the crude reaction mixture on silica gel gave a small quantity of a further product tentatively identified as **22**: ir (CCl_4) 5.47 μ; nmr δ 4.42 (m, 1), 3.36 (m, 1), and 2.2 (m, 12); mass spectrum m/e (rel intensity) 154 (6), 110 (15), 96 (121), 80 (18), 63 (42), 50 (64), and 46 (100).

A similar reaction using 3 equiv of peracid for 2 days gave a **20/21** ratio of 31:69.

Reaction of 19 with MCPBA.—To 1.8 g of **19** in 10 ml of CH_2Cl_2 at 0° was added 2.4 g (1 equiv) of MCPBA in 30 ml of CH_2Cl_2. After stirring for 40 min a copious white precipitate had formed and a negative starch–iodide test was obtained. The reaction mixture was filtered and the filtrate washed with $NaHCO_3$ solution after diluting with ether. The solution was dried and the solvent was removed to give 2.4 g of a light yellow oil which showed three peaks corresponding to **19**, **20**, and **21** in a 12:4:84 ratio by glpc. The addition of a small amount of ether resulted in the formation of crystalline **23b**: mp 96–97.5° (dec); ir (CCl_4) 2.85, 5.82, and 8.0 μ; nmr (220 MHz) δ 7.96 (s, 1), 7.89 (d, 1, J = 6 Hz), 7.52 (d, 1, J = 8 Hz), 7.36 (t, 1, J = 10 Hz), 5.22 (d of d, 1, J = 10, 3 Hz), 4.65 (d of d, 1, J = 6, 3 Hz), 3.34 (s, 1), and 2.4–1.8 (m, 12); mass spectrum m/e (rel intensity) 310 (11), 154 (54), 139 (57), 126 (64), and 98 (100).

Anal. Calcd for $C_{16}H_{19}O_4Cl$: C, 61.84; H, 6.16; Cl, 20.59. Found: C, 61.8; H, 6.4; Cl, 20.7.

Injection of pure **23b** unto a glpc column gave only **21**.

Reaction of 19 with PNPBA.—To 111 mg of **19** in 10 ml of CH_2Cl_2 at 0° was added 594 mg (3.5 equiv) of PNPBA in 5 ml of CH_2Cl_2. After stirring for 24 hr, ir indicated the absence of **19**. Excess peracid was destroyed by the addition of trimethylethylene, the mixture was filtered, and the filtrate was washed with $NaHCO_3$ solution and dried. Removal of the solvent gave 207 mg of a yellow oil. Glpc showed a **20/21** ratio of 18:72. The addition of CCl_4 resulted in the formation of a yellow solid which was recrystallized from ether–pentane to give light yellow **23c**: mp 92.5–93°; ir (CCl_4) 2.83, 5.79, and 7.85 μ; nmr δ 8.20 (s, 4), 5.38 (d of d, 1, J = 10, 4 Hz), 4.69 (d of d, 1, J = 7, 2 Hz), 4.6 (s, 1), and 2.6–1.1 (m, 12).

Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.81; H, 5.96. Found: C, 59.8; H, 5.8.

Injection of **23c** onto the glpc column gave a single peak with the retention time of **21**.

Epoxidation of 1,1-Dimethylallene.—To an ice-cold slurry of 16.7 g of acetic acid-free peracetic acid and 27 g of sodium carbonate was added slowly a methylene chloride solution of 2.0 g of the allene. After several hr the reaction mixture warmed to room temperature and stirring was continued for a total of 70 hr. The crude product was filtered, most of the solvent was removed by spinning band distillation, and the products were isolated by preparative glpc. The first component was **31**; the second, acetone. The third component was **30** [ir 5.75, 5.80, and 8.0 μ; nmr δ 2.03 (s, 6) and 1.41 (s, 6) (the 2.03 absorption split into two equivalent singlets upon the addition of benzene to the nmr sample)] and the fourth was 3-hydroxy-2,2-dimethylpropanoic acid β-lactone (**32**). In one experiment the ratio of acetone/**30**/**31**/**32** of 17:25:50:8 was determined by nmr. The appearance of absorption at δ 3.18 and 1.53 in a 1:3 ratio in the nmr of the crude product indicates the presence of **33**.

In a similar epoxidation the allene was treated with 40% peracetic acid, and the evolving gases were passed through a solution of barium chloride. Rapid evolution of carbon dioxide was noted.

Epoxidation of 1,1-Dimethylallene in Methanol.—To an ice-cold slurry of 1.0 g of allene and 15 g of sodium carbonate in 25 ml of methanol was added 3 equiv of acetic acid-free peracetic acid. After 3 hr the reaction mixture was filtered and washed with saturated sodium bicarbonate solution. The aqueous phase was extracted with methylene chloride, and the combined organic layers were dried. Nmr and glpc analysis indicated that the only significant products were acetone and methyl acetate in 1:1 ratio. These compounds were identified by isolation.

3-Hydroxy-2,2-dimethylpropanoic Acid β-Lactone.[23]—Dimethylketene was generated by the 700° pyrolysis of 10 g of **18** in a flow system and collected in a Dry Ice trap containing 50 mg of zinc chloride. Gaseous formaldehyde generated by heating 3.0 g of paraformaldehyde with a microburner was bubbled into the ketene–zinc chloride solution. The crude product was diluted with 20 ml of methylene chloride, stirred

(21) P. A. Leermakers, G. F. Vesley, N. J. Turro, and D. C. Neckers, *J. Amer. Chem. Soc.*, **86**, 4213 (1964).

(22) A. J. Blomquist, L. H. Liu, and J. C. Bohrer, *ibid.*, **74**, 3643 (1952).

(23) H. E. Zaugg, *Org. React.*, **7**, 305 (1954).

over sodium carbonate for 1 hr, and filtered. The filtrate was distilled to give 2 g of material, bp 56–61° (19 mm), containing starting dione. A pure sample of **32** was obtained by preparative glpc: ir 5.47, 9.1, and 10.9 μ; nmr δ 4.08 (s, 2) and 1.43 (s, 6).

Reaction of 32 with Acetic Acid.—To an nmr sample of **32** containing methylene chloride as an internal standard, was added 1 equiv of acetic acid. After 63 hr at room temperature, no reaction had occurred. In a similar experiment **32** was treated with excess 40% peracetic acid with the same result.

3-Hydroxy-3-Methylbutanoic Acid β-Lactone (33).—Lactone **33** was prepared as described:[24] ir 5.49, 9.3, and 12.6 μ (doublet); nmr δ 3.18 (s, 2) and 1.53 (s, 6).

Reaction of 33 with Peracetic Acid.—To an nmr sample of **33** in CH_2Cl_2 (containing benzene as an internal standard) was added 4 equiv of 40% peracetic acid. Gas evolution was immediate and in 45 min **33** was completely gone. No new peaks appeared in the spectrum.

Reaction of 36 with Acetic Acid.—A CH_2Cl_2 solution of **36** was treated with 1 equiv of glacial acetic acid at −70°. Glpc analysis showed a single component identified as **30**.

Reaction of 36 with Peracetic Acid.—A CH_2Cl_2 solution of **36** was treated with 2 equiv of 40% peracetic acid at −70°. As the reaction warmed to room temperature, vigorous CO_2 evolution was observed. Ir analysis of the crude product indicated that acetoxy ketone **30** was the predominant product.

Registry No.—**12**, 10008-69-2; **18**, 933-52-8; **19**, 1123-11-1; **23b**, 38202-51-6; **23c**, 38202-52-7; **32**, 1955-45-9; MCPBA, 937-14-4; PNPBA, 943-39-5; tetramethylallene, 1000-87-9; 1,2-dimethylallene, 598-25-4.

(24) T. L. Gresham, J. E. Jansen, F. W. Shaver, and W. L. Beears, *J. Amer. Chem. Soc.*, **76**, 486 (1954).

Photochemical Oxidations. VII. Photooxidation of Cyclohexylamine with Oxygen

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The presence of a charge-transfer ultraviolet absorption band for an oxygen-saturated cyclohexylamine solution has been reconfirmed. The absorption of light by this band causes cyclohexanone oxime and *N*-cyclohexylidinecyclohexylamine to be formed in the initial stages of the reaction, *i.e.*, to 0.6% conversion. The oxime is not the precursor of the imine. *N*-Cyclohexyl-1-hydroperoxycyclohexylamine, 1-hydroperoxycyclohexylamine, and the cyclohexylamine–hydrogen peroxide adduct give only the imine under the conditions of the reaction.

The destructive ability of a combination of oxygen and sunlight on organic substances is great and costly. We have been studying the consequences of light on charge-transfer (CT) complexes between various organic materials[1] and oxygen because these are instrumental in a number of degradations. The most dramatic demonstration to date is the fact that saturated hydrocarbons exhibit CT interactions[2a,b,c] with molecular oxygen and the excitation of this uv absorption band causes product formation.[1e-g]

A distinction must be made between those oxidation reactions initiated by sensitization and those by excitation of the CT band though similarities in products and product composition may occur. Among the reports of dye-sensitized oxygenation of amines, Gaffron[3] found that erythrosin photosensitized the oxygenation of *n*-propylamine and chlorophyll photosensitized the oxygenation of *n*-isoamylamine. More recently Schenck[4] reported that the dye-sensitized photooxygenation of primary, secondary, and tertiary amines resulted in the uptake of one, two, or three molecules of oxygen, respectively, indicating that the number of CH groups α to the nitrogen determines the stoichiometry. The products of these reactions were amine hydroperoxides. Others have reported that a variety of reactions occur when amines are irradiated in the presence of dyes and oxygen: α oxidation,[5-9] dehydrogenation,[10,11] and dealkylation.[10] Kinetic studies on the oxygen uptake in the photosensitized oxidation of triethylamine have also been done.[12]

In contrast, no work has been reported concerning the direct photooxidation of amines without sensitizers being present. Evans[2a] has suggested that oxygen charge-transfer complexes could provide a plausible initial stage in these photooxidations. Since it is known that amines also exhibit CT bands with oxygen, we wished to determine the chemical consequences of direct absorption of light by the oxygen–amine charge-transfer band. A number of aliphatic amines, *i.e.*, primary, secondary, and tertiary, were photochemically oxidized with oxygen in the initial studies. All of the aliphatic amines tested reacted; however, since the primary aliphatic amines gave more simple product mixtures than secondary and tertiary amines, these were selected for the initial study. For primary aliphatic amines, our attention was focused on the photooxidation of cyclohexylamine because a procedure for the synthesis of the α hydroperoxide of cyclohexylamine was available.

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(7) R. F. Bartholomew, R. S. Davidson, and M. J. Howell, *ibid.*, 2804 (1971).

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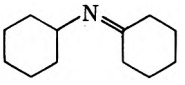
Results and Discussion

The spectral basis for the photooxidation of cyclohexylamine is illustrated in Figure 1. The absorption of oxygen-saturated cyclohexylamine begins at 380 nm and increases towards off scale at 265 nm. Nitrogen-saturated cyclohexylamine is included as a reference. Due to the intense absorption of cyclohexylamine beginning at 265 nm, the correct position of the CT maxima cannot be established. Though amines are known to undergo a slow nonphotochemical oxidation, this enhanced absorption conforms to that of the CT type in that it is reversibly formed, *i.e.*, it can readily be removed by displacing the oxygen by a more inert gas such as nitrogen.

The change transfer occurs with nitrogen as the donor and oxygen the acceptor. Of the three types of liquid phase CT phenomena we have been working with, the amine–oxygen CT absorption is most intense with the ether–oxygen CT band of intermediate strength and the saturated hydrocarbon–oxygen CT band the weakest.[1] This is in agreement with the correlation of increasing CT absorptivity with decreasing ionization potential of various donors.[2c,13a] Neither the presence of a ground state complex between oxygen and the amine nor the extent of its formation can be surmised from these data.

On irradiating the CT band of oxygen-saturated cyclohexylamine, the products, cyclohexanone oxime, *N*-cyclohexylidinecyclohexylamine (**1**), ammonia, and water, are formed. In addition, there are peroxides present in the irradiation solution.

Conceivably, absorption of light by the tail-end absorption of cyclohexylamine and not the CT band could have caused the observed reaction; *cf.* Figure 1. Then the excited state of the amino nitrogen could have entered into the reaction. However the irradiation of nitrogen-saturated cyclohexylamine using a Pyrex filter and a medium-pressure mercury lamp caused no detectable product formation yet these same conditions with oxygen give the observed products. Irradiation using the 350-nm phosphor, low-pressure lamps of the Rayonet reactor also gives the products. Irradiation of the oxygen–cyclohexylamine solution with a tungsten filament lamp did not give any product formation which narrows the wavelengths responsible for product formation to 280–375 nm, the region of the spectrum where the CT band is. Since the amine's absorption is below 280 nm and the direct irradiation of cyclohexylamine is known to give products albeit of a different type,[13b] absorption of light by the extended tail-end absorption of cyclohexylamine did not cause the observed reaction.



1

Cyclohexanone oxime is not the precursor of the imine **1** because the reaction rate of the oxime with cyclohexylamine is slow. Under the photochemical reaction conditions, no detectable amount of the imine is formed from the oxime during the time of the irradiation. Cyclohexanone, another possible precursor to the imine **1**, could not be found in the reaction solution.

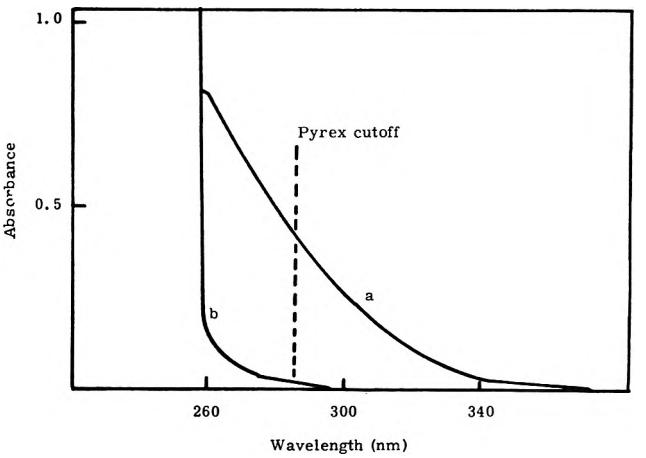


Figure 1.—Ultraviolet spectra of oxygen-saturated cyclohexylamine with nitrogen-saturated cyclohexylamine as a reference (curve a) and nitrogen-saturated cyclohexylamine with an empty cell as reference (curve b).

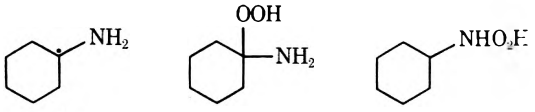
From CT theory the initiation of the product formation can be viewed according to reaction 1 most probably followed by the acid–base reaction 2. With

$$C_6H_{11}NH_2 + O_2 + h\nu \longrightarrow C_6H_{11}\dot{N}H_2^+ + \cdot O_2^- \quad (1)$$

$$C_6H_{11}\dot{N}H_2^+ + \cdot O_2^- \longrightarrow \underset{\mathbf{2}}{C_6H_{11}\dot{N}H} + \cdot O_2H \quad (2)$$

molecular oxygen being a ground state triplet, both insertion into a CH or NH bond and direct combination of the two radical products of reaction 2 are inhibited. Consequently the amine radical **2** is expected to have a finite lifetime in the reaction solution.

Though the possible presence of **3** in the reaction solution cannot be determined from these data, it has



3 **4** **5**

been postulated to be present for analogous photosensitized reactions and can reasonably be expected to form in this reaction solution as well either by rearrangement of **2** or by reaction of cyclohexylamine with a radical in solution. Noteworthy in this regard is the fact that the dissociation energy of the α-CH bond is slightly larger than that of the NH bond.[14]

With the expected presence of **2** and **3**, the hydroperoxides **4** and **5** are the probable candidates for the peroxides present in the reaction solution. Peroxides were shown to be present in the irradiation solution at 5×10^{-2} *M* by reaction with cobalt(II) acetate and iodometric titration. Treatment of the reaction solution with triphenylphosphine prior to titration proved to be effective in destroying the peroxide concentration. This strongly suggests that the peroxide in solution is there as a hydro- and/or hydrogen peroxide since dialkyl peroxides react only slowly with triphenylphosphine at room temperature whereas hydroperoxides react rapidly.[15]

(13) (a) H. Tsubomura and R. S. Mulliken, *J. Amer. Chem. Soc.*, **82**, 5966 (1960); (b) V. I. Stenberg and C. H. Niu, *Tetrahedron Lett.*, 4351 (1970).

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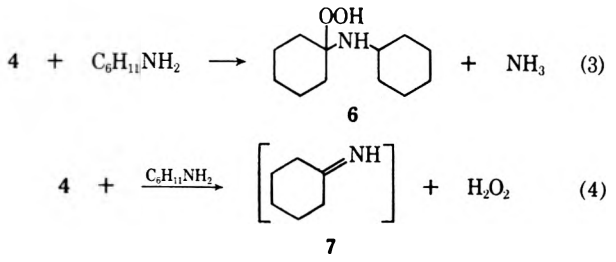
Surprisingly the imine **1** is not formed in so high yield with the triphenylphosphine treatment of the reaction mixture as without. To examine this, the hydroperoxide **4** was synthesized and reacted in cyclohexylamine in the absence of light. *N*-Cyclohexylidinecyclohexylamine was quantitatively formed with no cyclohexanone oxime. Hence **4** can be the precursor of the imine but not the oxime. When **4** is dissolved in cyclohexylamine and immediately treated with triphenylphosphine, cyclohexanone and the imine **1** are formed. The reason for the slight negative influence of triphenylphosphine on the imine yield in the reaction mixture could be due to the partial conversion of the hydroperoxide **4** into cyclohexanone rather than exclusively to the imine **1**. It must be mentioned that, though the hydroperoxide **4** has been isolated from the photosensitized oxidation of cyclohexylamine,[11] we have not been successful in isolating it from these CT-irradiated cyclohexyl-amine–oxygen solutions using the same technique. This is possibly due to its low concentration.

Since the hydroperoxide **4** is known to convert into *N*-cyclohexyl-1-hydroperoxycyclohexylamine, **6**, in cyclohexylamine–benzene, reaction 3,[11] **6** was also prepared to learn of its characteristics in our reaction solution. This peroxide, **6**, is also readily converted into the imine **1** in cyclohexylamine in the absence of light. Analogous to the reaction of **4** with triphenylphosphine, triphenylphosphine transforms **6** into a mixture of cyclohexanone, cyclohexylamine, and the imine **1**.

The mass balance of eq 4 which leads to the probable



precursor, **7**, of **1** suggests that hydrogen peroxide is in the reaction solution. Hydrogen peroxide is known to form an adduct **8** with cyclohexylamine according to eq 5.[11] Despite the fact that we were unable to isolate this compound from the reaction solution, **8** was made, dissolved in cyclohexylamine, and irradiated under nitrogen. With these conditions, it was quantitatively converted into the imine **1**. Consequently it can also be a precursor to **1** but cannot be to cyclohexanone oxime.

Reactions which are consistent with available data for the irradiation of oxygen–cyclohexylamine are summarized in reactions 1–10.

$$H_2O_2 + 2C_6H_{11}NH_2 \longrightarrow \underset{\mathbf{8}}{(C_6H_{11}NH_2)_2 \cdot H_2O_2} \quad (5)$$

$$2 + R\cdot \longrightarrow 7 + RH \quad (6)$$

$$7 + C_6H_{11}NH_2 \longrightarrow 1 \quad (7)$$

$$6 + C_6H_{11}NH_2 \longrightarrow 1 \quad (8)$$

$$4 + C_6H_{11}NH_2 \longrightarrow 1 + H_2O_2 \quad (9)$$

$$8 + h\nu \longrightarrow 1 \quad (10)$$

We must leave the origin of cyclohexanone oxime as a mystery with the suggestion that the *N*-hydroperoxide may have a role in its formation. Indirect evidence for oxidation on the nitrogen of the amine are (1) *N*-hydroperoxypiperidine found as a product during the radiolysis of piperidine,[16] (2) *N*,*N*-diethylhydroxylamine formed during the thermal oxidation of diethylamine,[17] and (3) triethylamine *N*-oxide formed during the irradiation of an oxygen–triethylamine solution.[18] Hence oxidation of the nitrogen clearly occurs under a variety of conditions. Though *N*-hydroxylcyclohexylamine could not be found in the cyclohexylamine–oxygen irradiation solution, it is converted into cyclohexanone oxime under these conditions.

Experimental Section

Materials.—Cyclohexylamine and cyclohexanone oxime were purchased from Aldrich Chemical Co. Cyclohexylhydroxylamine was synthesized by the method of Borch, *et al.*[19] The hydrogen peroxide–cyclohexylamine adduct and 1-hydroperoxycyclohexylamine were synthesized by the methods of Hawkins.[11,20] Cyclohexylamine (Aldrich Co.) was dried over potassium hydroxide, fractionally distilled from potassium hydroxide and sodium wire under nitrogen, and fractionally redistilled. The purity of the amine was checked by ultraviolet spectroscopy and flame-ionization gas chromatography.

Charge-Transfer Spectrum.—Purified cyclohexylamine was placed in a 1-cm quartz spectrophotometric cell fitted with ground glass stopper, nitrogen bubbled through for 2 min, the stopper put on, and the absorption spectrum recorded using a matched empty cell as a reference. The reference cell was then filled with purified amine and the nitrogen deoxygenating procedure repeated. The resulting spectrum established the base line. Oxygen was then bubbled into the amine in the sample cell for 2 min, the stopper placed on cell, and the spectrum again recorded to obtain the CT spectrum. Afterward, the base line could again be obtained by deoxygenating the sample.

Irradiation of the Oxygen-Saturated Cyclohexylamine Solution, Product Identification.—Oxygen gas was passed into magnetically stirred cyclohexylamine in an immersion well for 30 min prior to irradiation with a Hanovia 450-W medium-pressure lamp. The exit gases were passed first through a salt–ice trap and then a Dry Ice–acetone trap. The cyclohexylamine solution was irradiated for about 3 hr. Aliquots of the reaction mixture were injected into a Beckman GC-5 chromatograph equipped with two 20 ft × $^1/_8$ in., 5% KOH–20% Carbowax–Chromosorb columns[21] and a flame-ionization detector. *N*-Cyclohexylidenecyclohexylamine and cyclohexanone oxime were identified by retention times. The reaction mixture was concentrated by vacuum distillation and divided into two parts. One part was dissolved in absolute ethanol and hydrogenated with an excess 10% Pd/C. The solution was filtered, distilled, and analyzed by glpc. It showed a new peak not present in the original reaction mixture. By comparison of glpc retention time with a known sample and using spiking techniques, the new peak was found to correspond to dicyclohexylamine. Since the imine and oxime peaks were difficult to separate by preparative glpc. the remainder of the concentrated mixture was transferred in a 2 *N* hydrochloric acid solution and extracted with *n*-pentane. After washing with aqueous K_2CO_3 and drying over $MgSO_4$, the pentane solution was separated by preparative glpc into two products, cyclohexanone and cyclohexanone oxime, which were identified by comparing nmr and ir spectra with those of authentic samples.

When the reaction mixture from the photooxidation of cyclohexylamine was reacted with a 0.05 *M* cobalt(II) acetate solution,[22] the pink color of cobalt(II) ion turned to a black precipitate similar to the response of hydrogen peroxide in cyclo-

(16) A. P. Podsoblyaev and N. A. Bakh, *Chem. Abstr.*, **61**, 10220a (1964).
(17) C. F. Cullis and I. Isaac, *Trans. Faraday Soc.*, **48**, 1023 (1952).
(18) C. H. Niu and V. I. Stenberg, unpublished results, 1972.
(19) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971).
(20) E. G. E. Hawkins, *J. Chem. Soc. C*, 2663 (1969).
(21) H. Veening and G. D. Dupre, *J. Gas Chromatogr.*, **4**, 153 (1966).
(22) C. H. Sorum, "Introduction to Semimicro Qualitative Analysis," 4th ed, Prentice-Hall, Englewood Cliffs, N. J., 1960, pp 160–163.

hexylamine. The control, prepared by bubbling oxygen into cyclohexylamine for 3 hr in the absence of uv light, turned the pink Co(II) color to greenish brown. The quantity of peroxides in the irradiated oxygen-saturated cyclohexylamine was determined by the method of Vogel.[23] After the irradiated solution was treated with triphenylphosphine, the peroxide content was gone.

Anhydrous copper sulfate turned blue in contact with the oxygen-saturated, irradiated cyclohexylamine solution. By comparison of glpc retention times and spiking procedures using a 8 ft × 1/4 in. Porapak column, water was identified in the reaction mixture.

Ammonia was identified by its characteristic ir spectrum[24] and its glpc retention time using a Porapak column.

Irradiation of Oxygen-Saturated Cyclohexylamine Solution, Filter Studies.—A 1-cm quartz spectrophotometric cell was placed in a holder 2.5 cm from the outside surface of the Pyrex immersion well containing a 450-W lamp. Cyclohexylamine was flushed with oxygen and irradiated for 3 hr. The concentrations of *N*-cyclohexylidenecyclohexylamine and cyclohexanone oxime were 3.81×10^{-2} and 1.12×10^{-2} *M*, respectively, as determined by glpc. Upon repeating the procedure in a Rayonet reactor with the 350-nm phosphor, low-pressure lamps, the amounts of products were reduced to one-third that obtained with Pyrex. With a 100-W tungsten lamp, no products were obtained. Upon repeating the procedure with Pyrex using nitrogen rather than oxygen, no products were observed.

Thermal and Photochemical Reaction of Cyclohexanone Oxime in Cyclohexylamine.—Cyclohexanone oxime (4 g) was dissolved in 25 ml of cyclohexylamine, and 3 ml of this solution was transferred to a 1-cm quartz spectrophotometric cell. After irradiation with a 450-W lamp under nitrogen for 3 hr at a distance of 2.5 cm from the well, no *N*-cyclohexylidenecyclohexylamine was observed. The remaining solution was heated at 45° under nitrogen for 8 hr and a trace amount of *N*-cyclohexylamine was formed.

Oxidation of *N*-Cyclohexylhydroxylamine with Hydrogen Peroxide in Ethanol.—Hydrogen peroxide (30%, 50 ml) was gradually added to a stirred solution of 0.08 *M* *N*-cyclohexylhydroxylamine in ethanol. After being stirred under nitrogen at room temperature for 3 hr, the solution was then saturated with NaCl and extracted with chloroform. The mixture was dried over magnesium sulfate, filtered, concentrated, and poured into a small amount of water to form a white solid. The compound was recrystallized (petroleum ether) and identified as cyclohexanone oxime, mp 85–86° (lit.[25] mp 89–90°) and ir spectrum.

Photolysis of Hydrogen Peroxide–Cyclohexylamine Adduct in Cyclohexylamine.—Cyclohexylamine (3 ml) containing 0.162 mm of the hydrogen peroxide–cyclohexylamine adduct was irradiated in a 1-cm cell with the 450-W lamp in a Pyrex well. After 2.5 hr, 0.165 mm of *N*-cyclohexylidenecyclohexylamine was formed (glpc).

Thermal Decomposition of 1-Hydroperoxycyclohexylamine in Cyclohexylamine.—A 0.0394 *M* cyclohexylamine solution of 1-hydroperoxycyclohexylamine was stirred under nitrogen at 45° for 1 hr. *N*-Cyclohexylidenecyclohexylamine (0.0410 *M*) was produced (glpc).

Decomposition of *N*-Cyclohexyl-1-hydroperoxycyclohexylamine in Cyclohexylamine.—*N*-Cyclohexyl-1-hydroperoxycyclohexylamine (1.0 g) was added to 15 ml of cyclohexylamine, and the solution was stirred under nitrogen for 1 hr. *N*-Cyclohexylidenecyclohexylamine was found and isolated by gas chromatography. The product was identified by glpc retention times and comparing its ir spectrum with an authentic sample.

Registry No.—**1**, 10468-40-3; **4**, 24075-24-9; **6**, 2808-61-9; **8**, 37816-86-7; cyclohexylamine, 108-91-8; cyclohexanone oxime, 100-64-1; cyclohexylamine–oxygen adduct (1:1), 37817-06-4.

Acknowledgment.—We are grateful that this investigation was supported in part by a Public Health Service Research Career Development Award (1-K4-GM-9888; V. I. S.) and by a Sigma Xi research grant (to C. N.).

(23) A. I. Vogel, "A Textbook of Quantitative Inorganic Analysis," 3rd ed, Wiley, New York, N. Y., 1961, p 363.

(24) R. H. Pierson, A. N. Fletcher, and E. St. Clair Gantz, *Anal. Chem.*, **28**, 1218 (1956).

(25) R. C. Weast, S. M. Selby, and C. Hodgman, Ed., "Handbook of Chemistry and Physics," 45th ed, The Chemical Rubber Co., Cleveland, Ohio, 1964, p C-273.

The Effect of Biphenyl Geometry and Substituents on the Multiplicity and Efficiency of the Photocyclization Reactions of 2-Substituted Biphenyls

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The direct and sensitized photochemistry of the unsubstituted, 2′-, 3′-, 4′-, 4-, and 5-methoxy-2-biphenylyl isocyanates are reported. Direct excitation of these compounds yields carbazoles and 6(5*H*)-phenanthridinones. The carbazole arises from decomposition of the isocyanate in its singlet state to a nitrene which undergoes insertion into an aromatic C–H bond. The photocyclization of the isocyanates to 6(5*H*)-phenanthridinones occurs most efficiently *via* acetone sensitization in what is formally a nonoxidative cyclization to an aromatic ring. In contrast to the insensitivity of the singlet state decarbonylation to ring substituent, the photosensitized cyclization process is enhanced by a 4′-, 4-, or 5-methoxy group and dramatically retarded by a 2′- or 3′-methoxy substituent. The related acetone-sensitized photocyclizations of *N*-(2-propylidene)-2-aminobiphenyl and its 2′-, 3′-, and 4′-methoxy derivatives to the corresponding 6,6-dimethyl-5,6-dihydrophenanthridines were also studied. In this series the 3′-methoxy substituent markedly retarded the photocyclization reaction. In contrast to the photocyclization reactions of the isocyanate and imine groups, the imino ether linkage did not undergo the photocyclization reaction. The mechanism of these processes and the low intersystem crossing efficiency in these 2-substituted biphenyls is noted and discussed.

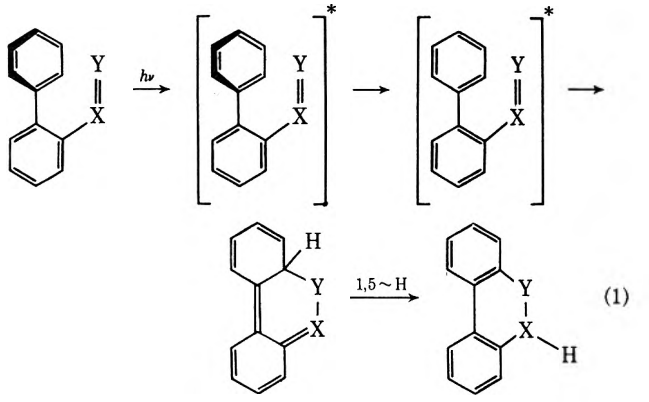
Our interest in the influence of ground- and excited-state geometry on photochemical reactivity[2] led us several years ago to initiate work on the photochemistry of biphenyl systems.[3] Aside from the consequences of markedly different equilibrium geometries of

(1) (a) Alfred P. Sloan Foundation Fellow, 1971–1973; (b) Camille and Henry Dreyfus Teacher Scholar, 1972–1977.

(2) For a discussion of these factors in diene photochemistry, see J. S. Swenton, J. A. Hyatt, T. J. Walker, and A. L. Crumrine, *J. Amer. Chem. Soc.*, **93**, 4808 (1971); **92**, 1406 (1970).

(3) (a) J. S. Swenton, *Tetrahedron Lett.*, 2855 (1967); (b) *ibid.*, 3421 (1968); (c) J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Amer. Chem. Soc.*, **92**, 3103 (1970); (d) J. S. Swenton, T. J. Ikeler, and B. H. Williams, "Excited State Chemistry," A Symposium, J. N. Pitts, Ed., Gordon and Breach, New York, N. Y., 1970, pp 93–106; (e) J. A. Hyatt and J. S. Swenton, *J. Heterocycl. Chem.*, **9**, 409 (1972); (f) J. A. Hyatt and J. S. Swenton, *J. Org. Chem.*, **37**, 3216 (1972).

the ground and excited states in modifying the photochemical and photophysical processes in biphenyls,[4] there was the synthetic potential of nonoxidative cyclization[5] in suitable 2-substituted biphenyls. The latter possibility seemed especially attractive, since the approach to planarity in the biphenyl excited state would favor bond formation between the ortho position of the biphenyl and an unsaturated 2-substituent (eq 1). In view of the convenient synthetic routes to

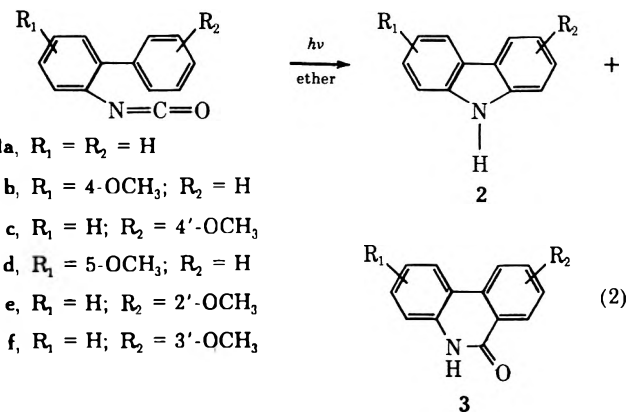


(1)

many 2-substituted biaryls, it was felt that these potential nonoxidative cyclizations would complement the well-studied photooxidative cyclizations[6] and were thus worthy of study in their own right. We wish to report here the nonoxidative photochemical cyclizations of 2-biphenylyl isocyanates and imines and the influence of substituents and biphenyl geometry on the efficiency and multiplicity of these processes.

Direct Irradiation of 2-Biphenylyl Isocyanates.—Our choice of the 2-substituted biphenyl system for study was based primarily on synthetic convenience and Yang's suggestion[7] that the ortho positions of excited biphenyl are electron rich. On this basis, it appeared that a weakly conjugating substituent, which would not markedly alter the nature of the biphenyl excited state yet had pronounced electrophilic character, would be an ideal test for the proposed photocyclization. Thus, the first system studied was a series of 2-biphenylyl isocyanates, **1a–f**.

The direct preparative irradiation of biphenyls **1a–f** produced in each case a mixture of carbazole(s) and phenanthridinone (Table I). The structures of the carbazoles were established by comparison of their melting points and ir spectra with those of the known carbazoles.[3c] Only the unsubstituted, **3a**, and 3-, **3b**; and 8-methoxy-6(5*H*)-phenanthridinones, **3c**, had been previously reported. The structures of the three remaining 6(5*H*)-phenanthridinones were established on the basis



1a, $R_1 = R_2 = H$
b, $R_1 = 4\text{-}OCH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = 4'\text{-}OCH_3$
d, $R_1 = 5\text{-}OCH_3$; $R_2 = H$
e, $R_1 = H$; $R_2 = 2'\text{-}OCH_3$
f, $R_1 = H$; $R_2 = 3'\text{-}OCH_3$

2

3

(2)

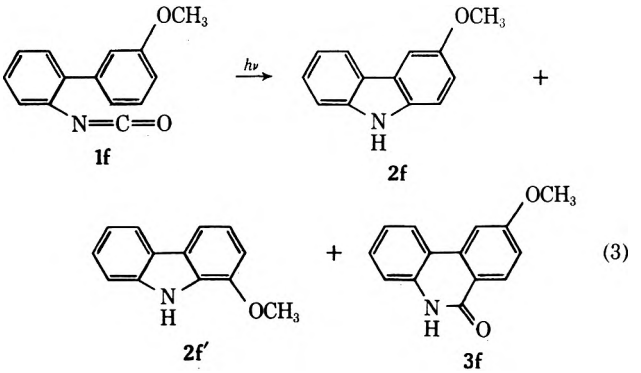
TABLE I
PREPARATIVE IRRADIATIONS FOR 2-BIPHENYLYL ISOCYANATES[a]

Compd	% Carbazole(s)[b]	% 6(5*H*)-Phenanthridinone[b]	% Recovered starting material[b,c]
1a	15	10	70
1b-4-OCH_3	15	55	34
1c-4'-OCH_3	20	29	46
1d-5-OCH_3	17	20	63
1e-2'-OCH_3	15	9	72
1f-3'-OCH_3	31	14	58

[a] Irradiations were performed for 3.5 hr using $\sim 10^{-2}$ *M* solutions under nitrogen with Vycor filtered light from a 450-W medium-pressure source. [b] The yields were calculated on the basis of crude weights eluted from the column and are uncorrected for the small amount of column residue. [c] Recovered as isocyanate and the corresponding urea.

of spectroscopic data (see Experimental Section for details).

In contrast to isocyanates **1a–e**, where only one carbazole and one 6(5*H*)-phenanthridinone were expected and observed, **1f** could produce two isomeric carbazoles and two isomeric phenanthridinones. While the two carbazoles **2f** and **2f'** were produced in identical amounts, only one 6(5*H*)-phenanthridinone could be isolated. This product was assigned as 9-methoxy-6(5*H*)-phenanthridinone (**3f**) on the basis of nmr de-



1f **2f** **2f'** **3f**

(3)

coupling experiments (see Experimental Section for details).

To evaluate the efficiencies of these reactive processes, quantum yield measurements were made (Table II). While the quantum yields for carbazole appearance and isocyanate disappearance could be measured by vpc, the production of the 6(5*H*)-phenanthridinones was less reliably determined. The determination for the latter was by uv analysis after correcting for carbazole absorption. The overlap of these two product absorp-

(4) In the ground state of biphenyl the rings are twisted to the extent of 20–30°.[4a] By contrast, elementary theory would predict a planar excited state,[4b] and experimental work supports a planar geometry for the excited triplet.[4c] (a) H. Suzuki, "Electronic Absorption Spectra and Geometry of Organic Molecules," Academic Press, New York, N. Y., 1967, pp 270–271; (b) A. Imamura and R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 5379 (1968); (c) P. J. Wagner, *ibid.*, **89**, 2820 (1967).

(5) For examples of nonoxidative cyclizations in heterocyclic systems, see (a) P. G. Cleveland and O. L. Chapman, *Chem. Commun.*, 1064 (1967); (b) O. L. Chapman and G. L. Eian, *J. Amer. Chem. Soc.*, **90**, 5329 (1968); (c) J. DeJong and J. H. Boyer, *Chem. Commun.*, 961 (1971); (d) R. A. Abramovitch and E. P. Kyba, *ibid.*, 265 (1969); (e) R. A. Abramovitch and E. P. Kyba, *J. Amer. Chem. Soc.*, **93**, 1537 (1971).

(6) For leading references see R. J. Hayward and C. C. Leznoff, *Tetrahedron*, **27**, 2085 (1971).

(7) N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, **88**, 5369 (1966).

tions varied with the substituent and thus only upper limits could be placed on some of the quantum yields for 6(5*H*)-phenanthridinone production. A complication in the direct irradiation is revealed by comparison of the quantum yields with the product ratios noted in preparative irradiations using Vycor-filtered light from a 450-W medium-pressure source. For each compound preparative irradiations showed a larger percentage of 6(5*H*)-phenanthridinone than would be expected from the quantum yield data at 253.7 nm. While control experiments established that secondary irradiation of 6(5*H*)-phenanthridinone to carbazole at 253.7 nm did not account for this discrepancy, studies at 300 nm[8] showed that the ratio of the 6(5*H*)-phenanthridinones to the carbazoles increased with length of irradiation. In view of the high triplet energy of carbazole (E_T = 70.1 kcal/mol),[9a] its moderate intersystem crossing efficiency (Φ_{ic} = 0.36),[9b] and its strong absorption in the near-uv, it appears reasonable that carbazole is acting as a triplet sensitizer to produce the 6(5*H*)-phenanthridinone (*vide infra*). This postulate is further strengthened by an independent experiment wherein carbazole sensitization of **1a** to **3a** was demonstrated. Thus, at 253.7 nm the major process observed is decarbonylation of the isocyanate resulting in production of the respective carbazole(s).

Sensitized Irradiations of 2-Biphenylyl Isocyanates. —To obtain evidence on the multiplicity of the excited state responsible for product formation, sensitization studies were undertaken. Owing to possible complications of inefficient energy transfer from low-energy sensitizers,[4c] the sensitization work was carried out using acetone as sensitizer and solvent.[10] In contrast to the direct irradiations, which yielded mixtures of carbazole(s) and 6(5*H*)-phenanthridinones, acetone-sensitized photolyses led primarily to phenanthridinones. To establish that these sensitizations were not due to singlet energy transfer from acetone,[11] sensitization experiments were performed on **1a** in the presence of piperylene as quencher. Should the singlet state of acetone be responsible for the sensitization, piperylene would have little effect on the reaction, since piperylene should not efficiently quench acetone singlets, while, if the triplet state of acetone were implicated in these sensitizations, piperylene would quench the triplet acetone with a diffusion-controlled rate and thus markedly lower the efficiency of the photocyclization

Table II

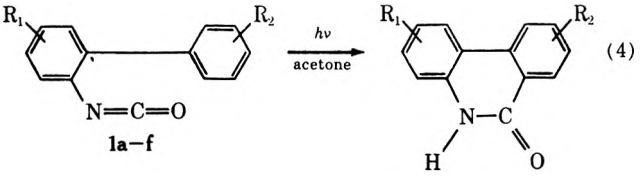
Quantum Yields for Direct Photolysis of 2-Biphenylyl Isocyanates

2-Biphenylyl isocyanate	$\Phi \times 10^{4}$ [a,b] isocyanate, 253.7 nm	$\Phi \times 10^{4}$ [a,c] phenanthridinone, 253.7 nm	$\Phi \times 10^{4}$ [a,c] carbazole, 253.7 nm
Unsubstituted, **1a**	115	*d*	66
4-OCH_3, **1b**	49	<3	34
4′-OCH_3, **1c**	52	<7	45
5-OCH_3, **1d**	86	*d*	65
2′-OCH_3, **1e**	39	<1	41
3′-OCH_3, **1f**		<1	55

[a] The estimated error in these numbers is 20%. [b] The quantum yields for disappearance of isocyanates were measured at 1–10% conversion. [c] The quantum yields were determined at 0.5–2% conversion. [d] The strong overlap of the respective carbazole and 6(5*H*)-phenanthridinone uv spectra prevented determination of this value.

of the isocyanate. Thus, the amount of phenanthridinone formed from low conversion irradiation of acetone solutions which were 0.10 *M* in isocyanate and 0.08 *M* in piperylene was compared with solutions containing no piperylene. In the presence of 0.08 *M* piperylene the yield of phenanthridinone was reduced by a factor of >5, while in 1.0 *M* piperylene runs the quenching of phenanthridinone formation was virtually complete (4% production relative to the unquenched irradiation could have been detected). These results support the proposal that singlet-state acetone is not responsible for the acetone sensitization results. While we believe that the most reasonable interpretation for the acetone sensitization work directly involves acetone triplet, attempts at employing sensitizers wherein singlet state energy transfer is not known to occur have met with only limited success. Thus, while acetophenone in benzene does sensitize the photocyclization of **1a** to **3a**, the quantum efficiency is only 5×10^{-4}, a factor of about 7.5 lower than the analogous acetone sensitization. Furthermore, acetophenone sensitizations of **1a** are of no preparative value.

As noted below, the sensitized reactions of **1a–d** proceed in high preparative yield, while in marked con-



(4)

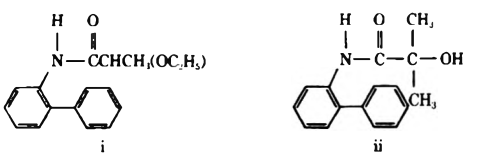
3a, 70% **3d**, 91%
b, 95% **e**, 10%
c, 91% **f**, 15%

trast the 2′- and 3′-OCH_3 compounds photocyclize in poor yields. The low reactivity of these compounds toward acetone sensitization is further confirmed from the quantum yields for these sensitizations recorded in Table III. Here the inherent efficiency of the triplet state cyclizations for the methoxy compounds spans a factor of about 30. Of special note is the much higher quantum yields for cyclization in the sensitized irradiations as compared to the direct photolyses. Where comparisons can be made (*i.e.*, **1b**, **1c**) the sensitized cyclization is approximately 20 to 40 times more efficient than the analogous process from direct irradiation.

(8) Quantum yield measurements at 300 nm suggested that there was a slight wavelength effect on the production of carbazole as its quantum efficiency decreased relative to the values at 253.7 nm. However, the interpretation of these results is unclear owing to the time dependence of the product ratios at this wavelength and the 253.7 contamination in the RPR-3000 Å source utilized.

(9) (a) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, p 298; (b) p 309.

(10) Sensitizations of **1a** in acetone (1–3 *M*)–ether gave, in addition to **3a**, i and ii. The structures for the latter compounds were assigned on the



basis of their ir and nmr spectra and their hydrolyses to 2-aminobiphenyl. While the mechanisms for formation of i and ii were not studied, they reasonably arise from radicals generated by hydrogen abstraction processes of acetone. Their formation suggests that, even with acetone, energy transfer to these biphenyls may not be diffusion controlled.

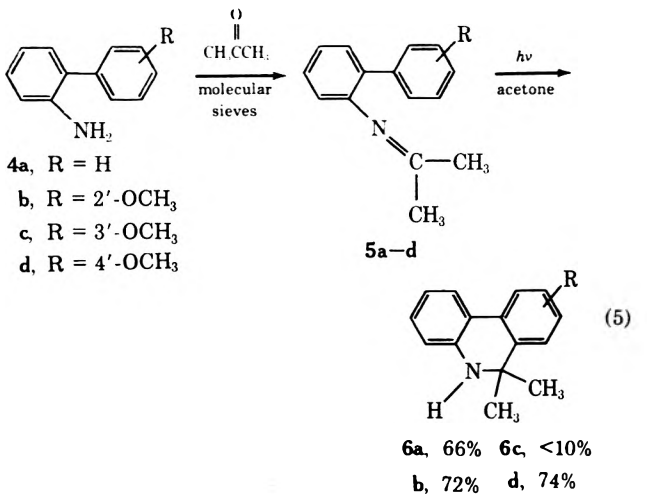
(11) M. A. Golub, *J. Amer. Chem. Soc.*, **92**, 2615 (1970).

TABLE III
QUANTUM YIELDS FOR ACETONE-SENSITIZED IRRADIATION AT 3000 Å[a]

2-Biphenylyl isocyanate	$\Phi \times 10^4$ [b] isocyanate	$\Phi \times 10^4$ [c] Phenanthridinone	$\Phi \times 10^4$ [c] carbazole
Unsubstituted, 1a	50	38	5
4-OCH_3, 1b	157	136	2
4'-OCH_3, 1c	120	118	*d*
5-OCH_3, 1d	65	45	1
2'-OCH_3, 1e	13	7	*d*
3'-OCH_3, 1f	10	3	1

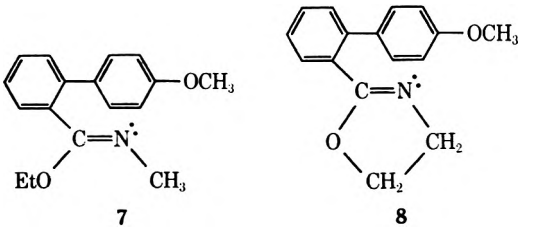
[a] See Table I, footnote *a*. [b] The isocyanate conversion was 10–15%. [c] The conversion to products was 1–15%. [d] No carbazole was detected for these compounds.

Irradiation Studies of *N*-(2-Propylidene)-2-aminobiphenyls.—The high yields of cyclized products in certain of the isocyanate cyclizations prompted us to briefly explore the chemistry of the simple imine linkage in these nonoxidative processes.[12] The ground-state polarity of the carbon–nitrogen double bond, while not so pronounced as that of the isocyanate, would certainly be in the proper direction for bonding interaction with the supposed electron-rich ortho positions of biphenyl. The imines **5a–d** were prepared in 50–70% yield by condensation of the appropriate aminobiphenyl with acetone in the presence of molecular sieves.[13] Isolation of the imines by distillation yielded material of >96% purity by vpc. Since the synthetic yields from these freshly distilled samples were comparable with those recorded from samples obtained by preparative vpc, the majority of the work was done on imines containing 1–3% of the corresponding amine as impurity.



In agreement with the isocyanate work, direct excitation of the imines in ether proceeded slowly and was of no preparative value. However, acetone-sensitized photolysis of the imines **5a**, **5b**, and **5c** produced cyclized products in moderate to good yield. The structures of the products were assigned as the respective 6,6-dimethyl-5,6-dihydrophenanthridines on the basis of analytical and spectroscopic data. It is noteworthy that, as in the case of the corresponding isocyanate, the 3'-methoxy substituent lowered reactivity such that no cyclization product could be isolated from **5c**. In contrast to the isocyanate system, the 2'-methoxy derivative **5b**, did afford the photocyclization product **6b** in good yield. In view of the difficulty of obtaining and maintaining 100% pure imine, no quantum yield studies on the imines were attempted. The length of preparative irradiations suggested quantum yields slightly less than those noted with the corresponding isocyanates.

Attempted Photocyclization of the Imino Ethers of 4'-Methoxybiphenyl.—While many of the nonoxidative cyclizations observed in the case of the isocyanates and imines were of good preparative yield, the quantum efficiencies were rather low. The recent demonstration of the importance of rotational freedom in reducing the reactivity of olefin systems suggested that the low quantum efficiency in these nonoxidative cyclizations might be related to a similar phenomenon.[2] For these nitrogen systems deactivation mechanisms could involve either rotation about the –N=C– linkage or an inversion mechanism involving the nitrogen lone pair. Unfortunately, neither the isocyanate nor the imine system allow a steric constraint to be placed on the rotational or inversion deactivation mechanism by incorporation of the linkage into a ring (if a neutral species is to be maintained). Thus, we briefly explored the photocyclization reactivity of the imino ethers **7** and **8**. If either of the deactivation processes noted above were important in these systems, **8** would be expected to be significantly more reactive than **7**. Unfortunately, the imino ethers **7** and **8** would have a markedly different polar character than the isocyanate or imine linkage. Apparently, the nature of the substituent has a pronounced effect on the photocyclization efficiency, since both **7** and **8**, as compared to the isocyanate or imine systems, were quite unreactive toward cyclization in either direct or acetone-sensitized photolysis.[14] Thus, the importance of rotational or inversion deactivation mechanisms in accounting for the low efficiency of the nonoxidative cyclizations remains unanswered.



Discussion

Direct Excitation in Biphenyl Systems.—The direct photolyses of the 2-biphenylyl isocyanates produces carbazoles in low quantum efficiency ($\Phi \cong 0.005$). The most obvious mechanism for carbazole formation is loss of CO in excited **1** followed by insertion of the nitrene into the adjacent C–H bond, producing carbazole.[15] This proposal is strengthened by the identity

(12) While this work was in progress, Abramovitch[5d] reported that **5a** generated from an azide precursor did photocyclize in low yield to 6,6-dimethyl-5,6-dihydrophenanthridine. By mutual consent we have explored the nature of the cyclization in more detail.

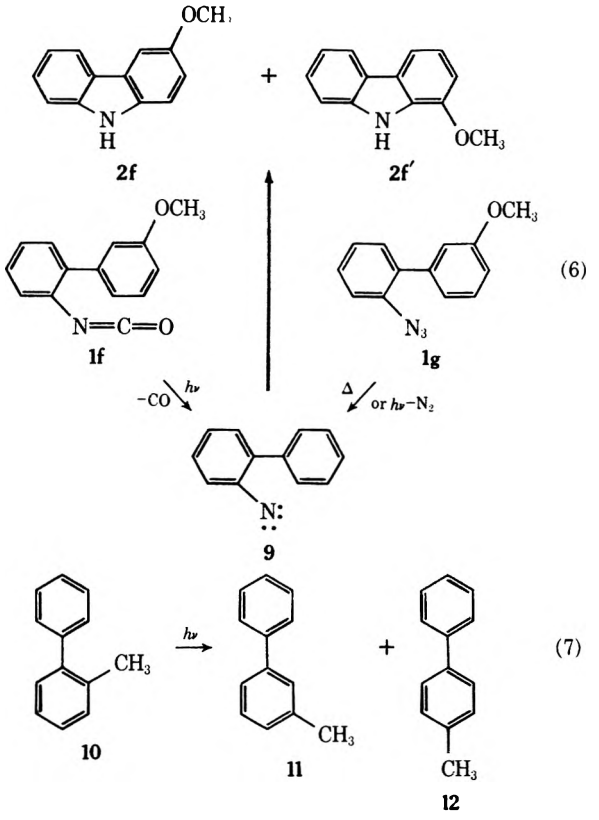
(13) Westheimer has independently noted the use of molecular sieves for imine formation: K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36**, 1570 (1971).

(14) We wish to thank Mr. John Hyatt for this series of experiments.

(15) This process has analogy with the gas-phase photodecarbonylation of isocyanic acid.[15a,b] (a) W. D. Woolley and R. A. Back, *Can. J. Chem.*, **46**, 295 (1968); (b) J. N. Bradley, J. R. Gilbert, and P. Svejda, *Trans. Faraday Soc.*, **64**, 911 (1968).

of the ratio of carbazoles produced from photolysis of **1f** and photolysis or thermolysis of the corresponding azide, **1g**. The nitrene has been directly implicated in the latter series of reactions.[3c] The differences in quantum efficiency in the azide *vs.* the isocyanate system (Φ = 0.42 *vs.* 0.005) seemingly reflects the much larger photostability of the isocyanate *vs.* the azide group.

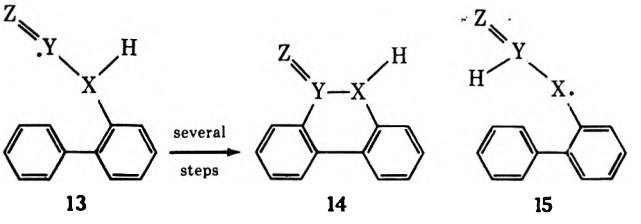
Recently, several investigators have reported that photolysis of 2-biphenyl derivatives produced isomerized biphenyls (eq 7).[16] In our studies such isomers



were not noted as major processes, although small amounts of such isomerizations may have gone undetected. It appears reasonable that the absence of such processes in our system is due to the even lower efficiency of these isomerizations *via* benzvalene intermediates than the decarbonylation reactions. Support for this comes from a recent study of Zimmerman and Crumrine,[16d] who showed that photoisomerization of 2,2′-dimethyl-6,6′-diethylbiphenyl *via* a benzvalene intermediate has a quantum yield of about 2×10^{-4}, a factor of about 30 lower than the decarbonylation efficiency of the isocyanates.

A final point worthy of mention concerns the efficiency of intersystem crossing in 2-substituted biaryl systems. As we noted several years ago[3d] for such varied compounds as the 2-azidobiphenyls and the isocyanate and imino systems reported here, the intersystem crossing efficiency based on quantum yields from direct and sensitized reactions is only 5–10%.[17] More recently Griffin and coworkers have concluded from their results on the photochemistry of 2-methylbiphenyls that intersystem crossing was low in these molecules also. The apparent low intersystem crossing noted in these systems could be a result of either exceptionally fast nonreactive decay processes of the singlet state or an especially slow rate of intersystem crossing. In view of the varied nature of 2-substituted derivatives which show this effect, it is tempting to conclude that the latter effect is operative. Since the equilibrium geometry of the biphenyl triplet should tend to be planar, and 2 substituents should exert steric hindrance toward planarity, an attractive postulate is that the low intersystem crossing in this system is related to a barrier to planarity in the excited state. Should this be the case, it provides another example of the importance of geometric factors in multiplicity-dependent photochemistry.

Sensitized Reactions of 2-Substituted Biphenyls.— Of the numerous mechanisms which can be envisioned for the formal nonoxidative photocyclization processes reported here, several deserve brief comment. One would involve the intermediate **13**, formed by hydrogen abstraction or hydrogen transfer processes.[18] While it seems reasonable that radical **15** would be formed in preference to **13**, the overall low quantum efficiency of the cyclization process would be explained if **15** were



formed reversibly while the more reactive species **13**, even though formed less readily, was more reactive toward cyclization. A modification of this mechanism involving electron transfer from sensitizer to biphenyl followed by cyclization is also an *a priori* possibility. If such a mechanism were operative, additional products from radical recombinations would be expected (see footnote 10). Partial evidence against this mechanism is the failure to isolate such products either in the preparative direct excitation of the isocyanates in ether (Table I) or the high-yield acetone sensitizations. While solvent[19] and sensitizer[20] effects would be expected to markedly influence both of these mechanisms, experimentally meaningful studies in these particular systems are quite difficult.

A fundamentally different mechanism would be photocyclization of **16** to **17** followed by 1,5-hydrogen shift to yield the aromatic species. While many electrocyclic processes bear formal analogy to the first step

(16) (a) R. A. Finnegan and D. Knutson, *Tetrahedron Lett.*, 3429 (1968); (b) R. A. Abramovitch and T. Takaya, *Chem. Commun.*, 1369 (1969); (c) U. Mende, J. L. Laseter, and G. W. Griffin, *Tetrahedron Lett.*, 3747 (1970); (d) H. E. Zimmerman and D. S. Crumrine, *J. Amer. Chem. Soc.*, **94**, 498 (1972).

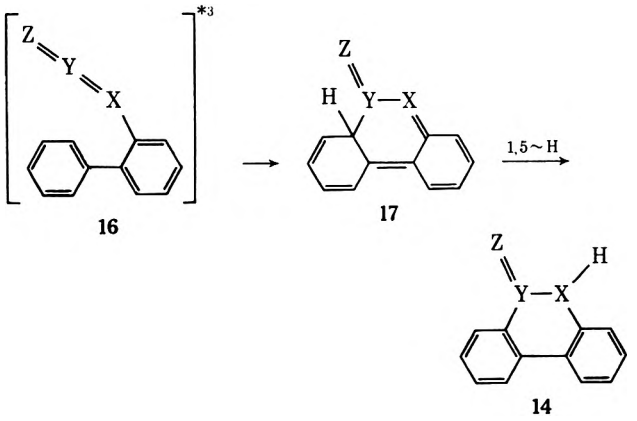
(17) A recent value for the intersystem crossing in benzene is 0.42,[17a] while most simple aromatic hydrocarbons have values greater than 0.2.[17b] (a) H. Morrison and R. Peiffer, *J. Amer. Chem. Soc.*, **90**, 3428 (1968); (b) ref 8b.

(18) While hydrogen abstraction by excited isocyanate or imine group does not appear to have been reported, hydrogen transfer from radicals to imine groups is well recognized. For leading references see A. Padwa, W. Bergmark, and D. Pashayan, *J. Amer. Chem. Soc.*, **90**, 4458 (1968); **91**, 2653 (1969).

(19) Solvent effect studies with the isocyanates are limited to nonnucleophilic media while a further complication is the low solubility of the products in many common solvents.

(20) In our experience acetone is the only good sensitizer for these cyclizations. While acetophenone in benzene does sensitize the reaction, the reaction is quite slow. The difficulty apparently rests with the high energy of the twisted biphenyl triplet.

(*i.e.*, **16** → **17**), these reactions are virtually exclusively singlet-state processes. In contrast, our evidence from



16 **17** **14**

acetone sensitization studies strongly suggests that the cyclization of the isocyanate and imine groups involves the triplet state. If the triplet state does produce **17**, it would be necessary for intersystem crossing to proceed or be concurrent with formation of **17**. While we consider it instructive to point out the more reasonable mechanistic possibilities of the cyclizations, the exact molecular details of these reactions remain to be established.

A final point is the effect of methoxy substituents and the nature of the ortho-unsaturated substituent on the yield of the photocyclization. While a detailed discussion of the effect of methoxy groups on the cyclization would be premature, since the mechanism has not been established, several relevant points can be made. In the case of 4-methoxy, **1b**, and 4′-methoxy, **1c**, substituents the reactivity as evidenced by the quantum yields is enhanced by a factor of 3–4 relative to the unsubstituted systems. Thus, experimentally, methoxy groups which are meta to either the position of cyclization or the position bearing the cyclizing substituent show enhancement of reactivity. This increased reactivity at positions meta to an electron-donating group is reminiscent of similar effects in photosolvolyses[21] and photodeuteration[22] studies of anisole derivatives and suggests the importance of substituents which enhance reactivity at these positions for good synthetic processes. The markedly lower reactivity of the 2′-methoxy (isocyanate series only), **1e**, and 3′-methoxy, **1f** and **5c**, is less readily rationalized, as it is probably due to a combination of steric and electronic effects. Interestingly, while a 3′-methoxy markedly retards reaction, a 5-methoxy substituent exerts very little effect on the efficiency of the process.

While photocyclizations involving only three unsaturated ortho substituents were noted here, it appears that the yield of the cyclization is markedly influenced by the nature of this group. Molecules undergoing successful cyclization have ground-state polarizations in which the cyclizing atom may be regarded as electron deficient. The one attempted cyclization of an electron-rich 2 substituent was unsuccessful and thus the character of the side chain as well as the ring substituents is important. Unfortunately, the importance of Yang's suggestion of the increased electron density at the ortho position of excited biphenyl is not readily assessed from either the methoxy substituent effects or the variation of cyclizing substituent.

Summary.—The direct irradiation of 2-substituted biphenyls results in poor intersystem crossing and inefficient nonoxidative cyclizations. The acetone-sensitized photolyses results in photocyclization reactions, whose efficiencies and yields vary with the position of ring substituent and the nature of the unsaturated 2 substituent. The high preparative yields noted in some of these systems suggest good synthetic utility for selected transformations.

Experimental Section

Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer. Uv spectra were determined with a Cary 14 recording spectrometer. The mass spectra were measured with an AEI MS-9 mass spectrometer. Nmr spectra were measured at 60 MHz using TMS as internal standard. All elemental analyses were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All photolyses were carried out in an atmosphere of purified nitrogen.

2′-Methoxy-2-biphenylyl Isocyanate (1e).—A solution of 7.4 g (37 mmol) of 2′-methoxy-2-aminobiphenyl[23] in 30 ml of dry ethyl acetate was added over 15 min to a stirred solution of 9 g of phosgene in 30 ml of dry ethyl acetate. Phosgene was bubbled through the solution for an additional 1.5 hr, after which the solvent was removed *in vacuo*. The residue was chromatographed on a 64 × 1.9 cm silica gel column slurry packed in 2% ether in hexane. Fractions (60 ml) were eluted with 2% ether in hexane. Removal of the solvent from fractions 3–8 followed by vacuum distillation of the residue yielded 5.3 g (63%) of the isocyanate as a colorless liquid: bp 116–117° (0.24 mm); ir (neat) 4.43 (vs) and 13.2–13.3 μ (vs); uv max (hexane) 277 nm (ε 4100).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.52; H, 5.04; N, 6.14.

3′-Methoxy-2-biphenylyl Isocyanate (1f).—A mixture of 10.0 g (44 mmol) of 3′-methoxy-2-biphenylcarboxylic acid[24] and 20 ml (0.28 mol) of thionyl chloride was refluxed for 1 hr. The excess thionyl chloride was removed by vacuum distillation, and the remaining traces of thionyl chloride were removed by gently heating the oil under vacuum for 4 hr. There remained 11.0 g of 3′-methoxy-2-biphenylcarbonyl chloride as a red oil, ir (neat) 5.61 (vs), 11.2–12.0 (vs), 12.96 (s), 13.25 (s), 14.02 (m), and 14.30 μ (m).

A solution of 11.0 g of the acid chloride in 10 ml of acetone was added to a stirred solution of 5 g (77 mmol) of sodium azide in 25 ml of water at 0°. Stirring was continued for 1 hr after which the phases were separated. The organic phase was dried over sodium sulfate at 0° for 5 min and was added to refluxing benzene (30 ml). The aqueous phase was extracted with benzene, and the benzene was dried and also added to the refluxing benzene. The benzene solution was refluxed for 1 hr, after which the benzene was removed *in vacuo*. Vacuum distillation of the red residue yielded 7.1 g (72%) of the isocyanate as a colorless liquid: bp 114–115° (0.15 mm); ir (neat) 4.40 (vs), 11.40 (m), 11.56 (m), 11.70 (m), 12.7 (s), 13.2 (vs), and 14.27 μ (s); uv max (hexane) 281 nm (ε 3900) and 251 (7100).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.72; H, 4.95; N, 6.27.

4′-Methoxy-2-biphenylyl Isocyanate (1c).—Using a procedure analogous to that of the 3′-methoxy isomer, a mixture of 4.21 g (18.5 mmol) of 4′-methoxy-2-biphenylcarboxylic acid[25] and 16 ml (0.22 mol) of thionyl chloride was converted to 4′-methoxy-2-biphenylcarbonyl chloride in 95% yield, mp (hexane) 60.0–61.5°. Reaction of 4.2 g (17 mmol) of the acid chloride with 2.7 g (42 mmol) of sodium azide in the usual manner yielded 2.62 g (64%) of the isocyanate as a colorless liquid: bp 111–112° (0.09 mm); ir (neat) 4.36 (vs), 11.92 (s), 12.30 (m), and 13.0–13.2 μ (vs); uv max (diethyl ether) 228 nm (ε 21,000) and 258 (12,000).

(21) H. E. Zimmerman and S. Somasekhara, *J. Amer. Chem. Soc.*, **85**, 922 (1963); H. E. Zimmerman and V. R. Sandel, *ibid.*, **85**, 915 (1963).

(22) E. Havinga and M. E. Kronenberg, *Pure Appl. Chem.*, **16**, 137 (1968).

(23) G. Smolinsky, *J. Amer. Chem. Soc.*, **83**, 2489 (1961).

(24) G. W. Kenner, M. H. Murray, and C. M. B. Tylor, *Tetrahedron*, **1**, 259 (1957).

(25) M. J. Malawski and T. Drapala, *Rocz. Chem.*, **34**, 1371 (1960).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.64; H, 4.89; N, 6.17.

4-Methoxy-2-biphenylyl Isocyanate (1b).—In a procedure analogous to that of the 2'-methoxy isomer, 10.3 g (52 mmol) of the amine[26] was treated with phosgene to yield 9.0 g (77%) of the isocyanate **1b** as a colorless liquid: bp 113–114° (0.12 mm); mp 25.0–25.5°; ir (neat) 4.38 (vs), 11.00 (m), 13.00 (s), and 14.23 μ (vs); uv max (diethyl ether) 228 nm (ε 18,000) and 257 (11,900).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.70; H, 5.04; N, 6.24.

5-Methoxy-2-biphenylyl Isocyanate (1d).—In an analogous fashion to that of the 2'-methoxy isomer, 8.8 g (44 mmol) of the amine[26] was treated with phosgene to produce 9.6 g (98%) of the isocyanate as a colorless liquid: bp 113–115° (0.13 mm); ir (neat) 4.40 (vs), 12.28 (br, m), 12.95 (s), and 14.24 μ (vs); uv max (diethyl ether) 226 nm (ε 26,000) and 295 (3200).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.25; H, 4.98; N, 6.47.

Preparative Direct Photolyses of Biphenylyl Isocyanates. General.—Direct photolyses of the isocyanates were performed in a stirred reactor under a nitrogen atmosphere with Vycor filtered light from a 450-W Hanovia medium-pressure source. After irradiation the solvent was removed *in vacuo* and the residue was chromatographed on a silica gel (2.3 × 75 cm) column slurry packed in 2% ether in hexane. Elution was carried out with increasing percentages of ether–hexane (E–H) to pure ether (E), 250-ml fractions being collected.

2'-Methoxy-2-biphenylyl Isocyanate (1e).—Photolysis of 0.96 g of the isocyanate in 300 ml of anhydrous ether for 3.5 hr followed by chromatography yielded these results: fraction 1–2, 2% E–H, nil; 3–4, 4% E–H, 0.30 g (33%) of recovered **1e**; 5–6, 8% E–H, nil; 7–8, 16% E–H, nil; 9–11, 16% E–H, 0.12 g (15%) of 4-methoxycarbazole; 12–18, E, 0.37 g (39%) of 2,2'-bis(2-methoxyphenyl)carbanilide; and 19–30, E, 0.08 g (9%) of 10-methoxy-6(5*H*)-phenanthridinone (**3e**): mp (acetone) 297.5–298.0°; ir (KBr) 2.90 (w), 6.03 (s), 6.22 (s), 11.1 (m), 12.23 (m), 12.92 (m), 13.47 (s), 13.59 (s), 14.15 (m), and 14.52 μ (s); uv max (diethyl ether) 233 nm (ε 51,000), 253 (12,000), 262 (11,000), 269 (9700), 278 (7400), 291 (4100), 302 (4900), 318 (7200), 331 (12,600), and 347 (11,700); nmr (100°, dimethyl sulfoxide-d_6) δ 11.30 (broad s, 1 H, –NH), 7.00–9.15 (m, 7 H, aromatic), and 4.06 (s, 3 H, $-OCH_3$).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.63; H, 4.91; N, 6.24.

3'-Methoxy-2-biphenylyl Isocyanate (1f).—Photolysis of 0.96 g of the isocyanate in 300 ml of anhydrous ether for 3.5 hr followed by chromatography gave these results: fraction 1, 20% E–H, 0.19 g (20%) of recovered **1f**; 2–3, 20% E–H, 0.13 g (15%) of 1-methoxycarbazole; 4, 20% E–H, 0.024 g (3%) of a mixture of 1- and 3-methoxycarbazoles; 5–8, 20% E–H, 0.11 g (13%) of 3-methoxycarbazole; 9–20, E, 0.38 g (38%) of 2,2'-bis(3-methoxyphenyl)carbanilide; and 21–36, E, 0.16 g (14%) of 9-methoxy-6(5*H*)-phenanthridinone: mp (acetone) 235–236°; ir (KBr) 2.90 (w), 6.03 (s), 6.23 (s), 11.84 (m), 13.35 (m), and 14.9 μ (m); uv max (diethyl ether) 242 nm (ε 47,000), 266 (16,000), 309 (4600) 320 (5900), and 334 (5700); nmr (100°, dimethyl sulfoxide-d_6) δ 11.0 (broad s, 1 H, –NH), 7.0–8.5 (m, 7 H, aromatic), and 3.98 (s, 3 H, $-OCH_3$).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.53; H, 4.86; N, 6.29.

4'-Methoxy-2-biphenylyl Isocyanate (1c).—Irradiation of 0.84 g of **1c** in 300 ml of anhydrous ether for 3.5 hr resulted in precipitation of a white solid. Concentration of the heterogeneous reaction mixture to 30 ml followed by filtration and washing of the collected white solid with ether afforded 0.19 g of 8-methoxy-6(5*H*)-phenanthridinone (**3c**), mp 271–273° (lit.[27] mp 271–272°). Chromatography of the combined mother liquors on silica gel yielded the following results: fraction 1–14, 8% E–H, nil; 15–17, 60% E–H, 0.144 g (20%) of 2-methoxycarbazole as a white solid; 18–24, 60% E–H, 0.40 g (46%) of 2,2'-bis(4-methoxyphenyl)carbanilide as a white solid; 25–27, E, nil; 28–33, E, 0.05 g of 8-methoxy-6(5*H*)-phenanthridinone as a white solid: mp (acetone) 271.5–273.0°; ir (KBr) 2.90 (w), 6.00 (s), 6.21 (s), 11.92 (m), 13.30 (s), 13.52 (w), 13.98 (w), and 14.35 μ (w); uv max (diethyl ether) 228 nm (ε 46,000), 233 (sh, 44,000), 242 (sh, 20,000), 264 (18,000), 272 (sh, 13,000), 280 (sh, 10,000), 312 (10,500), 328 (9600), and 343 (7600); nmr (100°, dimethyl sulfoxide-d_6) δ 11.10 (broad s, 1 H, –NH), 7.1–8.5 (m, 7 H, aromatic), and 3.97 (s, 3 H, $-OCH_3$).

4-Methoxy-2-biphenylyl Isocyanate (1b).—A stirred solution of 0.76 g of **1b** in 300 ml of dry diethyl ether was irradiated for 3.5 hr. After 1.75 and after 3.5 hr, the solution was filtered to remove the phenanthridinone which had formed (0.263 g). Chromatography yielded the following results: fractions 1–4, 4% E–H, nil; 5–8, 8% E–H, nil; 9–12, 16% E–H, 0.10 g (15%) of 2-methoxycarbazole; 13–18, E, 0.27 g (34%) of 5,5'-dimethoxy-2,2'-diphenylcarbanilide as a white solid; 19, E, nil; 20–31, E, 0.16 g (a total yield of 55%) of 3-methoxy-6(5*H*)-phenanthridinone (**3b**) as a white solid: mp (acetone) 255–256° (lit.[27] mp 251°); ir (KBr) 2.90 (w), 5.97 (vs), 6.22 (s), 13.00 (vs), and 13.86 μ (m); uv max (diethyl ether) 228 nm (ε 52,000), 237 (sh, 40,000), 246 (sh, 23,000) 263 (15,000), 278 (12,500), 312 (11,600), 325 (13,400), and 339 (9800); nmr (100°, dimethyl sulfoxide-d_6) δ 11.19 (broad s, 1 H, –NH), 6.75–8.40 (m, 7 H, aromatic), and 3.90 (s, 3 H, $-OCH_3$).

5-Methoxy-2-biphenylyl Isocyanate (1d).—Photolysis of 0.81 g of the isocyanate in 300 ml of anhydrous ether for 3.5 hr followed by chromatography on silica gel gave the following results: fractions 1–7, 4% E–H, nil; 8–12, 16% E–H, 0.12 g (17%) of 3-methoxycarbazole; 13–20, E, 0.53 g (63%) of 4,4'-dimethoxy-2,2'-diphenylcarbanilide; 21–23, E, nil; 24–40, E, 0.164 g (20%) of 2-methoxy-6(5*H*)-phenanthridinone as a white solid: mp (acetone) 231–232°; ir (KBr) 2.89 (w), 5.99 (s), 6.22 (s), 12.32 (m), 13.01 (s), and 14.73 μ (m); uv max (diethyl ether) 227 nm (ε 43,000), 233 (38,000), 242 (22,000), 264 (12,700), 273 (10,500), 343 (8500), and 357 (6930); nmr (100°, dimethyl sulfoxide-d_6) δ 11.11 (broad s, 1 H, –NH), 7.0–8.5 (m, 7 H, aromatic), and 3.93 (s, 3 H, $-OCH_3$).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.55; H, 4.86; N, 6.19.

Preparative Sensitized Irradiations of 2-Biphenylyl Isocyanates. General.—All sensitized irradiations were performed under an atmosphere of purified nitrogen in 300 ml of acetone using Corex filtered light from a 450-W medium-pressure source. Chromatographic separations were carried out as described for the direct irradiations unless otherwise noted.

2'-Methoxy-2-biphenylyl Isocyanate (1e).—A stirred solution of 0.92 g of the isocyanate was irradiated for 3.5 hr and the reaction mixture was chromatographed on silica gel. There was recovered 0.03 g (4%) of carbazole **2e**, 0.60 g (63%) of the carbanilide, and 0.09 g (10%) of the phenanthridinone **3e**. Prolonged irradiation did not lead to markedly different conversions.

3'-Methoxy-2-biphenylyl Isocyanate (1f).—Irradiation of 0.70 g of the isocyanate for 3.5 hr followed by chromatography of the reaction, gave 0.04 g (5%) of recovered isocyanate, 0.02 g (3%) of a mixture of carbazoles, 0.62 g (84%) of carbanilide, and 0.11 g (15%) of 9-methoxy-6(5*H*)-phenanthridinone (**3f**). Prolonged irradiation did not lead to substantially increased yields of cyclization product.

4'-Methoxy-2-biphenylyl Isocyanate (1c).—Irradiation of 0.80 g of the isocyanate led to rapid formation of phenanthridinone, which was filtered from the solution every 1.5 hr. After a total irradiation time of 6 hr, concentration of the acetone solution resulted in crystallization of additional phenanthridinone for a total yield of 0.73 g (91%) of **3c**, mp 271–273°.

4-Methoxy-2-biphenylyl Isocyanate (1b).—Irradiation of 0.72 g of the isocyanate for 3.5 hr followed by filtration of the precipitated phenanthridinone yielded 0.61 g of pure product. Chromatography yielded an additional 0.11 g for a total yield of 0.77 g (100%) of **3b**.

5-Methoxy-2-biphenylyl Isocyanate (1d).—Irradiation of 0.82 g of the isocyanate for 3.5 hr resulted in precipitation of 0.61 g of the phenanthridinone **3d**. Chromatography of the residue yielded 0.05 g of the carbanilide and 0.14 g of **3d**, a total yield of 0.75 g (91%).

Irradiation of 2-Biphenylyl Isocyanate in the Presence of Piperylene.—An acetone solution, 0.10 *M* in isocyanate and 0.08 *M* in piperylene, was prepared by dilution of 0.4885 g of isocyanate to 25 ml with a stock solution of freshly distilled piperylene in anhydrous acetone (0.551 g of piperylene in 100 ml of acetone). A 15-ml portion of this solution was transferred to a Pyrex test tube, degassed, sealed, and irradiated simultaneously with 15 ml of 0.1 *M* isocyanate in acetone containing no piperylene. The photolysis was performed for 1.5 hr in a merry-go-round apparatus with light from 16 RPR-3000 Å lamps. After irradiation the solvent was removed *in vacuo* and the residual oil

(26) P. A. S. Smith and J. H. Hall, *J. Amer. Chem. Soc.*, **84**, 480 (1962).
(27) L. P. Walls, *J. Chem. Soc.*, 1405 (1935).

was dissolved in anhydrous ether and diluted to an appropriate volume. Ultraviolet analysis as for the quantum yield determinations showed the production of 0.7% of phenanthridinone in the tube containing piperylene and 4% production of phenanthridinone in neat acetone. In an analogous series of experiments, quenching irradiations were performed on acetone solutions 1.0 *M* in piperylene and 0.08 *M* in isocyanate. These solutions were irradiated as above for 30 min. Ultraviolet analysis showed the production of 0.09% phenanthridinone in the solution containing piperylene while 1.5% of phenanthridinone was formed in neat acetone. Both in the presence and absence of piperylene measurable amounts of carbazole (<0.001%) could not be detected.

Irradiation of 6(5*H*)-Phenanthridinone (3a) at 254 nm.—A solution of 0.101 g (0.51 mmol) of **3a** in dry diethyl ether (60 ml) in a quartz tube was degassed for 5 min with purified nitrogen and irradiated for 6 hr in a Rayonet apparatus equipped with RPR 2537 Å lamps. Tlc indicated an absence of carbazole (**2a**) where less than 0.5 mg easily would have been detected. Removal of the solvent left a white solid, mp (before crystallization) 295–296° (lit.[3a] mp 295–296° for **3a**).

Quantum Yield Determinations for Biphenylyl Isocyanates. Acetone Sensitized Photolyses.—The quantum yields for acetone sensitizations were determined on 10^{-1} to 10^{-2} *M* solutions of the isocyanate in acetone using 16 RPR-3000 Å lamps and potassium ferrioxalate as actinometer in a merry-go-round assembly. In a typical determination the acetone solutions under nitrogen in quartz test tubes (13.5 ml of solution) were simultaneously irradiated with the actinometer (quartz test tube). The quantum yields for products were essentially invariant from 1 to 15% conversion. Owing to the difficult analysis for disappearance of starting material at very low conversion, $\Phi_{isocyanate}$ was determined only in the 10–15% conversion runs. Later, when a high intensity grating monochromator became available, spot checks of the quantum yields determined on the Rayonet were made. These determinations were found to be within ±15% of those using the unfiltered light from the RPR-3000 Å source. The quantum yields for products reported in Table III represent the average of 3–7 measurements, while those for the isocyanate disappearance are the average of two determinations.

Direct Photolyses at 254 nm.—The quantum yields were determined with light from 16 RPR-2537 Å lamps in a Rayonet photochemical reactor essentially as described for the sensitization runs. The measurements were performed on 10^{-1} to 10^{-2} *M* solutions of isocyanate under nitrogen in quartz test tubes (13.5 ml of solution). The quantum yields reported in Table II were determined at 1–10% conversion and showed no dramatic time dependence. The reported values represent the average of at least four measurements at different per cent conversions.

Analytical Procedure for Quantum Yields.—The analysis for unreacted isocyanate and carbazole was by flame ionization vpc (5 ft × 0.125 in., 5% SE-30 on 100–120 mesh Varaport 30) at 150–200° (depending on the isocyanate) using added benzophenone, fluorenone, or dimethyl diphenate as internal standard. The instrument was calibrated immediately prior to analysis using known mixture of the isocyanate, carbazole, and internal standard closely approximating the photolysis mixture. The amount of phenanthridinone was determined by uv analysis correcting for the known amount of carbazole in the irradiated solution. The average value of phenanthridinone present, determined from analysis at a minimum of two wavelengths, was used for calculating the quantum yield of phenanthridinones.

***N*-(2-Propylidene)-2-aminobiphenyl (5a).**—The following is typical of that used for preparation of the imines used in this work. A solution of 10.0 g (60 mmol) of 2-aminobiphenyl in 50 ml of acetone was refluxed with stirring over molecular sieves for 1 hr. The progress of imine formation was followed by vpc (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh Varaport 30) at 190°. After filtration and solvent removal *in vacuo*, 50 ml of hexane and an equivalent of phenyl isocyanate, as determined assuming equal thermal combustibility of amine to imine, was added to remove unreacted 2-aminobiphenyl. The solution was warmed for 5 min, cooled to 0°, and then filtered to remove the urea. After solvent removal *in vacuo*, the residue was distilled to afford 6.3 g (50%) of a slightly yellow viscous oil, **5a**: bp 94–95° (0.07 mm); λ_{max}^{EtOEt} 245 nm (ε 14,000), 283 (4600); ir (neat) 3.28 (s, broad), 6.00 (s), 6.25 (s), 6.70 (m), 6.80 (s), 7.00 (s), 7.24 (s), 8.10 (s), 8.23 (s), 8.67 (m), 9.03 (m), 9.34 (m), 9.62 (m), 9.93 (m), 10.92 (m), 11.80 (m), 12.55 (s), 12.91 (s), 13.4 (s, broad), 13.92 (m), and 14.30 μ (s, broad); nmr (CCl_4) δ 1.38 (s, 3 H), 1.87 (s, 3 H), 6.61 (m, 1 H), and 6.9–7.4 (m, 8 H). Exact mass measurement: theoretical 209.1204; observed 209.1201.

***N*-(2-Propylidene)-4'-methoxy-2-aminobiphenyl (5d).**—A solution of 5.06 g (25 mmol) of 4'-methoxy-2-aminobiphenyl in 25 ml of acetone was refluxed over 5 g of molecular sieves for 1 hr. After filtration and solvent removal *in vacuo*, the residue was distilled to yield 4.2 g (70%) of a slightly yellow viscous oil, **5d**. The product contained a slight trace (<3%) of starting material as analyzed by vpc (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh Varaport 30) at 190°: bp 121–125° (0.03–0.04 mm); ir (neat) 3.19 (m), 3.31 (m), 6.04 (s), 6.23 (s), 6.31 (m), 6.40 (m), 6.48 (m), 6.68 (s), 6.86 (s), 7.05 (s), 7.26 (m), 7.47 (s), 7.87 (s), 8.07 (s), 8.30 (s, broad), 8.63 (s), 9.28 (m), 9.85 (s, broad), 10.06 (m), 10.21 (m), 12.10 (s, broad), 12.56 (m), 12.66 (s), 13.30 (s, broad), 13.46 (s), and 14.50 μ (w, broad); nmr (CCl_4) δ 1.43 (s, 3 H), 1.92 (s, 3 H), 3.67 (s, 3 H), and 6.5–7.5 (m, broad, 8 H). Exact mass measurement: theoretical 239.1310; observed 239.1305.

***N*-(2-Propylidene)-2'-methoxy-2-aminobiphenyl (5b).**—A mixture of 3.9 g (20 mmol) of 2'-methoxy-2-aminobiphenyl, 5 g of molecular sieves, and 25 ml of acetone was refluxed for 1 hr. After filtration and solvent removal *in vacuo*, the residue was distilled to yield 2.72 g (60%) of a slightly yellow, viscous oil, **5b**: bp 118–122° (0.08 mm); product contained a slight impurity (<5%) as analyzed by vpc (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh on Varaport 30) at 172°; ir (neat) 3.44 (m, broad), 6.00 (s), 6.24 (m), 6.70 (s), 6.84 (s), 7.02 (s), 7.36 (s), 8.05 (s, broad), 8.95 (m), 9.54 (m), 9.76 (s), 10.00 (m), 12.60 (m, broad), and 13.30 μ (s, broad); nmr (CCl_4) δ 1.50 (s, 3 H), 1.80 (s, 3 H), 3.60 (s, 3 H), and 6.5–7.5 (m, broad, 8 H). Exact mass measurement: theoretical 239.1310; observed 239.1305.

***N*-(2-Propylidene)-3'-methoxy-2-aminobiphenyl (5c).**—A solution of 8.71 g (40 mmol) of 3'-methoxy-2-aminobiphenyl was dissolved in 25 ml of acetone. To this was added 5 g of molecular sieves and the solution was refluxed for 0.5 hr. An additional 5 g of molecular sieves was added and the solution was refluxed for an additional 0.5 hr. The solution was filtered and the solvent was removed by distillation. The remaining viscous residue was distilled [bp 124–126° (0.10 mm)] to yield 8.87 g (85%) of a slightly yellow, viscous oil, **5c**: product contained <1% starting material by vpc analysis (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh Varaport 30) at 165°; ir (neat) 3.40 (m, broad), 6.02 (s), 6.25 (s), 6.82 (s), 7.04 (s), 7.35 (s), 7.71 (s), 7.92 (s), 8.06 (s), 8.25 (s), 8.54 (s), 9.55 (s), 9.81 (s), 11.50 (m, broad), 12.68 (s, broad), 13.30 (s, broad), and 14.32 μ (m, broad); nmr (CCl_4) δ 1.45 (s, 3 H), 1.90 (s, 3 H), 3.68 (s, 3 H), and 6.5–7.5 (m, 8 H). Exact mass measurement: theoretical 239.1310; observed 239.1312.

Sensitized Irradiation of *N*-(2-Propylidene)-2-aminobiphenyl (5a).—A solution of 1.10 g (5.2 mmol) of **5a** in 150 ml of acetone was irradiated for 11 hr under a nitrogen atmosphere. The reaction was monitored by vpc analysis (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh Varaport 30) at 190° until no more starting material was detected as reacting (<10% remained as unreacted). The solvent was removed *in vacuo* from a slightly yellow reaction mixture and the dark, oily residue was chromatographed on a silica gel (3 × 50 cm) column slurry packed in 2% ether–hexane (E–H). Elution proceeded as follows: 900 ml, 2% E–H, nil; 1250 ml, 5% E–H, 0.72 g of a yellow oil which solidified. The product was then sublimed (100°, 0.10 mm) to afford 0.72 g (66%) of a yellow, crystalline solid, mp 96–98°. A portion was then recrystallized from hexane to yield white, crystalline 6,6-dimethyl-5,6-dihydrophenanthridine (**6a**): mp 102–103° (lit.[5d] mp 104–105°); ir (KBr) 6.24 (m), 6.73 (m), 6.96 (s), 13.07 (s), 13.28 (s), 13.39 (s), and 13.78 μ (s); nmr (CCl_4) δ 1.38 (s, 6 H), 3.45 (s, broad, 1 H), 6.2–7.2 (m, 6 H), and 7.55 (m, 2 H).

Anal. Calcd for $C_{15}H_{15}N$: C, 86.12; H, 7.18; N, 6.70. Found: C, 86.18; H, 7.48; N, 6.66.

Sensitized Irradiation of *N*-(2-Propylidene)-4'-methoxy-2-aminobiphenyl (5d).—A solution of 1.01 g (4.2 mmol) of **5d** in 150 ml of acetone was irradiated for 1 hr under a nitrogen atmosphere. After solvent removal *in vacuo* the dark, oily residue was impregnated on 10 g of silica gel and chromatographed on a silica gel (3 × 50 cm) column slurry packed in 2% ether–hexane. Elution proceeded as follows: 1 l. 2% E–H, nil; 1 l., 5% E–H, 0.04 g of a yellow oil; 1.25 l., 10% E–H, 0.74 g (74%) of a yellow oil which solidified, mp 95–100°. The solid was then sublimed (100°, 0.05 mm) to yield 0.73 g (73%) of **6d**, mp 103–106°. Recrystallization of this material from hexane yielded 8-methoxy-6,6-dimethyl-5,6-dihydrophenanthridine (**6d**) as a

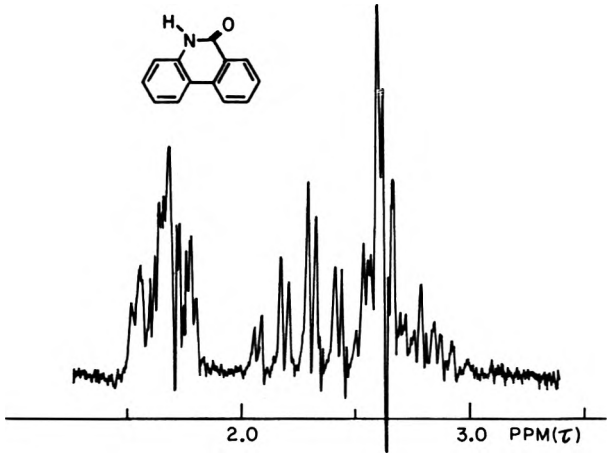


Figure 1.—Nmr spectrum of 6(5*H*)-phenanthridinone (**3a**) in the aromatic region.

white, crystalline solid: mp 108–109°; ir (KBr) 3.38 (m, broad), 6.21 (m), 7.06 (m), 7.68 (s), 7.78 (s), 8.20 (s), 8.48 (m), 9.56 (m), 9.63 (m), 11.42 (m), 12.13 (m), 13.08 (m), 13.43 (s), and 13.72 μ (m); nmr (CCl_4) δ 1.39 (s, 6 H), 3.61 (s, broad, 1 H), 3.74 (s, 3 H), 6.4–7.2 (m, broad, 5 H), and 7.45–7.7 (m, broad, 2 H).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.33; H, 7.11; N, 5.86. Found: C, 80.14; H, 7.13; N, 5.69.

Sensitized Irradiation of *N*-(2-Propylidene)-2′-methoxy-2-aminobiphenyl (5b).—A solution of 0.91 g (3.8 mmol) of **5b** in 150 ml of acetone was irradiated for 1.5 hr under a nitrogen atmosphere. The progress of the reaction was monitored by vpc analysis (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh Varaport 30) at 170°. After 1 hr the reaction had proceeded to greater than 90% conversion. After solvent removal *in vacuo*, a dark oil remained which was impregnated on 10 g of silica gel and chromatographed on a silica gel (3 × 48 cm) column slurry-packed in 10% ether–hexane. Elution proceeded as follows: 250 ml, 10% E–H, nil; 250 ml, 10% E–H, 0.08 g of a yellow oil which solidified, impure by vpc analysis; 1 l., 10% E–H, 0.65 g (72%) of a yellow oil which solidified pure as analyzed by vpc. The solid was then sublimed (100°, 0.02 mm) and recrystallized from hexane to yield 0.62 g (68%) of 10-methoxy-6,6-dimethyl-5,6-dihydrophenanthridine (**6b**): mp 108–109°; ir (KBr) 2.98 (m), 3.40 (m), 6.23 (m), 6.36 (m), 6.73 (m), 6.86 (s), 7.00 (s), 7.27 (m), 7.39 (m), 7.64 (m), 7.71 (m), 7.94 (s, broad), 8.36 (m), 8.45 (m), 8.58 (m), 8.74 (m), 9.50 (s), 8.60 (s), 10.01 (m), 10.67 (m), 12.55 (s), 13.20 (s, broad), and 13.83 μ (s); nmr (CCl_4) δ 1.38 (s, 6 H), 3.56 (s, broad, 1 H), 3.74 (s, 3 H), 6.5–7.4 (m, broad, 6 H), and 8.2–8.4 (m, 1 H).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.33; H, 7.11; N, 5.86. Found: C, 80.16; H, 7.15; N, 5.83.

Sensitized Irradiation of *N*-(2-Propylidene)-3′-methoxy-2-aminobiphenyl (5c).—A solution of 1.04 g (5.0 mmol) of **5c** in 150 ml of acetone was irradiated for 1 hr under a nitrogen atmosphere. The reaction was monitored by vpc (5 ft × 0.125 in., 5% SE-30 on 100/120 mesh Varaport 30) at 170° and was complete within 1 hr. From vpc analysis, two products were produced in the ratio of 2.86:1. The solvent was removed *in vacuo* from a slightly yellow reaction mixture and the dark, oily residue was chromatographed on silica gel. There were isolated two products in low yield. Owing to the low yield and the difficulty of purification, further work was not attempted.

1-(4′-Methoxy-2-biphenylcarbonyl)aziridine.[28]—To a rapidly stirred mixture of 20 ml of benzene, 0.65 g of sodium hydroxide, 25 g of crushed ice, and 1.70 g (39 mmol) of ethylene imine was added dropwise a solution of 0.95 g (3.9 mmol) of 2-(4-methoxyphenyl)benzoyl chloride in 10 ml of benzene. After the reaction mixture had warmed to room temperature, the phases were separated. The organic phase and ether washings of the aqueous phase were combined and dried over sodium sulfate. Removal of the solvent *in vacuo* yielded a light yellow solid which was recrystallized from ethanol to yield 0.8 g of the amide as white crystals: mp 126–128°; ir (KBr) 5.99 (s), 7.41 (s), 8.07 (s), 11.88 (s), and 13.02 μ (s); nmr ($CDCl_3$) δ 2.07 (s, 4 H), 3.85 (s, 3 H), and 6.8–8.0 (m, 8 H).

(28) H. Heine, M. Fetter, and E. Nicholson, *J. Amer. Chem. Soc.*, **81**, 2202 (1959).

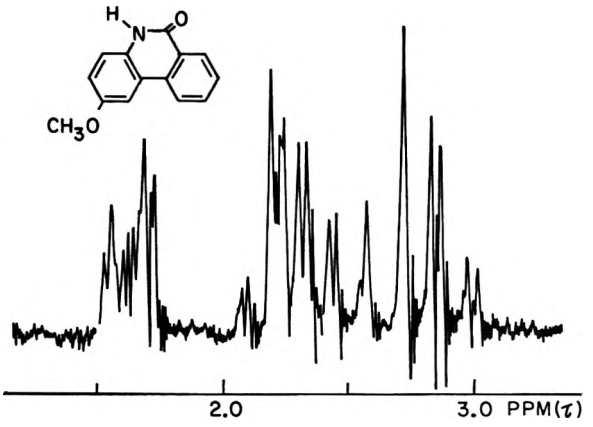


Figure 2.—Nmr spectrum of 2-methoxy-6(5*H*)-phenanthridinone (**3d**) in the aromatic region.

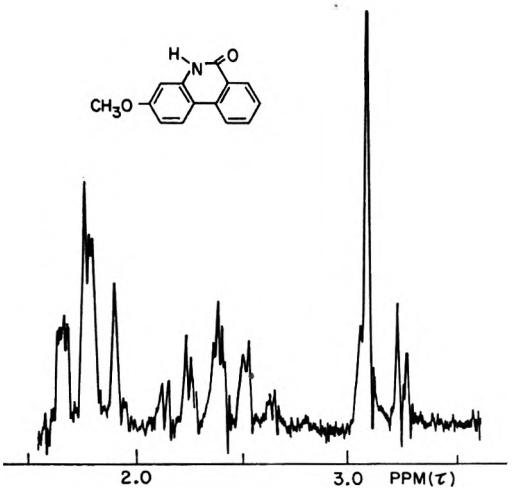


Figure 3.—Nmr spectrum of 3-methoxy-6(5*H*)-phenanthridinone (**3b**) in the aromatic region.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.67; H, 5.97; N, 5.53. Found: C, 75.41; H, 5.98; N, 5.50.

2-(4′-Methoxy-2-biphenyl)-2-oxazoline (8).—A solution of 2.30 g of sodium iodide and 1.06 g (4.2 mmol) of the aziridine in 100 ml of acetone was refluxed for 44 hr with protection from moisture. Work-up yielded a viscous yellow oil. Chromatography of this material on silica gel (ether–benzene elution) followed by molecular distillation yielded 1.5 g (65%) of a colorless, viscous oil, **8**: ir (neat) 6.05 (s), 8.08 (s), 8.52 (s), 9.67 (s), 10.67 (s), 12.02 (s), and 13.15 μ (s); nmr ($CDCl_3$) δ 3.86 (s, 3 H), 4.08 (center of A_2B_2, 4 H), and 6.8–8.0 (m, 8 H).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.67; H, 5.97; N, 5.53. Found: C, 75.24; H, 6.03; N, 5.55.

4′-Methoxy-*N*-methyl-2-biphenylcarboxamide.—The amide was prepared in the usual fashion by treating the acid chloride with methylamine. Recrystallization of the crude material from benzene gave white crystals: mp 133.0–134.5°; ir (KBr) 6.10 (s), 6.25 (s), 7.15 (s), 9.95 (s), 9.72 (s), and 13.09 μ (s); nmr ($CDCl_3$) δ 2.66 (d, J = 5 Hz, 3 H), 3.81 (s, 3 H), 5.5 (br s, 1 H), and 6.8–7.7 (m, 8 H).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.20; H, 6.21; N, 5.75.

Ethyl 4′-Methoxy-*N*-methyl-2-biphenylcarboximidate (7).—To a stirred, cold (0°) solution of 1.90 g (10.0 mmol) of triethyloxonium tetrafluoroborate in 50 ml of dry methylene chloride was added a solution of 2.0 g (8.3 mmol) of amide 19 in 10 ml of methylene chloride dropwise. The reaction mixture was stirred for 12 hr at room temperature followed by addition of 3 ml of 50% aqueous potassium carbonate, filtration, and evaporation of the solvent. The resulting crude oil was passed through a Florisil column (ether–benzene elution) and the resulting colorless oil (1.1 g, 49%) was stored under nitrogen. Further purification by either short-path distillation or preparative vpc resulted in

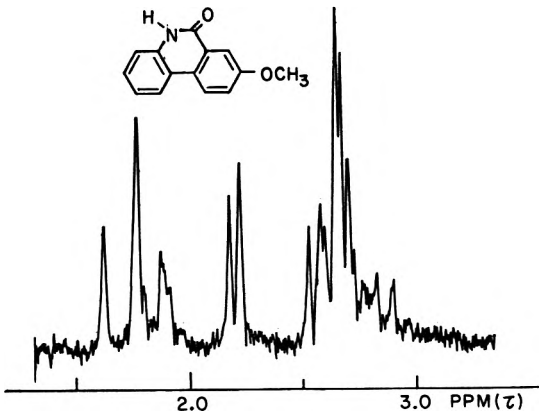


Figure 4.—Nmr spectrum of 8-methoxy-6(5*H*)-phenanthridinone (**3c**) in the aromatic region.

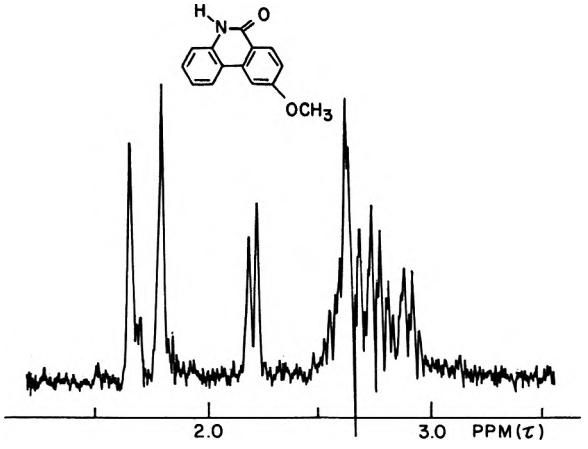


Figure 5.—Nmr spectrum of 9-methoxy-6(5*H*)-phenanthridinone (**3f**) in the aromatic region.

partial decomposition of the sample. The column-chromatographed material was homogeneous by vpc and showed ir (neat) 5.97 (s), 7.84 (s), 8.05 (s), 9.62 (s), 12.02 (s), and 13.4 (s); nmr ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 2.66 (s, 3 H), 3.81 (s, 3 H), 4.19 (q, J = 7 Hz, 2 H), and 6.8–7.5 (m, 8 H). Exact mass measurement: theoretical 269.1415; observed 269.1409.

Nmr Assignments of Phenanthridinone from 3′-Methoxy-2-biphenylyl Isocyanate.—An empirical table of chemical shifts for the 6(5*H*)-phenanthridinone aromatic hydrogens was constructed for the nmr spectra of the unsubstituted, 2-, 3-, 7-, 8-, 9-, and 10-methoxy compounds (Table IV). Good agreement with observed values (Figures 1–6) was obtained by assigning base values to the chemical shifts for the protons in **3a**: τ 1.7 region, H_1 and H_{10} (deshielding by the ring), H_7 (deshielding by the amide carbonyl); τ 2.3 region, H_8 and H_9; τ 2.6 region, H_2, H_3, and H_4. The observed chemical shift values of the remaining compounds, 2-, 3-, 8-, 9-, and 10-methoxy, were in good agreement with those calculated by assuming that the methoxy group would shield ortho protons by approximately τ 0.5 and meta protons by about τ 0.1.

The nmr spectrum of the product from irradiation of 3′-methoxy-2-biphenylyl isocyanate showed a two-proton doublet at τ 1.7 (J = 9 Hz), a one-proton doublet at 2.3 (J = 3 Hz), and a multiplet at 2.5–2.9. This nmr is most consistent with **3f**, since it shows two protons in the τ 1.7 region having ortho coupling and one proton in the τ 2.2 region showing meta coupling. Structure **3f′** would be expected to show only two protons below τ 2.3. In agreement with this assignment irradiation of the protons at τ 1.7 simplified the τ 2.8 region. Likewise, when irradiation was carried out in the τ 2.8 region, the doublets at 1.7 and 2.3 collapsed to singlets. It was concluded that this cyclization product was the 9-methoxy-6(5*H*)-phenanthridinone (**3f**).

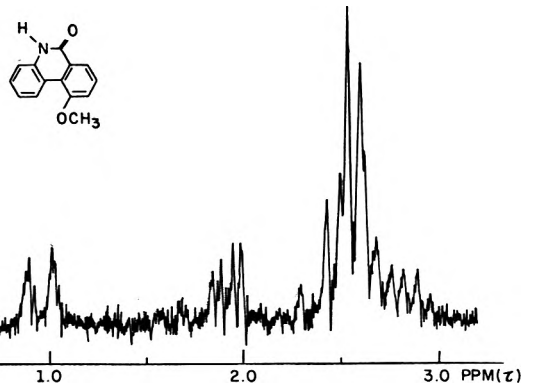
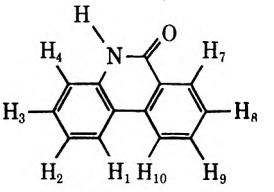


Figure 6.—Nmr spectrum of 10-methoxy-6(5*H*)-phenanthridinone (**3e**) in the aromatic region.

TABLE IV

EXPECTED τ VALUES FOR THE AROMATIC HYDROGENS IN SUBSTITUTED 6(5*H*)-PHENANTHRIDINONES



Compd	H_1	H_2	H_3	H_4	H_7	H_8	H_9	H_{10}
Unsubstituted (**3a**)	1.7	2.6	2.6	2.6	1.7	2.3	2.3	1.7
2-Methoxy (**3d**)	2.2		3.1	2.7	1.7	2.3	2.3	1.7
3-Methoxy (**3b**)	1.8	3.1		3.1	1.7	2.3	2.3	1.7
7-Methoxy (**3f′**)	1.7	2.6	2.6	2.6		2.8	2.4	1.7
8-Methoxy (**3c**)	1.7	2.6	2.6	2.6	2.2		2.8	1.8
9-Methoxy (**3f**)	1.7	2.6	2.6	2.6	1.8	2.8		2.2
10-Methoxy (**3e**)	1.7	2.6	2.6	2.6	1.7	2.4	2.8	

Registry No.—**1a**, 17337-13-2; **1b**, 38088-88-9; **1c**, 38088-89-0; **1d**, 38088-90-3; **1e**, 38088-91-4; **1f**, 38088-92-5; **3a**, 1015-89-0; **3b**, 38088-94-7; **3c**, 38088-95-8; **3d**, 38088-96-9; **3e**, 38088-97-0; **3f**, 38088-98-1; **3f′**, 38088-99-2; **4a**, 90-41-5; **4b**, 1206-76-4; **4c**, 38089-02-0; **4d**, 38089-03-1; **5a**, 29666-58-8; **5b**, 38089-05-3; **5c**, 38089-06-4; **5d**, 38087-93-3; **6b**, 38165-84-3; **6d**, 38087-94-4; **7**, 38087-95-5; **8**, 38087-92-2; acetone, 67-64-1; 3′-methoxy-2-biphenylcarboxylic acid, 38087-96-6; 3′-methoxy-2-biphenylcarbonyl chloride, 38087-97-7; 4′-methoxy-2-biphenylcarboxylic acid, 18110-71-9; 4′-methoxy-2-biphenylcarbonyl chloride, 38087-99-9; 4-methoxy-2-biphenylamine, 38088-00-5; 5-methoxy-2-biphenylamine, 38088-01-6; 1-(4′-methoxy-2-biphenylcarbonyl)aziridine, 38088-02-7; 4′-methoxy-*N*-methyl-2-biphenylcarboxamide, 35158-67-9.

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Derivatives of 1,8-Diphenylanthracene[1]

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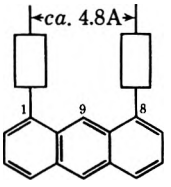
Two additional polyphenylated anthracenes, the 1,8,10-triphenyl derivative **5** and the 1,8,9,10-tetraphenyl derivative **6**, have been prepared by reaction of the diphenylquinone **2** with phenyllithium followed by reduction and dehydration. Mononitration of 1,8-diphenylanthracene (**1d**) yielded the 10-nitro derivative **13**. Derivatives **12** of 1,8-diphenylanthracene with a substituent at C-9, a location allowing interaction of the substituent with the π orbitals of the two phenyl rings, were obtained by the methylation or acetylation of the anthrone **11**. Studies of the oxidation and reduction of the various hydrocarbons **1**, **5**, **6**, and **20** by polarography and cyclic voltammetry provided a measure of the relative ease of adding or removing one or more electrons from these hydrocarbons. In general, the cation radicals and dianions formed were relatively unstable, but the anion radicals had substantial lifetimes even in partially aqueous solutions.

In earlier publications,[2] we have described the preparation of various derivatives of anthracene **1** and naphthalene **20** with phenyl substituents in one or more of the peri positions C-1, C-8, and C-9.[3] Of special interest were those compounds **1c**, **1e**, and **20b** with two or more adjacent phenyl substituents held in a sterically crowded face-to-face relationship to one another and 1,8-phenylanthracene (**1d**), a molecule that exists primarily in a conformation (see Chart I) with the two phenyl rings approximately perpendicular to the plane of the anthracene ring. This latter molecule offers the interesting possibility that appropriate substituents at C-9 will be in an environment that is shielded from attack by external reagents and yet in a favorable location for interaction with the π orbitals of the two phenyl rings. This paper describes several methods that we have explored for the introduction of substituents at the 9 position of the 1,8-diphenylanthracene system and describes certain physical properties of the derivatives prepared by us.

CHART I

CONFORMATION OF 1,8-DIPHENYLANTHRACENE (1d)



The most useful intermediate that we have found for preparing various 1,8-diphenylanthracene derivatives is the diphenylquinone **2** (Scheme I), prepared from the diodide **19d** and a lithium di- or triphenylcuprate.[2] Several other possible synthetic precursors (Chart II), including **18**, **19b**, and **19c**, were prepared but were found to be less satisfactory than the diiodoquinone **19d**. As expected from earlier reduction studies,[2] reaction of the quinone **2** with a limited amount of phenyllithium introduced a phenyl group at the less hindered C-10 carbonyl group to form the keto alcohol **3**. With excess phenyllithium the diol **4** became the major product. Each of these alcohols **3** and **4** could be reduced and dehydrated to form the polyphenylanthracene derivatives **5** and **6**. The nmr spectra of these derivatives (see Experimental Section) were analogous to those observed previously[2] for the phenylanthracene derivatives **1d** and **1e**. In the triphenyl

SCHEME I

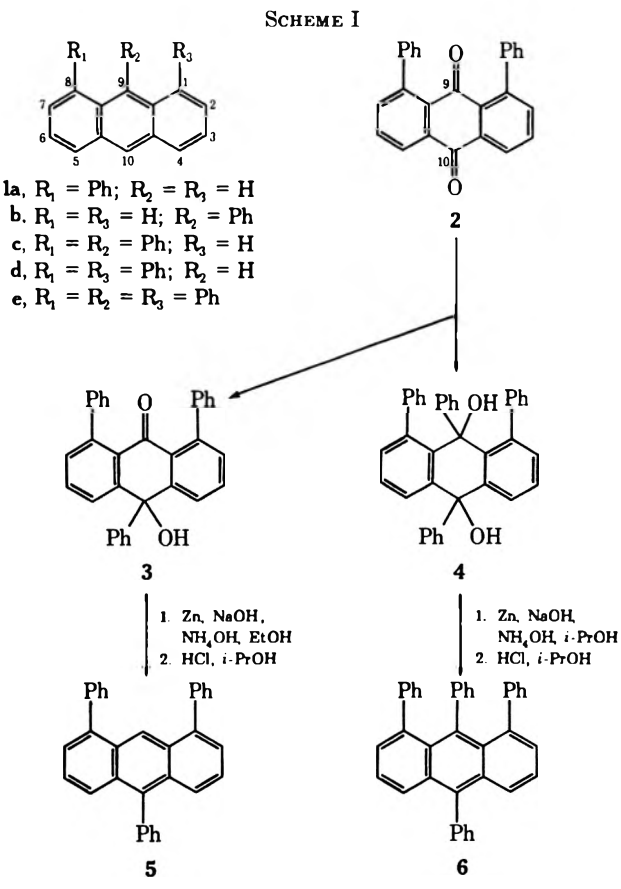
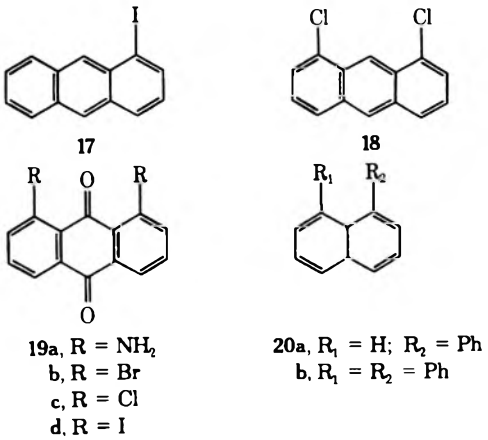


CHART II



(1) This research has been supported by Public Health Service Grant No. RO1-CA-12634 from the National Cancer Institute.

(2) H. O. House, D. G. Koepsell, and W. J. Campbell, *J. Org. Chem.*, **37**, 1003 (1972), and references cited therein.

(3) For a review of the properties of naphthalenes with peri substituents, see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

derivative **5**, with no phenyl rings in a crowded face-to-face arrangement, all of the phenyl signals were at relatively low field (δ 7.1–7.9) analogous to the spectrum observed for 1,8-diphenylanthracene (**1d**). In the tetraphenyl derivative **6**, the signal for one phenyl group (at C-10) was in the usual low-field location (δ 7.60) but the remaining three phenyl groups (at C-1, C-8, and C-9) exhibited relatively high-field signals (δ 6.3–6.9) analogous to the spectrum observed for 1,8,9-triphenylanthracene (**1e**).

One satisfactory method for preparing 1,8-diphenylanthracene derivatives with C-9 substituents consisted of the O-methylation or the O-acetylation of the anthrone **11** to form the derivatives **12** (Scheme II). Table I summarizes the locations of the nmr methyl

SCHEME II

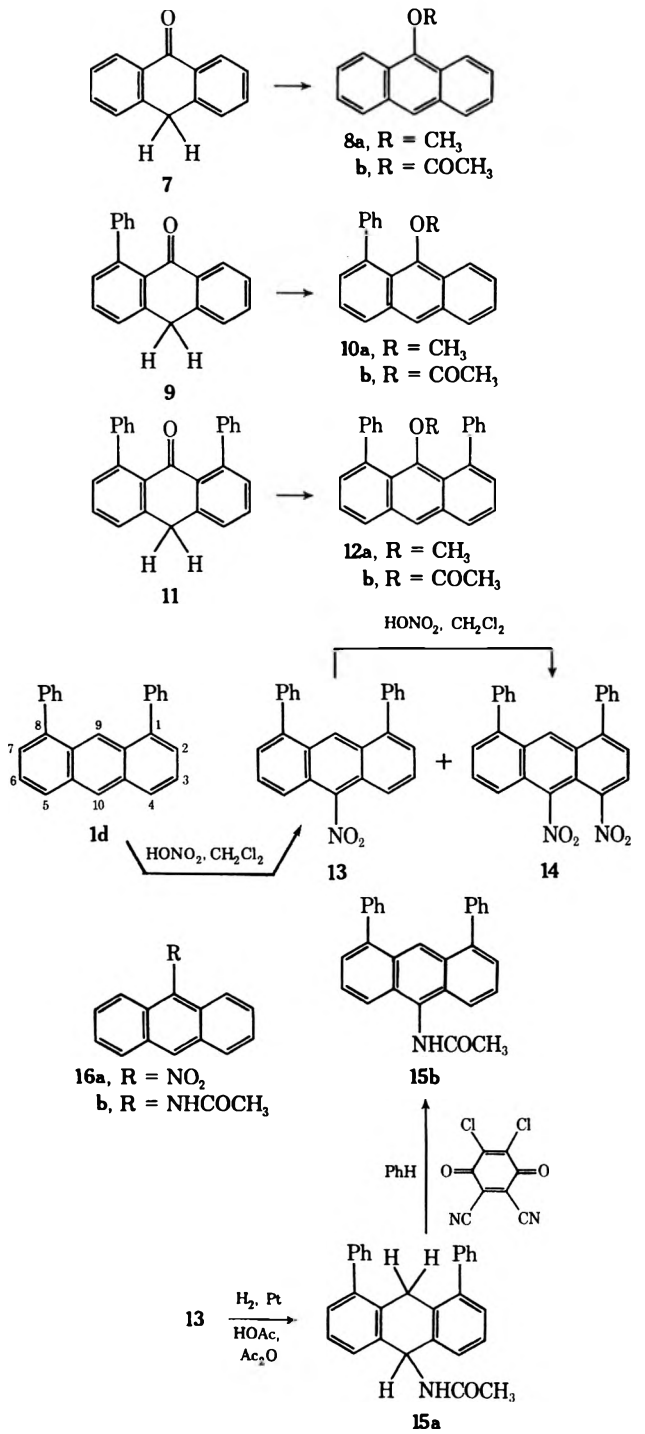


TABLE I

NMR METHYL SIGNALS FOR THE 9-METHOXYANTHRACENES AND THE 9-ACETOXYANTHRACENES

Functional group	δ values (CDCl3 solutions) 8	10	12
CH_3CO_2	2.53	1.52	0.28
CH_3O	4.10	3.25	2.37

signals for the C-9 methoxy or acetoxyl substituent when two (**12**), one (**10**), or no (**8**) adjacent phenyl substituents are present. The substantial upfield shift (*ca.* 2 ppm) of the methyl signal in the diphenylanthracene derivatives **12** indicates that the C-9 substituents are suitably located to be capable of interaction with the π orbitals of the two phenyl rings.[4]

To examine the preferred site of electrophilic substitution in 1,8-diphenylanthracene (**1d**), the hydrocarbon was subjected to nitration under mild conditions. Like anthracene, which undergoes nitration to form the 9-nitro derivative **16a**, we expected the major product to be either the 10-nitro derivative **13** or possibly the 9-nitro isomer. In fact, the mononitro compound proved to be **13** and further nitration led to substitution at C-4 in the anthracene ring to form the dinitro derivative **14**. Thus, there appears to be appreciable steric hindrance to electrophilic substitution at C-9 in the hydrocarbon **1d**. The location of the nitro group in **13** was established by hydrogenation and acetylation to form the dihydroamide **15a**. Dehydrogenation with dichlorodicyanobenzoquinone yielded the aromatic amide **15b**. Since the nmr spectrum of the amide **15b** exhibited a methyl signal (at δ 2.80) comparable in location to the signal from 9-acetamidoanthracene (2.34), we conclude that the acetamide function is at C-10 (structure **15b**) and not at C-9, where a distinct upfield shift (*ca.* 2 ppm) would be expected (*cf.* **12b**, Table I).

The ease of reduction and of oxidation of the various hydrocarbons **1**, **5**, **6**, and **20** were compared by the polarographic measurements summarized in Tables II and III. The potentials required for oxidation to the cation radical and for reduction to the anion radical were both relatively insensitive to the number and the location of the phenyl substituents. The second reduction potential (corresponding to reduction of the anion radical to a dianion) was also relatively insensitive to the location and number of phenyl substituents present except for the two anthracene derivatives **1e** and **6**. For these materials, each of which has three phenyl groups in adjacent peri positions (C-1, C-8, and C-9), the second reduction potential was *ca.* 0.3 V less negative than would be expected from the values for related materials. This second reduction step may be facilitated by the formation of a nonplanar dianion which relieves strain in these sterically crowded molecules.

The lifetimes of the various ions formed by oxidation and reduction were estimated from the cyclic voltammetry studies summarized in Table IV. In general, both the dianions and the cation radicals were very reactive with half-lives of the order of 10^{-2} sec or less. However, the anion radicals were relatively

(4) Because the two C-9 substituents described (CH_3O– and CH_3COO–) are not linear, the methyl groups are probably not located properly to exhibit the maximum upfield shift from the ring currents of the two adjacent phenyl rings.

TABLE II

POLAROGRAPHIC OXIDATION POTENTIALS FOR PHENYL DERIVATIVES OF NAPHTHALENE AND ANTHRACENE IN $CHCl_2$ CONTAINING 0.2 M n-$Pr_4N^+CF_3SO_3^-$

Compd (concn, $M \times 10^3$)	$E^1/_2$ vs. sce, V	n value
Naphthalene (0.60)	1.76[a]	0.7
20a (0.67)	1.67	0.7
20b (0.63)	1.64	0.7
Anthracene (1.2)	1.35[b]	0.8
1a (0.66)	1.35	0.7
1b (1.2)	1.32[b]	0.7
1c (0.61)	1.30	0.7
1d (1.6)	1.34	0.7
1e (0.46)	1.25[c]	0.6
5 (0.41)	1.30	0.7
6 (0.62)	1.21[d]	0.8

[a] The reported value in CH_3CN containing $NaClO_4$ is 1.54 V: E. S. Pysk and N. C. Yang, *J. Amer. Chem. Soc.*, 85, 2124 (1963). [b] The reported values in DMF containing n-Bu_4NI are 1.34 V for anthracene and 1.30 V for 1b: A. J. Bard, K. S. V. Santhanam, J. T. Maloy, J. Phelps, and L. O. Wheeler, *Discuss. Faraday Soc.*, 45, 167 (1968). [c] A second poorly defined wave was also observed at *ca.* 1.60 V. [d] A second poorly defined wave was also observed at *ca.* 1.67 V.

TABLE III

POLAROGRAPHIC REDUCTION POTENTIALS FOR PHENYL DERIVATIVES OF NAPHTHALENE AND ANTHRACENE IN DMF CONTAINING 0.5 M n-$Bu_4N^+BF_4^-$

Compd (concn, $M \times 10^3$)	$E^1/_2$ vs. sce, V (n value) First wave	Second wave
Naphthalene (15.2)[a]	−2.49 (0.9)	
20a (9.2–13.7)[a]	−2.37 (0.9)	−2.61 (1.3)
20b (3.5)[a,b]	−2.23 (1.0)	−2.50 (1.2)
Anthracene (8.9)[a]	−1.93 (1.0)	−2.48 (0.9)
1a (3.5)[a,c]	−1.86 (1.0)	−2.35 (1.1)
1b (7.8)[a]	−1.87 (1.0)	−2.43 (0.9)
1c (1.9)[a,d]	−1.83 (0.9)	−2.21 (1.0)
1d (3.2)[a]	−1.84 (0.9)	−2.34 (1.1)
1e (2.7)[a]	−1.83 (0.9)	−2.05 (1.2)
5 (0.50–0.64)	−1.79 (1.0)	−2.28 (1.0)
6 (0.91–1.1)	−1.77 (0.9)	−2.00 (1.2)

[a] Data from ref 11. [b] A third wave was observed at −2.78 V. [c] A third wave was observed at −2.70 V. [d] A third wave was observed at −2.69 V.

stable (half-lives typically 30 sec or more), not only in anhydrous media but also in the presence of added 1 M H_2O. Consequently, it would appear practical to isolate salts of certain of these anion radicals provided that they are kept in an oxygen-free environment. A study of the properties of certain of these anion radicals will be subject of a separate paper.

Experimental Section[5]

1,8-Diphenyl-9,10-anthraquinone (2).—The following procedure represents an improvement on the previously reported[2] method. The CuBr used in this procedure was purified by first dissolving 35 g of commercial CuBr (Fisher Scientific Co.) in 150 ml of saturated aqueous KBr followed by decolorizing with charcoal and dilution with 1000 ml of H_2O. The CuBr that precipitated was collected, washed successively with EtOH and with hexane, and then dissolved in 125 ml of freshly distilled n-Bu_2S [bp 74–75° (14 mm)]. The resulting solution was filtered through a sintered glass funnel to remove *ca.* 0.3 g of insoluble residue and the filtrate was then heated to 140–160° under 10–20 mm pressure to remove the n-Bu_2S, leaving 27.5 g of purified CuBr. Spectrographic analysis indicated that this procedure removed small amounts of impurities containing Fe, Mg, Ag, Pb, Sn, and Ca. A solution of Li_2Ph_3Cu was prepared by treating 3.50 g (24.4 mmol) of purified CuBr with 76.6 mmol of PhLi in 170 ml of Et_2O. This solution was cooled to −10° and a cold solution of 2.00 g (4.35 mmol) of the diiodoquinone **19d** in 600 ml of THF was added rapidly with stirring. After the resulting solution had been stirred at −10° for 4 min, a stream of oxygen was bubbled through the reaction solution for 7 min while the temperature was maintained at 0 to −10°. The resulting mixture was treated with aqueous NH_4Cl + NH_3 (pH 8), the organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic solutions were concentrated and the residual yellow semisolid was triturated with ether to remove 0.4 g of an insoluble, high-melting by-product. The Et_2O solution was concentrated and the residue was heated to 60–70° (0.05 mm) to remove the bulk of the relatively volatile biphenyl. The residue (1.567 g) was chromatographed on silica gel with CH_2Cl_2 as an eluent to separate 818 mg (52%) of the crude diphenylquinone **2**, mp 190–196°. Recrystallization (*i*-PrOH) afforded the pure quinone **2**, mp 200–201°. A small amount (20 mg) of the starting diiodide **19d** was also recovered from the chromatography column.

Preparation of the Triphenyl- and Tetraphenylanthracenes 5 and 6.—To a solution of 1.005 g (2.79 mmol) of the quinone **2** in 80 ml of PhH was added 3.0 ml of an Et_2O solution containing 3.3 mmol of PhLi. The resulting solution was stirred at 25° for 30 min and poured into aqueous NH_3 and NH_4Cl (pH 8). The combined organic layer and CH_2Cl_2 extract of the aqueous phase were concentrated to leave 1.34 g of yellow semisolid. Trituration with CH_2Cl_2 left 231 mg of the crude diol **4**, which was recrystallized (EtOH) to separate 149 mg (10%) of the diol **4** in fractions melting within the range of 266–271.5°.

Repetition of this reaction with 319 mg (0.89 mol) of the quinone **2** in 10 ml of PhH and excess PhLi (17.7 mmol in 16 ml of Et_2O) afforded 319 mg (70%) of the diol **4** as white needles from EtOH, mp 262–272.5°.

Recrystallization from EtOH separated one stereoisomer of the diol **4** as white needles: mp 282.5–283.5°; ir (KB pellet) 3480 and 3350 cm^{-1} (OH); uv (95% EtOH) intense end absorption (ϵ 80,000 at 210 mμ) with an inflection at 222 mμ (ϵ 53,300); mass spectrum m/e (rel intensity) 516 (M^+, 0.5) 483 (43), 482 (100), 405 (24), and 326 (18).

Anal. Calcd for $C_{38}H_{28}O_2$: C, 88.34; H, 5.46. Found: C, 88.15; H, 5.60.

The residue (1.088 g) from the mother liquors, after separating the diol **4**, was chromatographed on silica gel with $CHCl_3$ as the eluent. The early chromatographic fractions were triturated with hexane and fractionally recrystallized from EtOH to separate 82 mg (6%) of a second stereoisomer of the diol **4** as white needles: mp 276–277.5°; ir (KBr pellet) 3490 cm^{-1} (OH); uv (95% EtOH) intense end absorption (ϵ 62,000 at 210 mμ) with inflections at 223 mμ (ϵ 48,000) and 265 (7800); nmr (C_6D_6) δ 5.9–8.1 (multiplet, OH and aryl CH); mass spectrum m/e (rel intensity) 516 (M^+, 1), 501 (25), 500 (38), 499 (16), 483 (34), 469 (29), 468 (100), 424 (28), and 423 (67). On tlc (silica gel coating, CH_2Cl_2 eluent) the R_f values for the isomeric diols **4** were 0.76 (mp 276–277.5°) and 0.10 (mp 282.5–283.5°).

Anal. Calcd for $C_{38}H_{28}O_2$: C, 88.34; H, 5.46. Found: C, 88.22; H, 5.76.

The mother liquors from the early chromatographic fractions and the intermediate chromatographic fractions were crystallized from EtOH to separate 146 mg (15%) of the starting quinone **2**, mp 196–199°. The later chromatographic fractions were recrystallized from EtOH or from MeOH to separate 385 mg (32%) of the hydroxy ketone **3**, mp 221–225°. Recrystallization from MeOH afforded the pure ketol **3** as colorless prisms: mp 227–228°; ir ($CHCl_3$) 3570 (OH) and 1678 cm^{-1} (conjugated C=O); uv max (95% EtOH) 222 mμ (shoulder ϵ 43,000) and 291 (10,200); nmr ($CDCl_3$) δ 7.85 (2 H d of d, J = 1.8 and 8 Hz, aryl CH), 7.55 (2 H t, J = 8 Hz, aryl CH), 7.1–7.4 (17 H m, aryl CH), and 3.07 (1 H s, OH); mass spectrum m/e (rel intensity) 438 (M^+,

(5) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ units (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

TABLE IV

STUDIES OF THE OXIDATION (0.2 M n-$Pr_4N^+CF_3SO_3^-$ IN CH_2Cl_2) AND REDUCTION (0.5 M n-$Bu_4N^+BF_4^-$ IN DMF) OF PHENYL DERIVATIVES OF NAPHTHALENE AND ANTHRACENE BY CYCLIC VOLTAMMETRY

Compd (concn, $M \times 10^3$)	Potentials (vs. sce) and half-lives (values obtained with added H_2O)[a]					
	Reduction				Oxidation	
	$E_{1/2}$, V	$t_{1/2}$, sec	$E_{1/2}$, V	$t_{1/2}$, sec	$E_{1/2}$, V	$t_{1/2}$, sec
Naphthalene	−2.56	>30			1.81	<0.1
(3.0–13.5)	(−2.55)	(>30)				
20a (4.0–4.4)	−2.36	3	−2.59	$<10^{-2}$		
	(−2.37)	(2)	(2.37)			
20b (2.9–5.4)	−2.25	~13	−2.51[b]	$<10^{-2}$	1.59	$<10^{-2}$
	(−2.25)	(7)	(−2.50)			
Anthracene	−1.96	>30	−2.53	<0.02	1.35	<0.05
(1.0–12.0)	(−1.95)	(>30)	(−2.47)			
1a (2.3–2.9)	−1.91	>30	−2.40[c]	$<10^{-2}$		
	(−1.90)	(>30)	(−2.35)			
1b (1.0–6.2)	−1.93	>30	−2.47	<0.03	1.31	7×10^{-3}
	(−1.93)	(>30)	(−2.42)		(1.31)	(7×10^{-3})
1c (1.0–2.9)	−1.90	>30	−2.34[d]	<0.04		
	(−1.88)	(>30)	(−2.23)			
1d (1.9–4.1)	−1.88	>30	−2.37[e]	<0.04	1.30	7×10^{-3}
	(−1.88)	(>30)	(−2.30)		(1.29)	(3×10^{-3})
1e (2.9–4.4)	−1.85	3	−2.03[f]	$<10^{-2}$	1.26	0.05
	(−1.85)		(−2.00)		(1.23)	(0.04)
5 (0.6–0.7)	−1.81	~22	−2.31[c]	$<10^{-2}$		
6 (0.9–1.1)	−1.77	~8	−2.03[g]	$<10^{-2}$		

[a] The solutions for reduction contained 1.0 M H_2O and the solutions for oxidation contained 0.2 M H_2O. [b] An additional peak was observed at −2.80 V. [c] An additional peak was observed at −2.75 V. [d] An additional peak was observed at −2.72 V. [e] An additional peak was observed at −2.76 V. [f] An additional peak was observed at −2.79 V. [g] An additional peak was observed at −2.78 V.

48), 437 (39), 422 (60), 421 (100), 420 (39), 361 (24), 344 (29), and 171 (16).

Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.64; H, 5.06. Found: C, 87.43; H, 4.99.

A mixture of 253 mg (0.58 mmol) of the ketol **3**, 1.0 g of Zn dust (activated with 6 mg of $CuSO_4$),[6] 2 ml of aqueous 28% NH_3, 12 ml of aqueous 30% NaOH, and 20 ml of EtOH was refluxed with stirring for 24 hr. An additional 500 mg of Zn dust was added and refluxing and stirring were continued for 39 hr more. The reaction mixture was filtered and both the residue and the filtrate were extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were concentrated and a solution of the residual white solid and 3 ml of aqueous 12 M HCl in 100 ml of i-PrOH was refluxed for 45 min. The resulting solution was concentrated and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic phase was dried, concentrated, and chromatographed on silica gel with CH_2Cl_2 as the eluent. The early fractions contained 92 mg (38%) of the triphenylanthracene **5**, mp 189–192°. Recrystallization (EtOH) separated the pure hydrocarbon **5** as yellow needles: mp 194–195°; ir ($CHCl_3$) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; uv max (95% EtOH) 214 mμ (ϵ 44,800), 261 (101,000), 343 (shoulder, 3660), 361 (7720), 380 (11,800), and 400 (10,300); nmr ($CDCl_3$) δ 8.66 (1 H, partially resolved multiplet, aryl CH at C-9), 7.1–7.9 (21 H m, aryl CH); mass spectrum m/e (rel intensity) 406 (M^+, 100) and 325 (11).

Anal. Calcd for $C_{32}H_{22}$: C, 94.54; H, 5.46. Found: C, 94.24; H, 5.77.

The later chromatographic fractions from the reaction mixture afforded 47 mg (23%) of the quinone **2**, mp 195–199° (believed not to have been an impurity in the starting ketol **3**), and 44 mg (17%) of the starting ketol **3**, mp 217–220°.

A mixture of 319 mg (0.62 mmol) of the diol **4**, mp 262–272°, 2.5 g of Zn dust (activated with 15 mg of $CuSO_4$),[6] 5 ml of aqueous 28% NH_3, 25 ml of aqueous 30% NaOH, and 60 ml of i-PrOH was refluxed with stirring for 48 hr. The resulting mixture was filtered, the filtrate was treated with an additional 500 mg of Zn dust and 25 ml of i-PrOH, and refluxing and stirring were continued for 48 hr more. The previously described isolation procedure was followed, including reaction of the reduced intermediate with 3 ml of aqueous 12 M HCl in 100 ml of boiling i-PrOH for 45 min. The crude organic product was chromatographed on silica gel with a hexane–CH_2Cl_2 (7:3, v/v) eluent. Recrystallization of the early fractions from hexane separated 86 mg (29%) of the tetraphenylanthracene **6** as pale yellow plates: mp 220–221°; ir ($CHCl_3$) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; uv max (95% EtOH) 229 mμ (inflection, ϵ 34,000), 270 (71,500), 369 (inflection, 7750), 391 (11,800), and 409 (11,000); nmr ($CDCl_3$) δ 7.5–7.8 (7 H m, two anthracene CH and C-10 phenyl at δ 7.60), 6.9–7.4 (4 H m, anthracene CH), and 6.3–6.9 (15 H m, three phenyl groups at C-1, C-8, and C-9); mass spectrum m/e (rel intensity) 483 (20), 482 (M^+, 100), 405 (13), and 326 (10).

Anal. Calcd for $C_{38}H_{26}$: C, 94.57; H, 5.43. Found: C, 94.65; H, 5.40.

Later fractions from the chromatography of the reaction mixture contained (ir analysis) 205 mg (64%) of the crude diol **4**, mp 243–250°.

Preparation of the 9-Acetoxyanthracene Derivatives 8b, 10b, and 12b.—A mixture of 3.013 g (15.5 mmol) of anthrone (**7**), 5 ml of Ac_2O, and 20 ml of collidine was heated to 100° for 2.5 hr and then cooled and poured with stirring into a mixture of ice and aqueous HCl. The resulting suspension was filtered and the residue was fractionally crystallized from EtOH to separate 309 mg (10%) of the starting anthrone **7**, mp 286–288°, and 2.22 g (60%) of the acetate **8b** as white needles, mp 134–137°. Recrystallization afforded the pure acetate **8b**: mp 135.5–137° (lit.[7] mp 130–133°); ir ($CHCl_3$) 1765 cm^{-1} (ester C=O); uv max (95% EtOH) 216 mμ (ϵ 11,300), 219 (11,000), 246 (shoulder, 101,000), 252 (192,000), 315 (shoulder, 1320), 329 (2980), 345 (5800), 363 (8780), and 383 (8150); nmr ($CDCl_3$) δ 8.30 (1 H s, aryl CH at C-10), 7.2–8.1 (8 H m, aryl CH), and 2.53 (3 H s, CH_3CO); mass spectrum m/e (rel intensity) 236 (M^+, 3), 194 (51), 193 (31), 165 (100), 164 (24), 163 (43), 139 (17), and 43 (52).

The same reaction and isolation procedures were followed with 241 mg (0.89 mmol) of the anthrone **9**, 1 ml of Ac_2O, and 3 ml of collidine. Recrystallization of the crude product from EtOH separated 219 mg (79%) of the acetate **10b**, mp 188–194°. The pure acetate **10b** crystallized from EtOH as colorless prisms: mp 194–195°; ir ($CHCl_3$) 1764 cm^{-1} (ester C=O); uv max (95% EtOH) 214 mμ (ϵ 21,800), 256 (127,000), 319 (shoulder, 1270), 335 (3060), 351 (6090), 369 (9150), and 389 (7970); nmr ($CDCl_3$) δ 8.40 (1 H s, aryl CH at C-10), 7.1–8.2 (12 H m, aryl CH), and 1.52 (3 H s, CH_3CO); mass spectrum m/e (rel intensity) 312 (M^+, 3), 270 (80), 269 (42), 268 (84), 241 (38), 240 (20), 239 (100), 237 (38), 213 (20), and 43 (39).

(6) E. Martin, *J. Amer. Chem. Soc.*, **58**, 1438 (1936).

(7) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, **28**, 2572 (1963).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.59; H, 5.24.

A comparable reaction of 232 mg (0.802 mmol) of the anthrone **11** with 1 ml of Ac_2O and 3 ml of collidine for 4.5 hr yielded 258 mg of crude product. Recrystallization from EtOH afforded 203 mg (65%) of the acetate **12b**, mp 274–282°. An additional recrystallization from EtOH afforded the pure acetate as white needles: mp 282–282.5°; ir ($CHCl_3$) 1760 cm^{-1} (ester C=O); uv max (95% EtOH) 213 mμ (ε 31,000), 261 (133,000), 342 (shoulder, 3280), 359 (6520), 377.5 (9540), and 398 (7920); nmr ($CDCl_3$) δ 8.48 (1 H s, aryl CH at C-10), 8.02 (2 H d of d, J = 1.6 and 8.4 Hz, aryl CH), 7.1–7.6 (14 H m, aryl CH), and 0.28 (3 H s, CH_3CO); mass spectrum, m/e (rel intensity) 388 (M^+, 4), 347 (17), 346 (100), 345 (22), 344 (28), 313 (16), 268 (21), 239 (19), and 43 (19).

Anal. Calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.27; H, 5.10.

Preparation of the 9-Methoxyanthracene Derivatives 8a, 10a, and 12a.—To a refluxing solution of 259 mg (0.96 mmol) of the anthrone **9** and 6 ml of aqueous 20% NaOH in 8 ml of *i*-PrOH was added, portionwise with stirring, 1.21 g (6.5 mmol) of MeOTs. The resulting mixture was refluxed for 20 min and then diluted with 15 ml of H_2O and allowed to cool. The crude crystalline product (167 mg) that separated was collected and recrystallized from EtOH to separate 154 mg (57%) of the methoxyanthracene **10a** as pale yellow plates: mp 138.5–139.5°; ir ($CHCl_3$) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; uv max (95% EtOH) 212 mμ (ε 23,000), 258 (105,000), 340 (shoulder, 3090), 356 (5960), 375 (8620), and 394 (7720); nmr ($CDCl_3$) δ 8.30 (1 H s, aryl CH at C-10), 7.1–8.2 (12 H m, aryl CH), and 3.25 (3 H s, OCH_3); mass spectrum m/e (rel intensity) 285 (23), 284 (M^+, 100), 270 (18), 269 (99), 268 (91), 229 (15), and 124 (20).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.47; H, 5.95.

A comparable reaction with 190 mg (0.55 mmol) of the anthrone **11**, 6 ml of aqueous 20% NaOH, 8 ml of *i*-PrOH, and 1.21 g (6.5 mmol) of MeOTs yielded 115 mg (60%) of the methoxyanthracene **12a** as pale yellow needles from EtOH: mp 241–242.5°; ir ($CHCl_3$) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; uv max (95% EtOH) 215 mμ (ε 31,900), 254 (shoulder, 67,600), 262 (112,000), 346 (shoulder, 3280), 369 (6760), 384 (9530), and 406 (8300); nmr ($CDCl_3$) δ 8.35 (1 H s, aryl CH at C-10), 7.1–8.2 (16 H m, aryl CH), and 2.37 (3 H s, OCH_3); mass spectrum m/e (rel intensity) 361 (30), 360 (M^+, 100), 346 (16), 345 (69), 344 (49), and 268 (12).

Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.79; H, 5.70.

The same procedure was applied[8] to anthrone **7**) to produce 9-methoxyanthracene (**8a**) in 51% yield as yellow needles from *i*-PrOH: mp 95–96° (lit.[7] mp 95–96°); nmr ($CDCl_3$) δ 7.3–8.5 (9 H m, aryl CH) and 4.10 (3 H s, OCH_3).

Nitration of Anthracene and 1,8-Diphenylanthracene (1d).—A mixture of 968 mg (10.8 mmol) of aqueous 70% HNO_3, 8 ml of CH_2Cl_2, and 306 mg (1.72 mmol) of anthracene was stirred at 0–3° for 1 hr and then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried and concentrated and the residual yellow oil (432 mg) was chromatographed on silica gel with PhH as an eluent. The early fractions, containing (tlc) 9-nitroanthracene (**16a**), were recrystallized from EtOH to separate 208 mg (55%) of the nitro derivative **16a** as yellow needles: mp 145.5–147.5° (lit.[9] mp 146°); ir ($CHCl_3$) 1520 and 1370 cm^{-1} (NO_2); uv (95% EtOH) 217 mμ (ε 14,300), 245 (shoulder, 102,000), 250 (120,000), 333 (shoulder, 2480), 347 (3840), 364 (4640), 383 (3950), and 402 (shoulder, 2180); nmr ($CDCl_3$) δ 8.51 (1 H s, aryl CH at C-10) and 7.2–8.1 (8 H m, aryl CH); mass spectrum m/e (rel intensity) 223 (M^+, 100), 193 (48), 177 (69), 176 (76), 165 (51), 151 (21), and 88 (34).

To a refluxing solution of 1.018 g (4.52 mmol) of the nitro compound **16a** in 20 ml of HOAc was added, dropwise and with stirring, a solution of 8 g of $SnCl_2 \cdot 2H_2O$ in 8 ml of aqueous 12 *M* HCl. The resulting solution was refluxed for 30 min, cooled, and filtered to separate the amine–tin complex. This residue was washed with HOAc and then triturated with aqueous NH_3 and extracted repeatedly with Et_2O. The Et_2O extract was concentrated and the residual crude amine was dissolved in 30 ml of cold (0°) Ac_2O. This cold solution was stirred for 15 min and then poured onto ice and allowed to stand. The crude amide **16b** (835 mg or 78%, mp 282–284°) was collected and recrystallized from PhH to separate the pure amide **16b** as 737 mg of white needles: mp 283–284° dec (lit.[10] mp 280–281°); ir (KBr pellet) 3190 (amide NH) and 1637 cm^{-1} (amide C=O); uv max (95% EtOH) 214 mμ (ε 14,000), 247 (shoulder, 95,600), 253 (158,000), 315 (shoulder, 1160), 330 (2740), 346 (5350), 364 (7700), and 383.5 (6950); nmr ($C_6D_5NO_2$ at 120°) δ 8.34 (1 H s, aryl CH at C-10), 7.2–8.3 (8 H m, aryl CH), and 2.34 (3 H s, CH_3CO); in $Cl_2CHCHCl_2$ solution at *ca.* 35° the *C*-methyl singlet is located at δ 1.83. In $CDCl_3$ solution, the methyl signal appears as two peaks at δ 1.68 and 2.49, suggesting that in this solvent both the acetamido and acetimido tautomers are present. Exposure of this $CDCl_3$ solution to gaseous HCl resulted in a change in the relative positions and intensities of the peaks with the predominant peak appearing at δ 2.18, mass spectrum m/e (rel intensity) 235 (M^+, 38), 194 (18), 193 (100), 192 (28), and 43 (26).

A cold (0°) mixture (two phases) of 204 mg (0.619 mmol) of 1,8-diphenylanthracene (**1d**), 15 ml of CH_2Cl_2, and 500 mg (5.5 mmol) of aqueous 70% HNO_3 was stirred for 2 hr at 0° and then for 20 min at 25°. After the mixture had been treated with $NaHCO_3$, the CH_2Cl_2 solution was separated and stirred with an additional 500 mg (5.5 mmol) of aqueous 70% HNO_3 for 2 hr at 0° and 30 min at 25°. Solid $NaHCO_3$ was again added and the CH_2Cl_2 solution was separated, concentrated, and chromatographed on silica gel with CH_2Cl_2 as the eluent. The early fractions were combined and recrystallized from hexane to separate 111 mg (48%) of the nitro derivative **13**, mp 245–252°. Recrystallization from EtOH afforded the pure nitro compound **13** as yellow needles: mp 250.5–252°; ir ($CHCl_3$) 1525 and 1367 cm^{-1} (NO_2); uv max (95% EtOH) 257 mμ (ε 71,700), 359 (shoulder, 3840), 382 (5190), and 400 (shoulder, 4770); nmr ($CDCl_3$) δ 8.75 (1 H s, aryl CH at C-9), 7.95 (2 H, d of m, J = 8 Hz, aryl CH at C-4 and C-5), and 7.3–7.8 (14 H m, phenyl CH and aryl CH at C-2, C-3, C-6, and C-7); mass spectrum m/e (rel intensity) 376 (26), 375 (M^+, 100), 345 (11), 329 (14), 328 (14), and 326 (18).

Anal. Calcd for $C_{26}H_{17}NO_2$: C, 83.18; H, 4.56; N, 3.73. Found: C, 83.15; H, 4.65; N, 3.65.

The later chromatography fractions (41 mg or 16%) contained the crude dinitro compound **14**, mp 193.5–195°. Recrystallization from hexane and then from EtOH separated the pure dinitro compound **14** as orange prisms: mp 199–200°; ir ($CHCl_3$) 1530 and 1355 cm^{-1} (NO_2); uv max (95% EtOH) 245 mμ (ε 30,400), 272 (44,500), and 426 (8420); nmr ($CDCl_3$) δ 8.83 (1 H s, aryl CH at C-9), 8.0–8.4 [2 H, a doublet (J = 8 Hz) of multiplets for the proton at C-5 and a doublet (J = 7.5 Hz) for the proton at C-3], and 7.1–8.0 (13 H m, phenyl CH and aryl CH at C-2, C-6, and C-7); mass spectrum m/e (rel intensity) 420 (M^+, 26), 375 (18), 374 (71), 345 (21), 344 (82), 316 (66), 315 (100), 314 (28), 313 (70), and 239 (18).

Anal. Calcd for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found: C, 74.31; H, 3.87; N, 6.55.

A 21.2-mg (0.057 mmol) sample of the mononitro compound **13** was treated at 25° for 2.5 hr with a mixture of 2 ml of CH_2Cl_2 and 0.2 g (2 mmol) of aqueous 70% HNO_3. The crude product, isolated as previously described, was recrystallized from EtOH to separate 15.1 mg (63%) of the dinitro compound **14**, mp 197.5–198.5°, identified with the previously described sample by a mixture melting point determination and by comparison of nmr and mass spectra.

A solution of 113 mg (0.302 mmol) of the nitro compound **13** in 85 ml of HOAc and 15 ml of Ac_2O was hydrogenated for 10 hr at 25° and atmospheric pressure over the catalyst from 100 mg of Pt_2O. The resulting mixture was filtered and concentrated and the residue was chromatographed on silica gel with $CHCl_3$ as an eluent. Recrystallization of the appropriate chromatographic fractions from EtOH separated 95 mg (80%) of the crude dihydroamide **15a** as white needles: mp 235–240°; ir ($CHCl_3$) 3430 (NH) and 1670 cm^{-1} (amide C=O); uv (95% EtOH) shoulders at 235 mμ (ε 20,800) and 260 (7930) with intense end absorption (ε 64,100 at 210 mμ); nmr ($CDCl_3$) δ 7.0–7.6 (16 H m, aryl CH), 6.0–6.4 (2 H m, NH and CH), 3.5–4.2 (2 H m, benzylic CH_2), and 2.17 (3 H s, CH_3CO). A solution of 88 mg (0.23 mmol) of the crude dihydro amide **15a** and 58 mg (0.26 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in 7 ml of PhH

(8) This experiment was performed in our laboratories by Dr. David S. Crumrine.

(9) O. Dimroth, *Ber.*, **34**, 219 (1901).

(10) J. Rigaudy, H. Canquis, G. Izout, and J. Baranne-Lafont, *Bull. Soc. Chim. Fr.*, 1842 (1961).

was refluxed for 24 hr and then the solvent was removed. The residue was chromatographed on silica gel with first CH_2Cl_2 and then $CHCl_3$ as eluents. The fractions containing the crude amide **15b** were recrystallized from EtOH to separate 40 mg (46%) of the crude amide **15b** as colorless plates, mp 319–323°. Recrystallization afforded the pure amide **15b**: mp 324–325.5°; ir (KBr pellet) 3240 (NH) and 1650 cm^{-1} (amide C=O); uv max (95% EtOH) 212 mμ (ε 39,800), 260 (111,000), 362 (6880), 380.5 (10,500), and 400.5 (9030); mass spectrum *m/e* (rel intensity), 387 (M^+, 86), 345 (84), 344 (31), 190 (28), and 43 (100); nmr ($C_6D_5NO_2$) δ 7.2–8.6 (17 H m, aryl CH) and 2.80 (3 H s, CH_3CO); in $Cl_2CHCHCl_2$ solution the *C*-methyl singlet was at δ 1.89. As was the case with the model amide **16b**, a solution of the amide **15b** in $CDCl_3$ exhibited two peaks at δ 2.52 and 1.75; after exposure of the solution to gaseous HCl, the major peak was located at δ 2.03.

Anal. Calcd for $C_{28}H_{21}NO$: C, 86.79; H, 5.46; N, 3.62. Found: C, 86.52; H, 5.40; N, 3.45.

Preparation of the Halogenated Anthracene Derivatives 17, 18, and 19b.—A cold (0°) solution of 15.0 g (77.7 mmol) of 1-aminoanthracene in a mixture of 40 ml of concentrated H_2SO_4, 55 ml of H_2O, and 125 g of ice was diazotized at −10° by treatment with a solution of 14.0 g (203 mmol) of $NaNO_2$ in 60 ml of H_2O. The cold (−10°) slurry of the red diazonium salt was treated with a solution of 55 g (330 mmol) of KI in 75 ml of H_2O and the resulting mixture was warmed to complete the reaction with the diazonium salt. The crude solid product (37.5 g) was collected and chromatographed on silica gel with PhH as an eluent. The early fractions, containing (tlc) the iodide **17**, were washed with aqueous $Na_2S_2O_3$, dissolved in CH_2Cl_2, dried, concentrated, and triturated with Et_2O to separate 6.66 g (27%) of the iodide **17**, mp 81–96°. Recrystallization from EtOH separated the pure iodide **17** as yellow plates: mp 102.3–103°; ir ($CHCl_3$) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; uv max (95% EtOH) 217 mμ (ε 12,600), 252 (130,000), 317 (shoulder, 1340), 331 (3020), 347 (5770), 365 (8170), and 385 (7780); nmr ($CDCl_3$) δ 8.61 (1 H s, aryl CH), 8.23 (1 H s, aryl CH), and 6.9–8.1 (7 H m, aryl CH); mass spectrum *m/e* (rel intensity) 304 (M^+, 100), 177 (36), 176 (29), and 88 (14).

Anal. Calcd for $C_{14}H_9I$: C, 55.29; H, 2.98; I, 41.73. Found: C, 55.46; H, 2.99; I, 41.53.

A mixture of 2.515 g (9.10 mmol) of the dichloroquinone **19c**, 12.5 g of Zn dust, and 50 ml of aqueous 20% NH_3 was heated on a steam bath with stirring for 30 min and then cooled and filtered. The residue and the filtrate were each extracted with CH_2Cl_2 and the combined CH_2Cl_2 extracts were concentrated. A solution of the residual white solid in 250 ml of *i*-PrOH containing 2 ml of aqueous 12 *M* HCl was refluxed for 3 hr and then concentrated and partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was concentrated and the residue was recrystallized from *i*-PrOH to separate 1.655 g (74%) of the dichloride **18**, mp 149–157°. Recrystallization afforded the pure dichloride **18** as pale yellow needles: mp 156.5–158°;[11] ir ($CHCl_3$) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; uv max (95% EtOH) 218 mμ (ε 12,600), 252 (113,000), 256 (113,000), 319 (shoulder, 1340), 333 (2950), 350 (5550), 368 (8060), and 388 (7320); nmr ($CDCl_3$) δ 9.19 (1 H s, aryl CH), 8.35 (1 H s, aryl CH), and 7.2–8.0 (6 H m, aryl CH); mass spectrum *m/e* (rel intensity) 250 (12), 248 (70), 246 (M^+ for ^{35}Cl, 100), 176 (23), 123 (12), and 68 (13).

Anal. Calcd for $C_{14}H_8Cl_2$: C, 68.05; H, 3.22; Cl, 28.80. Found: C, 67.78; H, 3.26; Cl, 28.69.

An attempt to apply this same reduction procedure to the diiodoquinone **19d** resulted in the reductive cleavage of the C–I bonds to form anthracene in 68% yield.

A solution of 5.48 g (24.5 mmol) of the diamine **19a** in a mixture of 27 ml of concentrated H_2SO_4, 35 ml of H_2O, and 78 g of ice was diazotized at −15° by the slow addition of a solution of 8.8 g (128 mmol) of $NaNO_2$ in 38 ml of H_2O. To the resulting cold (−15°) suspension was added a slurry of CuBr, prepared from 4.70 g (18.8 mmol) of $CuSO_4 \cdot 5H_2O$, 1.5 g (23.6 mg-atom) of Cu, 11.6 g (113 mmol) of NaBr, 2.4 ml of concentrated H_2SO_4, and 100 ml of H_2O. The resulting mixture was heated to 80° and then cooled and made basic with NaOH. The crude solid product was collected, washed successively with aqueous 10% HCl, aqueous $NaHCO_3$, and water, and then dried. Chromatography on silica gel with PhH as the eluent separated 1.237 g (14%) of the crude dibromoquinone **19b**, mp 213–225°. Recrystallization from EtOH separated the pure dibromide **19b** as yellow needles: mp 233–234°; ir ($CHCl_3$) 1685 cm^{-1} (conjugated C=O); uv max (95% EtOH) 213 mμ (ε 28,800), 255 (33,800), 351 (4480), and 416 (shoulder, 774); nmr ($CDCl_3$) δ 8.28 (2 H, d of d, J = 7.6 and 1.3 Hz, aryl CH at C-4 and C-5), 8.06 (2 H, d of d, J = 1.3 and 7.6 Hz, aryl CH at C-2 and C-7), and 7.55 (2 H t, $J \cong 8$ Hz, aryl CH at C-3 and C-6); mass spectrum *m/e* (rel intensity) 368 (52), 366 (100), 364 (M^+ for ^{79}Br, 50), 150 (90), 75 (64), and 74 (29).

Anal. Calcd for $C_{14}H_6Br_2O_2$: C, 45.94; H, 1.65; Br, 43.66. Found: C, 45.89; H, 1.73; Br, 43.90.

Polarographic Measurements of Oxidation and Reduction Potentials.—These measurements were obtained at 25° with a Heath polarograph, Model EU-402V. The reductions were performed at a dropping Hg electrode with a Pt counterelectrode in purified DMF[12] employing 0.5 *M* n-$Bu_4N^+BF_4^-$[12] as the supporting electrolyte and with a saturated calomel reference electrode that made contact with the reaction solution through intervening salt bridges containing aqueous 1 *M* $NaNO_3$ and 0.5 *M* $Et_4N^+BF_4^-$ in DMF. The oxidations were performed at a rotating Pt wire anode (0.1 mm diameter, 600 rpm) with a fixed Pt counterelectrode in CH_2Cl_2 containing 0.2 *M* n-Pr_4N^+-$CF_3SO_3^-$[13] as the supporting electrolyte. The CH_2Cl_2 was purified by washing successively with aqueous 5% Na_2CO_3 and with H_2O and drying over $CaCl_2$. The solvent was then distilled under N_2 at atmospheric pressure and collected at 40–40.5°. The Pt wire anode was cleaned before each use by successive treatment with aqueous H_2CrO_4 and with aqueous 12 *M* HCl as described by Adams[14] and then rinsed successively with H_2O, acetone, and CH_2Cl_2. The reference was a saturated calomel electrode with intervening salt bridges containing aqueous 1 *M* $NaNO_3$ and 0.5 *M* n-$Bu_4N^+BF_4^-$ in DMF. The $E_{1/2}$ values (*vs.* sce) and the n values were obtained from plots of E *vs.* log $[i/(i_d - i)]$ and are presented in Tables II and III. Certain of the reduction potential values in Table III were described in an earlier paper.[2]

Oxidation and Reduction Measurements by Cyclic Voltammetry.—The polarographic module employed was a custom-made module utilizing solid-state amplifiers that followed the typical three-electrode design such as that found in a Heath polarograph. For slow scans the internal circuitry of the module was employed and for fast scans an external triangular wave form generator was employed to drive the polarography module. The current–potential curves were displayed on a storage oscilloscope (Tektronix RM 564 fitted with two differential amplifiers, type 2-A63) and were photographed with a Tektronix oscilloscope camera fitted with a Polaroid back. The potentials were calibrated against a previously calibrated digital voltmeter (United Systems Corp., Series 180) and the sweep time calibrations were made with the oscilloscope fitted with a previously calibrated time base (Tektronix type 2-B67). The oxidation measurements employed a spherical Pt anode (typical diameter 1.25 mm) that had been cleaned by heating it in an air–H_2 flame. For reduction measurements, the cathode was the same spherical Pt electrode described above that had been coated with Hg as previously described.[15] The same solvents, supporting electrolytes, counterelectrodes, and reference electrodes that were used in the above polarographic measurements were employed for these studies. The nitrogen was purified as previously described[15] and the electrolysis cell was of all-glass construction with provision for passing purified nitrogen either through or over the solution being measured. The entire electrolysis cell was kept in a grounded steel drum during measurements to minimize electrical interference. In those reduction measurements where cathodic (E_{pc}) and anodic (E_{pa}) waves were observed, the value of the reduction potential ($E_{1/2}$) was taken to be $^1/_2$ ($E_{pc} + E_{pa}$); as expected, the value corresponded to the cathodic potential where the cathodic

(11) E. Bergmann and A. Weizmann [*J. Amer. Chem. Soc.*, **60**, 1801 (1938)] have reported the dichloride **18** to melt at 185°.

(12) H. O. House, E. Feng, and N. P. Peet, *J. Org. Chem.*, **36**, 2371 (1971).

(13) K. Rousseau, G. C. Farrington, and D. Dolphin, *J. Org. Chem.*, **37**, 3968 (1972).

(14) R. N. Adams, "Electrochemistry at Solid Electrodes," Marcel Dekker, New York, N. Y., 1969, pp 201–202.

(15) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970).

current had reached 85% of its peak value (i_{pc}).[16] Where no anodic current peak (i_{pa}) was observed, an estimate of the value of $E_{1/2}$ was obtained from the cathodic potential at which i_c reached 85% of the maximum value, i_{pc}. Comparable procedures were followed to obtain the oxidation potentials. Half-life estimates for the various oxidized and reduced species were obtained by a previously described procedure[15] in which the scan rates and switching potentials (E_λ) in reductions were adjusted until $i_{pa} = 1/2(i_{pc})$. The half-life for reduced species was than taken to be the elapsed time as the potential was swept from E_{pc} to E_λ to E_{pa}. In instances where the intermediate was either too unstable or too stable to allow a variation in i_{pa} with time, the minimum or maximum values of the half-life were estimated. Comparable procedures were followed for the oxidations. The results of these measurements are summarized in Table IV. The effect of added H_2O on the stability of various oxidized and reduced species was explored by adding known amounts of H_2O (1.0 *M* for reductions and 0.2 *M* for oxidations) to the anhydrous solution and then repeating the measurements previously described.

(16) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964); **37**, 178 (1965).

Registry No.—**1a**, 1714-09-6; **1b**, 602-55-1; **1c**, 1714-19-8; **1d**, 33522-35-9; **1e**, 33522-39-3; **2**, 33522-27-9; **3**, 38305-27-0; *cis*-**4**, 38309-51-2; *trans*-**4**, 38309-52-3; **5**, 38305-28-1; **6**, 38305-29-2; **7**, 90-44-8; **8a**, 2395-96-2; **8b**, 784-04-3; **9**, 1714-15-4; **10a**, 38305-34-9; **10b**, 38305-35-0; **11**, 33522-37-1; **12a**, 38305-37-2; **12b**, 38305-38-3; **13**, 38305-39-4; **14**, 38305-40-7; **15a**, 38305-30-5; **15b**, 38305-31-6; **16a**, 602-60-8; **16b**, 37170-96-0; **17**, 22362-90-9; **18**, 14381-66-9; **19a**, 129-42-0; **19b**, 38313-16-5; **19c**, 82-43-9; **19d**, 30877-00-0; **20a**, 605-02-7; **20b**, 1038-67-1; anthracene, 120-12-7; 1-anthramine, 610-49-1.

The Reaction of Cyclic α-Ketal Acids with Phosphorus Pentachloride. A New Stereospecific Route to Esters of Halohydrins

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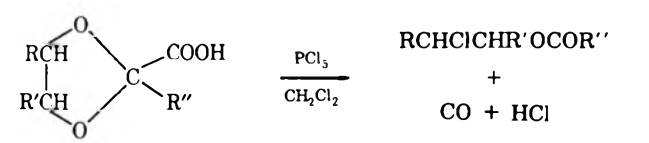
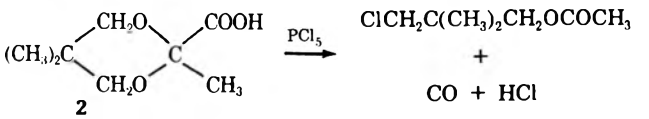
Treatment of a number of cyclic α-ketal acids containing 1,3-dioxolane, 1,3-dioxane, and 1,3-dioxepane rings with phosphorus pentachloride in methylene chloride yielded esters of 1,2-, 1,3-, and 1,4-chlorohydrins, respectively. Evidence is presented to show that 2-chloro-2-methyl-1,3-dioxolane (**5**) and 2-chloro-2,5,5-trimethyl-1,3-dioxane (**9**) are formed directly at −60° from 2-carboxy-2-methyl-1,3-dioxolane (**4**) and 2-carboxy-2,5,5-trimethyl-1,3-dioxane (**8**), respectively. On warming to 0° **5** and **9** rearrange to 2-chloroethyl acetate (**6**) and 3-chloro-2,2-dimethylpropyl acetate (**10**), respectively. Similar reactions with optically active 1,3-dioxolanes yield stereospecific products in which inversion of configuration occurs at the carbon–oxygen bond which is converted to a carbon–chlorine bond. In unsymmetrical 1,3-dioxolanes, the regiospecific products of the reaction are those predicted by assuming an SN2 type mechanism for opening of the 1,3-dioxolane ring. The synthetic utility of these reactions for the synthesis of optically active epoxides is demonstrated.

In a preliminary communication, the conversion of several 2-carboxy-1,3-dioxolanes (**1**) and a 2-carboxy-1,3-dioxane (**2**) into esters of halohydrins by treatment



1

4, R = R' = H; R'' = CH_3

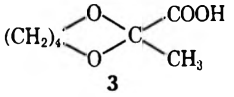


2

31, R = C_2H_5

with phosphorus pentachloride in methylene chloride were described.[2] A more detailed account of this and additional work is presented herein.

The preparation of the requisite 2-carboxy-1,3-dioxolanes and 1,3-dioxanes from diols and pyruvic and benzoylformic acids was accomplished in moderate yields under acid catalysis by either or both of two methods: A, treatment of the α-keto acid with excess diol; and B, treatment of the diol with excess α-keto acid.[3] When method A was used an alkaline treatment was needed during the work-up to hydrolyze any ester formed. Yields of 1,3-dioxanes were better than those of 1,3-dioxolanes (see Table I, Experimental Section). In the only case of a 1,4-diol studied, 1,4-butanediol and pyruvic acid reacted to give 2-carboxy-2-methyl-1,3-dioxapane (**3**) in 63% yield. In a few cases, benzoylformic acid afforded α-ketal acids in about the same yields as when pyruvic acid was used.



3

The reactions of the cyclic acids above described with phosphorus pentachloride or thionyl chloride in methylene chloride took place rapidly at room temperature or below. The evolution of hydrogen chloride and carbon monoxide occurred rapidly under all conditions. Comparable results were obtained when a suspension of the dried sodium salts of **1** and **2** in methylene chloride was treated with thionyl chloride or phosphorus pentachloride. In two cases when thionyl chloride was used, the results were qualitatively the same but the yields of pure halo esters obtained were inferior. Accordingly, in all further work only phosphorus pentachloride was used.

With regard to the mechanism of the reaction, we wished to know whether the acid chloride was formed and lost carbon monoxide or an alternate path was involved. Accordingly, a solution of 2-carboxy-2-

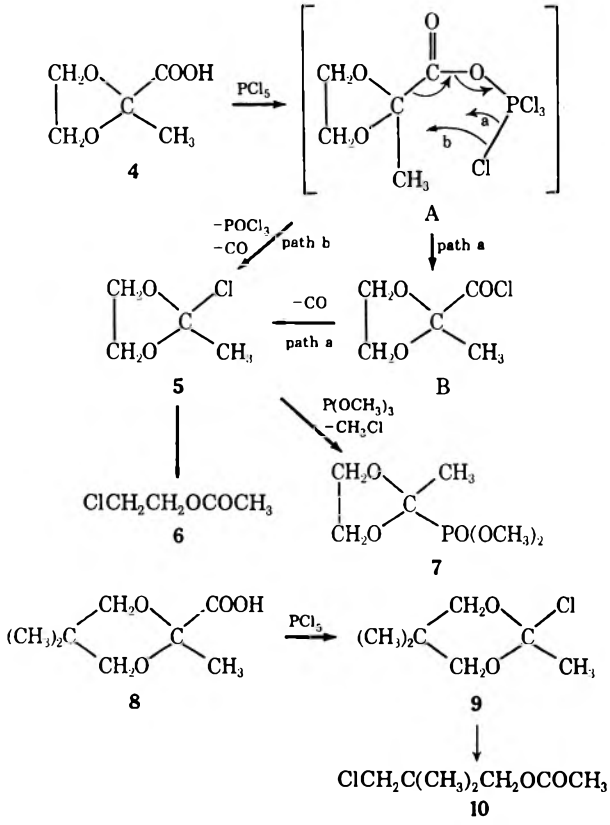
(1) Postdoctoral Fellow. This work was supported by Grant No. GP-12445X of the National Science Foundation.

(2) M. S. Newman and C. H. Chen, *J. Amer. Chem. Soc.*, **94**, 2149 (1972).

(3) E. Vogel and H. Schinz, *Helv. Chim. Acta*, **33**, 116 (1950).

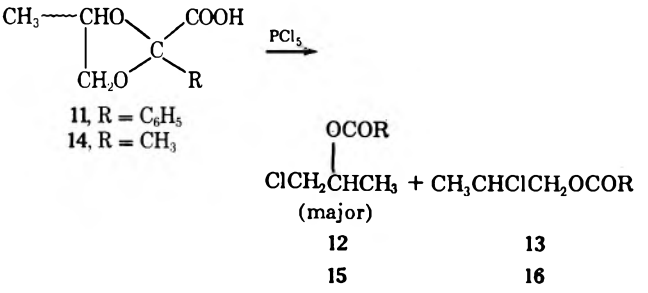
methyl-1,3-dioxolane (**4**) in methylene chloride was added to a suspension of phosphorus pentachloride in methylene chloride at −60°. Evolution of carbon monoxide and hydrogen chloride was instantaneous. The nmr spectrum of the product was consistent with the structure 2-chloro-2-methyl-1,3-dioxolane (**5**).[4] On warming to 0° the spectrum changed to one consistent with the structure 2-chloroethyl acetate (**6**), the product isolated. That **5** was present at −60° was confirmed by treatment of the product formed at −60° with trimethyl phosphite to yield dimethyl (2-methyl-1,3-dioxolanyl)phosphonate[4] (**7**). The lack of induction period observed in all the reactions of cyclic α-ketal acids with phosphorus pentachloride in methylene chloride, and the fact that the addition of galvinoxyl[5] to a reaction of the sodium salt of **4** with thionyl chloride in methylene chloride did not inhibit the reaction by which **4** was converted into **6**, make a free-radical path unlikely.

A similar result was obtained when phosphorus pentachloride was treated with 2-carboxy-2,5,5-trimethyl-1,3-dioxane (**8**) to yield 2-chloro-2,5,5-trimethyl-1,3-dioxane (**9**) at −60° which on warming rearranged into 3-chloro-2,2-dimethylpropyl acetate (**10**). As a result of the above facts the following mechanism for the formation of **5** and **9** is offered (illustrated only with **4**).

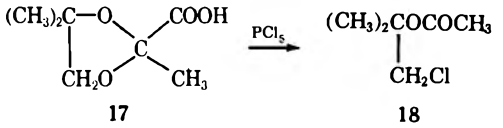


Reactions involving PCl_5 undoubtedly involve attack at oxygen by the PCl_4^+ ion.[6] In the case of ordinary acids this first-formed product usually collapses to yield the acid chloride (path a). However, in the cases of α-ketal acids, path b (as shown in A) involving loss of carbon monoxide with direct formation of **5** is apparently preferred, as judged by the fact that carbon monoxide is formed simultaneously with hydrogen chloride. At low temperatures **5** is stable (see Experimental Section for nmr spectrum). As warming occurs **5** rearranges to **6**.[4] The mechanism by which the rearrangement occurs is of interest and was examined further in substituted analogs.

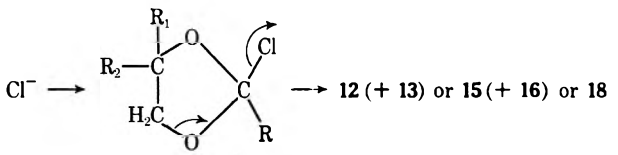
On treatment of 2-carboxy-4-methyl-2-phenyl-1,3-dioxolane (**11**) with phosphorus pentachloride there was obtained in 92% yield a mixture which consisted of 1-chloro-2-propyl benzoate (**12**) and 2-chloro-1-propyl benzoate (**13**) in the ratio of 19:1, respectively.[7] Similarly, 2-carboxy-2,4-dimethyl-1,3-dioxolane (**14**) afforded an 80% yield of a 93:7 mixture of 1-chloro-2-propyl acetate (**15**) and 2-chloro-1-propyl acetate (**16**).[7] In the case of 2-carboxy-2,4,4-trimethyl-1,3-



dioxolane (**17**) only 1-chloro-2-methyl-2-propyl acetate (**18**) was obtained.



These results suggested that the reactions proceed by the formation of 2-chloro-4-methyl-2-phenyl-1,3-dioxolane (**19**), 2-chloro-2,4-dimethyl-1,3-dioxolane (**20**), and 2-chloro-2,4,4-trimethyl-1,3-dioxolane (**21**), which open to **12** (and **13**), **15** (and **16**), and **18** by an SN2 type displacement by chloride ion (formed by the tendency of **19**, **20**, and **21** to ionize[8]) as shown. This

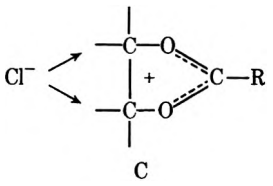


19, R_1 = H; R_2 = CH_3; R = C_6H_5
20, R_1 = H; R_2 = CH_3; R = CH_3
21, R_1 = R_2 = CH_3; R = CH_3

mechanism requires inversion at the carbon undergoing reaction with chlorine. Alternately, the chloride ion (or a chlorine-containing species) might react with ion C[8b] by an SN2 type reaction (inversion required) or an

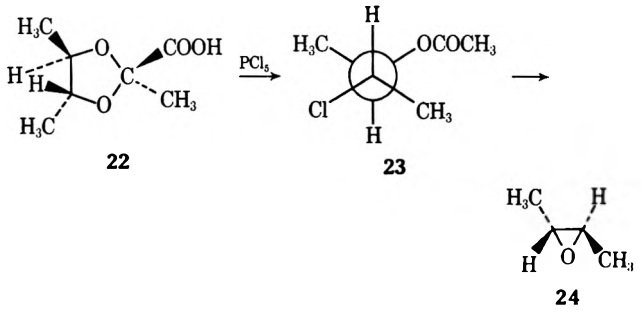
(4) H. Gross, J. Freiberg, and B. Costisella, *Chem. Ber.*, **101**, 1250 (1968).
(5) G. M. Coppinger, *J. Amer. Chem. Soc.*, **79**, 501 (1957).
(6) For examples involving ketones see M. S. Newman and L. L. Wood, Jr., *ibid.*, **81**, 4300 (1959). In A, an alternate formulation would place the phosphorus atom on the oxygen containing the hydrogen.
(7) We previously reported[2] the formation of pure **12**. However, by the use of Eu(DPM)$_3$, K. J. Eisentraut and R. E. Sievers, *ibid.*, **87**, 5254 (1965), the presence of a small amount of the isomer was estimated by nmr spectral studies.
(8) For references and a discussion of the type of cation produced by this ionization see (a) S. Winstein and R. E. Buckles, *ibid.*, **65**, 613 (1943), and (b) S. Hunig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964). Such ions were produced by participation of a neighboring acetoxy groups in the ionization of a halide or tosyl group, whereas in the present case ions are produced (we assume) by ionization of the chlorine of **5**, **19**, **20**, and **21**.

intimate ion pair involving C and a chloride ion might collapse to product (which would require mostly retention).



C

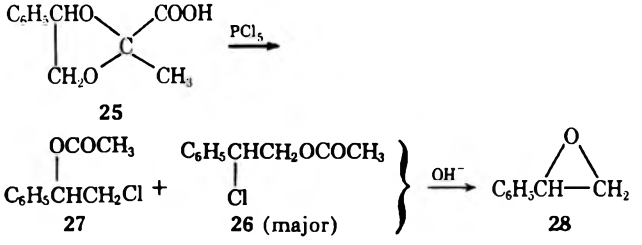
To test these hypotheses D-(−)-2,3-butanediol was converted into D-(−)-2-carboxy-2,4,5-trimethyl-1,3-dioxolane (**22**), which yielded L-(+)-*erythro*-3-chloro-2-butyl acetate (**23**) on treatment with phosphorus pentachloride. That inversion had occurred in going from **22** to **23** was established by the fact that treatment of **23** with strong base produced D-(+)-2,3-epoxybutane (**24**),



22 **23** **24**

a reaction known to proceed with inversion at the carbon–halogen bond.[9] This result excludes the intimate ion pair mechanism.

Further evidence about the mechanism was provided by the fact that treatment of (*R*)-(−)-2-carboxy-2-methyl-4-phenyl-1,3-dioxolane[10] (**25**) [prepared from (*R*)-(−)-phenyl-1,2-ethanediol] with phosphorus pentachloride yielded mainly (*S*)-2-chloro-2-phenyl acetate[11] (**26**) containing a small amount (*ca.* 4%) of 2-chloro-1-phenyl acetate (**27**) assumed to be the *R* isomer, as no cleavage of the bond to oxygen should occur. The conversion of **26** (and **27**) to (*R*)-styrene oxide (**28**),



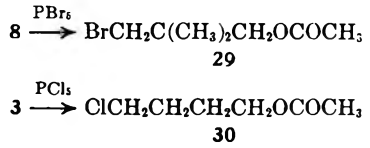
25 **27** **26** (major) **28**

a reaction involving inversion (nor for **27**), confirms the *S* assignment for **26**.

The structure of the major product (**26**) is that which would be predicted by an SN2 mechanism, since the ratio of rate of displacement of chlorine by iodide ion in benzyl chloride and 2-phenylethyl chloride is about 174[12a] or 196[12b] and the rate for 1-phenylethyl chloride (2.5×10^{-5}) is only slightly less than that for benzyl chloride (3.3×10^{-5}).[13]

The smooth stereospecific transformations of **22** to **24** and of **25** to **28** represent an excellent way to prepare optically active epoxides. Since the conversion of an optically active diol to a cyclic ketal does not involve a change in configuration at either carbon and the subsequent steps involve two inversions at one carbon (it may be either carbon if an unsymmetrical diol is used instead of 2,3-butanediol), the resulting epoxide must have the same configuration at each carbon as did the original diol. Thus, if a mixture of halo esters is obtained it need not be separated, as each component must yield the same epoxide.

Further examples of the utility of the reactions described are given by the conversion of 2-carboxy-2,5,5-trimethyl-1,3-dioxane (**8**) to 3-bromo-2,2-dimethylpropyl acetate (**29**), of 2-carboxy-2-methyl-1,3-dioxepane (**3**) to 4-chlorobutyl acetate (**30**), and of 2-carboxy-



5,5-diethyl-1,3-dioxane (**31**) to 3-chloro-2,2-diethylpropyl acetate.

Experimental Section[14]

General Methods of Synthesizing Cyclic α-Ketal Acids. Method A. Preparation of 2-Carboxy-2,5,5-trimethyl-1,3-dioxane (8).—In a typical reaction a mixture of 15.0 g (0.17 mol) of pyruvic acid, 26.6 g (0.256 mol) of 2,2-dimethyl-1,3-propanediol, 150 ml of benzene, and 3 g of acid resin (Amberlite IR-120, Mallinckrodt Chemical Co.) was heated to reflux in an apparatus having a phase-separating head. After 15 hr about 6.5 ml of water was obtained. The filtered reaction mixture was concentrated to give 38 g of residue, which was heated with strong aqueous alkali for 30 min on the steam bath. The resulting alkaline solution was carefully neutralized in the cold with HCl; at the end H_3PO_4 brought the pH to 1. The product was isolated by ether extraction and the dried ($MgSO_4$) extracts were concentrated to afford a creamy solid (33.4 g) which was recrystallized from 2 l. of heptane to give 23.0 g (77% based on pyruvic acid) of **8**** (dried *in vacuo* over P_2O_5): mp 115–116°; nmr ($CDCl_3$) δ 0.77, 1.22 (s, s, 6, 5,5-*gem*-dimethyl), 1.61 (s, 3, 2-Me), 3.58 (s, 4, CH_2), 9.47 (s, 1, COOH). Liquid products were vacuum distilled.

(9) H. J. Lucas and H. K. Garner, *J. Amer. Chem. Soc.*, **70**, 990 (1948). See also C. C. Price and P. F. Kirk, *ibid.*, **75**, 2396 (1953).

(10) The designation *R* refers to the carbon attached to the phenyl group. The compound designated as **25** is a mixture of diastereoisomers (about 3:2 as judged by nmr) because of the new asymmetric center at C-2. No attempt was made to separate these isomers or to determine which was the major component. The same is true for **14**.

(11) The sign of rotation of (*S*)-**26** is negative (neat) but positive in $CHCl_3$. Similarly (*R*)-**28** is positive (neat) but negative in $CHCl_3$. See G. Berti, F. Bottari, and B. Macchia, *Ann. Chim. (Rome)*, **52**, 1101 (1962).

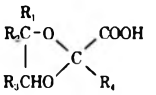
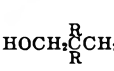
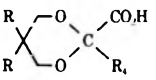
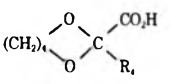
(12) (a) J. B. Conant and W. R. Kirner, *J. Amer. Chem. Soc.*, **46**, 232 (1924); (b) P. Beltrame, L. Olear, and M. S. Monetta, *Gazz. Chim. Ital.*, **89**, 2039 (1959).

(13) J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 885 (1956).

(14) Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer as films on NaCl plates. Nuclear magnetic resonance spectra were determined on a Varian 60 high-resolution spectrometer using TMS as an internal standard. The mass spectra were determined in an AEI MS-902 double-focusing mass spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter (accuracy to 0.001°) using a 10-cm Micro-cell with inner glass tube diameter of 3.4 mm and a cell volume of 1 ml. In a typical rotation determination, the sample was weighed on a Fisher Gram-Atic balance (accurate to 0.0001 g) and dissolved in a suitable solvent in a 1-ml Kimax volumetric flask, and the prepared solution of known concentration was transferred into the Micro-cell for immediate measuring in the instrument. Measuring accuracy with micro cells is claimed to be approximately ±0.2% for rotations >1° by the manufacturer. Elemental microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn., and by M-H-W Laboratories, Garden City, Mich. All new compounds designated by a double asterisk had analyses within ±0.3% of theory for the elements listed in parentheses by M-H-W Laboratories, or Galbraith Laboratories. All known compounds designated by * had nmr, ir, and mass spectra (parent peak) which were consistent with the assigned structures.

TABLE I

PREPARATION OF CYCLIC KETALS FROM α-KETO ACIDS

Registry no.	Diol $R_1COHCHOHR_3$ R_2	Keto acid $R_4COCOOH$	Bp.°C, of 1,3-dioxolane[a] 	Elemental analysis	Yield, %
107-21-1	$R_1 = R_2 = R_3 = H$	$R_4 = CH_3$[l]	**4**, 85–86**	$[(C_5H_8O_4),C,H]$	55[b]
57-55-6	$R_1 = R_2 = H$; $R_3 = CH_3$	$R_4 = CH_3$	**14**, 89–90[c]**	$[(C_6H_{10}O_4),C,H]$	70[d]
558-43-0	$R_1 = R_2 = CH_3$; $R_3 = H$	$R_4 = CH_3$	**17**, 91–92[e]**	$[(C_7H_{12}O_4),C,H]$	48[d]
5396-58-7	$R_1 = R_3 = CH_3$; $R_2 = H$[f]	$R_4 = CH_3$	**22**, 77.5–78**	$[(C_7H_{12}O_4),C,H]$	51[d]
93-56-1	$R_1 = R_2 = H$; $R_3 = Ph$[g]	$R_4 = CH_3$	**25**, 133–134[h]**	$[(C_{11}H_{12}O_4),C,H]$	51[d,k]
	$R_1 = R_2 = R_3 = H$	$R_4 = Ph$[m]	76.5–77.5[i]**	$[(C_{10}H_{10}O_4),C,H]$	53[b]
	$R_1 = R_2 = H$; $R_3 = CH_3$	$R_4 = Ph$	**11**, 147.0–150.5[c]**	$[(C_{11}H_{12}O_4),C,H]$	51[b]
					
126-30-7	$R = CH_3$	$R_4 = CH_3$	**8**, 115–116[j]**	$[(C_8H_{14}O_4),C,H]$	78[b]
115-76-4	$R = C_2H_5$	$R_4 = CH_3$	**31**, 90.5–91.5[j]**	$[(C_{10}H_{18}O_4),C,H]$	89[d]
110-63-4	$HO(CH_2)_4OH$				
		$R_4 = CH_3$	**3**, 105–107**	$[(C_7H_{12}O_4),C,H]$	63[d]

[a] All boiling points are in the range of 0.5–1.0 mm. [b] Prepared by method A. [c] A mixture of stereoisomers.[10] [d] Prepared by method B. [e] At 8.5 mm. [f] D-(−)-2,3-butanediol, $[\alpha]^{22}D$ −12.9°, neat. [g] (*R*)-(−)-phenylethanediol, $[\alpha]^{19.5}D$ −39.2° (*c* 0.0304, ethanol). [h] At 0.06 mm. [i] Melting point, recrystallized from hexane. [j] Melting point, recrystallized from heptane. [k] Crude product suitable for further reaction. [l] Registry no., 127-17-3. [m] Registry no., 611-73-4.

Method B. Preparation of D-(−)-2-Carboxy-2,4,5-trimethyl-1,3-dioxolane (22).—In a typical reaction, D-(−)-2,3-butanediol[15] [10.0 g, 0.11 mol, $[\alpha]^{22}D$ −12.9° (neat)] was added dropwise in 2.5–3 hr to a well-stirred mixture of 29.3 g (0.33 mol) of pyruvic acid and 1 g of acidic resin (Amberlite IR-120) in 150 ml of benzene held at reflux as in method A. After a further 30 min at reflux 2.8 ml of water had been collected. After cooling and filtration, distillation and redistillation afforded 8.9 g (50% based on diol) of **22**:** bp 77–78° (0.6 mm); $[\alpha]^{22}D$ −14° (neat); nmr δ 1.28 (d, *J* = 5.5 Hz, 6, 4-Me, 5-Me), 1.55 (s, 3, 2-Me), 3.81 (m, 2, 4-H, 5-H), 9.47 (s, 1, COOH).

(*R*)-(−)-2-Carboxy-2-methyl-4-phenyl-1,3-dioxolane (25).—By method B, (*R*)-(−)-phenylethanediol, mp 64.5–65.5° [from benzene–petroleum ether (bp 30–60°)], $[\alpha]^{19.5}D$ −39.24° (*c* 0.0304, ethanol),[16] was converted into **25**,[10] bp 133.5–134.5° (0.06 mm), $[\alpha]^{20}D$ −57.37° (*c* 0.0638, $CHCl_3$), in 51% yield. An analytically pure sample of **25**, having the same rotation, was obtained only after a cold aqueous alkaline solution of **25** was extracted with ether and **25** was liberated in the cold with phosphoric acid. The data for the other compounds synthesized are summarized in Table I.

General Methods of Synthesis of Esters of Chlorohydrins from Ketals of α-Keto Acids. A. Reaction of Ketals of α-Keto Acids with PCl_5.—In a typical experiment, 1 g (4.83 mmol) of the diastereoisomeric mixture[10] of **11** in 5 ml of CH_2Cl_2 was added dropwise to a solution of 1.05 g (5.83 mmol) of PCl_5 in 10 ml of CH_2Cl_2 at room temperature in a 50-ml flask fitted with a 10-ml pressure-equalizing dropping funnel and a gas outlet. The gas evolved was passed over a small amount of ammonia to detect HCl, through a test solution[17] to test for carbon monoxide, or measured by collection over water. Carbon monoxide and HCl were immediately detected. The reaction was essentially complete after 15 min. When the gas evolved was not passed through the CO testing solution, the reaction was monitored by the volume of CO collected. After standing at room temperature for 2 hr, dilute Na_2CO_3 was added (with cooling). The CH_2Cl_2 layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. Distillation afforded 0.80 g (84%) of **12**,‡ bp 98.0–99.5° (1.2 mm), containing about 5% of **13**.‡ The presence of a small amount of **13** was revealed by nmr analysis [with 15 mol % of $Eu(DMP)_3$ added[18]] and the precentage was estimated by integration. The methyl proton signal of **12** at δ 2.21 (d, *J* = 6.5 Hz) is shifted downfield more (because it is β to the ester function) than is the methyl of **13** at δ 1.8 (d, *J* = 6.5 Hz), which is γ to the ester function.[19]

In a similar manner, the proportions of **15**[20]‡ (93%) and **16**‡ (7%) were estimated in the product of reaction of **14** with PCl_5. In addition an authentic sample of a mixture of **15** and **16** was prepared by acetylation of a mixture of 1-chloro-2-propanol and 2-chloro-1-propanol (*ca.* 7:3) obtained from the Columbia Organic Chemicals Co.

B. Reaction of Sodium Salts of α-Ketal Acids with PCl_5 and $SOCl_2$.—In a typical reaction, 0.50 g of the dried sodium salt prepared from **8** (by neutralization with the equivalent of $NaHCO_3$ followed by rotary evaporation of water and drying of the salt by distillation of benzene therefrom) was suspended in 2 ml of CH_2Cl_2 and treated during 15 min with a solution of 0.465 g of PCl_5 in 10 ml of CH_2Cl_2 in an apparatus similar to that described above in part A. Carbon monoxide was evolved immediately and the reaction was complete shortly after the PCl_5 solution had been added. After a conventional work-up there was obtained 0.38 g (90%) of **10**,[21]‡ bp 95–96° (9.6 mm).

Similarly, when a solution of 5 g of $SOCl_2$ in 3 ml of dry ether at room temperature was added to a suspension of the dried sodium salt, prepared from 1.85 g of **1**, in ether, carbon monoxide[17] and sulfur dioxide[22] were immediately detected. After heating at reflux for 2 hr, the mixture was filtered. Distillation afforded 1.29 g (75%) of **6**,‡ bp 142.0–142.5°.

C. Reaction of Ketals of α-Keto Acids with $SOCl_2$.—The following is a typical example. Excess thionyl chloride (0.8 g, 6.7 mmol) in 5 ml of anhydrous ether was added to 0.88 g (4.58 mmol) of 2-carboxyl-2-phenyl-1,3-dioxolane at room temperature.

(15) Obtained from the Norse Laboratories, Santa Barbara, Calif. 93103.

(16) J. A. Dale and H. S. Mosher, *J. Org. Chem.*, **38**, 4002 (1970), report $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH) for (*R*)-phenylethanediol; hence our diol was about 100% optically pure. We thank Dr. J. D. Morrison for pointing this out to us.

(17) F. Feigl, "Spot Tests in Organic Analysis," 5th Translated English edition, Elsevier, Amsterdam, 1956, p 327.

(18) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).

(19) See R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1522 (1971), and references cited therein.

(20) A. N. Pudovik and E. M. Faizullin, *Zh. Org. Khim.*, **2**, 798 (1966); *Chem. Abstr.*, **65**, 15214*h* (1966).

(21) M. Bartok, B. Kozma, and A. S. Gilde, *Acta Univ. Szegod., Acta Phys. Chem.*, **11**, 35 (1965), give bp 96–98° (7 mm).

(22) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1966, p 553.

Carbon monoxide, SO_2, and HCl were immediately detected as described above.[17,22] The reaction mixture appeared yellow and was stirred at ambient temperature overnight. Distillation afforded 0.67 g (79%) of 2-chloroethyl benzoate,‡ bp 98.5–99° (1.4 mm).[23]

Reaction of (*R*)-(−)-2-Carboxy-2-methyl-4-phenyl-1,3-dioxolane (25) with PCl_5.—Addition of a solution of 0.9 g (4.32 mmol) of pure **25**, $[\alpha]^{23}D$ −57.26° (*c* 0.035, $CHCl_3$), in 8 ml of CH_2Cl_2 to a solution of 1.2 g of PCl_5 in 20 ml of CH_2Cl_2 in a similar manner as described above afforded 0.85 g (4.29 mmol) of (*S*)-(+)-2-chloro-2-phenylethyl acetate (**26**)[24]‡ [bp 92–93° (1 mm); $[\alpha]^{23.5}D$ 89.91° (*c* 0.032, $CHCl_3$); nmr (CCl_4) δ 2.0 (3, s, CH_3COO–), 4.36 (2, d, J = 7 Hz, –OCH_2–), 5.0 [1, m, –(C_6H_5)CHCl], and 7.32 (5, s, C_6H_5–)] containing *ca.* 3% **27**,[25]‡ nmr (CCl_4) δ 2.05 (3, s, CH_3COO–), 3.67 (2, d, J = 6.5 Hz, –CH_2Cl), 5.84 [1, t, J = 6.5 Hz, –$OCH(C_6H_5)$–], and 7.25 (5, s, C_6H_5). The percentage of **27** was estimated by integration of the acetyl methyl signal at δ 2.05 with respect to that of **26** at δ 2.0, through a 50-Hz sweep width. When the sodium salt prepared from crude **25**, $[\alpha]^{20}D$ −57.37° (*c* 0.0638, $CHCl_3$), was treated with PCl_5 as described above there was obtained (*S*)-(+)-**26** (containing *ca.* 4% of (*R*)-**27** as estimated above), $[\alpha]^{20}D$ 73.74° (*c* 0.0747, $CHCl_3$).

L(+)-*erythro*-**3-Chloro-2-butyl Acetate (23).**[26]—Treatment of D(−)-2-carboxy-2,4,5-trimethyl-1,3-dioxolane (**22**), $[\alpha]^{22}D$ −14° (neat) [made from D(−)-2,3-butanediol, $[\alpha]^{22}D$ −12.9° (neat)] with PCl_5 in CH_2Cl_2 as above afforded **23**,‡ bp 87–88° (52 mm), $[\alpha]^{21}D$ 12.74° (neat), in 90% yield. Reaction of **22** with $SOCl_2$ in CH_2Cl_2 afforded **23**, $[\alpha]^{21}D$ 15.16° (*c* 0.0483, CH_2Cl_2), in 80% yield.

3-Chloro-2,2-dimethyl-1-propyl Acetate (10).‡—Treatment of **8** with PCl_5 in CH_2Cl_2 gave **10**,[21] bp 70–71° (8.5 mm), in 85% yield. Yields of **10** were inferior when methods B and C were used.

4-Chlorobutyl Acetate (30).‡—Method A was used to prepare **30**,[27] bp 80–82° (11 mm), from **3** in 85% yield.

Reaction of 8 with PBr_3.—A solution of 1.0 g (3.7 mmol) of PBr_3 in 5 ml of dry ether was added dropwise to a solution of 1.0 g (5.75 mmol) of **8** in 15 ml of ether. The evolution of HBr and CO were detected immediately. After standing overnight, the readily volatile substances were removed under reduced pressure. Nmr analysis showed that the crude residue was essentially pure 3-bromo-2,2-dimethylpropyl acetate. On distillation an analytical sample of this bromo ester (**29**),‡ bp 80–81° (8 mm), was obtained.

Chemical and Nmr Evidence for 2-Chloro-2-methyl-1,3-dioxolane (5).—A mixture of 0.2 g of **4** and 0.32 g of PCl_5 in 0.6 ml of CH_2Cl_2 was stirred at −60 to −70° for 3 hr, during which time HCl (g) and CO were detected.[17] Low-temperature nmr (CH_2Cl_2) analysis of the product at −58° revealed that the major product had signals at δ 1.66 (s, 3, C-2 Me) and 4.14 (s, 4, –CH_2–CH_2–) consistent with the formulation as **5**,[4] which rapidly rearranged on warming to 0° to **6**, nmr (CH_2Cl_2) δ 2.08 (s, 3, CH_3–COO–), 3.68 (m, 2), and 4.32 (m, 2), an A_2M_2 pattern for $ClCH_2$–CH_2O ($COCH_3$). In a similar run the product from 1.85 g of **4** was stirred at −60° until no more CO was evolved (4 hr). Excess trimethyl phosphite was added and the mixture, after stirring at −60° for 4 hr, was allowed to come to room temperature overnight. After removal of methylene chloride and excess trimethyl phosphite, the residue was fractionated to give about 0.75 g (43%) of **6** and 0.78 g (50%) of dimethyl phosphonate,[28] nmr (neat) δ 3.75 [d, 6, J_{POCH} = 12 Hz, $(CH_3O)_2P$], 6.75 (d, 1, J_{PH} = 694 Hz, HP–), and 1.25 g (45%) of **7**,[4]‡ bp 73–74° (15 mm), slightly contaminated with dimethyl phosphonate, nmr (neat) δ 1.45 (d, 3, J_{PCCH} = 17 Hz, CH_3CP), 3.69 (d, 4, J_{PCOCH} = 11 Hz, –OCH_2–CH_2O–), 3.74 (6, d, J_{POCH} = 11 Hz, 2 CH_3O–).

Nmr Evidence for 9.—Addition of a solution of 0.2 g (1.15 mmol) of **8** in 0.4 ml of CH_2Cl_2 to 0.26 g of PCl_5 in 0.2 ml of CH_2Cl_2 at −70° as described above afforded essentially pure **9**, nmr (CH_2Cl_2, −57°) δ 1.30 [s, 6, $(CH_3)_2C$], 2.89 (s, 3, C-2 methyl), 4.87 (d, 4, J = 1.5 Hz, ring protons), in agreement with the formulation as **9**. On warming to 5° and finally to 35°, the ketal of the acid chloride slowly rearranges to **10**.[21]‡ In contrast to **5**, **9** appears to be stable at temperatures up to about −10°, and rearranges much more slowly than **5**.

(*R*)-(−)-Styrene Oxide (28).—A solution of 3.2 g (16.1 mmol) of **26**, $[\alpha]^{27}D$ 89.91° (*c* 0.032, $CHCl_3$), which contained about 3% of **27**, in 4 ml of methanol was added during 20 min to a stirred ice-cold solution of 20 g of NaOH in 25 ml of water. After 3 hr at 0° the product was isolated by $CHCl_3$ extraction. On removal of the $CHCl_3$ crude (*R*)-styrene oxide was obtained in almost quantitative yield. On distillation a center cut was obtained, bp 57.5–58.5° (4 mm), $[\alpha]^{25}D$ 34.1° (neat, 1 dm), $[\alpha]^{25}D$ −22.5 (*c* 2.390, $CHCl_3$), −21.5 ± 1.5° (*c* 0.330, $CHCl_3$).[29]

D-(+)-2,3-Epoxybutane.—A solution of 0.9 g of **23**, $[\alpha]^{22.5}D$ 12.48° (neat), in 1 ml of ethylene glycol was added during 25 min to a stirred solution of 13.5 g of KOH in 7.4 ml of water held at 117° (oil bath). The epoxide was distilled as formed. At the end the oil-bath temperature was raised to 145°. The distillate was thoroughly dried with $CaCl_2$ to yield 0.35 g (81%) of D-(+)-2,3-epoxybutane,‡ bp 50–51°, $[\alpha]^{21.5}D$ 76.22° (*c* 0.0613, xylene).[30]

Registry No.—**3**, 38088-73-2; **4**, 5736-04-9; **5**, 38088-74-3; **7**, 17997-31-8; **8**, 36294-83-4; **8** (Na salt), 38808-77-6; **10**, 2163-55-5; **11**, 38088-79-8; **12**, 36220-92-5; **13**, 7022-98-2; **14**, 6413-11-2; **17**, 38088-83-4; **22**, 36220-93-6; **23**, 36220-94-7; **24**, 1758-33-4; **25**, 38088-84-5; **26**, 6509-95-1; **28**, 20780-53-4; **31**, 38088-86-7; Cl_5P, 10026-13-8.

(23) M. V. Prokof'eva, S. R. Rafikov, and B. V. Suvorov, *Zh. Obshch. Khim.*, **32**, 1318 (1962); *Chem. Abstr.*, **58**, 1392e (1963), give bp 118–120° (2 mm).

(24) For the optically inactive compound, see Y. Yukawa and M. Sakai, *Bull. Chem. Soc. Jap.*, **39**, 827 (1966).

(25) An authentic sample, bp 87.0–87.5° (11 mm), was prepared by acetylation of 2-chloro-1-phenylethanol in pyridine. See V. R. Kartashov and I. V. Badrikov, *Zh. Org. Khim.*, **3**, 775 (1967); *Chem. Abstr.*, **67**, 43162e (1967).

(26) For racemic compound, see R. C. Fahey and C. Schubert, *J. Amer. Chem. Soc.*, **87**, 5172 (1965).

(27) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).

(28) Product resulting from dealkylation of $(CH_3O)_3P$ by HCl formed in the reaction. See Ye. L. Geffer and J. Burdon, "Organophosphorus Monomers and Polymers," Vol. 6, International Series of Monographs on Organic Chemistry, Pergamon Press, Elmsford, N. Y., 1962, p 114.

(29) The optical purity of our (*R*)-**28** was about 100% as judged by the fact that D. J. Pasto, C. C. Cumbo, and J. Fraser, *J. Amer. Chem. Soc.*, **88**, 2194 (1966), report $[\alpha]^{25}D$ −34.2° (neat, 1 dm) for (*S*)-**28**. All measurements were made on a Perkin-Elmer 141 polarimeter by Dr. Dan Olson, whom we thank for repeating this preparation.

(30) H. L. Lucas and H. K. Garner, *J. Amer. Chem. Soc.*, **70**, 990 (1948), give $[\alpha]^{25}D$ 59° (neat) for 2,3-epoxybutane.

Phosphorus Betaines Derived from Cycloheptene and Cyclooctene Oxides. Inversion of Cyclooctenes

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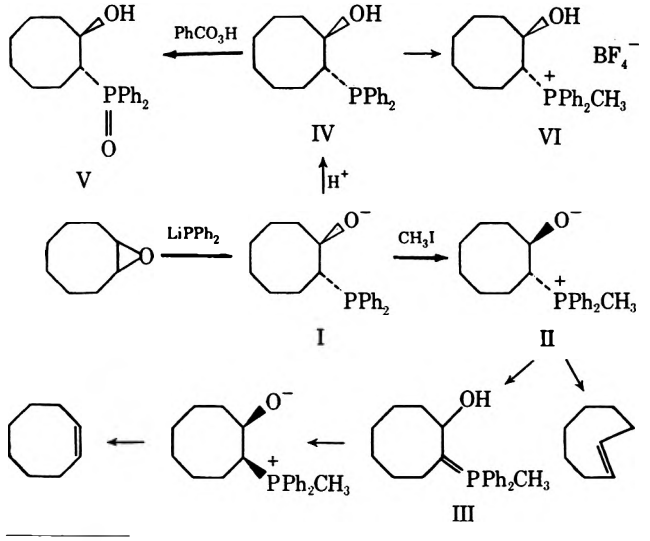
trans-Cyclooctene, *trans*-1-methylcyclooctene, *cis,trans*-1,4-cyclooctadiene, and *cis,trans*-1,5-cyclooctadiene can be prepared from the corresponding epoxides by treatment with lithium diphenylphosphide followed by methyl iodide. Similar treatment of cycloheptene oxide affords cycloheptenylmethyldiphenylphosphonium fluoroborate, but no *trans*-cycloheptene. Attempted deoxygenation of 1,2-dimethylcycloheptene oxide results in retro Wittig cleavage to the acyclic ketophosphonium salt XX instead of fragmentation to methyldiphenylphosphine oxide and 1,2-dimethyl-*trans*-cycloheptene. The "betaine" derived from cyclooctene oxide can be observed by ^{31}P nmr and is assigned the cyclic structure VII on the basis of its chemical shift of δ 62.8.

Deoxygenation of acyclic epoxides by treatment with lithium diphenylphosphide (LDP) followed by methyl iodide affords alkenes with overall inversion of stereochemistry.[3] Similar inversion in the case of cyclic epoxides would result in a simple route to strained *trans*-cycloalkenes; so we have studied the deoxygenation of several cyclooctene and cycloheptene oxides. The results of this study show that the relatively stable *trans*-cyclooctenes can be prepared, but that potential betaine precursors to *trans*-cycloheptenes readily find other reaction pathways when faced with the prospect of fragmentation to alkene and phosphine oxide.

Cyclooctene oxide reacts slowly with LDP at room temperature to form the expected SN2 product, the phosphine alkoxide I. Reaction of I with methyl iodide at 25° results in fragmentation to *trans*-cyclooctene (>90% yield, 70% isolated; >99.5% trans) provided that rigorously aprotic conditions are maintained throughout the experiment. Failure to dry the reagents has little effect on the overall yield, but the stereoselectivity drops from >99:1 to as low as 2:1 *trans*:*cis*-cyclooctene. Loss of stereochemistry under protic conditions is explained by formation of the hydroxy ylide III from the *trans*-betaine II followed by protonation to afford the *cis*-betaine.[4]



The first step in the sequence, cleavage of cyclooctene oxide by LDP, appears to be stereospecific and far less sensitive to reaction conditions than the betaine fragmentation step. Neutralization of the initial phosphine alkoxide I with acetic acid affords the phosphine alcohol IV, characterized as the oxide V or as the quaternary phosphonium fluoroborate VI. Within the limits of nmr or tlc analysis, other stereoisomers are not present. Treatment of the crystalline salt VI with *n*-butyllithium or diazabicycloundecene (DBU) in dry tetrahydrofuran affords *trans*-cyclooctene (80–85% yield, 99% trans). However, similar treatment of crude VI (at least 85% pure by nmr analysis) with DBU affords up to 30% *cis*-cyclooctene. Apparently, some minor side product from the epoxide cleavage step is able to catalyze interconversion of II and III under protic conditions with resulting loss of stereochemistry.

The reaction of VI with butyllithium can be followed conveniently by ^{31}P nmr spectroscopy. The ^{31}P resonance of VI occurs at δ −34.7 relative to external 85% phosphoric acid, as expected for a typical phosphonium salt.[5] Upon reaction of VI with butyllithium in tetrahydrofuran at −40°, a homogeneous solution is obtained which displays a single ^{31}P resonance at δ +62.8. This chemical shift is characteristic of pentavalent phosphorus[5] and is consistent with the cyclic structure VII but not with the betaine formulation II. Typical Wittig intermediates have not been studied previously by ^{31}P nmr, but the stable "betaine" produced by reaction between isopropylidenetriphenylphosphorane and diphenylketene appears to have considerable O–P bonding, as evidenced by the ^{31}P resonance at δ +36.[6] In other systems, pentavalent phosphorus structures have been distinguished from the isomeric betaines by ^{31}P chemical shifts of δ +35 to +67 for the former and *ca.* −7 for the latter.[7]

The broad ^{31}P resonance of VII begins to diminish perceptibly at 5° (rapidly at 20°) while a broadened quartet (J_{P-CH} = 13 Hz) appears at δ −33.8. The chemical shift and appearance of this signal can be duplicated precisely by a solution of authentic methyldiphenylphosphine oxide and lithium fluoroborate. Pure methyldiphenylphosphine oxide displays a broadened quartet at δ −25 (J_{P-CH} = 13 Hz) in tetrahydro-

(1) Alfred P. Sloan Fellow, 1971–1973.

(2) We thank the National Science Foundation for support of this work.

(3) E. Vedejs and P. L. Fuchs, *J. Amer. Chem. Soc.*, **94**, 822 (1972).

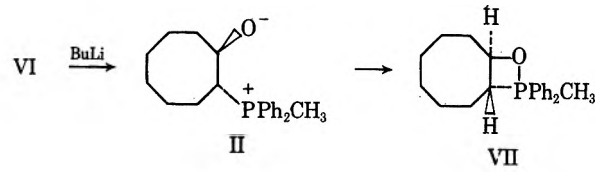
(4) Bissing and Speziale have suggested the formation of an analogous hydroxy ylide to explain partial loss of stereochemistry upon deoxygenation of 4-octene oxide with triphenylphosphine at 160°: D. E. Bissing and A. J. Speziale, *ibid.*, **87**, 2683 (1965).

(5) M. Grayson and E. J. Griffith, Ed., "Topics in Phosphorus Chemistry," Vol. 5, Interscience, New York, N. Y., 1967.

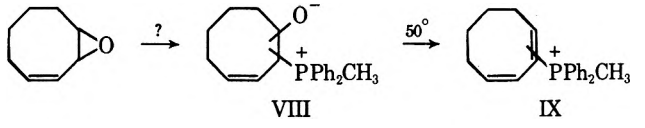
(6) G. Wittig and A. Haag, *Chem. Ber.*, **96**, 1535 (1963).

(7) I. Kawamoto, T. Hata, Y. Kishida, and C. Tamura, *Tetrahedron Lett.*, 2417 (1971); G. H. Birum and C. N. Matthews, *Chem. Commun.*, 137 (1967).

furan.[8] No other signals are observed in the temperature range −20 to 20°, indicating that the dipolar betaine structure II is unstable with respect to VII in tetrahydrofuran.



Deoxygenation of the monoepoxides of 1,4- or 1,5-cyclooctadienes under the usual conditions affords *cis,trans*-1,4-cyclooctadiene and *cis,trans*-1,5-cyclooctadiene in yields of 40 and 60%, respectively. Methyldiphenylphosphine oxide is isolated in >80% yield from both reactions; so it is likely that the low yield of cis,trans dienes is due to complications after betaine fragmentation. Addition of diphenylisobenzofuran along with the methyl iodide affords the expected Diels–Alder adducts from either *cis,trans*-1,5- or *cis,trans*-1,4-cyclooctadiene, but the yield of adducts is no higher than the yield of dienes in the absence of diphenylisobenzofuran. Attempted deoxygenation of 1,5-cyclooctadiene dioxide to the highly reactive *trans,trans*-cyclooctadiene affords only traces of hydrocarbon products. Treatment of the monoepoxide of 1,3-cyclooctadiene under the usual conditions also fails to form the hydrocarbon product. At 50° the presumed betaine VIII is converted into a phosphonium salt with a P–CH_3 doublet at δ 2.95 and olefinic hydrogens between δ 6 and 8, consistent with the cyclooctadienylphosphonium structure IX.



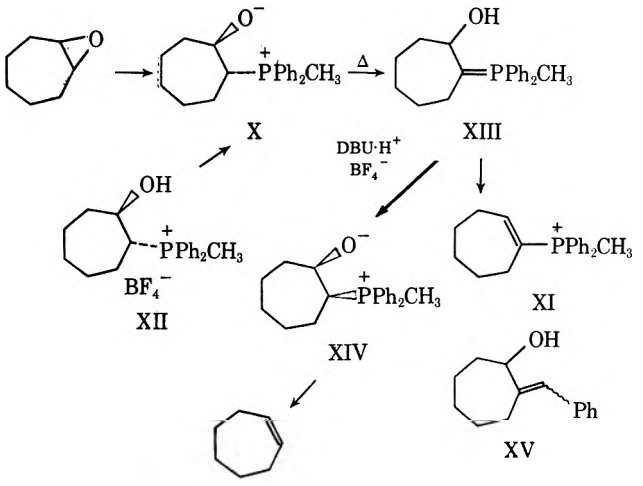
Reaction of 1-methylcyclooctene oxide with LDP followed by methyl iodide as usual affords a mixture of *cis*- and *trans*-1-methylcyclooctenes, even under scrupulously aprotic conditions. However, treatment of the corresponding crystalline hydroxyphosphonium salt with DBU in tetrahydrofuran affords only the trans isomer (70% isolated yield, 99% trans) characterized by exact mass, nmr, and formation of a diphenylisobenzofuran adduct. The factors causing loss of stereochemistry in the direct reaction have not been determined.

Cycloheptene oxide is converted into the betaine X under the usual conditions, but no evidence of fragmentation to *trans*-cycloheptene can be detected. In refluxing tetrahydrofuran, the betaine is converted into the methyldiphenylcycloheptenylphosphonium salt XI as the sole product observed by nmr. No trace of methyldiphenylphosphine oxide can be detected and addition of diphenylisobenzofuran does not result in the Diels–Alder adduct of *trans*-cycloheptene.[9] The structure of the salt XI is verified by independent synthesis from 1-lithiocycloheptene and chlorodiphenylphosphine followed by quaternization with methyl iodide.

(8) The $LiBF_4$ adduct of methyldiphenylphosphine oxide can be isolated if desired as a stable, crystalline, water-soluble substance.

(9) E. J. Corey, F. A. Carey, and R. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965).

The crystalline hydroxyphosphonium salt XII can be prepared in the usual way, and treatment of XII with *n*-butyllithium followed by heating affords XI as before.[10] However, reaction of XII with DBU in refluxing tetrahydrofuran affords *cis*-cycloheptene and methyldiphenylphosphine oxide in addition to XI. Formation of *cis*-cycloheptene and XI is explained by conversion of X into the hydroxy ylide XIII. In the presence of the proton donor DBU·$H^+BF_4^-$, XIII undergoes hydrogen transfer to form the *cis*-betaine XIV, which can fragment to *cis*-cycloheptene. Under aprotic conditions, XIII suffers elimination of hydroxide to form XI. Several other cases of vinylphosphonium salt formation from betaines have been reported recently.[11] The elimination of hydroxide is not reversible with or without added water, and cycloheptene is not formed from authentic XI under the DBU reaction conditions.

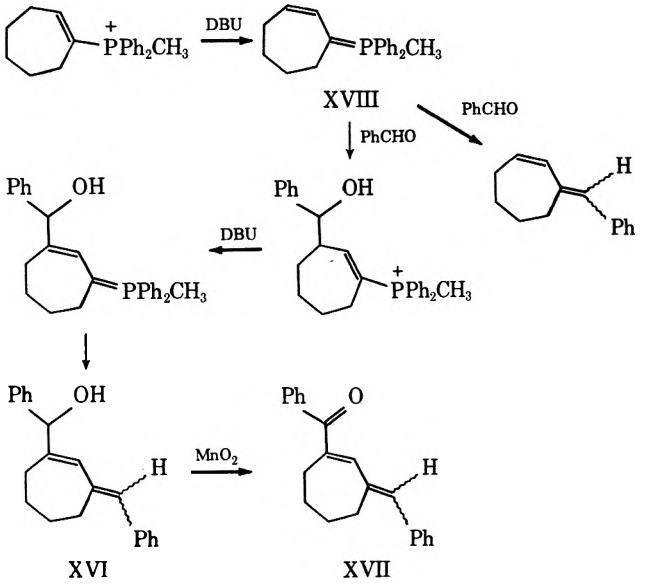


In an attempt to trap the hydroxy ylide XIII as the Wittig product, we have examined the reaction of XII with DBU in the presence of benzaldehyde. The simple product XV is not formed, however, and all of the new products are derived from further reactions of XI. In addition to cycloheptene, methyldiphenylphosphine oxide, and the obvious Wittig products styrene and benzylidenecycloheptene, the reaction mixture contains the dienol XVI ($C_{21}H_{22}O$) resulting from reaction of 2 mol of benzaldehyde with XI. Oxidation of XVI with active MnO_2 affords a cis,trans mixture of dienones, one of which has been isolated in pure form. The dienone is assigned the structure XVII on the basis of analysis, the nmr spectrum, and the ultraviolet chromophore (326 nm, ϵ 22,100; 255 nm, ϵ 15,000). Formation of the dienol XVI is explained by intial condensation of benzaldehyde at the γ position of the conjugated ylide XVIII followed by deprotonation and normal Wittig reaction. Benzyl-

(10) We have failed to detect X or its pentavalent phosphorane isomer by ^{31}P nmr under conditions which were successful in the analogous reaction of VI with butyllithium. The absence of ^{31}P signals at −20° is probably due to precipitation of the reaction intermediate(s). However, a homogeneous solution is obtained at *ca.* 0° which still has no observable ^{31}P signal even though an equally concentrated solution of XII displays an easily observed signal at δ −31.4. At present, we are inclined to suspect line broadening due to an equilibrium between two or more structures such as the betaine X, its $LiBF_4$ adduct, the cyclic phosphorane, etc., as the most plausible explanation.

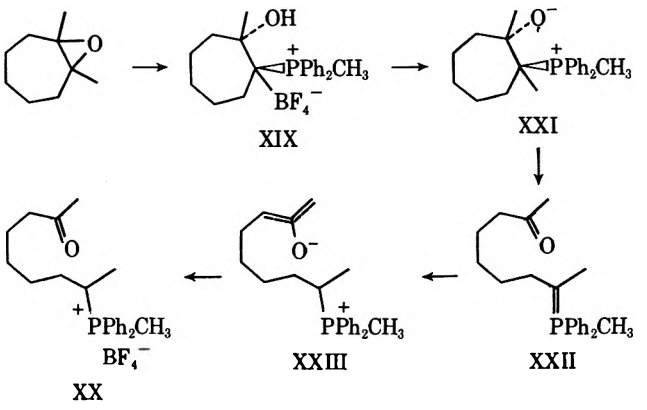
(11) (a) S. Trippett and B. S. Walker, *J. Chem. Soc. C*, 887 (1966); (b) E. E. Schweizer, T. Minami, and D. M. Crouse, *J. Org. Chem.*, **36**, 4028 (1971); (c) E. E. Schweitzer, D. M. Crouse, T. Minami, and A. T. Wehman, *Chem. Commun.*, 1000 (1971).

idenecycloheptene, styrene, and XVI are formed as expected from XI, benzaldehyde, and DBU. Although previous reports of γ attack on allyl ylides are rare,[12] we have found that the reaction is quite general and occurs to some extent with a variety of allyl ylides and aldehydes.[13]



From the above results, it is clear that highly strained *trans*-cycloalkenes cannot be generated by the betaine method unless the possibility of elimination to a vinylphosphonium salt is blocked. Elimination of hydroxide is not possible in the betaine derived from 1,2-dimethylcycloheptene oxide; so we have attempted to convert this precursor into 1,2-dimethyl-*trans*-cycloheptene. The tetrasubstituted epoxide reacts with LDP at 65°, but quaternization of the initial product with methyl iodide followed by aqueous work-up does not produce the expected hydroxyphosphonium salt XIX or any hydrocarbon products. Instead, an isomeric ketophosphonium salt XX is obtained (carbonyl infrared absorption at 5.86 μ). The nmr spectrum of XX has a methyl singlet at δ 2.05, a *P*-methyl doublet at 2.47 (J_{PCH} = 13 Hz), a broadened methylene triplet at 2.38 (J_{HCCH} = 6 Hz), and a methyl signal at 1.29 split into a doublet of doublets (J_{PCH} = 20 Hz, J_{HCCH} = 7 Hz). From the latter signal, it is clear that the *C*-methyl group next to phosphorus is attached to a carbon which also has one hydrogen substituent. These spectral features prove conclusively that XX is the ketophosphonium salt derived from retro Wittig cleavage of the betaine XXI.

The hydroxyphosphonium salt XIX can be isolated by treatment of 1,2-dimethylcycloheptene oxide with LDP, neutralization of the alkoxide with acetic acid, and quaternization of the resulting hydroxyphosphine with methyl iodide. The *C*-methyl signals of XIX are observed at δ 1.16 (singlet) and 1.60 (doublet, J_{PCH} = 20 Hz), and the ^{31}P nmr signal is observed at δ −28. Treatment of XIX with methanolic sodium carbonate or *n*-butyllithium in tetrahydrofuran followed by aqueous work-up affords XX as the only observable product.



Reaction of XIX with *n*-butyllithium in tetrahydrofuran at −70°, warming to 25°, and quenching with D_2O–DCl affords a sample of XX containing deuterium at both enolizable positions (pmr signals at δ 2.47 and 2.05). However, no change in coupling is observed in the doublet of doublets at δ 1.29 or in the intensity of the *P*-CH_3 doublet. Clearly, proton transfer to the ylide carbon in the initial retro Wittig product XXII occurs prior to D_2O–DCL work-up. On the basis of ^{31}P nmr evidence, we conclude that retro Wittig cleavage *and* proton transfer to form the enolates XXIII occur to some extent even at −20°. The only signal observed in the ^{31}P resonance spectrum of the solution obtained from XIX and butyllithium occurs at δ −26.5, and the signal is unchanged upon warming to 25°. The ^{31}P signal of the ylide XXII would be expected at higher field by δ 10–20 relative to the phosphonium salt.[14]

Neither methyldiphenylphosphine oxide nor 1,2-dimethyl-*cis*-cycloheptene is formed from XIX under any conditions examined. The absence of intra- or intermolecular Wittig products is somewhat surprising, since an equilibrium between XXIII and XXII might be anticipated from the comparable pK_a's of protons next to carbonyl or postive phosphorus.[15] Apparently, conversion of XXII to XXIII by proton transfer is rapid compared to Wittig condensation, and essentially irreversible in tetrahydrofuran solution.

The facile retro Wittig cleavage of XXI under aprotic conditions is an unusual example of such cleavage to a reactive ylide and a simple carbonyl fragment. Clearly established examples of betaine cleavage are limited to systems where the potential ylide is stabilized by carbonyl, phenyl, etc., systems where betaine fragmentation to olefin and phosphine oxide is retarded by electron-donating substituents at phosphorus,[16] or reactions which are conducted in hydroxylic solvents.[17]

Retro Wittig cleavage may also explain some of the nonstereoselectivity (formation of *cis*-cycloalkene) observed in decomposition of the betaines II and X under protic conditions. Although we cannot disprove this possibility rigorously, we doubt that internal Wittig reaction could account for the high material

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(14) S. O. Grim, W. McFarlane, and T. J. Marks, *Chem. Commun.*, 1191 (1967); G. H. Birum and C. N. Matthews, *ibid.*, 137 (1967).

(15) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 3.

(16) S. Trippett, *Pure Appl. Chem.*, **9**, 255 (1964); see also ref 4 and ref 15, Chapter 4; M. Schlosser and K. F. Christmann, *Justus Liebigs Ann. Chem.*, **708**, 1 (1967).

(17) M. E. Jones and S. Trippett, *J. Chem. Soc. C*, 1090 (1966); J. W. Rakshys, Jr., and S. V. McKinley, *Chem. Commun.*, 1336 (1971).

balance observed in these reactions, particularly in the experiments leading to cyclooctenes.

The betaine method holds considerable promise for synthesis of substituted *trans*-cyclooctenes, a subject which is under active investigation. However, the technique is not useful for preparation of more highly strained alkenes, since the intermediate betaines are readily converted into vinylphosphonium salts by elimination of hydroxide. Increased alkyl substitution at the epoxide carbons appears to facilitate retro Wittig cleavage; so it is unlikely that simple modifications of the technique will expand its scope to permit generation of *trans*-cycloheptenes.

Experimental Section

Epoxides were prepared by reaction of the appropriate alkenes with *m*-chloroperbenzoic acid in methylene chloride at 25°. The epoxides were worked up with sodium bisulfite and sodium carbonate and were distilled prior to use. Lithium diphenylphosphide (LDP) solution in tetrahydrofuran was prepared as described previously.[3] Hydrocarbon products were analyzed by glpc using a Varian Aerograph 90-P3 gas chromatograph. Proton nmr spectra were obtained using Varian A-60A and HA-100 spectrometers, and ^{31}P spectra were obtained using the Varian XL-100 system[18] with external water lock and without proton noise decoupling.

trans-**Cyclooctene.**—LDP solution[3] (4.15 ml, 1.15 *M*, 0.00476 mol) was injected into a flame-dried three-neck flask under positive argon pressure. Cyclooctene oxide (0.63 g, 0.005 mol) in dry tetrahydrofuran (15 ml) was added at 25° over several minutes using a dropping funnel. The solution was allowed to stand for 30 hr at room temperature, at which time the ruby-red phosphide color had faded to a pale yellow. Freshly distilled methyl iodide was then added (1.03 g, 0.0072 mol) and the mixture was allowed to stand for 0.5 hr at 25° under positive argon pressure. Pentane (100 ml) was then added, and the mixture was filtered to remove precipitated salts and washed several times with water. The pentane layer was dried over sodium sulfate and analyzed by glpc (10 ft × 0.25 in., 20% TCEP/Chromosorb P at 50°) using toluene as internal standard, 90% yield of cyclooctene based on epoxide, <99% trans. For preparative purposes, the pentane layer was concentrated under a Vigreux column and the *trans*-cyclooctene was distilled using a short-path distillation head to yield 0.41 g (75%) of material boiling at 68–72° (100 mm), typically contaminated by *ca.* 3% tetrahydrofuran and 1–2% *cis*-cyclooctene.

(*trans*-2-**Hydroxycyclooctyl**)**methyldiphenylphosphonium Fluoroborate (VI).**—Cyclooctene oxide was allowed to react with LPD as before. After the usual reaction period at 25°, the solution was cooled in Dry Ice–acetone, treated with 1.1 equiv of acetic acid, and stirred for 15 min. The cooling bath was then removed, methyl iodide was added, and the mixture was allowed to warm to room temperature and stirred for 0.5 hr. Most of the solvent was removed under vacuum at room temperature and the salts were precipitated with hexane and washed well to remove unreacted epoxide and traces of cyclooctene. The viscous residue was then dissolved in methanol (5 ml/g of crude salt) and added to a vigorously stirred aqueous solution of sodium fluoroborate (*ca.* 250 equiv).

After stirring for 1 hr, the crude VI was extracted with chloroform and dried over sodium sulfate, and the chloroform was evaporated under vacuum at 30°. Residual chloroform was removed under high vacuum and the resulting foam was crystallized from tetrahydrofuran to afford VI: mp 77–78°; nmr ($CDCl_3$) δ 7.5–8.0 (10 H, br m), 3.4–4.2 (3 H, br m), 2.60 (3 H, d, J = 13 Hz), 1.2–2.2 (12 H, br m), and residual tetrahydrofuran signals at *ca.* 1.8 and 3.7. Extensive efforts to remove the last traces of tetrahydrofuran failed. The nmr spectrum of crude VI was identical except that tetrahydrofuran was not present, and a residual chloroform signal could not be removed completely.

Conversion of VI into *trans*-**Cyclooctene. A. Using Diazabicycloundecene (DBU) as Base.**—Crystalline VI (0.296 g, 0.00071 mol) was stirred with dry tetrahydrofuran (7 ml) and DBU (0.11 g, 0.000714 mol) under nitrogen for 2 hr at room temperature. Aqueous pentane work-up and glpc analysis as before indicated *trans*-cyclooctene, 80% yield, and <1% *cis*-cyclooctene. Under identical conditions, a noncrystalline sample of VI (containing traces of $CHCl_3$) afforded *trans*- and *cis*-cyclooctene in a ratio of 7:3.

B. Using *n*-**Butyllithium.**—Crystalline VI (0.30 g, 0.00072 mol) was stirred in dry tetrahydrofuran (30 ml) at −70°, and *n*-butyllithium in hexane (1.62 *N*, 0.46 ml) was added dropwise. The mixture was stirred for 15 min after addition and allowed to come to room temperature. After 30 min at 25°, the reaction was worked up as before, and glpc analysis indicated 82% *trans*-cyclooctene as the sole volatile product.

C. Conversion of VI into VII. ^{31}P **Nmr Experiment.**—The reaction of VI (0.51 g) and *n*-butyllithium (0.76 ml) was conducted as above except that 4 ml of tetrahydrofuran was used. The mixture was opaque after addition of butyllithium at −70°, but warming to −20° produced a clear solution. The solution was transferred into a 12-mm XL-100 nmr tube under argon pressure and spectra were recorded at 5° intervals between −20 and 25°. A single resonance was observed initially at δ +62.8 relative to external 85% H_3PO_4. At 5°, a new signal was detected at δ −33.8 and integration of the signals indicated a corresponding decrease in the δ 62.8 signal. At 25°, disappearance of the high-field signal was complete within 20 min. The usual work-up and glpc analysis of the nmr sample indicated stereospecific conversion into *trans*-cyclooctene.

(*trans*-2-**Hydroxycyclooctyl**)**diphenylphosphine Oxide (V).**—Cyclooctene oxide (0.94 g, 0.0075 mol) was cleaved with LPD as usual. The resulting tetrahydrofuran solution was then treated with 2% hydrogen peroxide (30 ml) at 10° and allowed to stand for 1 hr at 25° after the initial exothermic reaction. The product was extracted with chloroform, dried ($MgSO_4$), and evaporated under vacuum. The residual oil was crystallized from benzene to afford V (1.5 g, 62% isolated), mp 159–160°. *Anal.* Found: C, 73.28; H, 7.59; P, 9.43. Calcd: C, 73.15; H, 7.67; P, 9.43. By tlc or nmr analysis, the mother liquors contained no other phosphine oxides.

cis,*trans*-**1,4-Cyclooctadiene.**—The same procedure was used as described for preparation of *trans*-cyclooctene, starting from the monoepoxide of *cis*,*cis*-1,4-cyclooctadiene. The product consisted of *cis*,*trans*-cyclooctadiene, 25% yield, and traces of the cis,cis isomer. The yield could be increased to 40% by adding the methyl iodide over 18 hr at 25°. After the usual pentane *vs.* water work-up, the aqueous phase was extracted with $CHCl_3$ to yield 85% of methyldiphenylphosphine oxide, mp 108° (lit.[19] mp 108–109°). The diene was isolated by preparative glpc of the concentrated pentane extracts and characterized by extract mass (calcd 108.0938 amu; found 108.0936 ± 0.001 amu): nmr ($CDCl_3$) δ 5.6–6.0 (4 H, m), 1.94–2.5 (8 H, m); ir ($CHCl_3$) 3.33, 3.40, 3.48, 6.94, 10.13 μ. The *cis*,*trans*-1,4-cyclooctadiene reacted with diphenylisobenzofuran at 25° to form an adduct in quantitative yield, mp 208–209° (recrystallized from $CHCl_3$–ether).

cis,*trans*-**1,5-Cyclooctadiene.**—The same procedure was used as described for preparation of *trans*-cyclooctene. The known *cis*,*trans*-1,5-cyclooctadiene was formed in 60% yield (>99% cis,trans isomer) and was identified by spectral features[20] and formation of an adduct (mp 178–179°) with diphenylisobenzofuran.

(*trans*-2-**Hydroxycycloheptyl**)**methyldiphenylphosphonium Fluoroborate (XII).**—The same procedure was used as described for preparation of VI. The product XII crystallized from $CHCl_3$–CCl_4, 65% in two crops, mp 154–156°. The analytical sample was recrystallized from $CHCl_3$–CCl_4, mp 159–160°. *Anal.* Found: C, 60.06; H, 6.67; F, 18.86; P, 7.81. Calcd: C, 60.02; H, 6.55; F, 18.99; P, 7.74. Nmr ($CDCl_3$): δ 7.5–8.0 (10 H, m), 3.0–4.1 (3 H, br m), 2.51 (3 H, d, J = 13 Hz), 1.61 (br s, 10 H).

Attempted Inversion of Cycloheptene Oxide.—Cycloheptene oxide was treated with LDP followed by methyl iodide as usual. The usual work-up afforded no pentane-soluble products. Extraction of the aqueous phase and pentane-insoluble residues with $CHCl_3$ afforded a crude product having no trace of the *p*-

(18) Provided by the National Science Foundation.

(19) A. E. Arbuzov and and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948).

(20) A. C. Cope, C. F. Howell, J. Bowers, R. C. Lord, and G. M. Whitesides, *J. Amer. Chem. Soc.*, **89**, 4024 (1967).

methyl doublet of methyldiphenylphosphine oxide at δ 1.98. A *P*-methyl doublet was observed at δ 2.8, consistent with the presence of (*trans*-2-hydroxycycloheptyl)methyldiphenylphosphonium iodide.

The experiment was repeated as above, except that the solution obtained after addition of methyl iodide was refluxed for 12 hr. No pentane-soluble products were obtained. The chloroform-soluble fraction displayed a single *P*-methyl doublet at δ 2.88 and other signals characteristic of (1-cycloheptenyl)methyldiphenylphosphonium iodide (see below). The above experiment was repeated in the presence of diphenylisobenzofuran. No trace of the adduct of *trans*-cycloheptene could be detected by tlc analysis.

(1-Cycloheptenyl)methyldiphenylphosphonium Iodide (XI).—Chlorodiphenylphosphine (5.2 g, 0.0236 mol) was stirred in dry ether (100 ml) at −60°. A solution of 1-lithiocycloheptane[21] in ether (85 ml, 0.25 *M*) was added dropwise at a rate such that the temperature did not exceed −55°. After 30 min at −60°, methyl iodide (8.5 g, 0.063 mol) was added and the solution was allowed to come to 25°. After 30 min the mixture was diluted with water and extracted with chloroform, and the organic phase was dried over sodium sulfate and evaporated. The residual oil was taken up in methanol (100 ml) and stirred with excess sodium iodide to ensure a homogeneous counterion.

Chloroform *vs.* water work-up afforded a yellow oil which crystallized from chloroform–ethyl acetate to yield XI (5.5 g, 55%, mp 85–88°). Four recrystallizations afforded pure material, mp 89–90°. *Anal.* Found: C, 56.77; H, 5.96; I, 29.88; P, 7.16. Calcd: C, 56.98; H, 5.73; I, 30.05; P, 7.33. Nmr ($CDCl_3$): δ 7.5–8.0 (10 H, m), 6.88 (1 H, dt, J = 24, 6 Hz), 2.88 (3 H, d, J = 13 Hz), 2.2–2.8 (4 H, m), 1.4–2.0 (6 H, m).

Reaction of XII and DBU.—A suspension of XII (0.39 g, 0.00094 mol) in dry tetrahydrofuran (5 ml) and 1,5-diazabicyclo[5.4.0]undec-5-ene (Aldrich, 0.36 g, 0.0024 mol) was refluxed for 24 hr. The solution was analyzed directly by glpc and was found to contain *cis*-cycloheptene (45%). Water was added and the products were extracted with chloroform to yield 0.35 g of yellow oil. By nmr analysis, the oil consisted of XI (50% yield) and methyldiphenylphosphine oxide (45%).

Reaction of XII, DBU, and Benzaldehyde.—The above experiment was repeated using 0.22 g of XII, 0.087 g of DBU, and 0.29 g (5 equiv) of benzaldehyde. Analysis by glpc indicated the presence of *cis*-cycloheptene (30%) and styrene (15%). The chloroform extracts were separated by preparative layer chromatography over silica gel (three developments with $CHCl_3$) and three zones were collected: R_f 0.9, benzylidenecycloheptene (0.016 g, 20%); R_f 0.1, methyldiphenylphosphine oxide (0.092 g, 85%); R_f 0.3, 3-(α-hydroxybenzyl)benzylidenecycloheptene (XVI) (0.038 g, 30%), viscous oil [ir (neat) 2.80, 2.96, 3.30, 3.40, 3.50 μ; nmr ($CDCl_3$) δ 7.1–7.4 (10 H, m), 6.3–6.7 (2 H, m), 5.16 (1 H, s), 1.5–2.8 (9 H, m)].

XVI (0.2 g, 0.0065 mol) was stirred with active MnO_2 (4 g) in ethyl acetate (25 ml) at 45° for 12 hr, the mixture was filtered and evaporated, and the crude oil was taken up in hexane. The dienone XVII (stereochemistry unknown) crystallized slowly: mp 91–92.5°; uv (methanol) λ_{max} 226 nm (ε 20,500), 255 (15,000), 326 (22,100); ir ($CHCl_3$) 3.31, 3.40, 3.50, 6.12, 6.26 μ; nmr ($CDCl_3$) δ 7.4–7.9 (5 H, m), 7.33 (5 H, s), 7.92 (1 H, s), 7.57 (1 H, s), 2.6–2.9 (4 H, m), 1.8–2.1 (4 H, m); *m/e* 288 amu.

Attempted Inversion of 1,2-Dimethylcycloheptene Oxide.—1,2-Dimethylcycloheptene oxide was treated with LDP at reflux in tetrahydrofuran for 72 hr followed by methyl iodide at 25° as usual. Aqueous work-up afforded no pentane-soluble products, and the chloroform extract contained no methyldiphenylphosphine oxide by nmr or tlc analysis. The oily product was dissolved in methanol and added dropwise to a vigorously stirred solution of aqueous sodium fluoroborate, and the fluoroborate salt was recovered by $CHCl_3$ *vs.* water work-up. The nmr spectrum of the product was identical with the spectrum of XX prepared from pure XIX (see below).

(1,2-Dimethyl-2-hydroxycycloheptyl)methyldiphenylphosphonium Fluoroborate (XIX).—The product of reaction between 1,2-dimethylcycloheptene oxide and LDP was converted into XIX by the same method used to prepare VI. The oily product crystallized inefficiently from tetrahydrofuran to afford colorless crystals: mp 137–140°; nmr ($CDCl_3$) δ 7.5–8.2 (10 H, m), 3.7 (1 H, br s), 2.72 (3 H, d, J = 13 Hz), 1.2–2.4 (*ca.* 11 H, br m), 1.60 (3 H, d, J = 20 Hz), 1.16 (3 H, s). Traces of residual tetrahydrofuran were evident and could not be removed completely under vacuum.

Conversion of XIX into XX.—A suspension of XIX (0.44 g, 0.0011 mol) in dry tetrahydrofuran (4 ml) was cooled to −70° under argon. *n*-Butyllithium in hexane (0.68 ml, 0.0011 mol) was added dropwise *via* syringe with vigorous stirring. The resulting mixture was stirred for 0.5 hr at −70° and then warmed to −22°. The solution was transferred into an XL-100 nmr tube under argon pressure and spectra were recorded between −20 and 25°. A single resonance at δ −26.5 was observed throughout which increased slightly in intensity as the sample was warmed to 25°. The solution was treated with aqueous 5% HCl, the product was extracted with chloroform, and the crude product was treated with excess aqueous sodium fluoroborate as usual. After $CHCl_3$ *vs.* water work-up, XX was obtained as a pale yellow oil which could not be induced to crystallize: ir ($CHCl_3$) 5.86 μ; nmr ($CDCl_3$) δ 7.6–8.2 (10 H, m), 3.9 (1 H, br), 2.47 (3 H, d, J = 13 Hz), 2.38 (2 H, br t, J = 6 Hz), 2.05 (3 H, s), 1.1–2.0 with partially overlapping doublet of doublets at 1.29, J = 20 and 7 Hz (11 H combined).

The experiment was repeated using D_2O–DCl instead of H_2O–HCl. The tetrahydrofuran solution was stirred vigorously with the aqueous phase for *ca.* 10 min, and worked up as before. The nmr spectrum of the resulting XX showed no change in the relative height or appearance of the methyl signals at δ 2.47 or 1.29, but the signals at 2.05 and 2.38 were diminished in intensity. Integration indicated *ca.* 1.6 D/mol of XX.

***trans*-1-Methylcyclooctene.**—1-Methylcyclooctene oxide (0.4367 g, 0.003116 mol) in dry THF (4 ml, distilled from $LiAlH_4$) was added to a solution of lithium diphenylphosphide (0.00279 mol) in dry THF (*ca.* 5 ml) under positive argon pressure. The solution was stirred for 95 hr at 25°; the red color slowly faded to pale yellow. The reaction mixture was cooled to −78° and glacial acetic acid (0.1675 g, 0.00279 mol) was added under argon flow. After stirring for 1 hr, the solution was allowed to warm to −25° and methyl iodide (0.596 g, 0.00419 mol) was added under argon flow. After 2 hr at −25° the product was allowed to warm to 25° over *ca.* 1 hr, and was then diluted with water (100 ml) and extracted with pentane (2 × 30 ml) to remove unreacted epoxide. The aqueous layer and pentane-insoluble material were then extracted with chloroform (6 × 80 ml), the chloroform was dried over sodium sulfate and evaporated under the aspirator, and the last traces of chloroform were removed under high vacuum. The foamy residue (1.24 g) was crystallized from THF to yield (2-hydroxy-2-methylcyclooctyl)methyldiphenylphosphonium iodide, mp 208–211°, first crop 0.69 g (light sensitive).

Conversion of the above salt to 1-methyl-*trans*-cyclooctene was effected by treatment with 1 equiv of DBU in dry THF under a nitrogen atmosphere for 2 hr at 25°. The product was isolated by aqueous pentane work-up, the pentane was removed using a Vigreux column at atmospheric pressure, and the hydrocarbon was isolated by preparative glpc in 70% yield (10 ft × 0.25 in. 20% TCEP on Chromosorb P) as a colorless liquid with a characteristic unpleasant odor: nmr ($CDCl_3$) δ 5.35 (1 H, d × d × q, J = 11, 5, 1.5 Hz), 1.9–2.3 (4 H, m), 1.7 (3 H, d, J = 1.5 Hz), 0.5–1.9 (8 H, br m); ir (neat) 3.45, 3.52, 6.95, 11.45 μ; exact mass found and calculated, 124.125190. The olefin reacts with diphenylisobenzofuran (2 hr, refluxing $CHCl_3$) to form an adduct, mp 125.5–127°.

Registry No.—V, 38202-37-8; VI, 38213-74-0; XI, 34170-10-0; XII, 34215-20-8; XVI, 38202-39-0; XVII, 38202-40-3; XIX, 38229-25-3; XX, 38213-76-2; LDP, 15968-89-5; cyclooctene oxide, 286-62-4; methyl iodide, 74-88-4; *trans*-cyclooctene, 931-89-5; monoepoxide of 1,4-cyclooctadiene, 38202-42-5; *cis,trans*-1,4-cyclooctadiene, 34218-69-4; Diels–Alder adduct of 1,4-cyclooctadiene and 1,3-diphenylisobenzofuran, 38202-43-6; 1,5-cyclooctadiene monoepoxide, 637-90-1; *cis,trans*-1,5-cyclooctadiene, 5259-71-2; Diels–Alder adduct of 1,5-cyclooctadiene and 1,3-diphenylisobenzofuran, 38202-45-8; cycloheptene oxide, 286-45-3; 1-lithiocyclohep-

(21) E. A. Brande, W. F. Forbes, and E. A. Evans, *J. Chem. Soc.*, 2202 (1953).

tene, 38202-46-9; 1,2-dimethylcycloheptene oxide, 38202-47-0; 1-methylcyclooctene oxide, 16240-40-7; (2-hydroxy-2-methylcyclooctyl)methyldiphenylphosphonium iodide, 38202-49-2; *trans*-2-methylcyclooctene, 38229-26-4; adduct of diphenylisobenzofuran and *trans*-2-methylcyclooctene, 38215-60-0.

Preparation and Reactions of Nitrate Esters of *N*-Acylserine and -threonine Derivatives

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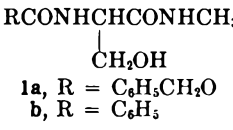
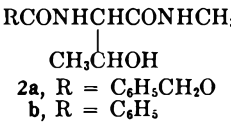
Nitrate esters of *N*-carbobenzoxyserinemethylamide, *N*-benzoylserinenmethylamide, *N*-carbobenzoxythreoninemethylamide, *N*-carbobenzoxyalanylserine methyl ester, *N*-benzoylallothreoninemethylamide, and *N*-carbobenzoxyglycylserylglycine ethyl ester were prepared from the corresponding amino acid derivatives and acetyl nitrate. Treatment of the first four compounds with ammonia causes an elimination of nitrate ion and formation of substituted acrylic acid and crotonic acid derivatives, respectively.

The reaction of acetyl nitrate with *N*-acylserine and -threonine derivatives has been studied to determine if the hydroxyl group present would cause the selective introduction of a nitro group on the amide nitrogen. Such a reaction would be important in the selective cleavage of peptides containing these amino acids. The resulting *N*-nitroamide bond would undergo cleavage with aqueous ammonia[2] more readily than the unmodified peptide bonds. The actual results obtained in the nitration were different from those expected and were considered important enough to report.

Treatment of *N*-acylserinemethylamide (1) and *N*-acylthreoninemethylamide (2) with fuming nitric acid

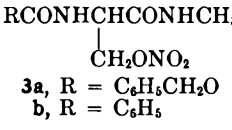


1a, R = $C_6H_5CH_2O$
b, R = C_6H_5

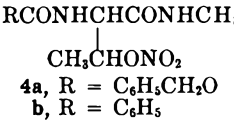


2a, R = $C_6H_5CH_2O$
b, R = C_6H_5

and acetic anhydride in acetic acid gave exclusively the *O*-nitrate derivative (**3**, **4**) rather than the *N*-nitro derivatives. The use of fuming nitric acid and acetic anhydride alone gave lower yields of the nitrate ester. The behavior of a mixture of cupric nitrate and acetic anhydride[3] was not general and gave the *O*-nitro derivative with **1b** and the *O*-acetyl derivative with **1a**.



3a, R = $C_6H_5CH_2O$
b, R = C_6H_5



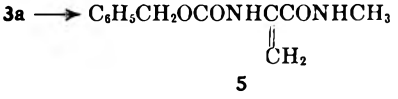
4a, R = $C_6H_5CH_2O$
b, R = C_6H_5

Evidence for the location of the nitro group on the oxygen rather than on the nitrogens was based on nmr and infrared spectra. The nmr spectrum of **3a** showed broad absorptions for the two NH groups at δ 5.53 and 6.21. The former was a doublet and would correspond to the NHCH group. The infrared spectra for the nitrates showed frequencies for amide groups which were not markedly different from the *N*-acylamino acid derivatives. In contrast, the frequency for the carbonyl of the *N*-nitrobenzamide derivatives[3] was reported to be in the 5.85-μ region.

(1) (a) Deceased. Inquiries should be addressed to S. Wawzonek. (b) Abstracted in part from the Ph.D. Thesis of F. E. B., Aug 1971.
(2) C. J. Peterson, Ph.D. Thesis, The University of Iowa, 1964.
(3) R. D. Campbell and C. J. Peterson, *J. Org. Chem.*, **28**, 2294 (1963).

Nitration on nitrogen is apparently slow under the conditions employed, since *N*-carbobenzoxyalaninemethylamide was not affected.

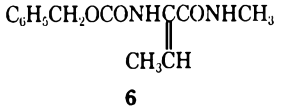
Treatment of **3a** with methanolic ammonia gave ammonium nitrate and α-*N*-carbobenzoxyaminoacrylmethylamide (**5**).



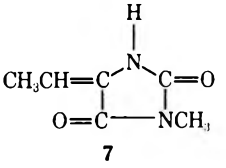
5

Proof for the structure of **5** was the spectra and chemical behavior. Treatment with dilute hydrochloric acid gave benzyl carbamate. The other hydrolysis product, *N*-methylpyruvamide, was difficult to isolate because of its high solubility in water. Catalytic hydrogenation gave alaninemethylamide. Oxidation with potassium dichromate gave *N*-carbobenzoxy-*N'*-methyloxamide, which on catalytic hydrogenation gave *N*-methyloxamide.

The reaction of alcoholic ammonia with **4a** gave ammonium nitrate, α-*N*-carbobenzoxyaminocrotonmethylamide (**6**), and 1-methyl-4-ethylidenehydantoin (**7**).



6



7

The structure of the hydantoin **7** was demonstrated by catalytic hydrogenation to 1-methyl-4-ethylhydantoin.

The hydantoin **7** is formed in this reaction by a base-catalyzed cyclization of the crotyl derivative **6**. The feasibility of such a reaction was demonstrated by cyclizing **6** with sodium hydroxide to **7**.

Changing the protecting group from carbobenzoxy to benzoyl did not change the course of the reaction with alcoholic ammonia but gave a more reactive species from **3b**; polymeric *N*-benzoylaminoacrylmethylamide was isolated. Substitution of sodium hydroxide in methanol for alcoholic ammonia in the reaction with **3b** gave *N*-benzoyl-*O*-methylserinemethylamide and benzamide.

The reaction of *N*-carbobenzoxyalanylserine methyl ester proceeded similarly and produced the *O*-nitrate,

TABLE I

N-ACYLAMINO ACID METHYLAMIDES

Compd	Mp, °C	Formula		C, %	H, %	N, %	Ir (Nujol), μ OH	NH	CO
1a	129–129.5[b]	$C_{12}H_{16}N_2O_4$	Calcd	57.13	6.39	11.10	2.96	3.02	5.95, 6.05
			Found	57.23	6.44	11.38			
1b	149–149.5[c]	$C_{11}H_{14}N_2O_3$	Calcd	59.45	6.35	12.61	2.88	2.98	5.96, 6.05
			Found	59.56	6.35	12.84			
2a	129–130[d]	$C_{13}H_{18}N_2O_4$	Calcd	58.63	6.81	10.52	2.78–2.85	2.92	5.86, 6.06
			Found	58.57	6.97	10.66			
2b	183.5–184[e]	$C_{12}H_{16}N_2O_3$	Calcd	60.91	6.82	11.84	2.90		6.00, 6.08
			Found	60.87	7.02	12.27			
CAMA[a]	113–115[f]	$C_{12}H_{16}N_2O_3$	Calcd	61.00	6.83	11.86		2.95	5.88, 6.00
			Found	60.89	6.75	11.59			

[a] *N*-Carbobenzoxyalaninemethylamide. [b] Recrystallized from acetone. [c] Recrystallized from ethanol–ether and twice from water. [d] Two recrystallizations from acetone–hexane. [e] Recrystallized from aqueous ethanol. [f] Two crystallizations from acetone–hexane.

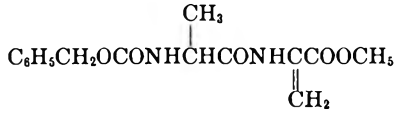
TABLE II

N-ACYL-*O*-NITROAMINO ACID METHYLAMIDES

Compd	Mp, °C	Formula		C, %	H, %	N, %	Ir (Nujol), μ NH	CO
3b	142–143[a]	$C_{11}H_{13}N_3O_3$	Calcd	49.35	4.89	15.70	3.97, 3.63	5.96, 6.10
			Found	49.84	5.05	15.60		
4a	148–149[a]	$C_{13}H_{17}N_3O_6$	Calcd	50.16	5.56	13.50	2.99	5.75, 6.05
			Found	50.10	5.56	13.45		
4b	158–159 dec[b]	$C_{12}H_{15}N_3O_5$	Calcd	51.24	5.38	14.94	2.93, 3.03	6.00, 6.10
			Found	50.79	5.41	14.81		

[a] Recrystallized from ethyl acetate–petroleum ether (bp 60–68°). [b] No further purification.

since treatment with alcoholic ammonia gave the acrylic acid derivative **8**. This structure was based on elemental analysis and the ir and nmr spectra.



8

Work with a tripeptide, *N*-carbobenzoxyglycylserylglycine ethyl ester, was carried out only through the nitration step.

The elimination reaction observed with the nitrate derivatives **3** and **4** proceeds more easily than when this group is absent. *N*-Carbobenzoxyserinemethylamide is stable toward methanolic ammonia. Substitution methanolic sodium hydroxide for the ammonia in this example caused elimination to a slight degree.

β elimination of the type described has been observed with cystine peptides,[4] and tosyl and phosphorylated serine derivatives.[5,6]

Experimental Section

General.—Melting points are corrected. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer and Infracord and nmr spectra were obtained using Varian A-60 and HA-100 spectrometers. DL-Amino acids were used in all reactions.

Amidation of Methyl Esters of *N*-Acylamino Acids.—The methyl ester (0.035 mol) was treated with anhydrous methylamine (20 ml) in a precooled glass-lined Parr bomb and the mixture was allowed to stand at room temperature for 12 hr. Removal of the methylamine gave a viscous oil, which upon trituration with ether gave a white solid. Yields of 99% were obtained for all the compounds listed in Table I except **2a** (79%).

Nitration of *N*-Acylamino Acid Methylamides.—A suspension of the methylamide (0.00734 mol) in glacial acetic acid (25 ml) and acetic anhydride (20 ml) at 0° was treated with fuming nitric acid (sp gr 1.52) (0.4 ml). The resulting solution was stirred at 0° for 6 hr and at room temperature for 1 hr and then was poured onto ice. The solid obtained was filtered, washed with water, and dried. The yields obtained for the compounds listed in Table II were as follows: **3b**, 79%; **4a**, 81%; and **4b**, 49%.

***N*-Carbobenzoxy-*O*-nitroserinemethylamide (3a)** was obtained in a 50% yield and in contrast to the other examples was extracted from the water mixture with methylene chloride. Removal of the solvent gave an oil which was crystallized from ether: mp 127–127.5° [two further crystallizations from petroleum ether (bp 86–100°) did not change the melting point]; ir (Nujol) 2.90 (NH), 5.98, 6.10 μ (CON); nmr ($DCCl_3$) δ 2.78 (d, CH_3N, J = 5 cps), 4.64 (m, $CHCH_2$), 5.10 (s, $C_6H_5CH_2$), 5.53 (broad d, NHCOO), 6.20 (broad s, $NHCH_3$), 7.30 (s, C_6H_5).

Anal. Calcd for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.10; N, 14.14. Found: C, 48.60; H, 5.17; N, 13.94.

***N*-Carbobenzoxy-*O*-acetylserinemethylamide.**—A mixture of cupric nitrate trihydrate (0.46 g) and acetic anhydride (70 ml) at 0° was treated dropwise with half of a suspension of *N*-carbobenzoxyserinemethylamide (0.453 g) in methylene chloride (20 ml) and acetic anhydride (20 ml). After completion of the addition more cupric nitrate trihydrate (0.255 g) was added and the second half of the amide suspension was added. The amide slowly dissolved and a homogeneous blue solution resulted and was allowed to stand at 0° for 2 hr and at room temperature for 2 hr. The resulting solution was poured onto ice and extracted with methylene chloride. Removal of the solvent gave a white, amorphous powder which after two crystallizations from ethyl acetate melted at 117.5–118°: yield 0.39 g (further purification by column chromatography using silica gel and a 1:1 ethyl acetate–benzene mixture as the eluent raised the melting point to 121–122°); ir (Nujol) 2.90 (NH), 5.70 ($OCOCH_3$), 5.90, 6.04 μ (CONH); nmr ($DCCl_3$) δ 1.99 (s, CH_3CO), 2.76 (d, CH_3N, J = 5 cps), 4.35 (m, OCH_2CH), 5.10 (s, $C_6H_5CH_2$), 6.03 (broad doublet, OCONH), 6.80 (broad singlet, $NHCH_3$), 7.31 (s, C_6H_5).

Anal. Calcd for $C_{14}N_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.14; H, 6.10; N, 9.69.

The *O*-acetyl derivative was also prepared by treating *N*-carbobenzoxyserinemethylamide (1.0 g) in ethyl acetate (10 ml) with 5 ml of a mixture containing perchloric acid, 2,4-dinitrobenzenesulfonic acid, and acetic anhydride in ethyl acetate.[7] The resulting solution, after standing for 15 min, was poured

(4) R. G. Hiskey, R. A. Upham, G. M. Beverly, and W. C. Jones, Jr., *J. Org. Chem.*, **35**, 513 (1970).

(5) I. Photaki, *J. Amer. Chem. Soc.*, **85**, 1123 (1963).

(6) G. Riley, J. Turnbull, and W. Wilson, *J. Chem. Soc.*, 1373 (1957).

(7) D. J. Pietrzyk and J. Belisle, *Anal. Chem.*, **38**, 1508 (1966).

into water and extracted with ethyl acetate. Removal of the solvent gave the *O*-acetyl derivative (0.85 g), which after crystallization from a mixture of ethyl acetate–petroleum ether (bp 86–100°) melted at 122–123°.

α-*N*-Carbobenzoxyaminoacrylmethylamide (5).—A solution of the methylamide **3a** (1.9 g) in methanol (50 ml) containing 15 *N* ammonium hydroxide (60 ml) was allowed to stand at room temperature for 24 hr. Removal of the solvent gave a solid (1.8 g) which was extracted with ethyl acetate. The insoluble portion was water soluble and proved to be ammonium nitrate (0.6 g).

Removal of the ethyl acetate gave a solid which was purified by chromatography on silica gel using benzene–ethyl acetate (8:2) as an eluent. The white solid obtained was recrystallized from benzene–petroleum ether (bp 86–100°): yield 1.2 g; mp 102.5–104.5°; ir (Nujol) 2.90 (NH), 5.72, 6.02 (CON), 11.35 μ (=CH_2); nmr ($CDCl_3$) δ 2.78 (d, CH_3N, J = 5 cps), 5.13 [singlet ($C_6H_5CH_2$) superimposed on a doublet (=CH)], 6.0 (d, =CH, J = 1.6 cps), 6.82 (broad singlet, $NHCH_3$), 7.32 (s, C_6H_5), 7.63 (broad singlet, OCONH).

Anal. Calcd for $C_{12}H_{14}N_2O_3$; C, 61.53; H, 6.02; N, 11.96. Found: C, 61.55; H, 6.01; N, 11.99.

Reactions of α-*N*-Carbobenzoxyaminoacrylmethylamide (5).

A. Catalytic Hydrogenation.—A solution of the acrylmethylamide **5** (0.5 g) in methanol (20 ml) and concentrated hydrochloric acid (1 ml) was reduced using palladium (10% on charcoal) (0.1 g) as a catalyst and hydrogen at 15 psi for 1.5 hr. Filtration of the solution followed by removal of the solvent gave a solid, which after two crystallizations from a mixture of isopropyl alcohol and ethyl acetate melted at 175.5–176°, ir (KBr) 2.80, 3.10 (NH), 5.90 μ ($CONHCH_3$).

Anal. Calcd for $C_4H_{11}N_2OCl$: C, 34.66; H, 8.00; N, 20.21. Found: C, 35.09; H, 7.78; N, 20.26.

The sample was identical with the hydrochloride of alaninemethylamide prepared by the catalytic hydrogenation of *N*-carbobenzoxyalaninemethylamide.

B. Hydrolysis.—A suspension of the acrylmethylamide **5** (1.5 g) in 6 *N* hydrochloric acid was allowed to stand at room temperature for 1.5 hr. The resulting solution was neutralized with sodium bicarbonate and extracted with ethyl acetate. Removal of the ethyl acetate gave a solid, which was dissolved in hot, aqueous methanol. Cooling gave benzyl carbamate (0.375 g), mp 87–88°. The filtrate gave no precipitate with 2,4-dinitrophenylhydrazine.

C. Oxidation.—A solution of the acrylmethylamide **5** (1.5 g) and chromium trioxide (1.7 g) in glacial acetic acid (25 ml) and water (1 ml) was treated at 0–5° with 6 drops of 36 *N* sulfuric acid and heated at 95° for 1 hr. The resulting solution was poured into water and gave *N*-carbobenzoxy-*N'*-methyloxamide, which was recrystallized from aqueous ethanol: yield 1.0 g; mp 166–167°; ir (Nujol) 2.84, 3.00, 3.09 (NH), 5.62, 5.92, 5.98 μ (CON).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.96. Found: 56.22; H, 5.21; N, 11.52.

Hydrogenation of the oxamide (0.4 g) in methanol (20 ml), water (5 ml), and acetic acid (2 ml) using palladium (10% on charcoal) catalyst at 18 psi of hydrogen for 3 hr gave *N*-methyloxamide (0.14 g), mp 230–231°. A mixture with an authentic sample[8] melted at the same point.

Ammonolysis of *N*-Carbobenzoxy-*O*-nitrothreoninemethylamide (4a).—A solution of the nitrate **4a** (0.76 g) in methanol saturated with ammonia was allowed to stand for 24 hr at room temperature. Removal of the solvent gave a solid which after crystallization from benzene–petroleum ether (bp 86–100°) melted at 128–131°. Chromatography on silica gel using benzene–ethyl acetate (9:1) as the eluent gave α-carbobenzoxyaminocrotonmethylamide (0.156 g), and benzene–ethyl acetate (8:2) as the eluent gave 1-methyl-3-ethylidenehydantoin (0.105 g). The crotonic acid derivative on crystallization from benzene–petroleum ether (bp 60–68°) melted at 137–139°, ir (KBr) 3.06 (NH), 5.81, 5.93 μ (CON).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.67; H, 6.53; N, 11.29.

The hydantoin upon crystallization from benzene–petroleum ether (bp 60–68°) melted at 206–207.5°: ir (KBr) 3.07 (NH), 5.56, 5.63, 5.69, 5.79, 5.93 (CO), 13.23 μ (=$CHCH_3$).

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.48; H, 5.75; N, 19.99. Found: C, 51.31; H, 5.72; N, 20.01.

(8) O. Wallach, *Justus Liebigs Ann. Chem.*, **184**, 67 (1877).

Catalytic hydrogenation of the hydantoin (0.1 g) in methanol (20 ml), water (20 ml), concentrated hydrochloric acid (1.5 ml) using palladium (10% on charcoal), and hydrogen at 18 psi gave 1-methyl-3-ethylhydantoin (0.1 g) which was recrystallized from benzene–petroleum ether (bp 86–100°): mp 99–100.5°; ir (KBr) 2.96, 3.15 (NH), 5.67, 5.84, 5.89 (CO).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.49; H, 7.29; N, 20.12.

A sample of 1-methyl-4-ethylhydantoin was prepared by refluxing 4-ethylhydantoin (1.0 g) in a solution of methanol (10 ml) containing sodium methoxide (6.47 g) with methyl iodide (1.0 ml) for 3 hr. The product melted at 99–100° and gave no lowering in melting point when mixed with the sample obtained by hydrogenation.

Cyclization of α-Carbobenzoxyaminocrotonmethylamide.—A solution of the crotonmethylamide (0.104 g) in methanol (20 ml) was treated with a 50% methanol solution (10 ml) containing sodium hydroxide (1.0 g) and the resulting solution was allowed to stand at room temperature for 24 hr. Removal of the solvent followed by extraction with ethyl acetate gave a solid which was purified by recrystallization from benzene–petroleum ether (bp 60–68°) and column chromatography on silica gel using benzene–ethyl acetate (8:2) as an eluent, yield 0.038 g, mp 207–207.5°. The ir spectrum was identical with that of 1-methyl-3-ethylidenehydantoin and the mixture melting point was the same.

Ammonolysis of *N*-Benzoyl-*O*-nitroserinemethylamide (3b).—A solution of the nitrate **3b** (0.90 g) in methanol (100 ml) and 15 *N* ammonium hydroxide (2 ml) was allowed to stand at room temperature for 24 hr. Removal of the solvent gave a solid (0.3 g), which was insoluble in water and ethyl acetate and melted above 340°: ir (Nujol) 2.90 (NH), 5.69, 5.75, 5.90, 6.00 (CON).

Anal. Calcd for $(C_{11}H_{12}N_2O_2)_x$: C, 64.69; H, 5.92; N, 13.72. Found: C, 63.87; H, 6.33; N, 13.71.

Reaction of *N*-Benzoyl-*O*-nitroserinemethylamide (3b) with Alcoholic Sodium Hydroxide.—A solution of the nitrate **3b** (2.7 g) in methanol (260 ml) and water (5 ml) containing sodium hydroxide (0.5 g) was allowed to stand for 24 hr. Removal of the methanol followed by extraction with ethyl acetate gave a viscous yellow oil which slowly crystallized. Chromatography on silica gel using benzene–ethyl acetate (1:1) as the eluent gave benzamide and ethyl acetate as the eluent gave *N*-benzoyl-*O*-methylserinemethylamide melting at 144.5–146° after one recrystallization from a mixture of benzene–petroleum ether (bp 86–100°), ir (Nujol) 2.85, 2.90 (NH), 5.96, 6.04 (CON), 8.90 μ (CH_2OCH_3).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.81; N, 11.86. Found: C, 61.22; H, 6.93; N, 12.09.

***N*-Carbobenzoxyalanyl-*O*-nitroserine Methyl Ester.**—*N*-Carbobenzoxyalanylserine methyl ester (3.0 g) was treated in a mixture of acetic acid (30 ml) and acetic anhydride (5 ml) at 0–5° with fuming nitric acid (1.0 ml). The mixture was stirred for 1.5 hr at 0–5° and for 5 hr at room temperature and then poured onto ice. The white solid obtained was recrystallized from ethyl acetate and melted at 123–124.5°: yield 3.3 g (a further recrystallization from benzene raised the melting point to 125–126.5°); ir (Nujol) 2.92 (NH), 5.64 ($COOCH_3$), 5.84, 5.96, 6.08 μ (CON).

Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.59; H, 5.15; N, 11.34.

Ammonolysis of *N*-Carbobenzoxyalanyl-*O*-nitroserine Methyl Ester.—A solution of the nitrate (0.32 g) in 15 *N* ammonium hydroxide (15 ml) was allowed to stand for 24 hr at room temperature. Removal of the ammonia was followed by extraction with ethyl acetate. Chromatography on silica gel using benzene–ethyl acetate (6:4) as the eluent gave a solid (0.12 g) which was crystallized from benzene–petroleum ether (bp 86–100°): mp 91–92°; ir (Nujol) 2.94 (NH), 5.74 ($COOCH_3$), 5.79, 5.94 (CON), 10.96 μ (=CH_2); nmr ($CDCl_3$) δ 1.37 (d, CH_3CH, J = 8 cps), 3.80 (s, $COOCH_3$), 4.33 (m, CH), 5.12 (s, $C_6H_5CH_2$), 5.89 (s, =CH), 6.58 (s, =CH), 7.32 (s, C_6H_5), 8.38 (broad s, C=CNH).

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.78; H, 5.97; N, 8.94.

***N*-Carbobenzoxyglycyl-*O*-nitroserylglycine Ethyl Ester.**—Fuming nitric acid (0.40 ml) was added to a suspension of *N*-carbobenzoxyglycylserylglycine ethyl ester (0.663 g) in acetic acid (30 ml) and acetic anhydride (1.0 ml) at 0–5° and the mixture was stirred at room temperature for 9 hr and poured onto ice. Extraction with ethyl acetate gave a solid which was chromatographed on silica gel using benzene–ethyl acetate (40:60) as an

eluent, yield 0.70 g. Crystallization from ethyl acetate–petroleum ether (bp 60–68°) gave a melting point of 58–60°; ir (Nujol) 2.85, 2.89 (NH), 5.56 ($COOC_2H_5$), 5.82, 5.86, 6.04 μ (CON).

Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.61; H, 4.92; N, 13.05.

Registry No.—**1a**, 38215-61-1; **1b**, 33628-81-8; **2a**, 38229-27-5; **2b**, 38215-63-3; CAMA, 38215-64-4; **3a**, 38215-65-5; **3b**, 38215-66-6; **4a**, 38215-67-7; **4b**, 38215-68-8; **5**, 38215-69-9; **6**, 38215-70-2; **7**, 38215-71-3; **8**, 38215-72-4; alaninemethylamide (HCl), 38215-73-5; *N*-carbobenzoxy-*N'*-methyloxamide, 38215-74-6; 1-methyl-3-ethylhydantoin, 36650-99-4; polymeric *N*-benzoylaminoacrylmethylamide, 38193-79-2; *N*-benzoyl-*O*-methylserinemethylamide, 38215-76-8; carbobenzoxyalanylserine methyl ester, 38660-05-8; *N*-carbobenzoxyalanyl-*O*-nitroserine methyl ester, 38660-06-9; *N*-carbobenzoxyglycylserylglycine ethyl ester, 33660-07-0; *N*-carbobenzoxyglycyl-*O*-nitroserylglycine ethyl ester, 38660-08-1.

A Kinetic Study of the Thermal Decomposition of 1,1-Diphenylpropyl Hydrogen Phthalate Ester in Solution

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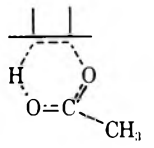
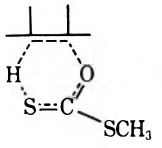
The rate of thermal decomposition of 1,1-diphenylpropyl hydrogen phthalate ester, using nmr techniques, was determined in DMSO solution over temperatures ranging from 65 to 92°. The pyrolysis reaction followed first-order kinetics. Values for the activation energy and the entropy of activation were calculated to be 30.2 kcal/mol and 7.3 eu, respectively. This positive entropy is indicative of a heterolytic or homolytic type cleavage and precludes a cyclic transition state for this decomposition. A decrease in rate was observed when the acid ester was converted to the corresponding methyl diester. Further, the reaction was completely curtailed when the acid ester was converted to the sodium salt. It seems evident that the proton of the orthocarboxylate acid function is playing a significant role in the mechanism of the decomposition of tertiary hydrogen phthalate esters, probably by intramolecular hydrogen bonding.

Ester pyrolyses have received a considerable amount of attention, both for their utility in the formation of olefinic compounds as well as for their mode of decomposition.[3] In general, the presently accepted mechanism for the decomposition of acetate esters, xanthate esters, and related esters involves a concerted six-membered cyclic transition state.



acetate ester



xanthate ester

The above mechanism can only account for cis-elimination products, even though there have been instances of varying amounts of trans-elimination products reported.[4] Briggs and Djerassi[5] have recently found in their pyrolysis studies of epimeric *cis*- and *trans*-9-methylcyclohexyl-*S*-methyl xanthates and acetates that the cis isomers yield considerable trans-elimination product. Kinetic deuterium isotope studies led these authors to propose an ionic mechanism for the net trans-elimination process. This is in agreement with Sixma and coworkers,[6] who reported predominantly positive entropies of activation for a number of tertiary acetate pyrolyses. In contrast, recent vapor-phase ^{18}O studies by Smith, *et al.*,[7] with ethyl acetate and Kwart and Slutsky[8] with *tert*-butyl *N,N*-dimethyl carbamate esters showed an absence of randomization of the ^{18}O label in the unreacted ester after pyrolysis, thus supporting a concerted transition state in these cases.

Recently, Rutherford[9] reported the pyrolyses of a new ester system, tertiary hydrogen phthalate esters, which decompose at low temperatures (less than 150°) to yield exclusively olefinic products and phthalic acid. On decomposition of *trans*-1,2-dimethylcyclohexyl hydrogen phthalate, 19% of trans-elimination product was obtained. It was, therefore, suggested that carbonium ion character was evident (at least in part) in the transition state during the pyrolysis. It was further found that *trans*-2-methyl-1-phenylcyclohexyl hydrogen phthalate ester yielded 6% trans product on pyrolysis[10] as well.

We later showed that partial decomposition of ^{18}O-enriched carbonyl oxygen of the *trans*-1,2-dimethylcyclohexyl hydrogen phthalate ester resulted in the enrichment of ^{18}O in the alkyl portion of the undecomposed ester.[11] This increase in ^{18}O abundance represents a 17% exchange, which was explained by invoking an ionic intermediate state in the decomposition.

More recently,[10] a detailed kinetic study was made of the decomposition of *cis*- and *trans*-1,2-dimethylcyclohexyl hydrogen phthalate esters and *cis*- and *trans*-2-methyl-1-phenylcyclohexyl hydrogen phthalate esters. Pyrolysis of these compounds, both neat and in DMF, showed that the rate-determining step involved ion pair formation.

(1) To whom correspondence should be addressed.

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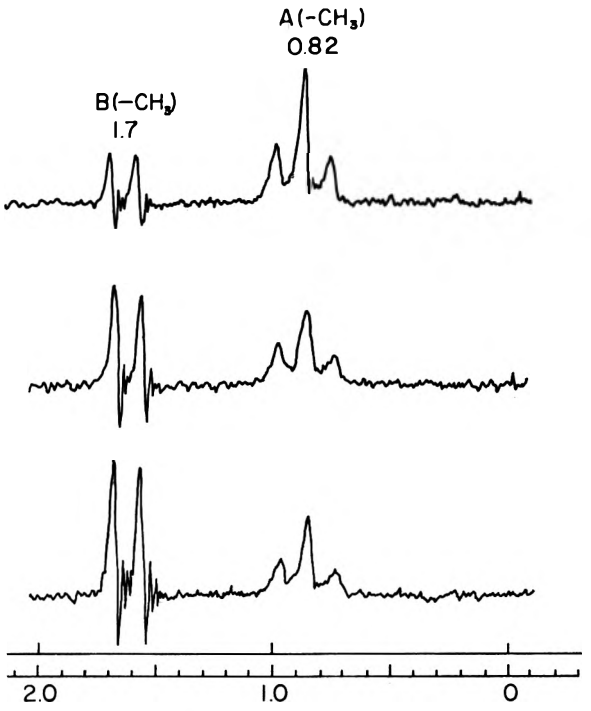
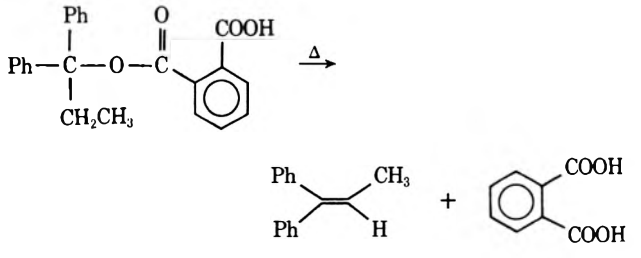


Figure 1.—Nmr spectra showing the decrease in methyl hydrogens (A) of the ester and the increase in methyl hydrogens (B) of the olefin with reaction time.

Simultaneously in our laboratory, a program was carried out to further substantiate ionic character in the low-temperature decomposition of the hydrogen phthalate ester of a tertiary alicyclic system. A system was designed in which a study of the rate of decomposition could be made over a much wider temperature range than previously recorded and which would employ a more effective means than titrimetry to follow the course of reaction. Thus, we wish to report a kinetic study of the thermal decomposition of 1,1-diphenylpropyl hydrogen phthalate ester in DMSO solution, using nmr techniques to determine the rate of decomposition.

Results

The decomposition of 1,1-diphenylpropyl hydrogen phthalate ester in DMSO at moderately low temperatures produces 1,1-diphenylpropene and phthalic acid, nearly quantitatively (98%).



This particular structure was employed for two reasons: first, the two phenyl groups on the alkyl–oxygen carbon should enhance the stability of any carbonium ion character that may be involved in the reaction mechanism; and secondly, the rate of the decomposition could be followed conveniently by nmr techniques. In the latter case, we were able to clearly distinguish between the triplet peak of the methyl group of the ester and the doublet peak of the olefin methyl group of the decomposition product (Figure 1). The sum of the integration values of these two peaks is always coequivalent to the amount of ester in the original sample, thus affording us with an internal standard to measure relative concentrations at all times during the experiment. The solvent, DMSO, was employed, as it readily dissolved both the reactants and the products, thus giving a homogeneous solution throughout the investigation.

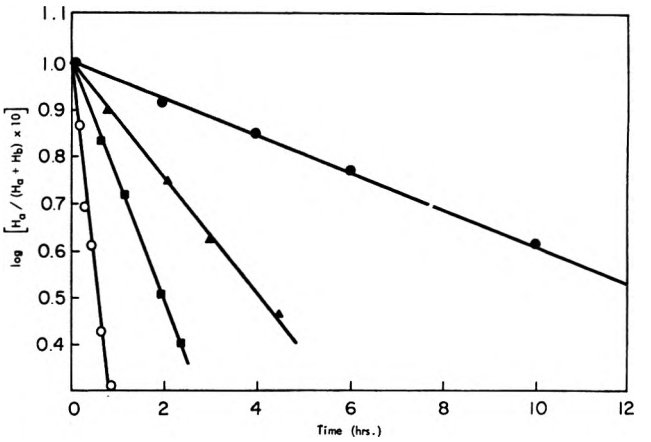


Figure 2.—Decomposition of 1,1-diphenylpropyl hydrogen phthalate in dimethyl sulfoxide: 65° (●), 75° (▲), 80° (■), and 92° (○).

Kinetics.—The rates of reaction were followed by measuring the integration curves for the disappearance of the methyl peak A (δ 0.82) of the hydrogen phthalate ester and the appearance of the methylene peak B (δ 1.7) of the 1,1-diphenylpropene (Figure 1). Stoichiometrically, the sum of the moles of olefin and ester at any time must be equal to the initial amount of ester (E_0) present in the solution. Therefore,

$$\frac{E}{E_0} = \frac{H_a}{H_a + H_b} \quad (1)$$

where E is the number of moles of ester at any time, t, and H_a and H_b are the height of the integrations of peaks A and B, respectively. As the decompositions were carried out under constant volume, the above equation was used to represent the concentration ratio of the solution. Application of this relationship to a first-order rate expression gives

$$\frac{dE}{dt} = -kE$$

$$\ln E = -kt + \ln E_0$$

$$\ln \frac{E}{E_0} = -kt$$

$$\ln \frac{H_a}{H_a + H_b} = -kt$$

Plots of $\log H_a/(H_a + H_b)$ *vs.* time for the decomposition of 1,1-diphenylpropyl hydrogen phthalate ester in DMSO at 65, 75, 80, and 92° (Figure 2) were obtained. It can readily be seen that first-order kinetics is followed in each case. The individual rate constants and averages for three separate runs at each of the four temperatures are listed in Table I.

The rate constants, k, were used in an Arrhenius plot to determine the activation parameters (Figure 3). The energy of activation was calculated to be 30.2 kcal/mol, and the entropy of activation was determined to

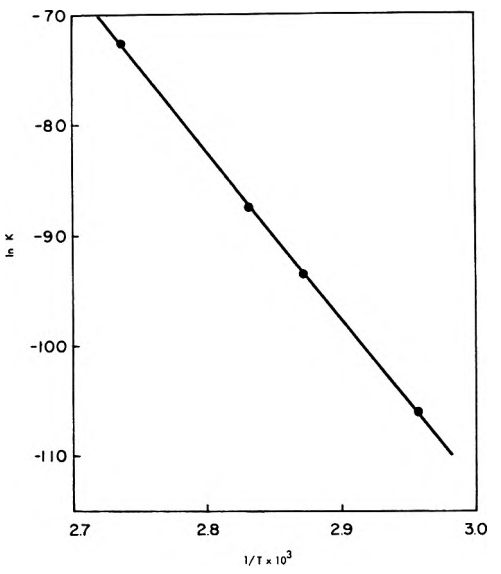


Figure 3.—Arrhenius plot for the decomposition of 1,1-diphenylpropyl hydrogen phthalate in DMSO.

TABLE I

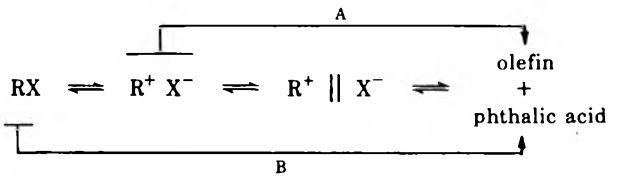
THE THERMAL DECOMPOSITION OF 1,1-DIPHENYLPROPYL HYDROGEN PHTHALATE ESTER IN DIMETHYL SULFOXIDE-d_6

Temp, °C	Rate constant 10^5 k, sec^{-1} [a]	10^5 SD[b]
65.0	2.46	0.01
75.0	8.65	0.10
80.0	15.9	0.3
92.0	68.0	1.1

[a] Average of three determinations. [b] Standard deviation.

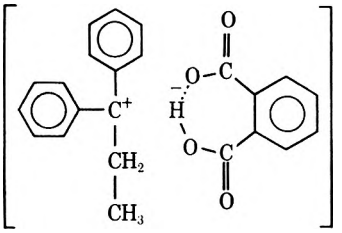
be 7.3 eu. This positive entropy of activation clearly indicates that the mechanism of decomposition involves a heterolytic or homolytic type cleavage, rather than a cyclic transition state that has been generally reported for most ester pyrolyses.

The results of this solution decomposition study directly support the previously postulated ion-pair mechanism proposed for the neat decomposition of tertiary hydrogen phthalate esters.[9-11] It also supports the generalized reaction scheme[12] recently proposed for the



decomposition of these types of compounds in which reaction paths A and B were indicated, based on the per cent ^{18}O in the reduced phthalic acid from which 2- and 4-oxygen equilibration of the phthalate moiety was determined for *cis*- and *trans*-1,2-dimethylcyclohexyl hydrogen phthalate esters. It therefore appears that this decomposition is also occurring heterolytically. Homolytic decomposition of these esters has not been observed but cannot be entirely ruled out and further studies are presently being carried out.

Hydrogen Bond Effects.—Intramolecular hydrogen bonding has been suggested to have some influence on the rate of decomposition of hydrogen phthalate esters;[13] however, no experimental evidence has been reported. To determine this effect, the acid ester of 1,1-diphenylpropyl hydrogen phthalate was converted to the corresponding sodium salt by reaction with sodium hydride. On heating this salt in DMSO for 40 hr at 65°, there was no indication that decomposition took place under these conditions (although it may be possible to effect decomposition at higher temperatures). There are two possibilities that could explain this inert behavior under our conditions. First, the decomposition may be impeded by the unavailability of the carboxylic hydrogen to stabilize the incipient anion of the ion pair through hydrogen bonding, as shown below, thus indicating that intramolecular hydrogen bonding could be significant.



Secondly, the carboxylate anion moiety is electron donating and consequently adversely affecting heterolytic cleavage of the alkyl–oxygen bond in the ester portion of the molecule.

In order to show that the anion inactivity was not totally due to the electrical effects of the carboxylic anion group, the acid portion of 1,1-diphenylpropyl hydrogen phthalate was methylated with diazomethane. The methyl ester group has similar electrical effects to an acid group but eliminates any hydrogen bonding. It was found that this diester compound did decompose on heating in DMSO but at a rate some 50-fold slower than the acid ester (Table II).

TABLE II

Compd	Solvent	Rate constant 10^5 k, sec^{-1}	Relative rate[a]
1,1-Diphenylpropyl hydrogen phthalate	DMSO	68.0	1
1,1-Diphenylpropyl methyl phthalate	DMSO	1.33	0.02
1,1-Diphenylpropyl hydrogen phthalate	Pyridine	15.0	1
1,1-Diphenylpropyl *p*-nitrobenzoate	Pyridine	1.01	0.07
1,1-Diphenylpropyl sodium phthalate	DMSO	No dec	

[a] Relative rates were determined for various compounds in the same solvents.

To further determine the importance of hydrogen bonding and electrical effects, the decomposition of 1,1-diphenylpropyl *p*-nitrobenzoate ester was studied. The decomposition again followed first-order kinetics. The reaction rate, compared to that of 1,1-diphenylpropyl hydrogen phthalate ester under the same conditions, was some 14 times slower (Table II). The nitro group is a much stronger electron-withdrawing group than the carboxylic acid group, and so one would expect a rate increase unless hydrogen bonding is in fact having

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a decided influence on the course of hydrogen phthalate ester decomposition.

It seems evident from the rates of decomposition of the *p*-nitrobenzoate ester and the methyl phthalate diester of 1,1-diphenylpropanol that intramolecular bonding does play an important role in the decomposition of hydrogen phthalate esters in solution.

Experimental Section

All melting points are uncorrected and were determined in a Thomas-Hoover melting point apparatus. Infared spectra were obtained on a Perkin-Elmer 257. Kinetic studies were performed in a mineral bath, maintained at ±0.1° by means of a Haake E-51 temperature controller. Kinetic measurements were made on a Varian A-60 nmr spectrometer in precision nmr tubes (507-PP-7 and 504-PP-7) obtained from Wilmad Glass Co. The deuterated solvents were obtained from Merck Sharp and Dohme. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

General Kinetic Procedure.—Ester was analytically weighed and a 0.75 *M* solution was prepared in dimethyl sulfoxide-d_6. At the beginning of each run, 0.4 ml of this solution was placed into each of six nmr tubes which immediately were sealed with pressure caps. The tubes were placed simultaneously in the constant-temperature bath. Tubes were withdrawn at appropriate intervals and quenched by plunging the tube into a beaker of crushed ice and water. The tube was allowed to return to room temperature and the nmr analysis was performed. Each nmr signal was integrated six times. The averaged value for $H_a/(H_a - H_b)$ had a mean deviation of less than 1%.

Preparation of 1,1-Diphenylpropanol.—Phenylmagnesium bromide was prepared by adding a solution of bromobenzene (94.2 g, 0.6 mol) and anhydrous ethyl ether (150 ml) to a stirred mixture of magnesium turnings in anhydrous ethyl ether. When reaction was complete, the flask was cooled in an ice–water bath and a solution of propiophenone (67 g, 0.5 mol) in anhydrous ether (100 ml) was added slowly over a period of 1 hr. After refluxing for an additional 30 min, the solution was cooled in an ice bath, and the Grignard complex was decomposed with a saturated aqueous solution of ammonium chloride. The ether layer was separated and the aqueous layer was extracted twice with 100-ml portions of ether. The combined ethereal solution was washed several times with water and then dried over anhydrous magnesium sulfate and filtered. The solution was then concentrated to approximately 200 ml with a rotary evaporator. The addition of petroleum ether (bp 30–60°) brought about the precipitation of a white, crystalline product which was collected by filtration. Recrystallization from ether–petroleum ether gave 97 g (91.5%) of 1,1-diphenylpropanol: mp 90–92° (lit.[14] mp 91–92°); ir (KBr) 3530 (free OH stretch), 1358 (OH bend), and 1165 cm^{-1} (CO stretch); nmr ($CDCl_3$, TMS) δ 0.88 (t, 3, J = 7 Hz, CH_3CH_2), 2.32 (q, 2, J = 7 Hz, CH_2CH_3), 2.13 (s, 1, OH), and 7.1–7.7 ppm (complex multiplet, 10, aromatic); the peak at 2.13 ppm disappeared upon the addition of D_2O.

Preparation of 1,1-Diphenylpropyl Hydrogen Phthalate Ester.—A solution of methylsulfinyl carbanion in dimethyl sulfoxide[15] was prepared in the following manner. A three-necked flask was fitted with an addition funnel, magnetic stirrer, and condenser, to which was attached a mercury pressure release trap. This apparatus was thoroughly dried and purged with nitrogen. Sodium hydride, 4.2 g (0.10 mol, as a 57% dispersion in oil), and 100 ml of dry dimethyl sulfoxide were added. The flask was heated to 55–65° in an oil bath until the evolution of hydrogen ceased (approximately 1 hr). This solution of methylsulfinyl carbanion was cooled to room temperature, and 1,1-diphenylpropanol (21.2 g, 0.10 mol) in 50 ml of dimethyl sulfoxide was added slowly with stirring. The mixture was stirred for 30 min at room temperature. Phthalic anhydride (14.8 g, 0.10 mol) was then added to the mixture as a solution in dimethyl sulfoxide. This addition produced considerable heat, and the flask was periodically cooled with cold tap water. After the addition of phthalic anhydride was completed, the solution was allowed to stir overnight. Formation of the desired hydrogen phthalate ester was accomplished by pouring the dimethyl sulfoxide solution of the sodium salt of the ester onto a crushed ice–water mixture containing concentrated hydrochloric acid (20 ml). In order to prevent the hydrolysis of the ester, a layer of ether was maintained over the ice–water mixture which was vigorously stirred. As the sodium salt was being poured, the ester was extracted rapidly into the ether layer. The ether layer was separated and the aqueous layer was extracted again with ether. The combined extracts were dried over magnesium sulfate and then concentrated to a small volume on a rotary evaporator. Careful addition of small portions of petroleum ether brought about the precipitation of a solid material (16.5 g, 46%). Recrystallization from benzene–petroleum ether gave a white material: mp 119° dec; ir (KBr) 3440 (broad peak, bonded OH stretch), 2660 and 2540 (OH stretch characteristic of hydrogen-bonded carboxylic acids), 1733 and 1710 (CO stretch), and 1305, 1266, 1235, and 1070 cm^{-1} (CO stretch); nmr (dimethyl sulfoxide-d_6, TMS) δ 0.81 (t, 3, J = 7 Hz, CH_3CH_2), 2.96 (q, 2, J = 7 Hz, CH_2CH_3), and 7.1–7.9 ppm (m, 14, aromatic).

Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.63; H, 5.60. Found: C, 76.55; H, 5.65.

Decomposition of Hydrogen Phthalate Esters. Characterization of the Products.—1,1-Diphenylpropyl hydrogen phthalate (1 g) was refluxed for 1 hr in chloroform. The phthalic acid which formed was collected, dried, and weighed (0.46 g, 98% of the theoretical yield), mp 211° dec (lit.[16] mp 210–211° dec). The chloroform was removed *in vacuo* and the resulting solid residue was recrystallized from methanol, yielding 0.54 g (98% of the theoretical yield) of 1,1-diphenylpropene, mp 46–47° (lit.[17] mp 48–48.5°). The olefin produced in the decomposition gave an ir spectra identical with that of a sample produced by the dehydration of 1,1-diphenylpropanol with acid: nmr ($CDCl_3$, TMS) δ 1.71 (d, 3, J = 7 Hz, CH_3CH), 6.07 (q, 1, J = 7 Hz, $CHCH_3$), and 7.1–7.6 ppm (m, 10, aromatic).

Preparation of 1,1-Diphenylpropyl-*p*-nitrobenzoate Ester.—Sodium hydride (2.1 g, 0.05 mol as a 57% dispersion in oil) was added to a reaction flask and the mineral oil was washed from the hydride with small portions of petroleum ether. The petroleum ether was removed by decantation and 150 ml of anhydrous benzene was added with 10.6 g of 1,1-diphenylpropanol. The mixture was allowed to react at refluxing temperature for 4 hr. A solution of *p*-nitrobenzoyl chloride (9.3 g, 0.05 mol) in anhydrous benzene (100 ml) was added slowly to the reaction flask with constant stirring. After the addition was completed, the contents were stirred for several hours and then filtered. The solution was washed with 5% sodium bicarbonate solution and then dried over anhydrous magnesium sulfate. After the solution was decolorized with charcoal, it was concentrated on a rotary evaporator. The addition of petroleum ether brought about the precipitation of light yellow crystals (11 g, 61%) which melted with decomposition at 135°: ir (KBr) 1735 (CO stretch), 1528 (NO asymmetric stretch), 1350 (NO symmetrical stretch), and 1272 and 1100 cm^{-1} (CO stretch); nmr (dimethyl sulfoxide-d_6, TMS) δ 0.82 (t, 3, J = 7 Hz, CH_3CH_2), 2.96 (q, 2, J = 7 Hz, CH_2CH_3), 7.2–7.7 (m, 1, aromatic), and 8.5 (s, 4, aromatic).

Anal. Calcd for $C_{22}H_{19}NO_4$: C, 72.94; H, 5.39. Found: C, 73.12; H, 5.30.

Esterification of 1,1-Diphenylpropyl Hydrogen Phthalate.—A freshly prepared ethereal solution of diazomethane was placed in a 250-ml beaker. To this solution was added 7.2 g (0.02 mol) of 1,1-diphenylpropyl hydrogen phthalate dissolved in ether. The disappearance of the yellow color of the ether solution and cessation of effervescence indicated the end of the reaction. The solution was concentrated *in vacuo* and the product was precipitated with petroleum ether. Recrystallization from benzene–petroleum ether yielded 2.1 g (28%) of material: mp 92° dec; ir (KBr) 1753 and 1733 (CO stretch) and 1297, 1274, 1125, and 1072 cm^{-1} (CO stretch); nmr ($CDCl_3$, TMS) δ 0.87 (t, 3, J = 7 Hz, CH_3CH_2), 2.95 (q, 2, J = 7 Hz, CH_3CH_2), 3.65 (s, 3, CH_3), and 7.1–8.0 ppm (m, 14, aromatic).

Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.77; H, 6.17. Found: C, 76.69; H, 6.03.

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Registry No.—1,1-Diphenylpropanol, 5180-33-6; phthalic anhydride, 85-44-9; 1,1-diphenylpropyl hydrogen phthalate ester, 37817-54-2; *p*-nitrobenzoyl chloride, 122-04-3; 1,1-diphenylpropyl-*p*-nitrobenzoate ester, 37816-59-4; 1,1-diphenylpropyl hydrogen phthalate methyl ester, 37816-61-8.

Thermolysis of Phenyl Glycosides

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Thermal analysis of several series of phenyl glycosides has shown that the pyrolytic cleavage of the glycosic group is facilitated by the participation of free hydroxyl groups in a transglycosidation reaction which releases the aglycone as a free phenol. The thermal stability of these compounds is considerably increased by complete acetylation of the molecule and is affected by the inductive effect of the substituents on both the phenolic aglycone and the sugar moiety.

Thermal cleavage of glycosidic bonds is of special interest in understanding the pyrolytic reactions of the carbohydrates and combustion of cellulosic materials.[1-7] In our previous studies of this subject, thermal analysis of analogous series of phenyl and substituted phenyl β-D-xylopyranosides,[4,5] β-D-glucopyranosides, and 2-deoxy-α-D-*arabino*-hexopyranosides,[6] selected as model compounds, has shown that the pyrolytic reactions proceed through the cleavage of the glycosidic group. In this process the aglycone group abstracts a proton to form free phenol, which evaporates, and the glycosyl group is condensed mainly as randomly linked oligosaccharides or an anhydro sugar which is decomposed on further heating. As in acid hydrolysis,[8] thermal cleavage of the aryl glycosides is influenced by the electron-withdrawing effect of the substituent on the phenolic group.[4,6] Furthermore, phenyl glucopyranoside is more stable than the corresponding 2-deoxyhexopyranoside or xylopyranoside.

These studies have been followed by thermal analysis of several phenyl and substituted phenyl 2-amino-2-deoxy-β-D-glucopyranosides, 2-acetamido-2-deoxy-β-D-glucopyranosides, and a variety of acetylated phenyl glycosides to determine the influence of the substituents in the sugar molecule and the availability of free hydroxyl and amino groups.

Results

The thermal analysis of phenyl 2-amino-2-deoxy-β-D-glucopyranoside (**3a**) is shown in Figure 1. The differential thermal analysis (dta), thermogravimetric analysis (tga), and derivative thermogravimetry (dtg) reflect the sequence of physical transformations and chemical reactions as the sugar is heated at a constant rate. As in the case of phenyl-β-D-glucopyranoside,[6] the first event at 80° is due to dehydration and the amount of water lost depends on previous treatment of the sample. Fresh crystals obtained from ethanol–water solution correspond to the dihydrate and contain 12% water that is lost at this temperature (see the tga curve in Figure 1). Storage in a dry atmosphere or under desiccation results in complete removal of the water. The endotherm at 178° is due to melting. At higher temperatures, these two physical transformations are followed by weight loss due to the cleavage of the glycosidic bond, evaporation of phenol, and decomposition of the sugar moiety. The tga and dtg curves show that the weight loss starts at about 225° and reaches a maximum rate at 284°. The dta curve shows only a slight thermal effect in this region due to the overlapping of endothermic and exothermic reactions. Following the rapid weight loss, there is a slow volatilization which leaves a fairly stable carbonaceous residue of 41% at 400°. This compares with 11% residue obtained from phenyl β-D-glucopyranoside.[6] The high yield of charred residue is characteristic for amino sugars, *O*-glycosides, with an amino group either in the aglycone or the glycosyl moiety, and *N*-glycosides. This aspect of the amino compound will be discussed in a following communication.

The thermal analysis features of phenyl and *p*-bromophenyl 2-amino-2-deoxy-β-D-glucopyranosides (**3a** and **3d**) are summarized in Table I. A comparison of these data with those obtained for the corresponding normal glycosides shows that the decomposition peaks for the amino compounds are about 15° lower and, as noted already, the residues are substantially higher.

The thermogram of phenyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**2a**) is shown in Figure 2. A comparison of this thermogram with Figure 1 shows that, after acetylation of the amino group, the melting point is shifted from 178° to 249° and is closely followed by a rapid decomposition indicated by the dtg peak at 261°.

Table I gives a summary of the dynamic thermal analysis data for a number of 2-acetamido glycosides (**2a–g**). For these compounds the melting process is accompanied or closely followed by decomposition. Consequently, the dta peak for decomposition is superimposed as a shoulder on the melting point endotherm or appears as an adjoining peak. The maximum rates of decomposition are still shown by distinct dtg peaks, but these show no discernible trend because the decomposition is controlled by physical transition of the crystalline materials to liquid rather than the

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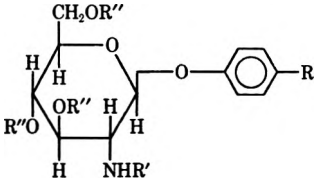
TABLE I

THERMAL ANALYSIS FEATURES OF GLYCOSIDES

Aglycone	Dta peaks: Change, °C	Mp, °C	Dec, °C	Dtg peaks: Change, °C	Dec, °C	Tga Residue,[a] %
2-Amino-2-deoxy-β-D-glucopyranosides						
Phenyl	80	178	264	80	284	41
p-Bromophenyl	124	165	285[b]	125	271	33
2-Acetamido-2-deoxy-β-D-glucopyranosides						
Methyl		202	307, 345[b]		318	30
p-Methoxyphenyl	74	252	263	75	264	26
p-Methylphenyl	105	241	255	106	266	27
Phenyl		249	Dec		261	32
p-Acetamidophenyl		244	266,[b] 317		266, 321	35
p-Bromophenyl	115, 130	254	Dec	116	262	25
p-Iodophenyl		248	Dec		250	28
p-Nitrophenyl	77	215	257[b]	75	220, 250	42
2-Acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranosides						
Methyl		159	337		343	2
p-Methoxyphenyl	158, 176, 182	191	355		357	4
p-Methylphenyl		201	345		349	6
Phenyl	182, 185	201	333		337	6
p-Acetamidophenyl		252	325		323	17
p-Bromophenyl	59	227	306		305	14
p-Iodophenyl	72	250	285		291	14
p-Nitrophenyl		245	268[b]		260	28
Tetra-*O*-acetyl-β-D-glucopyranosides						
p-Methoxyphenyl	98	103	364		364	0
p-Methylphenyl		119	347		350	0
Phenyl		126	345		347	0
p-Bromophenyl		132	362		365	0
Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosides						
p-Methoxyphenyl	34	100	351		352	0.5
p-Methylphenyl		94	333		336	0.4
Phenyl		86	325		327	0.0
p-Bromophenyl		136	349		351	0.1
p-Nitrophenyl		142	313[b]		312	27.0

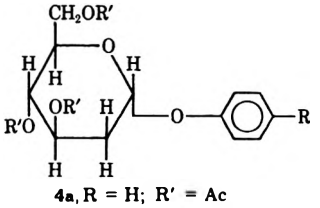
[a] Per cent residue at 400° based on anhydrous weight of the original material. [b] Exothermic.



1a, R = H; R′ = Ac; R″ = Ac
b, R = OCH_3; R′ = Ac; R″ = Ac
c, R = CH_3; R′ = Ac; R″ = Ac
d, R = Br; R′ = Ac; R″ = Ac
e, R = I; R′ = Ac; R″ = Ac
f, R = NO_2; R′ = Ac; R″ = Ac
g, R = NHAc; R′ = Ac; R″ = Ac

2a, R = H; R′ = Ac; R″ = H
b, R = OCH_3; R′ = Ac; R″ = H
c, R = CH_3; R′ = Ac; R″ = H
d, R = Br; R′ = Ac; R″ = H
e, R = I; R′ = Ac; R″ = H
f, R = NO_2; R′ = Ac; R″ = H
g, R = NHAc; R′ = Ac; R″ = H

3a, R = H; R′ = H; R″ = H
d, R = Br; R′ = H; R″ = H



4a, R = H; R′ = Ac
b, R = OCH_3; R′ = Ac
c, R = CH_3; R′ = Ac
d, R = Br; R′ = Ac
f, R = NO_2; R′ = Ac

chemical structure of the molecule. The tga curves show considerable residue at 400°, but not as much as was observed for the amino glycosides.

Since the dynamic thermal analysis data on relative stability of the acetamido compounds were not reliable because of the limitation imposed by melting, the decomposition of these compounds was investigated by isothermal tga at 250° to obtain the trend shown in Figure 3. This figure shows a slow rate of weight loss or high stability for the methyl glucoside as predicted by the dynamic thermal analysis data (Table I). The aryl acetamido glycosides, which are generally less stable, follow the order of Hammett's σ factor[6] and show an induction period before reaching the maximum rate of decomposition. This period is longer for *p*-methoxyphenyl and *p*-bromophenyl derivatives, which have melting points higher than 250°. Another isothermal experiment at 240° showed the same order for the maximum rates but even larger differences in the induction period.

The *p*-nitrophenyl compound again showed the peculiarities that have been observed in other series of glycosides.[4,6] The maximum rate of weight loss was reached rapidly but the pyrolysis slowed after a short

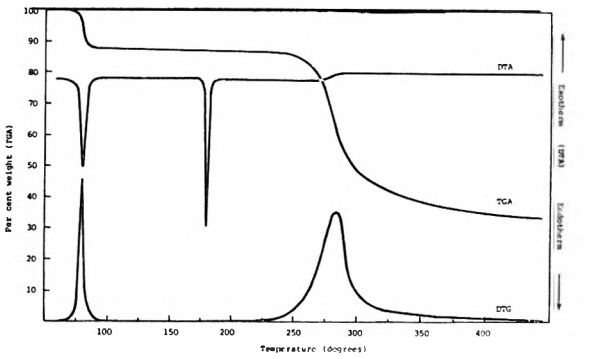


Figure 1.—Thermogram of phenyl 2-amino-2-deoxy-β-D-glucopyranoside

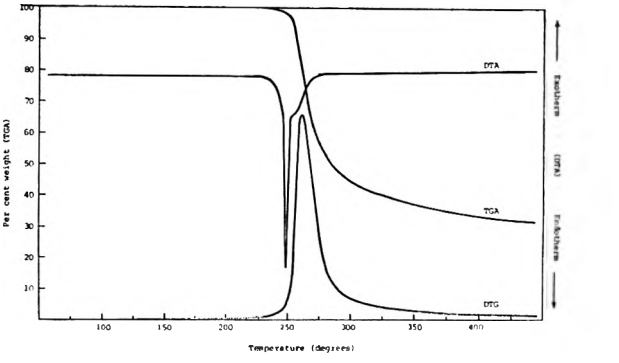


Figure 2.—Thermogram of phenyl 2-acetamido-2-deoxy-β-D-glucopyranoside.

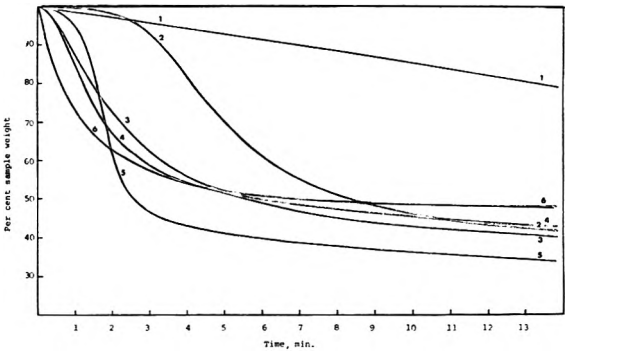


Figure 3.—Isothermal weight loss of 2-acetamido-2-deoxy-β-D-glucopyranosides at 250°: 1, methyl; 2, *p*-methoxyphenyl; 3, *p*-methylphenyl; 4, phenyl; 5, *p*-bromophenyl; 6, *p*-nitrophenyl.

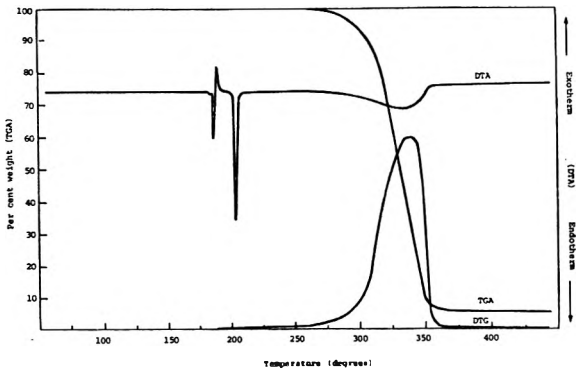


Figure 4.—Thermogram of phenyl 2-acetamido-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside.

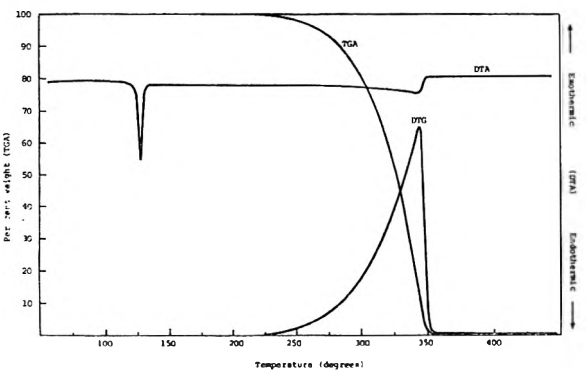


Figure 5.—Thermogram of phenyl tetra-*O*-acetyl-β-D-glucopyranoside.

while to leave more residue. Furthermore, as shown by dta (Table I), the overall decomposition process was exothermic instead of being endothermic, indicating that it proceeds differently.

Complete acetylation of the 2-aminoglucosides greatly increased the thermal stability of the products, as can be seen in the thermogram of phenyl 2-acetamido-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**1a**) (Figure 4). In this thermogram, the dta line shows a crystal transformation at 185° and melting at 201°. The dtg and tga curves show that the weight loss starts at about 250°, reaches a maximum at 337°, and leaves a residue of only 6% at 400°.

The thermal analysis data for a series of fully acetylated 2-amino glycosides are given in Table I. These data show that complete acetylation has greatly increased the stability of the glycosides and there is no longer the overlapping of the melting and decomposition processes.

The same phenomenon is observed on acetylation of the normal and 2-deoxy glycosides. Figures 5 and 6 show the thermograms of phenyl tetra-*O*-acetyl-β-D-glucopyranoside and phenyl tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside, respectively. In these cases, however, increased stability and volatility of the compound results in overlapping of the decomposition with evaporation of the intact molecule. Consequently, melting is followed by a broad endothermic weight loss which reaches a maximum rate at 347 and 327°, respectively, and leaves a negligible amount of residue at 400°.

Evaporation of the acetylated glycosides has been confirmed by analysis of the volatile products. The resulting data (see Table II) show that the free glycosides give a very high yield of free phenol and none or very little intact material, whereas the reverse is true for the acetylated compounds.

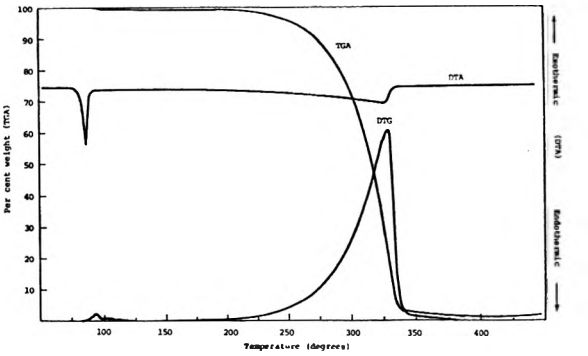


Figure 6.—Thermogram of phenyl tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside.

TABLE II
ANALYSIS OF VOLATILE PRODUCTS FROM DIFFERENT GLYCOSIDES

Glycoside	Free phenol, %	Starting material, %
Phenyl β-D-glucopyranoside	100[a]	0[a]
Phenyl 2-amino-2-deoxy-β-D-glucopyranoside	82	2
Phenyl 2-acetamido-2-deoxy-β-D-glucopyranoside	99	0
Phenyl 2-deoxy-α-D-*arabino*-hexopyranoside	82	4
Phenyl 2-acetamido-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside	29	42
Phenyl tetra-*O*-acetyl-β-D-glucopyranoside	0	62
Phenyl tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside	0	63

[a] Theoretical value.

The dynamic thermal analysis features of other fully acetylated normal and 2-deoxy glycosides are given in Table I. Because of the evaporation of these compounds their temperature of maximum rate of weight loss (dtg peak) does not necessarily correspond with the stability order. However, as discussed below, these data show that the acetylated compounds in general are considerably more resistant to thermal degradation than the corresponding unacetylated compound and remain intact at higher temperatures.

Discussion

The thermal stability of phenyl glycosides and the corresponding fully acetylated compounds of different series are compared in Table III and Figures 7 and 8. Table III gives the dynamic thermal analysis data for all these compounds, and isothermal weight loss is shown in Figure 7 for the glycosides at 260° and in Figure 8 for the acetylated compounds at 300°.

These data show that the acetylated compounds are considerably more stable than the parent compounds and that the free hydroxyl groups must play a significant role in the thermolysis of the glycosides. Considering that nearly 100% free phenol is generated by this process (see Table II), and after the cleavage of the glycosidic group the glycosyl moiety forms condensation products containing anhydro sugars and oligosaccharides,[6] it becomes clear that the thermoly-

TABLE III
COMPARATIVE THERMAL PROPERTIES OF PHENYL GLYCOSIDES

Glycoside	Dta peaks—Mp, °C	Dta peaks—Dec, °C	Dtg Dec, °C	Tga Residue, %
β-D-Glucopyranoside	175	305, 330	311, 336	11
Tetra-*O*-acetyl-β-D-glucopyranoside	126	344	348	0
2-Deoxy-α-D-*arabino*-hexopyranoside	165	296	299	7
Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside	86	324	327	1
2-Amino-2-deoxy-β-D-glucopyranoside	178	264	284	41
2-Acetamido-2-deoxy-β-D-glucopyranoside	249	255	261	32
2-Acetamido-tri-*O*-acetyl-β-D-glucopyranoside	201	333	337	6

sis process consists of inter- and intramolecular transglycosidation reactions. As shown before, the thermal reactions are less specific[7] and different hydroxyl groups could participate in the transglycosidation reaction to provide randomly linked condensation products.[5]

Substituents on the aglycone or glycosyl moiety produce an inductive effect on the cleavage of the glycosidic group, as in acid hydrolysis.[8] The para-substituted phenyl glycosides in each series follow the order of Hammett's σ factor, with the better leaving groups being less stable. This trend is clearly shown by the thermal analysis data, unless the thermolysis of the glycoside overlaps with melting or evaporation.

The substituents on the sugar moiety, however, in addition to the inductive effect on the glycosidic bond, could also change the availability or reactivity of the transglycosidation sites. Consequently, the net result is not necessarily parallel with the order of stability observed on acid hydrolysis. For the free glycosides, the combination of the two effects produces the order of stability shown in Table III and Figure 7, with normal glucoside being more stable than the 2-deoxy, 2-amino, and 2-acetamido compounds, respectively.

These data also show that, although C-2 hydroxyl groups could participate in the transglycosidation reaction, they do not play a specific role similar to that in the alkaline cleavage of the phenyl β-D-glucopyranoside,[9,10] because phenyl 2-deoxy-α-D-glucopyranoside is pyrolyzed at a comparative rate. This observation is in line with the random participation of the hydroxyl group discussed above.

The proposed mechanism for cleavage of the glycosidic group has further implications on the thermolysis of oligosaccharides and polysaccharides and the effect of water and nitrogen compounds on the course of pyrolytic reactions and flammability of cellulosic materials, that will be discussed in subsequent reports.

Experimental Section

Aryl 2-Acetamido-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside.—Phenol or a para-substituted phenol (5 g) and 2-acetamidotri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[11] (5 g) were dissolved in cold acetone (105 ml) and treated with 3.3% aqueous sodium hydroxide (45 ml).[12] The mixture was kept for 6 hr at room temperature and overnight at 5°. The acetone was removed at room temperature and the products were shaken with chloroform (100 ml). The chloroform layer was extracted with cold dilute alkali, washed with water, dried over $CaCl_2$, and evaporated *in vacuo*. The residue was recrystallized from 2-propanol, methanol, or 1:1 methanol–chloroform to give the compounds listed in Table IV.

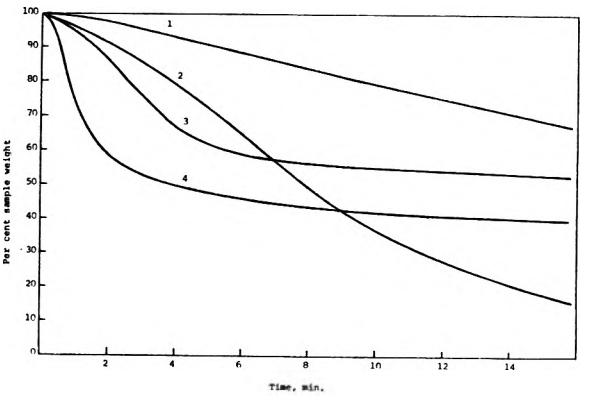


Figure 7.—Isothermal weight loss of phenyl glucosides at 260°: 1, phenyl β-D-glucopyranoside; 2, phenyl 2-deoxy-α-D-*arabino*-hexopyranoside, 3, phenyl 2-amino-2-deoxy-β-D-glucopyranoside; 4, phenyl 2-acetamido-2-deoxy-β-D-glucopyranoside.

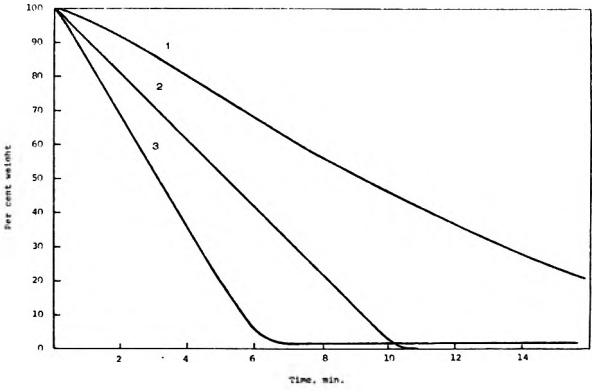


Figure 8.—Isothermal weight loss of fully acetylated phenyl glycosides at 300°: 1, phenyl 2-acetamido-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside; 2, phenyl tetra-*O*-acetyl-β-D-glucopyranoside; 3, phenyl tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside.

Aryl 2-Acetamido-2-deoxy-β-D-glucopyranosides.—Aryl 2-acetamido-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosides (1 g) were dissolved (suspended) in methanol (25 ml) and then treated with methanolic ammonia (50 ml) and left overnight at room temperature.[13] The acetamido derivatives that separated after evaporation were filtered, washed with cold water, and recrystallized from water or EtOH–H_2O to give the products listed in Table IV.

Aryl 2-Amino-2-deoxy-β-D-glucopyranosides.—Aryl 2-acetamido-2-deoxy-β-D-glucopyranoside (1 g) and hydrazine hydrate (85%) (5 ml) were kept in a sealed tube at 100–140° for 24–48 hr.[14] Excess hydrazine was then removed in an evacuated desiccator over H_2SO_4 for 2 days and the residue was triturated with EtOH. The resulting compounds are listed in Table IV.

Methyl 2-Acetamido-2-deoxy-β-D-glucopyranoside.—Methyl 2-acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranoside was prepared by the Leaback and Walker method in 40% yield, mp 163° (lit.[12] mp 163°). Treatment of this compound with ammonia gave the title compound, mp 204° (lit.[12] mp 204°), $[\alpha]_D$ −47.0° (c 1.0, H_2O).

Aryl Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosides.—Tetra-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranose (1 g) and para-substituted phenol (1 g) were mixed with powdered anhydrous $ZnCl_2$ (0.2 g) and stirred vigorously at 70–80° for 40 min.[15] At

(9) C. M. McCloskey and G. H. Coleman, *J. Org. Chem.*, **10**, 184 (1945).
(10) F. Shafizadeh, Y. Z. Lai, and R. A. Susott, *Carbohyd. Res.*, accepted for publication.
(11) D. Horton, *Methods Carbohyd. Chem.*, VI, 282 (1972).
(12) D. H. Leaback and P. G. Walker, *J. Chem. Soc.*, 4754 (1957).
(13) R. Kuhn and W. Kirschenlohr, *Chem. Ber.*, **86**, 1331 (1953).
(14) S. Hanessian, *Methods Carbohyd. Chem.*, **6**, 208 (1972).
(15) F. Shafizadeh and M. Stacey, *J. Chem. Soc.*, 4612 (1957).

TABLE IV

SYNTHESIS OF THE GLYCOSIDES

Compd	Yield, %	Solvent	Mp, °C	Found, % C	Found, % H	Found, % N	Empirical formula	Required, %[a] C	Required, %[a] H	Required, %[a] N
Aryl 2-Acetamidotri-*O*-acetyl-2-deoxy-β-D-glucopyranosides										
1a (H)	32	Propanol	204[b,c]							
1b (OMe)	28	MeOH	196	55.83	6.04	3.11	$C_{21}H_{27}NO_{10}$	55.60	6.01	3.09
1c (Me)	30	MeOH	197	57.48	6.21	3.16	$C_{21}H_{27}NO_9$	57.64	6.22	3.20
1d (Br)	35	MeOH	228-229	47.70	4.69	2.76	$C_{20}H_{24}BrNO_9$	47.80	4.82	2.79
1e (I)	31	MeOH	250	43.68	4.36	2.63	$C_{20}H_{24}INO_9$	43.71	4.40	2.55
1f (NO_2)	39	MeOH-$CHCl_3$	240[b]							
1g (NHAc)	26	MeOH	252-253	54.72	5.58	5.79	$C_{22}H_{28}N_2O_{10}$	54.97	5.88	5.83
Aryl 2-Acetamido-2-deoxy-β-D-glucopyranosides										
2a (H)	70	EtOH-H_2O	250[b]							
2b (OMe)	72	EtOH-H_2O	249	52.42	6.87	3.94	$C_{15}H_{21}NO_7 \cdot H_2O$	52.15	6.72	4.06
2c (Me)	73	EtOH-H_2O	238	54.53	7.05	4.15	$C_{15}H_{21}NO_6 \cdot H_2O$	54.68	7.04	4.25
2d (Br)	77	EtOH-H_2O	241	42.75	5.16	3.28	$C_{14}H_{18}BrNO_6 \cdot H_2O$	42.63	5.12	3.55
2e (I)	75	EtOH-H_2O	239	39.50	4.47	3.34	$C_{14}H_{18}INO_6$	39.71	4.29	3.31
2f (NO_2)	83	EtOH-H_2O	214[b]							
2g (NHAc)	65	EtOH-H_2O	236-237	53.95	5.98	7.84	$C_{16}H_{22}N_2O_7$	54.21	6.26	7.91
Aryl 2-Amino-2-deoxy-β-D-glucopyranosides										
3a (H)	72	EtOH	172[d]							
3d (Br)	75	EtOH	166.5	43.26	4.82	4.21	$C_{12}H_{16}BrNO_5$	43.11	4.83	4.19
Aryl Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosides										
4b (OCH_3)	40	EtOH	100	57.72	6.42		$C_{19}H_{24}O_9$	57.55	6.11	
4d (Br)	43	EtOH	134.5	48.71	4.74		$C_{18}H_{21}BrO_8$	48.53	4.76	

[a] Analysis is given for new compounds. [b] Reference 12. [c] B. Weissmann, *J. Org. Chem.*, **31**, 2505 (1966). [d] C. G. Greig, D. H. Leaback, and P. G. Walker, *J. Chem. Soc.*, 879 (1961).

short intervals the acetic acid generated was removed under diminished pressure. The mixture was extracted with benzene (100 ml). The extract was filtered, repeatedly washed with 5% NaOH solution and water, dried ($CaCl_2$), and evaporated to a syrup which crystallized on trituration with EtOH. The new products obtained are listed in Table IV.

Thermal Analysis.—The dta data were obtained with a Du Pont Model 990 thermal analyzer equipped with a calorimeter cell. All experiments were performed with 2-mg samples in covered 6-mm aluminum pans and an empty pan was used as the reference. A small hole was made in the cover to allow volatile products to escape. In all dta experiments, the samples were heated at the rate of 15°/min in a 75 ml/min flow of nitrogen.

For tga, a Cahn R-100 Electro-balance was used for weighing. The Du Pont thermal analyzer was used to program a furnace surrounding the sample tube. For dynamic tga the sample size, configuration, atmosphere, and heating rate were the same as in dta so that the two methods would be comparable. The derivative of the tga signal (dtg) was taken with a Cahn time derivative computer (Mark II). For isothermal tga the temperature was increased rapidly to the desired temperature and held within ±0.5°.

Decomposition Product Analysis.—The liberation of free phenol was determined under conditions identical with the dynamic dta and tga. Phenol which vaporized from the reaction pan was trapped quantitatively by bubbling the nitrogen purge gas through 1 *M* NaOH solution. The starting materials which were condensed in the cooler regions of the apparatus were washed out with ethanol. The resulting solutions were then analyzed by the uv absorption method to provide the data shown in Table II. Since some of the starting materials could have escaped condensation, the data gives only a lower limit for the evaporated starting materials.

Registry No.—**1a**, 13089-21-9; **1b**, 38229-72-0; **1c**, 38229-73-1; **1d**, 38229-74-2; **1e**, 38229-75-3; **1f**, 13089-27-5; **1g**, 14419-60-4; **2a**, 5574-80-1; **2b**, 38229-78-6; **2c**, 35694-99-6; **2d**, 38229-80-0; **2e**, 38229-81-1; **2f**, 3459-18-5; **2g**, 14419-61-5; **3a**, 38223-13-1; **3d**, 38223-14-2; **4a**, 20196-78-5; **4b**, 38223-16-4; **4c**, 38223-17-5; **4d**, 38223-18-6; **4f**, 38223-19-7; methyl 2-acetamido-2-deoxy-β-D-glucopyranoside, 3946-01-8; methyl 2-acetamido-2-deoxy-β-D-glucopyranoside triacetate, 2771-48-4; *p*-methoxyphenyl β-D-glucopyranoside tetraacetate, 14581-81-8; *p*-methylphenyl β-D-glucopyranoside tetraacetate, 14581-78-3; phenyl β-D-glucopyranoside tetraacetate, 4468-72-8; *p*-bromophenyl β-D-glucopyranoside tetraacetate, 14581-80-7.

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The Effect of Potassium Persulfate on the Reactions of 2-Butanol in Sulfuric Acid[1]

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An investigation of the formation and reactions of *sec*-butyl hydrogen sulfate in H_2SO_4 and D_2SO_4 at 0° was carried out. Either 2-butanol or 2-butene will dissolve in 98% H_2SO_4 (mole ratio 1:5) to form a stable mixture of *sec*-butyl alkoxonium ion and *sec*-butyl hydrogen sulfate if small amounts of $K_2S_2O_8$ are present. The proposed role of $K_2S_2O_8$ as a polymerization inhibitor is that of a scavenger of the traces of 2-butene in the system, thus blocking the initial step of the polymerization reaction, which is assumed to be the addition of *sec*-butyl cation to butene. *n*-Butane was formed in the presence of hydride donors such as methylcyclopentane, indicating the presence of 2-butyl cations in the system. When D_2SO_4 was used, incorporation of carbon-bound deuterium occurred, mostly at C-3, even when $K_2S_2O_8$ was used. It is proposed that H–D exchange occurs in a species which is formed prior to butene in the reaction sequence, and that the intermediate may be a π complex. Nmr spectra at two stages in the conversion of 2-butanol to 2-butylsulfuric acid are presented.

The reaction of simple alcohols and alkenes in sulfuric acid to produce alkylsulfuric acids is well known.[2-6] *sec*-Butyl alcohol also forms the ester, but after a short time, depending on acid strength and temperature, may begin the process of conjunct polymerization, which is the formation of acid-insoluble saturated and unsaturated hydrocarbons together with a series of stable acid-soluble cyclic allylic cations which are recoverable from the acid layer as cyclic hydrocarbons of varying complexity.[7-10]

The reaction may be followed by quenching and weighing of samples removed from the reaction mixture followed by titration of the samples with base. Formation of 1 equiv of $ROSO_3H$ corresponds to the disappearance of 1 equiv of titratable acid.

When the mole ratio of 2-butanol to 96–98% sulfuric acid is 1:5, and at 0°, 2-butylsulfuric acid builds up rapidly in the reaction mixture, reaching a maximum in 40–45 min at 60–70% of the theoretical amount of ester. By this time, the presence of polymer is clearly visible as oily droplets in quenched samples. Polymerization then proceeds rapidly, as indicated by reappearance of titratable acid in successive samples. At the same time the precision of the titration decreases because of the increasing heterogeneity of the mixture owing to the increasing amount of polymer present and the accompanying sampling difficulties.

If, however, a small amount of $K_2S_2O_8$ (0.25 mol % based on the alcohol used) is added to the chilled sulfuric acid just prior to addition of the alcohol, followed by like portions about every 15 min thereafter, the alkylsulfuric acid solution is stabilized against the polymerization reaction without any significant loss of material from the 2-butyl system. Polymer-free systems have been maintained routinely for over 2 hr, using a total of 2 mol % $K_2S_2O_8$. In one experiment, the system was maintained for over 7 hr without visible signs of polymerization by addition of a total of 7 mol % $K_2S_2O_8$. It was noted that excess persulfate was present when the mixture was quenched. Figure 1 shows titration results for composites of several experiments with and without potassium persulfate. Some variation between experiments is observed, but the general form of the curves shown is highly reproducible. The exact shape of any curve is dependent on the strength of acid used. Also, for those experiments in which $K_2S_2O_8$ was used (E-1 and E-2 in Figure 1), additional acidity was continually being produced through the oxidizing action of the persulfate. Accurate corrections could not be made readily for this effect, but they should be small. In spite of some variation in exact shape of the curves for similar reactions run at different times, there is no question about polymerization in the absence of $K_2S_2O_8$, and polymerization inhibition in its presence. The steady-state concentration of alkylsulfuric ester in these experiments appears to lie between 80 and 90% of the theoretical amount. This concentration range is approached when the experiment is begun with butanol and sulfuric acid or with equivalent amounts of butene, water, and sulfuric acid. It seems probable that the apparent steady-state concentration approximates an equilibrium concentration.

The conjunct polymerization reaction also can be observed by noting the appearance of absorption bands in the nmr spectra of the reaction mixtures. These are attributed by Deno[10] to the formation of cyclopentenyl cations. This method is much less sensitive for observing early stages of the reaction than is the observation of these same species by means of their absorption in the ultraviolet at about 305–310 mμ. When potassium persulfate is present, both of these criteria for the onset of conjunct polymerization are absent.

An intriguing feature of the action of $K_2S_2O_8$ on the system 2-butanol–sulfuric acid was the need for continuous addition of the persulfate. When the initial addition of $K_2S_2O_8$ was delayed until 20 min after mixing the alcohol and acid, the alcohol polymerized, and a curve very similar to E-3 in Figure 1 resulted. In other experiments, addition of persulfate was terminated after 45 min. The results of these experiments, when plotted, gave a curve that was similar to E-1 in the initial stages, but the concentration of ester reached a maximum at about 60 min, and then dropped rapidly as in E-3 of Figure 1. When all of the persulfate was added initially, there was some stabilization, but the

(1) Abstracted in part from the Ph.D. Thesis of George S. Clark, University of Maine, 1968.

(2) C. M. Suter and E. Oberg, *J. Amer. Chem. Soc.*, **56**, 677 (1934).

(3) (a) R. L. Burwell, Jr., *ibid.*, **64**, 1025 (1942); (b) *ibid.*, **71**, 1769 (1949).

(4) R. Robey, *Ind. Eng. Chem.*, **33**, 1076 (1941).

(5) M. S. Newman, *J. Amer. Chem. Soc.*, **63**, 2431 (1941).

(6) A. Tian, *C. R. Acad. Sci.*, **228**, 922 (1949); *Chem. Abstr.*, **56**, 9494 (1950).

(7) V. N. Ipatieff and H. Pines, *J. Org. Chem.*, **1**, 464 (1936). The general nature of the acid-soluble species, as well as the highly unsaturated character of the acid-insoluble products, appears to have been first recognized by these authors.

(8) W. Calkins and T. D. Stewart, *J. Amer. Chem. Soc.*, **71**, 4144 (1949).

(9) N. C. Deno and M. S. Newman, *ibid.*, **72**, 3852 (1960).

(10) N. C. Deno, D. Boyd, J. Hodge, C. Pittman, and J. Turner, *ibid.*, **86**, 1745 (1964).

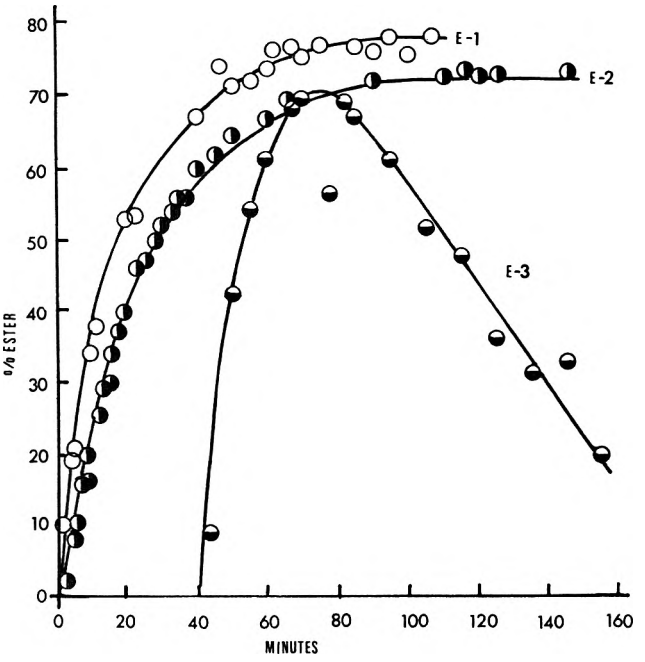


Figure 1.—Esterification of 2-butanol with sulfuric acid: E-1, with 98.1% acid plus $K_2S_2O_8$; E-2, with 95.6% acid plus $K_2S_2O_8$; E-3, 98.1% acid, $K_2S_2O_8$ absent. E-1 and E-2 are composites of two experiments, E-3 of four. The mole ratio of acid/alcohol was 5.0 in all runs. E-3 was displaced 40 min for clarity.

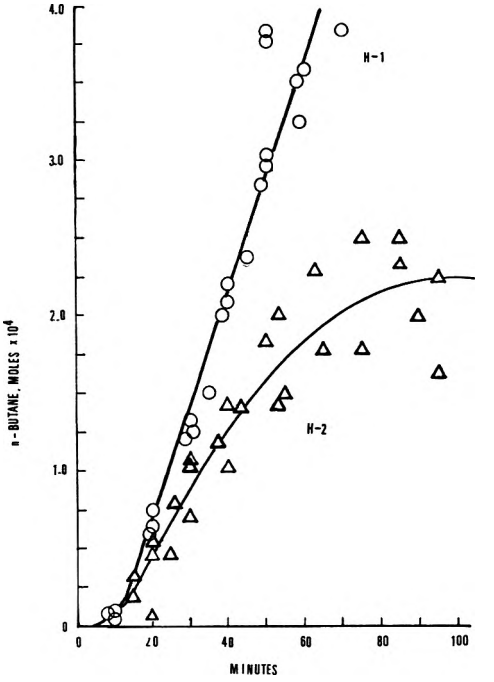


Figure 2.—Evolution of *n*-butane from esterification mixtures in presence of methylcyclopentane: H-1 with $K_2S_2O_8$; H-2 without. Both curves are composites of several experiments.

concentration of ester reached a maximum at 55 min, after which titratable acid reappeared as in unprotected mixtures. The requirement that a small portion of the persulfate be added at regular intervals rather than all of it initially suggests that the persulfate is being used up by a secondary reaction not necessarily related to its inhibiting action on polymerization.

Several experiments were carried out to help decide what step or intermediate in the polymerization reaction was being affected by the persulfate. The rate of alkylation of toluene by 2-butanol–sulfuric acid remained unchanged in the presence of persulfate. Persulfate did not prevent rapid racemization of optically active 2-butanol.[3a,9]

The presence of persulfate did not decrease the apparent initial rate of evolution of *n*-butane in the presence of small amounts of methylcyclopentane or methylcyclohexane (Figure 2), and the rate remains constant through the first hour (curve H-1). The apparent rate of evolution of butane from the system without $K_2S_2O_8$ drops off rapidly as polymerization sets in, presumably because the butane dissolves in the polymer, and its vapor pressure is lowered. This effect could be duplicated by the addition of a relatively large volume of cyclopentane or of inert hydrocarbon.

No isobutane is produced by the mixtures stabilized by persulfate. This is not really surprising, as the evolution of isobutane from unprotected mixtures is part of the complex process of conjunct polymerization.[8]

Because all of these reactions, alkylation, racemization, and butane formation, are believed to involve the 2-butyl cation, it seemed evident that this species was not being affected by the persulfate. These results could have been expected, as carbonium ions are formed relatively rapidly in this system, if the rate of racemization is taken as evidence. Although we have no direct measurement on the rate of racemization, it may be deduced from the combined data of Table I and

TABLE I
RELATIVE NUMBERS OF EXCHANGED PROTONS IN 2-BUTANOL[a] AND RETENTION OF OPTICAL ACTIVITY

	Free 2-BuOH		2-BuOH from ester	
Position	Run D-1	Run D-2	Run D-1	Run D-2
C-1[b]	0	0.3	0.2	0.2
C-2	0.27	0.19	0.61	0.55
C-3	1.00	0.93	1.53	1.55
C-4[b]	0	0.3	0.3	0.1
Retention of optical activity	37%	26%	<1%	<1%

[a] Recovered from solution in D_2SO_4 in presence of $K_2S_2O_8$. [b] C-1 represents the methyl group adjacent to the carbinol group. The small fractions of protons exchanged on C-1 and C-4 may not be real, but may result from difficulties in choosing a cutoff for the integrations in a region of the spectrum where signals overlapped. For the starting alcohol, $[\alpha]^{25}D$ was +8.80. Time of contact with D_2SO_4 (98%; 5:1 mole ratio of acid to alcohol) was 30 min at 0°.

Figure 1 that about 90% of the alcohol has been racemized in 30 min, for the concentration of ester at this time is about 60% of the theoretical amount, and essentially all of the ester has been racemized. Additionally, approximately 75% of the free alcohol, or another 30% of the total, is racemic. If the *sec*-butyl cation is formed rapidly, then its reaction with small amounts of persulfate could not be the step at which the polymerization reaction is stopped, for the persulfate would be used up rapidly, and the polymerization reaction then could proceed as usual.

The most reasonable initial step in the polymerization reaction is the addition of a cation to an alkene. Beyond the initial step the details become lost in a maze of rearrangements, hydride transfers, alkylations, and dealkylations. The formation of 2-butene in the

system under consideration must be relatively slow at low temperature, for the amounts of persulfate used to stabilize 2-butanol in sulfuric acid will not stabilize freshly prepared solutions of 2-butene in sulfuric acid unless special precautions are taken which will be discussed shortly. Similarly, when a small amount of *tert*-butyl alcohol is added to a mixture of acid and 2-butanol that is being stabilized, polymerization occurs in spite of continued addition of persulfate. The tertiary alcohol appears to dehydrate so much more rapidly than the secondary alcohol that the persulfate cannot cope with the alkene produced. Also, perhaps the branched structure of the isobutylene produced slows down its possible reaction with persulfate relative to its reaction to form polymer. If alkene can be scavenged from the system as rapidly as it is formed, then the progress of the polymerization is stopped in its initial stage. We have considered that the effect of the persulfate was to oxidize the butene to a glycol, which then might be dehydrated to 2-butanone. Traces of 2-butanone have been detected by comparison vapor–liquid chromatography in a fraction obtained by quenching and neutralizing the reaction mixture, followed by distillation of the volatile organic materials through an efficient column.[11]

Recently, a note has appeared which confirms our supposition that the persulfate may react with alkene. Deno and coworkers[12] have shown that significant yields of glycols may be obtained from appropriate precursors, including 2-butanol, and potassium persulfate in sulfuric acid.

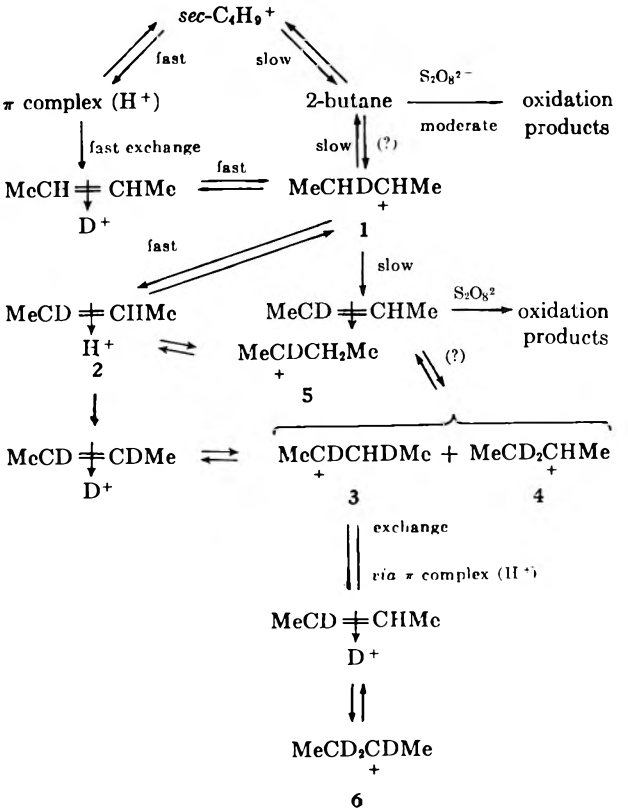
The proposed mechanism for the action of potassium persulfate as an inhibitor of polymerization suggests that the incorporation of carbon-bound deuterium into the molecule might be eliminated, or at least severely inhibited, by the presence of persulfate. Presumably such deuterium incorporation occurs *via* addition of D^+ from D_2SO_4 to alkene. If persulfate removes alkene as fast as it is formed, then deuterium incorporation could not occur. When 2-butanol was allowed to react with D_2SO_4 in the presence of potassium persulfate and then recovered, there was still extensive substitution by deuterium. This result is inconsistent with a mechanism requiring exchange at the alkene stage, but is consistent with a species which can exchange protons with the solvent, and which exists either as an intermediate between cation and alkene or builds up in some branching reaction. Dewar first proposed a species which was represented as a π complex.[13] Taft and coworkers,[14] and others,[15] have suggested such an intermediate from studies on the hydration of isobutene and on oxygen exchange rates for tertiary alcohols in acidic media.

We have considered the possibility that our data do not require the π complex, and that exchange does occur *via* the alkene, but that the reaction of the alkene with deuterium ion, with persulfate, or with carbonium ion to initiate polymerization are simply competitive reactions. An unequivocal answer to this question would require rate data for individual steps in the reaction scheme. In the absence of these data, we present semiquantitative arguments based on the comparative extents of racemization and deuteration, summarized in Table I.

Although hopes for a dramatic outcome of the H–D exchange reaction were frustrated, the data obtained are of interest. Incorporation of carbon-bound deuterium into the 2-butyl system under conditions similar to the ones employed in this work has been observed by Burwell,[3b] but no information was provided about the exchange location. Recovery of unreacted alcohol and alcohol from hydrolysis of alkylsulfuric acid was effected following Burwell's procedures, and examination by nmr spectroscopy of alcohol isolated from two separate experiments gave results similar to Burwell's. The unreacted alcohol, presumably present in the mixture as oxonium ion, was much less extensively exchanged and racemized than that recovered from ester. The protons most extensively exchanged were those on C-3, the carbon atom adjacent to the carbinol group. In order to exchange at C-2, any given molecule would have to go through the π complex stage at least twice. The small amount of exchange noted at C-1 is surprising.

Possible pathways for the exchanges at C-1 and C-2 in D_2SO_4, beginning at the carbonium ion stage, are shown in the reaction scheme presented in Scheme I.

Scheme I



The reactions outlined ignore the obvious extensions to include deuteration at C-1 and C-4, and the pathway to **6** by way of 2,3-dideuterio-2-butene is not shown.

(11) G. S. Clark, M.S. Thesis, University of Maine, 1966.

(12) N. C. Deno, W. E. Billups, J. S. Bingman, R. R. Lastomirsky, and R. G. Whalen, *J. Org. Chem.*, **34**, 3207 (1969).

(13) M. J. S. Dewar, *J. Chem. Soc.*, **406** (1946).

(14) (a) R. Taft, *J. Amer. Chem. Soc.*, **74**, 5372 (1952); (b) J. Levy, R. Taft, D. Aron, and L. P. Hammett, *ibid.*, **75**, 1253 (1953); (c) E. Purlee and R. Taft, *ibid.*, **78**, 5807 (1956); (d) P. Riesz, R. Taft, and R. Boyd, *ibid.*, **79**, 3724 (1957); (e) R. Boyd, R. Taft, A. Wolf, and D. Christman, *ibid.*, **82**, 4729 (1960).

(15) A. Shilov, R. Sabirova, and V. Gorshkov, *Dokl. Akad. Nauk SSSR*, **119**, 555 (1958); *Chem. Abstr.*, **53**, 6988 (1959).

Loss of proton is not considered reversible because of the low concentration of proton available. The deuterations of alkene are marked as questionable because it is this possibility that we are discussing. The notation "π complex (H^+)" means a species with a protonated, as opposed to deuterated, double bond.

All of the cations, $C_4H_9^+$ and **1**–**6**, may revert to ester or alcohol, and be recovered as "free" alcohol or as alcohol from hydrolysis of the ester. As mentioned earlier, there is very little alcohol present that has not been through one or more steps of this sequence, for a total of about 90% of the recovered alcohol is racemic.

Examination of Table I shows that of the "free" alcohol recovered in runs D-1 and D-2, an average of 23% has been deuterated at C-2, and therefore must have reached one or more of the stages **3**, **4**, and **5** if π complexes represent the major pathway for deuteration. The same table shows that an average of 96% of the alcohol molecules have undergone exchange at C-3. If 23% also is substituted at C-2, some must be doubly substituted, at the very least.

Now the degree of racemization of this material is in the range 63–75%, and we see that the number of molecules which have undergone substitution exceeds the number which have been racemized. In other words, *once a molecule reaches the cation stage, it will, on the average, undergo more than one substitution before reverting to alkylsulfuric acid.*

In the case of the alcohol recovered from ester, polydeuteration is the only explanation of the results, which show, on the average, 150% deuteration at C-3 and 58% at C-2. Clearly, some of these species must have arisen from cation **3** and perhaps from **6**.

The point of these arguments is that deuteration is relatively fast, as least as fast as cation formation. If deuteration occurs exclusively or principally by way of alkene, then alkene formation must be rapid. If the persulfate removes only a small part of the alkene, *i.e.*, reduces the steady-state concentration slightly, it cannot be an effective inhibitor, for then polymerization could still occur. However, if essentially all of the alkene is removed, *i.e.*, if its steady-state concentration is reduced by perhaps 90%, then persulfate would be used up rapidly because the alkene is formed rapidly. As we have seen, in 30 min essentially all of the molecules have been at the cation stage, and all have undergone exchange, some more than once. If substitution occurs by way of alkene, then alkene formation also has to be rapid. However, we already have seen that rapid alkene formation should render the small amounts of persulfate ineffective. Our conclusion is that the major pathway to H–D exchange in this system is not through alkene.

The interesting question remains as to the necessity for addition of the persulfate before the alcohol is added to the acid. Why cannot one wait until 15 min after the alcohol and acid are mixed before the first addition? No visible evidence of polymer is present at that time. The answer is that the process of polymerization has begun, even though it is not visible to the eye. One begins to note absorption in the ultraviolet after 4 or 5 min. For samples handled in a comparable manner, transmittances at 307–310 mμ were 0.90, 0.75, and 0.31 (concentrations $\sim 10^{-3}$ M in 96% H_2SO_4, approximately 0°) after 4, 37, and 43 min. Because polymerization, once begun, cannot be halted by the addition of small amounts of persulfate, it is believed that the reaction is autocatalytic.

Hoffman and Schriesheim[16] have suggested that "old" sulfuric acid, previously used as catalyst for butene–isobutene alkylations, and containing cyclopentenyl cations, was responsible for elimination of the inhibition period in that reaction. This investigation showed that neither "old" sulfuric acid, previously used in a polymerization reaction, nor solutions of cyclopentenyl cations prepared by dissolving alkylated cyclopentadienes in concentrated sulfuric acid had any noticeable influence on the rate at which polymer formed in our systems. When the supposed catalysts were used in the absence of $K_2S_2O_8$, the maximum formation of ester occurred at the same time as in the absence of the additives. When "old" acid or acid containing cyclopentenyl cations was added to systems stabilized by $K_2S_2O_8$, no polymerization occurred.

We propose that the acid-insoluble polymer is responsible for the autocatalytic nature of the polymerization process, and the characteristic responsible for its catalytic activity is its high degree of unsaturation.[7] Addition of some of the acid-insoluble polymer, prepared in a previous run, was shown to catalyze further polymerization, and to render ineffective the persulfate being added to the system. When the polymer was fractionated, it was found that only the higher boiling fractions, which were also highly unsaturated, were effective in promoting polymerization.

We believe that the reason the persulfate is unable to attack the alkene linkages in the polymer effectively is that the polymer is present in a separate organic phase even when present in trace amounts, and perhaps because the alkene linkage is sterically protected by branching methyl groups nearby. The persulfate is soluble only in the acid layer. Although persulfate is unable to attack the higher molecular weight alkenes, carbonium ions are able to do so by virtue of their being largely organic. They, together with the polymer, may form a micelle-like aggregate with the localized charge of the cation presented to the acid phase. The unsaturated linkages are protected within the polymer phase, but the cations may migrate along or within the micelle until they find suitable sites for reaction. The subsequent reactions may then include the hydride transfers, rearrangements, C–C chain splittings, deprotonations, cyclizations, etc., which result in the large number of relatively stable products.

Experiments with other alcohols showed that 2-pentanol was similar to 2-butanol, except that larger amounts of potassium persulfate were required to prevent polymerization. Several experiments with cyclohexanol indicated that persulfate could stabilize it against polymerization, although the alcohol did not show the same tendency as 2-butanol or 2-pentanol to polymerize. 2-Octanol did not polymerize within 2 hr in 96% H_2SO_4 at 0°, and the esterification curves with and without $K_2S_2O_8$ were superimposable. When the mole ratio of acid to alcohol was increased to 10:1, 2-octanol and 2-butanol polymerized even in the presence of $K_2S_2O_8$.

Experiments with 2-butene, an equimolar amount of water, and 98% sulfuric acid in the presence of $K_2S_2O_8$

(16) J. Hoffman and A. Schriesheim, *J. Amer. Chem. Soc.*, **84**, 958 (1962).

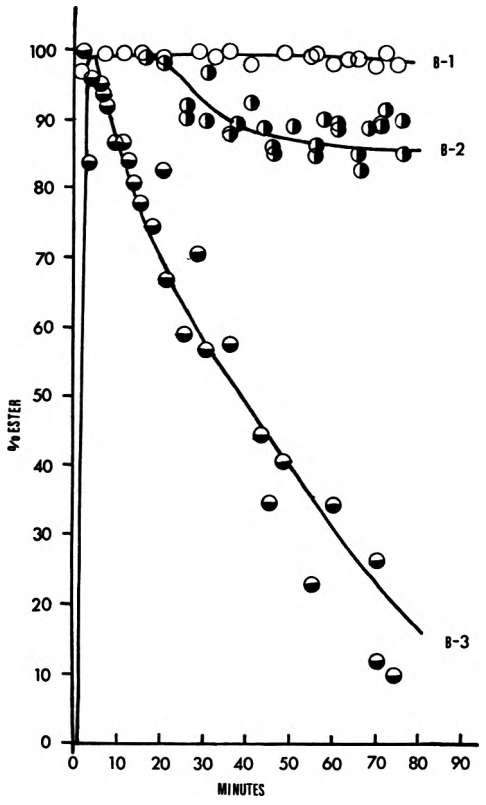


Figure 3.—Esterification of 2-butene with sulfuric acid: B-1, no $K_2S_2O_8$, −40°; B-2, with $K_2S_2O_8$, mixed and kept at −40° for 5 min, warmed to 0°; B-3, no $K_2S_2O_8$, mixed at −30°, warmed to 0°. The mole ratio acid/alcohol was 5.0 for all runs. Maximum per cent ester was normalized to 100 for all runs.

support our conclusions regarding the action of persulfate. Small amounts (1 mol % based on 2-butanol) of 2-butene introduced into a stabilized system of sulfuric acid–2-butanol at 15 min after starting the run did not cause polymerization, but large amounts of 2-butene mixed with H_2SO_4 and water polymerized despite the presence of $K_2S_2O_8$ unless special precautions were observed.

If 1 mol of butene was added to 5 mol of 96–98% sulfuric acid containing an additional 1 mol of water, at −40 to −60°, and if the temperature was kept very low, no inhibitor appeared to be necessary. If the mixture was allowed to warm up to 0°, polymerization occurred as with the alcohol. If the solution was prepared in the presence of $K_2S_2O_8$ but the initial temperature and rate of addition were adjusted so that the temperature quickly reached 0° after addition of the butene, polymerization occurred. On the other hand, if the mixture was allowed to stay at the low temperature for at least 5 min before warming to 0°, the persulfate was able to protect against polymerization. Evidently a little time is required for complete conversion of all of the butene to alkylsulfuric acid. Figure 3 shows the results of several experiments. Note that in curve B-2, the concentration of alkylsulfuric acid appears to be levelling off at between 80 and 90%, which is the concentration reached by stabilized mixtures of 2-butanol and sulfuric acid after several hours.

The nmr spectrum of such a system after 15 min was similar to that of a mixture of 2-butanol–sulfuric acid–$K_2S_2O_8$ after 90 min, and remained unchanged for at least 1.5 hr when stabilized with $K_2S_2O_8$ in the same manner as in the experiments with 2-butanol. An

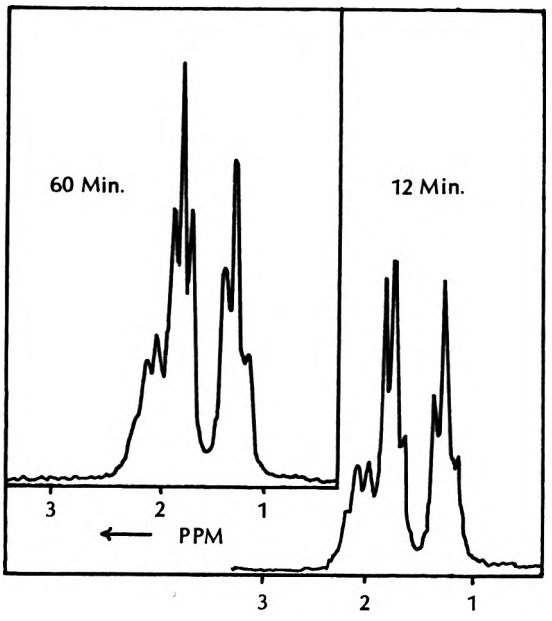


Figure 4.—Portions of nmr spectra of 2-butanol–H_2SO_4–$K_2S_2O_8$ after 12 and 60 min, showing conversion of RCH_2^+ to $ROSO_3H$.

interesting point which appears not to have been reported in the literature may be seen in the nmr spectra of stabilized solutions of 2-butanol after 12 and 60 min reaction time (Figure 4). The "triplet" centered at 1.76 ppm may be noticed to vary considerably with time. We interpret these peaks as due to the protons on C-1 of the oxonium ion of 2-butanol and of *sec*-butylsulfuric acid. Reading from the left, the first peak is due to alkylsulfuric acid. The middle peak is a combination of alkylsulfuric acid and alkoxonium ion. The third is due to alkoxonium ion. As the reaction proceeds, the intensity of signal due to the alkylsulfuric acid increases while that due to alkoxonium ion decreases. The same result may be observed in the two smaller peaks that are visible at just over 2 ppm. The right-hand peak increases with time. As might be expected, the oxonium ion deshields adjacent protons somewhat more effectively than does the sulfuric ester.

Experimental Section

Sulfuric Acid and Deuterium Sulfate.—Analyzed reagent grade H_2SO_4 was stored in a container that could be pressurized with dry air and that was fitted with a wash-bottle type adapter with a Teflon stopcock attached to the outlet. Deuterium sulfate was prepared by addition of 99.8 mol % D_2O to SO_3, following a modification of a method of Herber.[17] The product was 97.8% D_2SO_4 by weight; its isotopic purity, by nmr spectral analysis, was 99.8 mol %.

2-Butanol and Other Alcohols.—2-Butanol from various sources rapidly produced a yellow color when a few drops were mixed with concentrated sulfuric acid. Infrared examination showed the presence of a small absorption band, presumably due to the carbonyl group, at 1715 cm^{-1}. Purification was accomplished by washing the 2-butanol three times with aqueous $NH_2OH \cdot HCl$, then distilling the desired product away from the oximes and excess reagent under reduced pressure (pot temperature below 50°). The distillate was then dried (K_2CO_3) and redistilled through a 50-plate column, bp 99–100°. No evidence could be found for the presence of a carbonyl group, and a sharp hydroxyl proton doublet in the nmr spectrum at δ 5.1 ppm (neat) showed that the alcohol was dry.

(17) R. H. Herber, *Inorg. Syn.*, **7**, 155 (1963).

2-Pentanol and other alcohols were purified by standard procedures. All were examined by ir and nmr, and subjected to the color test with sulfuric acid.

(+)-2-Butanol.—α-Pinene, $[\alpha]^{25}D$ +47.40, was prepared from β-pinene[18] by the method of Richter and Wolff.[19] Brown's method[20] was used to convert *cis*-2-butene to the optically active alcohol. On our hands, the product instantly developed a brilliant orange-yellow color in contact with sulfuric acid, and showed a strong carbonyl peak in its infrared spectrum at 1670 cm^{-1}. Careful distillations improved the alcohol only slightly, so it was subjected to the purification described above. Optical rotation varied somewhat from batch to batch; the highest value was $[\alpha]^{25}D$ +10.40.

Apparatus.—The reaction vessel was a 500-ml four-neck flask, equipped with a ground stirrer shaft and bushing in the center neck. Other necks were adapted for a low-temperature thermometer, for admission of nitrogen gas when desired, and for a serum cap through which gas samples could be withdrawn with a syringe. One neck either supported a buret modified for rapid addition of the alcohol or was used for the periodic addition of $K_2S_2O_8$ and removal of samples for titration.

The stirrer and flask were both mounted on the same swiveling vertical support rod, making it possible to raise the flask quickly from a solid CO_2–ethanol bath, rotate it by 180°, and immerse it in a well-stirred ice–water bath. The stirrer blade for the reaction mixture was a modified Hershberg type made of tantalum wire.

Esterification of 2-Butanol with Sulfuric Acid.—A weighed amount of H_2SO_4 or D_2SO_4 was placed in the reactor, the stirrer was started (positive nitrogen pressure), and the acid was cooled to −20 to −30°. The acid often froze upon cooling, but this did not offer much of a problem if the stirrer was kept running.

The required amount of 2-butanol was then added as quickly as possible from a pressurized buret. Usually, the addition required 40–50 sec, and the temperature of the system would be just under 0° when addition was complete. The timer was started at this point, and the reactor was immersed in the 0° bath.

If $K_2S_2O_8$ was used as a polymerization inhibitor in a run, a portion equivalent to 0.25 mol % of the alcohol to be used was added just prior to addition of the alcohol, and like portions were added each 15 min thereafter, or as desired in special experiments. Other additives, such as methylcyclopentane, were used as desired.

Samples of the reaction mixture, about 2.0 g each, were periodically withdrawn from the flask, using a succession of cleaned and dried pipets each topped with a 2-ml dropper bulb, and quickly transferred into half-pint tared vacuum bottle fillers[21] containing about 30 g of ice. Sample weights were obtained by difference.

At the end of a run, each individual sample was titrated with standardized 1.0 *N* NaOH solution delivered from a weighing buret. The quenched samples showed no change in titratable acid over a period of several hours.

Esterification of 2-Butene with H_2SO_4.—Sulfuric acid was placed in the reactor and cooled as in the experiments with 2-butanol, and butene was allowed to run in from a trap in which an approximately weighed amount had been collected. The delivery tube was arranged so that the butene ran directly onto the surface of the frozen H_2SO_4–air emulsion. The addition time in all successful runs was between 45 and 60 sec. It appeared that avoidance of local heating and keeping the overall temperature below −20 or −25° was necessary to avoid polymerization. In some runs, the temperature was raised to 0° as quickly as possible. In the runs that were successfully stabilized against polymerization, the mixture was held at a low temperature (−40°) for at least 5 min before warming it to 0°. Samples of gases taken from over the mixture in the reaction flask and subjected to gas chromatographic examination after that period of time showed no traces of butene.

Samples of the mixture were then obtained and titrated as in the experiments with the 2-butanol.

Evolution of Gases from the 2-Butanol–H_2SO_4 System at 0°.—Runs were prepared as for the esterification experiments, except that no nitrogen flowed through the reaction flask. The vapor phase over the system was periodically sampled by removal of 5 ml of gas in a syringe and analysis by gas chromatography on a silica gel column. The same method was used for sampling for butene, isobutane, or *n*-butane in the experiments with hydride donors. The amount of gas found in the sample was converted to moles present in the vapor space over the sulfuric acid by application of a factor calculated using the volume of vapor space in the reaction flask, temperature, volume of sample, and the ideal gas laws. The method was calibrated using known mixtures.

Ultraviolet Spectra in H_2SO_4.—From mixtures of 2-butanol or 2-butene and sulfuric acid prepared as for esterification runs, either with or without $K_2S_2O_8$, samples were removed and diluted with cold concentrated sulfuric acid to approximately 2.5×10^{-3} *M* concentration of alcohol and the spectra were recorded immediately on a Perkin-Elmer Model 4000 Spectracord.

Nuclear Magnetic Resonance Spectra of 2-Butanol and Related Products in H_2SO_4.—Nmr spectra were recorded on a Varian A-60 instrument with tetramethylsilane sealed in a capillary tube as an external standard. Spectra in H_2SO_4 and D_2SO_4 were run at 0°.

Registry No.—Potassium persulfate, 7727-21-1; 2-butanol, 78-92-9; sulfuric acid, 7664-93-9; *n*-butane, 106-97-8; 2-butene, 107-01-7.

(15) We thank Dr. H. I. Enos, Jr., Pine and Paper Chemicals Research Division, Hercules Powder Company, Wilmington, Del., for a gift of optically active α- and β-pinenes.

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Hydrogen Exchange Studies. VIII.[1] Base-Catalyzed Hydrogen Exchange of 1,3,5-Trinitrobenzene in Aqueous Dimethylformamide

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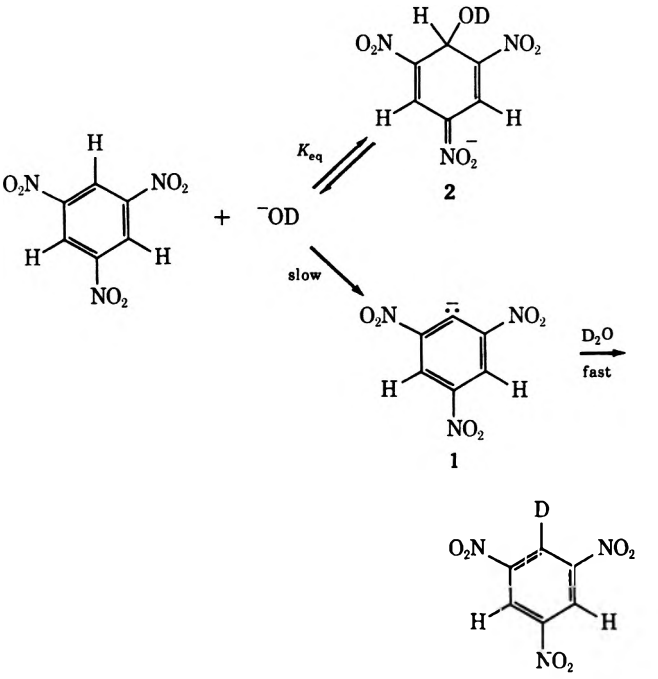
The rate of aromatic proton exchange between 1,3,5-trinitrobenzene (TNB) and dimethylformamide–D_2O containing sodium deuterioxide has been measured as a function of medium composition and reactant concentration. In contrast to the normally observed trend of base-induced exchange rates in protic–aprotic solvent mixtures, in this system the pseudo-first-order rate constants for exchange *decrease* with increasing DMF content over the range 25–80 mol % DMF, when the TNB is present in excess over the base. Also, for constant medium composition and base concentration, the rates are *halved* on doubling the TNB concentration. This unusual behavior is interpreted as arising from competition between proton exchange and Meisenheimer complex formation.

Aromatic hydrogen exchange induced by strong bases has been investigated in a variety of systems with a view to elucidating the structural and electronic factors governing the exchange process.[2] The currently accepted mechanism for proton exchange involves initial removal of the proton by base to form a carbanion in the slow step, followed by rapid neutralization of the latter by proton transfer from a solvent molecule.[3] Detailed kinetic schemes for proton transfer processes, involving also hydrogen-bonded carbanionic species, have been presented and their mechanistic implications discussed.[4]

Aromatic compounds containing two or more nitro groups are of special interest in studies of base-induced proton exchange, since with these compounds the base may take part in more than one type of interaction.[5-7] In the case of the 1,3,5-trinitrobenzene–hydroxide ion system the base can abstract a ring proton, giving the aryl carbanion **1** and leading to proton exchange with the medium, or it can add covalently to aromatic carbon to form the colored adduct **2**, known as a Meisenheimer complex.[8] In the general case still other processes, involving charge-transfer complexes[9] and radical anions,[10] are also possible.

The feasibility of proton exchange for 1,3,5-trinitrobenzene in dimethylformamide–D_2O–base systems was described previously, for deuterioxide[11a] and for other Brønsted bases.[11b] We have since carried out an investigation of σ-complex formation and proton exchange in the trinitrobenzene–hydroxide ion system. The equilibrium constant data have recently been reported.[11c] Our results on hydrogen isotope exchange are now presented and the relationship with complex formation is discussed, on the basis of the following reaction scheme.



Experimental Section

Reagents.—1,3,5-Trinitrobenzene (TNB) was recrystallized from ethanol and then from chloroform, mp 122.5–123.0° (uncorrected). Dimethylformamide (DMF) was purified by the method of Ritchie and Megerle.[12] Sodium deuterioxide solutions were prepared by dissolving freshly cut sodium metal in D_2O. The DMF and NaOD–D_2O solutions were transferred under nitrogen.

Kinetic Method.—The kinetic data were obtained by the sealed tube method, as follows. To a weighed quantity of TNB

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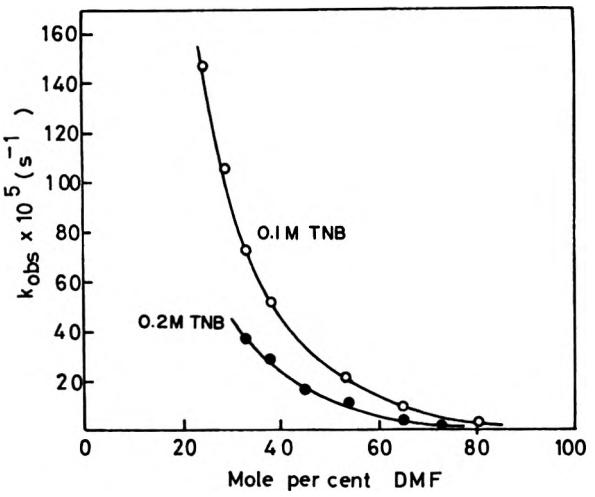

Figure 1.—Plots of k_{obsd} (50°) for hydrogen exchange in TNB in DMF–D_2O containing NaOD (0.02 *M*) as a function of medium composition: open circles, 0.1 *M* TNB; shaded circles, 0.2 *M* TNB.

(*ca.* 1 g) in a 50-ml volumetric flask were added DMF and D_2O in the requisite amounts, and the solution temperature was brought to 25°. Just prior to starting the run the NaOD–D_2O was added, resulting in instantaneous appearance of red color, and then DMF was added to the mark. The flask was cooled by means of a Dry Ice–acetone bath and transferred to a nitrogen-flushed drybox for filling of the Pyrex reaction tubes, which were then sealed and placed in unison in the constant-temperature bath. The tubes were withdrawn individually over a period corresponding to 1–2 half-lives for exchange and cooled, and the contents (*ca.* 6.5 ml) were added to *ca.* 30 ml of dilute sulfuric acid. The red color of the reaction solutions disappeared instantly on acidification, but in some cases a dark brown coloration remained, indicative of decomposition. (For solutions of high DMF content neutralization gave on occasion a transitory green color which was readily bleached in light.) The precipitated TNB was filtered, washed with distilled water, and dried. The yield of TNB was generally about 75% of theoretical and selected samples had mp 121–123°, indicating a satisfactory purity for isotopic analysis by infrared spectrometry. The extent of deuteration was determined by measuring the CH and CD[12] peak heights at 3100 and 2305 cm^{-1} for 1 *M* solutions in acetonitrile, using 0.1 mm calcium fluoride cells and a standard calibration curve. The instrument employed, a Perkin-Elmer Model 21, gave an estimated precision of 2–4%. Pseudo-first-order rate constants (k_{obsd}) were obtained from least squares calculations for linear plots of log (100 − % exchange at time *t*) *vs.* time; the estimated error is ±5%. The values of k_{obsd} refer to exchange of all three hydrogens in the TNB molecule.

Results and Discussion

Kinetic Results and Concentration Dependence of Proton Exchange.—The kinetic data for proton exchange in trinitrobenzene obtained by the method described above are given in Tables I and II. Pseudo-first-order rate constants measured as a function of medium composition at 25 and 50° for two values of TNB concentration, with constant NaOD concentration, are contained in Table I. The effect of varying the NaOD concentration is shown in Table II for two values of the medium composition.

It is apparent from the data of Table I (see also Figure 1) that for a given medium composition and NaOD concentration the rate of proton exchange is greater for the *lesser* of the two concentrations of TNB. This result, which may not have been expected, is tied

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TABLE I
PSEUDO-FIRST-ORDER RATE CONSTANTS FOR PROTON EXCHANGE IN TRINITROBENZENE AS A FUNCTION OF TNB CONCENTRATION AND MEDIUM COMPOSITION (DMF–D_2O)

	Mol % DMF	$10^5 k_{obsd}$, sec^{-1} 25°	50°
0.100 *M* TNB	24.8		147
0.020 *M* NaOD	28.8	4.20	105
	33.1		72.5
	38.2	1.85	51.5
		1.83	
	53.6	0.603	21.8
			19.3
	65.1	0.272	8.35
		0.253	
	80.5	0.054	2.03
0.200 *M* TNB	33.1		36.0
0.020 *M* NaOD			38.5
	38.2		30.7
			26.3
	45.0		16.6
			15.0
	53.6		10.7
			9.8
	65.1		3.65
			3.93
	72.9		1.67
	80.5		0.75

TABLE II
PSEUDO-FIRST-ORDER RATE CONSTANTS FOR PROTON EXCHANGE IN TRINITROBENZENE (0.200 *M*) AS FUNCTION OF DEUTERIOXIDE ION CONCENTRATION IN DMF–D_2O AT 50°

	$10^5 k_{obsd}$, sec^{-1} 38.2 mol % DMF	53.6 mol % DMF
[NaOD]		
0.0040	4.60	1.48
	5.17	1.51
0.0075	10.5	3.80
	10.7	
0.010	15.1	4.92
	14.4	4.82
0.0150	21.0	7.77
	22.2	
0.020	30.7	10.7
	26.3	9.8

intimately to the interdependence of the proton exchange process and Meisenheimer complex formation. It was shown previously[11c] that the equilibrium constant (K_{eq}) for formation of adduct 2 from TNB and hydroxide ion increases sharply with increasing DMF content of the medium, from its value of 3.0 l. mol^{-1} in purely aqueous medium to *ca.* 2×10^4 l. mol^{-1} in 34 mol % DMF. Thus for a given $[NaOD]_{stoich}$, the concentration of *free* deuterioxide ion is an inverse function of $[TNB]_{stoich}$. For example, for 33.1 mol % DMF, where K_{eq} is estimated as *ca.* 2×10^4, one calculates that for $[NaOD]_{stoich} = 0.02\ M$ and $[TNB]_{stoich} = 0.2\ M$, $[OD^-]_{free} \cong 6 \times 10^{-6}\ M$; on the other hand, for $[NaOD]_{stoich} = 0.02\ M$ and $[TNB]_{stoich} = 0.1\ M$, $[OD^-]_{free} \cong 13 \times 10^{-6}\ M$. This calculated increase of *ca.* 2 in $[OD^-]_{free}$ on decreasing [TNB] from 0.2 to 0.1 *M* compares favorably with an observed increase of 2.0 in the pseudo-first-order rate constant for exchange at this solvent composition at 50° (Table I). Although the K_{eq} data were measured in DMF–H_2O at 25° but applied to DMF–D_2O at 50° (*i.e.*, both temperature and solvent isotope effects were not

taken into account), moderate changes in the value of K_{eq} are not expected to have a significant effect on this result.

The data of Table II show that the rate of proton exchange is directly proportional, within experimental error, to $[NaOD]_{stoich}$ for both medium compositions. Because of the relatively large magnitude of K_{eq} for complex formation in these media and the use of excess TNB, the $[NaOD]_{free}$ which determines the proton abstraction process is proportional to $[NaOD]_{stoich}$ within experimental error, though of course $[NaOD]_{free} \ll [NaOD]_{stoich}$.

The extensive complexing of deuterioxide ion in these TNB–OD^-–DMF systems effectively eliminates the possible problem of limited solubility of NaOH in media rich in DMF.[14] This complexing also bears directly on the question of whether reaction of hydroxide ion with DMF (hydrolysis to formate ion and dimethylamine) interferes significantly with the proton exchange process. From previous work[14] one can estimate that for 38.2 mol % DMF, 0.02 *M* NaOH, 25°, the half-life for reaction of DMF with hydroxide ion is *ca.* 6.3 min. From the data of Table I, for 38.2 mol % DMF the half-life for the deuterioxide ion catalyzed proton exchange of TNB (0.1 *M*) at 25° is 630 min. A similar disparity in rates occurs at the other solvent compositions. However, the following consideration indicates that the DMF–OD^- reaction[15] does not interfere appreciably with the proton exchange process under the experimental conditions [TNB] > [NaOD]. For 38.2 mol % DMF and $[TNB]_{stoich}$ = 0.1 *M*, $[NaOD]_{stoich}$ = 0.02 *M*, one estimates[11c] from the K_{eq} data for complex formation that $[NaOD]_{free} \cong 6 \times 10^{-6}$ *M*. On the assumption that one-half of the *free* base is consumed by reaction with DMF for each hydrolysis half-life, and that this loss can be linearly extrapolated to an exchange half-life, then the net loss in base during the exchange half-life is *ca.* 2% of $[NaOD]_{stoich}$. The maximum calculated loss in OD^- over the solvent composition range studied is 5% per exchange half-life. Since σ-complex formation and breakdown is effectively instantaneous, the deuterioxide ion consumed in DMF hydrolysis is replaced from this reservoir, so that the free base concentration will remain essentially constant during the exchange run. It is important, however, to point to the necessity in the proton exchange studies to prepare reaction solutions in such a sequence that the TNB be present in the aqueous DMF solution *prior* to the addition of base; the reverse procedure would lead to premature loss of some base *via* hydrolysis.

Medium Dependence of Proton Exchange.—The effect of changing solvent composition on the rate of proton exchange of TNB is given by the data of Table I and is seen more clearly in Figure 1 (kinetic data at 25° yield a curve which is closely similar to that given in Figure 1 for the 50° data). It is apparent that the rate as given by the pseudo-first-order constants *decreases* sharply as the DMF content of the medium increases. This behavior is in contrast to the well-documented[17] general increase in rate of reactions of anionic nucleophiles with various substrates in mixtures of protic and dipolar aprotic solvents. By analogy with other proton transfer processes in DMSO–water or DMSO–methanol systems, to which most of the available literature data apply,[18] one might have expected a rate increase of *ca.* 10^4 in the present system on increasing the DMF content from 25 to 80 mol %.

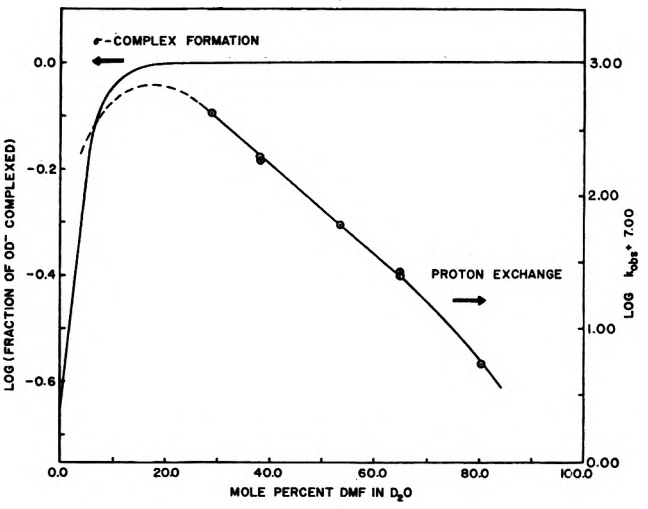

Figure 2.—Plots showing correlation between rate of proton exchange (25°) in TNB and the degree of σ-complex formation as a function of medium composition (0.1 *M* TNB, 0.02 *M* NaOD).

The reversed medium effect measured in this system can be explained by considering the medium effect on the two concurrent processes, proton exchange and complex formation. Directly relevant to our discussion is the study by Crampton and Gold[5] dealing with proton exchange and complex formation for 1,3-dinitrobenzene (DNB) in DMSO–methanol–sodium methoxide. Proton exchange in DNB was followed by measuring the tritium uptake from methanol-*t*, with NaOMe (0.25 *M*) in excess over DNB (0.17 *M*), over the range of medium composition 10–88 mol % DMSO. The rate of exchange was found to *increase* over the range 10–60 mol % DMSO and thereafter level off, remaining approximately constant. Parallel spectrophotometric measurement of apparent extinctions showed increasing complex formation up to *ca.* 70 mol % DMSO and then a levelling off, indicating virtually complete complexing of the DNB. The levelling off in rate of proton exchange was accounted for on the basis that the colored species (Meisenheimer complex formation by addition of MeO^- at C-4) represented an unreactive form of the substrate and that exchange occurred *via* a very small concentration of carbanion.

For the trinitrobenzene–deuterioxide ion system, the relationship between isotopic exchange and σ-complex formation is shown in Figure 2, in the form of plots of log k_{obsd} (exchange) and log (fraction of

(14) E. Buncel and E. A. Symons, *Chem. Commun.*, 164 (1970); E. Buncel, S. Kesmarky, and E. A. Symons, *ibid.*, 120 (1971).

(15) No account is taken here of the solvent isotope effect[16] on the DMF hydrolysis reaction.

(16) P. M. Laughton and R. E. Robertson, "Solute–Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 7.

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stoichiometric OD^- complexed)[19] *vs.* mol % DMF. The latter function shows that, for TNB, 99% of the base has already been complexed by 15–20 mol % DMF. In contrast, in the DNB–OMe^- system[5] the 99% complexing stage (of the component present in deficit which in this case was DNB) does not occur until *ca.* 88 mol % DMSO. In the DNB–OMe^- system there is less than 0.1% complexing in the medium of 20 mol % DMSO.

Crampton and Gold predicted[5] that in the DNB–OMe^- system the log (rate) *vs.* H_- (or solvent composition) profile should pass through a maximum and then decrease as the extent of complexing continued to increase. However, data were not available to demonstrate this point experimentally. In the present work we have been able to verify their prediction by employing the TNB–OD^- system, in which the degree of complexing is more extensive than for DNB under identical solvent conditions. In Figure 2 a maximum is sketched in for the TNB plot in the solvent composition region where the fraction of $[OD^-]_{stoich}$ removed by complex formation becomes significant.[20,21] Thus Crampton and Gold's study with DNB[5] and our own with TNB are complementary in their attempt to demonstrate and explain the competition which occurs between proton exchange and σ-complex formation for nitroaromatic substrate–base systems in solution. These results are also consistent with the recently reported[22] hydrogen exchange of DNB in MeONa–MeOD, in which system the degree of complexing is expected to be negligible.

(19) This function was determined as $\log([\text{complex}]/[\text{complex}]_{max})$, where the values of [complex] were calculated from the appropriate K_{eq} data.[11c] The $[\text{complex}]_{max}$ corresponds to complete complexing of NaOD, the species in lower concentration. For $K_{eq} > ca.\ 10^4$, the limit of experimental data (34 mol % DMF), this function takes the value 0.00.

(20) A maximum in the rate–medium composition profile will be predicted if the degree of complexing of OD^- increases more rapidly with increasing content of the dipolar aprotic component than does the effectiveness of OD^- for catalysis of proton exchange.

(21) Proton exchange measurements were not made for the low-DMF region because of increasingly limited solubility of TNB in these media.

(22) I. R. Bellobono and G. Sala, *J. Chem. Soc., Perkin Trans. 2*, 169 (1972).

Registry No.—1,3,5-Trinitrobenzene, 99-35-4; dimethylformamide, 68-12-2.

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A Facile Exchange of Aromatic Hydrogen with Deuterium in the Absence of Catalysts. Meta Aromatic Diamines

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m-Phenylenediamines exchange ring hydrogen with deuterium at room temperature in the absence of catalysts. At concentrations of 1 mmol of amine per 1 ml of methanol-d_4 equilibrium at 60–80% deuteration is established within 24–60 hr. Under the same conditions *o*- and *p*-phenylenediamines completely fail to react. Only hydrogens at ortho and/or para positions to *both* amine groups exchange. A third mechanism, involving the direct attack of a deuterium cation on the electron-rich carbon atom in the rate-determining step, is postulated.

Acid-catalyzed hydrogen exchange on aromatic nucleus is a reversible electrophilic substitution reaction (A-SE2) in which the rate-controlling step is the slow transfer of a proton to the substrate.[1] Several examples of base-catalyzed isotopic exchange of aromatic hydrogen support a rate-limiting proton abstraction,[2,3] but this mechanism has not yet been elucidated fully. On the other hand, in the absence of acidic or basic catalysts isotope exchange either does not occur or proceeds at extremely slow rates. For example, the extent of exchange between dimethylaniline and tritiated water in the absence of acids is negligible[4] after 24 hr at 80°. We have now found that a facile exchange does take place at room temperature in the absence of catalysts, provided that the aromatic hydrogens are activated by at least two amino groups.

The exchange was first observed with certain *m*-toluenediamines (**4**, **5**) prepared in connection with other studies as shown in the reaction scheme.

3,5-Dinitro-4-methoxytoluene (**3a**) can be obtained by the action[5] of diazomethane on **1**, the methylation of the silver or sodium salt of **1** by methyl iodide[6] or dimethyl sulfate,[7] and the nitration[8] of 4-methoxytoluene. In this work, **3a** and **3b** were prepared from 3,5-dinitro-4-chlorotoluene[9,10] (mp 115°) by displacing chloride with alkoxide ion (**2** → **3**). Hydrogenation of **3a** and **3b** in the presence of platinum catalyst proceeded smoothly to give diamines **4a** and **4b**, of which only the dihydrochloride of **4a** has been reported. Hydrogenation of **2** also afforded **5** in excellent yield.[10]

When diamines **4a**, **4b**, and **5** were dissolved in methanol-d_4 at concentrations of 1 mmol/ml, a nearly instantaneous, quantitative exchange of the four amine protons occurred. This was followed by the slow deuteration of both aromatic protons until equilibrium was established at *ca.* 78–81% deuterium exchange

(1) R. O. C. Norman and R. Taylor, "Reaction Mechanisms in Organic Chemistry," Monograph 3, C. Earbon, Ed., Elsevier, New York, N. Y., 1965, p 203.

(2) R. D. Guthrie and D. P. Wesley, *J. Amer. Chem. Soc.*, **92**, 4057 (1970).

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(4) B. B. P. Tice, I. Lee, and F. H. Kendall, *ibid.*, **85**, 329 (1963).

(5) W. Borsche and E. Faske, *Chem. Ber.*, **59**, 687 (1926).

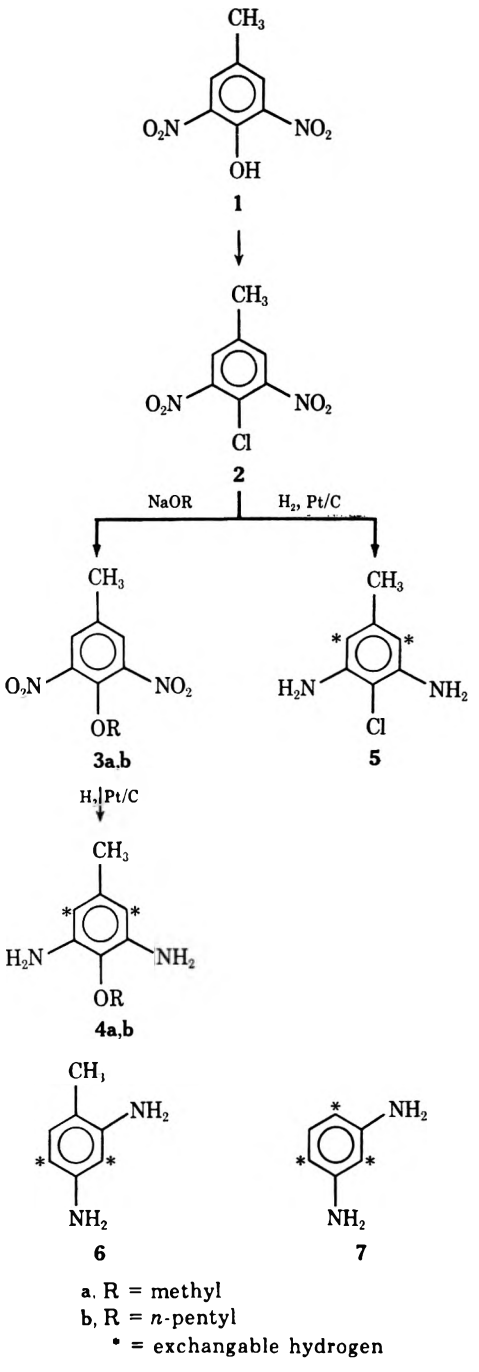
(6) W. Staedel, *Justus Liebigs Ann. Chem.*, **217**, 170 (1883).

(7) G. Schieman and M. Seyhan, *Chem. Ber.*, **70B**, 2396 (1937).

(8) W. E. Chamberlain, *Amer. Chem. J.*, **19**, 534 (1897).

(9) R. M. Vance, U. S. Patent 3,221,065 (Nov 30, 1965); *Chem. Abstr.*, **64**, 8082 (1966).

(10) An early publication [M. Hönig, *Chem. Ber.*, **20**, 2419 (1887)] describes the isolation of **2**, mp 48°, by nitrating 4-chlorotoluene. That nitration gave probably a mixture of isomers, which should account for the low melting point reported. Reduction of this mixture gave **5**, mp 111°.



within 24 hr for **4a** and **4b**, and 60 hr for **5** (Figure 1). In order to demonstrate that the two amino groups were primarily responsible for the exchange, 2,4-toluenediamine (**6**) and 1,3-phenylenediamine (**7**) were tested under the same conditions; compounds **6** and **7** behaved in a similar manner.

Of the three aromatic protons of **6**, the 6-H at 6.7 ppm remained unchanged over a period of 3 days. On the other hand, the overlapping signals for 3-H (singlet at 6.08 ppm) and 5-H (doublet near 6.03 ppm) showed exchange of 60% within 48 hr (Figure 1). In the case of **7**, the overlapping signals for 2-H, 4-H, and 6-H at 6.0–6.2 ppm decreased progressively, indicating deuteration, whereas the 5-H (multiplet near 6.7–6.9 ppm) did not exchange at all. In fact, the rate of exchange could be determined by comparing the total integration of 2-H, 4-H, and 6-H with that of 5-H. In addition, the methanol impurity peak of methanol-d_4 was employed as reference with the same results. With

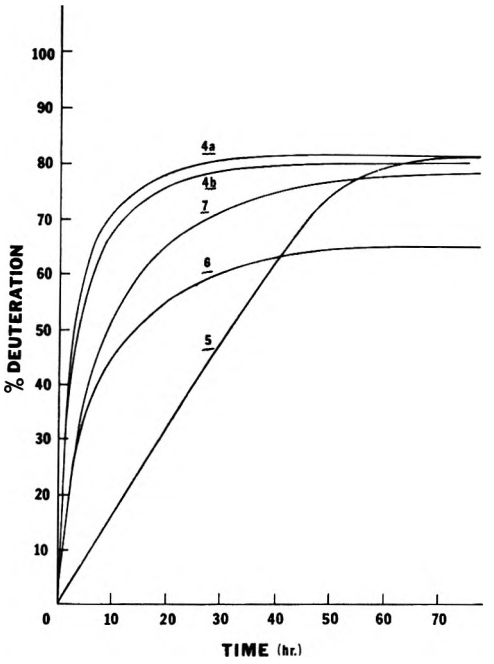
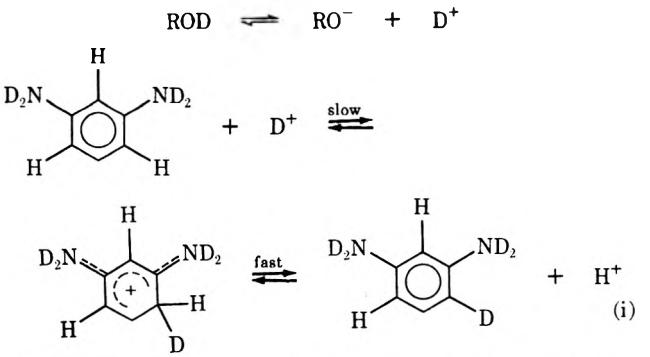


Figure 1.—Hydrogen–deuterium exchange of aromatic meta diamines **4a**, **4b**, **5**, **6**, and **7** at room temperature in the absence of catalysts (*c* 1 mmol/ml of methanol-d_4).

compounds **4a**, **4b**, **5**, and **6** the integral signal of the methyl group was used to follow rates of deuteration.

Surprisingly, the aromatic hydrogens of 1,2-phenylenediamine, 1,4-phenylenediamine, their *N*,*N*,*N*′,*N*′-tetramethyl derivatives, and 4-toluidine showed no exchange after 3 days of standing at room temperature. In fact, no exchange was noticed when the aforementioned compounds were kept at 70° for 6 hr in ethanol-d_6. This difference in reactivity between metadiamines on one hand, and ortho and para diamines on the other, as well as the difference in reactivity among the aromatic protons in **6** and **7**, point out conclusively that the facile exchange in the absence of catalysts requires the activation of aromatic hydrogens by at least two powerful, electron-donating amine groups.[11] One could predict that stronger activation *e.g.*, by three amine groups, would result in even faster exchange rates.

Because aromatic diamines are very weak bases, a base-catalyzed mechanism for the observed exchange should be excluded. Furthermore, if the reaction were base-catalyzed, the order of reactivity would be reversed, *i.e.*, ortho and para diamines would react



(11) Stronger deuteration conditions, for example higher temperature and concentration, can bring about an extremely slow deuteration of those hydrogens in aromatic diamines which are activated by only one amino group. Such an exchange has already been noticed.

faster than meta diamines. Acid catalysis[12] is not likely either. A third, heretofore unobserved mechanism involving the direct attack of deuterium cation on the activated, electron rich carbon atoms is now postulated (i).

Evidence in support of this mechanism was provided by comparing the reactivities of **4a** and **5** under exactly the same conditions whereby the reaction rates should be related to the electron clouds at C_2 and C_6. Since **4a** and **5** differ only by the substituent at C_4, this electron density should depend mainly on the inductive effect of the methoxy and chloro groups, the σ_m values[13] of which are +0.115 and +0.373, respectively. Thus, both groups are electron withdrawing at the meta positions, the methoxy group being weaker. Consequently, the electron densities at C_2 and C_6 are higher in **4a** than in **5**, and **4a** should react faster than **5**. This is in accord with our experimental evidence, as shown in Figure 1. Finally, additional evidence in support of the mechanism was provided by observing that an increase in deuteration rate occurred when the ratio of methanol-d_4 to amine was increased.

Experimental Section

Deuterium exchange was determined with a Varian HA-100 spectrometer using tetramethylsilane as internal reference. The compounds were dissolved in methanol-d_4 at concentrations of 1 mmol/ml and allowed to stand at room temperature. The appropriate nmr peaks were integrated at time intervals until equilibrium was established. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were determined with a Thomas-Hoover apparatus and were not corrected.

3,5-Dinitro-4-methoxytoluene (3a).—A solution of 4-chloro-3,5-dinitrotoluene[9,10] (**2**, 43.2 g, 0.2 mol) and sodium methoxide (12.5 g, 0.22 mol) in methanol (500 ml) was refluxed for 12 hr and cooled. The precipitated solid was filtered off, stirred in water (300 ml), refiltered, and dried, giving pure **3a**: yield 35.2 g (83%); mp 123–124° (lit.[6,7] mp 123°); nmr ($CDCl_3$) δ 7.84 (s, 2, aromatic H), 4.02 (s, 3, OCH_3), 2.48 (s, 3, CH_3).

3,5-Dinitro-4-pentoxytoluene (3b).—Sodium hydride (56.7% in oil, 14 g, 0.33 mol) was added portionwise with stirring to dry pentanol (400 ml). After the addition had been completed, chloride **2** (65 g, 0.3 mol) was added, and the reaction mixture was brought to 100–110° slowly (1 hr) by means of an oil bath, stirred at 100–110° for 3 hr, cooled, distilled *in vacuo* until all pentanol was removed, diluted with water (500 ml), and extracted with chloroform (three 500-ml portions). The combined chloroform extracts were clarified by gravity filtration, washed with water (two 200-ml portions), dried ($MgSO_4$), and evaporated to dryness. The crude product obtained was purified by two distillations at reduced pressure: bp 131–133° (0.15 mm); yield 44.6 g (55%); nmr ($CDCl_3$) δ 7.84 (s, 2, aromatic H), 4.12 (t, 2, $-OCH_2-$), 2.49 (s, 3, aromatic CH_3), 1.80 (m, 2, $-OCH_2CH_2-$), 1.40 (m, 4, $-OCH_2CH_2CH_2CH_2CH_3$), 0.94 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.93; H, 6.13; N, 10.37.

4-Methoxytoluene-3,5-diamine (4a).—3,5-Dinitro-4-methoxytoluene (**3a**, 33.4 g, 0.157 mol) in ethanol (500 ml) was hydrogenated at 25–50° (250 psi) in the presence of platinum catalyst (5% Pt/C, 1 g) in a 1-l. Parr autoclave, equipped with cooling coil and stirrer. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the oily residue was distilled at reduced pressure to give an oil, bp 98–105° (0.4 mm), which solidified upon standing, mp 72–74°, yield 18.5 g (68%). The analytical sample was obtained by one recrystallization from methylene chloride–hexane: mp 73–74°; nmr ($CDCl_3$) δ 5.98 (s, 2, aromatic H), 3.72 (s, 3, OCH_3), 3.62 (s, 4, NH_2), 2.12 (s, 3, CH_3).

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.1; H, 7.95; N, 18.41. Found: C, 62.98; H, 7.87; N, 18.30.

The dihydrochloride was prepared by bubbling hydrogen chloride through a solution of diamine **4a** in ethanol, mp 239–240° (lit.[7] mp 241°).

4-Pentoxytoluene-3,5-diamine (3b → 4b).—This compound was prepared as described for **4a**. The crude product obtained was purified by distillation at reduced pressure: bp 134–135° (0.25 mm); yield 85%; nmr ($CDCl_3$) δ 5.97 (s, 2, aromatic H), 3.80 (t, 2, $-OCH_2-$), 3.60 (s, 4, NH_2), 2.12 (s, 3, aromatic CH_3), 1.76 (m, 2, $-OCH_2CH_2-$), 1.42 (m, 4, $-OCH_2CH_2CH_2CH_2CH_3$), 0.92 (m, 3, $-CH_2CH_3$).

Anal. Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.34; H, 9.61; N, 13.58.

The dihydrochloride was prepared as in **4a**, and purified by crystallization from ethanol, mp 279–281° subl.

Anal. Calcd for $C_{12}H_{22}Cl_2N_2O$: C, 51.25; H, 7.88; N, 9.96; Cl, 25.22. Found: C, 51.42; H, 7.75; N, 9.93; Cl, 25.45.

4-Chlorotoluene-3,5-diamine (5).—Hydrogenation of **2** was carried out as in **4a**. The product was purified by recrystallization from benzene: mp 115–116°; yield 88%; nmr ($CDCl_3$) δ 5.97 (s, 2, aromatic H), 3.85 (s, 4, $-NH_2$), 2.11 (s, 3, aromatic CH_3).

Anal. Calcd for $C_7H_9ClN_2$: C, 53.68; H, 5.79; Cl, 22.64; N, 17.89. Found: C, 54.59; H, 5.80; Cl, 22.49; N, 17.95.

Registry No.—**2**, 5264-65-3; **3a**, 29455-11-6; **3b**, 37780-39-5; **4a**, 37780-40-8; **4b**, 37780-41-9; **4b** 2HCl, 37780-42-0; **5**, 34207-43-7.

Acknowledgments.—The author wishes to thank Dr. R. M. Vance for a sample of 4-chlorotoluene-3,5-diamine, and Mr. Marion Yeagle for nmr spectra.

(12) The hydrogen–deuterium exchange of the primary amine groups generates methanol, the hydroxyl protons of which conceivably may initiate an acid-catalyzed mechanism. Since methanol is a very weak acid, this possibility does not appear likely.

(13) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

1,3-Bridged Aromatic Systems. VIII. Rearrangements of Strained Systems[1]

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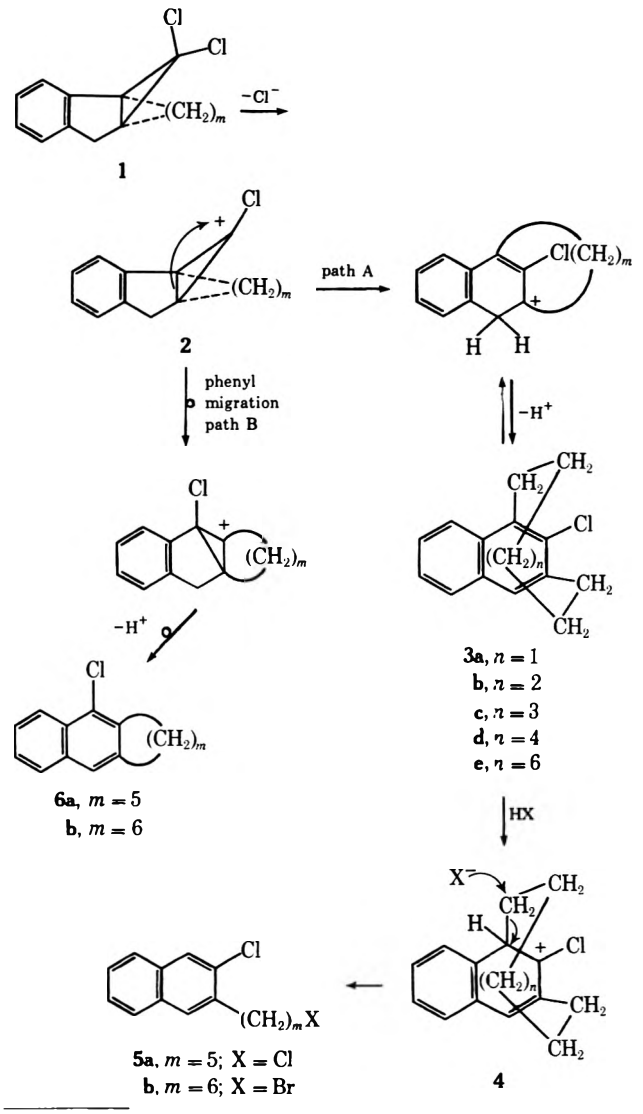
Received October 24, 1972

The strained metacyclophane **3b** is converted quantitatively into the rearranged naphthalene **6b** by action of a mixture of *p*-toluenesulfonic acid and trifluoroacetic acid in hot benzene. The mechanism of this rearrangement has been established by ^{13}C-tagging experiments and has been shown not to involve phenyl migration as previously suggested for the analogous naphthalene **6a**. The cyclophane **3c** has been prepared and its properties are compared with its analogs **3b**, **3d**, and **3e**.

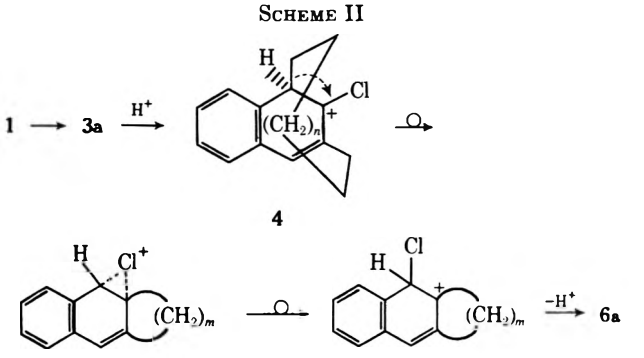
Metacyclophanes of type **3**, where $n = 2, 4, 6$, have been prepared[3] in high yield by addition of the elements of dihalocarbene to the corresponding indenes, and the effect of constraint and strain caused by the highly compacted methylene bridge on chemical reactivity has been discussed. The practical limiting value of n in **3** is 2; attempts[3b] to prepare **3a** ($n = 1$) gave the cleavage and rearranged products **5a** and **6a**, respectively. It was suggested[3b] that the rearranged product **6a** was formed by phenyl migration in the ion **2** (path B, Scheme I) and that the ring-opened product **5a** was formed from **3** through the intermediate **4**. It was also shown that the bromo analog of **3b** (Cl replaced by Br) reacts readily with hydrogen bromide in hot benzene to give the ring-opened product corresponding to **5b** (Cl replaced by Br).

Scheme I



While the mechanism suggested in path B of Scheme I for the formation of the rearranged product **6a** is reasonable, an alternate mechanism is shown in Scheme II. This mechanism assumes that the ring-opening reaction gives only **3a**; rearrangement occurs not by phenyl migration as shown in path B of scheme I, but by protonation of the metacyclophane to give cation **4** followed by rearrangement of alkyl with subsequent or concerted migration of the chlorine atom.

Scheme II



In order to evaluate this alternate mechanism we have reexamined reactions of **3b**, the highly strained homolog of **3a**, and have obtained data which substantiates the alternate mechanism of rearrangement outlined in Scheme II.

Reaction of **3b** in hot benzene with hydrogen bromide gave a mixture of **5b** (40.3% yield) and **6b** (52.5% yield). In order to minimize cleavage of **3b** to **5b**, acids were studied which contained anions less nucleophilic than halide. It was observed that **3b** was stable in hot benzene (21 hr) containing either anhydrous *p*-toluenesulfonic acid or trifluoroacetic acid; however, a mixture[4] of these two acids in hot benzene smoothly effected the conversion of **3b** into only the rearranged product **6b** (99.5% yield, 23 hr). These conditions also effected the conversion of 12-bromo-8,9-benzo[6]-metacyclophane (**3b**, chlorine replaced by bromine) into the bromo analog of **6b**.

The structure of **6b** was confirmed by its oxidation

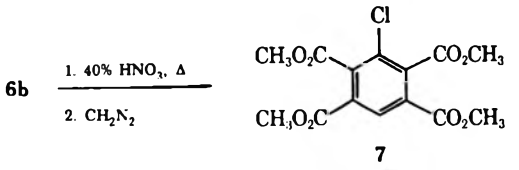
(1) Supported by the National Science Foundation Grant No. GB11918.

(2) Correspondence should be addressed to Duke University, Durham, N. C. 27706.

(3) (a) W. E. Parham and J. K. Rinehart, *J. Amer. Chem. Soc.*, **89**, 5668 (1967); (b) W. E. Parham, D. R. Johnston, C. T. Hughes, M. K. Meilahn, and J. K. Rinehart, *J. Org. Chem.*, **35**, 1048 (1970); (c) W. E. Parham, R. W. Davenport, and J. K. Rinehart, *ibid.*, **35**, 2662 (1970).

(4) The interesting synergetic effect of these two acids has not been previously reported and was not anticipated.

and conversion into **7**, a product which was identical with the ester similarly prepared from chlorodurene.



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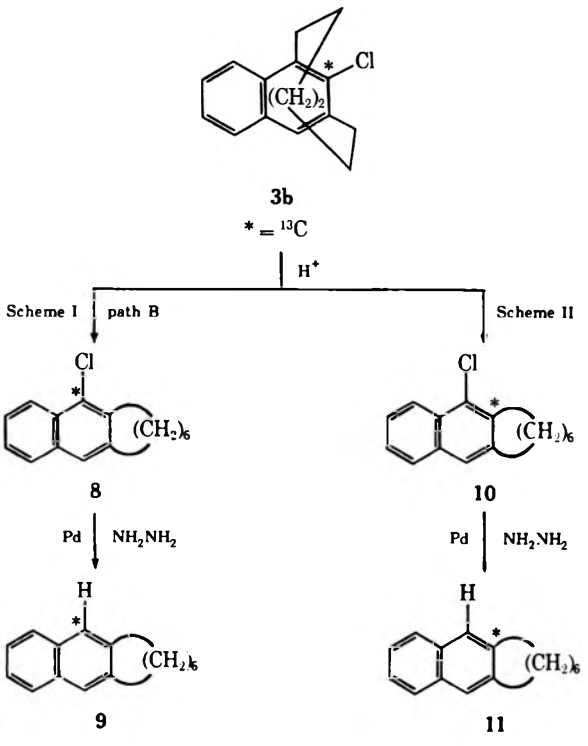
The procedure used to confirm the mechanism of rearrangement outlined in Scheme II is shown in Scheme III.

SCHEME III



The metacyclophane **3b** was prepared with 15% ^{13}C enrichment over natural abundance at C-12 by reaction of the corresponding indene with ^{13}C-enriched chloroform and potassium *tert*-butoxide. Examination of the carbon magnetic resonance spectra (cmr) of labeled and unlabeled **3b** revealed that the signal of carbon-12 occurred at 138.3 ppm downfield from tetramethylsilane. The sequence of reactions outlined in Scheme III was effected which led to **8** or **10** and to **9** or **11**. If the mechanism outlined in path B (Scheme I) is correct, then the chlorine atom in **8** and the additional hydrogen atom in **9** must be on the ^{13}C-enriched carbon atom. If the alternate mechanism outlined in Scheme II obtains, then the enriched ^{13}C will be at a quaternary carbon atom in both **10** and **11**.

Examination of the cmr spectra of labeled and unlabeled rearranged product (**6b**) showed that the labeled carbon atom occurred at 142.3 ppm downfield from tetramethylsilane; however, it was not possible to determine whether the labeled carbon was as shown in **8** or **10** in the naphthalene nucleus since both carbon atoms are quaternary (see Experimental Section for complete description of cmr spectra).

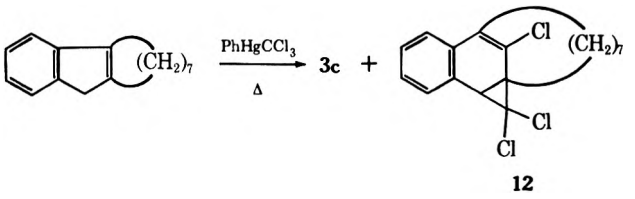
In order to make an absolute assignment of the position of ^{13}C-enriched carbon, the rearranged product was converted (93.5% yield) into the reduced derivative **9** or **11**. The aromatic region of the cmr spectrum of **9** or **11** showed carbon atoms contained in four peaks at 145.5, 138.0, 132.1, and 130.0 ppm downfield from tetramethylsilane. Of these, the peaks at 132.1 and 130.0 ppm integrated in the ratio of 2:1. Comparison of the cmr spectrum with the unlabeled derivative showed that absorption at 145.5 ppm was the ^{13}C-enriched carbon.

Application of selective off-resonance decoupling in **9** or **11**, as described by Ernst,[5-7] caused the peak at 132.1 ppm to split into a doublet with a residual coupling constant (J_r) of 46 Hz, and the peak at 130.0 ppm to split into a doublet with J_r = 50 Hz, as required for methine carbon. The peaks at 145.5 and 138.0 ppm remained centered on their original resonance frequencies, as required for quaternary carbon. The peak at 145.5 ppm did broaden, indicating long-range coupling with the benzylic protons. These results show that the labeled carbon atom in the reduced product is not bonded directly to H, and therefore that its structure is **11** and not **9**. Thus, the rearranged product is **10** and not **8**, and the alternate mechanism for rearrangement of **3b** to **6b** (Scheme II) is the correct one.

We have previously reported[3] that as the value of n in **3** is decreased from 6 to 2 the constraint of the methylene bridge is increased, and with small values of n the aromatic ring to which the bridge is attached is distorted. This distortion is evidence by spectral changes and by change in chemical reactivity. For example **3b** readily decolorizes neutral potassium permanganate and bromine in carbon tetrachloride at room temperature while the less strained analogs **3d** and **3e** are unaffected by these reagents.

The metacyclophane **3c** (n = 3) had not been examined and was prepared to evaluate qualitatively whether the changes in aromatic character of the ring, as a function of the value of n, are gradual, or whether there might be a pronounced break between n = 2 and n = 3.

The cyclophane **3c** was prepared (90% yield), accompanied by a small amount of **12** (1%), by reaction



12

of the appropriate indene with phenyl(trichloromethyl)-mercury.[3] The pmr spectrum of **3c** was characteristic of the benzo[n]metacyclophanes and showed one hydrogen in the shielding cone of the benzene ring at τ 12.0 (as compared to 10.9 for **3b** and 10.5 for **3d**); the ultraviolet spectrum of **3c** also reflected distortion of the benzene ring [most intense absorption λ_{max}, mμ (log ϵ): for **3e**, 235 (5.06); **3d**, 238 (4.91); **3c**, 241 (4.83); **3b**, 244 (4.76)].

The chemical reactivity of **3c** was examined under the same conditions employed for **3b**. In contrast to **3b**, the cyclophane **3c** did not react with neutral potassium permanganate or with bromine in carbon tetra-

(5) R. R. Ernst, *J. Chem. Phys.*, **45**, 3845 (1966).
(6) M. Tanabe, T. Hamasaki, D. Thomas, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 273 (1971).
(7) B. Birdsall, N. J. M. Birdsall, and J. Feeney, *J. Chem. Soc., Chem. Commun.*, 316 (1972).

chloride and did not undergo rearrangement by action of hot benzene containing *p*-toluenesulfonic acid and trifluoroacetic acid (100% recovery) or ring opening with hydrogen bromide. The cyclophane **3c** did, however, react with phenyl(trichloromethyl)mercury to give **12** which was isolated in 39% yield.

The rather pronounced break in chemical reactivity observed between **3b** (n = 2) and **3c** (n = 3) is not surprising when one considers that Allinger[8] and coworkers calculated a ground-state energy difference of approximately 10kc al/mol between the [8]paracyclophane and the [9]paracyclophane; a difference in strain energy comparable to cyclooctane and cyclobutane.

Experimental Section

All melting points are uncorrected. The carbon magnetic resonance spectra were taken at 25.2 MHz on a Varian XL-100 nmr spectrometer equipped with a Varian Fourier Transform controller coupled to a Varian 620i computer. The spectra were taken in 12-mm sample tubes using a 40-μsec pulse width. All chemical shifts are reported with respect to internal tetramethylsilane. Petroleum ether used was bp 60–70°.

14-Chloro-8,9-benzo[6]metacyclophane (3b) was prepared from hexahydrocyclooct[*b*]indene[9] as previously described (74% yield)[3b] and in 42% yield from the indene (0.0062 mol), potassium *tert*-butoxide (0.025 mol) and chloroform (0.0125 mol) in benzene by a procedure similar to that described[3a,b] for the preparation of 2-chloro-1,3-dimethylnaphthalene. The product was purified by preparative tlc (silica gel PF-254, petroleum ether as eluent), mp 43–46° (lit.[3b] 45.5–46.2°). The proton-decoupled carbon magnetic resonance (cmr) spectrum (2 M in acetone-d_6) showed ten aromatic peaks at 144.3, 143.6, 138.3, 137.9, 136.6, 132.7, 131.4, 130.8, 128.9, 128.5 ppm, and six aliphatic peaks at 35.9, 35.6, 34.4, 33.1, 31.7, 28.2 ppm, downfield from TMS.

^{13}C-Enriched 3b was made (61% yield) from the indene (0.0063 mol), ^{13}C-enriched chloroform (0.012 mol, Merck, diluted to 15% enrichment), and potassium *tert*-butoxide (0.025 mol) as described above (60.4% yield). The cmr spectrum was as described above; the enriched carbon (C-14) showed a peak at δ 138.3.

Reaction of 12-Chloro-8,9-benzo[6]metacyclophane (3b) with Hydrogen Bromide.—Cyclophane **3b** (0.215 g, 0.878 mol) and an internal standard (*n*-docosane, 0.210 g) were heated in dry (from CaH_2) benzene. Hydrogen bromide was passed through the hot (77°) mixture and the reaction progress was followed by glcp analysis (6 ft × 1/4 in. 5% DC 710 on 80–100 mesh Chromosorb W, 200°, He rate 60 ml/min). The reaction was complete after 135 min after which time the cooled mixture was washed with aqueous sodium bicarbonate (25 ml of saturated solution), dried ($MgSO_4$), and concentrated to a yellow solid (0.350 g). The mixture of **5b** and **6b** was separated by preparative tlc (silica gel PF-254, petroleum ether as eluent).

The highest band was removed from the plate with 5% methanol in chloroform and was identified as **5-chloro-6,7,8,9,10,11-hexahydrocycloocta[*b*]naphthalene (6b)**: oil, 52.5% yield; $\lambda_{max}^{95\% alc}$, mμ (log ε), 215 (sh, 4.46), 227 (sh, 4.87), 232 (5.06), 259 (sh, 3.38), 269 (sh, 3.59), 278 (3.74), 288 (3.78), 297 (3.60), 300 (sh, 3.58), 319 (2.52), 323 (2.52); pmr (10%) in $CDCl_3$ with areas relative to 17 protons) τ 1.54–1.90 (m, 0.9 aromatic 4 H, peri to chloro), 2.14–2.84 (m, 3.9, aromatic H), 6.70–7.26 (m, 3.8, benzylic CH_2), 7.97–9.17 (m, 8.4, bridge CH_2); mass spectrum m/e 244 (parent molecular ion), P + 2, proper intensity for one chlorine atom. The proton-decoupled cmr spectrum (2 M in acetone-d_6) showed ten aromatic peaks at 146.3, 142.3, 138.5, 135.1, 135.0, 132.7, 131.6, 131.3, 130.9, 129.1 ppm, and six aliphatic peaks at 34.2, 33.4, 29.4, 28.8, 26.7, 26.0 ppm downfield from TMS.

Anal. Calcd for $C_{16}H_{17}Cl$: C, 78.51; H, 7.00; Cl, 14.49. Found: C, 78.59; H, 6.92; Cl, 14.54.

The second band was removed from the plate with 5% methanol in chloroform and was shown to be **2-(6-bromohexyl)-3-chloronaphthalene (5b)**: white needles (from petroleum ether); mp 70–71°; $\lambda_{max}^{95\% alc}$, mμ (log ε), 288 (5.00), 252 (sh, 3.43), 260 (3.58), 269 (3.69), 279 (3.70), 289 (3.49), 306 (2.66), 320 (2.60); pmr (20% in $CDCl_3$, area relative to 18 protons) τ 2.04–2.70 (m, 5.8, aromatic H), 6.62 (t, J = 6 Hz, 2.1, CH_2Br), 7.14 (t, J = 7 Hz, 2.1, benzylic CH_2), 7.87–8.83 (c, 8.0, CH_2); mass spectrum m/e 324 (parent molecular ion), 35% of base peak, P + 2 (45% of base peak), P − 149 ($C_5H_{10}Br$, base peak).

Anal. Calcd for $C_{16}H_{18}BrCl$: C, 59.00; H, 5.57; total halogen as Cl, 21.78. Found: C, 58.93; H, 5.34; total halogen as Cl, 21.90.

Reaction of 3b with *p*-Toluenesulfonic Acid and Trifluoroacetic Acid in Benzene. Formation of 6b.—A mixture of **3b** (0.266 g, 1.08 mmol), anhydrous *p*-toluenesulfonic acid (0.022 g, 0.128 mmol), trifluoroacetic acid (0.459 g, 4.02 mmol), and dry benzene (28 ml) was heated at 78°. The reaction progress was followed by glpc analysis (as above) and showed, after 15 min, 11% reaction; 1 hr, 32%; 3 hr, 68%; 4 hr, 79%; 6 hr, 85%. After 18 hr of heating the cooled solution was washed with saturated aqueous sodium bicarbonate (25 ml) and with water (25 ml), dried ($MgSO_4$), and concentrated to give pure **6b** (0.260 g, 97.7% yield).

^{13}C-Enriched 6b (10) was prepared as above (73% yield from preparation tlc, silica gel PF-254, petroleum ether as eluent); the enriched aromatic carbon showed a signal at δ 142.3.

Reaction of 12-bromo-8,9-benzo[6]metacyclophane[3b] with *p*-toluenesulfonic acid and trifluoroacetic acid, as described for 3b, gave 5-bromo-6,7,8,9,10,11-hexahydrocycloocta[*b*]naphthalene as an oil (99.5% yield, one component by glpc): ir (neat) 3040 w, 2900 s, 2835 m, 1598 w, 1556 w, 1488 m, 1250 m, 915 m, 740 s cm^{-1}; $\lambda_{max}^{95\% alc}$, mμ (log ε), 215 (sh, 488), 233 (5.00), 259 (sh, 3.40), 269 (sh, 3.60), 278 (3.76), 289 (3.80), 297 (sh, 3.63), 300 (sh, 3.62), 318 (2.56), 322 (2.59); pmr ($CDCl_3$) τ 1.50–1.88 (m, 1.1 aromatic 4 H, peri), 2.14 2.70 (m, 4.0 aromatic H), 6.60–7.20 (m, 4.0, benzylic CH_2), 7.93–9.00 (c, 7.9 bridge CH_2).

Anal. Calcd for $C_{16}H_{17}Br$: C, 66.45; H, 5.92; Br, 27.64. Found: C, 66.32; H, 5.68; Br, 27.69.

Tetramethyl 3-Chloro-1,2,4,5-benzenetetracarboxylate (7). A.—Chlorodurene (0.201 g) was oxidized at 164–170° (22 hr) as previously described.[3b] The tetra acid (79% yield) melted at 305° dec instead of 248° as previously reported.

Anal. Calcd for $C_{10}H_5ClO_8$: C, 41.61; H, 1.75. Found: C, 41.34; H, 1.69.

The tetra ester (70% yield, pure) melted at 123.7–125.2° (reported,[3b] 122.6–123.1°).

B.—Rearrangement product **6b** (0.185 g) was oxidized as previously described:[3b] mp and mmp of derived 7 122–123°, ir and nmr identical with authentic.

6,7,8,9,10,11-Hexahydrocycloocta[*b*]naphthalene (11).—Reduction of **6b** (0.82 mmol) in ethanol (20 ml) with 10% Pd/C (0.10 g) with hydrazine (3 ml, 95%) was carried out essentially as described for analogous pyridinophanes.[10,11] The concentrate was dissolved in ether, washed (10% HCl and then water), and dried ($MgSO_4$). The oil was purified by preparative tlc (silica gel PF-254, petroleum ether as eluent) to give pure (tlc) unlabeled 11 (69% yield) as an oil which was crystallized from absolute ethanol (Dry Ice–acetone bath) to give unlabeled 11 as a white solid: mp 50–52° (51.5–52° after sublimation); pmr (CCl_4) τ 1.5–3.2 (m, 6, aromatic H), 6.8–7.5 (m, 3.85, benzylic CH_2), 7.6–9.6 (m, 12.1, CH_2); proton decoupled carbon magnetic resonance spectrum (2 M in acetone-d_6), which should show five aromatic signals, gave four aromatic peaks at 145.5, 138.0, 132.1 (wt 2), 130.0 ppm (wt 1), and three aliphatic peaks at 33.3, 32.6, 26.2 ppm downfield from TMS. Selective off-resonance proton decoupling of the aromatic region of the cmr spectrum gave a broad singlet at δ 145.5 and a singlet at 138.0, indicating quaternary carbons, and doublets at δ 132.1 (J_r^{CH} = 46 Hz) and 130.0 (J_r^{CH} = 50 Hz) for methine carbons; these results also showed the validity of the integration.

Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.48; H, 8.72.

^{13}C-Enriched 11 was prepared from ^{13}C-enriched **6b** as described above (93.5% yield). The enriched aromatic carbon nmr signal was at δ 145.5 (quaternary carbon).

13-Chloro-10,11-benzo[7]metacyclophane (3c) was prepared from 6,7,8,9,10,11,12-heptahydro-5*H*-cyclonon[*a*]indene[9] (1.52 g) and phenyl(trichloromethyl)mercury by a procedure similar to

(8) N. L. Allinger, L. A. Freiberg, R. B. Hermann, and M. A. Miller, *J. Amer. Chem. Soc.*, **85**, 1171 (1963).

(9) W. E. Parham and D. C. Egberg, *J. Org. Chem.*, **37**, 1545 (1972).

(10) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *ibid.*, **35**, 3775 (1970).

(11) W. L. Mosby, *Chem. Ind. (London)*, 1348 (1958).

that described[3a] for **3e**. The crude solid was chromatographed over 280 g of 80–200 mesh alumina (Matheson Coleman and Bell) using petroleum ether to 5% benzene in petroleum ether as eluent. The first compound from the column was **3c**: mp 64.5–66°; 90% yield; ir (neat), 3050 s, 2910 s, 1588 m, 1500 m, 1460 s, 1440 s, 1132 m, 1038 m, 1020 m, 872 m, 768 m, 739 s, cm^{-1}; $\lambda_{max}^{95\%\ alc}$, mμ (log ε), 235 (sh, 470), 241 (4.83), 271 (sh, 3.58), 282 (sh, 3.70), 289 (3.73), 300 (sh, 3.58), 320 (sh, 2.55), 333 (sh, 2.35); pmr (CCl_4) τ 1.84–2.83 (m, 4.9, aromatic H), 6.00–6.83 (m, 2.8, benzylic CH_2), 7.10–9.60 (c, 10.5, bridge CH_2), 12.0 (br S, 0.8, CH of bridge).

Anal. Calcd for $C_{17}H_{19}Cl$: C, 78.90; H, 7.40; Cl, 13.70. Found: C, 78.79; H, 7.37; Cl, 13.93.

Further elution of the column gave an oil (0.220 g) which was purified by preparative tlc (silica gel PF_{-254}, petroleum ether as eluent) to give additional **3c** (R_f 0.38) and **12** [mp 144–146.5° from pentane (−30°), 0.024 g, 10% yield]: $\nu_{C=C}$ 1620; $\lambda_{max}^{95\%\ alc}$, mμ (log ε), 228 (sh, 4.25), 235 (4.39), 242 (4.35), 299 (3.69); nmr ($CDCl_3$) τ 2.66 (br s, 4.0, aromatic H), 6.60–7.50 (c, 3.9, allylic CH_2 and benzylic CH), 7.63–9.27 (c, 11.1, bridge CH_2); mass spectrum *m/e* 340 (parent molecular ion, 22% of base peak), P + 2 (22%), P + 4 (7%), P + 6 (1%); relative intensities of P + 2, P + 4, P + 6 show three chlorine atoms.[12]

(12) R. F. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1963, p 17.

Anal. Calcd for $C_{18}H_{19}Cl_3$: C, 63.26; H, 5.60. Found: C, 63.16; H, 5.40.

The adduct **12** (purified as described above) was obtained in 39.4% yield from the reaction of **3c** (0.743 mm) with phenyl(trichloromethyl)mercury (1.55 mmol) in hot benzene (48 hr).

Registry No.—**3b**, 23069-15-0; **3c**, 38165-50-3; **5b**, 38165-51-4; **6b**, 37950-93-9; **7**, 37950-94-0; **11**, 16271-28-6; **12**, 37950-96-2; 12-bromo-8,9-benzo[6]metacyclophane, 37950-97-3; 5-bromo-6,7,8,9,10,11-hexahydrocycloocta[*b*]naphthalene, 37950-98-4; 6,7,8,9,-10,11,12-heptahydro-5*H*-cyclonon[*a*]indene, 37950-99-5; phenyl(trichloromethyl)mercury, 3294-57-3.

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The Cope Rearrangement of 9-Methylenebarbaralane. A Complete Line Shape Analysis

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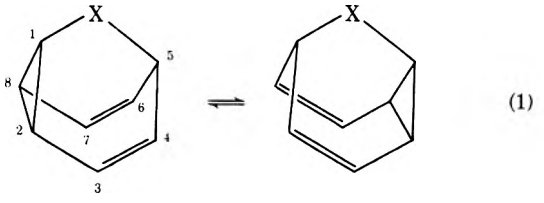
Below −100°, the methylene-proton resonance of 9-methylenebarbaralane splits into an AB quartet as the Cope rearrangement becomes slow on the nmr time scale. Analysis of these spectral changes by the complete line shape method gave the following activation parameters: $\Delta G^{\ddagger}$ (−89.5°) = 9.5 kcal/mol; E_a = 10.5 kcal/mol; log *A* = 13.7; $\Delta H^{\ddagger}$ = 10.0 kcal/mol; $\Delta S^{\ddagger}$ = 2.3 eu. A redetermination was made of the free energy of activation for the analogous process in barbaralone: $\Delta G^{\ddagger}$ (−41°) = 10.5 kcal/mol. The higher barrier for the ketone is attributed to π-electron withdrawal from the bishomobenzene transition state by the 9-keto substituent.

The barrier to the Cope rearrangement of bridged derivatives of 2,3-homotropilidene (eq 1) has been dis-



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cussed in terms of steric and electronic factors. Tricyclodecadienes, such as bullvalene[2a] (**1**, X = CH=CH) and dihydrobullvalene[2b] (**1**, X = CH_2CH_2), have generally higher barriers than tricyclononadienes, such as barbaralone[3] (**1**, X = C=O) and barbaralane[4] (**1**, X = CH_2), because of greater release of strain in the transition state to rearrangement in the latter cases. The trend continues in tricyclooctadienes, such as semibullvalene[5a] (**1**, X = null) and its annelated derivatives,[5b] in which ground-state strain is even larger and the barrier, as a result, is much lower than in the C_9 and C_{10} series.[6] The electronic effects of substituents have recently been treated in theoretical terms by Hoffmann[7] and by Dewar.[8] Electron-withdrawing groups at the 1 and 5 positions, or electron-donating groups at the 2, 4, 6, and 8 positions, raise the barrier to the Cope rearrangement. These conclusions were obtained by a comparison between the effect of substitution on the ground state and on the bishomobenzene-like transition state.

The tricyclononadiene series is particularly amenable to a study of these electronic effects, because the nature of the 9 substituent can be readily manipulated. Barriers have been reported for barbaralone[3] (E_a = 8.1, $\Delta G^{\ddagger}$ = 9.6 kcal/mol) and barbaralane[4] (E_a =

(1) (a) Northwestern University; (b) The Ohio State University; (c) Holder of a NATO Postdoctoral Fellowship (1970–1972) administered by the Science Research Council.

(2) (a) M. Saunders, *Tetrahedron Lett.*, 1699 (1963); A. Allerhand and H. S. Gutowsky, *J. Amer. Chem. Soc.*, **87**, 4092 (1965); (b) G. Schröder, J. F. M. Oth, and R. Merényi, *Angew. Chem., Int. Ed. Engl.*, **4**, 752 (1965).

(3) J. B. Lambert, *Tetrahedron Lett.*, 1901 (1963). This trivial name was given to the ketone by this author in 1962 to honor Dr. Barbara Ferrier, who performed its original synthesis.[4] The second syllable traditionally carries the accent.

(4) W. von E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967).

(5) (a) F. A. L. Anet and G. E. Schenck, *Tetrahedron Lett.*, 4237 (1970), measurements on the octamethyl derivative; (b) L. A. Paquette, R. E. Wingard, Jr., and R. K. Russell, *J. Amer. Chem. Soc.*, **94**, 4739 (1972).

(6) H. Iwamura, K. Morio, and T. L. Kunii, *Bull. Chem. Soc. Jap.*, **45**, 841 (1972). These authors have used MINDO/1 calculations to demonstrate that relief of strain in the transition state increases in the order C_{10}–C_9–C_8.

(7) R. Hoffmann and W.-D. Stohrer, *J. Amer. Chem. Soc.*, **93**, 6941 (1971).

(8) M. J. S. Dewar and D. H. Lo, *ibid.*, **93**, 7201 (1971).

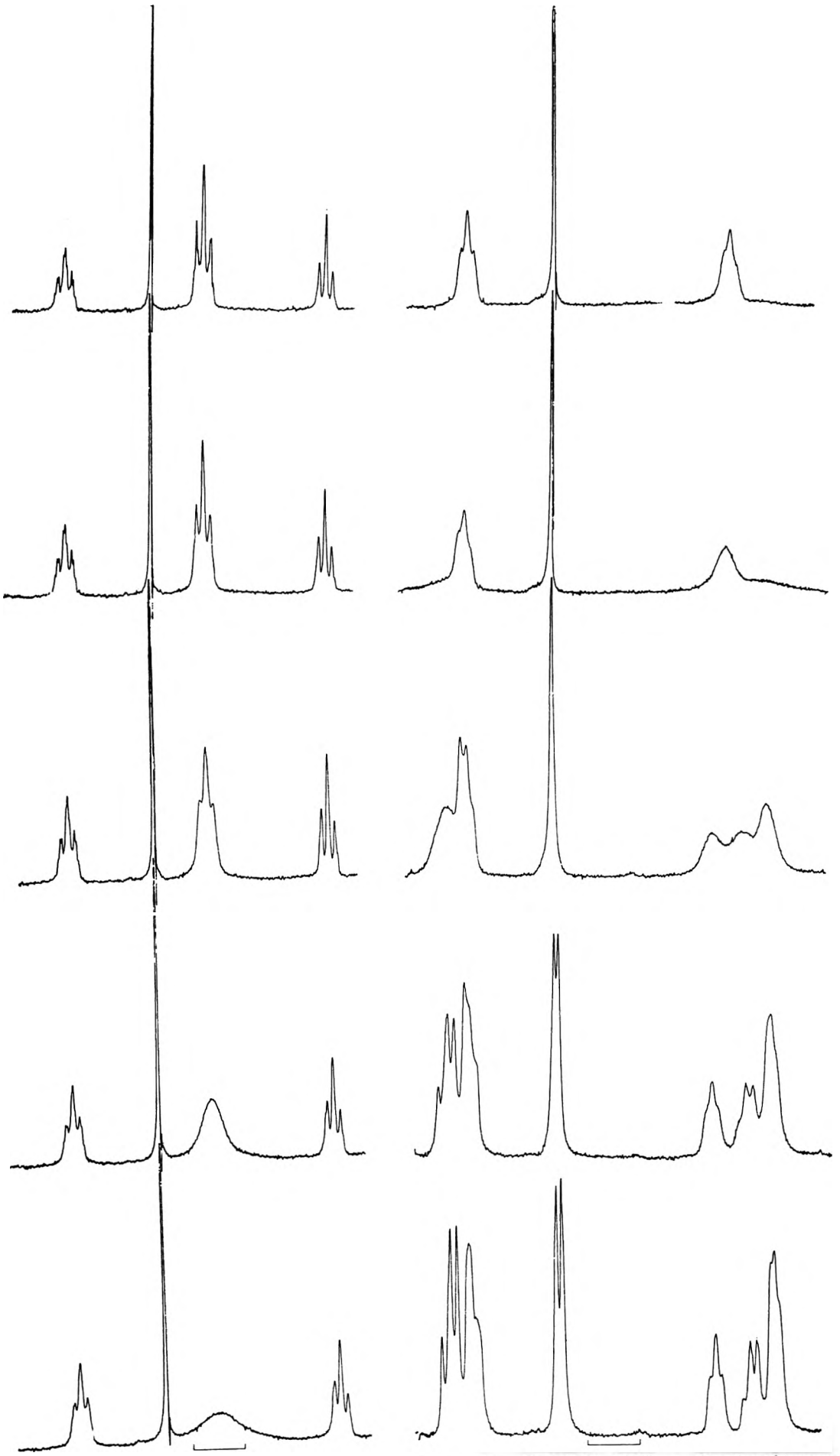

Figure 1.—The 90-MHz proton spectrum of 9-methylenebarbaralane (1, X = C=CH_2) in $CFCl_3$ as a function of temperature: (left column from the top) 25, −0.5, −20, −38.5, −48°; (right column from the top) −67, −74, −87, −96.5, −107°. The calibration bar represents 50 Hz. The resonance positions at slow exchange are δ 2.35 (br s, H-2, H-8), 2.58 (t, H-1), 2.94 (t, H-5), 4.58 (d, C=CH_2), 5.58 (br d, H-3, H-7), and 5.81 (t, H-4, H-6).

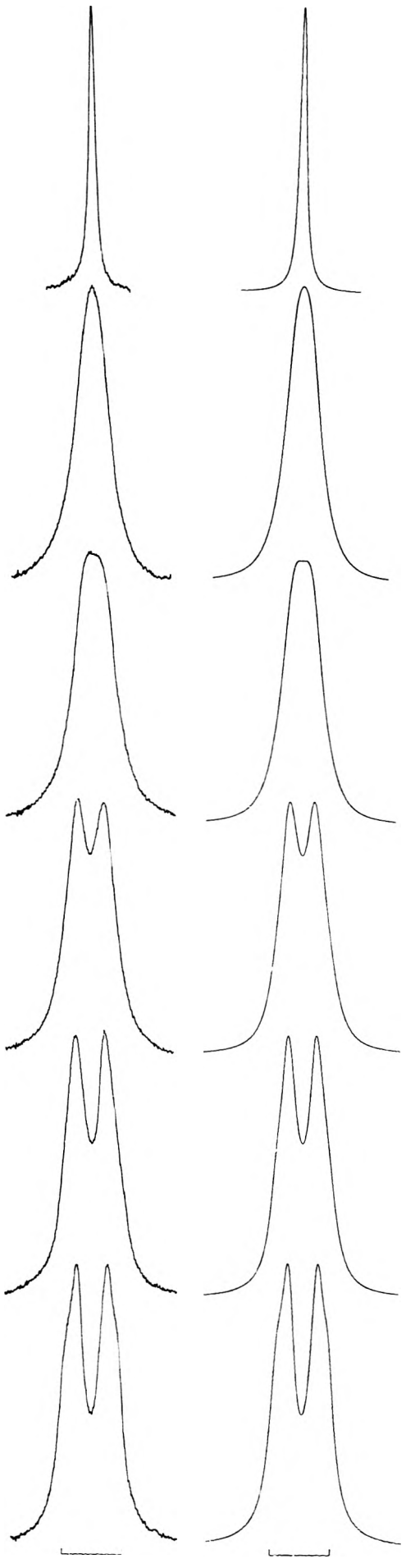

Figure 2.—The observed (left) and calculated resonances of the 9-methylene protons in 9-methylenebarbaralane. The temperatures are (top to bottom): −69 (fast exchange), −89.5, −91, −94, −98, and −108° (slow exchange). Rates were also determined at −93, −96, −101.5, −103.5, and −106° (Experimental Section), but the spectra are omitted. The calibration bar represents 10 Hz.

8.6, $\Delta G^{\ddagger}$ = 7.8 kcal/mol) by the use of approximate methods. Doering[4] noted that 9-hydroxy- and 9-chlorobarbaralane and the ethylene dithioketal of barbaralone rearrange at "comparable rates" to those of the parent ketone and hydrocarbon. A barrier for protonated barbaralone was found to be greater than 13.8 kcal/mol.[9] To date, no accurate barrier has been reported for a tricyclononadiene, because the complexity of the spectra precluded complete line shape analyses. We have prepared the 9-methylene derivative of barbaralane[10] (1, X = C=CH_2) and have examined the temperature dependence of its nmr spectrum. The methylene protons offer a simple resonance pattern that can be subjected to a complete line shape analysis. We report herein the derivation of accurate activation parameters for the Cope rearrangement of this compound. Critical examination of other barriers reported for this C_9 series reveals that the most important factor in determining the magnitude of the barrier is electronic perturbation of the bishomobenzene transition state by the group at the 9 position.[7,8] Differential steric factors (angle strain) within the series are either absent or negligible.

Results and Discussion

The room-temperature proton spectrum of 9-methylenebarbaralane (Figure 1) is made up of a singlet from the methylene protons, a low-field triplet from the 3 and 7 protons, a midfield triplet from the spectrally averaged 2, 4, 6, and 8 protons, and a high-field triplet from the averaged 1 and 5 protons. As the temperature is lowered, the spectrum passes through three distinct points of coalescence, as the various protons respond to slowing of the Cope rearrangement. Below −110°, the slow-exchange spectrum is obtained (Figure 1). The methylene resonance appears as a doublet at δ 4.58, or a broad AB quartet on scale expansion. The coalescence temperature for the A_2-to-AB process is −89.5°. The nonexchanging 3 and 7 protons maintain their resonance position at δ 5.58, but the fine structure is altered because of coupling to the 4 and 6 protons. At slow exchange, the 4 and 6 protons resonate at δ 5.81 and the 2 and 8 protons at δ 2.35, with coalescence occurring at −67°. Finally, the 1 resonance is located at δ 2.58 and the 5 resonance at δ 2.94, and their coalescence takes place at −75°. The 5 resonance is identified as the first-order downfield triplet, because of the large chemical shift from the 4,6 resonance, whereas the 1 resonance is a second-order triplet, because the 2,8 resonance is extremely close.

Free energies of activation can be calculated at the coalescence temperatures, since the slow-exchange chemical-shift differences are known. Analysis of the AB quartet of the methylene group gave $\Delta\nu$ = 6.35

(9) P. Ahlberg, J. B. Grutzner, D. L. Harris, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 3478 (1970).

(10) L. A. Paquette and M. J. Broadhurst, *ibid.*, to be submitted.

Hz (at 90 MHz) and J = 1.85 Hz. From standard equations,[11] the free energy of activation was calculated to be 9.5 kcal/mol at −89.5°. Similar analysis of the changes in the 2, 4, 6, and 8 resonances ($\Delta\nu$ = 310 Hz) yielded $\Delta G^{\pm}$ = 9.3 kcal/mol at −67°.

A more complete analysis was possible for the changes in the methylene resonances by the use of complete line shape techniques.[11] Rates were calculated for nine points (Figure 2, in which not all of the kinetic points are shown), and an Arrhenius plot of these data (Figure 3) gave the following activation parameters: E_a = 10.5 kcal/mol; log A = 13.7; $\Delta H^{\pm}$ = 10.0 kcal/mol; and $\Delta S^{\pm}$ = 2.3 eu. The correlation coefficient for the least-squares fit was 0.996. From these numbers, the free energy of activation was calculated at the coalescence temperatures discussed above: $\Delta G^{\pm} = \Delta H^{\pm} - T\Delta S^{\pm}$ = 9.5 kcal/mol at both −67 and −89.5°. This figure compares very favorably with those obtained from the coalescence-temperature equations.

Since the primary objective of this study was to examine the effect of the electron-withdrawing power of the 9 substituent on the barrier to rearrangement, a comparison was made between the barriers for 9-methylenebarbaralane and barbaralone. The literature contains only an approximation of the barrier for the latter compound.[3] We have reexamined the spectrum as a function of temperature (Figure 4). The spectrum at room temperature is similar to that of the methylene compound. The slow-exchange spectrum contains some differences in the chemical shifts. The 3 and 7 protons are found at δ 5.83, and the 4 and 6 protons just to lower field at δ 5.95. The 2,8 resonance is located at δ 2.92, just to high field of the 5 resonance (δ 3.05). The 1 proton gives a triplet of doublets (triplet coupling to the 2, 8 protons; doublet long-range W coupling to the 5 proton) at δ 2.37. A complete line shape analysis is not possible. Analysis of the changes in the 2, 4, 6, and 8 resonances of 9-methylenebarbaralane, however, gave nearly identical free energies of activation by both the coalescence-temperature and complete line shape methods (see above). Application of the coalescence-temperature method to barbaralone ($\Delta\nu$ = 270 Hz, T_c = −41°) gave $\Delta G^{\pm}$ = 10.5 kcal/mol. This value is about 1 kcal/mol larger than that reported previously,[3] but we feel that it is more reliable.

There should be little or no difference in strain between barbaralone and 9-methylenebarbaralane, since the 9-carbon atom in both compounds is sp² hybridized. The free energy of activation for the ketone is 1 kcal/mol higher than that for the methylene compound, and the coalescence temperature for the 2, 4, 6, and 8 resonances is about 25° higher. These differences are best explained by the molecular orbital theory developed by Hoffmann and Stohrer.[7] Examination of the individual molecular orbitals reveals that greater π-electron acceptance by the group at the 9 position raises the barrier to rearrangement. The approach of Dewar and Lo[8] leads to similar conclusions. The 9 carbon of barbaralone bears a larger partial positive charge than that in 9-methylenebarbaralane. The higher barrier to rearrangement therefore is due to the superior ability of the keto group to accept π electrons. This reasoning has previously been applied to the even

(11) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

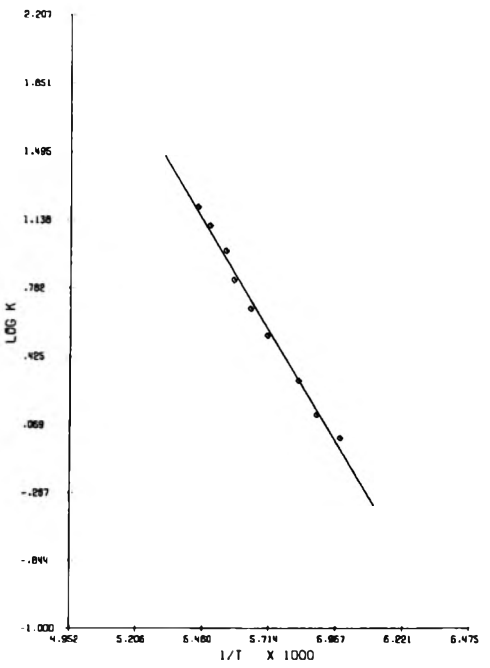

Figure 3.—The Arrhenius plot for the Cope rearrangement of 9-methylenebarbaralane.

higher barrier in protonated barbaralone, in which the 9 carbon can bear a full positive charge, and to the lower barrier in barbaralane, in which the sp³ 9 carbon is a very poor π-electron acceptor.[7,8] The data for these four compounds are gathered in Table I.

TABLE I
BARRIERS TO THERMAL REORGANIZATION OF BARBARALANES

X[a]	T_c, °C	$\Delta G^{\pm}$, kcal/mol	Source
CH_2	−77	7.8	Ref 5, 6
C=CH_2	−67	9.5	This work
C=O	−41	10.5	This work
$^+$COH	> −5	> 13.8	Ref 9

[a] Group attached to atoms 1 and 5 in structure 1.

In summary, we have measured the free energy of activation for Cope rearrangement in 9-methylenebarbaralane by both the coalescence-temperature and the complete line shape methods and found it to be 9.5 kcal/mol. We have redetermined the free energy of activation for barbaralone to be 10.5 kcal/mol by the coalescence-temperature method. The differences between the two systems are best explained in terms of the π-electron withdrawing ability of the group at the 9 position.

Experimental Section

Nmr spectra were taken on a Bruker 90-MHz HFX-10 spectrometer. Tetramethylsilane was used both for an internal standard and for a locking signal. Line shape calculations are carried out on a CDC-6400 computer with a CalComp 565 plotter. The relaxation times (T_2 = 2/line width at half-height) were fixed by interpolation between the fast- and slow-exchange values. The mean lifetime ($\tau = k^{-1}$) was then determined by a trial-and-error fit to the line shape, using $\Delta\nu$ = 6.35 and J = 1.85 Hz. The temperatures (mean lifetimes, relaxation times used for the Arrhenius plot) were −89.5° (τ = 0.062 sec, T_2 = 1.19 sec), −91 (0.078, 1.15), −93 (0.105, 1.10), −94 (0.150, 1.075), −96 (0.212, 1.025), −98 (0.29, 0.975), −101.5 (0.50, 0.88), −103.5 (0.75, 0.832), and −106 (1.00, 0.775).

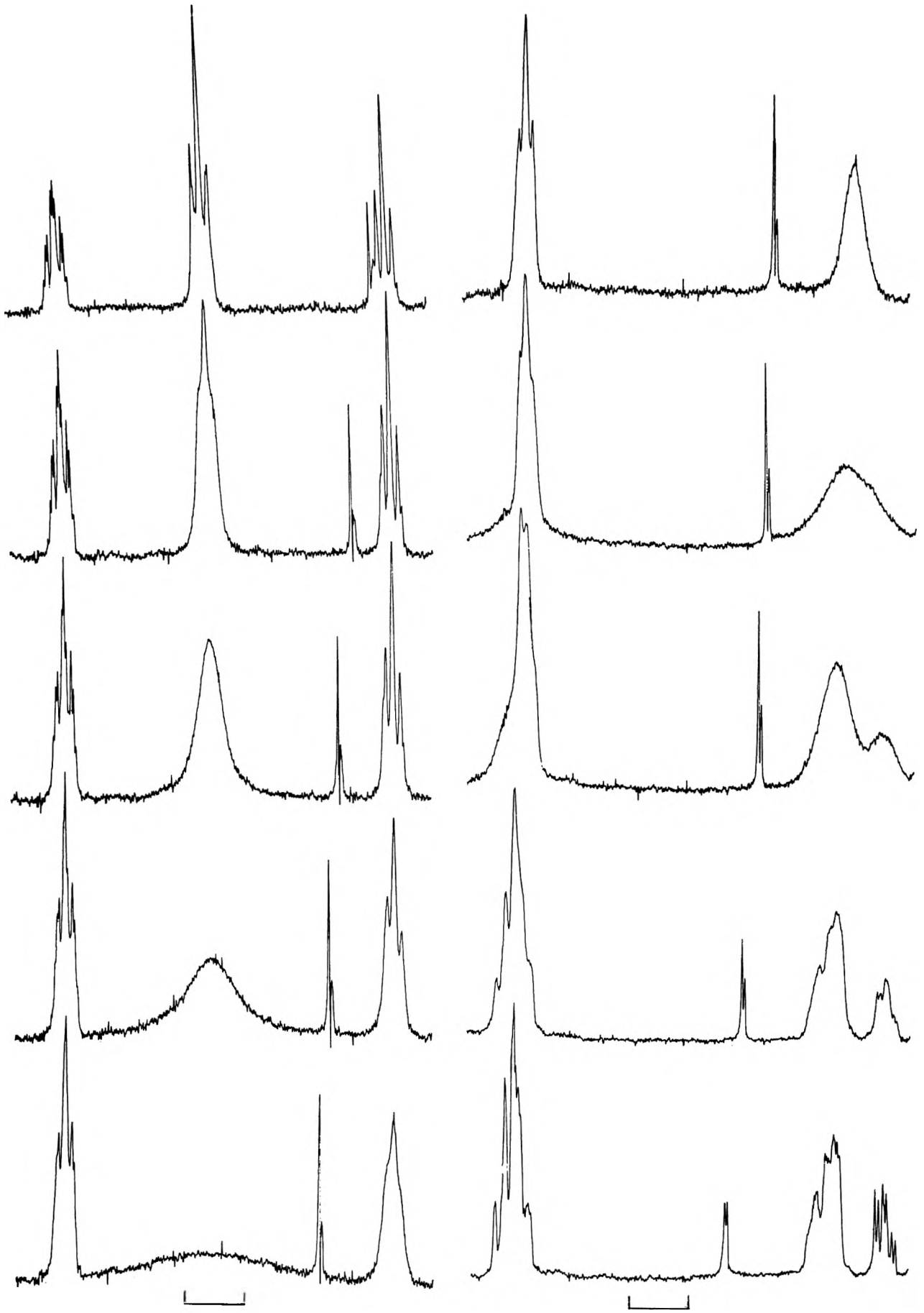

Figure 4.—The 90-MHz proton spectrum of barbaralone (1, X = C=O) in acetone-d_6 as a function of temperature: (left column from the top) 25, −0.5, −14.5, −26, −35.5°; (right column from the top) −41, −52, −60, −72, −87.5°. The calibration bar represents 50 Hz. The resonance positions at slow exchange are δ 2.37 (t of d, H-1), 2.92 (m, H-2, H-8), 3.05 (m, H-5), 3.9 (d, impurity), 5.83 (br m, H-3, H-7), 5.95 (t, H-4, H-6).

Barbaralone was prepared by Michler ketone sensitized photoisomerization of bicyclo[4.2.1]nona-2,4,7-trien-9-one in benzene solution.[12]

9-Methylenebarbaralane, bp 71–73° (5 mm), was prepared by reduction of barbaralone with methylenetriphenylphosphorane in ether solution[10] and purified for the present study by preparative vpc isolation from a 5 ft × 0.25 in. column packed with 5% SE-30 on Chromosorb G.

(12) L. A. Paquette, R. H. Meisinger, and R. E. Wingard, Jr., *J. Amer. Chem. Soc.*, **94**, 2155 (1972). See also T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Shechter, *ibid.*, **94**, 5366 (1972); K. Kurabayashi, and T. Mukai, *Tetrahedron Lett.*, 1049 (1972).

Registry No.—**1** (X = CO), 6006-24-2; **1** (X = CCH_2), 37816-60-7.

Acknowledgments.—The authors are grateful for support of this work by the National Science Foundation (Grants GP-22942, GP-34259X, and GP-8678) and by the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4).

Synthesis of 1-(2-Acetoxyethyl)bicyclo[4.3.0]non-5-en-4-one[1]

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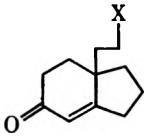
The synthesis of 1-(2-acetoxyethyl)bicyclo[4.3.0]non-5-en-4-one (1a), an intermediate in one synthetic route to the analogous enone bromide **1b** which was desired for intramolecular alkylation studies, is discussed. A novel method for determining the structure of the Michael adduct from ethyl 2-oxocyclopentaneacetate (2) and methyl vinyl ketone, using ^{13}C nmr spectroscopy, is described. An efficient method for ether fission of 9-oxatricyclo[4.3.3.0]dodecan-3-one (8) to yield the immediate precursor of 1a is reported.

We are presently studying the intramolecular alkylation of 1-(2-bromoethyl)bicyclo[4.3.0]non-5-en-4-one (**1b**) and related compounds. The acetoxy analog **1a**,



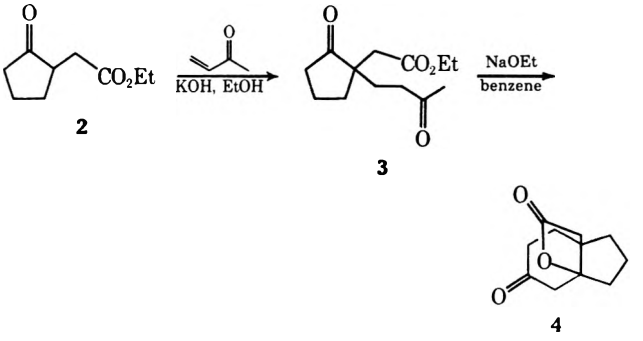
1a, X = OAc
b, X = Br

whose synthesis we report here, is an intermediate in one synthetic route to **1b**. Another synthetic route to **1b** and related compounds and a detailed analysis of their intramolecular alkylations will be reported shortly.[2]

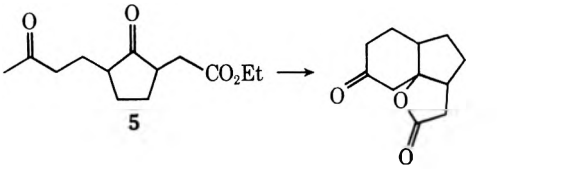
This synthesis began with ethyl 2-oxocyclopentaneacetate (2), which was condensed with methyl vinyl ketone to yield adduct **3**. Subsequent base-catalyzed condensation and lactonation gave keto lactone **4**,[3,4] as shown in Scheme I.

Although the structural assignments for compounds **3** and **4** have been made by Shchegolev and Kucherov,[3] and it is known that the Michael acceptor is usually introduced at the more highly substituted position of unsymmetrical ketones,[5] the possibility that **3** was actually the α,α'-substituted cyclopentanone **5** could not be eliminated. Spectral evidence did not distinguish between **3** and **5** (or **4** and **6**); the use of an nmr shift reagent was not useful for differentiation (see Experimental Section). Moreover, all subsequent reactions performed on **4** by us (*vide infra*) and Shchegolev and Kucherov[3] yield products whose spectral data are compatible with isomeric materials, originating from **5**. It seemed important, therefore, to unequivocally establish the structure of the Michael adduct.

SCHEME I



2 3 4



5 6

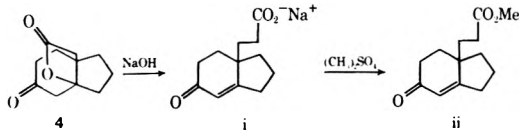
Since the chemical shift of a ^{13}C nucleus is increased in a downfield direction with increasing alkyl substitution,[6] we examined the proton-decoupled ^{13}C nmr spectrum of adduct **3**. Chemical shift assignments were made by comparing this spectrum with ^{13}C nmr spectra of model systems **2** and cyclopentanone.[7] The chem-

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research.

(2) (a) T. E. Jackson and R. L. Cargill, to be published; (b) presented in part by T. E. Jackson at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, ORGN 139.

(3) A. A. Shchegolev and V. F. Kucherov, *Izv. Akad. Nauk SSSR Ser. Khim.*, No. 7, 1456 (1969).

(4) Although the authors[3] claim that lactone **4** could be opened to enone carboxylate i and methylated to enone ester ii, which could serve as an intermediate in the synthesis of **1a**, they stated that ii was not stable and we chose not to pursue this route.

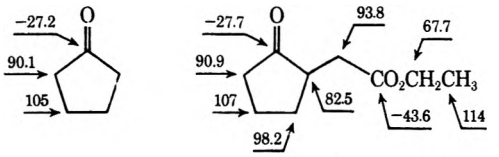


4 i ii

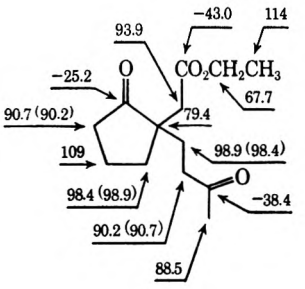
(5) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972.

(6) J. Mason, *J. Chem. Soc. A*, 1038 (1971).

(7) These proton-decoupled nmr spectra were run in benzene-d_6 with a deuterium lock on a Varian XL-100 spectrometer.



2

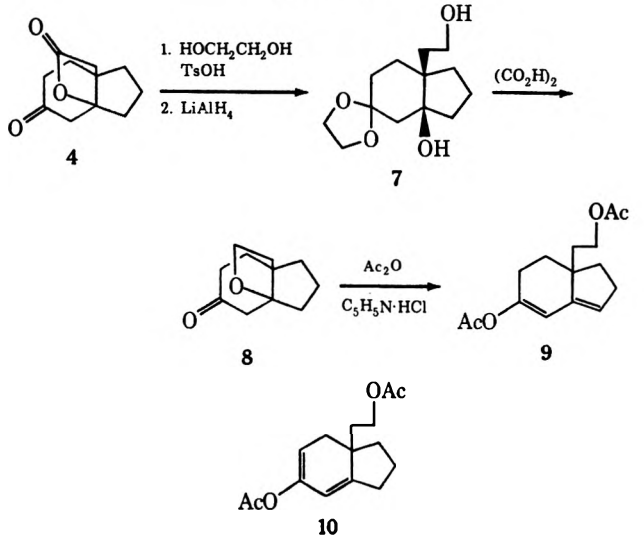


3

ical shift values in the diagram represent parts per million from benzene-d_6. By examining the chemical shift values for the α- and α'-cyclopentanone positions in the three compounds, we see that the values for **3** (90.7 and 79.4 ppm) are clearly consistent with only the α,α-disubstituted cyclopentanone. Structure **5** would be expected to display two signals in an intermediate range (*ca.* 82.5 ppm) for its α- and α'-cyclopentanone carbons. This novel method for structural determination should prove to be extremely useful.

Preparation of enone acetate **1a** was accomplished from diacetate **9**, whose synthesis is outlined in Scheme II. The ethylene ketal of keto lactone **4** was prepared

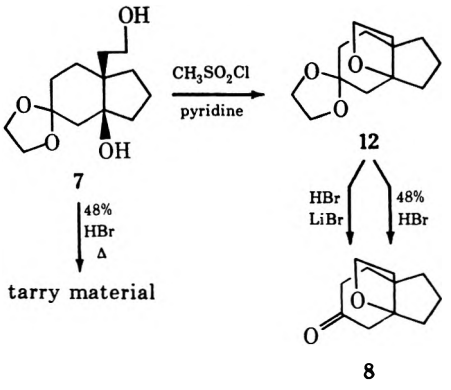
SCHEME II



4 7 8 9 10

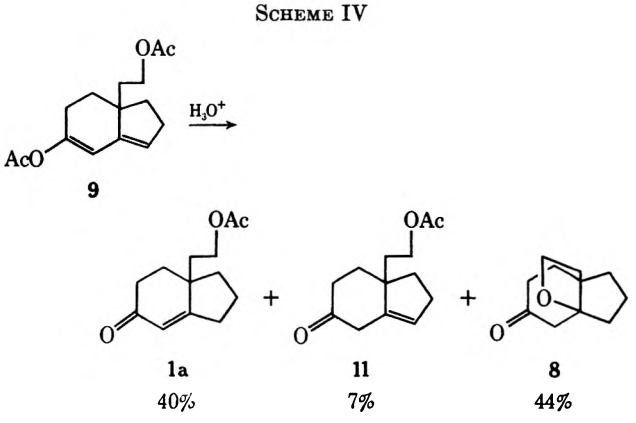
and reduced with $LiAlH_4$ to ketal diol **7**. It was not possible, in our hands (using a variety of mild acidic, conditions), to remove the ketal block from **7** without cyclizing the diol to the tetrahydrofuran, nor were we able to convert the primary alcohol functionality in **7** into a good leaving group, because of facile ether formation. Thus, treatment of ketal diol **7** under conditions which would remove the ketal group produced keto ether **8** (Scheme III). These results are not surprising in view of literature reports of the instability of a 1,4 diol monomesylate[8] with respect to the tetrahydrofuran, and of a 1,4 diol[9] which cyclizes under very mild, acidic conditions. Treatment of keto ether **8** with acetic anhydride and pyridine hydrochloride yielded diacetate **9**, which was distinguished from the homoannular diene isomer **10** by its uv spectrum (λ_{max} 242 nm). This experimental procedure is similar to that employed by Ireland and Mander[10] to open a tetrahydrofuran to a 1-chloro-4-acetoxybutane. This efficient (93%) method of ether cleavage to a useful intermediate is significant, since other standard methods of ether cleavage failed.

SCHEME III



Diacetate **9** was treated with aqueous acid to produce a mixture of enone acetate **1a** (40%), the β,γ-unsaturated enone acetate **11** (7%), and keto ether **8** (44%) (Scheme IV). Hydrolysis was monitored by ir

SCHEME IV



and discontinued when the enol acetate carbonyl band at 1760 cm^{-1} had disappeared. Enone acetate **1a** was easily separated from the mixture by glpc; other separation techniques would presumably work as well. It should be pointed out that this preparation of **1a** is very efficient, since coproducts **11** and **8** can be recycled to produce **1a**.

An attempt to monomesylate ketal diol **7** with methanesulfonyl chloride and pyridine resulted in the production of ketal ether **12** (Scheme III), whose ether linkage could not be opened with ether 48% HBr or a mixture of HBr–LiBr. Vigorous treatment of ketal diol **7** with HBr led to tarry material.

An alternate route to enone acetate **1a** involved the successful monoacetylation of ketal diol **7**, followed by

(8) H. W. Whitlock, Jr., *J. Amer. Chem. Soc.*, **84**, 3412 (1962).

(9) D. Becker and J. Kalo, *Tetrahedron Lett.*, 3725 (1971).

(10) R. E. Ireland and L. N. Mander, *J. Org. Chem.*, **34**, 142 (1969).

hydrolysis of the ethylene ketal with aqueous acid and dehydration of the resulting ketol with *p*-toluenesulfonic acid.

Experimental Section[11]

Ethyl 2-Oxocyclopentaneacetate (2).—The potassium salt of 2-carbethoxycyclopentanone was prepared and alkylated with ethyl bromoacetate in dimethyl sulfoxide.[12] Saponification and decarboxylation[13] yielded 2-oxocyclopentaneacetic acid, which was esterified[14] to yield **2** (33% overall). Alternate synthetic routes to **2** are available.[15]

9-Oxa[4.3.3.0]dodecane-3,8-dione (4).—Keto lactone **4** was prepared in two steps from **2** using the method of Shchegolev and Kucherov.[3] A 25.5-g (150 mmol) quantity of **2** and 12.1 g (172 mmol) of methyl vinyl ketone were condensed to give 19.8 g (55%) of ethyl 2-oxo-1-(3-oxobutyl)cyclopentaneacetate (**3**): bp 131° (0.45 mm); n^{28}D 1.4687 [lit.[3] bp 145–150° (2.5 mm), n^{20}D 1.4748]; ir (CCl_4) 1720 (C=O) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.00 (q, J = 7.2 Hz, 2, OCH_2CH_3), 2.55–1.35 (m, 13, all protons except OCH_2CH_3, with $COCH_3$ s at 2.04), 1.22 (t, J = 7.2 Hz, 3, OCH_2CH_3); nmr [CCl_4 + Eu(DPM)$_3$] δ 4.38 (t, J 7.2 Hz, 2, OCH_2CH_3), 3.45–3.00 (m, 6, $COCH_2$ groups), 2.90–1.97 (m, 9, CH_2 groups not adjacent to C=O and $COCH_3$ s at 2.57), 1.36 (t, J = 7.2 Hz, 3, OCH_2CH_3).

A 13.3-g (55.2 mmol) quantity of **3** was treated with excess sodium methoxide to yield 4.76 g (44%) of keto lactone **4**: mp 99–102° (lit.[3] mp 100–102°); ir (CCl_4) 1720 (C=O) and 1765 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 2.77 (m, 2, $COCH_2$), 2.68 (s, 2, CO_2CH_2), 2.56–1.50 (m, 10, remaining protons).

1-Hydroxy-6-(2-hydroxyethyl)bicyclo[4.3.0]nonan-3-one Ethylene Ketal (7).—A 4.65-g (23.9 mmol) quantity of keto lactone **4** was heated at reflux in benzene (175 ml) with 2.98 g (48.0 mmol) of ethylene glycol (Baker) and 0.2 g of *p*-toluenesulfonic acid monohydrate (Matheson, TsOH·H_2O). The reaction mixture was cooled, washed with 10% K_2CO_3 (20 ml), dried ($MgSO_4$), and concentrated to leave 5.70 g (theory) of ketal lactone: ir (CCl_4) 1775 cm^{-1} (lactone C=O); nmr ($CDCl_3$) δ 4.2–3.0 (m, 4, OCH_2CH_2O), 3.0–1.5 (m, 14, remaining protons).

The 5.70-g quantity of the ketal lactone was added, in ether (75 ml) over a 30-min period, to a slurry of 2.28 g (60.0 mmol) of $LiAlH_4$ (Foote) in ether (75 ml). After 16 hr, excess hydride was destroyed by the slow addition of ethyl acetate. The reaction mixture was diluted with 15% $(NH_4)_2SO_4$ (100 ml) and filtered (Celite), and the layers were separated. The aqueous phase was extracted with ether (3 × 40 ml) and the combined ether phases were dried ($MgSO_4$) and concentrated to leave 5.49 g (96% from keto lactone **4**) of ketal diol **7**: ir ($CHCl_3$) 3700–3050 (OH) and 3580 cm^{-1} (OH); nmr ($CDCl_3$) δ 4.12–3.36 (m, 8, OCH_2CH_2O, CH_2OH, and OH), 2.10–1.05 (m, 14, remaining protons).

9-Oxatricyclo[4.3.3.0]dodecan-3-one (8).—A solution of 1.48 g (6.11 mmol) of ketal diol **7** and 1.5 g of oxalic acid (Baker) in methanol (22 ml) and water (16 ml) was heated at reflux for 1 hr. Dilution of the cool reaction mixture with 10% K_2CO_3 (50 ml) and ether extraction (4 × 30 ml) followed by drying ($MgSO_4$) and concentration of the ether extracts left 0.979 g (89%) of pure keto ether **8**, which displayed a single peak on glpc (3% SE-30, 8 ft × 0.125 in., 150°, 30 cc/min of He): bp 89° (0.40 mm); n^{28}D 1.4945; uv[16] (95% EtOH) 239 nm (ε 75) and 288 (26); ir (CCl_4) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 3.92–3.56 (overlapping triplets, 2, OCH_2), 2.54 (m, 2, $COCH_2$), 2.42–1.23 (m, 12, remaining protons); nmr [CCl_4 + Eu(DPM)$_3$] δ 4.72 (t, J = 7.2 Hz, 2, OCH_2), 4.36–3.65 [m, 2, $COCH_2$ (4 position)], 3.47 [t, J = 7.2 Hz, 2, $COCH_2$ (2 position)], 2.72–1.83 (m, 10, remaining protons); mass spectrum (70 eV) m/e 180 (molecular ion).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.13; H, 8.81.

4-Acetoxy-1-(2-acetoxyethyl)bicyclo[4.3.0]nona-4,6-diene (9).—A solution of 0.340 g (1.88 mmol) of keto ether **8** and pyridine hydrochloride (1 g) in acetic anhydride (20 ml) was heated at reflux for 5.5 hr, poured onto crushed ice (50 g), and extracted with 1:1 pentane–ether (4 × 30 ml). The combined ether extracts were washed with 10% KOH until the washings were basic, dried (Na_2SO_4), and concentrated to leave 0.461 g (93%) of pure diacetate **9**, which displayed a single peak on glpc (3% SE-30, 8 ft × 0.125 in., 175°, 30 cc/min of He): uv max (95% EtOH) 245 nm (ε 11,000); ir (CCl_4) 1760 (C=O) and 1740 cm^{-1} (C=O); nmr (CCl_4) δ 5.87 (m, 1, vinyl), 5.40 (m, 1, vinyl), 4.05 (t, J = 7 Hz, 2, OCH_2), 2.7–1.2 (m, 16, remaining protons, with $COCH_3$ singlets at 2.06 and 1.96, and OCH_2CH_2 t, J = 7 Hz, at 1.70); mass spectrum m/e (rel intensity) 264 (3), 43 (100). Diacetate **9** appeared to decompose slowly upon standing, and was therefore not submitted for analysis.

1-(2-Acetoxyethyl)bicyclo[4.3.0]non-5-en-4-one (1a).—A solution of 0.659 g (2.49 mmol) of diacetate **9** in methanol (10 ml), water (10 ml), and concentrated HCl (1 ml) was stirred for 2.2 hr. Disappearance of the acetate C=O band at 1760 cm^{-1} was monitored by ir. The reaction solution was diluted with 10% K_2CO_3 (30 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and concentrated to afford 0.518 g of material which by glpc analysis (20% SE-30, 5 ft × 0.25 in., 175°, 85 cc/min of He) was 40% enone acetate **1a**, 7% β,γ-unsaturated isomer **11**, and 44% keto ether **8**. Enone acetate **1a** was collected from glpc for spectral analysis: uv max (95% EtOH) 242 nm (ε 11,200); ir (CCl_4) 3020 (vinyl CH), 1740 (ester C=O), and 1670 cm^{-1} (C=O); nmr (CCl_4) δ 5.64 (m, 1, vinyl), 4.07 (t, J = 7.2 Hz, 2, CH_2OAc), 2.8–1.2 (m, 15, remaining protons, with $COCH_3$ s at 1.98); mass spectrum (70 eV) m/e (rel intensity) 222 (19), 180 (5), 162 (16), 134 (100), and 43 (96). All spectral data for **1a** compared favorably with that for enone bromide **1b**.[2] Since enone acetate **1a** slowly converted, upon standing, to keto ether **8**, a satisfactory analysis was not obtained.

A sample of β,γ-unsaturated enone acetate **11** was also collected for spectral analysis: ir (CCl_4) 1755 (ester C=O) and 1715 cm^{-1} (C=O); nmr (CCl_4) δ 5.29 (m, 1, vinyl), 3.63 (t, J = 7.2 Hz, 2, CH_2OAc), 2.7–1.3 (m, remaining protons, with $COCH_3$ s at 2.05); mass spectrum (70 eV) m/e (rel intensity) 222 (2), 180 (18), 138 (100), and 43 (29).

9-Oxatricyclo[4.3.3.0]dodecan-3-one Ethylene Ketal (12).—A 0.907-g (3.74 mmol) quantity of ketal diol **7** was stirred with 0.593 g (5.18 mmol) of methanesulfonyl chloride (Matheson) and pyridine (4 ml) for 2 hr under an inert atmosphere. The reaction mixture was cooled, diluted with a cold mixture of water (5 ml) and pyridine (10 ml), and extracted with ether (3 × 30 ml). The combined extracts were dried ($MgSO_4$) and concentrated to leave 0.853 g (theory) of ketal ether **12**, which displayed a single peak on glpc (3% SE-30, 8 ft × 0.125 in., 170°, 30 cc/min of He): ir (CCl_4) showed no C=O; nmr ($CDCl_3$) δ 4.45–3.25 (m, 6, OCH_2CH_2O and CH_2OH), 3.02 (d, J = 6 Hz, 1, CH_2OH), 2.5–1.2 (m, 15, remaining protons).

A solution of 0.711 g (3.17 mmol) of ketal ether **12** in methanol (5 ml), water (5 ml), and concentrated HCl (0.2 ml) was stirred for 45 min, diluted with water (20 ml), and extracted with ether (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and concentrated to leave 0.554 g (98.5%) of keto ether **8**.

Attempted Cleavage of Ketal Ether 12 with HBr.—A 0.305-g (1.36 mmol) quantity of ketal ether **12** was stirred with 6 ml of 48% HBr (Baker) for 1 hr, diluted with water (25 ml), and extracted with ether (3 × 25 ml). The extracts were dried (K_2CO_3) and concentrated to leave 0.177 g (72%) of keto ether **8**. When ketal ether **12** was treated in a similar manner with 48% HBr and an equal volume of saturated LiBr, work-up afforded keto ether **8** quantitatively. Treatment of ketal diol **7** with 48% HBr at reflux for 2 hr afforded tarry materials.

Alternate Route to Enone Acetate 1a.—A 0.291-g (1.20 mmol) quantity of ketal diol **7** was stirred with acetic anhydride (2 ml) for 3 hr, diluted with cold 10% K_2CO_3 (50 ml), and extracted with ether (2 × 25 ml). The extracts were dried ($MgSO_4$) and concentrated to leave 0.201 g (59%) of 6-(2-acetoxyethyl)-1-hy-

(11) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach uber Engelskirchen, West Germany. Infrared spectra were recorded using a Perkin-Elmer Model 257 grating spectrophotometer. All nmr spectra were determined using tetramethylsilane as an internal standard, with a Varian A-60 spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph 1200 flame ionization chromatograph, and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph.

(12) D. M. Pond and R. L. Cargill, *J. Org. Chem.*, **32**, 4064 (1967).

(13) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

(14) R. Granger and P. F. G. Nau, *Bull. Soc. Chim. Fr.*, 1807 (1959).

(15) A. W. Noltes and F. Kogl, *Recl. Trav. Chim. Pays-Bas*, **80**, 1334 (1961).

(16) When 0.2 ml of 3 *N* NaOMe was added to the 0.0099 *M* uv sample and the spectrum was rerun at timed intervals, the absorption band at 239 nm steadily intensified. The addition of 0.1 ml of concentrated HCl to another sample had little effect on the spectrum.

droxybicyclo[4.3.0]nonan-3-one ethylene ketal: ir (CCl_4) 3600–3400 (OH) and 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.25–3.45 (m, 6, OCH_2CH_2O and CH_2OAc), 3.25 (broad s, 1, OH), 2.5–1.5 (m, 14, remaining protons).

A solution of 0.111 g (0.390 mmol) of the above acetate in methanol (10 ml), water (10 ml), and concentrated HCl (1 ml) was stirred for 30 min and worked up as above to yield 0.0771 g (82.3%) of 6-(2-acetoxyethyl)-1-hydroxybicyclo[4.3.0]nonan-3-one: ir (CCl_4) 3600–3300 (OH), 1735 (ester C=O), and 1720 cm^{-1} (C=O).

A solution of 0.0771 g (0.321 mmol) of the ketol acetate and 50 mg of $TsOH \cdot H_2O$ in benzene (60 ml) was heated at reflux for 2 hr with azeotropic removal of water. The benzene solution was cooled, washed with 10% K_2CO_3 (30 ml), dried ($MgSO_4$), and concentrated to leave 0.0713 g (theory) of crude (80% pure by glpc) enone acetate 1a.

Registry No.—**1a**, 38312-34-4; **2**, 20826-94-2; **3**, 24054-04-4; **4**, 24109-44-2; **7**, 38312-38-8; **8**, 38312-39-9; **9**, 38312-40-2; **11**, 38312-41-3; **12**, 38312-42-4; 9-oxatricyclo[4.3.3.0]dodecane-3,8-dione ethylene ketal, 38312-43-5; 6-(2-acetoxyethyl)-1-hydroxybicyclo[4.3.0]non-3-one ethylene ketal, 38312-44-6; 6-(2-acetoxyethyl)-1-hydroxybicyclo[4.3.0]nonan-3-one, 38312-45-7.

Acknowledgment.—The authors are grateful to Dr. P. D. Ellis for determining the ^{13}C nmr spectra.

Synthesis and Acid-Catalyzed Rearrangements of Tricyclo[4.3.2.0]undecanones[1]

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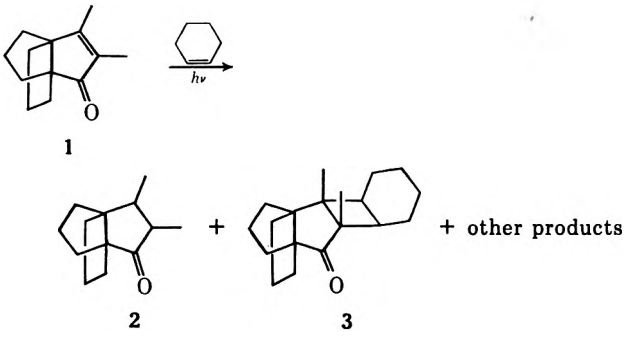
Received October 12, 1972

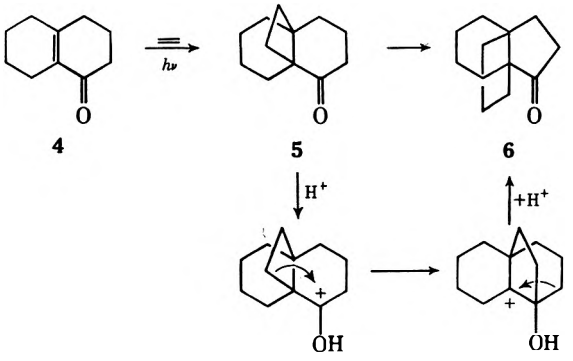
A novel synthesis of 3,4-dimethyltricyclo[3.3.3.0]undecan-2-one (2) from bicyclo[4.3.0]non-1(6)-en-2-one (7) is reported. A mechanistic interpretation for the different ratio of the three cycloadducts (8a–c) obtained from irradiation of 4 with *cis*- and *trans*-2-butene is presented. Cycloadducts 8a and 8b were found to undergo rearrangement to 2 at different rates. A synthesis of tricyclo[4.3.3.0]dodecan-7-one (6) is also reported.

In our recent investigation of cycloaddition reactions of crowded enones and olefins,[2] we irradiated 3,4-dimethyltricyclo[3.3.3.0]undec-3-en-2-one (1) in cyclohexene. In addition to the [2 + 2] cycloadduct **3** (and other products isomeric with **3**) was formed a product suspected to be 3,4-dimethyltricyclo[3.3.3.0]undecan-2-one (**2**), derived from photoreduction. In order to confirm this suspicion we chose to synthesize **2** independently. Although the saturated ketone **2** could undoubtedly be generated from enone **1** by reduction with lithium in ammonia,[3] we chose to use a less obvious approach which was suggested by some other work which will be described shortly. This decision led not only to a novel synthesis of **2**, but also yielded some mechanistic information on enone photoannulation (an area of study where information is sparse[4]) as well as interesting relative rate differences of Wagner–Meerwein shifts in isomeric systems.



The earlier results which suggested this alternate approach to **2** are shown in Scheme I. Although bicyclo[4.3.0]non-1(6)-en-2-one (**7**) undergoes photocycloaddition with 1,2-dichloroethylene readily,[5] preliminary results from our laboratory indicated that cycloaddition reactions of bicyclo[4.4.0]dec-1(6)-en-2-one (**4**) with olefins (other than ethylene) were not successful.[6] Enone **4**, however, does undergo sluggish photoannulation with ethylene to yield tricyclo[4.4.2.0]-dodecan-2-one (**5**). Ketone **5**, when treated with *p*-toluenesulfonic acid (TsOH) in benzene at reflux, undergoes two Wagner–Meerwein shifts to yield tricyclo[4.3.3.0]dodecan-7-one (**6**), quantitatively.

SCHEME I



The efficiency of the acid-catalyzed rearrangement of **5** to **6** suggested that the photoannulation of enone **7** with 2-butene, followed by acid-catalyzed rearrangement of the resulting isomers **8**, should comprise a good synthesis of ketone **2** (Scheme II). Execution of this reaction sequence (using *cis*-2-butene) resulted in the production of ketone **2** from a mixture of isomers **8**, in an overall yield of 82%. This product was identical with the photoreduced product obtained from the irradiation of enone **1** in cyclohexene. The trans relationship of the methyl groups in **2** was ascertained

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research.

(2) R. L. Cargill, N. P. Peet, D. M. Pond, A. B. Sears, W. A. Bundy, and M. G. Rosenblum, to be published.

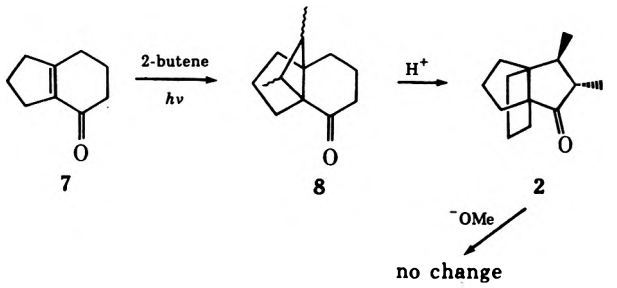
(3) (a) T. G. Halsall, D. W. Theobald, and K. B. Walshaw, *J. Chem. Soc.*, 1029 (1964); (b) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

(4) (a) R. M. Bowman, C. Calvo, J. J. McCullough, P. W. Rasmussen, and F. F. Snyder, *J. Org. Chem.*, **37**, 2084 (1972); (b) P. de Mayo, *Accounts Chem. Res.*, **4**, 41 (1971).

(5) R. L. Cargill and J. W. Crawford, *J. Org. Chem.*, **35**, 356 (1970).

(6) One explanation for this difference holds that the excited state of **4** is not as long-lived as the excited state of **7**, owing to rigidity differences, which would make decay of excited **4** to ground state a more favorable process than decay of **7** to ground state.

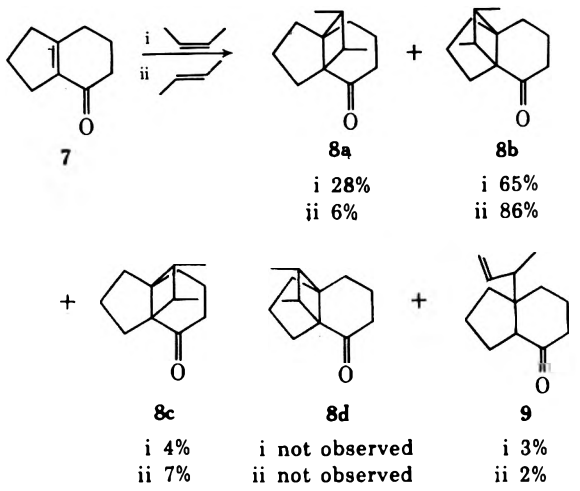
SCHEME II



by recovering **2** unchanged from NaOMe–MeOH at reflux. Had **2** been the cis isomer, base treatment would certainly have converted all or most of it into the thermodynamically more stable trans isomer.

By monitoring the conversion of **8** into **2** by glpc, we noticed that the two major isomers of **8** underwent the skeletal rearrangement at markedly different rates. In order to gain further insight into this difference in behavior, we first had to determine the stereochemistry of the isomers of **8** which were formed. At this point we suspected that the two major isomers of **8**, in the cycloaddition of enone **4** and *cis*-2-butene, were the two trans isomers, as one would predict from a nonconcerted cycloaddition process.[7] In order to confirm this suspicion we performed the cycloaddition with *trans*-2-butene as well, to determine whether the same two products were formed preferentially. The product ratios from photoannulations of enone **7** with *cis*-2-butene and *trans*-2-butene are shown in Scheme III. In each case, the same three cycloadducts (**8a**, **8b**, and **8c**) were formed, as well as small amounts of a keto olefin, thought to be **9**.

SCHEME III



In order to further establish that the two major isomers produced from cycloaddition of **7** with *cis*-2-butene were the trans isomers, and to determine which was which, an nmr study of these two adducts with a shift reagent [Eu(DPM)$_3$] was undertaken. Since the degree of deshielding suffered by a proton or group of protons is inversely proportional to r^3 [r being the average internuclear distance between the proton(s) and the bound Eu^{3+}],[8] it is evident that for the four possible positions of a methyl group, the degree of deshielding should decrease, going from a to d, as shown in the structure below. To carbon tetrachloride solutions of known concentrations of the two major cycloadducts from **7** and *cis*-2-butene were added known amounts of Eu(DPM)$_3$, incrementally. A plot of methyl group chemical shift against [Eu(DPM)$_3$]/[ketone] for the two ketones is shown in Figure 1. This graph shows that the structures given for these two ketones in Scheme III (**8a** and **8b**) are correct, since (i) no two lines in the plot coincide and (ii) the two inner lines correspond to the methyl groups in one ketone and the two outer lines correspond to the methyl groups in the other ketone.

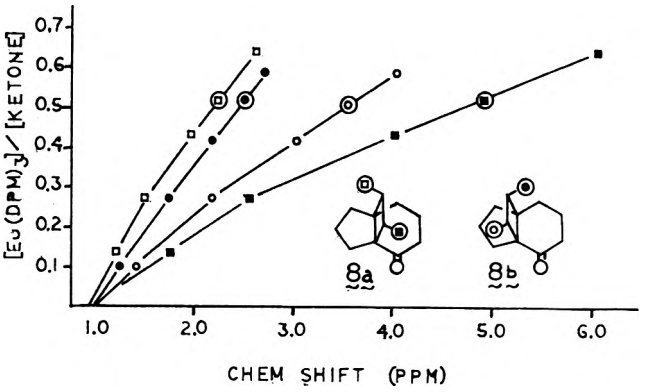
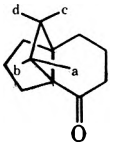
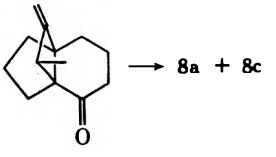


Figure 1.—Effect of nmr shift reagent on methyl groups at varying distances from binding site.



The structure of the minor cycloadduct was established as **8c** by its identity (glpc and mass spectrum) with one of the products obtained from catalytic hydrogenation of **10**.[9]



The results of these photoannulations of enone **7** with *cis*- and *trans*-2-butene agree well with the theory proposed by Dilling[10] in his study of cycloaddition reactions of *cis*- and *trans*-dichloroethylenes with cyclopentenone. Schemes IV and V show the mechanistic interpretations for initial β bonding and initial α bonding, respectively, where the diradical intermediates (**11** and **13**, **12** and **14**, **15** and **17**, and **16** and **18**) are rotationally equilibrated before ring closure. Percentages directly above and below the ketones **8a–d** are the observed yields of the products (from Scheme

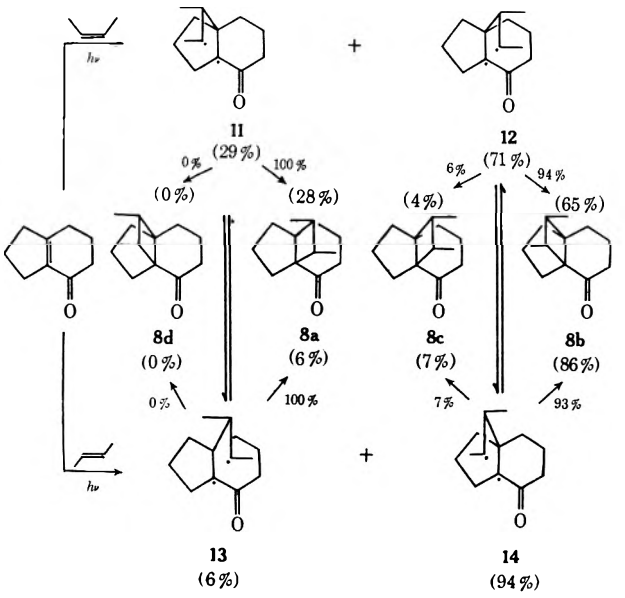
(7) It seemes reasonable to conclude that the 1,2 interactions of the methyl groups on the cyclobutane ring would have more to do with the resulting product stereochemistry than whether a methyl group lay over a five- or six-membered ring.

(8) M. R. Willcott, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972).

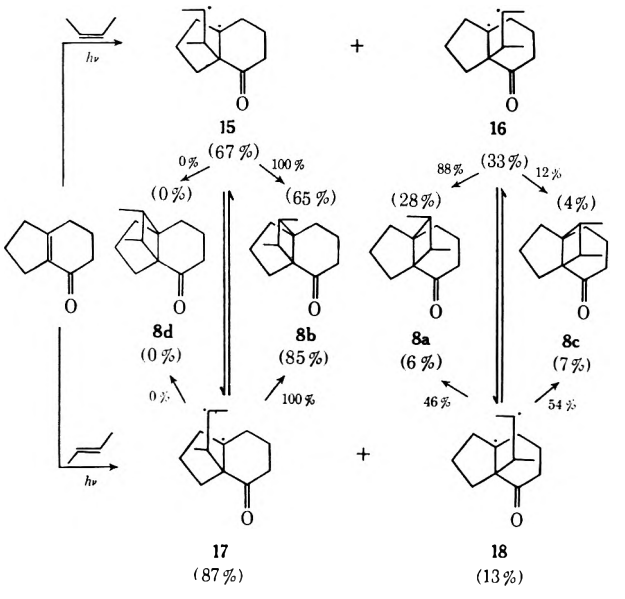
(9) The structure and stereochemistry of ketone **10** have been established: N. P. Peet, R. L. Cargill, and J. W. Crawford, *J. Org. Chem.*, **38**, 1222 (1973).

(10) W. L. Dilling, T. E. Tabor, F. P. Boer, and P. P. North, *J. Amer. Chem. Soc.*, **92**, 1399 (1970).

SCHEME IV



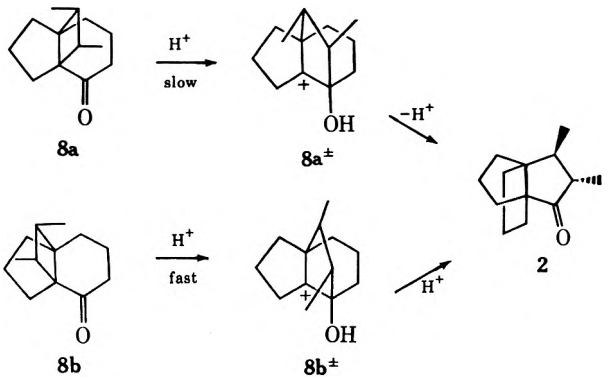
SCHEME V



III). Percentages under the diradical intermediates (**11**–**18**) represent relative amounts of each which must be formed to produce the ratios of ketones to which they close. Finally, the percentages over the arrows indicate the amounts of each diradical which close to each ketone. If α bonding occurs initially (Scheme V), a majority (88%) of diradical **16** from *cis*-2-butene must close to **8a**, whereas a majority (54%) of diradical **18** (in rotational equilibrium with **16**) from *trans*-2-butene must close to **8c**. Such an inconsistency does not arise in the mechanistic pathway involving initial β bonding (Scheme IV). For this reason, we favor the mechanistic pathway shown in Scheme IV.

Small amounts of a keto olefin, assigned structure **9**, were also formed in the photoannulations of enone **7** with both *cis*- and *trans*-2-butene. This photoproduct was not considered in the mechanistic interpretations of Schemes IV and V, but can be envisioned as arising from diradical intermediate **11** or **12** by intramolecular hydrogen abstraction.

As was previously mentioned, ketone **8b** rearranged to **2** much more rapidly than did ketone **8a** (see Experimental Section). These results are best interpreted by comparing the energetics of the processes leading to the intermediates **8a**$^{\pm}$ and **8b**$^{\pm}$ from the respective



ketones. In the formation of intermediate **8a**$^{\pm}$, both methyl groups are being positioned over the planes of the rings, or into sterically crowded environments. However, in the formation of intermediate **8b**$^{\pm}$, both methyl groups are being twisted away from these sterically crowded regions. Thus, since the ground-state energies of **8a** and **8b** must be similar, the activation energies for conversion of these two ketones into **2** should differ with that for **8a** → **2** being the larger.

Experimental Section[11]

Tricyclo[4.4.2.0]dodecan-2-one (5).—A solution of 1.01 g (6.72 mmol) of bicyclo[4.4.0]dec-1(6)-en-2-one (**4**)[12] in methylene chloride (150 ml) saturated with ethylene was irradiated (Pyrex filter) at low temperature[13] for 20.5 hr. Progress of the reaction was monitored by glpc (10% Carbowax 1000M, 6 ft × 0.125 in., 150°, 30 cc/min of He); the addition was 50% complete after 5 hr, and 95% complete when irradiation was terminated. The reaction solution was warmed to room temperature and dried ($MgSO_4$), and the solvent was removed by distillation to leave a clear oil which was short path distilled to yield 0.939 g (78%) of 95% pure **11**. Separation from the small amount of starting enone present by preparative glpc (10% Apiezon M, 8 ft × 0.25 in., 175°, 85 cc/min of He) afforded pure **5**: bp 69° (0.6 mm); uv max (95% EtOH) 292 nm (ϵ 14); ir (CCl_4) 1705 cm^{-1} (C=O); nmr δ 2.5–1.1 (m); mass spectrum (70 eV) *m/e* 178 (molecular ion).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.82; H, 10.04.

(11) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. Infrared spectra were recorded using a Perkin-Elmer Model 257 grating spectrophotometer. All nmr spectra were determined using tetramethylsilane as an internal standard, with a Varian A-60 nmr spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph 1200 flame ionization chromatograph, and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph. Irradiations were carried out using a Hanovia high-pressure mercury arc (450 W), internal probe, type L, with the filter specified.

(12) Enone **4** was prepared by G. W. Hanwell using the method of H. O. House and H. W. Thompson, *J. Org. Chem.*, **36**, 3729 (1971). For alternate methods, see R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1970), and R. G. Carlson and E. G. Zey, *J. Org. Chem.*, **37**, 2468 (1972).

(13) Low temperature was maintained by immersing the irradiation vessel in a Dry Ice–isopropyl alcohol bath, and circulating isopropyl alcohol, cooled indirectly with Dry Ice, through the probe.

Tricyclo[4.3.3.0]dodecan-7-one (6).—A solution of 0.252 g (1.41 mmol) of ketone **5** and 0.5 g of *p*-toluenesulfonic acid monohydrate (Baker, $TsOH \cdot H_2O$) in benzene (45 ml) was heated at reflux for 45 min. Progress of the reaction was monitored by glpc (10% Carbowax 1000M, 6 ft × 0.125 in., 150°, 30 cc/min of He). The cool reaction solution was washed with saturated $NaHCO_3$ (25 ml) and water (15 ml), dried ($MgSO_4$), and concentrated to leave 0.243 g (95%) of 95% pure **6**. Separation from the small amount of enone **4** (present initially in **5**) by preparative glpc (10% Apiezon M, 8 ft × 0.25 in., 175°, 85 cc/min of He) afforded pure **6**: mp 121–123°; uv (95% EtOH) 292 nm (ε 30); ir (CCl_4) 1735 cm^{-1} (C=O); nmr (CCl_4) δ 2.30 (t, J = 7 Hz, 2, $COCH_2$), 2.1–1.1 (m, 16, remaining protons); mass spectrum (70 eV) m/e 178 (molecular ion).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.88; H, 10.10.

Cycloaddition of Enone 7 and *cis*-2-Butene.—A solution of 1.47 g (10.8 mmol) of enone **7**[5] and *ca.* 20 ml of *cis*-2-butene (Matheson, CP grade) in methylene chloride (140 ml) was irradiated (Pyrex filter) for 8 hr at low temperature.[13] Progress of the reaction was monitored by the disappearance of **7** with glpc (3% SE-30, 8 ft × 0.125 in., 140°, 30 cc/min of He). The reaction solution was warmed to room temperature and dried ($MgSO_4$), and the solvent was removed by distillation to leave 2.08 g (theory) of a mixture containing isomeric 10,11-dimethyltricyclo[4.3.3.0]undecan-2-ones **8a** (28%), **8b** (65%), and **8c** (4%), and 6-(1-methylprop-2-enyl)bicyclo[4.3.0]nonan-2-one (**9**) (3%), as determined by glpc. All of these components were collected from glpc (10% Apiezon M, 8 ft × 0.25 in., 160°, 85 cc/min of He) for spectral analysis. Collected samples were reanalyzed on analytical glpc (10% Carbowax 1000M, 6 ft × 0.125 in., 150°, 30 cc/min of He) to ensure purity.

Ketone **8a** had ir (CCl_4) 1690 cm^{-1} (C=O); nmr (CCl_4) δ 2.5–0.8 (m, all protons, with CH_3 doublets, J = 7.2 Hz, at 0.90 and 0.87); mass spectrum (70 eV) m/e (rel intensity) 192 (1), 137 (92), and 108 (100).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.81; H, 10.28.

Ketone **8b** had ir (CCl_4) 1690 cm^{-1} (C=O); nmr (CCl_4) δ 2.5–0.8 (m, all protons, with CH_3 doublets, J = 7.2 Hz, at 0.99 and 0.93); mass spectrum (70 eV) m/e (rel intensity) 192 (15), 137 (70), and 108 (100).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.01; H, 10.36.

Ketone **8c** had ir (CCl_4) 1690 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 192 (6), 137 (94), and 108 (100). Insufficient quantities of **8c** were available for nmr and elemental analyses.

Ketone **9** had ir (CCl_4) 3060 (vinyl CH), 1705 cm^{-1} (C=O); nmr (CCl_4) δ 6.0–4.0 (m, CH_2=CH), 5.03 (m, CH_2=CH), 2.5–0.7 (m, remaining protons, with CH_3 d, J = 7.2 Hz, at 0.93); mass spectrum (70 eV) m/e 192 (molecular ion).

Cycloaddition of Enone 7 and *trans*-2-Butene.—A solution of 0.833 g (6.11 mmol) of enone **7**[5] and *ca.* 20 ml of *trans*-2-butene (Matheson, CP grade) in methylene chloride (140 ml) was irradiated (Pyrex filter) for 2.5 hr at low temperature.[13] Reaction progress was monitored as above and the reaction solution was worked up as above to leave 1.17 g (theory) of isomeric ketones **8a** (6%), **8b** (86%), **8c** (7%), and **9** (2%).

3,4-Dimethyltricyclo[3.3.3.0]undecan-2-one (2).—A solution of 1.41 g (7.34 mmol) of ketones **8a**, **8b**, **8c**, and **9** (in a ratio of 11:24:1.4:1.0, respectively) and $TsOH \cdot H_2O$ (0.5 g) in benzene (40 ml) was heated at reflux for 8 hr. Progress of the reaction was monitored by glpc (10% Carbowax 1000M, 6 ft × 0.125 in., 150°, 30 cc/min of He) and the four ketones in the initial mixture eluted at 8.0, 9.8, 12.2, and 15.5 min, respectively. After 8 hr the peaks at 9.8 (**8b**), 12.2 (**8c**), and 15.5 min (**9**) were absent,[14] and a new peak at 7.0 min had developed. A substantial amount of the ketone at 8.0 min still remained. The reaction mixture was cooled and 75% of the reaction solution was washed with saturated $NaHCO_3$ (25 ml) and water (20 ml), dried ($MgSO_4$), and concentrated to leave 1.02 g (96%) of a mixture of two ketones at 7.0 and 8.0 min. These ketones were collected from preparative glpc (10% Apiezon M, 8 ft × 0.25 in., 150°, 85 cc/min of He), a system in which the two ketones eluted in the same order. An infrared spectrum (CCl_4) of the smaller peak at 8.0 min was identical with that of ketone **8a**. An infrared spectrum of the large product peak at 7.0 min (ketone **2**) was identical with that of the photoreduction product from **1**. Ketone **2** had ir (CCl_4) 1730 cm^{-1} (C=O); nmr (CCl_4) δ 2.45–0.78 (m, with CH_3 doublets, J = 7.2 Hz, at 1.02 and 0.91); mass spectrum (70 eV) m/e 192 (molecular ion).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.93; H, 10.39.

The remaining 25% of the reaction mixture was heated at reflux for an additional 24 hr and worked up as above to yield 0.300 g (85%) of *pure* **2**.

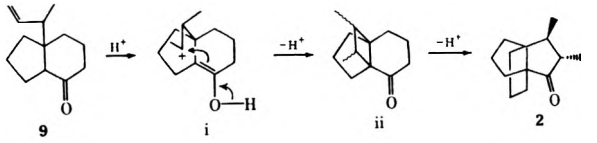
To determine the stereochemical relationship of the methyl groups in ketone **2**, a 0.300-g (1.56 mmol) quantity of **2** in 10 ml of 1.5 *N* NaOMe was heated at reflux under an inert atmosphere for 2 hr. The cool reaction solution was diluted with water (20 ml) and extracted with pentane (3 × 15 ml). The combined extracts were dried ($MgSO_4$) and concentrated to leave 0.208 g (70%) of unchanged **2**, as evidenced by its infrared spectrum. Analysis by glpc (10% Carbowax 1000M, 6 ft × 0.125 in., 150°, 30 cc/min of He) and coinjection with authentic **2** both gave a single peak.

Reduction of Ketone 10.—A solution of 16 mg of ketone **10**[9] (*ca.* 80% pure from preparative glpc) in 5 ml of methanol was hydrogenated at 46 psi for 2 hr using 3.2 mg of platinum oxide catalyst. The catalyst was filtered, and the filtrate was diluted with water, extracted with carbon tetrachloride, dried ($MgSO_4$), and concentrated. Analysis by glpc (coinjection) (DEGS) showed the presence of **8a** and **8c** (ratio *ca.* 2:1, respectively), along with small amounts of two products derived from the original impurity in **10**. The mass spectrum (70 eV) of **8c** obtained from **10** is identical with that obtained in the photoannulation experiments.

Registry No.—**2**, 38312-59-3; **4**, 18631-96-4; **5**, 38312-61-7; **6**, 38312-62-8; **7**, 22118-01-0; **8a**, 38312-64-0; **8b**, 38343-72-5; **8c**, 38312-65-1; **9**, 38312-66-2; **10**, 38312-67-3; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6.

Acknowledgment.—The authors are grateful to Dr. Wendell L. Dilling of Dow Chemical Company for help with the interpretation of the photoannulation results in a private communication, and for other valuable contributions.

(14) Ketone **9**, as well as ketones **8b** and **8c**, was apparently converted to ketone **2** during this 8-hr period. It is conceivable that **9** was converted to **2** *via* ii as follows.



Photochemistry of β,γ-Unsaturated Ketones. 10,11-Dimethyltricyclo[4.3.2.0]undec-10-en-2-one[1]

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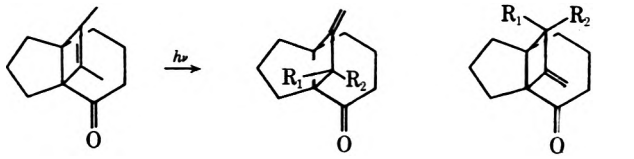
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received November 10, 1972

The photochemical 1,3-acyl migration[2] is a rearrangement common to β,γ-unsaturated ketones in which efficient mixing of carbonyl and olefinic orbitals occurs.[3] However, when this orbital mixing is inefficient (ϵ_{max} <150), olefin triplet reactions are usually observed.[3] Atom abstraction from solvent (photoreduction[3,4] being a special case), dimerization (or cycloaddition), and intramolecular atom abstraction reactions are viable olefin triplet reactions[5] of rigid olefins as well as β,γ-unsaturated ketones (ϵ_{max} <150) in which the olefinic group is rigid (*i.e.*, enones in which the olefinic group is in a five-membered or smaller ring). We have recently encountered an example of photochemically induced intramolecular hydrogen transfer



1
296 nm (ε 168)

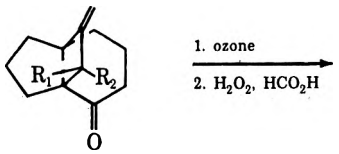
2a, $R_1 = H; R_2 = CH_3$
b, $R_1 = CH_3; R_2 = H$

3a, $R_1 = H; R_2 = CH_3$
b, $R_1 = CH_3; R_2 = H$

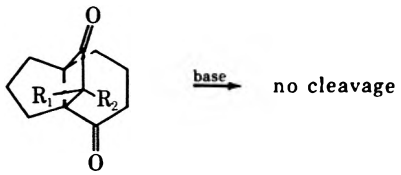
(a process which is well documented for rigid olefins[6]) in β,γ-unsaturated ketone **1**[7] (ϵ_{max} 168).[8]

Irradiation of 10,11-dimethyltricyclo[4.3.2.0]undec-10-en-2-one (**1**)[7] in hexane (Corex) produced a mixture of four new ketones in which 10-methyl-11-methylenetricyclo[4.3.2.0]undecan-2-one (**2a**) predominated (70%).[9]

Spectral information allowed us to initially determine the structure of the major photorearranged isomer as either **2** (**a** or **b**) or **3** (**a** or **b**). Oxidative cleavage of this major product produced diketone **4** (**a** or **b**), whose partial structure was verified by its resistance to base cleavage.[10]



2a, $R_1 = H; R_2 = CH_3$
b, $R_1 = CH_3; R_2 = H$



4a, $R_1 = H; R_2 = CH_3$
b, $R_1 = CH_3; R_2 = H$

The stereochemistry at the 10 position (methyl-bearing carbon) of **2** was then determined by comparing the effect of added shift reagent [Eu(DPM)$_3$] on the nmr chemical shift of the methyl group in **2** (**a** or **b**) with those of the methyl groups in model compounds **5** and **6**.[11] Plots of methyl group chemical shift against [Eu(DMP)$_3$]/[ketone] for the five methyl groups in these three ketones are shown in Figure 1. This graph clearly shows that the methyl group of the photorearrangement product is the same distance from the carbonyl group as is the 10-position methyl group in **5**;[12] thus its structure can be assigned as **2a**. In addition, the structure of the diketone obtained from ozonolysis of **2a** can be assigned as **4a**.

The hydrogen shift which produces **2** may be viewed as an orbital symmetry allowed [1,3] *suprafacial* sigmatropic reaction. The selectivity observed (70% of the reaction being migration of that hydrogen which is farthest from the carbonyl group and on the face of the π system away from the carbonyl) is a clear indication of some interaction between the carbonyl group and the olefinic group in the reacting species. The nature of this interaction remains to be ascertained.

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research.

(2) G. Büchi and E. M. Burgess, *J. Amer. Chem. Soc.*, **82**, 4333 (1960).

(3) R. L. Cargill, T. Y. King, and A. B. Sears, *J. Org. Chem.*, **36**, 1423 (1971), and references cited therein.

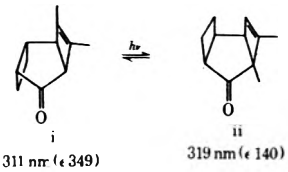
(4) (a) R. L. Cargill, J. R. Damewood, and M. M. Cooper, *J. Amer. Chem. Soc.*, **88**, 1330 (1966); (b) P. S. Engel and H. Ziffer, *Tetrahedron Lett.*, 5181 (1969); (c) R. L. Cargill and A. B. Sears, *ibid.*, 3555 (1972).

(5) H.-D. Scharf, *Fortschr. Chem. Forsch.*, **11**, 219 (1969).

(6) P. J. Kropp, *J. Amer. Chem. Soc.*, **89**, 3650 (1967).

(7) R. L. Cargill and J. W. Crawford, *J. Org. Chem.*, **35**, 356 (1970).

(8) Although ε 168 does not quite fit into the ε <150 category, the latter coefficient is only meant to roughly separate two categories of β,γ-unsaturated ketones. Another exception to this generalization is compound ii (ε <150), which does undergo photochemical 1,3-acyl migration.[2]



i
311 nm (ε 349)

ii
319 nm (ε 140)

(9) Irradiation of the unmethylated enone, λ_{max}^{EtOH} 296 nm (ε 85), in methylene chloride gave only the saturated ketone as expected. See Experimental Section.

(10) Had **4** (**a** or **b**) instead been a β diketone produced from oxidation of β,γ-unsaturated ketone **3** (**a** or **b**), treatment with base would have produced a keto acid.

(11) N. P. Peet, R. L. Cargill, and D. F. Bushey, *J. Org. Chem.*, **38**, 1218 (1973).

(12) M. R. Willcott, R. E. Lenkinkski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972).

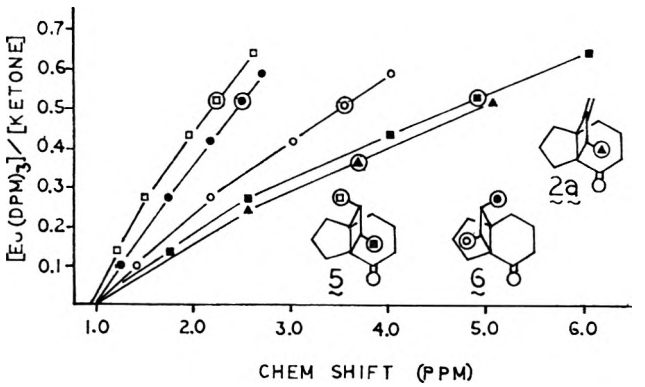


Figure 1.—Effect of nmr shift reagent on methyl groups at varying distances from binding site.

Experimental Section

10-Methyl-11-methylenetricyclo[4.3.2.0]undecan-2-one (2a).—A solution of 2.10 g (11.0 mmol) of 10,11-dimethyltricyclo-[4.3.2.0]undec-10-en-2-one (1)[7] in hexane (450 ml) was irradiated (Corex filter) for 5 hr. Progress of the reaction was monitored by the disappearance of 1 with glpc (3% DEGS, 8 ft × 0.125 in., 110°, 30 cc/min of He). The solvent was removed by distillation and the residue was short path distilled (68°, 0.20 mm) to afford 0.579 g of a four-component mixture. The major product **2a** (*ca.* 70% of mixture) was collected from glpc (20% Carbowax 1000M, 5.5 ft × 0.25 in., 150°, 85 cc/min of He): uv max (95% EtOH) 295 nm (ε 62); ir (CCl_4) 1690 cm^{-1}; nmr (CCl_4) δ 4.88 (m, 2, exo methylene), 2.3–1.1 (m, 13, all ring protons), 0.99 (d, J = 7.2 Hz, 3, methyl); mass spectrum (70 eV) m/e 190 (molecular ion).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.89; H, 9.63.

Infrared spectra (CCl_4) of the three minor components, each of which comprised *ca.* 10% of the isolated product mixture, were very similar to that of **2a**. An nmr spectrum of the crude reaction mixture indicated that **2a** was the major component before glpc analysis.[4c]

10-Methyltricyclo[4.3.2.0]undecane-2,11-dione (4a).—A 0.630-g (3.27 mmol) quantity of ketone **2** in methylene chloride (100 ml) was cooled (−78°) and ozone was passed through the solution until ozone was detected in the effluent gas. The reaction solution was concentrated, and the resulting yellow oil in formic acid (10 ml) and 30% hydrogen peroxide (5 ml) was heated at reflux for 30 min. Concentration of the reaction solution left 0.590 g (94%) of diketone **4a**: mp 108–109°; ir (CCl_4) 1770 (cyclobutanone C=O) and 1705 cm^{-1} (cyclohexanone C=O); nmr (CCl_4) δ 2.5–1.1 (m, 13, all protons except CH_3), 0.93 (d, J = 6 Hz, 3, CH_3).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.02; H, 8.46.

Attempted Base Cleavage of Diketone 4a.—A 0.590-g (3.07 mmol) quantity of **4a** and 10% Na_2CO_3 solution (200 ml) were heated at reflux for 2 hr. The cool reaction mixture was extracted with ether (2 × 40 ml) and the combined extracts were washed with saturated NaCl solution (20 ml), dried ($MgSO_4$), concentrated, and sublimed (80°, 0.2 mm) to yield 0.380 g (64%) of recovered **4a**. Acidification of the aqueous phase followed by work-up as above separated an additional 0.050 g (8%) of **4a**.

Irradiation of Tricyclo[4.3.2.0]undec-10-en-2-one.—A solution of 211 mg of tricyclo[4.3.2.0]undec-10-en-2-one[7] in 55 ml of methylene chloride was irradiated (Corex filter) for 30 min. The solvent was removed by distillation and the residual oil was purified by glpc (20% DEGS, 10 ft × 0.25 in., 200°, 50 ml/min He) to give 1,1,2,2-tetrachloroethane and 154 mg (72%) of tricyclo[4.3.2.0]undecan-2-one as the only volatile products: uv max (95% EtOH) 293 nm (ε 26); ir (CCl_4) 1700 cm^{-1}; the nmr spectrum (CCl_4) is a complex absorption centered at *ca.* δ 1.9. This ketone is identical with a sample prepared by catalytic hydrogenation.

The *p*-toluenesulfonylhydrazone was recrystallized from methanol–water, mp 140–140.5°.

Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.08; H, 7.25; N, 8.53.

Registry No.—**1**, 22241-70-9; **2a**, 38229-64-0; **4a**, 38229-65-1; tricyclo[4.3.2.0]undec-10-en-2-one, 22241-68-5; tricyclo[4.3.2.0]undecan-2-one, 38229-67-3; tricyclo[4.3.2.0]undecan-2-one *p*-toluenesulfonylhydrazone, 38229-68-4.

(13) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach uber Engelskirchen, West Germany. Infrared spectra were recorded using a Perkin-Elmer Model 257 grating spectrophotometer. All nmr spectra were determined using tetramethylsilane as an internal standard, with a Varian A-60 nmr spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph 1200 flame ionization chromatograph, and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph. Irradiations were carried out using a Hanovia high-pressure mercury arc (450 W), internal probe, type L, with the filter specified.

O-Alkyl Cleavage of Methyl Esters by 1,5-Diazabicyclo[5.4.0]undecene-5

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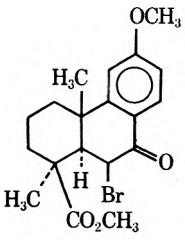
In connection with the synthesis of diterpenoid intermediates an improved yield of lactone **2** from bromo ketone **1** was required. The transformation of bromo ketone **1** to a mixture of lactone **2** (47% yield) and ester **3** (40% yield) by refluxing in collidine has been previously reported[2,3] along with the observation that treatment of bromo ketone **1** with sodium methoxide yields only elimination product **3**. The suggestion was offered that a major factor in the contrasting behavior of sodium methoxide and collidine might be the steric requirements of the bases for proton abstraction. Thus we initiated an investigation into the improvement of the yield of lactone **2** by utilizing a variety of bases that have greater steric requirements than collidine. As a result of this study, we now wish to report that the base 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) is useful for the *O*-alkyl cleavage of methyl esters.

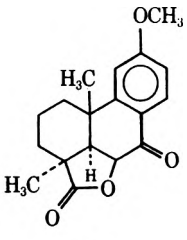
Reaction of bromo ketone **1** with 2 equiv of DBU in 10 equiv of *o*-xylene at 165° for 5 hr gave product **5** in 92% yield in the form of a white, crystalline solid, mp 122.5–123.5°. The infrared spectrum showed absorptions at 1650 and 1600 cm^{-1} for the α,β-unsaturated ketone system. The nmr spectrum exhibited resonance signals for a doublet (J = 6 Hz) at δ 1.41 for the C-4 methyl group, a singlet at 1.73 for the C-10 tertiary methyl group, a singlet at 4.33 for the methoxy group, a doublet (J = 1.8 Hz) at 6.91 for the vinylic proton, a multiplet at 7.39 for the C-13 and C-14 protons, and a doublet (J = 9 Hz) at 8.98 for the C-11 proton. Neither lactone **2** nor elimination product **3** were found in the reaction mixture.

Additional evidence for structure **5** was the observation that elimination product **3** could be isolated in 90.5% yield if bromo ketone **1** was allowed to react for only 15 min. Since DBU is known to be a facile de-

(1) National Defense Education Act Graduate Fellow, 1971–1973.
(2) E. Wenkert, *et al.*, *J. Org. Chem.*, **30**, 713 (1965).
(3) E. Wenkert, *et al.*, *Can. J. Chem.*, **41**, 1924 (1963).



1



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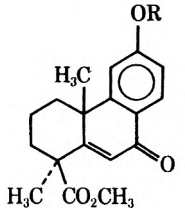
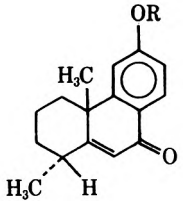


3, R = CH_3
4, R = H

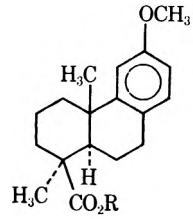


5, R = CH_3
6, R = H

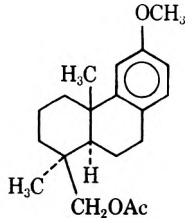
hydrohalogenating agent,[4-8] the isolation of intermediate ester **3** indicates that **5** must have arisen from **1** by dehydrobromination and subsequent decarbomethoxylation. Support for the stereochemistry assigned to **5** is provided by the report[3] that **6** can be obtained from **4** in approximately 33% yield by dealkylation and subsequent decarboxylation with lithium iodide in refluxing collidine.[9,10]

Evidence that decarbomethoxylation of compounds **1** and **3** proceeded through *O*-methyl cleavage of the methyl ester and subsequent decarboxylation was provided by the following results. Treatment of ester **7** with 10 equiv of DBU in 10 equiv of *o*-xylene at a reaction temperature of 165° for 48 hr gave pure white crystalline acid **8** in 96.7% yield, mp 159–160° (lit.[11] mp 158–161°). When acetate **9** was treated with DBU in the same manner only starting material could be recovered from the reaction mixture. These results rule out the possibility that the conversion of ester **7** to acid **8** could have proceeded by the hydrolytic route. If this route had been operative acetate **9** would have been easily cleaved in comparison to ester **7**. Ester **7** (methyl *O*-methylpodocarpate) requires extremely severe conditions for ordinary hydrolysis.[12]

The generality of the cleavage reaction is demonstrated by the application of DBU to the cleavage of methyl *O*-methylpodocarpate (**7**) and the four esters described below.



7, R = CH_3
8, R = H



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Methyl mesitoate is the classic example of a hindered ester. A solution of DBU (10 equiv) in 10 equiv of *o*-xylene was allowed to react at 165° for 48 hr to give a 94.6% yield of colorless crystals, mp 149–151° (lit.[13] mp 153–154°), which was identical by mixture melting point and ir with authentic mesitoic acid.

Methyl triisopropylacetate has also been utilized to confirm the ability of several reagents to cleave hindered esters.[11,14]

Triisopropylacetic acid was esterified with diazomethane, and the crude ester was treated with 10 equiv of DBU dissolved in 10 equiv of *o*-xylene at 165° for 48 hr to give a 91.2% yield of colorless crystals, mp 136–139°. One recrystallization from methanol–water gave material which was identical by mixture melting point and ir with an authentic specimen of triisopropylacetic acid.

In order to demonstrate that this reaction is not limited to hindered esters in very complex molecules, the simple ester, methyl palmitate, was treated with 10 equiv of DBU in 10 equiv of *o*-xylene at 165° for 48 hr. The resulting acid, mp 62–63°, was obtained in 93% yield and was identical by mixture melting point and ir with authentic palmitic acid.

Methyl 3β-acetoxy-Δ_5-etienate contains both a hydrolytically sensitive functionality and a relatively hindered ester group, and was used in the investigation of the lithium iodide/refluxing lutidine system as a selective ester cleavage reagent. With both iodide and DBU S_N2 displacement of the acetate group is sterically hindered and attack at the acetate carbonyl is energetically unfavorable; therefore, reasonable selectivity can be achieved. After 8 hr reflux, the lithium iodide method gave 25–28% of starting material, 49–51% of the desired acetoxy acid, and 5–10% of the hydroxy acid resulting from hydrolytic loss of the acetate group.[10]

A solution of DBU (10 equiv) and the acetoxy ester in 10 equiv of *o*-xylene was allowed to react at 165° for 3.5 hr. The reaction time was optimized for maximum selectivity. Glc comparison of the crude product with authentic samples showed that the DBU method gave 50% starting material, 41% of the desired acetoxy acid, 7% of the hydroxy acid resulting from hydrolytic loss of the acetate group,[10] and 2% of the diene acid resulting from elimination of the acetate group. Based on the material allowed to react, reasonable selectivity (82%) was achieved.

Reagents such as lithium iodide in refluxing pyridine, 2,6-lutidine, or 2,4,6-collidine,[10] lithium iodide in hot dimethylformamide,[15] potassium *tert*-butoxide in DMSO,[11] and lithium ethyl mercaptide in hexamethylphosphoramide[14] have been developed for effecting cleavage of methyl esters by nucleophilic displacement of the carboxylate anion from the methyl group. Although DBU does not cleave esters under the mild conditions reported for the mercaptide[14] and potassium *tert*-butoxide methods,[11] this reagent does cleave methyl esters without the utilization of ionic nucleophilic reagents.

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(14) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).
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Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained using a Jeolco minimar spectrometer. Tetramethylsilane was used as an internal standard. Infrared spectra were obtained using a Perkin-Elmer Model 137 G spectrophotometer. Gas–liquid chromatography (glc) was performed using a Hewlett-Packard Model 402 gas chromatograph with a hydrogen flame detector. A glass column (6 ft × 0.25 in. o.d.) bent in a U shape and packed with 3% SE-30 on 100/120 mesh GCQ at a column temperature of 270° with a helium flow rate of 90 ml/min was used for all glc analyses.

Dehydrobromination–Decarbomethylation of Bromo Ketone 1.—Bromo ketone 1 (500 mg, 1.27 mmol) was added to a solution of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) (390 mg, 2.56 mmol) and 1.51 ml of *o*-xylene. The temperature of the reaction solution was allowed to remain at 165° for 5 hr. The ether extract of the reaction mixture was acidified with 5% HCl and washed with 5% aqueous sodium carbonate and water, dried over anhydrous sulfate, and evaporated *in vacuo*. Crystallization of the residue from 20:1 methylene chloride–methanol solution yielded 299 mg (92%) of the white, crystalline compound **5**: mp 122.5–123.5° (lit.[16] mp 120–121°); λ_{max}^{KBr} 1650, 1600 cm^{-1}; δ^{CHCl_3} 1.41 (3 H, d, J = 6 cps), 1.73 (3 H), 4.33 (3 H), 6.91 (1 H, d, J = 1.8 cps), 7.39 (2 H, multiplet), 8.98 ppm (1 H, d, J = 9 cps). *Anal.* Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.90; H, 8.00.

Dehydrobromination of Bromo Ketone 1.—Bromo ketone 1 (500 mg, 1.27 mmol) was added to a solution of DBU (0.140 mg, 0.92 mmol) and 1.51 ml of *o*-xylene which was allowed to remain at 165° for 15 min. Following work-up in the manner described above, crystallization from aqueous methanol yielded 360 mg (90.5%) of the crystalline solid **3**: mp 175–177° (lit.[10] mp 173–175°); λ_{max}^{KBr} 1725, 1645, 1600, 1575 cm^{-1}; δ^{CHCl_3} 1.56 (3 H), 1.76 (3 H), 4.33 (3 H), 4.58 (3 H), 7.71 (1 H), 8.15 (2 H, multiplet), 9.58 ppm (1 H, d, J = 8 cps). *Anal.* Calcd for $C_{19}H_{22}O_4$: C, 72.50; H, 7.01. Found: C, 72.86; H, 7.14.

General Procedure for the *O*-Alkyl Cleavage of Methyl Esters. Methyl *O*-Methylpodocarpate, Methyl Mesitoate, and Methyl Triisophopylacetate, and Methyl Palmitate.—A solution of DBU (1.202 g, 8.30 mmol) and 0.83 mmol of the appropriate methyl ester was dissolved in 1.0 ml of *o*-xylene and the resulting mixture was allowed to remain at 165° for 48 hr. The usual work-up of the ether extract of the acidified carbonate layer yielded the corresponding acid, which was identical by ir, nmr, and mixture melting points with an authentic sample.

Attempted Cleavage of Acetate 9.—Acetate 9 (0.500 mg, 1.59 mmol) was dissolved in 1.9 ml of *o*-xylene and after the addition of DBU (2.42 g, 15.94 mmol) the solution was heated at 165° for 48 hr. The washed ether extract of the acidified reaction mixture yielded 0.489 mg (97.8%) of a white, crystalline material which was identical by glc, ir, nmr, and mixture melting points with an authentic sample of the starting material.

Selective Cleavage of Methyl 3β-Acetoxy-Δ^5-etienate.—Acetoxy ester (200 mg, 0.52 mmol) was added to a solution of DBU (740 mg, 4.86 mmol) in 0.62 ml of *o*-xylene and the resulting mixture was heated for 3.5 hr at 165°. The usual work-up yielded 154 mg of crude product. Glc comparison with authentic samples showed the product to be 50% of starting material, 41% of the desired acetoxy acid, 7% of the hydroxy acid resulting from hydrolytic loss of the acetate group, and 2% of the diene acid resulting from the loss of the acetate group.

Registry No.—**1**, 37931-64-9; **3**, 37931-65-0; **5**, 37931-66-1; DBU, 6674-22-2.

Acknowledgments.—We wish to thank the graduate school and the Biological and Physical Sciences Institute for partial financial support. We express our sincere appreciation to Dr. Ian K. Walker, Department of Scientific and Industrial Research, Wellington, New Zealand, for generous supplies of podocarpic acid.

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Synthesis of Benzo[*b*]-1,4-diazabicyclo[3.2.1]octane

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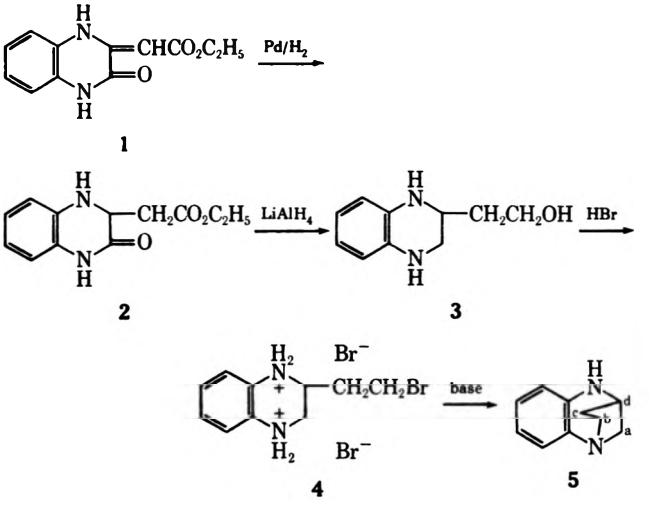
Benzo[*b*]1,4-diazabicyclo[3.2.1]octane (**5**), a new ring system, was prepared from 3-ethoxycarbonylmethylene-2-quinoxalone[1] as shown in Scheme I. Spectral data

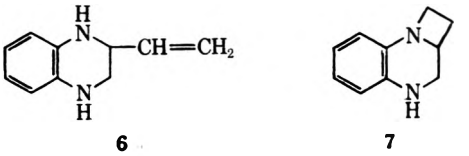
SCHEME I



support the keto structure shown above (**1**) rather than a tautomeric form. The infrared spectrum (KBr) shows conjugated ester carbonyl absorption at 1685 cm^{-1} and a lactam carbonyl at 1643 cm^{-1}, compared to the values 1705 and 1670 cm^{-1} for these bands in the dihydro compound **2**. The nmr spectrum of **1** (DMSO) showed a singlet at δ 5.55 which integrated for one proton. Protons on the α carbon atom of an α,β-unsaturated ester are known to absorb in this region.[2] Furthermore, no absorption was found in the region of δ 2.1 where protons in a methylene group adjacent to an ester group are known to absorb.[2] The uv spectrum (C_2H_5OH) was also in agreement with the assigned structure.

The free base corresponding to **4** could not be isolated due to the ease with which it undergoes cyclization to form **5**. The new compound (**5**) was formed by an intramolecular process as established by molecular weight determination.

Theoretically, two other compounds (**6** and **7**) might result from the treatment of compound **4** with bases.



6 **7**

Compound **6** was ruled out for two reasons. The infrared spectrum showed no alkene absorption. Further-

(1) Y. J. L'Italien and C. K. Banks, *J. Amer. Chem. Soc.*, **73**, 3246 (1951).

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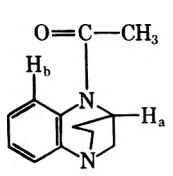
more, one would expect two N–H protons and three vinyl protons in the nmr spectrum of **6** but these were not observed. Thus, the choice is between **5** and **7**. One would expect the five-member ring to be more stable and hence the formation of **5** should be favored.

Comparison of the nmr spectrum of **5** or **7** with the nmr spectrum of the acetyl derivative **8** or **9** in $CDCl_3$



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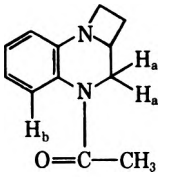

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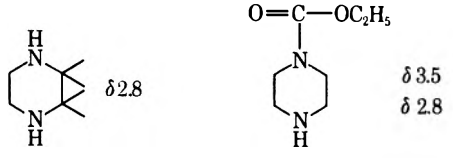
shows that the new ring compound has the structure shown as compound **5**. The nmr spectrum of **5** shows a multiplet at δ 2.06 (2 H, methylene protons at c in the bridge), a multiplet at 3.12 (4 H, methylene protons at a and b), a multiplet at 3.87 (1 H, bridgehead proton), a singlet at 4.15 (1 H, NH proton) and a multiplet at 6.8 (4 H, aromatic protons). When the nmr spectrum was determined in D_2O, the δ 4.15 peak disappeared.[3]

The nmr spectrum of the acetylated derivative showed some characteristic differences. The N–H proton peak disappeared and only three protons were found in the aromatic multiplet. One of the aromatic protons (H_b) was shifted downfield to δ 8.4 due to an anisotropic effect. More significant, the acetyl group would be expected to deshield the protons marked H_a. If the acetylated product were **9**, one would expect the multiplet for two protons to be shifted downfield and, if the acetylated product were **8**, the single H_a proton would be shifted downfield. Actually, it was the single proton at δ 3.87 that shifted to δ 4.83. It would appear therefore that structure **5** is correct and the product formed by intramolecular cyclization is benzo[*b*]-1,4-diazabicyclo[3.2.1]octane.

A similar shift has been observed in 1-carbethoxypiperazine.[4]



Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus. Infrared spectra (KBr) were obtained with a Perkin-Elmer Model 521 spectrophotometer. Ultraviolet spectra were determined with a Cary 14 ultraviolet spectrophotometer. Nuclear magnetic spectra were obtained at 60 MHz with a Varian Associates Model A-60A spectrometer.

Ultraviolet Spectrum of 3-Ethoxycarbonylmethylene-2-quinoxalone (1).[1]—Obtained was uv (C_2H_5OH), λ_{max} (E_{max}), 201 (2.82 × 10^4), 226 (2.07 × 10^4), 283 (5.84 × 10^3), 344 (6.45 × 10^3).

3-Ethoxycarbonylmethyl-2-quinoxalone (2).—3-Ethoxycarbonylmethylene-2-quinoxalone[1] (23.2 g, 0.1 mol) was added to 125 ml of glacial acetic acid. The mixture was hydrogenated at 50° over 10% palladium on carbon. Hydrogenation was rapid and the starting material dissolved rapidly as hydrogenation occurred (20–30 min). After the catalyst was removed, the acetic acid was removed *in vacuo* on a steam bath. A little petroleum ether was added to the residue to facilitate complete crystallization. The product was recrystallized from petroleum ether (60–110°): yield 41%, yellow solid, mp 106–108°.

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.03; N, 11.96. Found: C, 61.66; H, 5.85; N, 12.02.

2-(2-Hydroxyethyl)-1,2,3,4-tetrahydroquinoxaline (3).—3-Ethoxycarbonylmethyl-2-quinoxalone (18.5 g, 0.08 mol) was dissolved in 500 ml of dry tetrahydrofuran, and the solution was added dropwise to a stirred suspension of 9.5 g (0.25 mol) of lithium aluminum hydride. After the addition, stirring was continued for 2 hr and the mixture was then refluxed for 17 hr. The mixture was filtered and the inorganic salts were thoroughly extracted with tetrahydrofuran. The extract and filtrate were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residual oil solidified on standing a short time with petroleum ether. The product was recrystallized from benzene–petroleum ether (bp 60–110°) with the aid of decolorizing carbon: yield 65%; colorless solid; mp 97–98°; ir (KBr, cm^{-1}) 3370 (m), 3305 (m), 2580–2950 (vs), 1590 (s), 1455 (s).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.22; H, 7.94; N, 15.5.

2-(2-Bromoethyl)-1,2,3,4-tetrahydroquinoxaline Dihydrobromide (4).—2-(2-Hydroxyethyl)-1,2,3,4-tetrahydroquinoxaline (8.90 g, 0.05 mol) was added in small portions to 200 ml of 48% hydrobromic acid with stirring and some cooling. The mixture was refluxed for 8 hr. The mixture was reduced to a small volume by distillation and the dark, residual solid was washed with acetone to give a light gray solid (yield 69%). A colorless analytical sample was obtained by recrystallization from 48% hydrobromic acid with the aid of decolorizing carbon: mp >300°; ir (KBr, cm^{-1}) 2900–2100 (s), 1500 (s), 780 (s), 745 (s).

Anal. Calcd for $C_{10}H_{15}N_2Br_3$: C, 29.81; H, 3.75; N, 6.95; Br, 59.49. Found: C, 29.70; H, 3.81; N, 6.80; Br, 59.55.

Benzo[*b*]-1,4-diazabicyclo[3.2.1]octane (5).—2-(2-Bromoethyl)-1,2,3,4-tetrahydroquinoxaline dihydrobromide (10 g, 0.248 mol) was suspended in 50 ml of chloroform. A solution of 2.78 g (0.0496 mol) of potassium hydroxide in 100 ml of water was added and the mixture was stirred vigorously until solution was complete. The layers were then separated at once. The water layer was washed with chloroform and the extract and filtrate were dried ($MgSO_4$). The chloroform was removed on a steam bath leaving an oily residue which solidified on cooling. The product was recrystallized from benzene–petroleum ether (60–110°) with the aid of decolorizing carbon: yield 80%, colorless crystals, mp 131–134°.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48; mol wt, 160. Found: C, 74.88; H, 7.50; N, 17.53; mol wt, 165 (Rast).

1-Acetylbenzo[*b*]-1,4-diazabicyclo[3.2.1]octane (8).—Compound 5 (1.60 g, 0.01 mol), 0.8 g (0.011 mol) of acetyl chloride, and 1.01 g (0.01 mol) of triethylamine were dissolved in 100 ml of chloroform, and the solution was refluxed for 3 hr. The chloroform was removed by distillation and the residue was treated with dry ether to precipitate the triethylamine hydrochloride which was removed by filtration. The precipitate was extracted with warm benzene. The ether filtrate and benzene extract were combined and evaporated. The slightly sticky solid, so obtained, was recrystallized from petroleum ether (bp 60–110°): yield 70%, colorless crystals, mp 117–120°.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.36; H, 7.18; N, 13.81.

1-Benzoylbenzo[*b*]-1,4-diazabicyclo[3.2.1]octane (10).—This compound was prepared by the method used for **8**, using benzoyl chloride in place of acetyl chloride: yield 73%, colorless crystals, mp 158°.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.39; H, 6.01; N, 10.41.

1-Ethoxycarbonylbenzo[*b*]-1,4-diazabicyclo[3.2.1]octane (11).—The procedure for 10 was used again, using ethyl chloroformate in place of acetyl chloride: yield 30%, colorless crystals, mp 75–76°.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.09; H, 7.03; N, 11.93.

(3) The nmr spectrum of **5** with D_2O 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-73-1225. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

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Registry No.—1, 30681-63-1; 2, 37931-42-3; 3, 37931-43-4; 4, 37931-44-5; 5, 27023-72-9; 8, 37931-46-7; 10, 37931-47-8; 11, 37931-48-9.

Nitrogen Photochemistry. XI. Liquid Phase Irradiation of Primary Aliphatic Amines[1]

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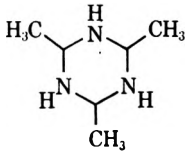
For some time, we have been studying the photochemistry of alkaloids and, as a direct consequence, it has been necessary to resolve some of the problems associated with amine photochemistry. The primary products from the liquid phase ultraviolet (uv) irradiation of several aliphatic amines have been isolated and identified to resolve existing questions on the probable (1) formation of imines and (2) existence of C–N bond cleavage in these photolyses.

Uncharacterized, unsaturated compounds are formed in equivalent amounts to hydrogen generated during the irradiation of hexane solutions of *n*-hexylamine and ethylmethylamine.[2] The irradiation of cyclohexylamine in cyclohexane produces exclusively cyclohexylcyclohexane in molar amounts.[3]

Pouyet reports that the irradiation of primary amines as 2-propylamine, *n*-butylamine, and isoamylamine in hexane provides hydrogen and 1-hexene in approximately equivalent amounts.[4,5] When the irradiation of primary amines is done in water, the corresponding alcohols and ammonia are formed.[4,6] Branching at the α carbon to the amino function enhances the reaction rate in both instances. Esr evidence has been given for presence of $CH_3CH{=}N\cdot$, $CH_3\dot{C}HNH_2$, and $CH_3CH_2\dot{N}H$ during the irradiation of ethylamine in an adamantane matrix while similar irradiations of *n*-propylamine and *n*-butylamine exhibit signals assigned to $RCH{=}N\cdot$ and $R\dot{C}HNH_2$.[7] At 77°K, Hadley and Volman have demonstrated that the irradiation of methylamine with 184.9-nm light gives esr signals for the $CH_3NH\cdot$ radical.[8]

In the vapor phase, irradiation of methylamine gives a trimer of methyl methylenimine, I, in addition to a polymer.[9-13] Mass spectrometric analysis of the gases has demonstrated the presence of a C_2H_5N compound which has been assigned the structure of ethylenimine.[10]



I

Experimental Section

Reagents.—The following lists the commercial sources of the chemicals used: Aldrich Chemical Co., cyclohexylamine, cyclopentylamine; Eastman, *n*-hexylamine, cyclohexylcyclohexane; and Chemical Samples Co., *n*-hexylcyclohexane, cyclopentylcyclopentane. Cyclohexane and cyclopentane were purified by known procedures.[14] *N*-1-(Hexylidene)hexylamine and *N*-cyclopentylidenecyclopentylamine were synthesized by the method of Campbell, *et al.*,[15] Dicyclopentylamine and *n*-hexylcyclohexylamine were prepared by reduction of the corresponding imines with excess 10% Pd/C in ethanol and vacuum distillation.

General Procedure for Products Accumulation Studies.—The irradiations were done in a quartz tube with a ground glass point using a 450-W medium-pressure Hanovia mercury arc lamp. Nitrogen gas free of oxygen was passed into the solution *via* a bubbler for 30 min prior to irradiation. The sample tube and the immersion well containing the lamp were placed in a 13.4 ± 0.1° water bath. Aluminum foil was placed around the upper part of the sample tube to avoid irradiating the vapors. The distance between the quartz tube and the edge of the immersion well was held constant at 3.5 cm. The reactions were monitored using a Beckman GC-5 equipped with flame ionization detectors, Disc integrator, and two 20 ft × 1/8 in. 5% KOH–20% Carbowax–Chromosorb W columns.[16] The cyclohexylamine study was done with 20 ft × 1/8 in. 18% Theed Chromosorb P columns. In order to restrict the number of products to a minimum, solvents with symmetrical molecules were employed.

General Procedure for Products Identification Studies.—The immersion well with lamp was surrounded by a Pyrex jacket containing *ca.* 1.5 g of sample in 300 ml of solvent. The solutions were irradiated for 4 hr with N_2 bubbling through and concentrated; the products were separated by an Aerograph A-700 glpc equipped with a 10 ft × 1/4 in. 5% KOH–20% Carbowax–Chromosorb W column. The product were identified by retention times and comparative nmr and ir spectra except for the air-oxidizable imine, *N*-cyclopentylidenecyclopentylamine. This imine was removed from its reaction solution by a 2 *N* HCl wash or hydrogenated to dicyclopentylamine with 10% Pd/C in ethanol. The latter compound was identified in the usual manner. Ammonia was trapped from the cyclohexylamine and *n*-hexylamine irradiation solutions by passing the effluent gas stream first through a NaCl–ice trap and subsequently through a Dry Ice trap. Ammonia was identified by its characteristic ir spectrum.[17]

Results

The products isolated and identified from the irradiations of cyclohexylamine, cyclopentylamine, and *n*-hexylamine are those represented in eq 1–3. The product accumulation data from these irradiations are illustrated in Tables I, II, and III.

Discussion

The four postulated cleavage patterns resulting from the irradiation of primary amines in the vapor phase are represented in eq 4a–d.[10] Pathway 4a is well ac-

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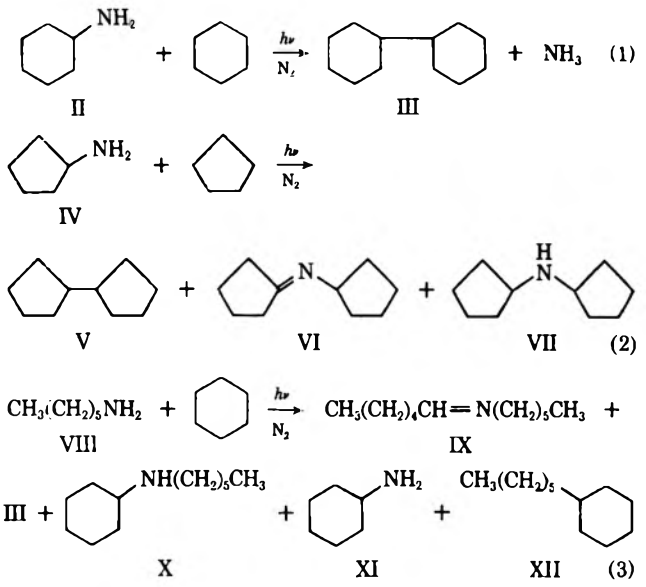


TABLE I

PHOTOCHEMISTRY OF CYCLOHEXYLAMINE IN CYCLOHEXANE

Time, min	II × 10^5 M	III × 10^5 M	ΔII × 10^5 M	III/ΔII
0	611			
10	590	18	21	0.85
20	573	39	38	1.03
40	554	75	57	1.31
60	480	132	121	1.09
120	438	182	173	1.05
180	295	193	316	0.61

TABLE II

PHOTOCHEMISTRY OF CYCLOPENTYLAMINE IN CYCLOPENTANE

Time, min	IV × 10^5 M	V × 10^5 M	VI × 10^5 M	VII × 10^5 M
0	570			
5	546	13	8	7
10	538	19	9	9
20	515	32	21	9
40	445	54	35	10
60	385	77	59	10
120	273	119	115	11

TABLE III

PHOTOCHEMISTRY OF *n*-HEXYLAMINE IN CYCLOHEXANE

Time, min	VIII × 10^5 M	IX × 10^5 M	III × 10^5 M	X × 10^5 M	XI × 10^5 M	XII × 10^5 M
0	611					
5	573	16	6	7	3	1
10	528	34	8		3	1
20	491	65	17	8	4	1
40	325	92	31		11	2
60	309	116	47	14	15	5
120	244	181	77	14	12	10

cepted; however, 4b is presently relegated to a minor role. There is indicative but not definitive evidence for 4c and 4d.

$$RR'CHNH_2 \xrightarrow{h\nu} RR'CHNH_2^* \begin{cases} \xrightarrow{a} RR'C\dot{N}H + H\cdot \\ \xrightarrow{b} RR'CH\cdot + \cdot NH_2 \\ \xrightarrow{c} RR'\dot{C}NH_2 + H\cdot \\ \xrightarrow{d} RR'C{=}NH + H_2 \end{cases} \quad (4)$$

If pathways 4a–d are functioning, the relative importance of each should be determined in part by the stability of the alkyl radical RR′ĊH. We now wish to report the results of testing this concept. The alkyl radicals of the amines selected have the following order of stability: $C_6H_{11} > C_5H_9 > C_6H_{13}$. The primary radical is less stable than the two secondary ones, and the bond hybridization accounts for the relative stability of the cyclohexyl and cyclopentyl radicals.[18] If the alkyl radical stability idea is correct, cyclohexylamine irradiation solutions should contain more products resulting from C–N cleavage than that of *n*-hexylamine with cyclopentylamine giving an intermediate amount.

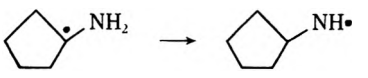
The C–N bond cleavage, 4b, is the dominant reaction resulting from the excited state of cyclohexylamine because the sole product in cyclohexane is cyclohexylcyclohexane. Further, the moles of cyclohexylcyclohexane equals the amount of amine decomposed within experimental error; *cf.* Table I. Although Booth and Norrish[2] were unsuccessful in finding ammonia during the irradiation of *n*-hexylamine in hexane, it has been found as a product in gas phase methylamine irradiations,[12] and we were successful in trapping it from the cyclohexylamine irradiation solution. Thus eq 4b, 5, and 6 adequately summarize the latter reaction.

$$\cdot NH_2 + C_6H_{12} \longrightarrow C_6H_{11}\cdot + NH_3 \quad (5)$$

$$2C_6H_{11}\cdot \longrightarrow C_{12}H_{22} \quad (6)$$

In contrast to the cyclohexylamine reaction, the irradiation of cyclopentylamine in cyclopentane produces a considerably different set of products; *cf.* reaction 2. Though cyclopentylcyclopentane is the major product, nitrogen-containing products as *N*-cyclopentylidenecyclopentylamine (VI) and dicyclopentylamine (VII) are also formed in good yields. The imine VI is not reduced in the reaction solution to the amine VII; however, the reverse reaction can and does occur. Consequently, dicyclopentylamine achieves a photostationary state in the reaction solution; *cf.* Table II. Although the irradiation of VII produces a high yield of VI, it is not the principal source of the imine because of the immediate and linear formation of VI during the irradiation of cyclopentylamine.

The appearance of dicyclopentylamine in the cyclopentylamine reaction solution implies that reaction 4a is functioning during the irradiation. It is unlikely that reaction 7 is occurring subsequent to reaction 4c as an alternative to 4a because 4c did not operate during the cyclohexylamine irradiation, and the rate of reaction 7 is expected to be slow since the C–H and N–H bond dissociation energies are nearly the same.[19]



(7)

The irradiation of *n*-hexylamine (VIII) in cyclohexane provides the imine, *N*-1-(hexylidene)-*n*-hexylamine (IX), as the major product, *i.e.*, 50% yield at all times measured; *cf.* reaction 3 and Table III. Both alkyl groups of the imine are derived from *n*-hexylamine in accordance with the well-accepted reaction 8.

$$CH_3(CH_2)_5NH_2 + CH_3(CH_2)CH{=}NH \longrightarrow IX \quad (8)$$

The remaining question of whether the imine, $CH_3(CH_2)_4CH{=}NH$, is formed by a two-step process

(18) For the relative reactivity of C_6H_{12} and C_5H_{10} towards Cl, *cf.*, C. Walling and P. S. Fredricks, *J. Amer. Chem. Soc.*, **84**, 3326 (1962).

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involving reaction 4a or a single-step one utilizing 4d can readily be decided by comparing the *n*-hexylamine and the cyclohexylamine reactions. Reaction 4d is expected to more readily occur during the irradiation of cyclohexylamine than with *n*-hexylamine whether one considers the relative bond dissociation energies of the α-CH bonds or the stability of the resulting imine double bonds. Yet imine formation does not occur with cyclohexylamine. Consequently, it appears the reaction of *n*-hexylamine is using reaction 4a.

It is now possible to conclude that N–H bond rupture is the dominant primary reaction of the excited state *n*-hexylamine whereas C–N bond rupture is most important for the excited state of cyclohexylamine. Though less clear, it appears that cyclopentylamine occupies an intermediate reactivity position as expected.

We have no evidence from this work to support the esr observation of Richerzhagen and Volman[7] on the presence of the imine radical >C=N· during the photolysis of primary alkylamines in an adamantane matrix. Since they have presented evidence that this species is generated from the excitation of another radical, we assume the precursor radical is not allowed to build up under the conditions of these experiments as it is in either a matrix or in cold solution.

All the amines of this study have absorption only at the far end of the near-uv range of the spectrum. The absorbance of the pure amines commonly reach 2 at about 240 nm with considerable tailing to about 300 nm when the spectra are obtained in a 1-cm cell. Therefore it is desirable to use quartz irradiation vessels with the full output of the mercury arc to effect these reactions.

Registry No.—Cyclohexylamine, 108-91-8; cyclopentylamine, 1003-03-8; *n*-hexylamine, 111-26-2.

Acknowledgments.—This investigation was supported in part by a Public Health Service grant (1 RO1 A108136) and a Public Health Service Research Career Development Award (1-K4-GM-9888) (V. I. S.).

Proton Magnetic Resonance Spectra of Aromatic *N*,*N*-Dimethylcarboxamides. Evidence for Hindered Rotation and Anisotropic Effects Caused by Additional Phenyl Rings[1]

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A previous publication from this laboratory[2] reported a large chemical shift difference (42 cps as compared to 10 cps for *N*,*N*-dimethylformamide) observed for the protons of the amide methyls in *N*,*N*-dimethyl-9-carboxamido-9,10-dimethylacridane. This seemingly abnormal chemical shift difference was explained on the basis of the preferred conformation of the amide function which places one of the methyls over the aromatic rings in the molecule. It was postulated that, owing to the diamagnetic anisotropic effect of the rings, the trans methyl experiences a long-range shielding effect, the methyl group cis to the carbonyl being unaffected. This then causes the net chemical shift difference to be large. As no report of the magnitude of such a shielding effect caused by additional phenyl rings has yet appeared, here we present a systematic study of the pmr spectra of aromatic *N*,*N*-dimethylcarboxamides containing up to three fused phenyl rings.

The results are summarized in Table I. The free energy of activation for rotation around the C–N bond ($\Delta G^{\ddagger}$) was calculated by the intensity ratio method.[3] It has been shown[4] that the $\Delta G^{\ddagger}$ values obtained by this method are quite reliable when the coalescence temperatures (T_c) are not too high. Unfortunately, the coalescence temperatures and hence $\Delta G^{\ddagger}$ for the anthracene (**5**) and acridine (**6**) amides could not be obtained, since these were much higher than the upper temperature limit for the solvent employed ($CDCl_3$). Use of a high-boiling solvent such as CBr_4 caused extensive decomposition before the coalescence temperatures were reached.

The pmr spectra of substituted *N*,*N*-dimethylbenzamides have been studied by Jackman, *et al.*[5] It has been shown that electron-donating substituents decrease $\Delta G^{\ddagger}$ while electron-withdrawing substituents increase it. As a nitrogen atom in an aromatic nucleus is known to be a strong electron withdrawer from the para position, it is expected to cause an increase in $\Delta G^{\ddagger}$. The data in Table I indicate that this expectation has been borne out. The ring-to-carbonyl group conjugation present in *N*,*N*-dimethylbenzamide is known to be responsible for its low C–N rotational barrier[5] (for example, $\Delta G^{\ddagger}$ for the benzamide[5] is 15.5 kcal mol^{-1} while for the formamide[3] it is 21 kcal mol^{-1}). The observed increase in T_c and $\Delta G^{\ddagger}$ with the increase in the number of phenyl rings (Table I) shows that the additional rings cause a decrease in this conjugation. The most likely explanation of this phenomenon probably lies in the steric interactions between the peri hydrogens of the additional rings and the methyl groups of the amide function. The resulting change in the conformation about the ring-to-carbonyl group bond causes an increase in the dihedral angle and hence reduction in the conjugation. This explanation is supported by the large $\Delta G^{\ddagger}$ (22.5 kcal mol^{-1}) observed for 2,4,6-trimethyl-*N*,*N*-dimethylbenzamide.[6] Steric factors are clearly seen to be predominant in this case.

In monosubstituted *N*,*N*-dimethylbenzamides, the values for $\Delta\delta$ increase with $\Delta G^{\ddagger}$ in a somewhat linear manner.[5] This is probably due to the increased rigidity with which the amide methyls are held over the phenyl ring. However, in the case of the amides in the present study, the increase in $\Delta\delta$ is too large to be accounted for by this effect alone. For example, $\Delta G^{\ddagger}$ for *p*-nitro-*N*,*N*-dimethylbenzamide[5] is 16.4 kcal mol^{-1}, compa-

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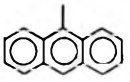
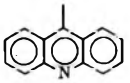
TABLE I

PMR DATA FOR AMIDES RC(=O)—NCHδ_2 (0.5 *M* SOLUTIONS IN $CDCl_3$)

No.	R	Mp, °C	Chemical shifts of the methyl protons[a] δ_1	δ_2	$\frac{\delta_1 + \delta_2}{2}$	$\Delta\delta$ ($\delta_2 - \delta_1$)	T_c, °C	$\Delta G^{\ddagger}$, 298.2 kcal/mol	Shifts[d] induced by —Eu(DPM)$_3$, cps— Downfield CH_3	Upfield CH_3
1[b]		42	2.955	3.085	3.02	0.13	30	15.5	138	88
2		55	2.89	3.01	2.95	0.12	46	16.0	90	62
3		59	2.67	3.15	2.91	0.48	66	16.6	127	80
4		37	2.67	3.15	2.91	0.48	86	17.2	108	73
5		139	2.55	3.26	2.91	0.71	>95	*c*	99	65
6		172	2.69	3.40	3.05	0.71	>95	*c*	98	63

[a] From TMS as internal standard. [b] Data from ref 4 and 5. [c] Not available; see text. [d] Eu(DPM)$_3$/amide ratio = 0.3; 0.3 *M* amide in CCl_4.

rable to that for the naphthalene amide in the present study (16.6 kcal mol^{-1}). Yet the former amide exhibits $\Delta\delta$ of 0.16 ppm, far lower than that for the latter amide, 0.42 ppm. This increase in the values of $\Delta\delta$ with an increase in the number of phenyl rings probably reflects the anisotropic effect exerted by the additional rings, resulting in considerable long-range shielding of one of the methyls. A progressive decrease in δ_1 (Table I) is clearly seen. A more curious observation is the increase in δ_2, indicating a stepwise deshielding of the second methyl group. A similar observation has been made in the spectra of benzamides.[5] A reasonable explanation of this phenomenon may be found in the conformation of the amide function with respect to the aromatic system which places the second methyl group in the deshielding zone of the ring currents exerted by the π-electron cloud. In this connection, the pmr spectrum of 2,4,6-tri-*tert*-butyl-*N*,*N*-dimethylbenzamide is most noteworthy.[7] The methyl protons of the amide function of this compound resonate at δ 2.64 and 2.96. This indicates that one of the methyls is being largely shielded while the other methyl is unaffected. Owing to the extreme crowding in this case, the conformation of the amide function may be quite different, which places the second methyl out of the deshielding zone of the aromatic ring.

If the above arguments are valid, then the upfield methyl must be trans and the downfield methyl must be cis to the carbonyl group. It was necessary to obtain experimental evidence in support of this statement, as in the case of simple aliphatic amides the assignments made have been the opposite.[8] Recently, Lewin has demonstrated the use of the lanthanide chemical shift reagent, Eu(DPM)$_3$, to make such structural assignments to the protons of some tertiary amides.[9] It was found that the complexation of the metal by the lone pair of the carbonyl oxygen causes the resonance associated with the cis group to suffer a larger induced shift than the resonance of the anti group. The pmr spectra of all the amides in the present study were examined after a gradual addition of Eu(DPM)$_3$ in carbon tetrachloride solution. Up to molar ratios of approximately 0.8 [Eu(DPM)$_3$/substrate] the relationship between the induced downfield shifts and the moles of the reagent was essentially linear. The values obtained for the induced shifts of the two methyl signals at reagent/substrate molar ratio of 0.3 are presented in Table I. The data show that in all cases the downfield signal suffered a larger induced shift than the upfield signal. In addition, the signal exhibiting greater shift sensitivity also broadened to a larger extent. These results indicate that the upfield signal can be assigned to the trans methyl and the downfield to the cis methyl, thus proving the assignments made above to be correct.

Experimental Section

All the amides were prepared from the commercially available carboxylic acids by the following reaction sequence.

$$\text{ArCOOH} \xrightarrow{\text{SOCl}_2} \text{ArCOCl} \xrightarrow{\text{NH(CH}_3)_2} \text{ArCON(CH}_3)_2$$

The general procedure was similar to that employed by Meltzer, *et al.*, for the synthesis of *N*,*N*-dimethylisonicotinamide.[10] Amides **1**, **3**, and **5** were prepared in 80–90% yield while the yields of amides **2**, **4**, and **6** were considerably lower,

(7) H. A. Staab and D. Lauer, *Chem. Ber.*, **101**, 864 (1968).
(8) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960).
(9) A. H. Lewin, *Tetrahedron Lett.*, 3583 (1971).
(10) R. I. Meltzer, A. D. Lewis, and J. A. King, *J. Amer. Chem. Soc.*, **77**, 4062 (1955).

40–50%. Their ir, pmr, mass spectra, and elemental analysis (within 0.3% for C, H, and N) provided sufficient evidence for the correct structure and purity. The 60-MHz spectra of 0.5 *M* solutions in $CDCl_3$ were studied in degassed sealed tubes between the temperatures of 40 and 95°. The spectra were obtained on a Varian A-60A spectrometer. Temperatures were calibrated with ethylene glycol according to established procedures.[2]

Registry No.—**2**, 1903-64-6; **3**, 3815-24-5; **4**, 30721-92-7; **5**, 38308-87-1; **6**, 38308-88-2.

The Synthesis of 3,5-Dicarbethoxy-1,2,4-cyclopentanetrione. A Correction

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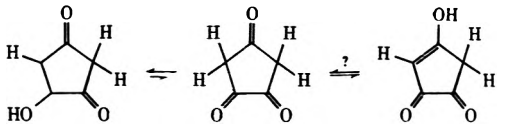
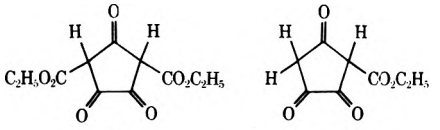
In connection with other work, we required 1,2,4-cyclopentanetrione (**1**), a material of some theoretical interest.[1] A convenient synthesis of **1** from 3,5-di-



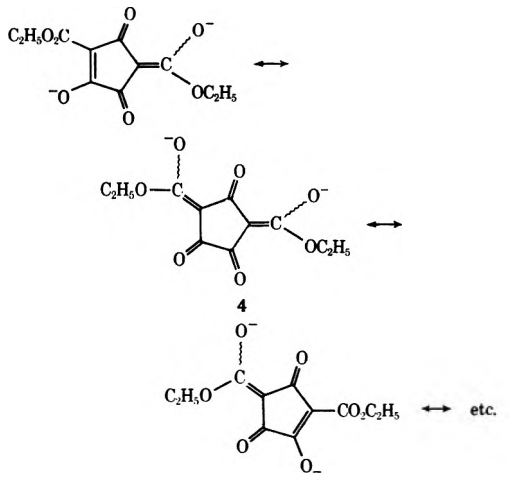
1

carbethoxy-1,2,4-cyclopentanetrione (**2**) has been reported.[2] In attempting to prepare **2**,[2-4] however, we encountered some experimental difficulty. In this process we have isolated and characterized 3,5-dicarbethoxy-1,2,4-cyclopentanetrione (**2**), an interesting and relatively unstable material with properties that differ considerably from those previously reported.[2-4] Furthermore, we would like to suggest that the properties previously reported for the title compound, **2**,[2-4] appear to best fit those for 3-carbethoxy-1,2,4-cyclopentanetrione (**3**), a hydrolysis product of **2**.



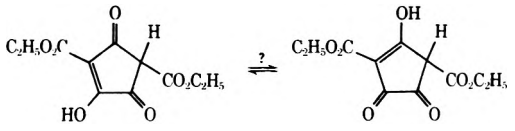
2 **3**

Treatment of diethyl acetonedicarboxylate, ethyl oxalate, and sodium or potassium ethoxide as reported[2,4] afforded a yellow salt which, following hydrolysis, could be converted to a viscous material which slowly crystallized. Trituration with a small amount of anhydrous ether gave **2** as a crude yellow solid. Recrystallization from anhydrous ether at 0° gave pure **2**, mp 107–109° dec. The nmr spectrum contained absorptions consistent with two nonequivalent ethoxy groups and a single methine hydrogen. The mass spectrum contained a parent peak at *m/e* 256 (calcd, 256). A neutralization equivalent of 127 (calcd, 128) was obtained by potentiometric titration. Two end points were clearly observable, with pK_a values of 2.1 and 5, estimated from the titration curve. In view of the similar enolic behavior of acylcyclopentanetriones[1c,5a] and related substances,[5b] the structure of this bis sodium or potassium salt, **4**, appears to be best represented as the following resonance hybrid.



4

The nmr spectrum of **4** in D_2O consisted of a single ethoxy resonance. Acidification of **4** regenerated the nmr spectrum of **2**, which appears to exist mainly in the diketone form **5** both in deuteriochloroform and in the solid phase (see Experimental Section).



5

In ethyl acetate, **2** readily dissolved and, upon standing, the solution darkened and a crystalline solid precipitated out, mp 145–147°. This new material, compound **3**, appears to be the material previously identified as the title compound.[2-4,6] The nmr and infrared spectra of this substance (**3**), which was isolated earlier by Wislicenus and Schöllkopf,[7] differs considerably from those of **2**. The nmr spectrum in acetone-d_6 consisted of a triplet and a quartet, characteristic of a single ethoxy group, and a singlet methine resonance which integrated as two protons, consistent with the enol form, **6**. In wet dimethyl-d_6 sulfoxide, two ethoxy resonances and a vinyl hydrogen were observed, suggesting an equilibrium between **6** and **7** or possibly **8** in this solvent. Compound **3** titrated (to a pH of 7) as a monoprotic acid, pK_a = 2.1, neut equiv 186 (calcd, 184). The mass spectrum of this material

(1) (a) C. F. Sheley and H. Schechter, *J. Org. Chem.*, **35**, 2367 (1970); (b) C. H. Depuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, **79**, 3923 (1957); C. H. DePuy and E. F. Zaweski, *ibid.*, **81**, 4920 (1959); C. H. Depuy and P. R. Wells, *ibid.*, **82**, 2909 (1960); (c) K. Hiraga, *Chem. Pharm. Bull.*, **13**, 1300 (1965).

(2) J. H. Boothe, R. G. Wilkinson, S. Kushner, and J. H. Williams, *J. Amer. Chem. Soc.*, **75**, 1732 (1953).

(3) v. P. Ruggli and K. Doebel, *Helv. Chim. Acta*, **29**, 600 (1946).

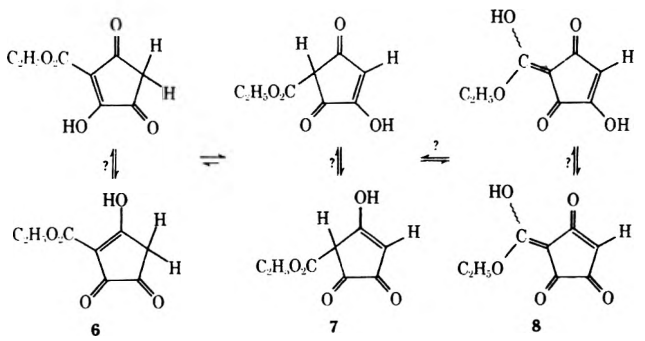
(4) E. Rimini, *Gazz. Chim. Ital.*, **26**, 374 (1896).

(5) (a) J. A. Elvidge and R. Stevens, *J. Chem. Soc.*, 2251 (1965); (b) S. Forsen and M. Nilsson in "Chemistry of the Carbonyl Group," Vol. 2, J. Zabicky, Ed., Interscience, New York, N. Y., 1970, p 157.

(6) We would like to thank Dr. R. G. Wilkinson[2] for kindly providing an infrared spectrum (solid phase) which confirmed the identity of the two materials.

(7) W. Wislicenus and K. Schollkopf, *J. Prakt. Chem.*, **95**, 269 (1917).

contained a parent peak at m/e 184 (calcd, 184). Upon standing at room temperature **3** slowly decomposes.



6 **7** **8**

When either **2** or **3** is refluxed in concentrated hydrochloric acid, **1** is obtained in good yield (70%), indicating that both **2** and **3** have the same gross structural features. The low yield in hydrolysis of **4** reported by earlier workers[3] is probably the result of **2** converting to **3**, which is accompanied by some decomposition. However, since **2** can easily be isolated in crude form and the hydrolysis to **1** proceeds in good yield, this represents an efficient synthesis of **1** (overall yield ~30%). Compound **3** (or **1**) could not be isolated from room-temperature hydrolysis of **2** in water.

Experimental Section

Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Microanalyses were determined by Galbraith Laboratories. Nmr spectra were recorded on a Varian T-60 spectrometer. Infrared spectra were measured using a Perkin-Elmer Model 137 spectrophotometer. Mass spectra were obtained on an Associated Electrical Industries MS12 instrument.

3,5-Dicarbethoxy-1,2,4-cyclopentanetrione (2).—Compound **2** was synthesized both according to the procedures of Rimini[4,8] and Boothe, *et al.*[2] Thus, potassium (2 g) was dissolved in absolute ethanol (7 g) in ether (50 ml), and ethyl oxalate (3.7 g) was added to the ice-cold solution. After a few minutes, diethyl acetonedicarboxylate[9] (5.2 g) was added dropwise and the mixture was stirred at room temperature for 24 hr. The reaction mixture was filtered and a yellow salt was isolated (9 g). A portion of this salt (2.3 g) was hydrolyzed with dilute sulfuric acid and immediately extracted with ethyl acetate. After drying ($MgSO_4$) and removal of the ethyl acetate under vacuum, the residue (1.33 g) slowly crystallized.[3] The nmr spectrum of this material in $CDCl_3$ indicated the presence of **2**, some diethyl acetonedicarboxylate, and a small but variable amount of **3** (*vide infra*). Washing the residue with a small amount of anhydrous ether afforded crude **2** (0.73 g), mp 85–90° dec. Additional amounts of **2** could be isolated by refrigerating the ether washings.

Hydrolysis of the yellow salt according to the method described by Ruggli and Doebel[3] gave similar results. Thus the potassium salt (2.6 g) in ether was ground up using a mortar and pestle and a few drops of concentrated hydrochloric acid were added. The ether layer was filtered and this process was repeated until the ether layer was colorless and the potassium salt was completely converted to potassium chloride. Evaporation of the ether, as before, afforded a residue similar in composition as previously reported.

Alternatively, sodium ethoxide [from sodium (1.6 g)], ethyl oxalate (5 cc), diethyl acetonedicarboxylate in benzene (200 cc), and anhydrous ether (50 cc) were refluxed under nitrogen for 1.75 hr.[2] The cooled solution was hydrolyzed with dilute sulfuric acid, the aqueous layer was extracted with ethyl acetate, and the organic fraction was distilled under reduced pressure. After standing under vacuum, the residue (6.78 g) solidified. The composition of this residue based on its nmr spectrum was basically the same as isolated above. Washing with anhydrous ether afforded crude **2** (3.22 g), mp 85–90° dec. An additional amount of **2** was isolated from the ether wash (0.5 g).

Compound **2** could be purified by recrystallizing from ether at 0°: mp 107–109°; nmr ($CDCl_3$, TMS) τ 8.24 (t, J = 7 Hz), 8.59 (t, J = 7 Hz, total of 6 H), 6.05 (s), 5.79 (q, J = 7 Hz), 5.56 (q, J = 7 Hz, total of 5.1 H), 0.23 (broad s, 0.9 H); ν_{max} (Nujol) 3105, 1770, 1740, 1710, 1680, and 1610 cm^{-1}; m/e 256 (calcd, 256); neut equiv 127 (calcd, 128, two end points observed potentiometrically). A yellow disodium salt was isolated after evaporation of the water: ν_{max} (Nujol) 1630, 1540 cm^{-1}; nmr (D_2O) τ 1.23 (t, 3 H, J = 7 Hz), 5.92 (q, 2 H, J = 7 Hz). Acidification of this salt regenerated **2** as identified by its nmr and infrared spectrum. Also present was a small amount of **3** (~10%).

The two preparations[2,4] gave, by the procedures outlined above, the same material, **2**, as determined by nmr, infrared, and melting point behavior.

Anal. Calcd for $C_{11}H_{12}O_7$: C, 51.56; H, 4.72. Found: C, 51.47; H, 4.68.

3-Carbethoxy-1,2,4-cyclopentanetrione (3).—Compound **2** (0.428 g, crude) was dissolved in ethyl acetate, or in an ether–ethyl acetate solution, and then allowed to stand. The solution gradually darkened, and after some 24 hr or more, crystals were deposited (200 mg). This material was recrystallized from ethyl acetate and sublimed: mp 145–147° dec, 145–158° ($CHCl_3$) (lit. mp 159–162°,[2,11] 140–156° dec,[4] 140° dec,[3] 145–150° dec[8]); pyridine salt mp 95–97° (lit.[8] mp 98°); nmr (acetone-d_6, TMS) τ 8.67 (t, J = 7 Hz, 3 H), 6.95 (s, 1.9 H), 5.67 (q, J = 7 Hz, 1.9 H), 1.45 (broad s, 1.07 H); nmr (wet DMSO-d_6, TMS) τ 8.77 (t), 7.0 (s), 5.85 (q), 8.84 (t), 5.94 (q), 3.63 (s). Based on the area ratio of the methine hydrogen (τ 7.0, 8) to the vinyl hydrogen (τ 3.63, 1), approximately 75% of the material is in the form of **2** in this solvent: ν_{max} (Nujol) 3210, 1760, 1710, 1670, and 1610 cm^{-1}; m/e 184 (calcd, 184). This material turned yellow and appeared to decompose upon standing at room temperature. It may also be hydroscopic. Attempts to obtain a satisfactory elemental analysis were not entirely successful. We obtained analysis for a hydrate of **3**, similar to those reported in the literature (for **2**)[2-4] when recrystallized from ethyl acetate.

Anal. Calcd for $C_8H_8O_5$: C, 52.17; H, 4.38. Calcd for $C_8H_8O_5 \cdot {}^1/_5H_2O$: C, 51.19; H, 4.47. Found: C, 51.24; H, 4.26.

The following analysis was obtained when a sample was recrystallized from chloroform and analyzed immediately:[10] C, 52.11, 51.79; H, 4.78, 4.55 (duplicate).

Conversion of 2 to 1,2,4-Cyclopentanetrione (1).[2]—Compound **2** (1.0 g, 3.9 mmol) was refluxed for 90 min in concentrated hydrochloric acid (80 ml). After the solution was concentrated to dryness, a dark brown material (0.38 g) was isolated. Compound **1** was separated by this material by sublimation (0.3 g, 70%) as reported: mp 172–174° dec (lit.[2] mp 172–173° dec); m/e 112 (calcd, 112) with major fragmentation at P − 42 (loss of C_2H_2O), P − 54 (loss of C_3H_2O), P − 57 (C_2HO_2), and a base peak at m/e 42 (C_2H_2O); nmr (TMS–DMSO-d_6) τ 7.09 (s, 2 H), 3.82 (s, 0.97 H), 1.17 (broad s, 1.06 H). The conversion of **2** (isolated in crude form) to **1** in 70% yield represents a very convenient synthesis of **1**.

Conversion of 3-Carbethoxy-1,2,4-cyclopentanetrione (3) to 1,2,4-Cyclopentanetrione (1).—Compound **3** (0.15 g) was dissolved in concentrated hydrochloric acid as reported above. A material identical with 1-hydroxy-1-cyclopentene-3,5-dione (**1**) isolated above was isolated in 80% yield.

Registry No.—**1**, 15849-14-6; **2**, 37951-06-7; **2** (2Na), 37950-90-6; **3**, 37950-91-7.

Acknowledgment.—I would like to thank the Research Corporation for a Cottrell Grant and the University of Missouri, St. Louis, for a summer fellowship.

(8) See also W. Wislicenus and F. Melms, *Justus Liebigs Ann. Chem.*, **436**, 101 (1924).

(9) R. Adams and H. Chiles, "Organic Syntheses," Collect. Vol. I, A. H. Blatt, Ed., Wiley, New York, N. Y., 1964, p 237.

(10) We would like to thank Dr. Craig Warren and The Monsanto Chemical Co., St. Louis, Mo., for the analysis.

Improved Synthetic Routes to Prostaglandins Utilizing Sulfide-Mediated Oxidation of Primary and Secondary Alcohols

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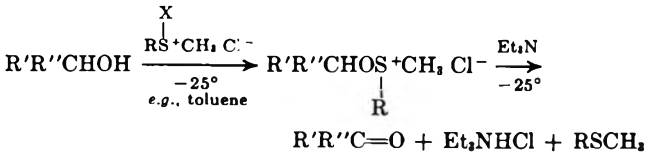
We have recently reported a new and highly effective method for the synthesis of aldehydes and ketones by oxidation of primary and secondary alcohols which utilizes complexes of a sulfide such as methyl sulfide with chlorine or *N*-chlorosuccinimide.[1] The general process may be outlined as

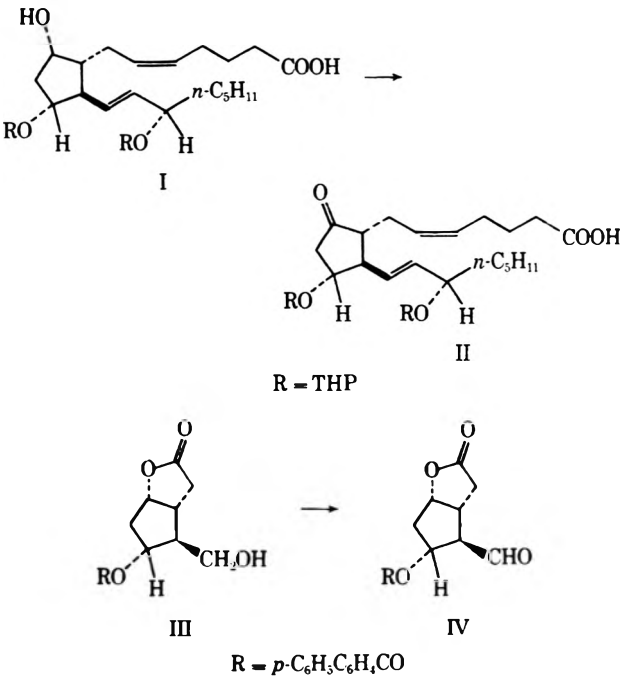


X = Cl or *N*-succinimido

We have now ascertained that this method of oxidation is highly advantageous in the generation of two key intermediates for the synthesis of prostaglandins, the keto acid II (prostaglandin E_2 11,15-bistetrahydropyranyl derivative), and the lactone ester aldehyde IV. In each of these cases the lability of the synthetic intermediates imposes severe restrictions on the reagents and reaction conditions which may be utilized.

The oxidation of the hydroxy acid I to the keto acid II has previously been accomplished using the Jones (CrO_3) reagent[2] at −20° in yields of *ca.* 70%.[3,4] The conditions of the reaction are quite critical, since there are several acid-sensitive units in II (*e.g.*, β-ketal system, tetrahydropyranyl ether system) which become involved to a substantial degree if reaction temperature and time are not carefully controlled. All previously known nonacidic oxidizing agents (*e.g.*, Collins reagent[5]) which were tried originally[3] were found to fail. In contrast, the use of the newly developed methyl sulfide–*N*-chlorosuccinimide reagent[1] under simple, standard conditions allowed the oxidation of I to II in >90% yield. Furthermore, the process is extremely convenient and clearly suitable for use on a multimolar scale.

In order to avoid reaction of the carboxyl function of I with an equivalent of the oxidizing agent, the isopropyldimethylsilyl ester[6] of I was prepared for use *in situ* from equivalent amounts of I, triethylamine, and isopropyldimethylsilyl chloride in toluene. The solution of this ester of I in toluene was then subjected to oxidation using the *N*-chlorosuccinimide–methyl sulfide to afford the silyl ester of II as a chromatographically homogeneous oil, which upon hydrolysis under mildly acidic conditions (pH ~4.5) furnished



R = THP

the 11,15-bistetrahydropyranyl derivative of prostaglandin E_2.

The oxidation of the hydroxy lactone III using the methyl sulfide–*N*-chlorosuccinimide reagent in toluene–methylene chloride solution produced the aldehyde IV contaminated by variable amounts of the starting alcohol III even when an excess of oxidizing agent was employed, perhaps because of insolubility of the sulfoxonium intermediate. Much better results were obtained, however, using as reagent the 1:1 complex of chlorine with methyl phenyl sulfide in carbon tetrachloride–methylene chloride mixture. Using essentially the standard procedure,[1] the aldehyde IV[4] could be isolated simply in crystalline form in >90% yield. The original[3,4] preparation of IV from III, which involved the use of Collins reagent,[5] afforded IV in 90% yield, but suffered from the disadvantage of being difficult to carry out on a multimolar or even molar scale.[7]

Experimental Section

Oxidation of I to II.—To a stirred solution of 56 mg (0.11 mmol) of the 11,15-bistetrahydropyranyl derivative of prostaglandin $F_{2\alpha}$ (I) in 0.5 ml of dry toluene and 0.11 ml of a 1.0 *M* solution of isopropyldimethylsilyl chloride in toluene was added dropwise at 0° 0.11 ml of a 1.0 *M* solution of triethylamine in toluene *via* syringe under an argon atmosphere. The reaction mixture was used immediately for oxidation.

To a solution of 64 mg (0.50 mmol) of *N*-chlorosuccinimide in 2 ml of toluene was added at 0° 45 μl (0.6 mmol) of methyl sulfide *via* microsyringe under an argon atmosphere. The stirred mixture was cooled to −25° (carbon tetrachloride–Dry Ice), and the

(1) E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, **94**, 7586 (1972).

(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2555 (1953).

(3) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).

(4) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971).

(5) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(6) See E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 7319 (1971). The trimethylsilyl ester was found to be too labile for use in this case, since some silyl transfer to the alcohol function occurs.

(7) The oxidation of III and IV has also been carried out in very good yield by Dr. N. M. Weinshenker and coworkers at the Alza Co. (personal communication) using Moffatt's method [K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965); **88**, 1762 (1966)] with *N,N'*-diethylcarbodimide–dimethyl sulfoxide.

above-described solution of the silyl ester of I in toluene was added dropwise by syringe. Stirring was continued for 2 hr at −25°, and then a solution of 100 mg (0.99 mmol) of triethylamine in 0.2 ml of pentane was added dropwise. The cooling bath was removed, and after 5 min 5 ml of ether was added. The organic layer was washed with 2 ml of ice-cold 1% aqueous hydrochloric acid and twice with 3 ml of cold water. Removal of dried (magnesium sulfate) solvents under vacuum produced 59 mg (92%) of the silyl ester of II as a colorless oil (homogeneous by tlc; R_f 0.40, silica gel–methylene chloride): ir max (neat) 2970 (m), 1745 (s), 1710 (s), and 1150 cm^{-1} (br s).

To a solution of 246 mg (3.00 mmol) of sodium acetate in 3 ml of acetone and 1 ml of water was added 180 mg (3.00 mmol) of acetic acid to give a standard solution of pH 4.5. To a solution of 59 mg of above-described silyl ester of II in 1 ml of acetone and 0.3 ml of water was added at 0° 0.4 ml of sodium acetate–acetic acid standard solution, and the mixture was stirred for 45 min. After warming to 25°, stirring was continued for 30 min, at which time tlc analysis indicated the absence of silyl ester. The solution was poured into 2 ml of ice–water and extracted with three 5-ml portions of ether. Removal of dried (magnesium sulfate) solvents under reduced pressure produced 48 mg (91% yield based on I) of the 11,15-bistetrahydropyranyl ether of prostaglandin E_2, chromatographically identical with authentic material. The infrared and nmr spectra were also identical with those of an authentic sample which had been prepared previously in this laboratory.[3,4]

Oxidation of III to IV.—To a solution of 21.3 mg (0.30 mmol) of chlorine in 1.5 ml of carbon tetrachloride was added at −10° a solution of 37.2 mg (0.30 mmol) of thioanisole in 0.5 ml of methylene chloride under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to −25°, and a solution of 56 mg (0.16 mmol) of the lactone alcohol III in 1 ml of methylene chloride was added dropwise. Stirring was continued for 90 min at −25°, and then a solution of 60.6 mg (0.60 mmol) of triethylamine in 0.5 ml of methylene chloride was added dropwise. The cooling bath was removed, and after 5 min 5 ml of ether was added. The organic layer was washed with 1 ml of ice-cold 1% aqueous hydrochloric acid. Removal of dried (magnesium sulfate) solvents produced a white solid which was washed twice with 3 ml of cold pentane to give 52 mg (93%) of IV as colorless crystals (R_f 0.25, silica gel–chloroform): nmr ($CDCl_3$) δ 2.0–3.6 (m, 6 H), 5.20 (br t, J = 5 cps, 1 H), 5.6–5.8 (m, 1 H), 7.3–8.4 (m, 9 H, aromatic protons), 9.89 (s, 1 H, aldehyde); ir ($CHCl_3$) 2950 (m), 2850 (m), 1775 (s), 1725 (s), 1720 (s), 1610 (m), 1270 (s), 1100 (br), 910 cm^{-1} (s). The chromatographic and spectral data agreed with those obtained for IV which had been prepared by Collins oxidation. The product IV could be used for the synthesis of prostaglandins as previously described[3,4] without further purification.

Registry No.—I, 37786-09-7; II, 38123-52-3; III, 32233-39-9; IV, 32233-41-3.

Acknowledgment.—We are indebted to the National Institutes of Health and the U. S. Agency for International Development for financial assistance.

The Synthesis of 9-Ketotridecanolide and Related 13- and 16-Membered Ketolactones[1]

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We have shown that keto lactones, including 7-ketoundecanolide, the parent system present in methymycin, can be synthesized by the oxidation of bicyclic enol ethers derived from the acid-catalyzed closure of 2-(ω-hydroxyalkyl)cycloalkanones.[2-4] Previously, six- to eight-membered ring ketones have been utilized. We now demonstrate the further utility of this method in the synthesis of 8-ketododecanolide (**1**), 9-ketotridecanolide (**2**), and 12-ketopentadecanolide (**3**) from cyclooctanone, cyclononanone, and cyclododecanone, respectively, in overall yields of 46, 35, and 19%.

The C-alkylations of carbethoxycyclooctanone (**4**) and cyclononanone (**5**) *via* their sodium enolates with 1-bromo-4-acetaoxybutane (**6**) proceed as previously described for smaller ring ketones[2] to lead to 2-(4′-hydroxybutyl)cyclooctanone (**7**) and the corresponding cyclononanone **8**. Hemiketal formation and dehydration of **7** proceeds readily upon acid catalysis or slow distillation *in vacuo*. The corresponding closure of **8** is more difficult and is best performed by distillation from potassium pyrosulfate.[3]

The oxidation of the resultant bicyclic enol ethers **9** and **10** with excess *m*-chloroperbenzoic acid (MCPBA)[2-4] must be done for a short time period in order to keep Bacyer–Villiger oxidation of the product ketolactone to dilactones as a minor side reaction. The utilization of other oxidation procedures (which avoid dilactone formation but are not as good in yield) such as reaction with *tert*-butylhydroperoxide and molybdenum hexacarbonyl[4b] or lead tetraacetate oxidation of the corresponding glycol[5] was only briefly investigated for these cases.

It is noteworthy that **2** represents the parent system of the erythromycin macrolides.[6]

Finally, **3** is readily synthesized from 2-(3′-hydroxypropyl)cyclododecanone (**12**), which is formed from the pyrrolidine enamine of cyclododecanone (**11**) upon reaction with ethyl acrylate, followed by lithium aluminum hydride reduction.[3,7]

Experimental Section[8]

8-Ketododecanolide (1).—Treatment of the sodium enolate of 2-carbethoxycyclooctanone[9] (from 4 and sodium hydride in toluene at reflux for 30 min) with 1-bromo-4-acetoxybutane (**6**, 1.1 equiv) for 2 days at reflux gave crude 2-carbethoxy-2-(4′-acetoxybutyl)cyclooctanone, which was hydrolyzed with potassium hydroxide in aqueous ethanol at reflux for 48 hr to give 2-(4′-hydroxybutyl)cyclooctanone (**7**, 62% yield): bp 127–129°

(1) This investigation was supported by Public Health Service Research Grant AI 07455 from the National Institute of Allergy and Infectious Diseases and by the Eli Lilly Co. This is part 8 of the series, Medium Ring Compounds.

(2) I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, *J. Org. Chem.*, **37**, 581 (1972).

(3) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *ibid.*, **33**, 2013 (1968).

(4) (a) I. J. Borowitz and R. Rapp, *ibid.*, **34**, 1370 (1969); (b) I. J. Borowitz and R. Rapp, *Chem. Commun.*, 1202 (1969).

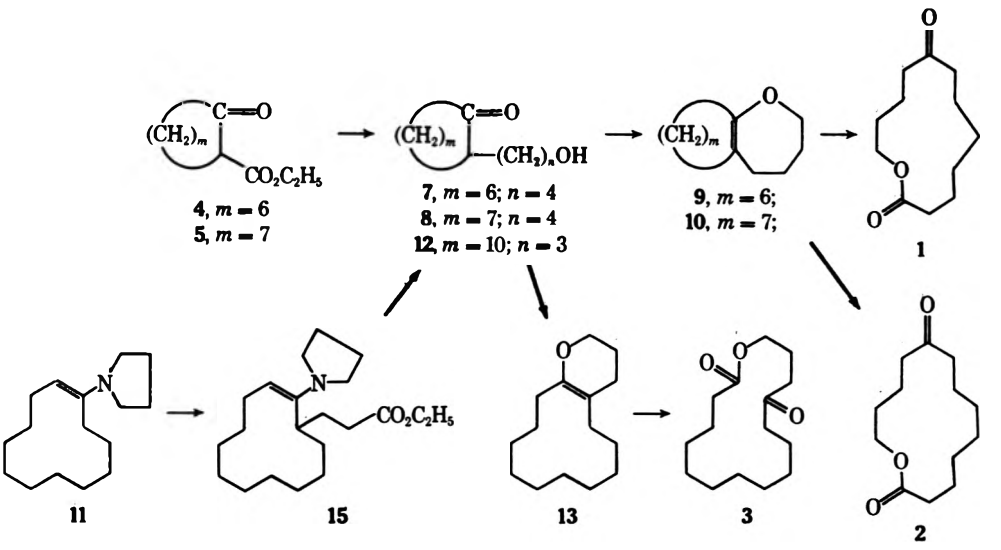
(5) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

(6) M. Berry, *Quart. Rev. Chem. Soc.*, **17**, 343 (1963).

(7) (a) G. Stork and S. Etheredge, unpublished; (b) S. Etheredge, Ph.D. Thesis, Columbia University, 1965; *Diss. Abstr.*, **26**, 4232 (1966).

(8) Infrared spectra were recorded on Perkin-Elmer 257 and Beckman IR-8 spectrophotometers. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Melting points were taken on Mel-Temp and Thomas-Hoover apparatus and are corrected while boiling points are uncorrected. Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical College, N. Y., and Columbia University. Solvents were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions involving carbanions were conducted under prepurified nitrogen. All vpc columns employed Chromosorb W and were 5 or 10 ft × 0.25 in.

(9) A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Syn.*, **47**, 20 (1967).



(0.55 mm); nmr (CCl_4) τ 8.55 (m, 16), 7.70 (m, 3, α-H), 6.54 (t, 2, CH_2O), 6.02 (s, 1, OH).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.40; H, 10.92.

Slow distillation of crude **7** *in vacuo* gave 2-oxabicyclo[5.6.0]-tridec-1(7)-ene (**9**, 58% from **4**): bp 70–75° (0.15 mm); ir (film) 1660 cm^{-1} (C=CO–), no OH; nmr (CCl_4) τ 6.1 (t, 2, CH_2O), 7.88 (m, 6, allylic H), and 8.2–8.5 (m, 12).

Addition of **9** to 85% pure MCPBA (2.2 equiv) in CH_2Cl_2 for 5 min, followed by reaction for 10 min at 25° and work-up,[3,5] gave crude **1** (80%, 95% purity by vpc at 210° on 10% SE-30). Repeated molecular distillation at 90° (0.1 mm) gave **1** as an oil: single peak by vpc as above; nmr ($CDCl_3$) τ 6.0 (t, 2, CH_2O), 7.7 (m, 6, α-CH), 8.4–8.6 (m, 12).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 67.89; H, 9.50. Found: C, 67.66; H, 9.56.

Oxidation of **9** (1.0 g, 0.0056 mol) in benzene (50 ml) containing $Mo(CO)_6$ (0.003 g) with 60% *tert*-butyl hydroperoxide (1.9 g, 0.012 mol)[4b] at reflux for 48 hr gave a mixture (by vpc) which was chromatographed on silica to give **1** (90% purity, 50% yield).

9-Ketotridecanolide (2).—Pyrrolidinocycloheptene (**14**) was consistently formed in *ca.* 68% yield from cycloheptanone and pyrrolidine by the use of benzene *and hexane* (4:1) as the azeotropic solvent. Other procedures gave generally lower yields, as previously noted.[3] Cyclononanone (from **14** in 37% overall yield[10]) was converted to carbethoxycyclononanone (**5**, 82% mixture of keto and enol forms): bp 85–100° (0.1 mm); nmr (CCl_4) τ −2.7 (3, 0.3 H, enolic OH), 5.8 (2 q, 2, OCH_2CH_3), 6.5 (t, 0.7, C_2H), 7.4–8.8 (m, 17). Alkylation of the sodium enolate of **5** with **6** (procedure as for **4**) gave 2-(4′-hydroxybutyl)-cyclononanone (**8**, 74% from **5**): bp 125° (0.02 mm); ir (film) 3400, 1695 cm^{-1}; nmr (CCl_4) τ 6.3–6.8 (m, 3, CH_2OH), 7.8–9.1 (m, 21); mass spectrum (80 eV) *m/e* 212 ($M^{\cdot+}$), 194 ($M - H_2O$), 165, 140, 112, 98, 84, 67, and 55.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.58; H, 11.48.

A mixture of **8** (1.3 g, 0.006 mol) and potassium pyrosulfate (0.13 g, 0.0005 mol) was slowly distilled (5 hr) through a short coiled column at bath temperature 110° (0.01 mm) to give 2-oxabicyclo[5.7.0]tetradec-1(7)-ene (**10**, 0.6 g, 0.003 mol, 50%), which was trapped at −70°: ir (film) 1660 cm^{-1}, no OH; nmr (CCl_4) τ 6.1 (t, 2, OCH_2), 7.85 (m, 6, allylic H), 8.53 (m, 14). A repetittion on a larger scale gave 77% of **10**. Conversion of **10** to a dimer (*m/e* 388) of unknown structure occurred if it was kept at room temperature for more than several hours.

Addition of crude **10** (0.55 g, 0.0028 mol) to 85% pure MCPBA (1.5 g, 0.0074 mol, 2.6 equiv) in CH_2Cl_2 (7 ml) as described for **9** (see above) gave an oily mixture (0.6 g) from which was crystallized 0.085 g of a solid: mp 84–85°; vpc (20% SE-30 at 275°), 85% dilactones (*m/e* 242) and 15% 9-ketotridecanolide (**2**, *m/e* 226). Molecular distillation of the mother liquor gave **2** (0.42 g, *ca.* 60%) containing 10% of dilactones (by vpc). An aliquot was separated by preparative vpc (20% SE-30 at 245°) to give pure **2**: mp 28°; high-resolution mass spectrum[11] (70 eV) *m/e* calcd for $C_{13}H_{22}O_2$ 226.1569, found 226.1543; *m/e* (rel intensity) 226 (3), 111 (20), 101 (36), 98 (100), 84 (13), 83 (30), 69 (15), 55 (70); ir (Nujol mull) 1740, 1710 cm^{-1}; nmr (CCl_4) τ 5.95 (t, 2, OCH_2), 7.5–7.9 (m, 6, $CH_2C{=}O$), 8.1–8.9 (m, 14).

The semicarbazone had mp 172–172.5°. *Anal.* Calcd for $C_{14}H_{25}N_3O_3$: C, 59.34; H, 8.89; N, 14.83. Found: C, 59.54; H, 9.30; N, 15.08.

A larger scale oxidation of **10** utilizing 2.0 equiv of MCPBA gave 15% of dilactones and 69% of **2**.[12]

12-Ketopentadecanolide (3).—Pyrrolidinocyclododecene (**11**)[13] was treated with ethyl acrylate (1.3 equiv) in benzene to give the pyrrolidine enamine of 2-(2′-carbethoxyethyl)cyclododecanone (**15**, 72%, procedure previously described):[3,7] bp 165–175° (0.2 mm); ir (neat) 1727, 1640, 1610 cm^{-1}; nmr (CCl_4) τ 5.94 (t, 2, $CO_2CH_2CH_3$), 6.53 (m, 1, vinyl H),[14] 7.04 (t, 4, NCH_2), 8.0–8.87 (m, 30).

The enamine ester **15** gave the 2,4-dinitrophenylhydrazone of 2-(2′-carbethoxyethyl)cyclododecanone: mp 102–104° [diethyl ether–petroleum ether (bp 30–60°)]; ir ($CHCl_3$) 3330, 1730, 1615, 1600, 1520, 1350 cm^{-1} (NO_2). *Anal.* Calcd for $C_{23}H_{34}N_4O_6$: C, 59.70; H, 7.41; N, 12.11. Found: C, 59.48; H, 7.46; N, 12.13.

Reduction of **15** with lithium aluminum hydride[3,7] gave 2-(3′-hydroxypropyl)cyclododecanone (**12**, 84%): bp 150–170° (0.17 mm); ir (neat) 3360, 1700 cm^{-1}; nmr (CCl_4) τ 6.52 (t, 2, CH_2O), 6.72 (s, OH), 7.53–8.7 (m, 25), Slow distillation of **12** from *p*-toluenesulfonic acid *in vacuo* gave 2-oxabicyclo[4.10.0]hex-1(6)-ene (**13**, 85%): bp 102–105° (0.33 mm); vpc (5% SE-30), one peak at 160–173°; ir (neat) 1670 cm^{-1}; nmr (CCl_4) τ 5.18 (t, 2, OCH_2), 7.87–8.64 (m, 24); mass spectrum (7 eV) *m/e* (rel intensity) 222 ($M^{\cdot+}$, 10), 123 (33), 111 (29), 110 (17), 98 (56), 67 (40), 55 (65).

Addition of **13** to MCPBA (2.6 equiv) in CH_2Cl_2 over 10 min followed by reaction at room temperature for 30 min and work-up[5] gave 12-ketopentadecanolide (41%): bp 127–132° (0.2 mm);

(10) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

(11) High-resolution mass spectra were done by Dr. R. Feltz, Battelle Memorial Institute, Columbus, Ohio, on an MS-9 mass spectrometer under NIH contracts 69-2226 and 71-2483.

(12) Reaction of **10** with MCPBA (3 equiv) in CH_2Cl_2 for 30 min gave a mixture of 76% of dilactones (*m/e* 242; vpc one peak with a shoulder; not further characterized) and 24% of **2** (by vpc relative areas).

(13) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(14) Enamine **15** apparently exists mainly as the less substituted isomer, as is the case for the pyrrolidine enamines of 2-alkylcyclohexanones.[15]

(15) (a) M. E. Kuehne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959); (b) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

ir (neat) 1715, 1735 cm^{-1}; nmr ($CDCl_3$) τ 5.94 (t, 2, OCH_2), 7.61 (m, 6, $CH_2C{=}O$), 8.0–8.65 (m, 18); mass spectrum (10 eV) *m/e* (rel intensity) 254 ($M^{\cdot+}$, 72), 236 (78), 226 (18), 222 (13), 208 (30), 156 (87), 153 (10), 139 (10), 112 (28), 111 (11), 98 (34), 97 (30), 86 (57), 85 (100).

The semicarbazone (79%) had mp 156.5–158°. *Anal.* Calcd for $C_{16}H_{29}N_3O_3$: C, 61.71; H, 9.39; N, 13.49. Found: C, 61.71; H, 9.43; N, 13.66.

Registry No.—**1**, 38223-26-6; **2**, 38223-27-7; **2** semicarbazone, 38223-28-8; **3**, 38223-29-9; **3** semicarbazone, 38223-30-2; **4**, 4017-56-5; **5**, 4017-57-6; **6**, 4753-59-7; **7**, 38223-49-3; **8**, 38223-50-6; **9**, 38223-51-7; **10**, 38223-52-8; **12**, 32539-82-5; **13**, 32539-83-6; **15**, 38223-55-1; 2-(2′-carbethoxyethyl)cyclododecanone dinitrophenylhydrazone, 38223-56-2; cyclononaone, 3350-30-9; 1,6-dioxacyclopentadeca-1,15-dione, 38223-57-3; 1,7-dioxacyclopentadeca-2,8-dione, 38223-58-4.

Acknowledgment.—We are indebted to Dr. Gary Koppel for experimental assistance.

Selective C-Alkylation of Phenylacetylureas through 1,3,5-Trialkali Salt Intermediates[1]

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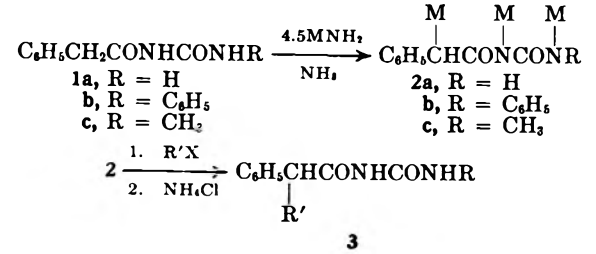
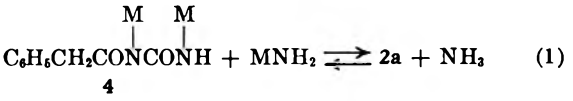
Recently,[4-6] we have found that 1,3,5 trianions derived from certain imides and β-keto imides can serve as useful synthetic intermediates by virtue of the high degree of regioselectivity accompanying their reactions with electrophilic reagents. During the course of these studies it occurred to us that arrangement of potential anion-stabilizing groups in phenylacetylurea (**1a**) might permit conversion of this compound into the 1,3,5-trialkali salt **2a**, which would represent the first example of a ureide trianion. It was anticipated that alkylation might then be directed selectively to the carbanion site of **2a** to afford *C*-alkyl derivatives **3**, a class of compounds which continue to attract considerable attention as anticonvulsant agents.[7] Moreover, such a direct new synthesis involving a single precursor, **2a**, could offer a more expedient method for certain structural variations than the multistep procedures[8] currently used for the preparation of compounds **3**.



3

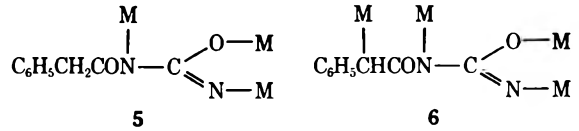
Treatment of **1a** with 2 mol equiv of potassium amide in liquid ammonia resulted in essentially complete consumption of the base as evidenced by the absence of stilbene formation upon addition of benzyl chloride.[9] Removal of the ammonia, followed by quenching with excess deuterium oxide, gave a good recovery of **1a** containing only N-bonded deuterium, indicating that 2 equiv of base produced the weakly nucleophilic dianion **4**, which failed to undergo appreciable alkylation at −33°.[10] Reaction of **1a** with 3 mol equiv of potassium amide in liquid ammonia followed by benzyl chloride afforded a mixture of *C*-benzyl derivative **3a**, unreacted **1a**, and stilbene. Since these results appeared to be consistent with an unfavorable equilibrium involving abstraction of a benzylic proton from dianion **4** to form trianion **2a** (eq 1), attempts were made to increase the



(1)

concentration of **2a** by replacing the ammonia with ether. This proved to be unsatisfactory because of extensive ammonolysis of the trianion during solvent exchange.[11] However, treatment of **1a** with 4.5 mol equiv of potassium amide in liquid ammonia, followed by a series of representative halides, afforded C-alkylation derivatives **3a–e** in good yields (Table I). Similarly, reaction of *N′*-phenyl- and *N′*-methylureides **1b** and **1c** with excess potassium amide in liquid ammonia followed by benzyl chloride afforded *C*-alkyl products **3f** and **3i** in good yields, while attempted benzylations in the presence of stoichiometric amounts of base gave mixtures consisting of **3f** and **3i**, unreacted starting materials, and stilbene.

It is conceivable that reaction of dianion **4** with a third equivalent of potassium amide could lead to a mixture of intermediates more complex than that illustrated in eq 1, possibly consisting of **2a** and the isomeric trianion **5**.[12] The excess amide necessary for



(1) This investigation was supported by the National Institutes of Health Grants GM-14340 and NS-10197.

(2) Abstracted from the Ph.D. dissertation of J. D. T., Virginia Polytechnic Institute and State University, July 1971.

(3) NSF undergraduate research participant, summer 1971.

(4) J. F. Wolfe, C. L. Mao, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, **31**, 3726 (1966).

(5) J. F. Wolfe and C. L. Mao, *ibid.*, **32**, 1977 (1967).

(6) J. F. Wolfe and C. L. Mao, *ibid.*, **32**, 3382 (1967).

(7) J. M. Delgado and E. I. Isaacson, "Medicinal Chemistry," 3rd ed, A. Burger, Ed., Interscience, New York, N. Y., 1970, Chapter 52; C. D. Lunsford, *Annu. Rep. Med. Chem.*, **4**, 30 (1969).

(8) For examples of traditional synthesis of compounds **3**, see (a) E. H. Volwiler and D. L. Tabern, *J. Amer. Chem. Soc.*, **58**, 1352 (1936); (b) M. A. Spielman, A. O. Geiszler, and W. J. Close, *ibid.*, **70**, 4189 (1948); (c) H. Takamatsu, S. Umemoto, S. Kanoh, and T. Isozaki, U. S. Patent 3,110,728 (1963); *Chem. Abstr.*, **60**, 2861*a* (1964); (d) H. Takamatsu, S. Umemoto, T. Tatsumi, and T. Isozaki, Japan, Patent 22,932 (1965); *Chem. Abstr.*, **64**, 3432*d* (1966).

(9) C. R. Hauser, W. R. Barsen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

(10) D. R. Bryant, S. D. Work, and C. R. Hauser, *J. Org. Chem.*, **29**, 235 (1964).

(11) W. S. Murphy and C. R. Hauser, *Chem. Ind. (London)*, 832 (1969).

(12) For examples of related trianions, see E. M. Kaiser, R. L. Vaux, and C. R. Hauser, *J. Org. Chem.*, **33**, 3640 (1967).

TABLE I

ALKYLATIONS OF TRIALKALI SALTS 2

Trialkali salt (M)	Halide R'X (registry no.)	Product	Mp, °C	Yield, %
2a (K)	$PhCH_2Cl$ (100-44-7)	3a	209–210	66
2a (Na)	$PhCH_2Cl$	3a	209–210	52
2a (Li)	$PhCH_2Cl$	3a	209–210	47
2a (K)	CH_3I (74-88-4)	3b	156–157[a,b]	73
2a (K)	C_2H_5Br (74-96-4)	3c	148–149[c,d]	76
2a (K)	$CH_2=CHCH_2Br$ (106-95-6)	3d	139–141[c,e]	76
2a (K)	$ClCH_2CO_2Na$ (3926-62-3)	3e	210–202[f,g]	60
2b (K)	$PhCH_2Cl$	3f	158–160[f,h]	73
2b (K)	CH_3I	3g	180–181[f,i]	52
2b (Li)	C_2H_5Br	3h	144–146[j,k]	57
2c (K)	$PhCH_2Cl$	3i	125–127[l,m]	57

[a] Recrystallized from aqueous ethanol. [b] Lit.[8b] mp 158–159°. [c] Recrystallized from acetone–heptane. [d] Lit.[8a] mp 137°. [e] Lit.[8a] mp 133–134°. [f] Recrystallized from absolute ethanol. [g] *Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.93; H, 5.22; N, 11.91. [h] *Anal.* Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.59; H, 5.94; N, 8.17. [i] *Anal.* Calcd for $C_{16}H_{16}N_2O_2$: C, 71.65; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.19. [j] Recrystallized from aqueous methanol. [k] Lit.[8d] mp 143–144°. [l] Purified by chromatography on silica gel and recrystallized from heptane. [m] *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.61; H, 6.38; N, 9.96. Found: C, 72.61; H, 6.39; N, 9.68.

successful alkylation might then be utilized in conversion of both trianions into a common 1,1,3,5 tetraanion (6), which reacts with halide to afford products 3. Alternatively, the use of excess base might result in kinetically favored formation of trianion 2a at the expense of trianion intermediate 5. However, the absence of N-substituted derivatives in alkylations of 1a and the requirement for excess amide in alkylations of 1b–c, neither of which can form trianions such as 5 or tetraanions like 6, appear to rule out both of the foregoing possibilities. Thus, excess potassium amide apparently exerts a simple mass law effect as shown in eq 1, and the appropriate 1,3,5-trialkali salts are the actual reactive intermediates in the observed C-alkylations.

In a brief study of the scope and limitations of the present reactions it was found that they were subject to a metallic cation effect, with tripotassio 2a being more reactive toward benzyl chloride than the corresponding sodio or lithio salts (Table I). Trilithio 2b could be generated in concentrations suitable for alkylation by means of 4 mol equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF)–hexane, but formation of 2a (M = Li) under similar conditions was less satisfactory as evidenced by incomplete alkylation with several halides. Therefore LDA, which is often superior to alkali amides for multiple anion formation,[13] appears to offer no advantage in these alkylations. Attempts to effect alkylation of trianion 1a (M = K) with secondary halides were unsuccessful. Finally, it should be mentioned that, although N'-aryl and N'-alkyl substituents appear to be generally compatible with the present trianion approach to C-alkylation, such was not the case with phenylacetyl ureides possessing an alkyl substituent at the benzylic position. For example, reaction of 3a with excess potassium amide in liquid ammonia followed by ethyl bromide afforded a mixture of products in which starting material predominated. Attempted C-alkylation of 3a with ethyl bromide in the presence of excess LDA gave none of the desired dialkyl derivative; instead 3a underwent extensive decarboxamidation to yield 2,3-diphenylpropionamide (7) (eq 2). Although elucidation of the mechanism and

$$\mathbf{3a} \xrightarrow[2.\ C_2H_5Br]{1.\ LDA} C_6H_5CH_2\underset{\displaystyle C_6H_5}{\underset{|}{C}}HCONH_2 \qquad (2)$$

7

generality of this reaction must await further study, preliminary results indicate that it may proceed in a manner similar to that described by Smith and Hauser[14] for the butyllithium-catalyzed decarboxamidation of certain primary amides.

Experimental Section[15]

Formation and Alkylations of Trialkali Salts 2a–c with Excess Alkali Amide.—The following synthesis of 2,3-diphenylpropionylurea (3a) is typical of the procedure used for the preparation of compounds 3a–g and 3i (Table I).

To a stirred solution of 0.09 mol of potassium amide, prepared from 3.52 g (0.09 g-atom) of potassium in 300 ml of anhydrous liquid ammonia, was added 3.57 g (0.02 mol) of solid phenylacetylurea (1a). The resulting green–yellow reaction mixture was allowed to stir for 20 min to ensure complete formation of trianion 2a (M = K). A solution of 6.58 g (0.052 mol) of benzyl chloride in 40 ml of anhydrous ether was added and the reaction mixture was stirred for 1 hr. During the addition of the halide the bright purple color associated with stilbene formation was evident. The reaction mixture was neutralized with excess solid ammonium chloride and the liquid ammonia was removed (steam bath) as an equal volume of ether was added. Addition of 200 ml of water to the resulting ethereal suspension resulted in separation of a considerable amount of solid material between the layers. This was collected by suction filtration and combined with a second portion of crude product obtained by concentration of the

(13) See T. M. Harris and G. P. Murphy, *J. Amer. Chem. Soc.*, **91**, 517 (1969), and references cited therein.

(14) H. A. Smith and C. R. Hauser, *ibid.*, **91**, 7774 (1969).

(15) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed in this laboratory by Miss Q. H. Tan using a Perkin-Elmer Model 240 C, H, and N analyzer. Thin layer chromatography (tlc) analyses were carried out with Eastman chromagram sheets, Type 6060 (silica gel), with fluorescent indicator. Spots were detected with ultraviolet light. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer using potassium bromide pellets and chloroform solutions. Proton magnetic resonance (pmr) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to tetramethylsilane, were measured to the center of a singlet or multiplet. Unless specified otherwise, chemicals were commercial reagent grade, and were used without further purification. *n*-Butyllithium was obtained from Foote Mineral Co., New Johnsonville, Tenn., as a solution in hexane and was standardized prior to use. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately prior to use. Diisopropylamine was distilled from calcium hydride and stored over molecular sieves. Phenylacetylurea (1a), mp 211–213° (lit.[16] mp 209°), was prepared by heating an equimolar mixture of phenylacetyl chloride and urea at 160° for 20 min and then recrystallizing the resulting crude solid from absolute ethanol. Similarly, 1-phenyl-3-(phenylacetyl)urea (1b), mp 170.5–171° (lit.[8d] mp 164–166°), and 1-methyl-3-(phenylacetyl)urea (1c), mp 188.5–190° (lit.[17] mp 190°), were prepared from the appropriately substituted urea and phenylacetyl chloride.

(16) S. Basterfield and M. E. Greig, *Can. J. Res.*, **8**, 450 (1933).

(17) J. Lebreau and P. Poignant, French Addn., 83,764; *Chem. Abstr.*, **64**, 644*h* (1966).

original ethereal layer and two 100-ml ethereal extracts of the aqueous layer. The total crude product was recrystallized from absolute ethanol to afford 3.55 g of **3a**: pmr (DMSO-d_6) δ 10.68 (s, 1, NH), 7.56 (m, 12, NH_2 and Ph), 4.28 (m, 1, CHCO), and 3.28 ppm (m, 2, CH_2Ph); ir (KBr) 2.93 (NH_2), 3.07 (NH), 5.95 (imide C=O), and 6.31 μ (amide C=O).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.79; H, 6.10; N, 10.27.

Alkylations of **1a** with benzyl chloride in the presence of 4.5 equiv of sodium amide or lithium amide were carried out in a similar manner.

Alkylation of tripotassio salt **2a** with sodium chloroacetate to afford 3-carboxy-2-phenylpropionylurea (**3e**) was conducted as described above except that the reaction time was extended to 2 hr and the product was isolated by acidification of the basic aqueous phase.

Attempted alkylation of 2,3-diphenylpropionylurea (**3a**) with ethyl bromide in the presence of excess potassium amide as described above afforded a mixture of products. Analysis of this mixture by tlc (THF–heptane) revealed the presence of unreacted **3a** along with traces of 2,3-diphenylpropionamide.

Although the observed melting points of alkyl derivatives **3c** and **3d** were somewhat higher than previously reported values (Table I), both of these compounds had analytical and spectral properties consistent with the assigned structures.

Formation and Attempted Benzylation of Dianion 4.—To a stirred suspension of 0.02 mol of potassium amide in 150 ml of liquid ammonia was added 1.78 g (0.01 mol) of **1a**. The resulting mixture was allowed to stir for 1 hr, and 1.26 g (0.01 mol) of benzyl chloride in 20 ml of ether was added; there was no evidence of stilbene formation. After 1 hr the ammonia was replaced by 200 ml of anhydrous ether and the resulting suspension treated with 10 ml of deuterium oxide. Filtration of the ethereal suspension and recrystallization of the residue from acetone–heptane afforded 1.36 g (76%) of recovered **1a**, the pmr (DMSO-d_6) spectrum of which had no absorption for imide or amide protons, but still retained a singlet (2 H) at 3.68 ppm for benzylic hydrogens. Analysis of the ethereal layer by tlc (ether–heptane) revealed traces of **1a** but no stilbene. Concentration of the ethereal layer afforded a nearly quantitative recovery of benzyl chloride.

Attempted Formation and Benzylation of Trialkali Salts 2a–c with 3 Equiv of Potassium Amide.—Each of the ureides **1a–c** (0.01 mol) was treated with 0.03 mol of potassium amide in liquid ammonia for 1 hr. Benzyl chloride (0.011 mol) was added, stirring was continued for 1 hr, and the reaction mixture was neutralized with ammonium chloride and processed in the usual fashion. In all cases addition of the halide resulted in appearance of the purple color accompanying stilbene formation. Each of the crude product mixtures was analyzed by tlc (THF–heptane), which revealed the presence of unreacted starting material, the appropriate *C*-benzyl derivative, and stilbene.

Formation and Alkylation of 1b (M = Li) Using LDA.—To a solution of 12.14 g (0.12 mol) of diisopropylamine in 200 ml of THF, maintained at 0° under a nitrogen atmosphere, was added 0.12 mol of *n*-butyllithium in hexane. The reaction mixture was allowed to stir for 15 min to form LDA and 7.62 g (0.03 mol) of solid **1b** was added. The resulting yellow solution was allowed to stir for 20 min, and 6.87 g (0.063 mol) of ethyl bromide in 50 ml of THF was added. The reaction mixture was stirred for 1 hr at 25° and then poured into a slurry of 200 g of ice and 15 ml of 12 *N* HCl. The THF layer was separated and combined with three 100-ml ethereal extracts of the aqueous solution. The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized to give 4.8 g of **3h** (Table I).

In a similar experiment **1a** (0.015 mol) was treated with 0.07 mol of lithium diisopropylamide and 0.03 mol of ethyl bromide to afford a mixture (tlc) of ethyl derivative **3c** and unreacted **1a**.

Attempted Ethylation of 3a by Means of LDA.—To a solution of 0.07 mol of LDA in 160 ml of THF–hexane, maintained at 0° under nitrogen, was added 4.02 g (0.015 mol) of **3a**. After 20 min, 3.43 g (0.03 mol) of ethyl bromide was added, the reaction mixture was allowed to warm to 25°, and stirring was continued for 1 hr. The reaction was processed as described above and the solid residue remaining after concentration of the organic extracts was analyzed by tlc (benzene–acetone) to reveal the presence of traces of **3a** and one other product. The crude product mixture was chromatographed on silica gel (benzene–acetone) to afford, after one recrystallization from aqueous ethanol, 2.3 g (66%) of 2,3-diphenylpropionamide, mp 131–132° (lit.[18] mp 133–134°). The ir spectrum of this material was identical with that of an authentic sample of 2,3-diphenylpropionamide. The aqueous layer was freeze-dried. The ir spectrum of the resulting solid has an intense band at 4.48 μ attributable to cyanate.[14]

Registry No.—**2a** (K), 37991-57-4; **2a** (Na), 37991-58-5; **2a** (Li), 37991-59-6; **2b** (K), 37991-75-6; **2b** (Li), 37991-76-7; **2c** (K), 37991-77-8; **3a**, 37991-66-5; **3b**, 37991-67-6; **3c**, 90-49-3; **3d**, 37991-69-8; **3e**, 37991-70-1; **3f**, 37991-71-2; **3g**, 37991-72-3; **3h**, 4287-43-8; **3i**, 37991-74-5.

(18) A. Meyer, *Chem. Ber.*, **21**, 1306 (1888).

Studies on Lactams. XXII.[1] An Unusual Reaction of Some 6-Azidopenams

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As a continuation of our work on the synthesis of penicillin analogs *via* α-azido-β-lactams,[2] we prepared the 6-azidopenams **3** and **4** by the reaction of azidoacetyl chloride and triethylamine on the appropriate thiazolines (**1** and **2**). Catalytic reduction of **3** led to the disappearance of the ir band characteristic of the azido group and gave a material which was used without further purification for reaction with phenoxyacetyl chloride and triethylamine. We had expected to obtain the penicillin V analog **5**, but, to our surprise, the crystalline product formed in high yield was found to be **6**, a penam that is readily synthesized from the thiazoline **1**, phenoxyacetyl chloride, and triethylamine. Similarly, **4** was transformed into **7** in about 80% yield by catalytic reduction followed by treatment with phenoxyacetyl chloride and triethylamine.

In a recent communication Bell and coworkers[3] have described the degradation of penicillin G methyl ester (**8**) and penillonic acid methyl ester (**11**) in refluxing trifluoroacetic acid to the thiazoline D-5,5-dimethyl-2-thiazoline-4-carboxylic acid methyl ester (**12**). This cleavage of the β-lactam in **8** is reminiscent of the fragmentation of 6-aminopenicillanic acid (**9**) under photolytic conditions. Gotfredsen and coworkers[4] observed that photolysis of an aqueous solution of the potassium salt of **9** resulted in a new penicillin, **10**. They proposed that the β-lactam ring was cleaved with the generation of the thiazoline **13** and amino ketene or its equivalent which reacted with 6-APA (**9**) to give **10**.

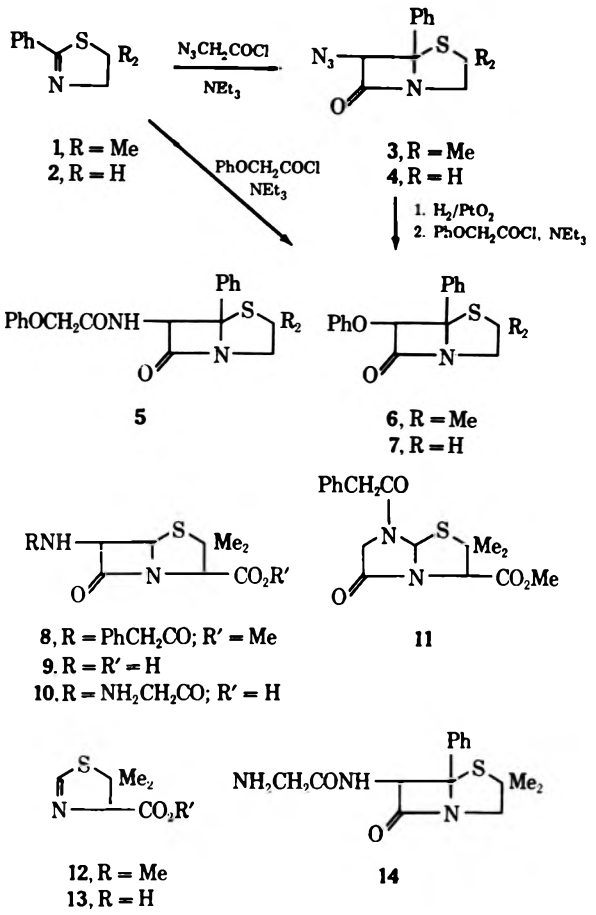
Our own observations on the formation of **6** and **7** from **3** and **4** can be easily accounted for if by analogy with 6-aminopenicillanic acid fragmentation we assume

(1) For part XXI, see A. K. Bose, Y. H. Chiang, and M. S. Manhas, *Tetrahedron Lett.*, 4091 (1972).

(2) (a) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967), and subsequent papers in this series.

(3) M. R. Bell, J. C. Carlson, and R. Oesterlin, *J. Amer. Chem. Soc.*, **92**, 2177 (1970).

(4) W. O. Godtfredsen, W. von Daehne, and S. Vangedal, *Experientia*, **23**, 280 (1967).



that the amino compounds formed by the reduction of **3** and **4** undergo β-lactam ring scission to the thiazolines **1** and **2**, respectively. To test this possibility, **1** in ethyl acetate solution was shaken with hydrogen for about 70 hr at room temperature in presence of Adams catalyst. From this reaction mixture a small amount of a solid and a yellow liquid were isolated. The solid, which was insoluble in common organic solvents, showed the highest peak in its mass spectrum at *m/e* 305 and a strong peak at *m/e* 191. We believe this product to be **14** (mol wt 305) by analogy with **10**. The main constituent of the liquid was deduced to be the thiazoline **1** on the basis of the mass spectrum (M^+, *m/e* 191), nmr peaks, and tlc comparison with authentic **1**. Further studies on this unusual β-lactam cleavage are necessary for establishing the exact pathway from the α-azido-β-lactams to the thiazolines under our reaction conditions.

Experimental Section

The melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer, the nmr spectra were taken on a Varian A-60A instrument, and the mass spectra were obtained on a Hitachi Perkin-Elmer RMU-7 mass spectrometer. The microanalysis were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

6-Azido-7-oxo-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptane (4).—A solution of triethylamine (7.2 g) in 250 ml of CH_2Cl_2 was added dropwise with constant stirring and under anhydrous conditions to a refluxing solution containing 12.65 g of 2-phenyl-2-thiazoline in 800 ml of CH_2Cl_2 and 9.2 g of azidoacetyl chloride in 750 ml of CH_2Cl_2. The addition of triethylamine was completed in 1 hr and the reaction mixture was stirred for an additional period of 17 hr. The solvent was then evaporated and the residue was extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to a viscous residue. Chromatography of this residue over a Florisil column using benzene as the eluent afforded 12.73 g (70%) of the pure title compound: mp 65–67°; ir (Nujol) 4.75 (azide), 5.64 μ (β-lactam carbonyl); nmr ($CDCl_3$) τ 2.55 (s, 5), 5.07 (s, 1), 5.67 (m, 1), 6.75 (m, 3 H); mass spectrum M^+ at *m/e* 246.

Anal. Calcd for $C_{11}H_{10}N_4OS$: C, 53.66; H, 4.09; N, 22.76; S, 13.39. Found: C, 53.72; H, 4.06; N, 22.83; S, 13.13.

6-Azido-3,3-dimethyl-7-oxo-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptane (3).—This penam was prepared in 87% yield from 5,5-dimethyl-2-phenyl-2-thiazoline and azidoacetyl chloride using the procedure outlined above: mp 102–104°; ir (Nujol) 4.7 (azide), 5–6 μ (β-lactam carbonyl); nmr (CDCl) τ 2.58 (s, 5), 4.98 (s, 1), 5.92 (d, 1, J = 12.5 Hz), 7.05 (d, 1, J = 12.5 Hz), 8.43 (s, 3), 8.56 (s, 3); mass spectrum M^+ at *m/e* 274.

Anal. Calcd for $C_{13}H_{14}N_4OS$: C, 56.97; H, 5.14; N, 20.43; S, 11.63. Found: C, 56.97; H, 5.27; N, 20.47; S, 11.67.

Reduction of 3 and Its Reaction with Phenoxyacetyl Chloride.—6-Azido-3,3-dimethyl-7-oxo-5-phenyl-4-thia-1-azabicyclo-[3.2.0]heptane (3.5 g) was dissolved in 50 ml of ethyl acetate and 2.1 g of Adams catalyst was added to it. The mixture was stirred in an atmosphere of hydrogen (41 psi pressure) for 54 hr. Solvent and the catalyst were removed and the product was used for the next operation without further purification.

The reduced material was dissolved in 200 ml of CH_2Cl_2, and 2 g of triethylamine was added to it. Phenoxyacetyl chloride (2.15 g) in 50 ml of CH_2Cl_2 was then added dropwise over a period of 0.5 hr. The reaction mixture was stirred overnight, then washed with water and dried ($MgSO_4$). Removal of solvent and chromatography over Florisil using methylene chloride–hexane (2:1) provided 3 g (70%) of 3,3-dimethyl-7-oxo-5-phenyl-6-phenoxy-4-thia-1-azabicyclo[3.2.0]heptane (6): mp 93–95°; ir (Nujol) 5.6 μ (β-lactam carbonyl); nmr ($CDCl_3$) τ 2.92 (broad, 10), 4.38 (s, 1), 5.9 (d, 1, J = 12 Hz), 7.08 (d, 1, J = 12 Hz), 8.4 (s, 3), 8.52 (s, 3); mass spectrum M^+ at *m/e* 325.

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 68.68; H, 5.09; N, 4.71; S, 10.76. Found: C, 68.70; H, 5.12; N, 4.60; S, 10.80.

Reduction of **4** using Adams catalyst followed by treatment with phenoxyacetyl chloride under conditions outlined above afforded **7**, mp 132–134°, in 80% yield: ir (Nujol) 5.65 μ; nmr ($CDCl_3$) τ 2.9 (broad, 10), 4.5 (s, 1), 5.65 (m, 1), 6.7 (m, 3); mass spectrum M^+ at *m/e* 297.

Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 70.14; H, 5.89; N, 4.31; S, 9.83. Found: C, 70.31; H, 5.86; N, 4.24; S, 9.74.

Registry No.—**1**, 37950-61-1; **2**, 2722-34-1; **3**, 37950-63-3; **4**, 37950-64-4; **6**, 37950-65-5; **7**, 37950-66-6; azidoacetyl chloride, 30426-58-5; phenoxyacetyl chlorides, 701-99-5.

Synthesis and Some Properties of *O*-Acyl- and *O*-Nitrophenylhydroxylamines

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O-Acyl- and *O*-nitrophenylhydroxylamines, useful aminating agents,[1,2] have usually been prepared by the following two methods:[3] (i) Carpino's method[2]

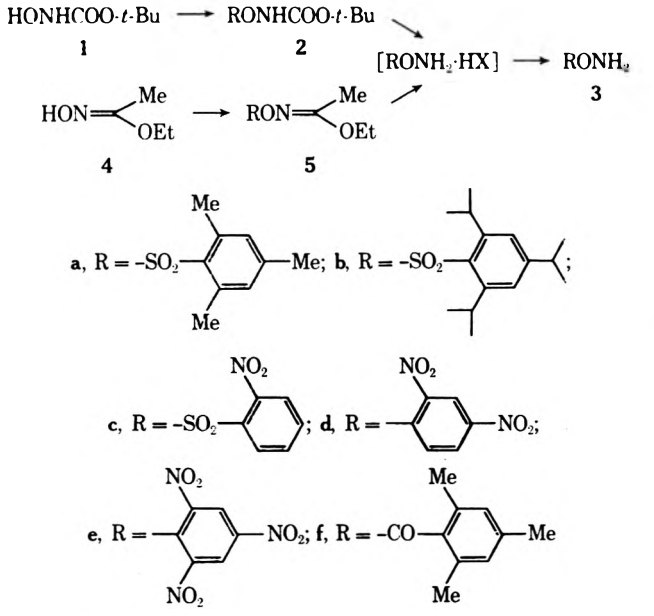
(1) (a) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Lett.*, 4133 (1972); (b) Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *ibid.*, 4137 (1972).

(2) (a) L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Amer. Chem. Soc.*, **81**, 955 (1959); (b) L. A. Carpino, *ibid.*, **82**, 3133 (1960); (c) J. G. Kraus, *Synthesis*, 140 (1972); (d) T. Sheradsky, *J. Heterocycl. Chem.*, **4**, 413 (1967); *Tetrahedron Lett.*, 1909 (1968); T. Sheradsky and Z. Nir, *ibid.*, 77 (1969).

(3) Other methods include (a) S. E. Meyer and T. Bellman, *J. Prakt. Chem.*, [II] **33**, 18 (1886); A. W. Scott and B. L. Wood, Jr., *J. Org. Chem.*, **7**, 508 (1942); (b) W. P. Jencks, *J. Amer. Chem. Soc.*, **80**, 4581, 4585 (1958); (c) L. Francesconi and A. Paracozzani, *Gazz. Chim. Ital.*, **31II** 334 (1901); O. Exner, *Collect. Czech. Chem. Commun.*, **23**, 272 (1958); G. Zinner, *Arch. Pharm. (Weinheim)*, **291**, 1 (1959); (d) G. Zinner, *ibid.*, **293** 657 (1960); (e) G. Zinner, *ibid.*, **296**, 57 (1963).

using *tert*-butyl *N*-hydroxycarbamate (**1**) and (ii) Zinner's method[4] using ethyl acetohydroxamate (**4**). Carpino's method has been successfully applied to the preparation of *O*-aryloyl-,[2a] *O*-arylsulfonyl-,[2b,c] and *O*-2,4-dinitrophenylhydroxylamines,[2d] but it has the disadvantage of rather high cost of the starting material, *tert*-butyl azidoformate. Zinner's method appears to be more economical, but has been restricted only to the preparation of *O*-aryloyl- and *O*-carbalkoxyhydroxylamines.

In this paper an improved preparation of *O*-arylsulfonyl- and *O*-nitrophenylhydroxylamines (**3**) by a modification of Zinner's method is described. Some of their properties are also described.



Ethyl *O*-arylsulfonylhydroxamates (**5a–c**), prepared from the readily accessible ethyl hydroxamate (**4**)[5] and arylsulfonyl chloride, were treated with 70% perchloric acid at 0° for 10 min. The reaction mixture was poured into ice water to give crystalline *O*-arylsulfonylhydroxylamines (**3a–c**) in high yields. The products were characterized by ir and nmr spectra, details of which are given in the Experimental Section. Compound **3c** decomposes quickly on exposure to air, so that no further investigation was carried out. In contrast, compounds **3a** and **3b** are noticeably more stable and can be kept in a freezer for several weeks. The products **3a** and **3b** obtained by this method usually contain 20–30% of water (estimated by iodometry) but can be used without further purification. If necessary, they can be recrystallized from ether and petroleum ether, as suggested by Carpino.[2b] They were found to be soluble in common organic solvents.

Using the same procedure as described above, *O*-(2,4-dinitrophenyl)-[2d] and *O*-picrylhydroxylamines (**3d** and **3e**) were also prepared in high yields. Compound **3e** is stable enough to be recrystallized from hot chloroform, and sparingly soluble in most organic solvents at room temperature. For comparison *O*-mesitoylhydroxylamine (**3f**) was also prepared according to the Zinner method.

The reactivity of these O-substituted hydroxylamines (**3**) was compared by their ability to aminate various substrates such as tri-*n*-butylamine, pyridine, diphenyl sulfide, diphenyl sulfoxide, and triphenylphosphine. The reactions were generally carried out in the methylene chloride solution at room temperature, but in some cases this procedure was modified as shown in the footnotes of Table I. The structures of the new compounds were proved by elemental analysis (Table II) and spectral data. The yields of the products listed in Table I revealed the marked dependency upon the nature of the leaving group.

TABLE I

COMPARISON OF YIELDS (PER CENT) IN REACTIONS OF **3** WITH VARIOUS NUCLEOPHILES

Starting material	Product	3a	3b	3d	3e[a]	3f
(*n*-Bu)$_3$N	(*n*-Bu)$_3$N$^+$NH$_2$ $^-$OR (**7**)	87[f]	72	85	0	15
C$_5$H$_5$N	C$_5$H$_5$N$^+$NH$_2$ $^-$OR (**8**)	80[g]	68	55	80[g]	Trace
Ph$_2$S	Ph$_2$S$^+$NH$_2$ $^-$OR (**9**)	90[j]	79	61[b]	87	
Ph$_2$S(O)	Ph$_2$S$^+$(O)NH$_2$ $^-$OR (**10**)	65[j]	40[c]	<20[d]	<30[e]	
Ph$_3$P	Ph$_3$P$^+$NH$_2$ $^-$OR (**11**)	86	76	92	91[h]	

[a] Amination effected in methylene chloride–ethanol (5:1) solution. [b] The reaction mixture was heated at 40–50° for 5 min, followed by allowing the mixture to stand at room temperature until the product separated. [c] The product was characterized by conversion[1b] to diphenylsulfoximine, mp 101–102° [lit. mp 103–104°: M. Barash, *Chem. Ind.* (*London*), 1261 (1964)]. [d] S-Amination was accompanied by the formation of high-melting by-product. [e] The reaction mixture was heated at 50–60° for 2–3 min, and then allowed to stand at room temperature for 2 days. A mixture of **10e** and **3e**, mp 129–130°, was obtained. Attempts to separate **10e** from **3e** were unsuccessful. [f] Y. Tamura, J. Minamikawa, Y. Kita, J. H. Kim, and M. Ikeda, *Tetrahedron*, in press. [g] Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm Bull.*, **19**, 130 (1971). [h] R. Appel, W. Buchner, and E. Guth, *Justus Liebigs Ann. Chem.*, **618**, 53 (1958). [i] Reference 1a. [j] Reference 1b.

TABLE II

ANALYTICAL DATA OF THE AMINATED PRODUCTS[a]

Compd	Mp, °C (recrystd from)	Empirical formula
7b	259–260 (CH_2Cl_2–Et_2O)	$C_{27}H_{32}N_2O_3S$
7d	81–82 (CH_2Cl_2–pet. ether)	$C_{18}H_{22}N_4O_5$
7f	213–215 (CH_2Cl_2–pet. ether)	$C_{22}H_{40}N_2O_2$
8b	183–184 (CH_2Cl_2–Et_2O)	$C_{20}H_{30}N_2O_3S$
8d	160–161 (EtOH–Et_2O)	$C_{11}H_{10}N_4O_5$
9b	239–240 (CH_2Cl_2–pet. ether)	$C_{27}H_{35}NO_3S_2$
9d	123–124 (CH_2Cl_2–pet. ether)	$C_{18}H_{15}N_3O_5S$
9e	137–138 (CH_2Cl_2–pet. ether)	$C_{18}H_{14}N_4O_7S$
11a	154–155 (CH_2Cl_2–Et_2O)	$C_{27}H_{28}NO_3PS\cdot H_2O$
11b	214–216 (CH_2Cl_2–pet. ether)	$C_{33}H_{40}NO_3PS$
11d	141–142 (CH_2Cl_2–pet. ether)	$C_{24}H_{20}N_3O_5P$

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in this table.

In summary, on the basis of this result, together with its relative stability and solubility in organic solvents, *O*-mesitylenesulfonylhydroxylamine (**3a**) is recom-

(4) G. Zinner, *Arch. Pharm.* (*Weinheim*), **293**, 42 (1960); **303**, 317 (1970).
(5) J. Houben and E. Schmidt, *Chem. Ber.*, **46**, 3616 (1913).

mended as the most convenient general reagent for amination.

Experimental Section[6]

Ethyl *O*-(Mesitylenesulfonyl)acetohydroxamate (5a).—Mesitylenesulfonyl chloride (72 g) was added to a solution of ethyl acetohydroxamate[5] (4) (34 g) and triethylamine (33 g) in dimethylformamide (90 ml) in portions with stirring under ice cooling. After addition was complete, the reaction mixture was stirred for 20 min at 0° and then poured into ice water. A white precipitate was filtered and recrystallized from petroleum ether (bp 30–60°) to give colorless needles (83 g, 86%) of **5a**: mp 57–58°; ir (KCl) 1635, 1600, 1200, 1180, and 670 cm^{-1}; nmr ($CDCl_3$) τ 8.85 (3 H, t, J = 8 Hz), 8.02 (3 H, s), 7.75 (3 H, s), 7.42 (6 H, s), 6.15 (2 H, q, J = 8 Hz), and 3.08 (2 H, b s).

Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.66; H, 6.44; N, 4.95.

Ethyl *O*-(2,4,6-Triisopropylbenzenesulfonyl)acetohydroxamate (5b).—Using the procedure described above for **5a**, **5b** was prepared from **4** (10.3 g) and 2,4,6-triisopropylbenzenesulfonyl chloride (30.3 g). Recrystallization from ethanol–water (20:1) gave colorless prisms (32 g, 87%) of **5b**: mp 75–76°; ir (KCl) 1630, 1600, 1350, 1195, and 670 cm^{-1}; nmr ($CDCl_3$) τ 8.88 (3 H, t, J = 6.8 Hz) 8.79 (18 H, d, J = 6.8 Hz), 8.00 (3 H, s), 7.13 (1 H, m), 6.09 (2 H, m), 5.83 (2 H, m), and 2.86 (2 H, s).

Anal. Calcd for $C_{19}H_{31}NO_4S$: C, 61.76; H, 8.46; N, 3.79. Found: C, 61.77; H, 8.34; N, 3.85.

Ethyl *O*-(*o*-Nitrobenzenesulfonyl)acetohydroxamate (5c).—Using the procedure described for **5a**, **5c** was prepared from **4** (1.0 g) and *o*-nitrobenzenesulfonyl chloride (2.1 g). Recrystallization from ligroin afforded white prisms (2.0 g, 73%) of **5c**: mp 79–80°; ir (KCl) 1615, 1530, 1380, 1325, and 1195 cm^{-1}; nmr ($CDCl_3$) τ 8.83 (3 H, t, J = 6.9 Hz), 7.96 (3 H, s), 6.09 (2 H, q, J = 6.9 Hz), and 2.28 (4 H, m).

Anal. Calcd for $C_{10}H_{12}N_2O_6S$: C, 41.67; H, 4.20; N, 9.72. Found: C, 41.68; H, 4.16; N, 9.81.

Ethyl *O*-Picrylacetohydroxamate (5e).—Utilizing the previously reported procedure for the preparation of ethyl *O*-2,4-dinitrophenylacetohydroxamate,[7] **5e** was prepared from **4** (6.2 g) and picryl chloride (15.0 g). Recrystallization from ethanol afforded pale yellow needles (15.3 g, 81%) of **5e**: mp 93.5–94.5°; ir (KCl) 1600, 1525, 1460, and 1340 cm^{-1}; nmr ($CDCl_3$) τ 8.75 (3 H, t, J = 6.9 Hz), 7.88 (3 H, s), 6.10 (2 H, q, J = 7.2 Hz), and 1.28 (2 H, s).

Anal. Calcd for $C_{10}H_{10}N_4O_8$: C, 38.22; H, 3.21; N, 17.83. Found: C, 38.34; H, 3.27; N, 17.55.

***O*-Mesitylenesulfonylhydroxylamine (3a).**—To a solution of **5a** (75 g) in dioxane (50 ml) was added 70% perchloric acid (30 ml) with stirring at 0° over 10 min. The reaction mixture was poured into ice water to give a white solid, which was filtered and washed with water. Although the product (64 g) thus obtained contains 20% of water (by iodometry), it can be used simply by filtration of a methylene chloride solution to remove water separated. The solid was dissolved in ether and precipitated by the addition of petroleum ether to give white needles of **3a**: mp 93–94°; ir (KCl) 3340, 3250, 1600, 1350, 1190, 1180, and 780 cm^{-1}; acetone oxime mp 95–96° (lit.[2b] mp 95–96.5°).

***O*-(2,4,6-Triisopropylbenzenesulfonyl)hydroxylamine (3b).**—To a solution of **5b** (30 g) in dioxane (50 ml) was added 70% perchloric acid (30 ml) with stirring at 0° over 10 min. The reaction mixture was stirred for an additional 2 hr and poured into ice water. A white precipitate was treated as described for **3a** to give white crystals of **3b** (30 g, containing 31% of water): mp 137–138°; ir (KCl) 3340, 3260, 1600, 1350, 1200, 1190, and 665 cm^{-1}; acetone oxime mp 112–113° (from ethanol).

Anal. Calcd for $C_{18}H_{29}NO_3S$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.84; H, 8.84; N, 4.03.

***O*-(*o*-Nitrobenzenesulfonyl)hydroxylamine (3c).**—Using the same procedure described for **3a**, **3c** was prepared from **5c**[11] (3.0 g). Yellow crystals (0.35 g) of **3c** were obtained and characterized by its ir spectrum: ir (KCl) 3340, 3250, 1600, 1530, 1370, and 1200 cm^{-1}. Because this compound was found to decompose on exposure to air, no further investigation was carried out.

***O*-(2,4-Dinitrophenyl)hydroxylamine (3d).**—Using the same procedure described for **3a**, **3d** was prepared from **5d** (21.7 g). Recrystallization from ethanol gave pale yellow needles (12.5 g, 78%) of **3d**: mp 112–113° (lit.[2d] mp 112°); ir (KCl) 3325, 3250, 1600, 1510, and 1340 cm^{-1}; nmr ($CDCl_3$) τ 3.63 (2 H, b s, NH_2), 2.03 (1 H, d, J = 10 Hz), 1.62 (1 H, dd, J = 10 and 3 Hz), and 1.26 (1 H, d, J = 3 Hz).

***O*-Picrylhydroxylamine (1e).**—Using the same procedure described for **3a**, **3e** was prepared from **5e** (1.45 g). Recrystallization from chloroform gave yellow prisms of **3e** (0.7 g, 62%): mp 98–100° dec; ir (KCl) 3300, 3250, 1610, 1530, and 1350 cm^{-1}.

Anal. Calcd for $C_6H_4N_4O_7$: C, 29.52; H, 1.65; N, 22.95. Found: C, 29.56; H, 1.79; N, 23.08.

The acetone oxime had mp 122–123° (from ethanol).

Anal. Calcd for $C_9H_8N_4O_7$: C, 38.03; H, 2.84; N, 19.72. Found: C, 38.03; H, 2.89; N, 19.93.

Reactions of 3a,b,d,e,f with Nucleophiles. General Procedure.—To a stirred solution of substrate (tri-*n*-butylamine, pyridine, diphenyl sulfide, diphenyl sulfoxide, and triphenylphosphine) (1 mmol) in methylene chloride (5 ml) was added a solution of **3** (1 mmol) in methylene chloride (5 ml) at 0°. After the reaction mixture was allowed to stand at room temperature for 10 min, ether or petroleum ether was added to precipitate the product. In some cases this procedure was modified (see the footnotes of Table I). The results are summarized in Tables I and II.

Registry No.—**3a**, 36016-40-7; **3b**, 38202-21-0; **3c**, 38202-22-1; **3d**, 17508-17-7; **3e**, 38100-34-4; **3f**, 37477-17-1; **4**, 10576-12-2; **5a**, 38202-27-6; **5b**, 38202-28-7; **5c**, 38202-29-8; **5e**, 38202-30-1; **7b**, 38202-31-2; **7d**, 38202-32-3; **7f**, 38202-33-4; **8b**, 38202-34-5; **8d**, 38202-35-6; **9b**, 38229-23-1; **9b**, 38202-36-7; **9e**, 38215-55-3; **11a**, 38215-56-4; **11b**, 38309-16-9; **11d**, 38229-24-2; $(n\text{-Bu})_3N$, 102-82-9; pyridine, 110-86-1; Ph_2S, 139-66-2; $Ph_2S(O)$, 945-51-7; Ph_3P, 603-35-0; triethylamine, 121-44-8; 2,4,6-triisopropylbenzenesulfonyl chloride, 6553-96-4; *o*-nitrobenzenesulfonyl chloride, 1694-92-4; picryl chloride, 88-88-0; *O*-picryl acetone oxime, 13194-03-1; *O*-(2,4,6-triisopropylbenzenesulfonyl) acetone oxime, 38215-59-7.

(6) Melting points are uncorrected. Nmr spectra were recorded on a Hitachi R-20 spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Hitachi EPI-G2 instrument.

(7) A. O. Ilvespää and Q. Marxer, *Helv. Chim. Acta*, **46**, 2009 (1963).

Synthesis of Some 5-Carboxy-5-hydroxymethyl-1,3-dioxanes

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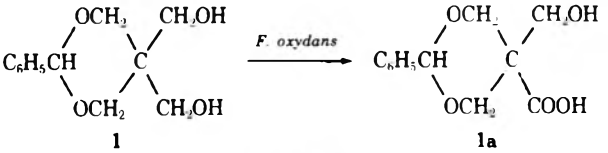
Oxidation of pentaerythritol with a mutant strain of *Flavobacterium oxydans* produces tris(hydroxymethyl)acetic acid, whereas the parent strain completely degrades pentaerythritol.[1]

Recent studies on the limits of oxidizing capability of the bacterium indicated that freeze-dried cells of the parent and mutant strains oxidized 2-phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane (1) to 2-phenyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (1a).[2]



1 1a

(1) C. T. Goodhue and J. R. Schaeffer, *Biotechnol. Bioeng.*, **11**, 1173 (1969).

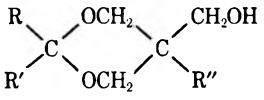
(2) The conversion of **1** to **1a** was first observed during an unpublished investigation carried out in collaboration with Dr. C. T. Goodhue, of these laboratories.

This observation suggested the possibility of an alternative synthesis of tris(hydroxymethyl)acetic acid by oxidation of a derivative of pentaerythritol with the parent strain of the bacterium. We undertook the synthesis of several acetal and ketal derivatives of tris(hydroxymethyl)acetic acid from the corresponding derivatives of pentaerythritol with freeze-dried cells of the parent strain as the oxidizing agent in order to examine the feasibility of this synthesis.[3]

In connection with this study we wish to report that with freeze-dried parent cells, in addition to the oxidation of **1** to **1a**, 2-isopropyl-5,5-bis(hydroxymethyl)-1,3-dioxane (**2**), 3,3-bis(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane (**3**), and 2,2-dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (**4**) were oxidized to the corresponding monocarboxylic acids, which were identified as their trimethylsilyl derivatives by a combination of gas chromatography and mass spectrometry (Table I).

TABLE I

MASS SPECTRA OF TRIMETHYLSILYLATED OXIDATION PRODUCTS AND AUTHENTIC SAMPLES



Substituents	Peak temp on glc, °C	Peaks in mass spectrum of oxidation product and authentic sample	
1a, R = C_6H_5; R′ = H; R″ = COOH	245	382	261
		381	231
		367	147
		297	105
			103
2a, R = $(CH_3)_2CH$; R′ = H; R″ = COOH	201	333	147
		305	103
		233	75
		231	73
3a, R = R′ = $(CH_2)_5$; R″ = COOH	190	319	75
		247	73
		159	59
			43
4a, R = R′ = CH_3; R″ = COOH	232	374	
		331	
		73	
4b, R = R′ = CH_3; R″ = H[a]	152	203	
		103	
		73	

[a] Authentic sample was not available. Molecular weight and cracking pattern are consistent with **4b**.

Although **4** was oxidized to **4a**, both compounds gradually disappeared from the oxidation medium over a 7-day period. During the same period of incubation, a new compound, 2,2-dimethyl-5-hydroxymethyl-1,3-dioxane (**4b**), was formed and accumulated as the only final product.

Synthesis of the dioxanes with freeze-dried mutant cells was also investigated. Higher yields of monocarboxylic acids were obtained with mutant cells than with parent cells (Table II). With mutant cells ketals **3** and **4** were converted to tris(hydroxymethyl)acetic acid in addition to **3a** and **4a**.

Decarboxylation product **4b** was not produced when **4** was oxidized with mutant cells.

Addition of calcium carbonate to the incubation media improved the yields of monocarboxylic acids in all cases studied (Table II); however, a slight decrease in the yield of **4b** was observed. Suppression of tris(hydroxymethyl)acetic acid production from **3** and **4** occurred with mutant cells in the presence of carbonate.

In one case, that of oxidation of **2** to **2a**, the product was isolated from a scaled-up preparation with parent cells. The yield of pure acid was 15.5%.

The variation observed in the yields of the different acids (Table II) is due to a combination of enzymatic and hydrolytic stability[4] effects.

TABLE II

YIELDS OF ACETALS AND KETALS OF TRIS(HYDROXYMETHYL)ACETIC ACID

	Per cent yield (68 hr)			
	Parent cells		Mutant cells	
Oxidation product	With $CaCO_3$	Without $CaCO_3$	With $CaCO_3$	Without $CaCO_3$
1a	41	25[a]	87	54[b]
2a	37	29[a]	78	67[a]
3a	79	36[b]	91	37
4a	35	29	91	48

[a] 92 hr. [b] 164 hr.

Enzymatic effects are evidenced by the generally lower yields of acids obtained with parent cells compared with those produced by mutant cells. Accumulation of **4b** probably occurred through decarboxylation of the normal oxidation product **4a**. It is reasonable to propose that decarboxylation of **4a** resulted from some unique effect of **4** or **4a** on the enzymes in the parent organism or from differences in the enzymes in the two organisms.

Evidence of hydrolytic stability effects on product yield can be found in the observation that the ketals appear less stable than the acetals. Lower yields of products and substantial amounts of tris(hydroxymethyl)acetic acid were observed in the oxidation mixtures of **3** and **4** with mutant cells, whereas higher yields of products accompanied by trace amounts of tris(hydroxymethyl)acetic acid were observed with **1** and **2** under the same conditions.

The general yield improvement obtained with carbonate may be due to greater acetal and ketal stability at a higher pH. When carbonate was present in the media, the pH ranged from 7.4 to 8.2. In the absence of carbonate, incubation media with parent cells had a pH between 5.2 and 6.6 and with mutant cells between 6.5 and 6.8. It should be pointed out, however, that carbonate also maintains the pH of the medium at a level where the oxidizing enzymes appear to work more efficiently.[1]

The utility of this synthesis as a method of preparation of 5-carboxy-5-hydroxymethyl-1,3-dioxanes is limited to those acetal and ketal derivatives of pentaerythritol and tris(hydroxymethyl)acetic acid that are stable enough to survive both the oxidation and method of isolation.

(3) Acetals and ketals of pentaerythritol were examined because of their ease of synthesis and hydrolysis.

(4) E. Berlow, R. H. Barth, and J. E. Snow, "The Pentaerythritols," Reinhold, New York, N. Y., 1958, p 143.

Experimental Section[5]

2-Isopropyl-5,5-bis(hydroxymethyl)-1,3-dioxane (2).—Isobutyraldehyde (26.5 g, 0.38 mol) and 23 ml of concentrated hydrochloric acid were added to a stirred solution of 50 g (0.37 mol) of pentaerythritol in 2.9 l. of water. After the mixture had been stirred for 24 hr at room temperature, insoluble solids were removed and the pH was adjusted to 8 with solid sodium carbonate. Water was evaporated and the solid residue was extracted with 800 ml of boiling *p*-xylene. After filtration, the extract stood overnight at 5°. The product weighed 25.3 g (36.4%), mp 97–99°.

Anal. Calcd for $C_9H_{18}O_4$: C, 56.8; H, 9.5; mol wt, 190.2. Found: C, 56.7; H, 9.4; mol wt, 188.

3,3-Bis(hydroxymethyl)-1,5-dioxaspiro[5.5]undecane (3).—The compound was prepared in 3.5% yield by the procedure of Issidroides and Gulen,[5] mp 125–127°.

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.1; H, 9.3; mol wt, 216.2. Found: C, 61.1; H, 9.1; mol wt, 216.

2-Phenyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (1a).—Dioxane **1a** was prepared according to a procedure published by Sulzbacher, *et al.*,[6] in 67.2% yield, mp 176–178°.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 6.0; mol wt, 238.2. Found: C, 60.5; H, 6.1; mol wt, 229.

2-Isopropyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (2a).—The dioxane was prepared in 29% yield, mp 149–151°.

Anal. Calcd for $C_9H_{16}O_5$: C, 52.9; H, 7.9; mol wt, 204. Found: C, 52.9; H, 7.9; mol wt, 226.

3-Carboxy-3-hydroxymethyl-1,5-dioxaspiro[5.5]undecane (3a).—Compound **3a** was prepared in 47.3% yield, mp 132–134°.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; mol wt, 230.2. Found: C, 57.8; H, 7.9; mol wt, 247.

2,2-Dimethyl-5-carboxy-5-hydroxymethyl-1,3-dioxane (4a).—Compound **4a** was prepared in 79% yield with a 20:1 molar ratio of ketone to acid, mp 128–130°.

Anal. Calcd for $C_8H_{14}O_5$: C, 50.5; H, 7.4; mol wt, 190.2. Found: C, 50.5; H, 7.5; mol wt, 185.

Preparation of Cells.—Growth of the parent strain was carried out on a medium containing 10.0 g of pentaerythritol, 2.0 g of acetic acid, 10 g of ammonium sulfate, 1.0 g of dipotassium hydrogen phosphate, 1.0 g of yeast extract, and 10 ml of mineral salts solution in 1 l. of distilled water adjusted to pH 7 with potassium hydroxide prior to sterilization.

The medium used for growth of the mutant strain has been reported.[1]

Flask culturing was carried out at 30° in 2.3-l. Fernbach flasks fitted with gauze closures. The inoculum was prepared in 25-ml erlenmeyer flasks fitted with Morton closures. The flasks were inoculated under sterile conditions from slants of either the parent strain[7] or the mutant strain (ATCC No. 21,245) and shaken on a rotary shaker at 400 rpm for 72 hr. Fernbach flasks were shaken at 150 rpm for 72 hr, after addition of a 5% (v/v) inoculum. Cells were harvested by centrifugation with a Sorvall refrigerated centrifuge operated at 9000 rpm for 20 min at 5°, freeze-dried in 0.4% potassium phosphate buffer, and stored at 5°.

Analysis of Oxidation Mixtures.—Acetals and ketals were estimated as the trimethylsilyl derivatives by gas–liquid chromatography.[1] Trimethylsilyl derivatives were prepared directly from freeze-dried samples of the oxidation mixtures. Standard curves were prepared with the chemically synthesized compounds using *n*-octadecane as the internal standard, with the exception of compounds **3** and **3a**, in which case *n*-dodecane was used. The accuracy of the estimation was 10%.

Biooxidation Reactions.—The oxidations were performed in 125-ml erlenmeyer flasks fitted with Morton closures. Cells (200 mg) and compound (225 mg) were suspended in 25 ml of nonsterile phosphate buffer. The mixtures were incubated at 30° on a shaker operated at 400 rpm. One-milliliter samples were removed at 24-hr intervals over a period of 7 days and analyzed.

Yield of product was reported based on the highest concentration observed during the incubation.

Product Identification.—Oxidation products were identified by comparison of the mass spectra of trimethylsilylated products isolated by gas–liquid chromatography with those of trimethylsilylated authentic samples (Table I).

Isolation of 2a.—Compound **2a** was prepared by a 20-fold scale-up of the biooxidation procedure. The cells were removed by centrifugation at 9000 rpm for 20 min at 5°. Ion exchange of the clarified solution was carried out on a column of Dowex 1 × 8 resin (100 ml in formate form). Elution was made with 4 *N* formic acid. Fractions containing pure product were freeze-dried. The product weighed 0.84 g (15.5%), mp 154–156°. A mixture melting point with an authentic sample was not depressed.

Registry No.—**1**, 2425-41-4; **1a**, 37951-01-2; **2**, 37951-03-4; **2a**, 37951-04-5; **3**, 714-88-5; **3a**, 38165-52-5; **4**, 770-74-1; **4a**, 16837-15-3; isobutyraldehyde, 78-84-2; pentaerythritol, 115-77-5.

Acknowledgment.—We wish to thank Dr. C. T. Goodhue for helpful advice, Mr. H. A. Risley for several samples of mutant cells, Mr. D. P. Maier for interpretation of the mass spectra, and Mr. R. E. Sceusa for technical assistance.

(5) Melting points are uncorrected. Molecular weights were obtained in acetone by the ebulliometric method. All evaporations were carried out under reduced pressure. The drying agent was sodium sulfate. Compounds **1** and **4** were prepared by published procedures [C. H. Issidroides and R. Gulen in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 679; L. Orther and G. Freyss, *Justus Liebigs Ann. Chem.*, **484**, 131 (1930)]. Gas chromatography was carried out with an F & M Model 810 gas chromatograph equipped with a thermal conductivity detector. The column was stainless steel 6 ft × 0.125 in. o.d. packed with SE-30 on Chromosorb W. A 30°/min column temperature rise from 100 to 300° was employed. Mass spectra were determined on either a Hitachi Perkin-Elmer RMS-4 or a C. E. C. 21-110B mass spectrometer.

(6) M. Sulzbacher, E. Bergman, and E. R. Pariser, *J. Amer. Chem. Soc.*, **70**, 2828 (1948); dioxanes **2a**, **3a**, and **4a** were also prepared by this method.

(7) This strain is maintained by Dr. C. T. Goodhue, Research Laboratories at Kodak Park Division of Eastman Kodak Co., Rochester, N. Y. 14650.

A Regiospecific Synthesis of 4-Chloroalkylbenzenes

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Although 4-chloro-1,2-dimethylbenzene (**1**) has been prepared in several different ways, each route has disadvantages as a practical synthetic method. Direct chlorination in the presence of Lewis acids results in formation of approximately equal amounts of the 3- and 4-chloro isomers.[1,2] These have been separated only by sulfonation, formation and fractional crystallization of the barium salts of the sulfonic acids, conversion of the barium salts to the sodium salts, and then desulfonation.[1] A multistep synthesis terminating in a Sandmeyer reaction of 3,4-dimethylbenzenediazonium chloride produces pure **1**,[3] but the yields are poor since nitration of *o*-xylene in the first step gives more 3- than 4-nitro-1,2-dimethylbenzene.[4,5]

Similar difficulties occur in the synthesis of other 4-haloalkylbenzenes, although separation of isomers is often simpler than in the case of **1**.

This paper reports a regiospecific synthesis of 4-

(1) A. Krüger, *Chem. Ber.*, **18**, 1755 (1885).

(2) A. Claus and O. Bayer, *Justus Liebigs Ann. Chem.*, **274**, 305 (1893).

(3) D. R. Lyon, F. G. Mann, and G. H. Cookson, *J. Chem. Soc.*, 662 (1947).

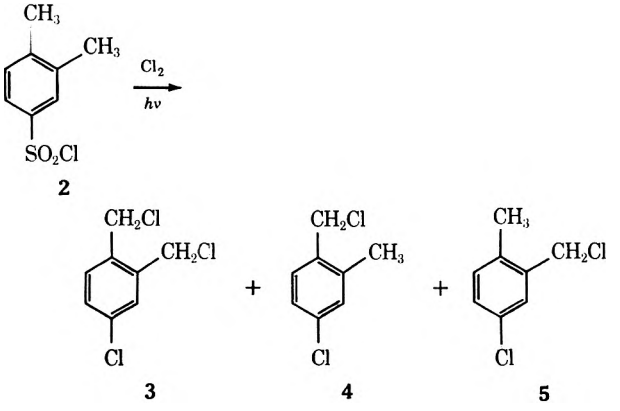
(4) A. W. Crossley and N. Renouf, *ibid.*, 202 (1909).

(5) Formation of **1** by reaction of 3,4-dimethylbenzenesulfonic acid with cuprous chloride has been reported: P. S. Varma, N. B. Parekh, and V. K. Subramanium, *J. Indian Chem. Soc.*, **16**, 460 (1939). I have been unable to reproduce this work.

chloro-1,2-dimethylbenzene and of 4-chlorotoluene. This method seems likely to be of general utility in the synthesis of 4-chloroalkylbenzenes.

It has been reported that chlorosulfonation of *o*-xylene gives 4-chlorosulfonyl-1,2-dimethylbenzene, with no mention of the 3 isomer being formed.[6] This reaction seemed a likely starting point for the specific formation of **1**, since conversion of aromatic chlorosulfonyl groups to chlorides has previously been reported.[7] Chlorosulfonation of *o*-xylene did indeed give 4-chlorosulfonyl-1,2-dimethylbenzene (**2**) as the major product, but nmr analysis indicated the presence of *ca.* 8–9% of a second isomer, presumably 3-chlorosulfonyl-1,2-dimethylbenzene. Recrystallization from ether gave pure **2** (mp 52–53°) in approximately 55% recovery from the crude sulfonation product.

Photochlorination of **2** was carried out until vpc analysis showed that less than 3% of the original sulfonyl chloride remained unreacted. Work-up of the reaction mixture gave a lachrymatory brown oil, whose ir spectrum showed the essential absence of sulfonyl peaks. The nmr spectrum similarly showed that the chlorosulfonyl group had been displaced by chlorine, but showed that, not unexpectedly, the methyl groups had also been chlorinated. The nmr spectrum of the crude product showed a strong singlet at δ 4.7, attributed to the methylene group of a benzyl choride, as well as peaks at δ 2.25 and 2.4 (in the area ratio 3:2) attributed to unreacted aromatic methyl groups. No signals appeared between δ 6 and 7, indicating the absence of any benzal chlorides. The area of the methylene signal was 2.6 times that of the combined methyl signals. If the assumption is made that no dimethyl compound remains in the mixture (an assumption supported by vpc analysis), and if the presence of small amounts of unreacted sulfonyl chloride is neglected, the spectrum indicates the photochlorination products to consist of 60% of **3** and 40% of a mixture of **4** and **5**.



Reduction of the crude chlorination product with zinc and hydrochloric acid gave (after distillation) pure **1** in overall 68% yield from **2**.

Repetition of the chlorination and reduction steps with the crude product of chlorosulfonation of *o*-xylene gave a product whose vpc, on several different columns, showed a single peak with a retention time identical with that of **1**. Its ir and nmr spectra, however, indicated that it contained about 8% of a second component, presumably 3-chloro-1,2-dimethylbenzene.

A similar sequence of chlorination and reduction steps (using iron in hydrochloric acid as the reducing agent) gave a 61% yield of *p*-chlorotoluene starting from *p*-toluenesulfonyl chloride.

While the goal of finding an essentially regiospecific path to 4-chloroalkylbenzenes had been accomplished, the overall yield of pure **1** from *o*-xylene was disappointing, owing to difficulties in recrystallizing the low-melting **2**. To overcome this difficulty, the crude product from chlorosulfonation of *o*-xylene was converted to bis(3,4-dimethylphenyl) sulfone.[8] The high-melting sulfone crystallized from the reaction mixture in high yield. Chlorination and reduction of the sulfone proceeded in essentially the same manner as did the reactions of the sulfonyl chloride to give **1** in an overall yield of 58% from *o*-xylene. Thus, despite the necessity for an extra step in the overall sequence, preparation of **1** *via* the sulfone seems the method of choice.

Experimental Section

Preparation of 3,4-Dimethylbenzenesulfonyl Chloride (2).—*o*-Xylene (20.0 g, 0.188 mol) in 200 ml of chloroform was cooled in an ice bath and stirred while chlorosulfonic acid (60 g, 0.51 mol) was added drop by drop. The solution was stirred for 1 hr at room temperature, and then for 1 hr at 50°. It was then cooled and poured onto ice. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to give 40.0 g of pale yellow oil, which crystallized on standing in the cold to give an oily solid, mp 41–48°. Three recrystallizations from ether gave 21.1 g (0.103 mol, 55%) of 3,4-dimethylbenzenesulfonyl chloride, mp 52–53° (reported[8] mp 51–52°).

Preparation of Bis(3,4-dimethylphenyl) Sulfone.—A solution of crude 3,4-dimethylbenzenesulfonyl chloride (20.0 g, 0.098 mol) in *o*-xylene (10.4 g, 0.098 mol) was stirred at room temperature. Aluminum chloride (anhydrous) was added slowly, until the mixture became too viscous to stir. Water was added cautiously, and the mixture was then extracted with chloroform. The organic layer was washed with water and then with sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent gave 26.1 g of pale yellow solid. Recrystallization from ethanol gave 22.3 g of bis(3,4-dimethylphenyl) sulfone (0.081 mol, 82%), mp 169–171° (reported[8] mp 162°).

Preparation of 4-Chloro-1,2-dimethylbenzene (1). A.—A stream of chlorine was passed through a solution of 3,4-dimethylbenzenesulfonyl chloride (10.0 g, 0.0487 mol) in 100 ml of chloroform. The solution was mechanically stirred and illuminated by a 150-W bulb at a distance of 2 in. At intervals, the chlorine stream was stopped and a sample of the solution was analyzed by vpc on a 6 ft, 3% SE-30 on Chromosorb W column at 185°. When the peak for 3,4-dimethylbenzenesulfonyl chloride (8.0 min) had essentially disappeared (2.5 hr) the reaction mixture was poured into sodium bisulfite solution, and the organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 9.3 g of a lachrymatory brown oil, which was dissolved in 25 ml of ethanol, and poured into 100 ml of concentrated hydrochloric acid which was rapidly stirred. Zinc dust (30.0 g, 0.46 g-atom) was added slowly to the mixture, with the evolution of much gas and an appreciable exotherm. The mixture was stirred for 1 hr after completion of the addition of the zinc, and was then extracted with chloroform. The organic layer was washed with sodium bicarbonate solution and with water and dried over magnesium sulfate. Evaporation of the solvent left 6.2 g of brown fluid, which was distilled under vacuum to give 4.65 g (0.033 mol, 68%), of 4-chloro-1,2-dimethylbenzene as a colorless liquid, bp 131–134° (25 mm).

B.—Chlorine gas was bubbled through a solution of bis(3,4-dimethylphenyl) sulfone (10.0 g, 0.0365 mol) in 200 ml of chloroform as described in part A. The course of the reaction was followed by ir spectroscopy. Introduction of chlorine was halted and the reaction was worked up as described above when the

(6) J. H. Uhlenbroek and M. Slagt, *Recl. Trav. Chim. Pays-Bas*, **80**, 1057 (1961).

(7) B. Miller and C. Walling, *J. Amer. Chem. Soc.*, **79**, 4187 (1957).

(8) O. Jacobsen, *Chem. Ber.*, **10**, 1009 (1877).

(9) H. Drews, S. Meyerson, and E. K. Fields, *J. Amer. Chem. Soc.*, **83**, 3871 (1961).

peak at 1090 cm^{-1} had essentially disappeared. The brown oil (13.2 g) obtained from the reaction was reduced as described above to give (after distillation) 7.28 g (0.052 mol, 71%) of 1.

Preparation of 4-Chlorotoluene.—*p*-Toluenesulfonyl chloride (15.0 g, 0.079 mol) was dissolved in 100 ml of chloroform, and the solution was stirred mechanically and irradiated by a 150-W incandescent bulb. Chlorine gas was passed through the solution until vpc analysis on a 6 ft, 3% SE-30 on Chromosorb W column showed that the *p*-toluenesulfonyl chloride was essentially completely reacted. The chlorine flow was stopped and the reaction mixture was worked up as described for the preparation of 1, to give 14.0 g of dark oil. The oil was suspended in 100 ml of rapidly stirred concentrated hydrochloric acid. Iron powder (7.0 g, 0.125 g-atom) was added slowly. The reaction mixture was stirred for 2 hr, filtered, and extracted with methylene chloride. The extract was washed with water and dilute sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give 6.1 g (0.048 mol, 61%) of brown fluid, whose ir and nmr spectra were identical with those of 4-chlorotoluene.

Registry No.—**1**, 615-60-1; **2**, 2905-30-8; bis(3,4-dimethylphenyl) sulfone, 28361-43-5; 4-chlorotoluene, 106-43-4; *o*-xylene, 95-47-6; *p*-toluenesulfonyl chloride, 98-59-9.

The Cyclization of 2-Benzamido-1-phenyl-1-propanol to 1-Phenyl-3-methylisoquinoline

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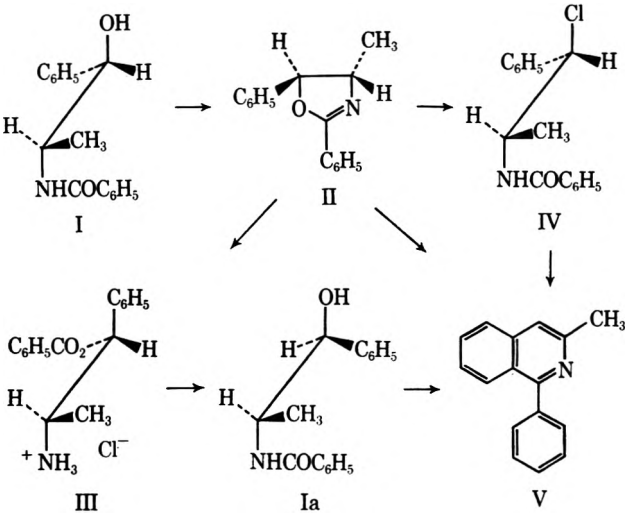
Received August 7, 1972

The cyclization of 3,4-diphenylbut-3-en-2-one oxime benzoate in nitrobenzene solution led unexpectedly to the formation of 1-phenyl-3-methylisoquinoline.[1] It was of great importance to us to confirm the identity of this cyclization product with a specimen obtained by a different route. The synthesis of 1-phenyl-3-methylisoquinoline by cyclization of 2-benzamido-1-phenyl-1-propanol given as a checked procedure,[2] based on the proposal earlier published,[3] furnished in our hands a product with mp 128–129°. On the other hand, our cyclization product obtained from 3,4-diphenylbut-3-en-2-one oxime benzoate had mp 89–90°, very close to that reported by Dobrovsky[4] and Gosh, *et al.*[5]

The uv, nmr, and mass spectra fully confirm the isoquinoline structure with the phenyl in the 1 and methyl in the 3 position. Our present task was to elucidate the structure of the compound obtained by Whaley and Hartung (mp 123–125°), quoted by Fitton and Smalley as having mp 126–127° and found by us to have mp 128–129°. In our opinion these were the same product, and the small differences in the melting points are caused by varying states of purity. The elemental analysis suggested the presence of oxygen and the data were in full agreement with those calculated for the starting material, 2-benzamido-1-phenyl-1-propanol. In addition the nmr spectrum was almost identical with that of starting amide and that of the product obtained after its treatment with P_2O_5 and $POCl_3$ in boiling xylene according to ref 2 and 3.

The only rational explanation is that the product claimed by Whaley and Hartung to be 1-phenyl-3-methylisoquinoline is in fact the threo isomer of the original erythro amide. The change of configuration in a series of analogous amides is well known.[6] The reaction pathways may be illustrated as follows.



The Whaley and Hartung product, in our opinion, is Ia, formed as a result of transformation I → II → III → Ia, and the reported derivatives were the hydrochloride and picrate of III. Our point of view has been confirmed by cyclization of both I and Ia in boiling decalin in the presence of phosphorus pentoxide. We have also synthesized 2,5-diphenyl-4-methyloxazoline (II) and 2-benzamido-1-chloro-1-phenylpropane (IV) and then we have refluxed them in decalin with P_2O_5. In all cases the only basic product was 1-phenyl-3-methylisoquinoline, mp 89–90°. The isolation of III after treatment of I with phosphorus oxychloride gives further support for our point of view. Our final conclusion, therefore, is that the cyclization of I does not take place under the conditions reported by Whaley and Hartung and quoted by Fitton and Smalley. The ring closure of 2-benzamido-1-phenyl-1-propanol takes place only when the amide is heated with phosphorus pentoxide at the much higher temperature of boiling decalin.

Experimental Section

Melting points were determined using a Thiele capillary melting point apparatus and are uncorrected. Uv spectra were determined with a C. Zeiss VSU-2P spectrophotometer, nmr spectra were recorded on a Tesla 80-MHz spectrometer, and ir spectra were recorded on a Unicam SP-200G spectrophotometer.

2-Benzamido-1-phenyl-1-propanol (I) was obtained from propiophenone by a three-stage synthesis according to ref 2: mp 143–144°; ir (Nujol) 3375, 3305 (NH, OH), 1640 (C=O), 1550 cm^{-1} (NH); nmr (DMSO-d_6) δ 1.05 (d, 3, CH_3), 4.13 (m, 1, C^2H), 4.69 (m, 1, C^1H), 5.39 (d, 1, OH), 7.08–7.88 (m, 10, aromatics), 8.12 (d, 1, NH).

2,5-Diphenyl-4-methyloxazoline (II) was obtained according

(1) S. Goszczyński and E. Salwińska, *Tetrahedron Lett.*, 5027 (1971).
(2) A. O. Fitton and R. K. Smalley, "Practical Heterocyclic Chemistry," Academic Press, New York, N. Y., 1968.
(3) W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949).
(4) A. Dobrovsky, *Monatsh. Chem.*, **82**, 140 (1951).
(5) T. N. Gosh and B. Bhabatosh, *J. Indian Chem. Soc.*, **36**, 425 (1959).
(6) J. Farkas and J. Sicher, *Collect. Czech. Chem. Commun.*, **20**, 1391 (1955).

to Nagai and Kanao:[7] bp 155° (5 mm); picrate mp 140–141°; nmr (CCl_4) δ 1.34 (d, 3, CH_3), 4.03 (m, 1, C^4H), 4.88 (d, 1, C^5H), 7.00–8.01 (m, 10, aromatics).

2-Benzamido-1-chloro-1-phenylpropane (IV) was prepared as described by Kojima:[8] mp 112–113°; ir (Nujol) 3375, 3305 (NH, OH), 1620 (C=O), 1550 cm^{-1} (NH).

2-Amino-1-benzoyloxy-1-phenylpropane Hydrochloride (III).—A 1-g portion of I dissolved in 10 ml of $POCl_3$ was allowed to stand at room temperature for 1 hr. Crushed ice was added, and the mixture was heated, boiled for 10 min, and cooled to give white needles. After recrystallization from water 0.9 g (79%), mp 220–221°, was obtained, ir (KBr) 2900 (NH_3^+), 1717 cm^{-1} (C=O). The hydrochloride when treated in alcoholic solution with picric acid gave picrate, mp 188–189°. The suspension of hydrochloride in water alkalized with dilute sodium hydroxide furnished Ia, mp 128–129°.

Treatment of 2-Benzamido-1-phenyl-1-propanol with P_2O_5 and $POCl_3$ in Boiling Xylene (I → Ia).—A 2-g portion of the amide was refluxed in 50 ml of xylene with 20 g of phosphorus pentoxide and 20 ml of phosphorus oxychloride for 2.5 hr. The further work-up used was similar to that described by Fitton and Smalley.[2] After recrystallization from ethanol, Ia had mp 128–129°; yield 1.3 g (65%); nmr (DMSO-d_6) δ 0.94 (d, 3, CH_3), 4.18 (m, 1, C^2H), 4.64 (m, 1, C^1H), 5.40 (d, 1, OH), 7.08–7.99 (m, 11, aromatics and NH); ir (Nujol) 3350 (NH, OH), 1637 (C=O), 1543 cm^{-1} (NH).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 75.28; H, 6.71; N, 5.48. Found: C, 75.36; H, 6.80; N, 5.44.

Cyclization of 2-Benzamido-1-phenyl-1-propanol (I, Ia) to 1-Phenyl-3-methylisoquinoline (V).—To 2.0 g of the amide I suspended in 50 ml of decalin, 20 g of phosphorus pentoxide was added. The mixture was refluxed for 3 hr, then cooled and 100 g of crushed ice was added. The decalin layer was separated and the aqueous solution was extracted with 50 ml of ether. The aqueous layer was made alkaline with 130 ml of 30% potassium hydroxide solution and then extracted with ether. The extracts were washed once with water and dried over KOH, and the solvent was removed, leaving 1.3 g (70%) of pale yellow oil which crystallized on standing.

Crystallization from ethanol gave colorless crystals, mp 89–90°, picrate mp 200–201°, hydrochloride mp 228–229°.

The free base had uv max (MeOH) 332 nm (ε 6000); uv (0.01 *N* HCl) 351 nm (ε 8900); nmr (CCl_4) δ 2.7 (s, 3, CH_3), 7.3–8.1 (m, 10, aromatics).

Anal. Calcd for $C_{16}H_{13}N$: C, 87.67; H, 5.98; N, 6.39. Found: C, 87.85; H, 6.15; N, 6.40.

The structure was further confirmed by mass spectral analysis,[9] which gave the correct molecular ion at *m/e* 219. The cyclization of the isomeric amide, mp 128–129° (Ia) (obtained after treatment of amide, mp 143–144°, with P_2O_5 and $POCl_3$ in boiling xylene or from III) gave the same result.

Cyclization of 2,5-Diphenyl-4-methyloxazoline.—A 2-g portion of II dissolved in 50 ml of decalin was treated with 20 g of P_2O_5 and refluxed for 3 hr. After cooling, 100 g of crushed ice was added, the decalin layer was removed, and the water layer was extracted several times with ether. The acidic water solution was made alkaline with 130 ml of 30% potassium hydroxide and extracted with ether. The combined ether extracts were washed with water and dried over KOH. The evaporation of ether left 1.13 g (60%) of pale yellow oil which crystallized on scratching. Recrystallization from ethanol gave colorless crystals, mp 89–90°. The uv and nmr spectra were identical as given above.

Cyclization of 2-Benzamido-1-chloro-1-phenylpropane.—A 2-g portion of IV was heated in boiling decalin with 20 g of phosphorus pentoxide for 3 hr. The further work-up was similar to that described for cyclization of II. The yield was 0.78 g (37%), mp 89–90°. The spectral data were in accordance with those found for V.

Registry No.—I, 38222-75-2; Ia, 38222-76-3; II, 38222-77-4; III, 38222-78-5; III picrate, 38222-79-6; V, 1616-50-8; V picrate, 38222-81-0; V HCl, 38222-82-1; propiophenone, 93-55-0.

(7) W. N. Nagai and S. Kanao, *Justus Liebigs Ann. Chem.*, **470**, 157 (1929).

(8) M. Kojima, *Yakugaku Zasshi*, **79**, 11 (1959).

(9) S. Goszczyński, E. Salwińska, and M. Łożyński, *Zesz. Nauk. Pol. Pozn.*, in press.

Communications

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

Friedel–Crafts Reactions of Amino Compounds. New Method for the Preparation of 1-Amino-4-hydroxyanthraquinone[1]

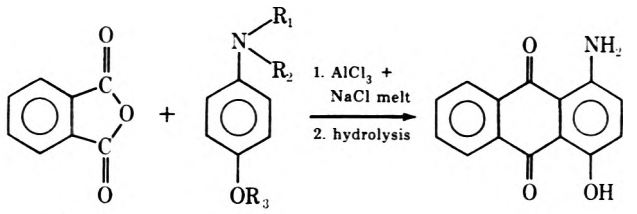
Summary: Friedel–Crafts reaction of substituted amines has resulted in a new method for the preparation of 1-amino-4-hydroxyanthraquinone.

Sir: The Friedel–Crafts acylation and cyclization reactions have been used for the direct synthesis of anthraquinones and related compounds.[2-5] However, no aminoanthraquinones have yet been prepared by this method where amino derivatives are directly involved as reaction species.

We wish to report the direct synthesis of 1-amino-4-hydroxyanthraquinone (III), commercially known as Celliton Fast Pink B and used as dye for all classes of fibers.[6] The dye has been prepared earlier from anthraquinone derivatives.[7-9]

The reaction of 4-aminophenol and its derivatives was studied in detail where aminophenols IIa–e were condensed with phthalic anhydride I in presence of $AlCl_3$–NaCl melt (Scheme I).

SCHEME I



I II III

IIa, $R_1 = R_2 = R_3 = H$
b, $R_2 = R_3 = H$; $R_1 = COCH_3$
c, $R_2 = R_3 = H$; $R_1 = COC_6H_5$
d, $R_1 = R_2 = R_3 = COC_6H_5$
e, $R_1 = R_2 = R_3 = COCH_3$

The reactions were carried out at various temperature ranges, between 170 and 210°, and time durations, 15 to 45 min, yielding compound III, 3% from 4-aminophenol (IIa), 10% from *N*-acetyl-4-aminophenol (IIb), 15% from *N*-benzoyl-4-aminophenol (IIc), 20% from tribenzoyl-4-aminophenol (IId), and 45% from triacetyl-4-aminophenol (IIe).

1-Amino-4-hydroxyanthraquinone (III) from IIe.—An intimate slurry of IIe (4 g) and I (4 g) was gradually added with stirring to a clear melt of anhydrous $AlCl_3$ (40 g) and NaCl (10 g) at 170–180°. The mixture was further stirred at 200–210° for 45 min, cooled, and digested with 2 *N* hydrochloric acid. The reaction product was thoroughly washed with water and dried and its benzene extract was chromatographed over silica gel. The pink band obtained, after eluting the column with benzene–acetone mixture (90:10), and on crystallization from benzene gave pink plates III, 2.5 g, mp 215°. The purity of the compound was checked by tlc (R_f 0.32; silica gel–benzene), analytical data (Calcd for $C_{14}H_9O_3N$: C, 70.29; H, 3.76; N, 5.85. Found: C, 70.42; H, 3.69; N, 5.78.) and spectral results [ir ν_{max} 3500, 3400, 1640, 1600, 1540, 1470, 1250, 1190, 840, 800, 740 cm^{-1}; mass spectrum ($M\cdot^+$) *m/e* 239, 212, 211, 183, 182, 107, 100, 76].

It was observed that fully protected amino groups yield better results as is evident from reactions with IId and IIe. It is interesting to note that IIe gave the best yield (45%) of the anthraquinone III. The lesser yield of III with IId may possibly be due to steric factor, the benzoyl group shielding the reactive center.

Acknowledgments.—We are indebted to Professor R. C. Kapoor for providing facilities and to Professor Paul J. Scheuer, University of Hawaii, for spectral analysis.

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Preparation of 7-*cis*-Ionyl and -Ionylidene Derivatives and Other Sterically Hindered Olefins by One-Way Sensitized Geometric Isomerization[1]

Summary: Quantitative preparations of many sterically hindered olefins have been achieved by selective triplet sensitization.

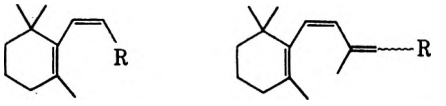
Sir: The severe steric hindrance (methyl–methyl or methyl–hydrogen interaction) present in the 7- and 11-cis isomers of vitamin A and carotenoids once cast doubt on their possible existence,[3] but, since then, 11-cis vitamin A (the less hindered of the two) and other compounds with similar steric interactions have been routinely prepared by selective hydrogenation of the corre-

(1) Presented in part at the Chemists Convention Bombay, India, 1971.
(2) C. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley, New York, N. Y., 1970, p 737.
(3) N. S. Dokunikhim, Z. Moisoeva, and U. A. Maytrikova, *Zh. Org. Khim.*, **2** (3), 516 (1966).
(4) V. M. Chari, S. Neelkantan, and T. R. Seshadri, *Indian J. Chem.*, **4**, 330 (1966).
(5) N. S. Bhide and A. V. Rama Rao, *Indian J. Chem.*, **7**, 997 (1969).
(6) K. Venkatraman, "The Chemistry of Synthetic Dyes," Academic Press, New York, N. Y.: Vol. II, 1952, p 805; Vol. III, 1970, p 391.
(7) I. G. Farbenindustrie, A. G., German patent 558,459 (1930); *Chem. Abstr.*, **27**, 309 (1933).
(8) Y. Bansho and K. Kondo, *J. Chem. Soc. Jap.*, **57**, 751 (1954).
(9) V. I. Gadzenko, V. A. Lavrishchev, N. I. Shuliko, and V. Z. Maslosh, U. S. S. R. patent 243,118 (1969); *Chem. Abstr.*, **71**, 82640 (1969).

(1) Photochemistry of Polyenes. III. The material on which this communication is partially based was presented in a plenary lecture at the 23rd IUPAC Congress, Boston, Mass, July 1971. The proceedings of this congress have been published.[2]
(2) R. S. H. Liu, *Pure Appl. Chem., Suppl. (23rd Congr.)*, **1**, 335 (1971).
(3) L. Pauling, *Fortschr. Chem. Org. Naturstoffe*, **3**, 203 (1939).

sponding dehydro compounds.[4] A similar method, however, failed to give 7-cis vitamin A,[5] in fact up to now there is no general method for preparation of this class of sterically hindered olefins.[6] Naturally the properties of such compounds are virtually unknown. In this communication we wish to report a simple photochemical method that shows promise as a general route to these compounds.

The method of choice is photosensitized isomerization under conditions where selectivity of energy transfer to the trans isomer is such that the eventual stationary state consists entirely of the hindered cis isomer. Selective energy transfer to the geometric isomer of lower triplet energy resulting in enrichment of the higher energy one is a well-known phenomenon in mechanistic studies of sensitized isomerization of olefins,[7] but, previously, in no case was the synthetically desirable condition of complete conversion to the high energy isomer reached.[7b] Now, we have found that in the series of β-ionyl derivatives (I), because of the high energy required for excitation of the skewed cis isomer,[8] conditions for selective energy transfer to the trans isomer can be easily found. For example, irradiation of a dilute solution of *trans*-β-ionol in the presence of 2-acetonaphthone, under the usual conditions for sensitized isomerization, results in rapid and quantitative formation of the cis isomer. The product is readily identified by its pmr spectrum ($J_{7,8}$ = 11.2 Hz with the remaining features similar to that of *trans*-ionol).[2] Similarly, other *trans*-β-ionyl derivatives are quantitatively converted to the corresponding cis isomers and, with fluorenone, β-ionone to an equilibrium mixture of *cis*-ionone and the related α-pyran[9] (Table I).



I II

That the observed one-way sensitized isomerizations are indeed due to selective energy transfer to the trans isomers can be inferred from a study of the dependence of photostationary state compositions on sensitizer triplet excitation energy, a method commonly employed in such mechanistic studies.[7] Results with β-ionol are shown in Figure 1. Clearly, the plot indicates that any sensitizer with energy below ~65 kcal/mol produces one-isomer stationary states. With higher energy sensitizers, larger amounts of the trans isomer are present, presumably because increased rates of energy transfer to the cis isomer reduce the selectivity of transfer to the trans. The plot also suggests that the triplet energy of *cis*-ionol is ~75 kcal/mol, expectedly higher

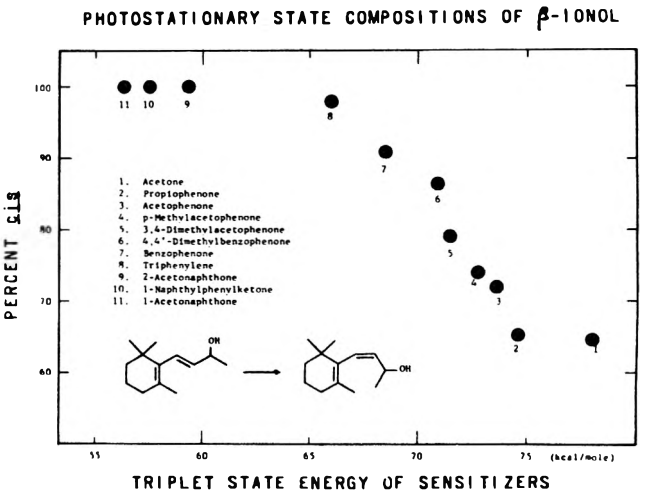


Figure 1.

TABLE I
PRODUCTS FROM ONE-WAY SENSITIZED GEOMETRIC ISOMERIZATION[a]

Product	R	Critical sensitizer (E_T, kcal/mol)[b]
I	CH_3	2-Acetonaphthone (59.3)
	C_2H_5	
	CH_2OH	
	$CH(CH_3)OH$	
	CN	
	$COCH_3$	9-Fluorenone (51)
	CO_2H	
	C_6H_5	Benzanthrone (47)
II[c]	CO_2CH_3	Benzanthrone (47)
	$CO_2C_2H_5$	
	CO_2H	
	CN	
2,4,6-Trimethylstyrene	β-Methyl	Benzophenone (68.5)
	β-Ethyl	
2,4,6-Trimethylstilbene		2-Acetonaphthone (59.3)

[a] Starting from the corresponding trans isomer or, in II, mixtures of 7-trans isomers. [b] Reference 7a. [c] Mixtures of 7-cis isomers, *e.g.*, for R = $CO_2C_2H_5$, 7-*c*-9-*t* (56%), 7-*c*-9-*c* (44%).

than the values for common conjugated dienes (55–60 kcal/mol).[10]

The usefulness of this method for preparing hindered olefins has been further demonstrated by preparing mixtures of 7-*cis*-ionylidene derivatives (II), *cis*-2,4,6-trimethylstyryl derivatives, and *cis*-2,4,6-trimethylstilbene[11] (Table I). Clearly in some cases sensitizers of lower E_T have to be used to achieve quantitative conversion to the cis isomer.[12]

cis-ionyl and -ionylidene derivatives show remarkable thermal stability. For example, *cis*-β-ionol is stable below 150° and dehydrates at higher temperatures, while ethyl ionylideneacetate is stable below 100° and cyclizes at higher temperatures. Being thermally stable and now readily available, these compounds are clearly potential intermediates to the presently unknown iso-

(4) For a up-to-date treatise on carotenoids see "Carotenoids," O. Isler, Ed., Birkhauser Verlag, Basel and Stuttgart, 1971.

(5) G. Wald, P. K. Brown, R. Hubbard, and W. Oroshnik, *Proc. Nat. Acad. Sci.*, **41**, 438 (1955); **42**, 578 (1956).

(6) Photochemically 7-*cis*-ionylidene compounds have been observed as intermediates or components of a complex product mixture; see M. Mousseron, *Advan. Photochem.*, **4**, 195 (1966). In only one case was selective hydrogenation reported to give an ionyl derivative; see J. Redel, J. Boch, and S. Tchen, *C. R. Acad. Sci. Paris*, **259**, 2466 (1964).

(7) (a) G. S. Hammond, *et al.*, *J. Amer. Chem. Soc.*, **86**, 3197 (1964); (b) J. Saltiel, *et al.*, *Org. Photochem.*, in press.

(8) From values of long range coupling constants the ring–chain dihedral angle in *cis*-β-ionol has been estimated to be 40–52°: V. Ramamurthy, T. T. Bopp, and R. S. H. Liu, *Tetrahedron Lett.*, 3915 (1972).

(9) The equilibrium was reported by E. N. Marvell, G. Caple, T. A. Gosnik, and G. Zimmer, *J. Amer. Chem. Soc.*, **88**, 619 (1966).

(10) R. S. H. Liu, N. J. Turro, and G. S. Hammond, *ibid.*, **87**, 3406 (1965).

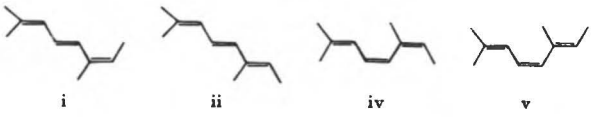
(11) Isomerization of hindered stilbenes by high energy sensitizers was reported by D. Gegiou, K. A. Muszkat, and E. Fischer, *ibid.*, **90**, 3907 (1968).

(12) As pointed out by a referee with low energy sensitizers these systems behave differently as in stilbenes where nonvertical excitation was postulated to account for the results. Mechanistic implications of our results are being examined in detail and will be reported in detail.

mers of 7-cis vitamin A and carotenoids. Such possibilities are being examined in our laboratory.

For less hindered compounds the method of selective sensitization for quantitative conversion to the cis isomer apparently does not apply. For example, in the case of alloocimene,[13] a model for the C_9–C_{13} fragment of carotenoids containing the less hindered C_{11}–C_{12} double bond, sensitization by a variety of sensitizers fails to give mixtures containing entirely the central cis isomers even though some enrichment is noted (Table II).[14]

TABLE II
PHOTOSTATIONARY STATE MIXTURES OF ALLOOCIMENE



Sensitizer (E_T)	Alloocimene i	ii	iv	v
Benzophenone (68.5)	25	39	19	15
Benzanthrone (47)	25	34	25	15
Dimethylbenzanthracene (44)	19	38	26	18

Acknowledgment.—The work was partially supported by grants from the Sloan Foundation, The Public Health Service (RO1 EY-AM 00918-01), and the U. H. Biomedical Research Program.

(13) R. S. H. Liu and Y. Butt, *J. Amer. Chem. Soc.*, **93**, 1532 (1971).

(14) In this case there is a dependence of stationary composition on triene and sensitizer concentrations; therefore values extrapolated to zero sensitizer and triene concentration are reported.

(15) (a) NSF Undergraduate Summer Research Fellow (b) Alfred P. Sloan Research Fellow, 1970–1972.

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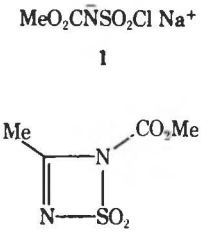
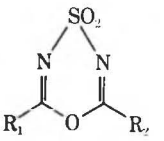
DECEMBER 15, 1972

The Fragmentation of Substituted 1,4,3,5-Oxathiadiazine Dioxides to *N*-Sulfonylamines

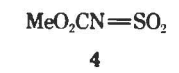
Summary: Certain nitriles react with the sodium salt of carbomethoxysulfamoyl chloride to afford 6-substituted 2-methoxy-1,4,3,5-oxathiadiazine dioxides, **2**, whose thermal cycloreversion gives methyl-*N*-sulfonylurethane, **4**, which participates in subsequent cycloadditions with alkenes.

Sir: In connection with synthetic studies[1,2] on the generation of *N*-sulfonylamines *via* dehydrohalogenation of sulfamoyl chlorides we investigated the chemistry of adducts derived from nitriles and this heterocumulene. The salt (**1**) derived[2] from reaction of carbomethoxysulfamoyl chloride with sodium hydride at −78° reacts with acetonitrile at 0–30° to afford (75%) an adduct,[3] mp 102–102.5° dec, which displayed nmr[4] singlets at δ 4.08 and 2.37 and intense ir ($CHCl_3$) absorption at 1705 and 1615 cm^{-1}, and underwent facile hydrolysis (H_2O/THF, 30°) to *N*-acetyl-*N'*-carbomethoxysulfamide, mp 149–150° dec. Although such spectral[5,6] and chemical evidence is consistent with either structure **2a** or **3** for this adduct, the former was shown to be correct based on the following results. The reaction of *N*-chlorosulfonyl-*N'*-methyl-*N'*-phenylurea[7] with an excess of phenylmethylcyanamide in THF at 30° gave (80%) of the symmetrically disubstituted oxathiadiazine **2b**, mp 175–176°, which exhibited the same C=N ir double absorption at 1685 and 1605 cm^{-1} but had symmetry consistent with the observed unsplit 6 H methyl group signal at δ 3.26 in the nmr. As final support for this argument, **1** reacts



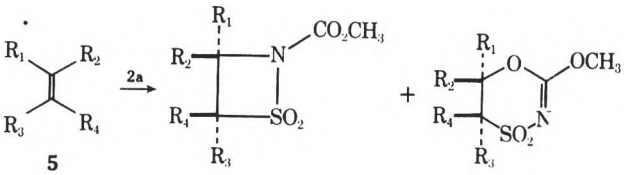


2a, R_1 = Me; R_2 = OMe
b, R_1 = R_2 = $C_6H_5(CH_3)N$
c, R_1 = *p*-$MeOC_6H_5$; R_2 = OMe
d, R_1 = Me_2N; R_2 = OMe



with dimethylcyanamide to give **2d**, mp 162–163°, whose ir (in $CHCl_3$, 1700 and 1620 cm^{-1}) and nmr [δ 4.08 (s, 3 H), 3.13 (s, 6 H)] are similar to those of **2a**.

These substituted 1,4,3,5-oxathiadiazine dioxides apparently undergo a thermal [2 + 4] cycloreversion at moderate temperatures in a variety of solvents to provide, along with the corresponding nitrile, *N*-sulfonylurethane **4** as evidenced by the isolation of cycloadducts by reaction with appropriate alkenes. Reaction of **2a** with **5a**, **5b**, and **5c** in THF or acetonitrile at



5 6 7

Compd	R_1	R_2	R_3	R_4
a	Ph	Ph	H	H
b	Ph	H	H	H
c	Me	Me	Me	H
d	Ph	H	Ph	H

30–60° gave the 2-carbomethoxy-1,2-thiazetidines[2] **6a**, **6b**, and **6c** and the 2,3-dihydro-6-methoxy-1,4,5-oxathiazines[2] **7b** and **7c** whose distribution was both

(1) E. M. Burgess and G. M. Atkins, Jr., *J. Amer. Chem. Soc.*, **94**, 6135 (1972).

(2) E. M. Burgess and W. M. Williams, *ibid.*, **94**, 4386 (1972).

(3) Satisfactory elemental analyses and exact mass spectra were obtained on the new compounds reported herein.

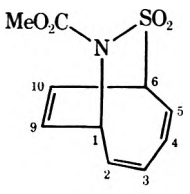
(4) All nmr spectra were recorded in $CDCl_3$ at 60 MHz.

(5) The possibility that the oxathiadiazine **2a** has a coupled C=N vibration leading to resonance splitting to give the 1705 cm^{-1} ir signal could not be discounted at this point.

(6) The nitrogen core binding energy signal observed in the ESCA spectrum was so broad that no definitive structural assignment could be made. We thank Dr. David Hercules at the University of Georgia for this measurement.

(7) This precursor is available from the reaction of chlorosulfonylisocyanate and *N*-methylaniline: R. Graf, *Angew. Chem. Int. Ed. Engl.*, **7**, 172(1968).

temperature and solvent dependent.[8] Employing the advantage of higher reaction temperature accessible by this method of *N*-sulfonylamine generation, cycloadducts were obtained from otherwise unreactive alkenes. For example, a mixture of *cis*-stilbene (**5d**) and 2a when melted (105°) affords the adduct **7d**, mp 157–159°, whose cis stereochemistry is evident from the benzylic hydrogen doublet nmr signals at δ 6.42 and 4.60 with a J = 3.0 Hz.[9] Cyclooctatetraene and 2a in acetonitrile at 80° led in low yield to the bicyclic sulfonamide **8**, mp 172–173° dec, whose structural fea-



8

tures were revealed by nmr signals at δ 6.09 (m, $H_{2-5,9,10}$), 5.07 (d of d, J = 6.5 Hz, H_6), 4.45 (d of d, J = 8.0 Hz, H_2), 3.85 (s, 3 H); uv λ_{max}^{EtOH} 261 nm (ϵ 2050); and ir absorption ($CHCl_3$) at 1735 cm^{-1} (C=O); and whose genesis probably involves closure of an appropriately substituted dipolar homotropylium cation intermediate.[10] Finally, new oxathiadiazines result from a cycloreversion–addition interchange of the incipient nitrile function in 2a. A melt (60°) of *p*-methoxybenzonitrile and 2a results in the formation of **2c**, mp 138–139°, whose thermal decomposition at 160° likewise provides **4**.

Acknowledgments.—We sincerely wish to thank the National Institutes of Health (GM-12672) and the National Science Foundation (GP-27956) for support.

(8) The mechanistic explanation for these effects on the cycloaddition mode has been advanced in ref 2.

(9) Some *trans*-stilbene is formed in the reaction but no cycloadducts with this stereochemistry were present.

(10) L. A. Paquette, J. R. Malpass, and T. J. Barton, *J. Amer. Chem. Soc.*, **91**, 4714 (1969).

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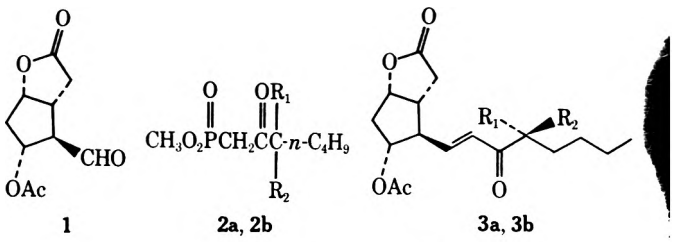
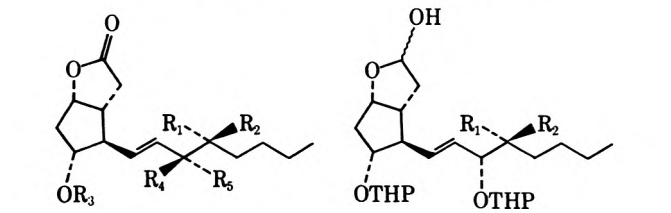
The Synthesis of 16(*R*)- or 16(*S*)-Methylprostaglandins

Summary: The synthesis of 16(*R*)- or 16(*S*)-methylprostaglandins and their C-15 epimers has been accomplished starting from the lactone **1**, the intermediate for the synthesis of natural prostaglandins.

Sir: We have recently investigated the synthesis of compounds having a prostanoic acid skeleton. The present paper describes the synthesis of 16(*R*)- or 16(*S*)-methylprostaglandins. Recently, synthesis and biological activities of 16,16-dimethylprostaglandins have been reported by Robert, *et al.*[1]

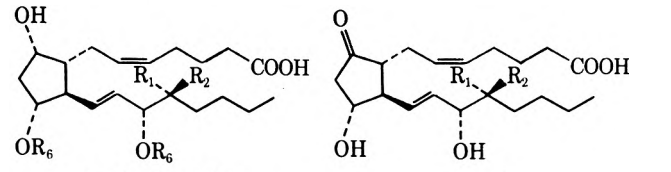


1 **2a, 2b** **3a, 3b**



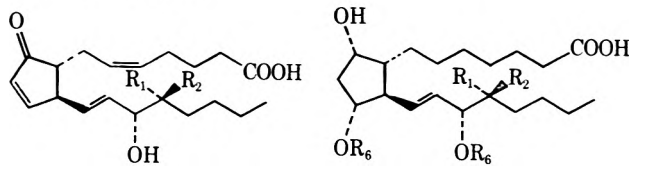
4c, 4b, R_3 = Ac; R_4 = H; R_5 = OH
4'a, 4'b, R_3 = Ac; R_4 = OH; R_5 = H

5a, 5b



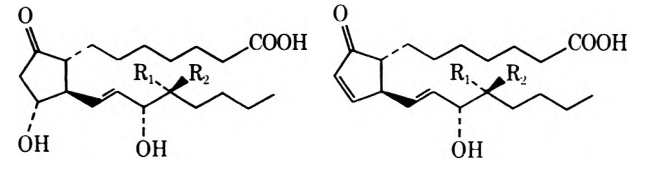
6a, 6b, R_6 = THP
7a, 7b, R_6 = H

8a, 8b



12a, 12b

9a, 9b, R_6 = THP
10a, 10b, R_6 = H



11a, 11b **13a, 13b**

2a–13a, R_1 = CH_3; R_2 = H [16(*R*)-methyl series]

2b–13b, R_1 = H; R_2 = CH_3 [16(*R*)-methyl series]

For the synthesis of 16(*R*)- or 16(*S*)-methyl-PGs, we used as starting material β-acetoxyaldehyde (**1**), which was prepared by Corey, *et al.*,[2] for the synthesis of natural PGs. Synthesis of 16(*R*)-methyl-PGs was initiated by the reaction of **1** with the sodium derivative of the 2-oxophosphonate **2a** $\{[\alpha]^{25}D$ −11.6° (*c* 8.6, Et_2O)$\}$ in THF at room temperature for 1 hr to form trans enone lactone **3a** [ir (liquid film) ν 1775, 1740, 1690, 1640, 1625 cm^{-1}] in 62% yield. Similarly, **3b** [ir (liquid film) ν 1780, 1740, 1690, 1660, 1630 cm^{-1}] was obtained from **1** with the sodium derivative of the 2-oxophosphonate **2b** $\{[\alpha]^{25}D$ +15.1° (*c* 6.11, Et_2O)$\}$ in 55% yield. **2a** and **2b** were prepared from the α-lithio derivative of dimethyl methylphosphonate and ethyl 2(*R*)-methylhexanoate[3] and 2(*S*)-methylhexanoate,[3] respectively.

3a and **3b** were reduced with excess $NaBH_4$ and separated from the 15β-hydroxy compounds by column chromatography on silica gel. This gave **4a** [ir (liquid

(1) A. Robert and B. J. Magerlein, International Conference on Prostaglandins, Vienna, Sept 25, 1972.

(2) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

film) ν 3400, 1780, 1740 cm^{-1}] in 37% yield and **4b** [ir (liquid film) ν 3400, 1775, 1740 cm^{-1}] in 44% yield. From **4a** and **4b** the synthesis of the target PGs was carried out using essentially the same experimental conditions as described earlier by Corey, *et al.*[2] Thus **4a** or **4b** was converted into the diol by hydrolysis of the acetyl group, the two hydroxy groups were protected with dihydropyran and a catalytic amount of *p*-toluenesulfonic acid, and the lactone ring was reduced with diisobutylaluminium hydride to obtain the corresponding lactol **5a** in 100% yield from **4a** or **5b** in 97% yield from **4b**.

5a and **5b** were condensed with 4-carboxy-*n*-butylidenetriphenylphosphorane in dimethyl sulfoxide to form bis(tetrahydropyranyl) ethers (**6a** and **6b**) in 52 and 63% yield, respectively. Hydrolysis of **6a** and **6b** using AcOH–H_2O (2:1) afforded 16(*R*)-methyl-PGF$_{2\alpha}$[4] (**7a**), $[\alpha]^{21}D$ +26.7° (*c* 0.493, EtOH), in 77% yield and 16(*S*)-methyl-PGF$_{2\alpha}$[4] (**7a**), $[\alpha]^{21}D$ +45.2° (*c* 0.438, EtOH), in 75% yield.

Oxidation by chromic acid reagent and hydrolysis using AcOH–H_2O (2:1) of **6a** and **6b** afforded 16(*R*)-methyl-PGE$_2$[4] (**8a**), $[\alpha]^{21}D$ −56.4° (*c* 0.841, EtOH), in 56% yield and 16(*S*)-methyl-PGE$_2$[4] (**8b**), $[\alpha]^{21}D$ −66.9° (*c* 0.797, EtOH), in 62% yield.

Selective reduction[5] of the cis double bond of **6a** and **6b** using 5% palladium/carbon catalyst afforded **9a** and **9b** in 96 and 96% yield, respectively.

Hydrolysis of **9a** and **9b** using AcOH–H_2O (2:1) afforded 16(*R*)-methyl-PGF$_{1\alpha}$ (**10a**) in 62% yield and 16(*S*)-methyl-PGF$_{1\alpha}$ (**10b**) in 61% yield. Oxidation by chromic acid reagent and hydrolysis of **9a** and **9b** afforded 16(*R*)-methyl-PGE$_1$[4] (**11a**), $\alpha^{21}D$ −44.8° (*c* 0.592, EtOH), in 50% yield and 16(*S*)-methyl-PGE$_1$[4] (**11b**), $\alpha^{21}D$ −53.4° (*c* 0.608, EtOH), in 72% yield.

Dehydration[6] of **8a**, **8b**, **11a**, and **11b** in AcOH–H_2O (9:1) afforded respectively 16(*R*)-methyl-PGA$_2$ (**12a**), in 81% yield, 16(*S*)-methyl-PGA$_2$[4] (**12b**), $[\alpha]^{21}D$ +165.4° (*c* 0.256, EtOH), in 74% yield, 16(*R*)-methyl-PGA$_1$ (**13a**), in 77% yield, and 16(*S*)-methyl-PGA$_1$ (**13b**), in 71% yield.

In a similar manner the 16(*R*)-methyl-15-epi-PGs and 16(*S*)-methyl-15-epi-PGs were obtained from acetoxy alcohols **4'a** and **4'b**. Ir and nmr spectra of these 15-epi-PGs were essentially identical with those of 16-methyl-PGs, but R_f values of 15-epi-PGs on tlc on silica gel were slightly larger than those of the corresponding 16-methyl-PGs.

The 16(*R*)- and 16(*S*)-methyl-PGs showed much stronger PG-like biological activities than the natural PGs. For example, 16(*R*)-methyl-PGE$_2$ was 100–200 times more active than PGE$_2$ in gastric juice inhibition (rat). 16(*R*)- and 16(*S*)-methyl-15-epi-PGs also showed strong activity. It is of interest that compounds with different C-15 stereochemistry show similar bioactivity.

Biological activities of these PGs will be described in a subsequent paper.

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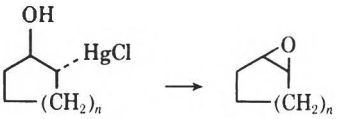
RECEIVED JANUARY 4, 1973

The Base-Catalyzed Decomposition of β-Hydroxyalkylmercuric Chlorides

Summary: A series of β-hydroxyalkylmercuric chlorides undergo decomposition to epoxides and ketones upon treatment with base in diglyme.

Sir: Although the addition of mercuric salts to olefins in the presence of water to give β-hydroxyalkylmercuric salts was discovered at the turn of the century, these compounds have received little consideration as synthetic intermediates.[1,2] Indeed, their best known transformation is a facile reversion to starting olefin under a variety of conditions.[1b] In view of the fact that mercury has been demonstrated to function as a leaving group in the solvolysis of alkylmercuric salts,[4] β-hydroxyalkylmercuric salts would be anticipated to undergo reactions similar to those of 1,2-halohydrins and β-hydroxy tosylates. Although early reports indicate that mercury-free products are not formed on exposure of these compounds to bases,[5] we have treated a series of β-hydroxyalkylmercuric chlorides with a variety of bases in diglyme at elevated temperature and wish to report that they undergo facile decomposition to epoxides and ketones (Table I).

In analogy to the corresponding 1,2-halohydrins,[6] *trans*-2-hydroxycyclopentylmercuric chloride (**1a**) and



1a, $n = 1$ **2a**, $n = 1$
b, $n = 2$ **b**, $n = 2$
c, $n = 3$ **c**, $n = 3$

trans-2-hydroxycyclohexylmercuric chloride (**1b**), on treatment with base, provide a convenient and high yield source of cyclopentene oxide (**2a**) and cyclohexene oxide (**2b**), respectively. The cycloheptyl derivative

(1) For reviews, see (a) N. S. Zefirov, *Russ. Chem. Rev.*, **34**, 527 (1965); (b) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(2) Hydroxymercuration followed by demercuration with NaBH$_4$ has recently been shown to be a useful procedure for the Markovnikov hydration of olefins.[3]

(3) (a) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967); (b) H. C. Brown and W. J. Hammar, *ibid.*, **89**, 1524 (1967); (c) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967); (d) S. Moon and B. H. Waxman, *Chem. Commun.*, 1283 (1967).

(4) (a) F. R. Jensen and R. J. Ouellette, *J. Amer. Chem. Soc.* **83**, 4478 (1961); (b) F. R. Jensen and R. J. Ouellette, *ibid.*, **83**, 4477 (1961).

(5) (a) K. A. Hofmann and J. Sand, *Chem. Ber.*, **33**, 1340 (1900); (b) J. Sand and K. A. Hofmann, *ibid.*, **33**, 1358 (1900); (c) W. Manchot and A. Klüg, *Justus Liebigs Ann. Chem.*, **420**, 170 (1920).

(6) (a) L. Goodman, A. Benitez, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 1680 (1958); (b) A. E. Osterberg, "Organic Syntheses," Collect. Vol I, Wiley, New York, N. Y., 1941, p 185.

(3) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **84**, 584 (1929).

(4) Ir and nmr (at 100 MHz) spectra were in agreement with the assigned structure and 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-73-1250. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(5) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970).

(6) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

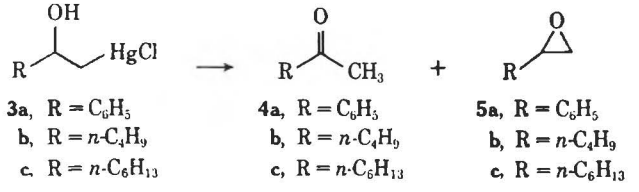
TABLE I

DECOMPOSITION OF REPRESENTATIVE β-HYDROXYALKYLMERCURIC CHLORIDES WITH VARIOUS BASES IN DIGLYME[a]

Hydroxymercurial	Base[b]	Temp, °C	Time, hr	Product yield, %[c] Epoxide	Ketone	Olefin	Mercury
1a	NaOMe	90	1	22	0	39	
			21.5	56	5		
1a	$KOCMe_3$	90	1	69	24	8	
1b	K_2CO_3[d]	120	25	33		18	23[e]
1b	NaH[f]	125	19	45		8	44[e]
1b	NaOMe[g]	120	0.75	81 (43[e])			
1b	$KOCMe_3$	117	0.75	99			88[h]
1c	NaOMe	115	0.75		<2	56	
			2.5		10	58	
			23	15	35	57	51[e]
1c	$KOCMe_3$[g]	100	19	19	70	5	
3a	$KOCMe_3$	107	6	0	31	25	
3b	NaOMe	120	2.5	0	18	39	
			23	<2	50		
3b	$KOCMe_3$	100	1.2	0	5	45	
			24.5	0	22[i]		
3c	NaOMe	120	21		40	48	

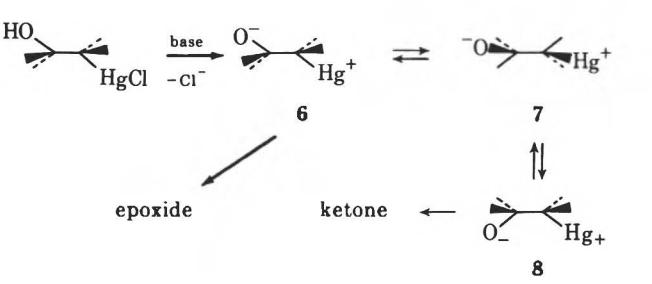
[a] The reactions were carried out under a nitrogen atmosphere. [b] A 1.1 mol ratio of base to hydroxymercurial was employed unless otherwise specified. [c] Determined by quantitative gas chromatography unless otherwise specified; structural assignments were made by comparison with authentic samples. [d] A 1.0 mol ratio of base to hydroxymercurial was employed. [e] Isolated yield. [f] A 3.1 mol ratio of base to hydroxymercurial was employed. [g] A 1.3 mol ratio of base to hydroxymercurial was employed. [h] Isolated yield after a 19-hr reaction period. [i] Based on incomplete reaction. There was a 29% recovery of **3b**.

1c,[7,8] however, affords primarily cycloheptanone, the product of a 1,2-hydride shift. The acyclic hydroxymercurials **3a**, **3b**,[7] and **3c**[7] also afforded ketone rearrangement products **4a**, **4b**, and **4c** in good yield while essentially none of the corresponding epoxides **5a**, **5b**, and **5c** were obtained. Aldehyde formation, which would result from alkyl or aryl migration, was not observed. This, therefore, provides a convenient synthetic procedure for carrying out a directed pinacol-type rearrangement under basic conditions in acyclic compounds or cycloheptyl derivatives, a transformation for which there are no satisfactory existing methods. Analogous 1,2-halohydrins, β-hydroxy tosylates, and related compounds afford epoxides under basic conditions.[9]



3a, R = C_6H_5 **4a**, R = C_6H_5 **5a**, R = C_6H_5
b, R = n-C_4H_9 **b**, R = n-C_4H_9 **b**, R = n-C_4H_9
c, R = n-C_6H_{13} **c**, R = n-C_6H_{13} **c**, R = n-C_6H_{13}

The base-catalyzed reaction of β-hydroxyalkylmercuric chlorides to give either epoxides or ketones presumably occurs through an initial proton abstraction to give a zwitterion[5a] which could adopt conformations **6**, **7**, or **8**. With the cyclopentyl and cyclohexyl derivatives **1a** and **1b**, the rigidity of the ring system permits the resulting zwitterion to exist in conformations **6** or **7** but not **8**. The trans relation of oxygen and mercury in **6** would permit displacement of mercury by oxygen and result in epoxide formation. The cycloheptyl ring system, however, is sufficiently flexible to adopt conformation **8**. The electrostatic interaction between the charged oxygen and mercury atoms would be anticipated to render this conformation more stable than **6** or **7**, where it is permitted by steric and geometric considerations.[10] In conformation **8**, the substituents on the carbon bearing oxygen approach the trans relationship to mercury necessary for the observed rearrangements.[11]



Some dehydroxymercuration was also observed in each of the reactions examined. Olefin formation was very rapid in comparison to rearrangement and epoxide formation. This side reaction could be suppressed, however, by proper selection of base. The sterically hindered base potassium *tert*-butoxide was found to be most satisfactory for this purpose.

(7) Satisfactory C and H analyses were obtained for all new compounds.

(8) The stereochemistry of **1c** is assumed on the basis of a normal trans addition to the double bond of cycloheptene.[1a]

(9) (a) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, pp 1–523; (b) S. Winstein and R. B. Henderson, *Heterocycl. Compounds*, **1**, 1 (1950).

(10) Indeed, some covalent bond character would be expected between oxygen and mercury.

(11) The absence of aldehyde formation suggests that rearrangement of an intermediate epoxide is not responsible for the observed ketones.[9] This unusual type of epoxide isomerization is, however, catalyzed by dicobalt octacarbonyl.[12]

(12) J. L. Eisenmann, *J. Org. Chem.*, **27**, 2706 (1962).

(13) National Science Foundation Undergraduate Research Participant, 1972.

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E. D. MIHELICH[13]

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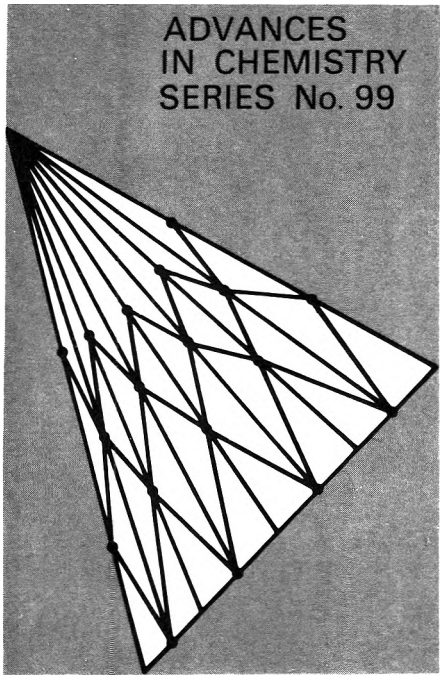

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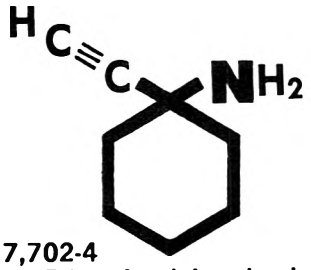

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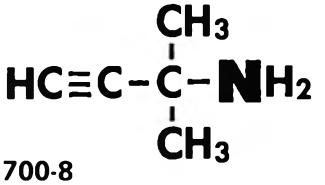

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1, 1-Dimethylpropargylamine

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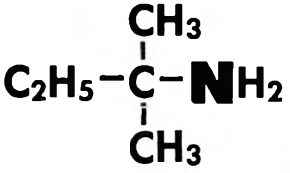

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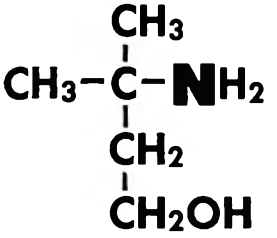

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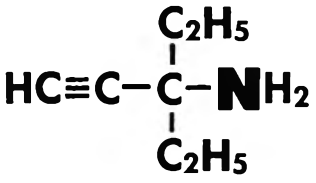

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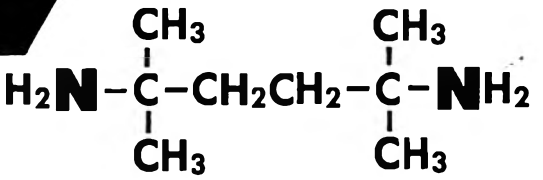

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