VOLUME 38 MARCH 9, 1973 NUMBER 5 JOCEAH

THE JOURNAL OF Organic Chemistry

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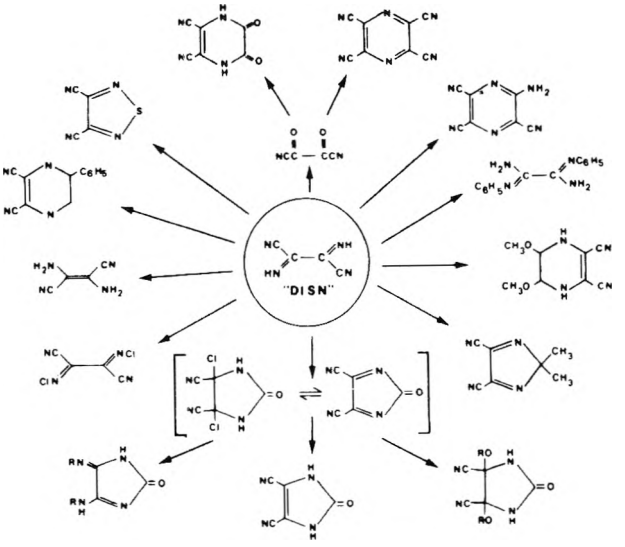

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Ref 1: R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard, & O. W. Webster J. Amer. Chem. Soc., 93, 4953 (1971)
Also: J.Org.Chem. 37 4133, 4136 (1972)

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 5 MARCH 9, 1973

Pesticides Identification
at the Residue Level

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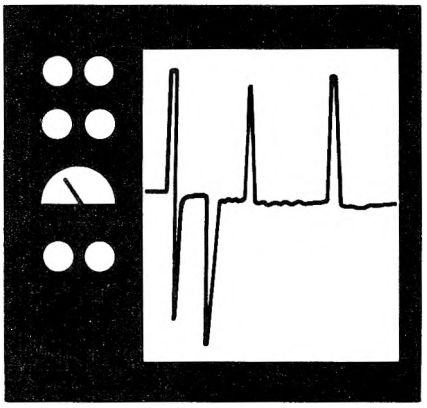
Ten papers from a symposium by the Division of Pesticide Chemistry of the American Chemical Society chaired by Francis J. Biros.



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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 5

MARCH 9, 1973

Solvolysis of 7-Substituted Bicyclo[3.3.1]non-3-yl Tosylates. A Kinetic Proof of σ(C–H) Participation

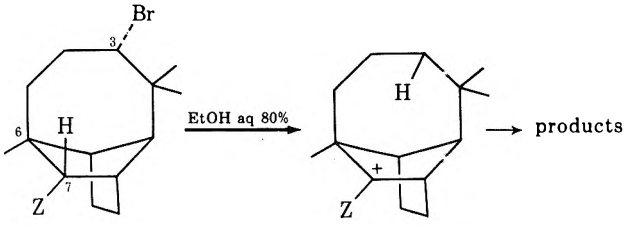
LILIANE STÉHELIN, LEONIDAS KANELLIAS, AND GUY OURISSON*

Institut de Chimie, Université Louis Pasteur, Strasbourg-67, France[1]

Received March 2, 1972

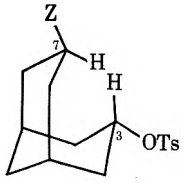
By solvolysis, substances of type **3** undergo at least in part (depending upon the nature of the substituent Z) a 1,5 hydride shift. This solvolysis was studied kinetically. A transannular σ(C–H) participation to ionization is proved by the nonlinearity of a Taft–Hammett plot; this is analogous to results obtained previously in the longifolene series, but less marked. The lesser magnitude of this participation appears to be linked with conformational equilibria in the bridged skeleton.

In the longifolene series, we have recently shown that the transannular 1,5 H migration **1** → **2** provides kinetic assistance to the ionization of the C–Br bond.[2] This was demonstrated by studying the solvolysis of a series of derivatives of type **1**, with Z varying from electron-attracting groups such as CN to electron-releasing groups such as CH_3.



1 **2**

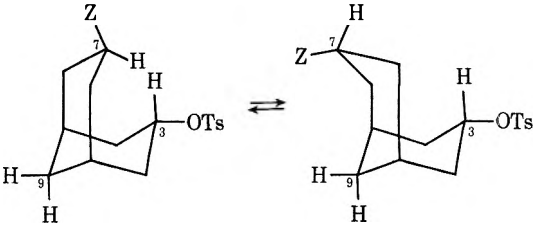
We now describe a similar study in a less exotic system than that of longifolene, with bicyclo[3.3.1]nonane derivatives **3**. As we shall see, the results obtained in



3

the first series have been confirmed; yet they are quantitatively less striking here; and this will form the basis of the concluding discussion.

The ring system of bicyclo[3.3.1]nonane is structurally very closely related to that of longifolene. In longifolene derivatives, C-3 and C-7 are only 3.17 Å apart;[3] in the bicyclo[3.3.1]nonane derivatives, C-3 and C-7 are also in van der Waals contact.[4] This leads to two consequences, in both series: any $sp^3 \rightarrow sp^2$ change at C-3, such as that resulting from the solvolysis, will be favored, and the short C-3–C-7 distance favors transannular hydride 1,5 shifts, as is well known in both series.[5–7] However, while longifolene derivatives are practically constrained to one conformation, bicyclo[3.3.1]nonane derivatives can display some conformational mobility. One extreme case would be the chair–boat equilibrium **3** ⇌ **4**, but this may be the



3 **4**

source of even more severe steric interactions, between Z and C-9.

It is therefore more probable that the rings are only flattened.[8] Anyway, this implies that, in the series **3**,

(1) Laboratory associated with the National Center of Scientific Research (France).

(2) L. Stéhelin, J. Lhomme, and G. Ourisson, *J. Amer. Chem. Soc.*, **93**, 1650 (1971).

(3) J. Cl. Thierry and R. Weiss, *Tetrahedron Lett.*, 2663 (1969).

(4) (a) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc. C*, 1844 (1965); (b) N. C. Webb and M. R. Becker, *J. Chem. Soc. B*, 1317 (1967); (c) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); (d) J. Laszlo, *Recl. Trav. Chim. Pays-Bas*, **84**, 251 (1965).

(5) D. Helmlinger and G. Ourisson, *Justus Liebigs Ann. Chem.*, **686**, 19 (1965).

(6) (a) R. A. Appleton and S. H. Graham, *Chem. Commun.*, 297 (1965); (b) R. A. Appleton, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 805 (1967); (c) W. A. Ayer, and K. Piers, *Chem. Commun.*, 541 (1965); H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner and C. M. Wong, *Tetrahedron Lett.*, 1279 (1965).

(7) (a) M. A. Eakin, J. Martin, and W. Parker, *Chem. Commun.*, 298 (1968); (b) M. A. Eakin, J. Martin, W. Parker, C. Egan, and S. H. Graham, *Chem. Commun.*, 337 (1968).

(8) M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, 2847 (1971).

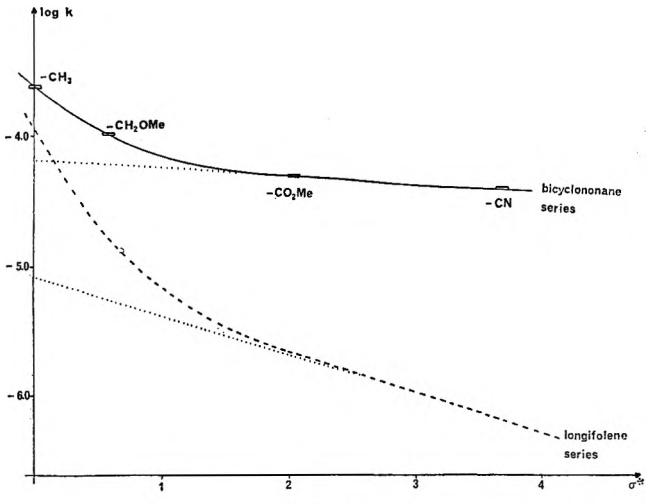


Figure 1.

the distance C-3–C-7 is less rigidly held to the van der Waals contact, and transannular hydride shifts may be less favored. Furthermore, any kinetic consequence of the H assistance to solvolysis in derivatives such as **3** should be weaker than in the longifolene series.

By methods discussed below, we have prepared the four derivatives **3**, Z = CN, CO_2CH_3, CH_2OCH_3, and CH_3. By analogy with our results in the longifolene series, we should expect to observe *no* hydride shift in the first two cases, with electron-attracting groups, and therefore we should expect to get, by solvolysis, exclusively the Δ^2 substances. By contrast, with Z = CH_2OCH_3 or CH_3, one should expect to get some H transfer, and to obtain a mixture of Δ^2 and Δ^6 isomers, as was already known in the case Z = CH_3.[7b] This is indeed confirmed by experiment (Table I). We have

TABLE I

	Solvolysis Products	
Starting material **3**	Without H shift	With H shift
OTs(C-3), CN(C-7)	Δ^2, CN(C-7): 100%	
OTs(C-3), CO_2CH_3(C-7)	Δ^2, CO_2CH_3(C-7): 100%	
OTs(C-3), CH_2OCH_3-(C-7)	Δ^2, CH_2OCH_3(C-7): 90%	Δ^6, CH_2OCH_3(C-7): 10%
OTs(C-3), CH_3(C-7)	Δ^2, CH_3(C-7): 45%	Δ^6, CH_3(C-7): 55%

therefore studied the kinetics of solvolysis of the four substances **3**, and analyzed the results in a Taft–Hammett plot.[9] Table II summarizes the kinetic results in aqueous ethanol at 25°.

TABLE II

Z	σ^*	k, sec^{-1}
CN	+3.64	$(3.92 \pm 0.04)\ 10^{-5}$
CO_2CH_3	+2.00	$(4.89 \pm 0.07)\ 10^{-5}$
CH_2OCH_3	+0.52	$(1.04 \pm 0.02)\ 10^{-4}$
CH_3	0	$(2.28 \pm 0.02)\ 10^{-4}$

The plot $\log k = f(\sigma^*)$ is clearly nonlinear (Figure 1). We have reproduced on the same plot the results previously obtained with longifolene derivatives.

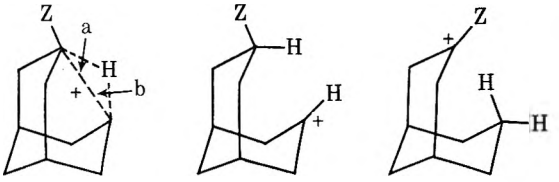
(9) (a) Reference 2; see ref 14, 15, and 16a therein. (b) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556. (c) For a recent example in the phenyl participation problem, see H. C. Brown and C.-J. Kim, *J. Amer. Chem. Soc.*, **93**, 5765 (1971).

It can be seen that, in the bicyclo[3.3.1]nonane series, (1) the slope for the reaction *without* H migration ($\rho_1^* \sim -0.06$) is less steep than in the longifolene series ($\rho_1^* \sim -0.3$); (2) the deviation from ρ_1^* accompanying the reaction with hydride shift is less marked than in the longifolene series; k_{CH_3} is only four times larger than k extrapolated for a linear plot, instead of 15 times in the longifolene series.

The first observation is in agreement with what can be expected for a system more flexible than that of longifolene: any increase of the distance C-3–C-7 should lead to a decrease of the influence, by a field inductive effect, of the Z group (leading to a lesser influence of the nature of Z on the rate of solvolysis, and therefore to a less steep curve).

The lesser deviation of linearity may be due only to the lesser propensity of H-7 to migrate: in the longifolene series, it is an exo nucleofuge in a bicyclo[2.2.1]-heptane system, and furthermore the transition $sp^3 \rightarrow sp^2$ eliminates, on C-7, the eclipsing of the methyl at C-6 and of Z at C-7. So, the near-quantitative hydride migration, as observed in the longifolene series, is far from being reached in the bicyclo[3.3.1]nonane series (Table I).

The interpretations given in our study of longifolene derivatives hold also in this case, as well as their ambiguity: the phenomenon of H assistance appears to be compatible with the intervention of a nonclassical ion **5** as the first intermediate, or of the transannular ion **6** derived from an intramolecular SN2 reaction by the σ(C–H) bond, or from an intimate rearranged ion pair.



5 **6** **7**

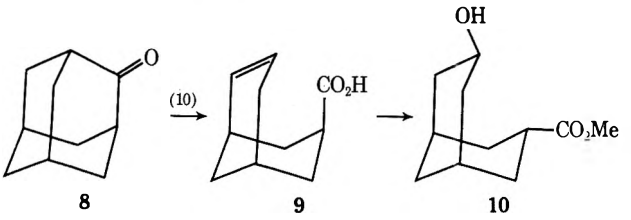
It is not possible to choose between these two hypotheses by comparing the rates and the product distribution. By extrapolating the linear portion of the curve to $\sigma^* = 0$, one obtains a "theoretical" k_{CH_3}, which would correspond to solvolysis without migration. This "theoretical" k_{CH_3} is one-fourth of the observed k_{CH_3}, which would lead to a "theoretical" distribution of products of one-fourth without and three-fourths with H migration, instead of the observed distribution (45% without and 55% with H migration).

This discrepancy would be easily explained by an asymmetric opening of the nonclassical ion **5**, collapsing competitively by cleavage a (for 55%) and by cleavage b (for 20%). However, the second hypothesis would also be compatible with the observed facts: the classical ion **6**, kinetically formed, could be equilibrated with the isomeric ion **7**, in a subsequent step; the relative collapse rate of ions **6** and **7** would then have to be similar to that postulated for the competitive cleavages of **5**.

Our results can therefore not help to define the structure of the first intermediate in the solvolysis of the products studied. However, they demonstrate clearly the effect of the migration of H to increase the rate of solvolysis at the site, across the ring, toward which H migrates. σ(C–H) assistance to solvolysis can now be taken as a general phenomenon, and this is

why we are now extending this study to 9,9-dimethyl derivatives of the series **3**, which should be conformationally blocked, and for which we therefore predict a closer similarity with the longifolene series.

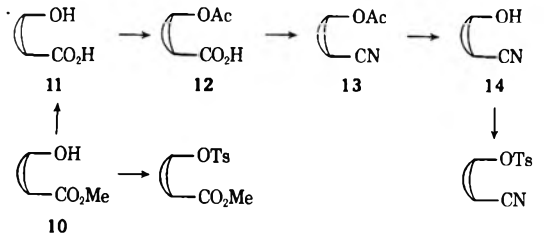
Synthesis of the Substrates.—The substrates selected for the study require a convenient precursor with the exo,exo configuration of the substituents at C-3 and C-7. Such a precursor was found in the exo,exo hydroxy ester **10**, obtained from adamantanone **8** *via* the



8 **9** **10**

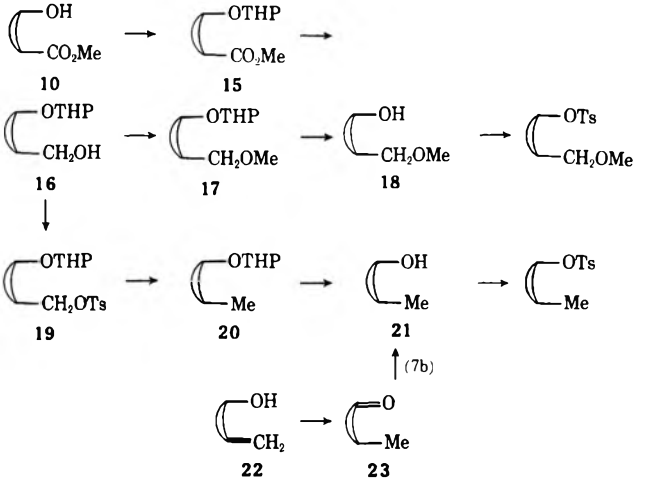
unsaturated endo ester **9**. Charts I and II summarize the reactions giving the four substances used for the

CHART I



11 **12** **13** **14** **10**

CHART II



10 **15** **16** **17** **18** **19** **20** **21** **22** **23**

kinetic study; these reactions are described in the Experimental Section.

Experimental Section

The following instruments were used: melting points, Reichert heating stage and microscope; infrared spectra (ir), Beckman IR-8A spectrophotometer; nuclear magnetic resonance spectra (nmr), Varian A-60, tetramethylsilane as internal reference; mass spectra, Thomson-Houston THN-208 double focusing spectrometer, direct inlet, 70 eV; gas chromatography, Aerograph Hy-Fi 600. Microanalyses were run by the Strasbourg Division of the Service Central of Microanalyse of CNRS.

***endo*-7-Carboxybicyclo[3.3.1]non-3-Ene (5) (3-Ene, *endo*-7-CO_2H).**—Adamantanone **8** (2 g) was dissolved in methanesulfonic acid (50 ml), and sodium azide (1.3 g) was added in small portions at 0° over 30 min. After the reaction was allowed to stand for 1 hr, the solution was poured onto ice and neutralized with a 5% aqueous sodium hydroxide solution. When the mixture was clearly alkaline, extra pellets of sodium hydroxide were added to make the medium strongly basic. The solution was stirred for 2 hr and then acidified with concentrated hydrochloric acid. Extraction by the usual method gave crude white crystals of the unsaturated acid **9** (2 g, 91%), recrystallizable from cyclohexane and identified by comparison with an authentic sample.

7-Carbomethoxybicyclo[3.3.1]nonan-3-ol (10) (3-OH, 7-CO_2CH_3).—The methyl ester of **9** (30.4 g) was dissolved in a solution of sodium methoxide in methanol (15 g of sodium in 1300 ml of methanol). Freshly distilled hexamethylphosphotriamide (HMPT) (270 ml) was added and the mixture was refluxed under nitrogen for 20 hr. After it was cooled and acidified with 1 *N* aqueous hydrochloric acid, the mixture was extracted in the normal way to give a crude liquid product (23.2 g) whose nmr spectrum showed it to be a mixture of acid and ester, both 7-exo. The yield was 82%. The crude product was esterified with boron trifluoride etherate in methanol to provide the 7-exo unsaturated ester, which was purified by sublimation and then submitted to hydroboration (see below): bp 58° (0.5 mm); ir ($CHCl_3$) 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.77 (m, 2, HC=CH), 3.65 (s, 3, CO_2CH_3); mass spectrum *m/e* 180, 165, 148, 121.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.98; H, 8.93.

A solution of diborane in tetrahydrofuran was prepared by the method of Zweifel and Brown.[11] The 7-exo unsaturated ester (0.5 g) was dissolved in tetrahydrofuran (11 ml), freshly distilled from lithium aluminum hydride. The apparatus was carefully purged with nitrogen. Then a solution of diborane in tetrahydrofuran (1.75 ml of 0.6 *M* solution) was slowly added *with continuous shaking* from a syringe. The reaction mixture was left to stir for 1 hr at room temperature and then 3 *N* aqueous sodium hydroxide (1.75 ml) was cautiously added, followed by hydrogen peroxide (30%, 1.75 ml), the reaction mixture being maintained at room temperature. The mixture was left to stir for 1 hr, and then most of the tetrahydrofuran was evaporated off under reduced pressure, and, after saturation of the aqueous phase with sodium chloride, extraction was carried out in the usual way. The crude product was a very viscous liquid (0.485 g, 88%), identified by nmr as a 55:45 mixture of 3-hydroxy ester **10** and corresponding 2-hydroxy ester.

Note that the molecular ratio ester/diborane is 3:1; from the volume of water necessary to destroy the excess diborane, it can be calculated that 1 mol of diborane reacts with 4 mol of ester. If too much diborane is added, the ester is reduced to a hydroxy compound. The stirring must be vigorous and the nitrogen flow not too violent to prevent entrainment of the diborane.

The 3-hydroxy ester **10** was separated from the 2-hydroxy ester by chromatography on neutral alumina (Woelm, activity II) by eluting with mixtures of increasing polarity of ethyl acetate in benzene, and then recrystallized from petroleum ether (bp 30–60°): mp 74–75°; ir ($CHCl_3$) 3600, 3440 (OH), 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 4.28 (m, 1, CHOH), 3.65 (s, 3, CO_2CH_3); mass spectrum *m/e* 198, 180, 167, 166, 139,

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.61; H, 9.15.

The 2-hydroxy ester was characterized as follows: bp 100° (0.01 mm); ir ($CHCl_3$) 3600, 3420, (OH), 1720 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 3.88 (m, 1, CHOH), 3.65 (s, 3, CO_2CH_3); mass spectrum *m/e* 198, 180, 166, 138.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.60; H, 9.06.

The 2-hydroxy ester (0.1 g) was readily dehydrated in anhydrous pyridine (4 ml); phosphorus oxychloride (0.2 ml) was added and the reaction was left for 20 hr at room temperature. A crude product was obtained (0.075 g, 82%), identified by nmr as the 7-*exo*-unsaturated ester.

7-Cyano-3-hydroxybicyclo[3.3.1]nonane (14) (3-OH; 7-CN). A. Hydroxy Acid 11 (3-OH; 7-COOH).—Saponification of the hydroxy ester **10** in the usual way (potassium hydroxide in

(10) (a) M. A. McKervey, personal communication, 1970; (b) D. J. Raber, G. J. Kane, and P. v. R. Schleyer, *Tetrahedron Lett.*, 4117 (1970).

(11) G. Zweifel and H. C. Brown, "Organic Reactions," Vol. 13, Wiley, New York, N. Y., 1962, p 33.

TABLE III

Product	Mp, °C	Ir ($CHCl_3$), cm^{-1}	Nmr ($CDCl_3$), δ	Mass spectrum: Calcd	Mass spectrum: Found
3 (Z = CN)	102–103	2240 (CN)	4.93 (m, 1, CHOTs)	$C_{17}H_{21}O_3NS$ M+ 319	319, 172, 147
3 (Z = CO_2CH_3)	72–73	1730 (ester C=O)	5.14 (m, 1, CHOTs) 3.66 (s, 3, CH_3CO_2)	$C_{18}H_{24}O_6S$ M+ 352	352, 180, 172 148
3 (Z = CH_2OCH_3)	67–68		5.20 (m, 1, CHOTs) 3.30 (s, 3, CH_3OCH_2) 3.11 (d, 2, J = 5 Hz, CH_2OCH_3)	$C_{18}H_{26}O_4S$ M+ 338	338, 172, 166, 121
3 (Z = CH_3)	64 dec		5.23 (m, 1, CHOTs) 0.83 (d, 3, J = 5 Hz, CH_3CH)	$C_{17}H_{24}O_3S$ M+ 308	(TsOH)+ 172 dec

methanol) gave the hydroxy acid 11 (98.5%), slightly soluble in ether and almost insoluble in chloroform: ir (KBr) 3420 (OH), 1700 cm^{-1} (acid C=O); nmr (CH_3OD) δ 4.24 (m, 1, CHOH).

B. Acetoxy Acid 12 (3-OAc; 7-COOH).—The hydroxy acid 11 was treated with acetic anhydride in pyridine in the usual way to give the acetoxy acid 12 (85%) (under no circumstances should methanol be used to destroy excess acetic anhydride, which is sufficient to esterify the acid function): ir ($CHCl_3$) 1720 (ester C=O), 1700 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 5.37 (m, 1, CHOAc), 2.09 (s, 3, CH_3CO_2).

C. Acetoxy Nitrile 13 (3-OAc; 7-CN).—The acetoxy acid 12 (2.5 g) was dissolved in anhydrous benzene (140 ml) and freshly distilled thionyl chloride (2.5 ml) was added. After refluxing for 4 hr followed by evaporation to dryness under reduced pressure, the residue was taken up again in benzene (150 ml) and saturated with ammonia. The solution was evaporated to dryness again and the residue was dissolved in anhydrous ether (70 ml) and filtered to remove the precipitated ammonium chloride. The product was added to a solution of phosphorus oxychloride (5 ml) in anhydrous ether (70 ml) with anhydrous pyridine (20 ml) and refluxed overnight. Excess phosphorus oxychloride was destroyed by the addition of water at 0°. Extraction in the usual way gave a crude, viscous product (2.15 g, 94%), the acetoxy nitrile 13: ir ($CHCl_3$) 2240 (CN), 1720 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 5.37 (m, 1, CHOAc), 2.09 (s 3, CH_3CO_2).

D. Hydroxy Nitrile 14 (3-OH; 7-CN).—Saponification of the acetoxy nitrile 13 in the usual way (potassium hydroxide in methanol) gave the hydroxy nitrile 14 (71%), recrystallizable from petroleum ether: mp 108–109°; ir ($CHCl_3$) 3590, 3420 (OH), 2240 cm^{-1} (CN); nmr ($CDCl_3$) δ 4.13 (m, 1, CHOH); mass spectrum *m/e* 165, 147, 120.

Anal. Calcd for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.34; H, 9.17; N, 8.72.

7-Methoxymethylbicyclo[3.3.1]nonan-3-ol (18) (3-OH; 7-CH_2OCH_3). A. Ether Ester 15 (3-OTHP; 7-CH_2OCH_3).—Dihydropyran (1.4 ml) was added to a solution of the hydroxy ester 10 (2.58 g) in anhydrous benzene (10 ml), followed by several rigorously dried crystals of *p*-toluenesulfonic acid. After the reaction was complete a few crystals of sodium bicarbonate were added. When the benzene and excess dihydropyran were evaporated off the tetrahydropyranyl derivative 15 was obtained as a viscous liquid (3.6 g, 98%): ir ($CHCl_3$) 1720 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 4.32 (m, 1, CHOTHP), 3.65 (s, 3, CH_3CO_2).

B. Hydroxy Ether 16 (3-OTHP; 7-CH_2OH).—Usual reduction of the ether ester 15 with lithium aluminum hydride in refluxing ether gave the hydroxy ether 16 (90%): ir ($CHCl_3$) 3610, 3420 cm^{-1} (OH); nmr ($CDCl_3$) δ 4.32 (m, 1, CHOTHP), 3.38.

C. Diether 17 (3-OTHP; 7-CH_2OCH_3).—The hydroxy ether 16 (1.4 g) was dissolved in 1,2-dimethoxyethane (28 ml) containing methyl iodide (1.4 ml). Sodium hydride (2.74 g) in a 50% dispersion in paraffin oil was added at 0° and the reaction mixture was stirred at room temperature. Excess sodium hydride was cautiously destroyed by the addition of water, at 0°, and the mixture was extracted in the usual way, saturating the aqueous phase with sodium chloride. A liquid volatile product (2.51 g, 77%) was obtained which was a mixture of the diether 17 and paraffin oil: nmr ($CDCl_3$) δ 4.28 (m, 1, CHOTHP), 3.30 (s, 3, CH_3OCH_2), 3.11 (d, 2, J = 5 Hz, CH_2OCH_3).

D. Hydroxy Ether 18 (3-OH; 7-CH_2OCH_3).—Treatment of the diether 17, dissolved in acetone, with a 5% solution of perchloric acid in water gave the hydroxy ether 18 (90%): mp (*p*-nitrobenzoate) 81–82°; ir ($CHCl_3$) 3600, 3420 cm^{-1} (OH); nmr ($CDCl_3$) δ 4.32 (m, 1, CHCH), 3.28 (s, 3, CH_3OCH_2), 3.11 (d, 2, J = 5 Hz, CH_2OCH_3); mass spectrum *m/e* 184, 166, 152, 139.

Anal. (*p*-nitrobenzoate). Calcd for $C_{18}H_{23}O_5N$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.86; H, 6.89; N, 4.41.

7-Methylbicyclo[3.3.1]nonan-3-ol (21) (3-OH; 7-CH_3). A. Tosylate Ether 19 (3-OTHP; 7-CH_2OTs).—Usual treatment of the hydroxy ether 16 with *p*-toluenesulfonyl chloride in anhydrous pyridine gave the ether tosylate 19 (92%): nmr ($CDCl_3$) δ 3.76 (d, 2, J = 6 Hz, CH_2OTs), 2.45 (s, 3, CH_3PhS).

B. Alcohol 21 (3-OH; 7-CH_3).—Usual reduction of the ether tosylate 19 with lithium aluminum hydride in ether gave the alcohol 21 (95%): mp 72–75°; ir ($CHCl_3$) 3600, 3420 cm^{-1} (OH); nmr ($CDCl_3$) δ 4.13 (m, 1, CHOH), 8.33 (d, 3, J = 5 Hz, CH_3CH); mass spectrum *m/e* 154, 136, 121.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.35; H, 11.57.

The tosylates of the derivatives 14, 10, and 18, and 21 were all prepared by a method identical with that described for the preparation of the tosylate 19. The physical characteristics of these tosylates are shown in Table III.

Kinetics.—Each solvolysis was carried out with nine titrations at appropriate time intervals. The 80% aqueous ethanol was prepared by the addition, at 20°, of 1 volume of distilled water to 4 volumes of freshly distilled absolute ethanol. The substance studied was ground in an agate mortar, weighed in a graduated 50-ml flask (0.5 or 0.25 mmol was weighed to ±0.1 mg), and then rapidly dissolved at room temperature by stirring. For each derivative studied, 50 ml of the solution, prepared as above, was placed in the thermostat bath (Colora ultrathermostat, ±0.1°). When temperature equilibrium at 25° had been reached, a 5-ml sample was withdrawn using a pipette and titrated. Seven samplings of the remaining solution were thus titrated at appropriate time intervals (the seventh at about 85% degree of completion of reaction). The remaining solution was left in the thermostat for at least 10 times the reaction half-life so as to measure the "experimental infinity." Each titration used a 0.01 *M* solution of sodium methoxide in methanol (standardized with a solution of potassium hydrogen phthalate). The indicator used was *p*-bromothymol blue, at the point of turning blue. A Manostat–Greiner micrometric buret was used, giving an accuracy of 0.001 ml. The products of the solvolytic reactions were determined by examination of 0.1 *M* solutions which had either been heated or allowed to stand for 10 times the reaction half-life, in the presence of 1 equiv of sodium carbonate.

For the derivative 3 (Z = CH_3) the kinetics were determined also by following the reaction in ultraviolet.[12] Results from both methods (titration and spectrography) were consistent.

The solvolysis products in the bicyclo[3.3.1]nonane series are very volatile. As we had only small quantities of starting

(12) C. G. Swain and C. R. Morgan, *J. Org. Chem.*, **29**, 2097 (1964).

TABLE IV

Starting material	Solvolysis product (registry no.)	Nmr ($CDCl_3$), δ	Mass spectrum: Calcd	Mass spectrum: Found
3 (Z = CN)	Δ^2, CN(C-7) (37741-58-5)	5.80 (m, 2, HC=CH)	$C_{10}H_{13}N$ M^+ 147	147, 120
3 (Z = CO_2CH_3)	Δ^2, CO_2CH_3(C-7)	5.76 (m, 2, HC=CH) 3.63 (s, 1, CO_2CH_3)	$C_{11}H_{16}O_2$ M^+ 180	180, 165, 148, 121, 120
3 (Z = CH_2OCH_3)	Δ^2, CH_2OCH_3(C-7) (37741-60-9)	5.71 (m, 2, HC=CH) 3.28 (s, 3, CH_3OCH_2) 3.17 (d, 2, J = 6 Hz, CH_2OCH_3)	$C_{11}H_{18}O$ M^+ 166	166, 124
	Δ^6, CH_2OCH_3(C-7) (37741-61-0)	5.48[a] (m, 1, HC=C–)		
3 (Z = CH_3)	Δ^2, CH_3(C-7) (2721-44-0)	5.73 (m, 2, HC=CH) 0.82 (d, 3, J = 6 Hz, CH_3)	$C_{10}H_{16}$ M^+ 136	136, 121
	Δ^6, CH_3(C-7) (2721-36-0)	5.40 (m, 1, HC=C–) 1.67 (s, 3, CH_3)		

[a] The nmr signal of this hydrogen is too weak to be assigned an unambiguous shift value; the shift (δ 5.48), here indicated, is compatible with the homolog multiplet on the solvolysis product of **3** (Z = CH_3).

materials, the solvolyses for preparative purposes were run with solutions 0.1 *M* in 80% aqueous acetone, in the presence of sodium carbonate, to avoid a thermodynamic equilibrium between the products of the reaction. Evaporation of the reaction mixture was easier than with aqueous ethanol, so that quantitative extraction of the reaction products was facilitated. Aqueous acetone is slightly less nucleophilic and less ionizing than 80% aqueous ethanol.[13]

We checked by vpc that the same products were obtained as those from solvolyses 0.01 *M* run in aqueous ethanol in the presence of sodium carbonate. The ratio of product without H shift/product with H shift was determined by a direct vpc evaluation of the crude product of such solvolyses. Table IV gives the nmr and mass spectral data of the products of those solvolyses studied.

(13) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962.

Registry No.—**3** (Z = CN), 37741-64-3; **3** (Z = CO_2CH_3), 37731-04-7; **3** (Z = CH_2OCH_3), 37731-05-8; **3** (Z = CH_3), 19912-54-0; **8**, 700-58-3; **9**, 21932-98-9; **9** *exo*-methyl ester, 37741-59-6; **10**, 37731-09-2; **11**, 37731-10-5; **12**, 37731-11-6; **13**, 37731-12-7; **14**, 37731-13-8; **15**, 37731-14-9; **16**, 37731-15-0; **17**, 37731-14-9; **18**, 37731-17-2; **18** *p*-nitrobenzoate, 37731-18-3; **19**, 37731-19-4; **21**, 37741-57-4; 7-carbomethoxybicyclo[3.3.1]nonan-2-ol, 37731-21-8.

Acknowledgment.—We thank Dr. M. A. McKervey (Belfast) for a generous gift of the unsaturated acid **9**.

Solvolysis of 9,9-Dimethylbicyclo[3.3.1]non-3-yl Tosylate. Enhancement of σ (C–H) Participation by Steric Blocking

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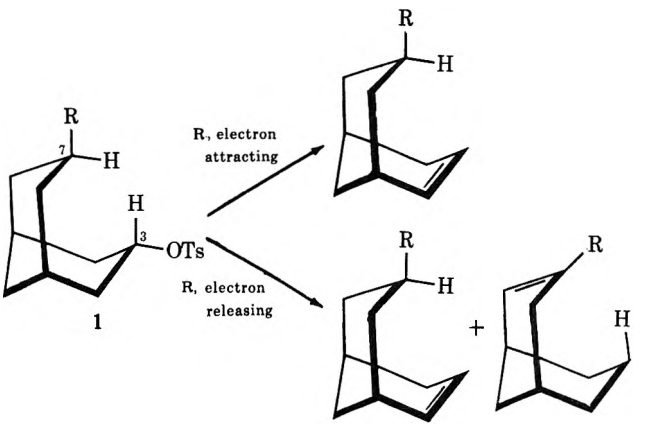
7,9,9-Trimethylbicyclo[3.3.1]non-3-yl tosylate (**2**, R = CH_3) undergoes solvolysis with quantitative 7–3 hydride transfer. The rate of solvolysis of **2** (R = CH_3) is four times higher than that of the lower homolog **1** (R = CH_3). This is interpreted by an anchoring of the conformation of both rings of **2** in a chair form, ensuring favorable geometry for H transfer.

We have recently shown that transannular H migrations accompanying solvolysis can produce a rate enhancement in the longifolene series[1] and in the bicyclo[3.3.1]nonane series.[2] In this last series, for instance, solvolysis of 7-substituted bicyclononyl tosylates **1** has been shown, by a Taft–Hammett treatment,[3] to be accelerated when it is accompanied by hydride migration from C-7 to C-3; there is a σ(C–H) participation in the step determining the rate of solvolysis.



However, in the bicyclononane series, this kinetic effect is less marked than in the longifolene series, and

(1) L. Stéhelin, J. Lhomme, and G. Ourisson, *J. Amer. Chem. Soc.*, **93**, 1650 (1971).

(2) L. Stéhelin, L. Kanellias, and G. Ourisson, *J. Org. Chem.*, **38**, 847 (1973).

(3) (a) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556; (b) A. Streitwieser, Jr., *J. Amer. Chem. Soc.*, **78**, 4935 (1956); "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 122, 146; (c) C. J. Lancelot, J. J. Harper, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4294 (1969); (d) P. G. Gassman, J. L. Marshall, J. G. Macmillan, and J. M. Hornback, *ibid.*, **91**, 4282 (1969).

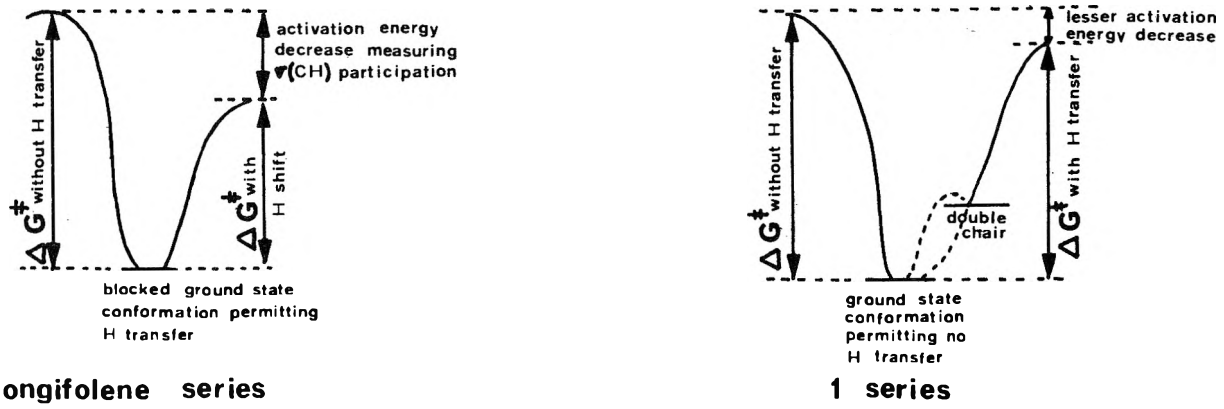
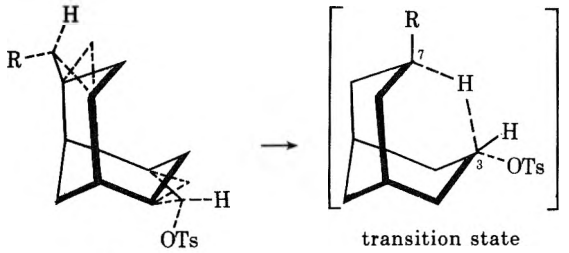


Figure 1.

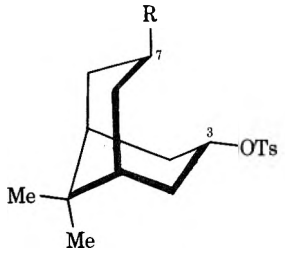
we have discussed several factors which can play a role in this quantitative difference;[2] we had concluded that it was probably due to a conformational difference. The longifolene skeleton is for all practical purposes anchored in a fixed conformation,[4] the one permitting hydride transfer from C-7 to C-3. On the contrary, both rings of bicyclononane derivatives can display conformational mobility, ranging from flattening of the rings to outright chair–boat interconversion.[5] It is only in the double-chair conformation of the solvolysis transition state that hydride transfer can take place.



1

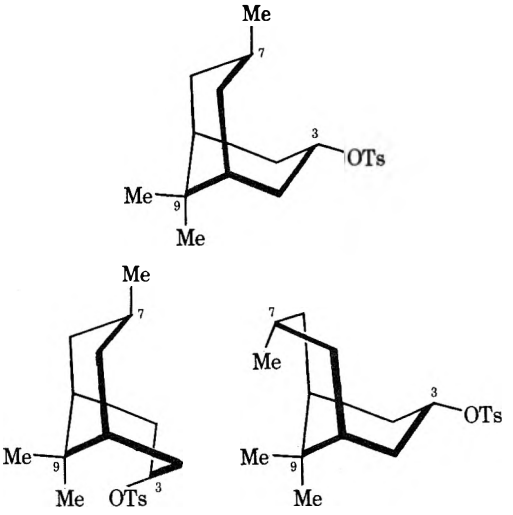
This double-chair conformation is certainly not the most stable one, owing to the H-3/H-7 interaction, and, whatever the exact geometry of the ground state, the necessary passage through the double-chair conformation must lead to an increase of the activation energy for that part of the reaction proceeding with hydride transfer during the rate-determining step. Figure 1 represents schematically the kinetic difference between the longifolene and the bicyclo[3.3.1]nonane series.

To check the validity of this interpretation, we have synthesized the 9,9-dimethyl tosylate 2 (R = CH_3).



2

In this substance, the *gem*-dimethyl group on the bridge blocks both rings into a chair conformation, effectively preventing a boat conformation from providing a way to eliminate the H-3/H-7 interaction.



The rate of solvolysis of the tosylate 2 (R = CH_3) is indeed four times higher (100% H transfer[6a]) than that of its lower homolog 1 (R = CH_3) (55% H transfer) (Table I), itself four times higher than that of the nitrile 1 (R = CN) (0% H transfer).

TABLE I

Derivative	k at 25° (80% aqueous EtOH)	H transfer, %	No H transfer, %
1 (R = CH_3)	2.28×10^{-4}	55	45
2 (R = CH_3)	9.28×10^{-4}	100	

We attribute this rate enhancement, at least in a large measure, to a σ(C–H) participation as efficient in series 2 as in the longifolene series, where a rate factor of 16 had also been found between the derivatives with a cyano and a methyl group[1] (Table I and Figure 2).

In fact, this is based on the assumption that the reaction rate in series 2 is not affected by the presence of the methyl groups as long as there is no hydride transfer, *i.e.*, for the plain solvolyses observed, in series 1, when R is an electron-withdrawing group like CN or CO_2CH_3. This leads one to the prediction, in particu-

(4) (a) J. C. Thierry and R. Weiss, *Tetrahedron Lett.*, 2663 (1969); (b) D. Helmlinger and G. Ourisson, *Justus Liebigs Ann. Chem.*, **686**, 19 (1965).

(5) (a) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc. C*, 1844 (1965); N. C. Webb, and M. R. Becker, *J. Chem. Soc. B*, 1317 (1967); M. R. Vegar, and R. J. Wells, *Tetrahedron Lett.*, 2847 (1971); (b) I. Fleming, S. W. Hanson, and J. K. M. Sanders, *ibid.*, 3733 (1971); J. A. Peters, J. D. Remijnse, A. van der Wiele, and H. van Bekkum, *ibid.*, 3065 (1971); P. D. Cradwick and G. A. Sim, *J. Chem. Soc. B*, 2218 (1971).

(6) (a) The product, 3,9,9-trimethylbicyclo[3.3.1]non-2-ene, was isolated, found homogeneous by gas chromatography, and characterized by nmr; (b) S. Winstein and J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

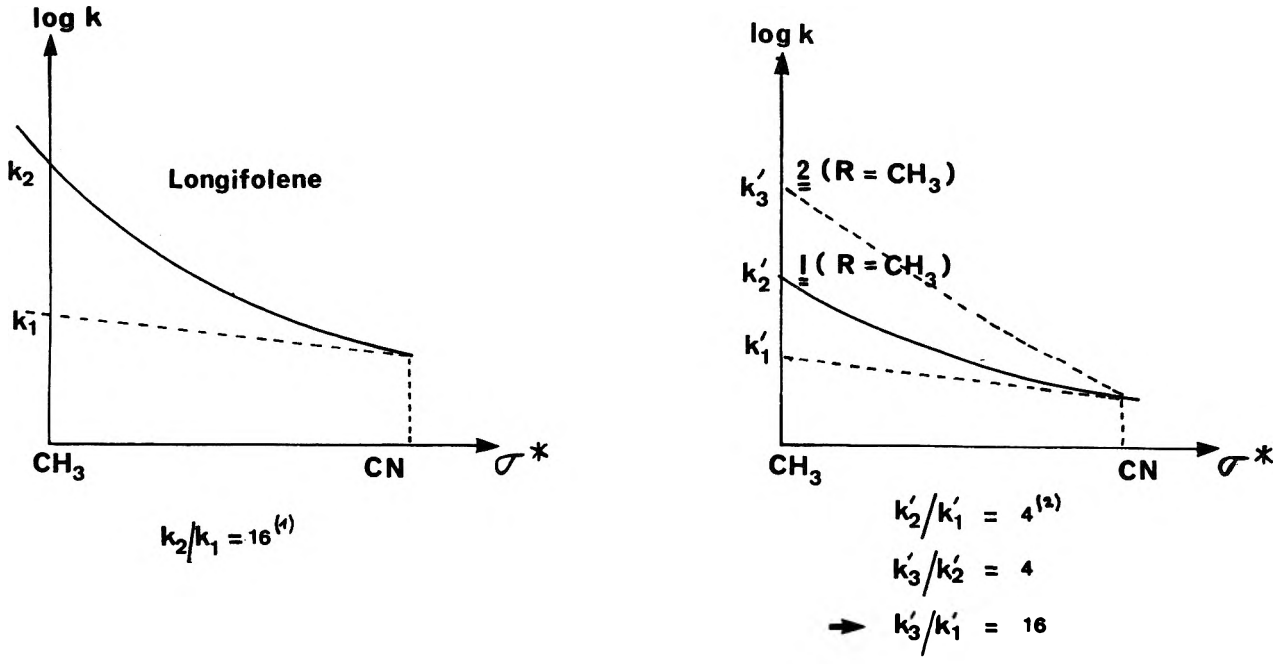
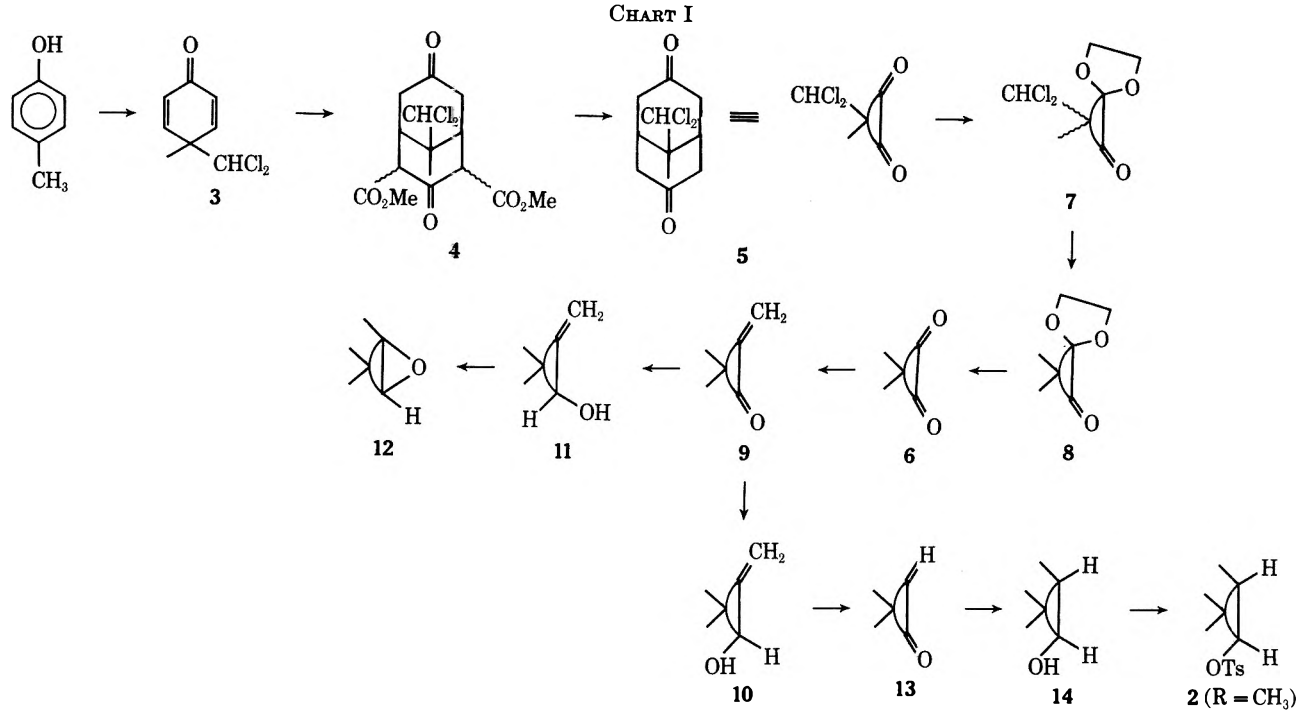


Figure 2.

CHART I



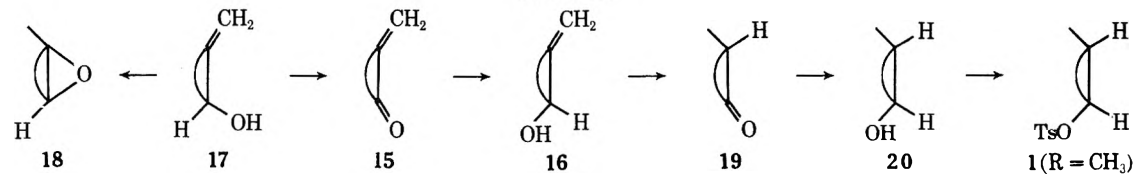
lar, that the reaction rate for solvolysis of **1** (R = CN) and **2** (R = CN) is the same. We have shunned the lengthy synthesis of **2** (R = CN) and accepted the correctness of the prediction just mentioned, on the basis of the following arguments.

The *inductive* effect of the methyl groups is certainly negligible, as even *tert*-butyl groups, in *trans*-4-*tert*-butyl and *cis*-3-*tert*-butylcyclohexyl tosylates, have practically no kinetic effect.[6b] The *field* effect of the cyano group may be more efficient in **2** (R = CN) than in **1** (R = CN), owing to the blocked conformations ensuring close proximity between C-3 and C-7; this should lead to a slight decrease of the solvolysis rate of **2** compared with **1** (R = CN), which would further increase the rate factor considered.

The other effects resulting from the presence of the axial methyl group in the ring undergoing solvolysis are taken as negligible. It appears therefore that the extent of σ(C–H) participation to the rate-determining step of solvolysis is comparable in the two series, that of longifolene and that of 9,9-dimethylbicyclo[3.3.1]-nonane, where (a) the two carbon atoms involved are situated at approximately identical distances[2] and (b) the conformations of the flexible parts of the molecules are anchored by additional substituents.

Synthesis of 2 (R = CH_3).—The synthetic route followed is summarized on Charts I and II, and described in the Experimental Section. The structures indicated are all in agreement with their physical characteristics, in particular with their nmr spectra.

CHART II



Experimental Section

We have included in some detail the preparation and/or properties of known substances, when this was found to be needed [1 (R = CH_3), 3, 4, 5, 16, 19, 20]. Microanalytical data are in agreement within ±0.3% with the calculated values for C, H, and Cl, for the indicated molecular formulas, unless explicitly indicated.

4-Dichloromethyl-4-methylcyclohexa-2,5-dienone (3).[7]—*p*-Cresol (54 g) and 15% aqueous sodium hydroxide (600 ml) were heated at 65° in a three-necked flask, with dropping funnel, stirrer, and condenser. Over 2 hr, chloroform (80 ml) was added dropwise with vigorous stirring. Stirring was maintained at the same temperature for 30 min. After cooling, the solution was extracted with chloroform, which was washed with saturated brine, dried over sodium sulfate, and evaporated. The dark, viscous residue was distilled *in vacuo*. The distillate was freed of phenols by stirring with a 1 *N* sodium hydroxide solution. The solid product was separated from the red alkaline solution by filtration and was abundantly washed with water. It was then dried *in vacuo* at room temperature. 4-Dichloromethyl-4-methylcyclohexa-2,5-dienone (3) (19.5 g, yield 20%) can be recrystallized in hexane: mp 55° (lit.[7] mp 55°); bp 70° (0.05 mm); ir ($CHCl_3$) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.05 (m, 1), 6.85 (m, 1), 6.45 (m, 1), 6.30 (m, 1, HC=CH), 5.75 (s, 1, $CHCl_2$), 1.47 (s, 3, CH_3); mass spectrum *m/e* 190, 192, 194, 175, 177, 155, 157, 107. *Anal.* Calcd for $C_8H_8Cl_2O$: 191.06.

Methyl 9-Dichloromethyl-9-methyl-3,7-dioxobicyclo[3.3.1]nonane-2,4-dicarboxylate (4).[8]—Sodium (1.7 g) was dissolved in anhydrous methanol (40 ml) under nitrogen in a three-necked flask, with dropping funnel, stirrer, and condenser. Over 10 min, the cyclohexadienone 3 (26 g), dissolved in methanol (120 ml), was added with stirring at room temperature. Methyl acetonedicarboxylate (23.6 g) was added. The mixture was heated at reflux during 48 hr with stirring, cooled, and acidified with 1 *N* sulfuric acid (80 ml). On standing at 0°, a white precipitate was formed; it was filtered and washed at 0° with methanol and water. The diester 4 (36 g, yield 72%) was recrystallized from methanol: mp 195–197° (lit.[8] mp 189°); ir ($CHCl_3$) 1715 (ketone C=O), 1745 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.45 (s, 1, $CHCl_2$), 3.81 3.79 (s, 6, $COOCH_3$), 1.36 (s, 3, CH_3); mass spectrum *m/e* 364, 366, 368, 332, 334, 336, 297, 299, 261. *Anal.* Calcd for $C_{15}H_{18}O_6Cl_2$: 365.21.

9-Dichloromethyl-9-methylbicyclo[3.3.1]nonane-3,7-dione (5).[8]—The diester 4 (24.5 g) was heated at reflux temperature for 3 hr in a mixture of acetic acid (250 ml) and sulfuric acid (25 ml). After cooling at 50°, most of the acetic acid was evaporated *in vacuo*. Water (250 ml) was added at about 0°. After 12 hr at 0°, the precipitate was filtered, washed wth cold water, and dried. The decarboxylated product 5 (12.6 g, yield 75%) was dissolved in methanol at 50° and treated with carbon black. The filtered solution was evaporated to give the pure diketone 5, which was recrystallized in ethyl acetate: mp 205° (lit.[8] mp 201°); ir (KBr) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.55 (s, 1, $CHCl_2$), 1.65 (s, 3, CH_3); mass spectrum *m/e* 248, 250, 252, 213, 215, 177. *Anal.* Calcd for $C_{11}H_{14}O_2Cl_2$: 249.14.

9,9-Dimethylbicyclo[3.3.1]nonane-3,7-dione (6). A.[9]—The diketone 5 (0.25 g) was dissolved in a 10% solution of sodium hydroxide in methanol (20 ml). In the presence of 5% palladium on barium sulfate (0.5 g), the solution was stirred in an atmosphere of hydrogen during 6 days. Water (4 ml) was added before filtration over Celite, which was washed with methanol. The filtrate was evaporated, water (10 ml) was added, and the product was extracted with chloroform. The product of hydrogenolysis 6 is obtained (0.155 g, yield 86%), but can be purified only with great difficulty, the crystals obtained from ethyl acetate, for instance, retaining impurities. The product is characterized by an exceptionally high polarity (R_f 0.1), tlc on silica gel, cyclohexane–ethyl acetate (1:1).

B.—The monodioxolane 8 (*vide infra*), treated with a mixture of methanol and a 5% solution of hydrochloric acid, gave quantitatively the same diketone 6: mp 180–190° dec; ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.42 (s, 6, CH_3); mass spectrum *m/e* 180, 165.

9-Dichloromethyl-9-methyl-7,7-ethylenedioxybicyclo[3.3.1]nonan-3-ones (7) [9-(*R*)- and 9-(*S*)-].—The diketone 5 (0.1 g) was treated in benzene (7 ml) with ethylene glycol (0.2 ml) and *p*-toluenesulfonic acid (6 mg). The solution was heated under reflux during 3 hr, with periodic withdrawal of the distillate to remove the water. After evaporation, the residue was treated with a 5% sodium carbonate–water solution and extracted with chloroform. The mixture of epimers of 7 (0.11 g, yield 93%) was obtained crystalline. Successive fractional crystallizations in a 1:9 mixture of ethyl acetate and cyclohexane give the individual 9 epimers, 7a, and 7b.

7a had mp 166–168°; ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.45 (s, 1, $CHCl_2$), 3.90 (m, 4, OCH_2CH_2O), 1.35 (s, 1, CH_3); mass spectrum *m/e* 292, 294, 296, 257, 259. *Anal.* Calcd for $C_{13}H_{18}Cl_2O_3$: 293.19.

7b had mp 162–164°; ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.15 (s, 1, $CHCl_3$), 3.86 (m, 4, OCH_2CH_2O), 1.40 (s, 1, CH_3); mass spectrum *m/e* 292, 294, 296, 257, 259. *Anal.* Calcd for $C_{13}H_{18}Cl_3O_3$: 293.19.

9,9-Dimethyl-7,7-ethylenedioxybicyclo[3.3.1]nonan-3-one (8).—The mixture of 9 epimers 7 (6 g), dissolved in a 10% solution of sodium hydroxide in methanol (250 ml), was stirred under hydrogen in the presence of 5% palladium on barium sulfate (2.6 g). After 8 hr, the solution was filtered over Celite, which was washed with methanol. After evaporation, water (25 ml) was added, and the product 8 (4.5 g, yield 98%) was extracted with chloroform. It was sublimed (80°, 0.5 Torr) and recrystallized in petroleum ether (bp 30–60°): mp 88–90°; ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.88 (m, 4, OCH_2CH_2O), 1.2 (s, 3, CH_3), 1.15 (s, 1, CH_3); mass spectrum *m/e* 224, 209. *Anal.* Calcd for $C_{13}H_{20}O_3$: 224.29.

9,9-Dimethyl-7-methylenebicyclo[3.3.1]nonan-3-one (9).[10]—Sodium hydride suspended in paraffin oil (0.755 g) was introduced into a perfectly dry three-necked 100-ml flask, with condenser, stirrer, and serum cap. Under nitrogen, it was washed with pentane and dried. Freshly distilled dimethyl sulfoxide (7.5 ml) was injected with a syringe, and the mixture was heated at 80°, until evolution of hydrogen stops (45 min). After cooling at 0°, a solution of triphenylmethylphosphonium bromide (5.35 g) in dimethyl sulfoxide (15 ml) was injected with a syringe. After 10 min at room temperature, the diketone 6 (2.7 g), dissolved in the smallest possible volume of dimethyl sulfoxide, was slowly injected with stirring and temperature control. After one night, cold water was added, then petroleum ether, and the product was extracted. It was isolated by very careful evaporation, as it is very easily sublimable (1.853 g, yield 65%). The monoketone 9 was purified by chromatography on silica gel, and recrystallized in methanol at −20°: mp 102–105°; ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.8 (m, 2, $=CH_2$), 1.25 (s, 3, CH_3), 1.20 (s, 3, CH_3); mass spectrum *m/e* 178, 163.

9,9-Dimethyl-7-methylenebicyclo[3.3.1]nonan-3-*exo*-ol (10).—The monoketone 9 (0.293 g) was reduced with lithium aluminum hydride in the usual way. The crude product (0.280 g, yield 93%) was shown by its nmr spectrum to consist of a 35:65 mixture of 3-exo and 3-endo alcohols 10 and 11. The exo alcohol 10 was obtained by chromatography on neutral alumina (Merck, activity II–III). It was recrystallized from petroleum ether at 0°: mp 106–107°; ir ($CHCl_3$) 3600, 3400 (OH), 1640, 890 cm^{-1} ($=CH_2$); nmr ($CDCl_3$) δ 4.70 (m, 2, $=CH_2$), 4.55 (m, 1,

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CHOH), 1.13 (s, 3, CH_3), 1.08 (s, 3, CH_3); mass spectrum *m/e* 180, 165. *Anal.* Calcd for $C_{12}H_{20}O$: 180.28. Chromatography on silica gel transforms **11** [nmr ($CDCl_3$) δ 4.93 (m, 2, $=CH_2$), 3.66 (m, 1, CHOH), 1.08 (s, 3, CH_3), 0.97 (s, 3, CH_3)] into the cyclic ether **12**, evaporated at 25° (0.01 Torr): nmr ($CDCl_3$) δ 3.95 (m, 1, CHO), 1.22 (s, 9, CH_3); mass spectrum *m/e* 180, 165. *Anal.* Calcd for $C_{12}H_{20}O$ (180.28): C, 79.94; H, 11.18. Found: C, 79.44; H, 11.32.

9,9,7-*exo*-Trimethylbicyclo[3.3.1]nonan-3-one (13).[11,12]—To the exo alcohol **10** (0.28 g) in methanol (4 ml) was added a 50% solution of sulfuric acid in water. After a few minutes, water was added, and the product was extracted by continuous ether extraction. It was ketone **13**: mp 54–55°; ir ($CHCl_3$) 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.15 (s, 6, CH_3), 0.88 (degenerate d, 3, CH_3); mass spectrum *m/e* 180, 165.

9,9,7-*exo*-Trimethylbicyclo[3.3.1]nonan-3-*exo*-ol (14).—By reduction of ketone **13** (0.1 g) with lithium in liquid ammonia, followed by chromatography on silica gel, alcohol **14** was obtained (0.07 g, yield 70%): mp 101–102°; ir (KBr) 3300 cm^{-1} (OH); nmr ($CDCl_3$) δ 4.35 (m, 1, CHOH), 1.07 (s, 3, CH_3), 0.97 (s, 3, CH_3), 0.88 (degenerate d, 3, CH_3); mass spectrum *m/e* 164 $(M - H_2O)^+$.

9,9,7-*exo*-Trimethylbicyclo[3.3.1]nonyl 3-*exo*-Tosylate (2) (R = CH_3).—A solution of alcohol **14** (0.035 g) in pyridine (1.5 ml) was treated with *p*-toluenesulfonyl chloride (0.054 g). The product **2** (R = CH_3) was isolated in the usual way, pyridine being removed only with water (no acid wash!). It is very unstable, but can be recrystallized in petroleum ether at −20°: mp 58° dec; nmr (CCl_4) δ 5.13 (m, 1, CHOTs), 1.17 (s, 3, CH_3), 1.07 (s, 3, CH_3), 1.03 (degenerate, d, 3, CH_3); mass spectrum *m/e* 172 ($TsOH^+$), 155 (Ts^+).

7-Methylenebicyclo[3.3.1]nonan-3-*exo*-ol (16).—7-Methylenebicyclo[3.3.1]nonan-3-one (**15**), obtained by fragmentation of 1,3-dibromoadamantane[13] was reduced with lithium aluminum hydride in ether.[14] The crude product was shown by nmr spectroscopy to be a 15:85 mixture of the 3-exo alcohol **16** and the 3-endo alcohol **17**. By chromatography on neutral alumina (Merck, activity II–III), the exo alcohol **16** was obtained pure. It was recrystallized from petroleum ether at 0°: mp 93–94°; ir ($CHCl_3$) 3600, 3400 (OH), 1640, 880 cm^{-1} ($=CH_2$); nmr ($CDCl_3$) δ 4.63 (m, 2, $=CH_2$), 4.56 (m, 1 CHOH); mass spectrum *m/e* 152, 137.

By chromatography on silica gel, the endo alcohol **17** [nmr (CCl_4) δ 4.95 (m, 2, $=CH_2$), 3.78 (m, 1, CHOH)] was transformed into the cyclic ether **18**, evaporated at 26° (0.1 Torr): nmr ($CDCl_3$) δ 4.05 (m, 1, CHO), 1.07 (s, 3, CH_3); mass spectrum *m/e* 152, 137, 134. *Anal.* Calcd for $C_{10}H_{16}O$: 152.23.

7-*exo*-Methylbicyclo[3.3.1]nonan-3-one (19).—The exo alcohol **16**, treated with acid in the manner described above for the obtention of **13** from **10**, gives the ketone **19**:[11] mp 57–58°; ir ($CHCl_3$) 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.82 (d, 3, *J* = 5 Hz, CH_3); mass spectrum *m/e* 152, 137. *Anal.* Calcd for $C_{10}H_{16}O$ (152.23): C, 78.89; H, 10.59. Found: C, 78.54; H, 10.50.

7-*exo*-Methylbicyclo[3.3.1]nonan-3-*exo*-ol (20).—Ketone **19**, reduced with lithium in liquid ammonia, gives the exo alcohol **20**: mp 72–75°; ir ($CHCl_3$) 3600 and 3420 cm^{-1} (OH); nmr ($CDCl_3$) δ 4.34 (m, 1, CHOH), 0.83 (d, 3, *J* = 5 Hz, CH_3); mass spectrum *m/e* 154, 136, 121. *Anal.* Calcd for $C_{10}H_{18}O$ (154.24): C, 77.86; H, 11.76. Found: C, 77.35; H, 11.57.

7-Methylbicyclo[3.3.1]nonyl 3-*exo*-Tosylate (1) (R = CH_3).—The exo alcohol **20**, treated with *p*-toluenesulfonyl chloride in pyridine, gives after extraction (avoiding any acidic washing), the corresponding, very unstable tosylate **1** (R = CH_3), which is recrystallized in hexane: mp 64° dec; nmr ($CDCl_3$) δ 5.24 (m, 1, CHOTs), 0.82 (d, 3, *J* = 5 Hz, CH_3); mass spectrum *m/e* 172 ($TsOH^+$), 155 (Ts^+).

Kinetics.—Solvolysis was carried out in a 80:20 (v/v) mixture of ethanol and water on solutions 0.002 *M*. After orientation runs, at least duplicate measurements were carried out for the determination of rate constants, up to more than 95% of completion. The progress of reaction was followed by the decrease of extinction at 262 nm,[15] on a Cary 14 spectrophotometer.

Registry No.—**1** (R = CH_3), 19912-54-0; **2** (R = CH_3), 37741-04-1; **3**, 6611-78-5; **4**, 37741-06-3; **5**, 22899-25-8; **6**, 37741-08-5; **7a**, 37741-09-6; **7b**, 37805-66-6; **8**, 37741-10-9; **9**, 37741-11-0; **10**, 37741-12-1; **11**, 37741-13-2; **12**, 37741-14-3; **13**, 37741-15-4; **14**, 37741-16-5; **15**, 19933-29-8; **16**, 1712-41-0; **17**, 1905-15-3; **18**, 6508-22-1; **19**, 37741-56-3; **20**, 37741-57-4; *p*-cresol, 106-44-5.

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Condensation–Cyclization Reactions of Electron-Deficient Aromatics. V. Formation of Enolic Bicyclononanone and Benzobicyclononanone Nitronates by Intramolecular Cyclization in Benzenoid and Naphthalenoid σ Complexes[1]

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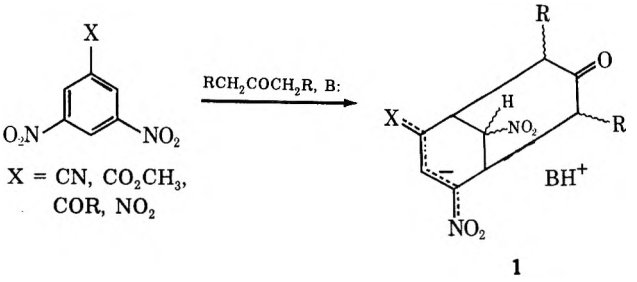
Intramolecular cyclizations in naphthalenoid σ complexes have been observed to occur, analogous to those previously observed in benzenoid systems. The condensation–cyclization reactions of 1,3-dicarbomethoxyacetone with *sym*-trinitrobenzene, 1,3,6,8-tetranitronaphthalene, and 1,3-dinitronaphthalene are compared, and the products isolated in each case are characterized. The reaction in the latter two instances yields interesting benzobicyclic nitronates.

The recent and rapidly growing interest in the chemistry of anionic σ complexes has been enhanced during the past few years by a number of interesting reports of structures prepared from several different types of aromatic compounds. Included in these studies have been characterizations of σ complexes prepared from electron-deficient benzenes,[2] naphthalenes,[2,3-11] anthracenes,[8] thiophenes,[12] purines,[13] pyridines, and diazines.[9,14-19] Two years ago we reported that simple anionic σ complexes formed from electron-deficient benzenes and carbanions readily undergo internal cyclization to yield novel new bicyclic nitronates which are remarkably stable.[1] Our initial studies were extended using a variety of different electron-deficient benzenes and ketonic carbanion sources, and we have found the reaction to be quite general.[1] It occurs readily with 1-X-3,5-dinitrobenzenes when X is electron withdrawing[1] and with 1-X-2,4,6-trinitrobenzenes when X is electron withdrawing or donating.[20] In the latter case isomeric products containing the X substituent on the bridgehead and on the nitronate function can be isolated when X is electron withdrawing, but only on the nitronate function when X is electron donating. Almost any active ketone or keto ester will bridge sufficiently electron-deficient benzenes. The mechanistic details of this stepwise process have been discussed previously.[1,21]



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As a logical extension of the study of benzenoid σ complexes, characterization of naphthalenoid complexes was reported by Fendler and others in the latter part of the 1960's.[2,6-9] This interesting work is continuing, as evidenced by very recent reports.[3-5,10,11] Since we supposed that our originally reported internal cyclization reactions would not be unique to benzenoid systems, we thought it of interest to investigate the possibility of preparing benzobicyclic nitronates from naphthalenoid σ complexes. Such systems would be of considerable value in comparative studies of simple bicyclic nitronates, much as the studies of benzenoid and naphthalenoid σ complexes have complemented each other. In addition, the observation of internal cyclization in naphthaleonoid systems would provide substantial evidence that such cyclizations may well occur in other systems, *i.e.*, pyridine, purine, thiophene σ complexes, etc. Since nitronates can easily be hydrolyzed to ketones in certain instances, the synthetic value of such a reaction for the preparation of bicyclic systems cannot be overlooked. We report here the first example of internal cyclizations in naphthalene σ complexes, and characterization of the isolated crystalline products.

We have found that 1,3-dicarbomethoxyacetone (DCA) is one of the most reactive ketonic substrates in condensation–cyclization reactions with benzenoid aromatics. We therefore decided to study the reactions of naphthalenoid systems using DCA. Since the detailed structure of bicyclic nitronate DCA adducts with electron-deficient benzenes had not been established previously, we found it necessary to first

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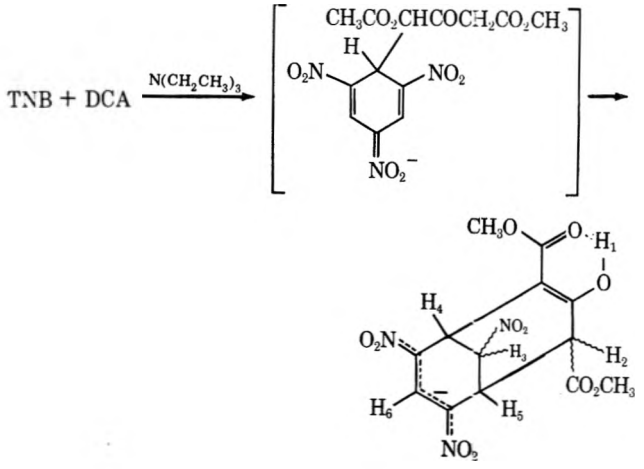
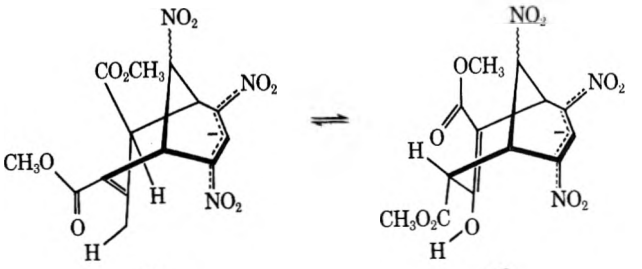
characterize the detailed structure of the *sym*-trinitrobenzene (TNB) adduct with DCA. This nitronate was found to be completely enolic, in contrast to the previously reported nitronates analogous to **1**, which are ketonic.

In dimethyl sulfoxide (DMSO) a 1:1 equivalent mixture of DCA, TNB, and triethylamine shows visible and pmr spectral absorptions characterizing the rapid formation of a benzenoid σ complex and subsequent cyclization to bicyclic nitronate.[2,22] Bright red crystals of this latter product can be isolated (see Experimental Section). The pmr ($CDCl_3$) and ir (KBr) spectra, as well as the elemental analysis, are consistent with structure **2**. The strong maximum at 500 nm in the

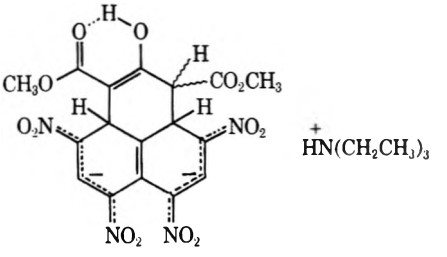


visible spectrum is characteristic of the nitropropene nitronate function of **2**.[1,2,23] Two intense bands in the ir spectrum at 1730 and 1648 cm^{-1} provide strong evidence for the ester-enol structure of **2**. The 1730-cm^{-1} absorption results from the unconjugated CO_2CH_3 carbonyl, whereas the 1648-cm^{-1} absorption results from the other CO_2CH_3 carbonyl bonded to the enolic hydroxyl group. These bands are almost of equal intensity, whereas in neat DCA the 1730-cm^{-1} band is broader and much more intense. The pmr spectrum ($CDCl_3$) provides confirming evidence for the total structure of **2**. The triplet and quartet of the $(CH_3CH_2)_3NH^+$ cation are centered at δ 1.36 and 3.18 ppm. The H-2 proton appears as a sharp doublet (1 H, $J < 3$ cps) at δ 3.78 ppm. The significance of the small J value will be discussed later. Two very sharp and closely spaced singlets for the CO_2CH_3 methyls appear at δ 3.84 and 3.86 ppm (3 H each). The H-3 proton α to NO_2 appears as a double doublet centered at δ 4.10 ppm (1 H). It is coupled to the bridgehead protons H-4 and H-5, with $J_{3,4}$ and $J_{3,5}$ both less than 2.5 cps. Both bridgehead protons appear centered at δ 5.31 ppm as an unsymmetrical broadened doublet (2 H). The nitropropene nitronate proton H-6 appears as a sharp singlet at δ 8.52 as expected.[1] The enolic proton H-1 and the cationic NH absorptions appear as a very broad symmetrical absorption at δ 12.25 (2 H). The configuration at the carbons bonded to H-2 and H-3 cannot be determined from this pmr data. It is known that the bridging $CHNO_2$ carbon remains configurationally stable in DMSO, however,[1] and the profound changes in the pmr spectrum of **2** in this solvent provide additional evidence for the enolic structure and the possibility for epimerization at the $CHCO_2CH_3$ carbon. In DMSO-d_6, the nitropropene nitronate proton H-6 no longer appears as a singlet as in $CDCl_3$, but as two singlets of unequal intensity. The rest of the spectrum becomes quite complex, except for the cation absorptions, which remain a sharp triplet and quartet. The two CO_2CH_3 singlets in $CDCl_3$ are transformed into three broader absorptions of unequal intensity in DMSO-d_6. A complex multiplet occurs centered at δ 3.8 ppm for H-2 instead of the sharp doublet observed in $CDCl_3$. Four separate absorptions appear in the region from δ 4.1 to 6.0 ppm. These are complex multiplets of nonintegral intensity individually, and result from H-3, H-4, and H-5. Because absorptions from one isomer (**2a** or **2b**) overlap with those of the



other in this region, it is impossible to assign all these peaks. Such a solvent effect on the spectrum may simply be related to the increased basicity of nitronate anions in DMSO relative to $CHCl_3$, resulting in intermolecularly catalyzed epimerization.

We have carried out a similar reaction of DCA with 1,3,6,8-tetranitronaphthalene (TNN) in order to characterize the kind of product which might be iso-



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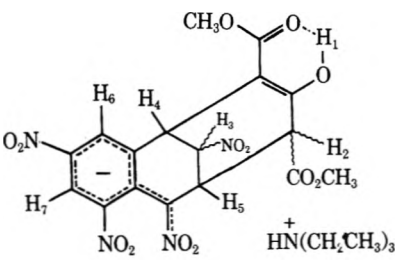

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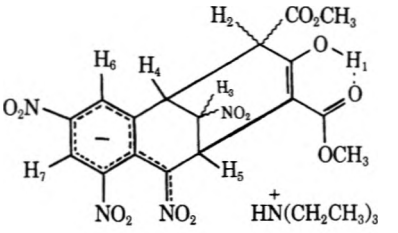

4b

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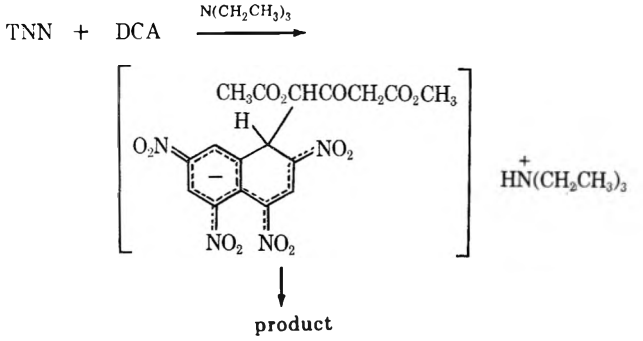
lated in this instance. Since twofold addition to tetranitroacenaphthalene has previously been reported to give a double σ complex,[11] and since the peri positions in TNN were both expected to be quite reactive, a 4, 5 condensation product, **3**, in addition to the two isomeric 2, 4 bridged products, **4a** and **4b**, seemed possible. When the reaction was carried out in neat DCA in the presence of excess triethylamine, two distinct visible spectral changes occurred in rapid succession. The instantaneous change occurring upon addition of triethylamine to a colorless saturated solution of TNN in DCA is the appearance of a strong maximum at 490 nm. This spectral development is similar to that described by Fendler for the formation of hydroxide and methoxide σ complexes of TNN.[3] In the present system, however, the 490-nm maximum rapidly diminishes and is replaced by another strong maximum at 526 nm. The changes are much too rapid to follow conveniently by pmr, but are undoubtedly due to formation of the intermediate σ complex, followed by



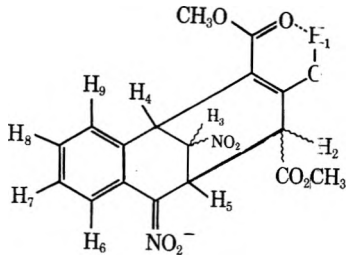
cyclization to product. Washing the reaction mixture with anhydrous ether to remove the excess DCA and triethylamine leaves a red-orange oil, which when worked up (see Experimental Section) yielded bright red crystals, mp 140.5–141°, which analyzed correctly for a 1:1:1 adduct of DCA, TNN, and amine. The infrared spectrum of this product (KBr) in the 1650–1740-cm^{-1} range is identical with that of **2**, again providing substantial evidence for an enol–ester structure. The pmr spectrum ($CDCl_3$) confirms the structure as **4**. There are significant differences between this pmr spectrum and that of **2**, caused by the benzo fusion in **4**. Nevertheless, the overall similarity of the two spectra provides additional evidence for analogous structures. The cation triplet and quartet again appear centered at δ 1.32 and 3.10 ppm. The next high field peaks are the two CO_2CH_3 absorptions at δ 3.74 and 3.83 ppm. The H-2 doublet in **4** is shifted downfield about 1 ppm from the corresponding resonance in **2**, and appears at δ 4.55 ($J_{2(4or5)} \cong 2.5$ cps). The H-3, H-4, and H-5 protons absorb in the region from δ 4.3 to 5.4 ppm and appear as two poorly resolved four-peak multiplets and one sharp double doublet. These peaks, centered at δ 4.4, 4.7, and 5.3 ppm, respectively, integrate for one proton each. The complexity of the absorptions results from the fact that in such bicyclic compounds containing nonequivalent bridgehead protons, long-range coupling can commonly occur.[1] Several sets of $J_{4,5}$, $J_{3,4}$, and $J_{2(4or5)}$ coupling constants within the range of 2 to 3 cps can account qualitatively for the observed splitting patterns, but decoupling experiments proved difficult owing to the close proximity of irradiated and observed peaks. Downfield at δ 8.2 ppm the AB system of the benzo fusion shows the expected double doublet. The $^+HNEt_3$ and enolic hydroxyl protons appear as a very broad band centered at δ 11.0 ppm. Using DMSO-d_6 as the pmr solvent does not change the pmr spectrum substantially, in contrast to the observations made with **2**. This must result from considerable stability associated with the isomer isolated.

It is impossible to unambiguously assign the structure of **4** to either **4a** or **4b** from the pmr spectral data. There is one feature of the spectrum of particular interest, however. The $J_{2(4or5)}$ coupling constant of 2.5 cps suggests that the CO_2CH_3 group is trans to the $CHNO_2$ bridge. If it were cis, a value of 5–7 cps would be expected since the dihedral angle (based on Dreiding models) in this latter case is ~30°. In the case of a trans system, the dihedral angle is ~50°, resulting in the expected J value of ~2.5 cps. These angles apply to models of both **4a** and **4b**. The configuration of H_2 in **2** is likely the same as in **4** for similar reasons (*vide supra*).

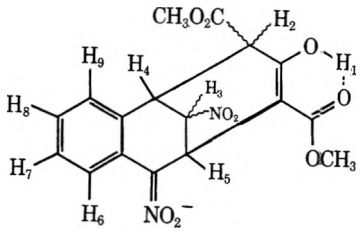
The condensation–cyclization reaction of 1,3-dinitronaphthalene (DNN) parallels that of TNN. Although development of visible absorption characterizing a DNN σ complex intermediate occurs quite rapidly on mixing the reagents, transformation to product occurs more slowly than with TNN. These qualitative reactivity changes are related to the stability of σ complexes formed from TNN and DNN, which are determined for the most part by the number of nitro groups on each system.[5] An initially colorless saturated solution of DNN in DCA turns violet on addition of triethylamine. The color corresponds to a maximum at 548 nm, similar to that previously reported for carbanionic σ complexes of DNN.[2,9] This maximum eventually disappears and the solution turns pale yellow, with a maximum at 322 nm. Washing the solution with copious quantities of ether to remove the excess amine and ketone results in a viscous, yellow-brown oil. When this oil is dissolved in a minimum amount of a hot 4:1 mixture of ether–ethanol, colorless crystals are formed when the solution is cooled to 0°. These contain solvent of crystallization. After filtration and drying at 0.5 mm for several hours, the crystals turn opaque, and melt sharply at 84–84.5°. The ir spectrum of this product is essentially identical with that of **4** in the 1600–1750-cm^{-1} range. The visible spectrum (MeOH) shows a maximum at 322 nm. The pmr spectrum ($CDCl_3$) provides definitive evidence for structure **5**. The triplet and quartet cation absorptions appear at δ 1.3 and 3.1 ppm, and the two CO_2CH_3 absorptions at δ 3.85 and 3.9 ppm. The H-2 proton doublet absorbs at δ 4.48, and the two bridgehead protons (H-4, H-5) are centered at δ 4.59 and 4.68 ppm. The latter two absorptions are complex multiplets with a total of over ten transitions. The H-3 proton α to NO_2 is again a clearly resolved double doublet at δ 5.40 ppm. The H-7, H-8, and H-9 protons of the fused benzene ring occur as a complex multiplet centered at δ 7.2 ppm. Interestingly, the H-6 proton absorbs far downfield at δ 9.20 ppm as a double doublet ($J_{6,7} = 8$, $J_{6,8} = 1.5$ cps). The unusually low field resonance for this proton is likely due to deshielding by the closely positioned peri nitrogen atom of the nitronate function. In this regard, it should be pointed out that the charge

density on nitronates is greatest on oxygen, and that nitrogen carries a formal positive charge. The chemical shifts for a series of previously prepared nitropropene nitronates support this supposition.[1,2] The $^{+}$NH and OH absorption appears as a broad symmetrical band at δ 10.48 ppm.

The very small coupling constant for H-2 in **5** again suggests that the CO_2CH_3 group is trans to the $CHNO_2$ bridge (*vide supra*). A distinction between **5a** and **5b**



5a



5b

cannot be unambiguously made. As with **4**, DMSO does not induce epimerization, again suggesting that the isomer obtained (**5a** or **5b**) is much more stable than its epimer. We have no explanation for such a stability difference.

The characterization of bridged naphthalenes provides support for the possibility that a large number of other types of electron-deficient aromatics may also be bridged by ketones, keto esters, and other potential biscarbanions. The types of new and interesting bicyclic nitronate structures which may be prepared might well approach the number of carbanionic σ complexes studied thus far, since any aromatic substrate reactive enough to form a carbanionic addition complex could theoretically be bridged. The synthetic possibilities for such reactions could well be of substantial importance in carbobicyclic and heterobicyclic synthesis. These possibilities will be considered in future work.

Experimental Section

Pmr spectra were obtained on JEOL MH-100 and C-60 HL nmr spectrometers. Chemical shifts are relative to internal TMS. Visible and infrared spectra were measured on Perkin-Elmer 402 and 21 spectrophotometers, respectively. Elemental analyses were performed by G. I. Robertson, Jr., Florham Park, N. J. 07932, and Galbraith Laboratories, Knoxville, Tenn. 37921. All melting points are uncorrected.

Preparation of 2.—A mixture of 1.3 ml of DCA and 2.13 g (0.01 mol) of TNB was warmed until the aromatic compound dissolved, and *ca.* 3 ml of triethylamine was then added. The greenish, tarlike mixture was kept at room temperature for 4 hr and 5 ml of methanol was added. The resultant slurry was added to 75 ml of anhydrous ether and the mixture was cooled. The crude product which precipitated was filtered and recrystallized from a 1:1 ether–methanol mixture to give a 30% yield of brilliant red crystals, mp 119–122°.

Anal. Calcd for $C_{19}H_{28}N_4O_{11}$: C, 46.71; H, 5.78; N, 11.47. Found: C, 46.84; H, 5.83; N, 11.36.

Preparation of 4.—Triethylamine (1 ml) was added to a saturated solution of 1 g (0.005 mol) of TNN in DCA at 40°. After 10 min, the oily red-orange reaction mixture was washed with copious amounts of dry ether to remove the excess amine and ketone. The resulting oil was dissolved in hot ether containing just enough ethanol to effect dissolution. Upon cooling at 0°, large red crystals of **4**, mp 140–141°, were obtained in 60% yield. These were quite stable and showed no evidence for decomposition after several weeks at room temperature.

Anal. Calcd for $C_{23}H_{29}N_5O_{13}$: C, 47.34; H, 5.01; N, 12.00. Found: C, 47.44; H, 5.26; N, 12.00.

Preparation of 5.—A solution of DNN, DCA, and triethylamine was prepared in a fashion similar to that described for **4**. The initially dark violet solution turned yellow after 15 min at room temperature. Washing this yellow solution with three 25-ml portions of dry ether yielded a yellow-brown oil, which was dissolved in hot ether by adding just enough ethanol to effect dissolution. After standing at 10° for 12 hr, large colorless crystals were deposited. When these were filtered and dried over $CaCl_2$ at 0.1 mm and 40° for 2 hr they turned pale yellow and opaque. This change is likely due to a loss of solvent of recrystallization. The yield of dry recrystallized product was *ca.* 50%. The crystals of **5** are quite sensitive to moisture, and after standing for 12 hr decompose to a brown tar.

Anal. Calcd for $C_{23}H_{31}N_3O_9$: C, 55.98; H, 6.33; N, 8.51. Found: C, 55.80; H, 6.15; N, 8.43.

Registry No.—**2**, 37703-25-6; **4a**, 37767-75-2; **4b**, 37703-26-7; **5a**, 37767-79-6; **5b**, 37767-80-9; DCA, 1830-54-2; TNB, 99-35-4; TNN, 28995-89-3; DNN, 606-37-1; triethylamine, 121-44-8.

Acknowledgments.—This research was supported by the Army Research Office at Durham, Grant No. 69C 0064, and by the Petroleum Research Fund administered by the American Chemical Society.

Reactions of the Classical 3-Bicyclo[3.1.0]hexyl Cation. Preparation and Acetolysis of the *endo*- and *exo*-2-Bicyclo[3.1.0]hexyl *p*-Toluenesulfonates[1a,b]

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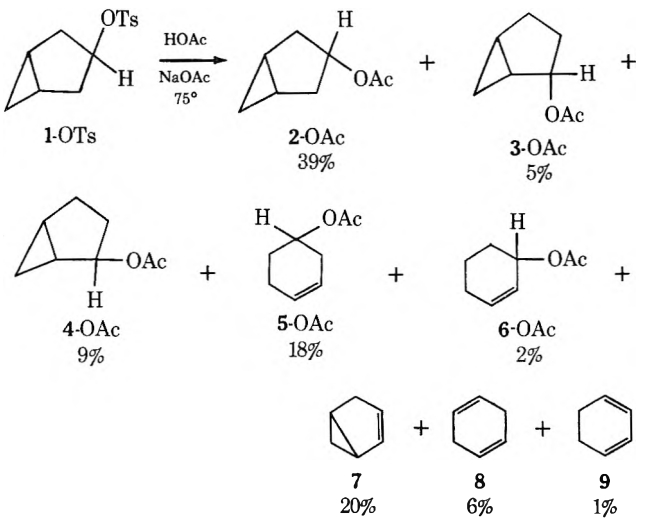
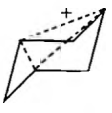
Preparation of the isomeric *endo*- and *exo*-2-bicyclo[3.1.0]hexyl *p*-toluenesulfonates (**3**-OTs and **4**-OTs) and determination of their kinetics and products of acetolysis are described. Both **3**-OTs and **4**-OTs react at similar, high rates, and give within experimental error identical product mixtures consisting of about 16% **3**-OAc, 36% **4**-OAc, and 48% cyclohexen-4-yl acetate at 24°. Using the product results from acetolysis of **3**-OTs and **4**-OTs, together with those reported in the literature for acetolysis of cyclohexen-4-yl *p*-toluenesulfonate, postulation of the nature of the processes involved in formation of the complex mixture of products from acetolysis of *trans*-3-bicyclo[3.1.0]hexyl *p*-toluenesulfonate is made.

In connection with their investigation of the nature and behavior of the unsubstituted trishomocyclopropenyl cation, Winstein and coworkers[3] observed that acetolysis at 75° of *trans*-3-bicyclo[3.1.0]hexyl *p*-toluenesulfonate (**1**-OTs) gave the complex mixture of products shown in Scheme I. On the other hand, acetolysis of *cis*-3-bicyclo[3.1.0]hexyl *p*-toluenesulfonate (**2**-OTs) at 75°, which proceeds primarily *via* formation of the symmetrical trishomocyclopropenyl cation intermediate (**10**), gave only **2**-OAc and **1**-OAc in yields of 99 and 1%, respectively.

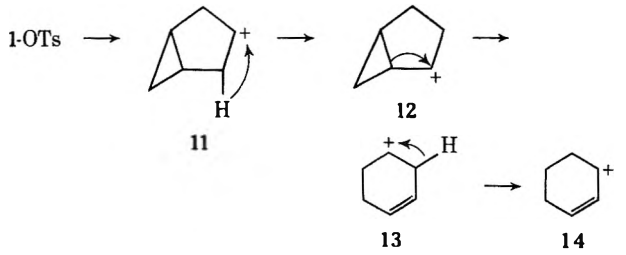
SCHEME I





10

Isotopic labeling studies[3] showed that the 39% yield of **2**-OAc obtained on acetolysis of **1**-OTs must have arisen simply from SN2 displacement by solvent acetic acid on **1**-OTs rather than *via* intermediate formation of **10**. However, the exact natures of the processes leading to the other seven products are not readily apparent, although their formation can be rationalized in simple classical terms by the series of rearrangements yielding the cation intermediates **12** to **14** shown below,



from each of which products are obtained. Thus, to obtain further information regarding the nature of the processes involved in product formation in acetolysis of **1**-OTs, we initiated a study involving direct generation of the 2-bicyclo[3.1.0]hexyl cation (**12**) by acetolysis of the *endo*- and *exo*-2-bicyclo[3.1.0]hexyl *p*-toluenesulfonates (**3**-OTs and **4**-OTs).

Results

Preparation of 3-OTs and 4-OTs.—The *endo*-2-bicyclo[3.1.0]hexanol (**3**-OH) precursor of **3**-OTs was prepared for this study by stereospecific addition of the Simmons–Smith reagent to cyclopenten-3-ol.[4] This was then equilibrated with aluminum isopropoxide in refluxing isopropyl alcohol to a mixture containing 65% of the exo alcohol **4**-OH, which was purified by glpc. Preparation of the *p*-nitrobenzoate or 3,5-dinitrobenzoate ester derivatives of these isomeric alcohols presented no difficulties. However, attempts to prepare the *p*-toluenesulfonate ester derivatives through reaction of **3**-OH or **4**-OH with *p*-toluenesulfonyl chloride by the usual method in pyridine at 0°, or using a special technique[5] at −78°, failed. In these cases only the presumed alkylpyridinium tosylate salts could be isolated.

Both **3**-OTs and **4**-OTs were finally prepared using the technique of Wiberg and coworkers[6] involving reaction of the alcohols with *p*-toluenesulfonyl chloride and powdered potassium hydroxide in ether. Upon addition of pentane and cooling both crystallized as white

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. (b) A portion of the work reported was carried out by E. C. F. while a Postdoctoral Fellow in Chemistry during 1961–1962 at the University of California, Los Angeles. The remainder was taken in part from the Ph.D. Dissertation of M. A. S., University of California, Davis, 1971.

(2) Deceased, November 23, 1969.

(3) S. Winstein, E. C. Friedrich, R. Baker, and Y. Lin, *Tetrahedron, Suppl 8, Part II*, 621 (1966).

(4) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963).

(5) E. C. Friedrich and S. Winstein, *ibid.*, **86**, 2721 (1964).

(6) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *ibid.*, **83**, 3998 (1961).

solids which, however, after a few minutes at room temperature or a few hours at −25° decomposed to deep blue liquids. These after a few days resolidified to tan solids, which were shown in both cases to consist entirely of cyclohexen-4-yl *p*-toluenesulfonate (**5**-OTs). This is similar to the behavior observed by Wiberg and coworkers[6] for their *endo*-5-bicyclo[2.1.1]hexyl *p*-toluenesulfonate, which also rearranged on standing at room temperature to **5**-OTs *via* melting to a deep blue liquid and resolidification. Thus, because of this extremely low stability of **3**-OTs and **4**-OTs it was not possible to obtain their microanalyses and spectra Also, it was necessary to store and employ them as solutions in ether for both the kinetic and product studies which follow.

Kinetic Studies.—The rates of acetolysis of **3**-OTs and **4**-OTs were observed to be much too fast to measure using the usual titrimetric techniques even at 25°. Therefore, only "one-point half-life" rate constants could be obtained as described in the Experimental Section. These are shown in Table I. Within experimental error, both **3**-OTs and **4**-OTs underwent acetolysis at the same rate. However, both were highly reactive, as is evidenced by the observation that in acetolysis they are approximately 10^5 times faster than cyclopentyl *p*-toluenesulfonate[7] and 10^4 times faster than nortricyclyl *p*-toluenesulfonate.[8]

Table I
Rates of Acid Production in Acetic Acid and Acetone

ROTs	Solvent	Temp, °C	k_1, sec^{-1}
3-OTs	98% HOAc 2% Et_2O	24.6	$(6.7 \pm 0.2) \times 10^{-2}$ [a]
4-OTs	98% HOA 2% Et_2O	25.1	$(7.0 \pm 0.2) \times 10^{-2}$ [a]
3-OTs	97% Acetone 3% Et_2O	25.0	$(3.53 \times 0.05) \times 10^{-5}$ [b]
4-OTs	97% Acetone 3% Et_2O	25.0	$(2.66 = 0.09) \times 10^{-5}$ [c]

[a] Calculated from averages of triplicate "one-point half-life" runs; errors are the maximum deviations from the averages. [b] Infinity is *ca.* 95% of that in acetic acid. [c] Infinity is *ca.* 100% of that in acetic acid.

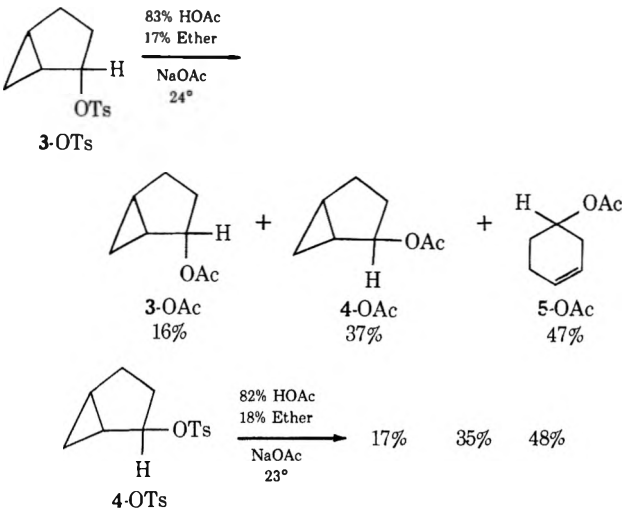
Although the rates of **3**-OTs and **4**-OTs in acetic acid were too fast for highly accurate measurement, they were quite manageable in dry acetone at 25.0°. In this solvent the rates of acid production for both isomers followed good first-order kinetics, with the endo isomer **3**-OTs being 1.3 times faster than the exo isomer **4**-OTs. These results are also shown in Table I.

In connection with the question of whether possible ion-pair return occurs during reaction of **3**-OTs or **4**-OTs to give unreactive **5**-OTs, it is important to note that in the rate runs in the poor ionizing solvent dry acetone the experimental infinities obtained were almost identical with those observed in acetolysis. Thus, it is reasonable to conclude that neither in acetic acid nor in dry acetone is ion-pair return to give unreactive **5**-OTs an important process. This could not be determined directly from experimental infinity titer data, since it was not possible to know the exact concentrations of **3**-OTs or **4**-OTs in the ether stock solution in which they were stored and used.

Although it was not possible to directly prove the structures of **3**-OTs and **4**-OTs by microanalytical and spectral methods, the kinetic results given above clearly show that we are dealing with the correct compounds. In subsequent work it has been found that in the solvolyses of the well-defined *endo*- and *exo*-2-bicyclo[3.1.0]-hexyl 3,5-dinitrobenzoates in 80% aqueous acetone at 80°[9] and the corresponding *N*-methyl-4-oxopyridinium iodides in 80% aqueous ethanol at 86°[10] the endo isomers react at rates approximately 1.2 to 1.3 times faster than the exo isomers, and they are faster in rate by factors of 10^4 to 10^5 over the cyclopentyl derivatives. Also, in neither of these other systems is ion-pair return to unreactive cyclohexen-4-yl derivatives observed.

Product Studies.—For product studies, **3**-OTs and **4**-OTs were allowed to react in acetic acid buffered with sodium acetate at room temperature for about 10 half-lives. Because it was necessary to use the tosylates as solutions in ether, this resulted in 17–18 volume % ether also being present in the acetic acid during the acetolysis product runs. Both **3**-OTs and **4**-OTs gave, within experimental error, by glpc analysis of runs carried out in duplicate, the same mixture of three acetates shown in Scheme II.[11] Less than 1% of any hydrocarbon elimination products were observed. Also, no evidence for any cyclohexen-4-yl tosylate (**5**-OTs) ion-pair return product was obtained. Based on the infinity titers obtained in acetolysis of **3**-OTs and **4**-OTs as a measure of their concentrations in the ether stock solutions in which they were employed, use of internal standards in the glpc analyses showed that the combined yields of **3**-OAc, **4**-OAc, and **5**-OAc were close to theoretical starting with either **3**-OTs or **4**-OTs.

Scheme II



To be able to properly compare the nature and ratio of the acetolysis products obtained from **3**-OTs and **4**-OTs with those obtained from **1**-OTs, it would have

(7) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235 (1961).
(8) Unpublished work of H. J. Schmid and S. Winstein.

(9) (a) E. C. Friedrich and M. A. Saleh, *Tetrahedron Lett.*, 1373 (1971); (b) E. C. Friedrich and M. A. Saleh, *J. Amer. Chem. Soc.*, in press.
(10) G. H. Schmid and A. Brown, *Tetrahedron Lett.*, 4695 (1968).
(11) These product results have already been quoted as unpublished work of Friedrich and Winstein by K. B. Wiberg, R. A. Fenoglio, V. Z. Williams, and R. W. Ubersax, *J. Amer. Chem. Soc.*, **92**, 568 (1970).

been better to also do acetolysis product studies on 3-OTs and 4-OTs in pure acetic acid at 75°, the conditions used in acetolysis of 1-OTs. However, this was not possible owing to the high reactivities of 3-OTs and 4-OTs and the fact that it was necessary to employ them as solutions in ether. Nevertheless, to obtain data of use in telling us something about the effects of solvent and temperature on the nature of the products obtained on acetolysis of the 2-bicyclo[3.1.0]hexyl cation (12), we carried out acetolysis product studies on the 2-bicyclo[3.1.0]hexyl 3,5-dinitrobenzoates 3-ODNB and 4-ODNB at 100°.

Initial controls carried out on the most reactive of the possible acetolysis products 3-OAc showed that it was not stable under the acetolysis reaction conditions at 100°. Heating a pure sample of 3-OAc in acetic acid buffered with sodium acetate and containing 3,5-dinitrobenzoic acid at 100° for 54 hr resulted in 54% rearrangement to give a mixture of 4-OAc and 5-OAc. However, this product instability does not present any serious problems, since on rearrangement only 4-OAc and 5-OAc are obtained and, in any case, direct comparison of the product ratios obtained from 3,5-dinitrobenzoate acetolysis with those obtained from tosylate acetolysis is not possible because of the differences in leaving groups. The primary purpose for doing the 3,5-dinitrobenzoate acetolysis at 100° was to learn something of the effects of temperature on the nature of the products, and this should be relatively independent of the nature of the leaving group.

Thus, samples of 3-ODNB and 4-ODNB were allowed to react in acetic acid buffered with sodium acetate at 100° for 50 hr. This period of time was estimated to be sufficient for approximately 5 half-lives for acetolysis of the dinitrobenzoates at 100°. Both isomeric dinitrobenzoates were found to give, within experimental error, identical product mixtures consisting of approximately 24% 3-OAc, 28% 4-OAc, 37% 5-OAc, 1% 6-OAc, and 10% of ion-pair return product 5-ODNB. It is reasonable that ion-pair return to unreactive 5-ODNB is seen here but is not observed in acetolysis of the *p*-toluenesulfonates, since the 3,5-dinitrobenzoate anion is more nucleophilic than is the *p*-toluenesulfonate anion.

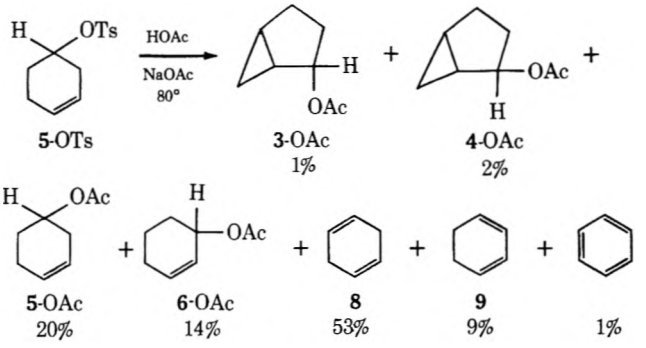
From the results obtained in acetolysis of 3-ODNB and 4-ODNB in acetic acid at 100° several important conclusions may be drawn regarding what might be predicted to be the product-forming behavior of 3-OTs and 4-OTs on acetolysis in pure acetic acid at 75°. First, it is apparent that even at 75° the product mixtures obtained from acetolysis of either 3-OTs or 4-OTs should be identical. Second, one would expect that at 75°, as at 25°, only 3-OAc, 4-OAc, and 5-OAc should be formed in significant yields from acetolysis of 3-OTs or 4-OTs, although the product ratios at 75 and 25° may be different.

Discussion

The kinetic and product results obtained in acetolysis of the *endo*- and *exo*-2-bicyclo[3.1.0]hexyl *p*-toluenesulfonates (3-OTs and 4-OTs) indicate that ionization of these systems must proceed with cyclopropyl participation, and that the 2-bicyclo[3.1.0]hexyl cation intermediate or intermediates involved in product formation must be considerably stabilized *via* charge delocalization from C_2 into the cyclopropane ring. The observation that 3-OTs and 4-OTs on acetolysis reacted at similar rates and gave identical mixtures of products was initially unexpected for stereoelectronic reasons.[12] However, a likely explanation now available for this behavior is that both isomeric tosylates react *via* similar activated complexes and a single bisected bishomoallyl cation intermediate in which delocalization of positive charge on C_2 simultaneously involves both the 1,5 and 1,6 bonds of the cyclopropane ring.[9]

It is readily apparent from the acetolysis product studies on 3-OTs and 4-OTs that the 2-bicyclo[3.1.0]-hexyl cation (12, or better as a charge-delocalized structure) is a reasonable source for the 2-bicyclo-[3.1.0]hexyl acetate (3-OAc and 4-OAc) and at least a portion of the cyclohexen-4-yl acetate (5-OAc) products obtained on acetolysis of 1-OTs. However, another intermediate must be involved in formation of the cyclohexen-3-yl acetate (6-OAc) and the 1,3- and 1,4-cyclohexadiene (9 and 8) products. This intermediate is most likely the cyclohexen-4-yl cation (13), and this conclusion is supported by product studies which have been reported. Thorton and Moore[13] found that acetolysis of cyclohexen-4-yl tosylate (5-OTs) at 80° gives the mixture of products summarized in Scheme III.

SCHEME III



Also, in a similar study carried out independently at 100° by Friedrich, Battiste, and Winstein[14] the substantially identical results 1% 3-OAc, 1% 4-OAc, 22% 5-OAc, 14% 6-OAc, 47% 8, 11% 9, and 4% benzene were obtained.[15]

Thus, if one now makes the reasonable assumption that the nature and ratios of the products obtained *via* acetolysis of the independently generated 2-bicyclo-[3.1.0]hexyl (12) and cyclohexen-4-yl (13) cations are indicative of the nature and ratios of the intermediates involved in formation of the products obtained from acetolysis of the *trans*-3-bicyclo[3.1.0]hexyl tosylate (1-OTs), Scheme IV for the reaction pathway in acetolysis of 1-OTs may be written. Based on this scheme, it may be concluded that, of the products obtained from acetolysis of 1-OTs, 59% arises either *via* the classical

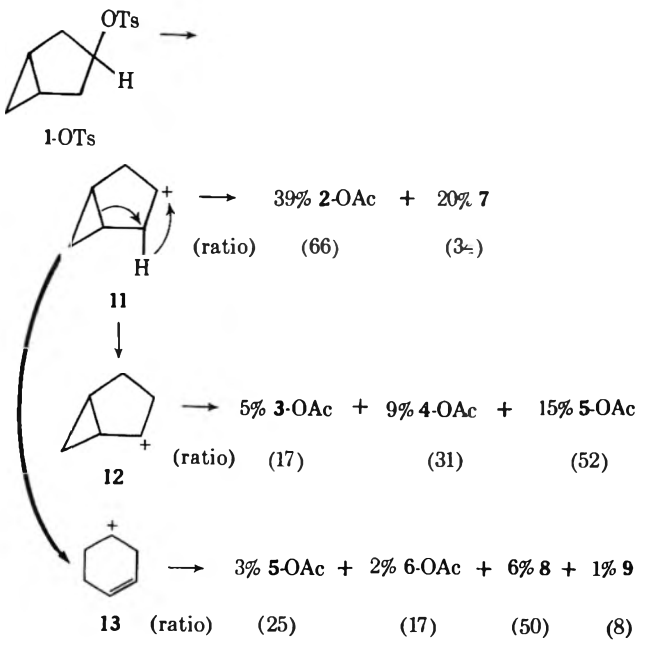
(12) C. D. Poulter, E. C. Friedrich, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4274 (1970), and references cited therein.

(13) R. L. Thornton, Ph.D. Thesis, Massachusetts Institute of Technology, 1961. Thesis supervisor: W. R. Moore.

(14) Unpublished work of E. C. Friedrich, M. A. Battiste, and S. Winstein.

(15) M. Hanack and W. Keberle, *Chem. Ber.*, **96**, 2937 (1963), also reported obtaining the acetates 3-OAc and 6-OAc in similar ratio from acetolysis of 3-OTs at 70°, but did not investigate the yields or nature of the hydrocarbon products.

Scheme IV



3-bicyclo[3.1.0]hexyl cation (**11**) or *via* Sn2 and E2 reactions by solvent on **1**-OTs, 29% arises from the 2-bicyclo[3.1.0]hexyl cation (**12**), and 12% results from the cyclohexen-4-yl cation (**13**). It is also of interest to note that the reaction scheme requires cyclopropane ring opening to be concerted with 2,3-hydride shift in **11** in giving **13**, since rearrangement of **12** to **13** was not observed. Formation of **12** and **13** may furthermore be concerted with ionization of **1**-OTs, although consideration of the effects of 2-alkyl substituents on the rates of solvolysis of **1**-OTs[16] casts some doubt on the likelihood of this possibility.

Experimental Section

All melting points and boiling points are uncorrected. Elemental analyses were performed by Miss Heather King, University of California, Los Angeles.

endo-2-Bicyclo[3.1.0]hexanol (3-OH).—Using a procedure similar to that reported by Dauben and Berezin,[4] 40 g (0.047 mol) of cyclopenten-3-ol was reacted with 83 g (1.33 mol) of zinc–copper couple, 250 g (0.93 mol) of methylene iodide, and 0.4 g of iodine in 600 ml of ether. The product was distilled under vacuum through a 30-cm glass spiral column to obtain, along with about 5 g of unreacted starting material, 20 g of *endo*-2-bicyclo[3.1.0]hexanol, bp 75–76° (20 mm), n^{25}D 1.4771, which was better than 99% pure [lit.[17] bp 76° (17 mm); n^{20}D 1.4788]. The *p*-nitrobenzoate derivative was prepared in the usual manner using a 10% excess of *p*-nitrobenzoyl chloride in cold pyridine and was recrystallized twice from warm methylcyclohexane, mp 81.5–83.0°.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.43; H, 5.27; N, 5.90.

endo-2-Bicyclo[3.1.0]hexyl *p*-Toluenesulfonate (3-OTs).—A magnetically stirred solution containing 1.0 g (0.0102 mol) of 3-OH in about 25 ml of anhydrous ether was cooled in an ice bath and 1.95 g (0.0102 mol) of *p*-toluenesulfonyl chloride was added. After the tosyl chloride dissolved, 2.0 g of powdered potassium hydroxide (95%) was added in 1-g portions. Stirring was then continued for 1 hr at 0°. At the end of this time the odor of tosyl chloride could no longer be detected in the solution. About 1 g of anhydrous potassium carbonate was added and stirring was continued for another 15 min. The reaction mixture was filtered with suction and the solids were washed well with ether. Titration of a 0.5-ml aliquot of the combined ether solutions (*ca.* 40 ml) in 20 ml of acetic acid to a stable bromophenol blue end point required 8.0 ml of 0.01527 *M* sodium acetate in acetic acid. Storage of the ether solution of **3**-OTs was done at −25° over solid potassium carbonate.

Because of the extremely low stability of **3**-OTs, it was impossible to isolate it in pure form for microanalysis or determination of spectra. Concentration of the ether solution, addition of pentane, and cooling to −25° produced white crystals which when filtered melted after a few minutes at room temperature to a deep blue liquid. This again resolidified after a few days to tan crystals melting at 47–49° after recrystallization from methylcyclohexane. Mixture melting point behavior and ir spectrum indicated that this material was pure cyclohexen-4-yl tosylate (**5**-OTs) (lit.[15] mp 50–50.5°).

exo-2-Bicyclo[3.1.0]hexanol (4-OH).—A solution of 5.0 g of *endo*-2-bicyclo[3.1.0]hexanol, 5.0 g of freshly distilled aluminum isopropoxide, and 1 ml of dry acetone in 100 ml of anhydrous isopropyl alcohol was heated under reflux for 114 hr. The resulting equilibrium mixture contained 65% 4-OH and 35% **3**-OH. The reaction mixture was then worked up by the addition of 30 ml of saturated ammonium chloride solution and 150 ml of ether. The ether solution was washed with several 50-ml portions of water, dried over magnesium sulfate, and concentrated. Purification of **4**-OH was accomplished by preparative scale glpc techniques in two passes through a 2 m × 1 in. 30% NMPN on 40/60 mesh firebrick column run at 120°. The *exo*-2-bicyclo[3.1.0]hexanol fraction collected was flash distilled under vacuum to give 1.0 g of **4**-OH, n^{25}D 1.4754, which was contaminated with < 9% **3**-OH [lit.[17] bp 73.5° (17 mm), n^{20}D 1.4801].

Anal. Calcd for $C_6H_{10}O$: C, 73.47; H, 10.20. Found: C, 73.19; H, 10.44.

The *p*-nitrobenzoate derivative of **4**-OH was prepared in the usual manner using a 10% excess of *p*-nitrobenzoyl chloride in cold pyridine and recrystallized twice from warm methylcyclohexane, mp 66.5–68.5°.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.13; H, 5.28; N, 5.88.

exo-2-Bicyclo[3.1.0]hexyl *p*-Toluenesulfonate (4-OTs).—An ether solution of **4**-OTs was prepared by the same procedure as that described for **3**-OTs from 1.0 g of **4**-OH, 1.95 g of *p*-toluenesulfonyl chloride, and 2.0 g of powdered potassium hydroxide in about 25 ml of ether. Titration of a 0.5-ml aliquot of the combined ether solutions (*ca.* 40 ml) in acetic acid required 7.8 ml of 0.01527 *M* sodium acetate solution. The tosylate **4**-OTs exhibited the same extremely low stability and melting behavior on isolation as did **3**-OTs.

Tosylate Acetolysis Kinetics.—Anhydrous acetic acid was prepared as previously described.[18] Because the rates of acetolysis of **3**-OTs and **4**-OTs were observed to be much too fast to measure using the usual titrimetric techniques even at 25°, only "one-point half-life" rates could be obtained. As an example of the usual procedure, 2.35 ml of 0.01527 *M* sodium acetate in dry acetic acid was added to 20 ml of dry acetic acid containing 4 drops of bromophenol blue indicator in a 50-ml erlenmeyer flask. Then, while the solution was being vigorously stirred, 0.25 ml of an ether solution of *exo*-2-bicyclo[3.1.0]hexyl tosylate (**4**-OTs) was added rapidly from a hypodermic syringe and the time for the indicator change was measured with a stopwatch. The temperature of the solution was then immediately determined and titration was continued until a stable end point was reached. This end point titer, which had also been previously measured on a separate sample, was 4.70 ml. Runs were always done in triplicate and the average reaction half-lives thus obtained were 10.4 ± 0.2 sec for **3**-OTs at 24.6° and 10.0 ± 0.2 sec for **4**-OTs at 25.1°.

Tosylate Kinetics in Dry Acetone.—Dry acetone was prepared as follows. About 1 l. of reagent grade acetone was dried by allowing it to slowly percolate through a 2 ft × 1 in. column packed with 1/16-in. pellets of type 4A Linde Molecular Sieve and distilling it from powdered type 4A Molecular Sieve through a glass helices column. Tests for dryness with Karl Fischer reagent showed that it contained less than 1 mg of water per 1 ml. The dried acetone was then stored under dry nitrogen before use. Kinetics were run using the usual sealed ampoule procedure, and titration of aliquotes for acid formed was done rapidly after

(16) T. Norin, *Tetrahedron Lett.*, 37 (1964).
(17) M. Hanack and H. Allmendinger, *Chem. Ber.*, **97**, 1669 (1964).
(18) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2770 (1956).

dilution in cold, dry acetone using standardized sodium methoxide in methanol to a bromothymol blue endpoint.

Tosylate Acetolysis Products.—As an example of the usual procedure, 1 ml of the ether stock solution of **3**-OTs or **4**-OTs was added rapidly from a hypodermic syringe to 5 ml of rapidly stirred 0.1 *M* sodium acetate in acetic acid containing about 10 mg of benzene internal standard at room temperature. After reacting at room temperature for about 2 min, the reaction mixture was worked up and the acetolysis products were determined by glpc using a similar procedure to that described earlier[3] for analysis of the acetate and olefin products obtained from acetolysis of *trans*-3-bicyclo[3.1.0]hexyl tosylate.

endo- and *exo*-**2-Bicyclo[3.1.0]hexyl-3,5-Dinitrobenzoates (3-ODNB and 4-ODNB).**—These were samples, mp 122–124° (lit.[17] mp 124–124.8°) and 96–98° (lit.[17] mp 98–98.6°), respectively, prepared as described elsewhere.[9b]

Stability of *endo*-2-Bicyclo[3.1.0]hexyl Acetate (3-OAc) under Acetolysis Conditions at 100°.—A small sample of **3**-OAc was prepared by the reaction of pure **3**-OH with acetic anhydride in pyridine, bp 103–104° (20 mm), n^{25}D 1.4530 [lit.[19] bp 65–68° (15 mm)]. Two separate Pyrex ampoules were made up, each containing about 0.15 g (1.1 mmol) of **3**-OAc, 0.1 g (0.5 mmol) of 3,5-dinitrobenzoic acid, and 0.1 g (1.2 mmol) of sodium acetate dissolved in 5 ml of dry acetic acid. The ampoules were sealed, heated at 100° for periods of 10 and 54 hr, respectively, and then worked up and analyzed by glpc using the procedure described below for studying the acetolysis products of **3**-ODNB and **4**-ODNB at 100°. The mixtures were found to consist of 82% **3**-OAc, 5% **4**-OAc, and 13% **4**-OAc and 46% **3**-OAc, 23% **4**-OAc, and 31% **5**-OAc, respectively.

3,5-Dinitrobenzoate Acetolysis Products.—As an example of the usual procedure, 0.23 g (0.8 mmol) of **3**-ODNB was dissolved in 8 ml of 0.11 *M* sodium acetate in dry acetic acid, sealed in a Pyrex ampoule, and heated at 100° for 50 hr. The ampoule was then opened, and a cyclohexyl acetate internal standard was weighed in. The contents of the ampoule were poured into 40 ml of *n*-pentane, and the pentane solution was washed with water and 5% aqueous sodium carbonate, dried over magnesium sulfate, and concentrated to about 3 ml by careful distillation through a short glass helices column. Cooling the pentane solution in ice caused **5**-ODNB to crystallize out. This was filtered and weighed, and its structure was determined by comparing its melting point and nmr spectrum with those of an authentic sample[20] prepared by us from **5**-OH. The acetate products were then analyzed by glpc on a 4 m × 0.25 in. column packed half with 20% diethylene glycol succinate (DEGS) and half with 20% diglycerol on 60/80 mesh Chromosorb P. The remaining acetates were then reduced in 50 ml of dry ether with 0.3 g of $LiAlH_4$. After work-up by adding saturated NH_4Cl solution, drying over magnesium sulfate, and concentrating the ether solution to about 4 ml, the resulting alcohols were also analyzed on glpc on the column described above. The reasons for this double analysis procedure and the methods used to identify the volatile products are described elsewhere.[9b] It was found that acetolysis of **3**-ODNB gave 24% **3**-OAc, 28% **4**-OAc, 37% **5**-OAc, 1% **6**-OAc, and 10% **5**-ODNB, and acetolysis of **4**-ODNB gave 23% **3**-OAc, 25% **4**-OAc, 41% **5**-OAc, 1% **6**-OAc, and 10% **5**-ODNB.

Registry No.—**3**-OH, 822-58-2; **3**-OH *p*-nitrobenzoate, 37816-89-0; **3**-OTs, 37816-90-3; **3**-OAc, 698-56-6; **3**-ODNB, 34272-26-9; **4**-OH, 822-59-3; **4**-OH *p*-nitrobenzoate, 37816-94-7; **4**-OTs, 37816-95-8; **4**-ODNB, 34272-27-0.

(19) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965).

(20) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

Monocyclic Allenes. The Synthesis of 3,8,9-Cycloundecatriene-1,6-dione and 12-Oxabicyclo[7.2.1]dodeca-5,6,9,11-tetraen-3-one, a Furanophane Containing an Allene Group

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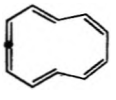
3,8,9-Cycloundecatriene-1,6-dione (**5**) can be prepared from the readily available 4,4,9,9-tetramethoxy-1,6-cyclodecadiene (**2**) *via* the dibromocarbene adduct **3**. The adduct **3** can also be converted into 4,4,10,10-tetramethoxy-6,7-cycloundecadiene-1,2-diol (**8**), which on acid treatment gives 12-oxabicyclo[7.2.1]dodeca-5,6,9,11-tetraen-3-one (**9**), a novel furanophane containing an allene group.

Only a few monocyclic allenes have been prepared in which other functional groups are present. Such molecules are of interest, since the interactions between the functional group and the allene moiety might be unusual. Further, these systems serve as potential precursors of the fully unsaturated monocyclic systems containing an allene group. Heilbronner[1] has suggested that the "Möbius" array of π orbitals in the [4*n*]annulenes might be favored over the "Hückel" array. The introduction of an allene group into a fully conjugated cycle provides an enforced dislocation of the π system. Furthermore, if the allene group is treated as a Möbius array, as suggested by Zimmerman,[2] the possibility exists for a Möbius interaction around the cyclic unsaturated system. The present paper describes the preparation of a number of 11-membered monocyclic allenes containing functional groups, together with a preliminary investigation into methods of converting these molecules into the 12π–11C monocyclic allene **1**.



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The precursor for the synthesis of the allenes was the bicyclic dibromide **3**. This molecule is obtained[3] by the reaction of dibromocarbene with tetramethoxycyclodecadiene **2**, the latter compound being readily available from naphthalene.[4] Treatment of **3** with methyllithium at −10° gave the allene **4**, mp 75–76°, in 73% yield. The ir spectrum of **4** showed a band at 1980 cm^{-1}, characteristic of an allene,[5] and the nmr

(1) E. Heilbronner, *Tetrahedron Lett.*, 1923 (1964).

(2) H. E. Zimmerman, *Accounts Chem. Res.*, **4**, 272 (1971).

(3) P. J. Garratt, K. C. Nicolaou, and F. Sondheimer, submitted for publication in *J. Amer. Chem. Soc.*

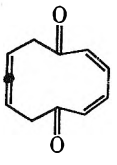
(4) C. A. Grob and P. W. Schiess, *Helv. Chim. Acta*, **43**, 1546 (1960).

(5) L. J. Bellamy, "Infra-Red Spectra of Complex Molecules," 2nd ed, Methuen, London, 1958, p 61.

spectrum was consistent with the assigned structure. Catalytic hydrogenation of **4** in ethyl acetate over palladium on charcoal occurred with concomitant hydrolysis, and cycloundecane-1,6-dione was obtained, identified as its dioxime, mp 229–230°.[6] Hydrolysis of **4** with dilute sulfuric acid in ether yielded 74% of 3,8,9-cycloundecatriene-1,6-dione (**5**), mp 66–67°. The assignment of this structure to **5** was made on the basis of its spectral properties and derivation from **4**. The ir spectrum of **5** had bands at 1960 (allene) and 1705 cm^{-1} (carbonyl), and the nmr spectrum showed signals at τ 4.14–4.44 (m, 2 H, olefin), 4.46–5.00 (m 2 H, allene) and 6.44–7.36 (8 H, methylene). The electronic spectrum of **5** had maxima at 227 (sh) (ϵ 200) and 294 nm (230) and is similar to that of 3,8-cyclodecadiene-1,6-dione[4,7] and related systems.[3] The long wavelength band presumably arises from a transannular chromophore interaction involving the carbon–carbon double bonds and the carbonyl groups.

Reaction of **5** with tosylhydrazine led to the corresponding bistosylhydrazone, mp 173–174°, in *ca.* 90% yield. Reduction of **5** with lithium aluminum hydride gave the diol **6** as an oil, presumably a mixture of stereomers. Attempts to dehydrate the diol **6** were unsuccessful, either **6** being recovered, or a complex mixture of products being formed. Treatment of **6** with acetic anhydride in pyridine yielded the corresponding diacetate, but pyrolysis of this diacetate led only to dimeric products (mass spectrum).

The dione **14**, formally derived from **5** by the introduction of an additional double bond, appeared to be a suitable precursor of the fully unsaturated allene **1**, and the synthesis of **14** was therefore investigated. Treatment of the dibromide **3** with osmium tetroxide and subsequent hydrolysis of the resulting osmate ester gave the cis diol **7**, mp 81–82°, in 80% yield. The assigned structure **7** was confirmed by the spectral properties, but the relative stereochemistry of the cis hydroxyl groups to the cyclopropyl ring is not known.



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Treatment of **7** with a large excess of methyllithium at −10° yielded 70% of the corresponding allene **8**, mp 109–110°. The nmr spectrum of **8** was consistent with the assigned structure and showed the presence of two types of hydroxylic protons (τ 7.00, 7.41), and two types of protons adjacent to hydroxyl (5.60, 6.07). The difference in chemical shift of these sets of protons presumably arises from their relative relationship to the allene group and consequent different magnetic environment.

When **8** was treated with 80% sulfuric acid in ether, 12-oxabicyclo[7.2.1]dodeca-5,6,9,11-tetraen-3-one (**9**), mp 69–70°, was isolated in 63% yield, rather than the anticipated dione **14**. The structure of **9** was confirmed by its chemical and spectral properties. Thus reaction of **9** with 2,4-dinitrophenylhydrazine gave a monohydrazone, mp 202–203°, while catalytic hydrogenation over palladium on charcoal yielded 69% of the bicyclic ketone **10**, mp 38–40°. The ir spectrum of **9** had bands at 1945 (allene) and 1697 cm^{-1} (carbonyl). The nmr spectrum ($CDCl_3$) showed signals at τ 3.90–4.06 (m, 2 H, furan), 4.50–4.70 (m, 1 H, H^7), 5.10–5.43 (m, 1 H, H^5), 6.04–6.88 (m, 5 H, methylene), and 7.07–7.32 (m, 1 H, methylene). The large difference in chemical shift of the allenic protons, H^5, H^7, is presumably due to the shielding of the H^5 proton by the furan ring, similar effects being observed in the metacyclophanes.[8] The high-field methylene proton is attributed to one of the H^4 protons, which is situated in a similar environment to H^5.

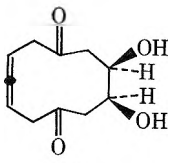
Compound **9** is an interesting substance and appears to be the first bridged aromatic system containing an

(6) D. Devaprabhakara and P. D. Gardner, *J. Amer. Chem. Soc.*, **86**, 648 (1963).

(7) R. C. Cookson and N. S. Warigar, *J. Chem. Soc.*, 2302 (1956); J. Labhart and G. Wagnière, *Helv. Chim. Acta*, **42**, 2219 (1959); K. Kosower, W. D. Closson, H. L. Goering, and J. C. Cross, *J. Amer. Chem. Soc.*, **83**, 2013 (1961); R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962).

(8) S. Fujita and T. Mori, *Bull. Chem. Soc. Jap.*, **42**, 1163 (1969); S. Fujita and H. Nozaki, *ibid.*, **44**, 2827 (1971); S. Fuiita, S. Hirano, and H. Nozaki, *Tetrahedron Lett.*, 403 (1972); S. Bradamante, A. Marchesini, and G. Pagani, *ibid.*, 4621 (1971).

allene group. The formation of **9** may occur directly from the ketal **8** or *via* the dione **15**. Protonation on



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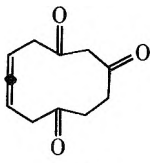

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the ketal oxygen in **8** or the carbonyl oxygen in **15**, followed by transannular substitution by the remote hydroxyl group, and subsequent dehydration would give **9**. Alternatively dehydration and hydrolysis of **8** may lead to the trione **16**, which would be expected readily to give **9** under acidic conditions.

In a second approach to the dione **14**, the dibromide **3** was oxidized with *m*-chloroperoxybenzoic acid to the epoxide **11**, mp 127–128°, in essentially quantitative yield. The relative stereochemistry of the oxirane and cyclopropane rings is not known, but in view of the findings with related systems,[3] **11** is likely to be the trans stereomer. Treatment of **11** with methyllithium at −10° led to 92% of the allene **12**, mp 122–123°, which on hydrolysis with *p*-toluenesulfonic acid and boron trifluoride etherate in acetone gave the dione **13**, mp 143–144°, in 85% yield. The ir spectrum of **13** showed bands at 1965 (allene) and 1700 cm^{-1} (carbonyl), and the nmr spectrum was consistent with the assigned structure. The electronic spectrum of **13** [λ_{max}^{EtOH} 232 (sh) (ϵ 550), 290 nm (260)] again showed the long wavelength band corresponding to a transannular chromophore interaction characteristic of molecules of this type.[3,4,7]

Attempts to convert **13** into **14** under a variety of conditions were unsuccessful. The only conditions leading to an isolable product were 30% perchloric acid in tetrahydrofuran, which gave the previously isolated furan **9** in 11% yield.

These results indicate that it is difficult to synthesize the dione **14** by a route involving acidic conditions. Other methods for preparing the fully unsaturated allene **1** are now under investigation.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Ir spectra were recorded on either a Unicam SP 200 or a Perkin-Elmer 257 spectrophotometer, and only strong and medium bands are reported. Nmr spectra were recorded on a Varian HA-100 spectrometer as solutions in $CDCl_3$, unless stated otherwise, with TMS as internal standard, and are reported in τ units. Mass spectra were recorded on either an AEI MS 9 or MS 12 spectrometer, and were taken at 70 eV, unless stated otherwise.

Silica for preparative thick layer chromatography (ptlc) was Merck Kieselgel GF_{254}, and that for column chromatography was Hopkins and Williams silica gel (MFC). Bromoform was dried ($CaCl_2$) and freshly distilled over P_2O_5 under N_2. Methyllithium in ether was obtained commercially from Alfa Inorganics. Solvents were May and Baker "R" grade and were purified and dried by standard methods.

11,11-Dibromo-3,3,8,8-tetramethoxybicyclo[8.1.0]undec-5-ene (3).—The diene **2** (12.8 g, 50 mmol)[4] was suspended in pentane (1.5 l.) and potassium *tert*-butoxide (42 g, 373 mmol) was added. The mixture was stirred under N_2 and cooled to 0°; bromoform (63.25 g, 250 mmol) was added slowly over 4 hr. The reaction mixture was allowed to warm to room temperature and was stirred for a further 12 hr. The precipitate was collected and identified as *anti*-6,6,12,12-tetrabromo-3,3,9,9-tetramethoxytricyclo[9.1.0.0^{5,7}]dodecane (19.2 g, 60%).[3] The filtrate was concentrated and chromatographed on silica eluting with ether–pentane, when **11,11-dibromo-3,3,8,8-tetramethoxybicyclo[8.1.0]undec-5-ene (3)** (3.15 g, 18%), mp 134–135° dec (pentane), was obtained: mass spectrum *m/e* 430, 428 (1%), 426, 398, 396 (9%), 394, 367, 365 (15%), 363, 317, 315, 285, 283, 129 (100%), 128, 105, 75; ir (KBr) 2950, 2830, 1435, 1314, 1283, 1195, 1143, 1125, 1075, 1055, 1026, 1015, 950, 915, 835, 762, and 748 cm^{-1}; nmr 4.57 (m, 2 H, olefin) 6.73, 676 (s, 12 H, OCH_3), 7.52–7.70 (m, 4 H, CH_2), 7.98 (m, 2 H), 8.23 (m, 2 H), 8.81 (m, 2 H).

Anal. Calcd for $C_{15}H_{24}O_4Br_2$: C, 42.05; H, 5.60; Br, 37.38. Found: C, 42.37; H, 5.92; Br, 36.98.

Reactions of 3 with Methyllithium. 5,5,10,10-Tetramethoxy-1,2,7-cycloundecatriene (4).—Compound **3** (4.28 g, 10 mmol) was dissolved in dry ether (20 ml), stirred under N_2, and cooled to −80°. Methyllithium (15 ml, 1 M, 15 mmol) was added in one portion; the reaction mixture was allowed to warm to −10° and stirred for 1 hr. Water (15 ml) was then added, the layers were separated, and the aqueous phase was washed with ether (50 ml). The combined organic layers were washed with water (10 ml) and dried ($MgSO_4$), and the solvent was removed by evaporation. The crystalline residue was recrystallized (CH_3OH) to give **5,5,10,10-tetramethoxy-1,2,7-cycloundecatriene (4)** (1.96 g, 73%): mp 75–76°; mass spectrum *m/e* 268 (3%), 253, 236, 221, 205, 204, 173, 147, 141, 109, 101, 88 (100%), 59, 43, 41; ir (KBr) 2960, 2830, 1980, 1458, 1437, 1319, 1268, 1244, 1220, 1192, 1117, 1105, 1078, 1048, 1035, 959, 932, 880, 806, 767, 713, and 622 cm^{-1}; nmr 4.56 (*t*, *J* = 5 Hz, 2 H, olefin), 4.87–5.14 (m, 2 H, allene), 6.80 (s, 12 H, OCH_3), 7.40–8.04 (m, 8 H, CH_2).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.00; H, 9.02.

3,8,9-Cycloundecatriene-1,6-dione (5).—Compound **4** (268 mg, 1 mmol) was dissolved in ether (10 ml), sulfuric acid (5%, 4 ml) was added, and the mixture was shaken for 1 hr. The ethereal layer was separated, the aqueous phase was extracted with ether (2 × 20 ml), and the combined ethereal layers were dried ($MgSO_4$). The solvent was removed by evaporation and the crystalline residue recrystallized (ether–pentane) to give **3,8,9-cycloundecatriene-1,6-dione (5)** (130 mg, 74%, prisms): mp 66–67°; mass spectrum *m/e* 176 (2.5%), 158, 148, 94 (100%), 81, 78, 66, 54; ir (KBr) 2980, 1960, 1705, 1339, 1279, 1256, 1220, 1102, 1003, 892, 885, 734, 700, and 673 cm^{-1}; nmr, see discussion; electronic spectrum, see discussion.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.89; H, 6.94.

Hydrogenation of 4.—Compound **4** (134 mg, 0.5 mmol) was dissolved in ethyl acetate (5 ml); palladium on charcoal (10%, 20 mg) was added and the mixture stirred for 2 hr under an atmosphere of H_2. The catalyst was removed by filtration and the filtrate evaporated. Ptlc of the oily residue, eluting with pentane–ether (1:1) gave **cycloundecane-1,6-dione** (47 mg, 51%):[6] mass spectrum *m/e* 182 (58%), 164, 140, 101, 98, 97, 84, 55; nmr (60 MHz, CCl_4) 7.43–7.90 (m, 8 H, CH_2CO) and 7.90–8.77 (m, 10 H, CH_2).

Treatment of cycloundecane-1,6-dione with $NH_2OH \cdot HCl$ and CH_3CO_2Na gave **cycloundecane-1,6-dioxime**, mp 229–230° (lit.[6] mp 228–229.5, 232–234°).

Reaction of 5 with Tosyl Hydrazide.—Compound **5** (0.53 g, 3 mmol) and tosyl hydrazide (1.12 g, 6 mmol) were dissolved in CH_3OH (20 ml), and concentrated HCl (2 drops) was added. After shaking for 1 hr, the crystalline residue was removed by filtration, washed (CH_3OH), dried, and recrystallized (ethyl acetate) to give **3,8,9-cycloundecatriene-1,6-dione ditosylhydrazone** (1.32 g, 86%): mp 173–174°; mass spectrum *m/e* 328, 278, 246, 173, 156, 139, 92, 91 (100%), 65; ir (KBr) 3220, 3060, 2950, 1628, 1505, 1470, 1430, 1410, 1348, 1332, 1312, 1297, 1188, 1172, 1095, 1040, 1030, 930, 898, 878, 825, 720, 710, and 680 cm^{-1}.

Reduction of 5 with Lithium Aluminum Hydride. 3,8,9-Cycloundecatriene-1,6-diol (6).—$LiAlH_4$ (38 mg, 1 mmol) was suspended in ether (10 ml) and stirred under N_2; a solution of the dione **5** (150 mg, 0.85 mmol) in ether (5 ml) was added dropwise over 20 min. After stirring for an additional 2 hr the mixture was neutralized with dilute HCl, the organic layer separated, and the aqueous phase extracted with ether (2 × 20 ml). The combined ethereal layers were washed with water (3 ml) and dried ($MgSO_4$); the solvent was removed by evapora-

tion. The oily residue was chromatographed on silica eluting with ether to give **3,8,9-cycloundecatriene-1,6-diol** (**6**) (130 mg, 85%) as a colorless oil: mass spectrum M^+ 180.1144, $C_{11}H_{16}O_2$ requires M^+ 180.1150, *m/e* 180 (0.7%), 162, 144, 129, 118, 105, 91, 79, 55, 53, 41 (100%); ir ($CHCl_3$) 3450, 3010, 2930, 1970, 1453, 1395, 1243, 1045, 957, 898, and 880 cm^{-1}; nmr 4.38–4.71 (m, 2 H, olefin), 4.73–5.17 (m, 2 H, allene), 5.78–6.42 (m, 2 H, CHOH), 7.46–7.92 (m, 8 H, CH_2), and 8.28 (s, 2 H, OH).

3,8,9-Cycloundecatriene-1,6-diol Diacetate.—The diol **6** (90 mg, 0.5 mmol) was added to a mixture of acetic anhydride (1 ml) and pyridine (1 ml) and the mixture heated to reflux for 30 min. After cooling, the mixture was poured into hydrochloric acid (1 *N*, 20 ml) and extracted with ether (2 × 50 ml). The ethereal extract was washed with water (5 ml) and dried (K_2CO_3); the solvent was removed by evaporation. Chromatography of the residue on silica gave **3,8,9-cycloundecatriene-1,6-diol diacetate** (115 mg, 87%) as a colorless oil: mass spectrum M^+ 264.1369, M^+ requires 264.1362, *m/e* 144, 143, 129, 117, 92, 79, 67, 66, 55, 43 (100%); at 20 eV 264, 204, 162 also observed; ir 3000, 2950, 1970, 1735, 1450, 1440, 1385, 1245, 1028, 960, 885, 855, 735, and 715 cm^{-1}; nmr (CCl_4) 4.36–4.73 (m, 2 H, olefin), 4.84–5.13 (m, 2 H, allene), 5.0–5.5 (m, 2 H, $CHOCOCH_3$), 7.12–7.92 (m, 8 H, CH_2), and 8.05 (s, 6 H, $OCOCH_3$).

Reaction of 3 with Osmium Tetroxide. 11,11-Dibromo-3,3,8,8-bicyclo[8.1.0]undecane-5,6-diol (**7**).—Compound **3** (2.14 g, 5 mmol) was dissolved in pyridine (50 ml), and a solution of osmium tetroxide (1.27 g, 5 mmol) in benzene (25 ml) was added. The reaction mixture was stirred for 2 hr, diluted with pentane (750 ml), and filtered. The precipitate of osmate ester (4.2 g) was suspended in ethanol (100 ml), and a solution $Na_2SO_4 \cdot 7H_2O$ (12.6 g, 50 mmol) in water (50 ml) was added. The mixture was heated to reflux for 1 hr, cooled, and filtered. $CHCl_3$ (250 ml) and water (100 ml) were added to the filtrate; the organic layer was separated, washed with water (10 ml), and dried ($MgSO_4$). The solvent was removed by evaporation and the crystalline residue recrystallized ($CHCl_3$–ether) to give **11,11-dibromo-3,3,8,8-tetramethoxybicyclo[8.1.0]undecane-5,6-diol** (**7**) (2.15 g, 80%): mp 81–82; mass spectrum *m/e* 367, 365 (5%), 363, 337, 335 (3%), 333, 300, 298, 287, 285, 268, 266, 254, 252, 177, 174, 146, 145, 132, 128, 108, 96 95, 94 (100%); ir (KBr) 3450, 2955, 1465, 1415, 1308, 1287, 1207, 1160, 1145, 1125, 1055, 1036, 1016, 975, 832, 725, and 685 cm^{-1}; nmr 6.10–6.29 (m, 2 H, CHOH), 6.76 (s, 6 H, OCH_3), 6.78 (s, 6 H, OCH_3), 7.19 (s, 2 H, OH), 7.60–8.38 (m, 8 H, CH_2), and 8.60–8.90 (m, 2 H, cyclopropane).

Anal. Calcd for $C_{15}H_{26}O_6Br_2$: C, 38.98; H, 5.67; Br, 34.58. Found: C, 38.74; H, 5.67; Br, 34.24.

Reaction of 7 with Methyllithium. 4,4,10,10-Tetramethoxy-6,7-cycloundecadiene-1,2-diol (**8**).—Compound **7** (462 mg, 1 mmol) was suspended in dry ether (40 ml) under N_2, stirred, and cooled to −80°. Methyllithium (6 ml, 1 *M*, 6 mmol) was added in one portion; the mixture was allowed to warm to −10° and was stirred for 30 min. Water (5 ml) was added and the mixture separated. The ethereal layer was washed with water (5 ml) and dried ($MgSO_4$) and the solvent removed by evaporation. The crystalline residue was recrystallized (ether–pentane) to give **4,4,10,10-tetramethoxy-6,7-cycloundecadiene-1,2-diol** (**8**) (210 mg, 70%): mp 109–110°; mass spectrum *m/e* 270, 239, 224, 220, 207, 206, 189, 174, 170, 147 (100%), 146, 118, 117, 109, 94, 57; ir (KBr) 3450, 2950, 2930, 1965, 1460, 1440, 1355, 1335, 1320, 1300, 1260, 1227, 1200, 1128, 1069, 1045, 988, 900, 880, 836, 815, 840, and 685 cm^{-1}; nmr 4.75–5.16 (m, 2 H, allene), 5.48–5.72 (m, 1 H, CHOH), 5.97–6.16 (m, 1 H, CHOH), 6.78 (s, 6 H, OCH_3), 6.82 (s, 6 H, OCH_3), 7.00 (s, 1 H, OH), 7.41 (s, 1 H, OH), and 7.46–8.26 (m, 8 H, CH_2).

Anal. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.17; H, 8.49.

12-Oxabicyclo[7.2.1]dodeca-5,6,9,11-tetraen-3-one (**9**).—Compound **8** (151 mg, 0.5 mmol) was dissolved in ether (50 ml), and sulfuric acid (80%, 2 ml) added. The mixture was shaken for 5 min; the ethereal layer was separated, washed with water (3 × 2 ml), and dried ($MgSO_4$). The solvent was removed by a stream of N_2, and the crystalline residue was recrystallized (pentane) to give **12-oxabicyclo[7.2.1]dodeca-5,6,9,11-tetraen-3-one** (**9**) (55 mg, 63%): mp 69–70°; mass spectrum M^+ 174.0677, $C_{11}H_{10}O_2$ requires M^+ 174.0681, *m/e* 174 (36%), 146, 94 (100%); ir (KBr) 2920, 1945, 1697, 1665, 1605, 1558, 1436, 1405, 1310, 1260, 1237, 1222, 1213, 1158, 1150, 1020, 1009, 988, 970, 940, 928, 903, 875, 858, 840, 783, and 710 cm^{-1}; nmr, see discussion; λ_{max}^{EtOH} 227 nm (ε 3000), 251 (1500), 310 (230), 318 (260), and 330 (180).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.91; H, 5.93.

Hydrolysis of the epoxide **13** (96 mg, 0.5 mol) in THF (10 ml) with perchloric acid (30%, 5 ml) at room temperature for 3 hr also gave **9** (11%), identical in all observed respects with that obtained from the diol.

Treatment of **9** with 2,4-dinitrophenylhydrazide and concentrated HCl in glyme at 70° gave the corresponding **2,4-dinitrophenylhydrazone**, (76%), mp 202–203°, pale orange crystals, mass spectrum *m/e* 354 (54%).

Anal. Calcd for $C_{17}H_{14}N_4O_5$: C, 57.62; H, 3.98; N, 15.81. Found: C, 57.19; H, 4.23; N, 15.48.

Hydrogenation of 9.—Compound **9** (34.8 mg, 0.2 mol) was dissolved in ethyl acetate (5 ml), palladium on charcoal (10%, 10 mg) was added, and the mixture was stirred under an atmosphere of hydrogen for 30 min. The catalyst was removed by filtration, and the filtrate was evaporated to give an oily residue. Ptlc on silica with pentane–ether (1:1) gave **12-oxabicyclo[7.2.1]-dodecan-3-one** (**10**), (24 mg: 69%): mp 38–40°; mass spectrum M^+ 182.1299, $C_{11}H_{18}O_2$ requires M^+ 182.1307, *m/e* 182 (25%), 180, 164, 153, 139, 125, 113, 98, 82, 80, 69, 55, 41 (100%); ir (CCl_4) 2930, 2860, 1702, 1473, 1450, 1365, 1354, 1275, 1200, 1140, 1090, 1065, and 1040 cm^{-1}; nmr 5.58–5.84 (m, 1 H), 5.88–6.20 (m, 1 H), 7.70–7.50 (m, 2 H), and 7.60–8.92 (m, 14 H).

Treatment of **10** with hydroxylamine hydrochloride and CH_3CO_2Na in CH_3OH–H_2O gave the oxime (82%): mp 123–124°; mass spectrum M^+ 197.1424, $C_{11}H_{19}NO_2$ requires M^+ 197.1416, *m/e* 197 (25%).

Reaction of 3 with *m*-Chloroperoxybenzoic Acid. 12,12-Dibromo-3,3,9,9-tetramethoxy-6-oxatricyclo[9.1.0.0^{5,7}]dodecane (**11**).—Compound **3** (2.14 g, 5 mmol) was dissolved in chloroform (50 ml) and *m*-chloroperoxybenzoic acid (12.0 g, 80%, 5.5 mmol) was added. The solution was stirred for 15 hr, excess of a saturated solution of sodium sulfite was added, and the mixture was neutralized with aqueous potassium hydroxide. The organic layer was separated, washed with water (2 × 5 ml), and dried ($MgSO_4$); the solvent was removed by evaporation. The crystalline residue was recrystallized ($CHCl_3$–pentane) to give **12,12-dibromo-3,3,9,9-tetramethoxy-6-oxatricyclo[9.1.0.0^{5,7}]-dodecane** (**11**) (2.0 g, 90%): mp 127–128°; mass spectrum *m/e* 382, 380 (22%), 378, 364, 362, 333, 331, 301, 299, 237, 221, 219, 129, 101 (100%), 89, 88; ir (KBr) 2960, 2840, 1465, 1455, 1315, 1275, 1162, 1140, 1120, 1077, 1050, 1012, 975, 962, 840, 818, 780, and 727 cm^{-1}; nmr 6.74 (s, 12 H, OCH_3), 7.04 (d, J = 10 Hz, 2 H, epoxide), 7.57–7.97 (m, 4 H, CH_2), 8.17–8.62 (m, 4 H, CH_2), and 8.80 (ddd, J = 2, 7, 13 Hz, 2 H, cyclopropane).

Anal. Calcd for $C_{15}H_{24}O_5Br_2$: C, 40.56; H, 5.45; Br, 35.98. Found: C, 40.34; H, 5.30; Br, 35.90.

Reaction of 11 with Methyllithium. 3,3 9,9-Tetramethoxy-12-oxabicyclo[9.1.0]dodeca-5,6-diene (**12**).—Compound **11** (888 mg, 2 mmol) was suspended in ether (50 ml), stirred under N_2, and cooled to −80°. Methyllithium (3 ml, 1 *M*, 3 mmol) was added in one portion, and the reaction mixture was allowed to warm to −10° and stirred for 30 min. Water (5 ml) was added; the organic layer was separated, washed with water (2 × 3 ml), and dried ($MgSO_4$). The solvent was removed by evaporation and the crystalline residue recrystallized (ether-pentane) to give **3,3,9,9-tetramethoxy-12-oxabicyclo[9.1.0]dodeca-5,6-diene** (**12**) (525 mg, 92%): mp 122–123°; mass spectrum *m/e* 284 (2%), 269, 253, 252, 237, 221 ,185, 161 148, 136, 129, 117, 101, 88 (100%), 59, 58, 57, 55, 43; ir (KBr) 2950, 2830, 1965, 1475, 1445, 1420, 1395, 1350, 1342, 1315, 1285, 1254, 1241, 1200, 1190, 1162, 1142, 1125, 1105, 1082, 1060, 1040, 1018, 995, 970, 948, 912, 904, 835, 825, 795, 782, 767, and 715 cm^{-1}; nmr 4.92 (m, 2 H, allene), 6.76, 6.78, 6.81 (s, 12 H, OCH_3), 6.84–7.12 (m, 2 H, epoxide) and 7.24–8.60 (m, 8 H, CH_2).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.32; H, 8.50.

12-Oxabicyclo[9.1.0]dodeca-5,6-diene-3,9-dione (**13**).—Compound **12** (142 mg, 0.5 mmol) was dissolved in acetone (25 ml), and a solution of *p*-toluenesulfonic acid (10 mg) in water and boron trifluoride etherate (1 drop) were added. The mixture was shaken for 10 min, the solvent was removed by evaporation, and water (1 ml) added; a precipitate formed. Ether (200 ml) was added and the mixture was shaken. The ethereal layer was

separated, washed with water (20 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a crystalline residue which was recrystallized (ether–pentane) to give **12-oxabicyclo[9.1.0]-dodeca-5,6-diene-3,9-dione (13)** (82 mg, 85%): mp 143–144°; mass spectrum (15 eV) *m/e* 192 (2.5%), 174, 164, 150, 120, 110, 108, 107 (100%), 94, 66, 65, 55; ir (KBr) 2980, 2930, 2880, 1965, 1700, 1467, 1438, 1418, 1390, 1340, 1300, 1270, 1249, 1200, 1112, 1090, 1027, 986, 968, 931, 886, 842, 793, and 714 cm^{-1}; nmr 4.44–4.80 (m, 2 H, allene), 6.40–6.64 (m, 2 H, epoxide), and 6.69–7.56 (m, 8 H, CH_2); electronic spectrum, see discussion.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.42; H, 6.38.

Registry No.—**2**, 37709-72-1; **3**, 37709-73-2; **4**, 37780-37-3; **5**, 37709-74-3; **5** ditosylhydrazone, 37709-75-4; **6**, 37709-76-5; **6** diacetate, 37709-77-6; **7**, 37709-78-7; **8**, 37709-79-8; **9**, 37709-80-1; **9** dinitrophenylhydrazone, 37709-81-2; **10**, 37709-82-3; **10** oxime, 37709-83-4; **11**, 37709-84-5; **12**, 37709-85-6; **13**, 37709-86-7.

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Addition Reactions of *cis,trans*-1,5-Cyclodecadiene[1]

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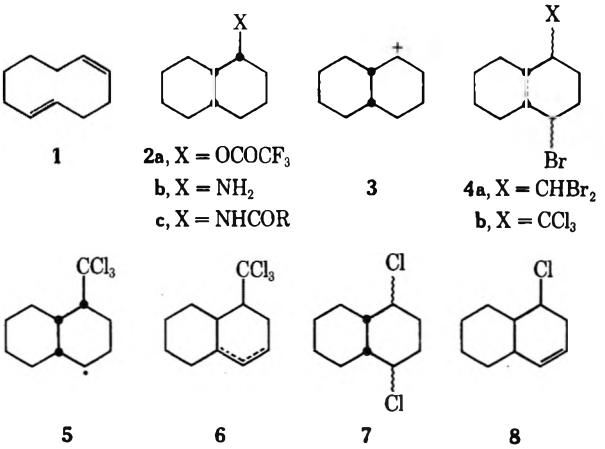
A variety of cationic, radical, and methylene reagents add selectively to *cis,trans*-1,5-cyclodecadiene. Noncyclic reagents (multistep addends), whether cationic or radical, lead to substituted *cis*-decalins, while methylene reagents give cyclopropane derivatives (preferred attack on trans C=C). The stereochemistry of the products has been established by nmr techniques and delineates to a substantial degree such mechanistic details of the addition process as position of initial attack and degree of concertedness. The stereoselectivity in product formation is usually higher with the cationic than with the radical reagents, and, in several reactions, it is sufficiently high to be useful in synthesis.

A few years ago, a report from our laboratory demonstrated the potential of *cis,trans*-1,5-cyclodecadiene (**1**) for differentiating between single-step and multistep attack of addends on the two carbons of an olefinic linkage.[3] Subsequently, several short communications showed much the same potential in the relative rates of exo addition to norbornene and to 7,7-dimethylnorbornene.[4] Both studies led to the conclusion, among others, that oxymercuration proceeds in steps rather than by a cyclic mechanism, even though cis additions are reported.

Our original investigation was limited to several reagents which add by a cyclic or single-step mechanism and to several ionic reagents. We have now extended the investigation to include radical addends as well as other ionic and methylene reagents. Additions to **1** by noncyclic reagents, whether cationic or radical, lead to substituted *cis*-decalins, usually with a substantial degree of stereoselectivity that can be useful in syntheses. This paper reports, we believe, the first examples of cycloadditions of radical reagents with the C_{10} ring system. Methylenes and other reagents which add to both carbons in the olefinic linkage without forming a trivalent carbon intermediate give 5,6-disubstituted cyclodecenes, with preference for addition to the trans rather than the cis C=C.[3] Frequently the two courses of addition can be differentiated easily by monitoring the C=CH nmr absorptions by an equimolar mixture of the diene **1** and the addend. The various addends are discussed in groups according to potential synthetic usefulness as well as to mechanism.

We have previously reported the photoisomerization of **1** to *cis,cis*-1,5-cyclodecadiene and the relative reactivities of the isomeric dienes toward trifluoroacetic acid and with respect to thermal isomerization to *cis*-1,2-divinylcyclohexane (**1** reacts faster than its isomer in both cases).[5]



Ionic Reagents. Trifluoroacetic Acid.—When a sample of diene **1** is added to trifluoroacetic acid, a spontaneous, exothermic reaction produces *cis*-1-*cis*-decalyl trifluoroacetate (**2a**) in nearly quantitative yield. Saponification of the ester yields *cis*-1-*cis*-decalol, an alcohol for which several preparations have been described. We believe this preparation to be the easiest

(1) (a) Based upon the Ph.D. dissertation of H. H. H., Louisiana State University, Baton Rouge, Aug 1970. (b) The maior portion of this manuscript was prepared while J. G. T. was a NATO Senior Fellow in Science at the Institut für organische Chemie, Universität des Saarlandes, Saarbrücken, Germany; J. G. T. acknowledges with appreciation the courtesies extended to him by Professor M. Hanack and other members of the institute. (c) Supported in part by a grant from the National Science Foundation (NSF GP 8228).

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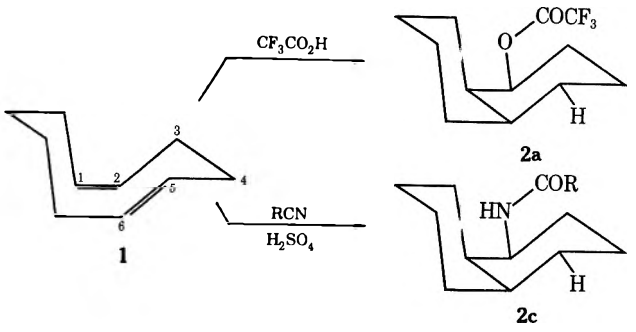
to use for small or large quantities of stereoisomerically pure alcohol.

The stereochemistry in this addition is not only useful for synthesis, but it is also of interest so far as details of the addition sequence are concerned. It seems unlikely that a 1-*cis*-decalyl cation (**3**) is actually formed at any time. Free 4-*tert*-butyl-1-cyclohexyl cations exhibit little regioselectivity in product formation,[6] and the neighboring methylene group in **3** would be expected to hinder rather than favor the formation of cis product. On the other hand, a process initiated by addition of a proton to the 5 position (trans C=C) and involving reasonably concerted bonding of trifluoroacetic acid at the 2 position while bridging between positions 1 and 6 is taking place accounts quite clearly for the observed stereoselectivity. Initial attack by proton at the 2 position (cis C=C) followed by a parallel sequence of events would lead to *trans*-1-*cis*-decalyl trifluoroacetate rather than the cis,cis isomer obtained. Dreiding models help significantly in picturing the alternative consequences.



Nitriles.—When a small amount of concentrated sulfuric acid is added to a solution of diene **1** in acetonitrile or in benzonitrile, the Ritter reaction proceeds smoothly at room temperature to form *N*-(*cis*-1-*cis*-decalyl) amides (**2c**) in moderate yield (58–64%). No evidence for the formation of an isomer (or other product) was obtained. Again, the stereoselectivity in this addition strongly implies initial protonation at C-5 in the diene followed by substantially concerted attack of the nitrile at C-2 and bond formation between C-1 and C-6.

Mercury(II) Azide.—An aqueous tetrahydrofuran solution of mercury(II) azide[7] reacted with diene **1** to form a mixture of products which was reduced by alkaline sodium borohydride[7] to a mixture of *cis*-1-*cis*-decalyl azide (11%), *cis*-1-*cis*-decalol (39%), and another saturated azide yet unidentified. The *cis*-1-*cis*-decalyl azide was reduced by hydrogen and platinum oxide to *cis*-1-*cis*-decalylamine (**2b**).

Chlorine.—Both molecular chlorine and iodobenzene dichloride react with alkenes to add the elements Cl–Cl by both polar and radical mechanisms, depending on the reaction conditions.[8a,b] An oxygen (or air) atmosphere inhibits the radical process and favors the polar one, but a nitrogen atmosphere favors the radical one. A molecular addition process (cyclic transition state; attack on both carbons of the C=C at the same time) has been proposed for the nonradical reaction of iodobenzene dichloride.[8c] We find, however, that all four reactions give only cycloaddition products; there is no evidence for the formation of substituted cyclodecenes.

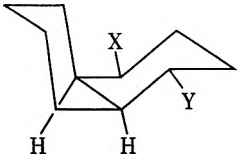
The reactions of both chlorine and iodobenzene dichloride with **1** in a nitrogen atmosphere were much more rapid than those in the presence of oxygen. The product mixtures from each reagent were similar but not identical for the two conditions. The spectra of the mixtures revealed only a little absorption for C=CH, which was identified in each case with 5-chlorobicyclo[4.4.0]dec-2-ene (**8**). The major products (~80% of the total gc area of the product mixture) are 1,4-dichloro-*cis*-decalins (**7**). Some minor products in the mixtures, particularly those from iodobenzene dichloride, have not been identified, but they do not appear to be substituted cyclodecenes or cyclodecanes.

The apparent formation of a mixture of 1,4-dichloro-*cis*-decalins (**7**) in these reactions implies that the concertedness of the additions described earlier is missing in these. Since some of the radical additions to be described below also gave stereoisomeric mixtures of substituted *cis*-decalins, the results with chlorine additions may imply that, in spite of the presence of oxygen, the (fast) radical mechanism prevailed. Alternatively, polar attack of sources of chlorine on the initially formed cationic intermediate may not accompany bridging between the 1 and 6 positions by the π electrons of the transannular C=C.[9]

In any event, it appears clear that iodobenzene dichloride does not react with diene **1** by a cyclic, molecular addition process.

Radical Reagents. Bromoform and Bromotrichloromethane.—Photoinitiated (3500-Å) addition of $BrCHBr_2$ to diene **1** in a nitrogen atmosphere produced a product mixture from which a single product, identified on the basis of spectral data as 1-bromo-4-dibromomethyl-*cis*-decalin (**4a**), was isolated by column chromatography in 45% yield. The minor components of the mixture were not identified. The nmr spectrum of the major product includes a triplet of doublets at δ 3.95 for HCBr, a pattern which requires vicinal coupling of an axial HCBr to two axial protons (J = 9.5 Hz) and to one equatorial proton (J = 2.5 Hz); that is, the ring bromine must be equatorial and trans to the ring juncture.

That same stereochemical result was obtained in the major product from photoinitiated addition of bromotrichloromethane to diene **1**. This solid adduct, identified as *trans*-1-bromo-4-trichloromethyl-*cis*-decalin (**4b**) on the basis of spectral data, was obtained in 61% yield. Its nmr spectrum included a triplet of doublets at δ 3.92 (J = 9.5 and 2.5 Hz, HCBr) and a multiplet at δ 2.65 ($HCCCl_3$). The patterns require that HCBr be axial with two vicinal axial protons (that is, bromine is equatorial and trans to the ring juncture) and that



X equatorial, cis to ring fusion
Y equatorial, trans to ring fusion

(6) S. D. Elakovich and J. G. Traynham, *Tetrahedron Lett.*, 1435 (1971).

(7) C. H. Heathcock, *Angew. Chem., Int. Ed. Engl.*, **8**, 134 (1969).

(8) (a) Molecular chlorine: M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2161 (1965). (b) $PhICl_2$: D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33**, 38 (1968) and references cited therein. (c) D. E. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 370 (1950).

(9) Initial attack at either the cis or the trans C=C, followed by concerted 1,6 bridging and uptake of the second chlorine, will give the same *trans*-1,4-dichloro-*cis*-decalin.

$HCCCl_3$ be axial with one axial and two equatorial vicinal couplings (that is, trichloromethyl is also equatorial but cis to the ring juncture).

The nmr spectrum of the total reaction product mixture with no treatment other than removal of excess bromotrichloromethane at reduced pressure (25°) included absorptions for C=CH and an absorption at δ 4.46 with a pattern indicative of an equatorial HCBr vicinal to one axial and two equatorial protons. No product responsible for this absorption was ever isolated; all attempts to isolate it, as well as treatment of the original product mixture with 0.5 equiv. of base, resulted in formation of unsaturated products. We believe that these data are consistent with the structure *cis*-1-bromo-4-trichloromethyl-*cis*-decalin (**4b**), with the bromine axial and cis to the ring juncture. This compound (*ca.* 40% yield on the basis of nmr data) would be expected to lose HBr readily to form olefinic products (5-trichloromethylbicyclo[4.4.0]decenes, **6**).

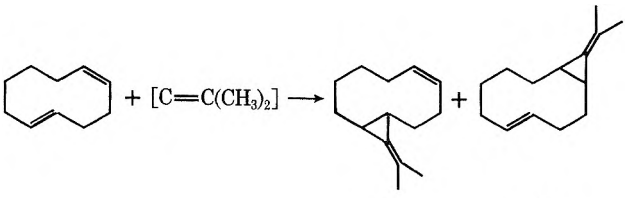
These stereochemical results have interesting implications for the details of these radical additions to **1**. One side of each alkene linkage (one lobe of each π orbital) in **1** is substantially less accessible to attack because it is oriented toward the interior of the ring. Attack on the exposed side of each alkene linkage will, without intervening inversion, lead to equatorial bonds to the substituents in the *cis*-decalin product. In order for the ring bromines to be *both* equatorial and trans to the ring juncture, dibromomethyl or trichloromethyl attack must come on the cis rather than the trans alkene linkage. Since the cationic addition reagents appear to attack the trans alkene linkage preferentially, this contrasting behavior of the radical reagents, $\cdot CHBr_2$ and $\cdot CCl_3$, is intriguing. We have no explanation for this contrast at present.

When the reaction was carried out with molar equivalents of bromotrichloromethane and **1** in methylene chloride solution, the product mixture appeared to consist of the same compounds as were obtained in excess bromotrichloromethane, but in different proportions. The nmr spectrum included the two six-line absorptions at δ 4.46 and 3.92, but the relative intensities were 1:4 rather than 1:1.4. If we have correctly identified the δ 4.46 absorption with *cis*-1-bromo-4-trichloromethyl-*cis*-decalin, this less stable, axial bromo isomer is formed more extensively with excess bromotrichloromethane than in the moderately dilute methylene chloride solution. The fact that both stereoisomers appear to be formed from **1** and in proportions which are dependent on bromotrichloromethane concentration shows that the addition of $BrCCl_3$ is not concerted; that is, that a *cis*-4-trichloromethyl-1-*cis*-decalyl radical (**5**) is an intermediate.

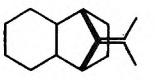
Methylenes.—While our work was in progress, the additions of dibromomethylene and of dichloromethylene to **1** were reported by others.[10] In each case the yield of dihalocyclopropane was about 75%, and the addition occurred preferentially at the trans-alkene linkage (about 3:1, trans:cis).[10] Our addition of dibromomethylene confirms that result, and we find quite similar results with methylene and with isopropylidenemethylene.

With methylene iodide and zinc–copper couple,[3,11] the yield of bicyclo[8.1.0]undec-4-enes was 60%, and 89% of the product was formed by attack on the trans-alkene linkage (11% on the cis C=C). When methylene was generated from diazomethane and copper, the yield of cyclopropanes was poor; the product which was formed resulted from 73% addition to the trans C=C, 27% to the cis C=C. With $C{=}C(CH_3)_2$, generated from 5,5-dimethyl-*N*-nitrosooxazalidone and lithium alkoxide,[12] we obtained a 75% yield of cyclopropanes; 70% of the addition occurred at the trans C=C (**9**) and 30% at the cis C=C (**10**).

The addition of isopropylidenemethylene was of particular interest to us, because its addition to certain acyclic olefins has been described as a sequential rather than simultaneous formation of the two bonds to the carbons in the alkene linkage.[12] The stereochemical results on which that description is based do not require that an intermediate be formed, only that bond development to the two alkene carbons occur unequally along the reaction coordinate. If a true intermediate were formed with **1**, we would expect a decalin derivative (which would presumably be 11-isopropylidenetricyclo[6.2.1.$0^{2,7}$]undecane, **11**); if no intermediate were formed, we would expect a cyclopropane (an 11-isopropylidenebicyclo[8.1.0]undec-4-ene). Since the cyclopropane product is formed exclusively, we infer that this methylene reagent does not generate a true intermediate in its addition to an alkene. The development of bonds to the two alkene carbons may well be sequential,[12] but the reaction coordinate is characterized by a single transition state between methylene reagent and cyclopropane product.



9 **10**



11

Experimental Section

Analytical gas chromatography (gc) utilized Beckman GC-5 and Hewlett-Packard Model 700 instruments equipped with flame ionization detectors and with 0.125-in. columns packed with the specified phase on 60–80 mesh solid support. Preparative gc utilized an Aerograph Autoprep Model A-700 instrument. Infrared (ir) spectra were obtained with a Beckman IR-10 instrument. Nuclear magnetic resonance (nmr) spectra were recorded on Varian Associates A-60A and HA-100 instruments with the assistance of W. Wegner; all chemical shifts are reported relative to internal tetramethylsilane. Element microanalyses were performed by R. Seab in these laboratories.

Addition of Trifluoroacetic Acid to 1.—To stirred trifluoroacetic acid (15 ml) was added 1[13] (2.72 g, 20 mmol) drop by drop

(10) J. Graefe and M. Muhlstadt, *Tetrahedron Lett.*, 3431 (1969).

(11) R. D. Smith and H. E. Simmons, *Org. Syn.*, **41**, 72 (1961).

(12) M. S. Newman and A. D. M. Okorodudu, *J. Amer. Chem. Soc.*, **90**, 4189 (1968). We acknowledge with appreciation the receipt of detailed procedures from Professor Newman in advance of publication.

(13) Prepared from butadiene, ethylene (150 psig), and bis(1,5-cyclooctadiene)nickel at room temperature: G. Wilke, *Angew. Chem., Int. Ed. Engl.*, **2**, 105 (1963). For us, ethylene pressures below 75 psig did not lead to much cyclodecadiene formation. At 150-psig pressure, we obtained almost quantitative conversion to a mixture (approximately 1:1) of **1** and cyclododecatrienes. The boiling point of **1** is 51–53° (5 mm).

in 30 sec. The temperature of the reaction mixture rose to 58° in 1 min and began to decrease a few minutes later. After 30 min the solution, which had become brown, was poured into 100 ml of ice water. The aqueous mixture was extracted several times with ethyl ether. The ether solution was washed with 10% sodium bicarbonate solution and with water, dried ($CaCl_2$), and distilled. The ester **2a** was obtained in 80% yield: bp 99–100.5° (9 mm); ir strong absorptions at 3.38, 3.48, 5.57, 8.10, and 8.51 μ, no absorptions at 10.29 (*trans*-cyclodecene) or 14.25 μ (*cis*-cyclodecene); nmr (CCl_4) δ 5.0 (b m, 1, HCO), 2.4–1.1 (b m, 16, decalin ring). When a portion of the ester was saponified with 2 *M* sodium hydroxide solution, *cis*-1-*cis*-decalol[3] was obtained in 93% yield, mp 90–91°.

Addition of Nitriles. A.—A solution of 1 (2.72 g, 20 mmol), acetonitrile (10 ml), and concentrated sulfuric acid (2 ml) was stirred overnight at room temperature and was poured into ice water (20 ml). Acetonitrile was removed by rotary evaporation under reduced pressure, and the aqueous mixture was extracted thoroughly with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated. The white, crystalline residue (2.5 g, 68%) was purified by recrystallization from acetone and by vacuum sublimation (64%): mp 178.6–180° (lit.[14] mp 181°); nmr (CCl_4) δ 5.83 (b m, 1, NH), 3.90 (m, 1, HCN), 1.96 (s, 3, $NCOCH_3$), 2–1 (b m, 16, decalin ring); ir (KBr) strong absorptions at 3.06, 3.23, 6.08, and 6.41 μ (primary amide). These data are consistent with the structure *N*-(*cis*-1-*cis*-decalyl)acetamide.[14]

B.—When a nearly identical procedure was used with benzonitrile in place of acetonitrile, *N*-(*cis*-1-*cis*-decalyl)benzamide[15] was obtained in 58% yield: mp 205–206° (lit.[15] mp 206°); nmr (CCl_4) δ 7.86–7.60 (m, 5, ArH), 6.08 (m, 1, NH), 4.16 (m, 1, HCN), 2.2–1.0 (m, 16, decalin ring); ir (KBr) 2.99, 3.06, 6.12, 6.32 μ (primary amide).

Mercury(II) Azide.—The diene 1 (4.0 g, 30 mmol) was added to a solution[7] of mercury(II) azide in tetrahydrofuran. The two-phase mixture was stirred at room temperature for 2 hr, reduced with sodium borohydride in 15% aqueous potassium hydroxide solution,[7] and extracted three times with ethyl ether. The ether solution was dried ($MgSO_4$) and concentrated under reduced pressure. A portion (4.0 g) of the residue (5.0 g) was chromatographed on Merck alumina (150 g, acid washed); petroleum ether (bp 30–60°), petroleum ether–ethyl ether mixtures (3:1, 1:1, and 1:3), and methanol were used sequentially as eluting solvents. Only a few of the 34 30-ml fractions collected contained any solute. The first eluent was 1 (0.1 g). The second one was identified as *cis*-1-azido-*cis*-decalin: 0.6 g (11%); ir 4.75 μ (azido); nmr (CCl_4) δ 3.45 (m, 1, HCN_3), 2.1–1.0 (16, decalin ring). A sample of this azide (0.3 g) was reduced in ethanol solution with hydrogen (45 psig) and platinum oxide to the amine (**2b**), which was converted to the benzamide,[15] mp 205–206°, identical with the benzamide obtained from the benzonitrile reaction. The third eluent (1.2 g) has not been identified: ir 4.75 μ (azido) but no absorption for OH or C=C; nmr (CCl_4) multiplets at δ 3.36 and 2.2–1.0, ratio 1:4. The last eluent, mp 90–91°, was identified as *cis*-1-*cis*-decalol[3,14] (1.8 g, 39%) by comparison of its ir and nmr spectra with those of an authentic sample.[3]

Molecular Chlorine Additions. Radical Conditions.[8a]—Chlorine (2.0 g, 28 mmol), which had been condensed in a chilled finger condenser, was swept by a stream of dry nitrogen into an irradiated (300-W lamp) solution of 1 (2.72 g, 20 mmol) in carbon tetrachloride (100 ml) under a nitrogen atmosphere. The temperature of the mixture was kept below 40° by external cooling; the reaction appeared to be complete after 10 min. The mixture was washed with water, dried ($MgSO_4$), concentrated (4.3 g of residue), analyzed by gc (12-ft Carbowax 20M column) and nmr methods, and subsequently distilled (2.4 g of distillate, 1.6 g of undistilled residue). About 80% of the mixture gc trace area was contained in a peak with a small shoulder of longer retention time; the nmr spectrum showed little absorption for C=CH. The lower boiling distillate fraction [bp 44–44.5° (0.2 mm), 0.7 g] was further purified by preparative gc. Its ir and nmr spectra included absorptions for C=CH: nmr (CCl_4) δ 5.52 (m, 2, C=CH), 4.18 (m, 1, HCCl), 2.8–1.3 (13, remainder of H). This minor constituent appears to be 5-chloro-2-bicyclo[4.4.0]-decene (**8**). The higher boiling distillate fraction [bp 70–76° (0.2 mm), 1.7 g] was shown by gc to consist of two components in about equal proportions. The ir spectrum indicated no unsaturation; nmr (CCl_4) δ 4.10 (m, 2, HCCl), 2.6–1.3 (14, decalin ring). When a sample of this fraction was treated with alcoholic potassium hydroxide, the elimination product obtained was readily dehydrogenated by palladium on carbon at 140° to tetralin.[16] These data show that this chlorine adduct is most probably a mixture of stereoisomeric 1,4-dichloro-*cis*-decalins (**7**).

B. Ionic Conditions.[8a]—The above experiment was repeated, except that air rather than nitrogen was used to sweep chlorine into the solution of 1, and the mixture was not irradiated. Approximately 2 hr was required for the disappearance of the yellowish color of chlorine. Besides this difference in apparent reaction times, we found no other substantial differences between the nitrogen-sweep and air-sweep reactions. The major products had identical gc retention times in both cases.

Iodobenzene Dichloride. A. Radical Conditions.[8b]—A mixture of 1 (1.36 g, 10 mmol), iodobenzene dichloride[17] (2.75 g, 10 mmol), and carbon tetrachloride (25 ml) was degassed by a freeze–thaw method and sealed. When the mixture was warmed to room temperature, a spontaneous, exothermic reaction occurred, and the solid iodobenzene dichloride disappeared within a few seconds. The mixture was cooled to room temperature, washed with water, dried ($MgSO_4$), and analyzed by gc on a 6-ft UCON column at 160°. Six products, with relative gc trace areas of 17, 18, 17, 15, 29, and 4, in order of increasing retention time, were present in the mixture. By comparison of gc characteristics with those of products obtained from molecular chlorine additions, the first component in this mixture was identified as 5-chloro-2-bicyclo[4.4.0]decene (**8**) and the fourth and fifth components as the stereoisomeric 1,4-dichloro-*cis*-decalins (**7**). The other components in the mixture were not identified.

B. Ionic Conditions.[8b]—Iodobenzene dichloride (2.75 g, 10 mmol) was added in one portion to a stirred solution of 1 (1.36 g, 10 mmol) in carbon tetrachloride (25 ml). The mixture was protected from atmospheric moisture by a calcium chloride tube, but air was not excluded. After 4.5 hr, the mixture had become homogeneous. It was washed with water, dried, and analyzed by gc (6-ft UCON column, 160°). Peaks with the same six retention times as were obtained from the radical product mixture were obtained; their relative areas, in order of increasing retention times, were 23, 13, 13, 19, 27, and 5.

Addition of Bromoform.—A solution of 1 (5.0 g, 37 mmol) in bromoform (47 g, 190 mmol) was irradiated with 3500-Å light for 15 hr. When most of the remaining reactants had been removed at reduced pressure, 11.5 g of residue remained. The nmr and ir spectra of this residue included weak absorptions for olefin (cis), but otherwise the chemical shifts and multiplicities were identical with those in the nmr spectrum of the purified product. Elution chromatography of 3.0 g of the residue on 90 g of Florisil led to the isolation of one product (1.7 g, 45%), identified on the basis of spectral data as 1-bromo-4-dibromomethyl-*cis*-decalin (**4a**): ir (neat) 14.49 and 14.93 μ (CBr); nmr (CCl_4) δ 5.76 (d, J = 4 Hz, 1, $HCBr_2$), 3.95 (t d, J = 9.5, 2.5 Hz, 1, HCBr), 3–1 (complex m, 15, decalin ring).

Anal. Calcd for $C_{11}H_{17}Br_3$: C, 34.0; H, 4.4. Found: C, 34.3; H, 4.4.

Addition of Bromotrichloromethane.—A solution of 1 (10 g, 73.5 mmol) in bromotrichloromethane (80 g, 404 mmol) under nitrogen was irradiated for 1 hr with 3500-Å lamps in a Rayonet apparatus. The nmr spectrum of the mixture then no longer included absorptions characteristic of 1, but it and gc analysis did show that a small amount of chloroform had formed. Removal of excess bromotrichloromethane at 25° (0.7 mm) left 25 g of residue, whose nmr spectrum included signals for C=CH and two sets of six-line signals (not identical) at δ 4.46 and 3.92 (relative intensities 0.7:1). Distillation of the concentrate gave 17 g of a slightly yellow material [bp 152–156° (0.7 mm)] which crystallized, and 3.8 g of viscous residue. The distillate was recrystallized from pentane to colorless crystals, 15 g: mp 67–69°; ir (KBr) 12.8–13.5 μ (CCl_3); nmr ($DCCl_3$) δ 3.92 (t d, 1, J = 9.5 and 2.5 Hz, HCBr), 2.65 (b m, 1, $HCCCl_3$), 2.5–1.0 (complex, 16, decalin ring). This major product was identified as *trans*-1-bromo-4-trichloromethyl-*cis*-decalin (61% yield).

(14) W. Hückel, R. Danneel, A. Gross, and H. Naab, *Justus Liebigs Ann. Chem.*, **502**, 99 (1933).

(15) W. Hückel, *ibid.*, **441**, 1 (1925).

(16) This dehydrochlorination–dehydrogenation experiment was performed by Dr. E. E. Green, to whom we express our appreciation.

(17) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 482.

Anal. Calcd for $C_{11}H_{16}BrCl_3$: C, 39.5; H, 4.8. Found: C, 39.7; H, 5.0.

Several attempts to isolate the component of the original mixture responsible for the nmr signal at δ 4.46 were unsuccessful. When a portion of the original, concentrated reaction mixture was treated with 0.5 molar equiv. of potassium hydroxide in methanol–water–dimethyl sulfoxide solvent[18] at room temperature, the resulting product mixture no longer gave nmr absorptions at δ 4.46, but it did give stronger absorptions in the olefin region. We inferred that the δ 4.46 signal most likely belonged to *cis*-1-bromo-4-trichloromethyl-*cis*-decalin, the easily dehydrobrominated (axial Br) stereoisomer of the major product.

Chromatography of a portion (5 g) of an original, concentrated reaction mixture on acid-washed alumina with pentane solvent gave, in addition to the major component and some minor unidentified components which were eluted early, a small amount (0.2 g) of a component whose spectral characteristics led us to identify it tentatively as 6-bromo-5-trichloromethyl-*cis*-1-cyclodecene: ir (neat) 12.8 (CCl_3) and 14.0 μ (cis C=C); nmr (CCl_4) b m at δ 5.75–5.33 (C=CH), 4.3 (HCBr), and 3.5–0.8 ($HCCCl_3$ + CH_2) in an approximate ratio of 2:1:13. None of the fractions eluted from the chromatography column gave an nmr absorption at δ 4.46.

Irradiation (3500 Å) of a solution of **1** (2.72 g, 20 mmol), bromotrichloromethane (3.96 g, 20 mmol), and methylene chloride (200 ml) under a nitrogen atmosphere for 3.5 hr produced a product mixture whose nmr spectrum was quite similar to that of the mixture obtained in excess bromotrichloromethane, except for the ratio of the δ 4.46 and 3.92 absorptions and the relative intensities of the C=CH absorptions. The mixture from methylene chloride solution gave a ratio of 1:4 (δ 4.46:3.92) and less intense C=CH absorption.

Methylenation[11] of 1.—From a mixture of zinc–copper couple (8.6 g, 132 mmol), anhydrous ethyl ether (40 ml), **1** (18 g, 132 mmol), and methylene iodide (35 g, 130 mmol), which had been stirred at reflux temperature for 24 hr, was obtained a product mixture concentrate which contained **1**, *cis*-1,2-divinylcyclohexane,[3] and the stereoisomeric methylenation products (*ca.* 60% yield) in a ratio of 89:11 (*trans*-bicyclo[8.1.0]undec-*cis*-4-ene:*cis*-bicyclo[8.1.0]undec-*trans*-4-ene). The major component was isolated by preparative gc: nmr (CCl_4) δ 5.40 (m, 2, C=CH), 2.5–1.3 (12, CH_2 in decalin ring), 0.48 (m, 2, bridgehead H), and 0.10 (m, 2, cyclopropane CH_2); ir 14.2 μ (strong, *cis* C=C).

A solution of diazomethane in ether (prepared from 34 mmol of *N*-methyl-*N*-nitrosourea;[19] *ca.* 24 mmol of diazomethane) and copper powder (0.5 g) were added sequentially to chilled **1** (3.5 g, 26 mmol) with stirring. With continued stirring, the mixture was kept at 0 to −5° for 3 hr and then at room temperature overnight. Addition of a few drops of acetic acid produced no gas evolution. The filtered solution was washed, dried, concentrated by rotary evaporation, and analyzed by gc. Only a small amount of methylenation had occurred. The stereoisomeric bicyclo[8.1.0]undec-4-enes were identified by the identity of their gc characteristics to those of the Simmons–Smith[11] products. The ratio of additions to the trans:cis alkene linkages was 73:27.

Addition of Dibromomethylene.[10]—Bromoform (8.5 g, 33 mmol) was added dropwise to a stirred, ice–salt chilled slurry of **1** (4.4 g, 32 mmol), potassium *tert*-butoxide (4.2 g, 38 mmol), and pentane (50 ml). The mixture, which became tan, was allowed to warm to room temperature and was stirred overnight. Conventional work-up and distillation led to the isolation of 70–75% yield of a mixture of addition products. Gc analysis indicated that two adducts were formed in a ratio of 3:1. The major component was isolated by preparative gc: ir (neat) 14.25 μ (strong, cis C=C); nmr (CCl_4) δ 5.40 (m, 2, C=CH), 2.25 (m, 8, C=C-CH_2 and CH$\mathbf{CH_2}$), 1.65 (4, $CH_2\mathbf{CH_2}CH_2$), and 1.15 (m, 2, bridgehead H). These data are consistent with the identification, 11,11-dibromo-*trans*-bicyclo[8.1.0]undec-*cis*-4-ene.

Addition of Isopropylidenemethylene.[12]—Lithium 2-ethoxyethoxide[12] (5.0 g, 51 mmol) was added in three portions to a stirred mixture of 5,5-dimethyl-*N*-nitrosooxazolidone[12] (5.0 g, 35 mmol) and **1** (20 ml) at 45–50°. Each addition caused vigorous gas evolution. After 30 min of stirring, the mixture was poured into ice water and extracted into ethyl ether. Conventional work-up and reduced pressure distillation gave a 75% yield of a mixture of adducts in a 7:3 ratio (gc), bp 71–73° (0.7 mm). The products were separated by preparative gc (6 ft × 0.25 in. column, 30% SE-30 silicone on Chromosorb P, 140°). The major product (shorter gc retention time) was identified by its spectral characteristics as 11-isopropylidene-*trans*-bicyclo[8.1.0]-undec-*cis*-4-ene (**9**): ir (neat) 14.20 μ (cis C=C); nmr (CCl_4) δ 5.40 (m, 2, C=CH), 1.70 (s, 6, CH_3), 2.5–1.4 (12, CH_2), and 0.95 (m, 2, bridgehead H). The minor product was identified by its spectral characteristics as 11-isopropylidene-*cis*-bicyclo[8.1.0]-undec-*trans*-4-ene (**10**): ir (neat) 10.4 μ (trans C=C); nmr (CCl_4) δ 5.55 (m, 2, C=CH), 1.66, 1.70 (2 s, CH_3), 2.3–0.8 (other H).

Registry No.—**1**, 1124-78-3; **2** (X = OH), 14759-74-1; **2** (X = N_3), 37710-16-0; **2a**, 37710-17-1; **2c** (R = CH_3), 37710-18-2; **2c** (R = Ph), 37710-19-3; *trans*-**4a**, 37710-22-8; *cis*-**4b**, 37710-23-9; *trans*-**4b**, 37710-24-0; **7**, 37710-20-6; **8**, 37710-21-7; 6-bromo-5-trichloromethyl-*cis*-1-cyclodecene, 37710-25-1; *trans*-bicyclo[8.1.0]undec-*cis*-4-ene, 24381-94-0; *cis*-bicyclo-[8.1.0]undec-*trans*-4-ene, 24315-98-8; 11,11-dibromo-*trans*-bicyclo[8.1.0]undec-*cis*-4-ene, 24315-95-5; **9**, 38821-32-8; **10**, 38821-33-9.

(18) J. G. Traynham and T. M. Couvillon, *J. Amer. Chem. Soc.*, **87**, 5806 (1965).

(19) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, pp 165, 461.

A Stereochemical Study of Product Formation from Some 4-*tert*-Butylcyclohexyl Cations[1]

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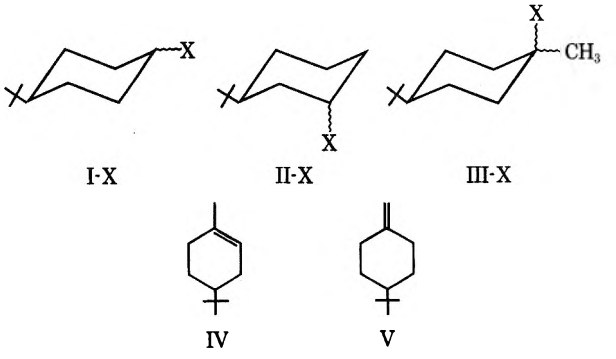
To assess the preferred stereochemistry of product formation from cyclohexyl carbonium ions, we have investigated the ratio of cis and trans products formed from several 4-*tert*-butylcyclohexyl systems. The reactions included lead tetraacetate and anodic oxidative decarboxylations of carboxylic acids, chlorinolyses of 2,4-dinitrobenzenesulfenates (products identified with both intimate and solvent-separated ion pairs), thermolyses of chlorocarbonates, and reactions of hydrogen chloride with tertiary alcohols and with olefins. Most carbonium ion processes with cyclohexyl systems, even those which involve solvent-separated ion pairs, are so strongly influenced by the stereochemistry of the reactant that they offer little information about the preferred stereochemistry of product formation from cyclohexyl cations. Secondary carbonium ions generated by lead tetraacetate oxidative decarboxylation and tertiary ones derived from alcohols, however, are apparently free so far as the stereochemical influence of the leaving group is concerned. For cyclohexyl cationic reactions in which the stereochemistry of the leaving group is not influential, and in which there is substantial bond making in the transition state, the preferred reaction path will lead to axial bond formation. The predominance of axial products in these reactions can be rationalized on the basis of torsional interactions, which hinder equatorial-like attack on the intermediate carbonium ions.

Several studies have established that the less stable, axially substituted products are formed preferentially or exclusively from cyclohexyl radical intermediates.[3] Our attempt to compare these results with those reported for other trivalent carbon intermediates was thwarted. Although there is a substantial volume of literature describing carbonium ion reactions of cyclohexyl systems, few of the papers illuminate the preferred stereochemistry of product formation from cyclohexyl cations.[4] Several cationic reactions involving cyclohexyl systems have been reported,[5] but in all of them the stereochemistry of the major products is directly tied to that of the reactant, even when the intervention of cationic intermediates is revealed by the 1,2-hydride shifts which occur.[5b] In order for the stereochemistry of product formation from cyclohexyl cations to be revealed, the counterion must be far enough removed so that it does not influence the direction of attack on the cation. Evidence of such a free carbonium ion[6] would be the formation of identical product mixtures from isomeric axial and equatorial reactants. In the present study, the preferred stereochemical paths of product formation from a number of different cyclohexyl cation precursors have been determined and compared.



In our study, we have used 4-*tert*-butylcyclohexyl systems and reactions which are expected to involve cyclohexyl cations. We have assumed that the cyclohexane rings are in the chair conformation and that the *tert*-butyl substituent (bulkiest substituent used) is always equatorial.[5a] Carbonium ion like reactions were effected by lead tetraacetate and anodic oxidations of carboxylic acids (Ia-COOH and Ie-COOH),[8] thermolyses of chlorocarbonates (Ia-OCOCl and Ie-OCOCl), chlorinolyses of 2,4-dinitrobenzenesulfenates (Ia-OSAr and Ie-OSAr), chlorodehydroxylations of tertiary alcohols (IIIa-OH and IIIe-OH), and additions of anhydrous hydrogen chloride to the isomeric olefins IV and V. The results are summarized in Table I. Of the systems which lead to secondary cyclohexyl cations, only the lead tetraacetate oxidations of Ia-COOH and Ie-COOH yielded identical product mixtures from the stereoisomeric reactants. In that reaction, the products consist of olefin and alkyl acetate, and axial acetate (Ia-OAc) is slightly favored over equatorial acetate (Ie-OAc). The chlorodehydroxylations of

(1) (a) Based on the Ph.D. dissertation of S. D. E., Louisiana State University—Baton Rouge, Jan 1971. Grateful acknowledgment is made to the Dr. Charles E. Coates Memorial Fund of the LSU Foundation donated by George H. Coates for financial aid toward the preparation of that dissertation. (b) Presented in part at the Combined Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 2, 1970, Paper ORGN 340. (c) A brief summary of a portion of these data has been published: S. D. Elakovich and J. G. Traynham, *Tetrahedron Lett.*, 1435 (1971).

(2) National Aeronautics and Space Administration Trainee, 1966–1969.

(3) (a) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968), and references cited therein; (b) J. G. Traynham, A. G. Lane, and N. S. Bhacca, *J. Org. Chem.*, **34**, 1302 (1969).

(4) Some discussions of the nomenclature of carbonium ions, in this journal and elsewhere, have been misleading because of the authors' failure to appreciate the distinction between one-word and two-word names. *Cyclohexyl carbonium ion* and *cyclohexyl cation* are both correct names for the same ion, and both (particularly the *cation* name) are preferred by us to *cyclohexenium ion* [G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972)], which is not formed in accord with usual IUPAC practice and emphasis. For a clear, definitive discussion of this matter, see C. D. Hurd, *J. Chem. Educ.*, **48**, 490 (1971).

(5) (a) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955); (b) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968); (c) D. S. Noyce, B. E. Johnson, and B. Weinstein, *J. Org. Chem.*, **34**, 463 (1969); (d) J. B. Lambert, G. J. Putz, and C. E. Mixan, *J. Amer. Chem. Soc.*, **94**, 5132 (1972); (e) J. E. Nordlander and T. J. McCrary, Jr., *ibid.*, **94**, 5133 (1972); (f) A. Streitwieser, Jr., and C. E. Coverdale, *ibid.*, **81**, 4275 (1959); (g) W. Hückel and K. Heyder, *Chem. Ber.*, **96**, 220 (1963).

(6) By "free," we refer only to the influence of the leaving group, not to association with solvent. Our discussion and data do not bear on the important nucleophilic role of solvent in the ionization process.[7]

(7) For a review, see D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49**, 60 (1972).

(8) In formula designations such as these, a and e will signify axial and equatorial bonding, respectively, of the functional group specified. The Roman numeral designates the substituted cyclohexyl group according to the illustrations in the text, and X is an unspecified functional group (not necessarily the same in all cases).

TABLE I
SUMMARY OF REACTIONS WITH 4-*tert*-BUTYLCYCLOHEXYL SYSTEMS

Reactant[a]	Reaction[d]	Substitution products[e]	% Axial product
Ia-COOH	$Pb(OAc)_4$, HOAc	I-OAc	53
Ie-COOH		I-OAc	53
Ia-COOH	$Pb(OAc)_4$, LiCl[f]	I-Cl	67
Ie-COOH		I-Cl	67
Ia-COOH	Anodic oxidation	I-OH	46
Ie-COOH		I-OH	30
		I-Cl (7.0)	36
Ia-OSAr[c]	Cl_2, HOAc	I-OAc (5.7)	19
		II-OAc (9.0)	83
		I-Cl (<1)	<50
Ia-OSAr[c]	Cl_2, HOAc, $LiClO_4$	I-OAc (5.6)	29
		II-OAc (8.7)	83
		I-Cl (35)	57
Ie-OSAr	Cl_2, HOAc	I-OAc (43)	33
		II-OAc (0.5)	100
		I-Cl (16.5)	62
Ie-OSAr	Cl_2, HOAc, $LiClO_4$	I-OAc (33)	48
		II-OAc (1.8)	100
Ia-OCOCl	Thermolysis	I-Cl	63
Ie-OCOCl		I-Cl	21
IIIa-OH	HCl	III-Cl	80
IIIe-OH		III-Cl	80
IV	HCl	III-Cl	65
V	HCl	III-Cl	70
Ia-OTs[b,c]	HOAc, 100°	I-OAc (8.1)	9
	0.05 *M* NaOAc	II-OAc (4.8)	94
Ie-OTs[b,c]	HOAc, 100°	I-OAc (19.9)	98
	0.05 *M* NaOAc	II-OAc (2.0)	25
Ia-OSO_2Me[b,c]	HOAc, 70°	I-OAc (9.3)	13
	0.1 *M* NaOAc	II-OAc (5.0)	92
Ie-OSO_2Me[b,c]	HOAc, 70°	I-OAc (20.9)	95
	0.1 *M* NaOAc	II-OAc (1.4)	21
Ia-NH_2[b,c]	H_2O, HONO	I-OH	44
Ie-NH_2[b]	H_2O, HONO	I-OH	14

[a] See ref 8. [b] From the literature (I-OTs,[5b] I-OSO_2Me,[5c] and I-NH_2[5g]). [c] More than 65 mol % of product mixture was olefin. [d] All reactions except one presumably involve carbonium ion intermediates. [e] Numbers in parentheses represent yield of product obtained in reactions by which multiple substitution products were produced. [f] Product formation from radical intermediate.

IIIa-OH and IIIe-OH also gave product mixtures (alkyl chlorides) indistinguishable from each other, with axial product predominating 4:1. The predominance of axial products in these two systems, as well as in the hydrochlorination of the olefins IV and V, is explained on the basis of torsional strain in the transition state, which hinders equatorial-like attack on the intermediate cation.[3a] The differences in the product mixtures from the other systems investigated indicate the difficulty of generating a cyclohexyl cationic center free from the influence of the leaving group.

Results

Oxidations of I-COOH.—Hydrogenation of 4-*tert*-butylbenzoic acid over platinum oxide catalyst produced a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acids, which were separated by the use of thiourea.[9] Separate **lead tetraacetate oxidative decarboxylations**, carried out at 80° in benzene containing pyridine, converted the acids to a mixture of olefin and alkyl acetates (Ia-OAc and Ie-OAc) through alkyl cation intermediates.[10] The product mixtures were analyzed by comparison of gas chromatographic (gc) and nuclear magnetic resonance (nmr) data with those of authentic samples. The same proportions of Ia-OAc and Ie-OAc (53:47, respectively) were obtained from both stereoisomeric carboxylic acids. The yields of olefin (30 and 38%) were not the same from the two isomeric reactants, but they were both moderately low and contrast with the high ones (76–87%) obtained by acetolysis of 4-*tert*-butyl-1-cyclohexyl toluene- and methanesulfonates.[5b,c]

Since the alkyl cation intermediate in this reaction is presumably generated from an alkyl radical,[10b] the stereochemistry of product formation from this radical precursor is of immediate interest and concern. The halodecarboxylation of a carboxylic acid by use of lead tetraacetate and lithium halide provides an alkyl halide formed from an alkyl radical which is generated under conditions which are quite similar to those for the cationic oxidative decarboxylations.[11] Separate halodecarboxylations of Ia-COOH and Ie-COOH by lead tetraacetate in the presence of lithium chloride give alkyl chloride mixtures indistinguishable from each other, with axial chloride (Ia-Cl) predominating 2:1.[12a] The thermal decompositions of the tertiary hypochlorites, Ia-$C(CH_3)_2OCl$ and Ie-$C(CH_3)_2OCl$, give this same 2:1 cis:trans chloride product ratio,[12b] indicating that the same type of radical intermediate is formed in both reactions. Since in the halodecarboxylation reaction the same radical is formed from both acids, it follows that the oxidation of this radical would lead to a single type of carbonium ion intermediate. Therefore, both the radical and the cationic lead tetraacetate reactions are independent of the configuration of the starting acid (so far as product stereochemistry is concerned), but product formation from the apparently free cationic intermediate is appreciably less stereoselective than it is from the apparently free radical from which the cation is formed.[13]

Recent studies of **anodic oxidations** of carboxylic acids identify the ester, alcohol, and olefin products with cationic intermediates.[14] Although a combination of radical and cationic processes may be involved in the formation of these products in aqueous solutions,

(9) H. van Bakkum, P. E. Verkode, and B. M. Wepster, *Kon. Ned. Akad. Wentensch. Proc., Ser. B*, **62**, No. 3 (1959); *Chem. Abstr.*, **54**, 2209*f* (1960).

(10) (a) E. J. Corey and J. Casanova, Jr., *J. Amer. Chem. Soc.*, **85**, 165 (1963); (b) J. K. Kochi, *ibid.*, **87**, 1811 (1965).

(11) J. K. Kochi, *ibid.*, **87**, 2500 (1965); *J. Org. Chem.*, **30**, 3265 (1965).

(12) (a) Since the completion of our study, the same results for these reactions have been reported by R. D. Stolow and T. W. Giants, *Tetrahedron Lett.*, 695 (1971); (b) F. D. Greene, C.-C. Chu, and J. Walia, *J. Amer. Chem. Soc.*, **84**, 2463 (1962).

(13) A referee has suggested that the identity of the product mixtures from the isomeric acids may "indicate no more than conformational equilibration of counterspecies at some point prior to product formation." Even this point of view does not reduce the stereochemical significance of our results, however. Because the configurational compositions of the radical and cationic product mixtures are quite different from one another, the cationic result cannot be dictated directly by the radical one, and configurational preferences of cation–counterion pairs would be as independent of those of precursor species as would those of free carbonium ions. Whether one advocates a free carbonium ion[6] or an ion pair intermediate, the ratio of acetate products (53 axial:47 equatorial) demonstrates that there is little configurational preference at this cationic stage and the configuration of the original reactant has no influence. The results which we have obtained with the tertiary alcohols IIIa-OH and IIIe-OH lead us to favor the free carbonium ion[6] interpretation.

(14) For example, see (a) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *J. Amer. Chem. Soc.*, **82**, 2645 (1960); (b) W. H. Koehl, Jr., *ibid.*, **86**, 4686 (1964); (c) J. G. Traynham and J. S. Dehn, *ibid.*, **89**, 3129 (1967); (d) J. G. Traynham, E. E. Green, and R. F. Frye, *J. Org. Chem.*, **35**, 3611 (1970), and references cited therein.

Table II

Product Distributions[a] from the Chlorinolysis in Acetic Acid of *cis*- and *trans*-4-*tert*-Butylcyclohexyl 2,4-Dinitrobenzenesulfenates

Sulfenate	Ia-Cl	Ie-Cl	Ia-OAc	Ie-OAc	IIa-OAc	IIe-OAc	Olefin[b]	R-OAc / R-Cl
Ie-OSAr	20	15	14	29	0.5		22	1.2
Ie-OSAr ($LiClO_4$)	10	6.2	16	17	1.8		48.5	2.1
Ia-OSAr	2.5	4.5	1.1	4.6	7.5	1.5	78	2.1
Ia-OSAr ($LiClO_4$)	<0.5	<0.5	1.6	4.0	7.2	1.5	85	>15

[a] Figures represent an average of two runs which gave numbers differing from the average by no more than 3% of the average figure. [b] Detected as the addition product mixture formed by reaction of 4-*tert*-butylcyclohexene and chlorine in acetic acid solvent (See Experimental Section for details).

the major portions of alcohol and olefin products appear to come from cationic intermediates,[14d] which are considered to be higher in energy than those generated by solvolysis reactions.

We have electrolyzed 0.5 *M* aqueous solutions of Ia-COONa and Ie-COONa at graphite anodes. The conversion was quite low for both isomers, and yields were not calculated. The product mixtures were complex, and only the stereochemical ratios of the major components, the *cis*- and *trans*-4-*tert*-butylcyclohexanols, were examined. While Ie-OH is the predominant product from both acids, its predominance in the mixture from Ie-COOH is substantially greater than it is from Ia-COOH. The intermediate carbonium ions in these electrolyses are generated from alkyl radicals absorbed on the anodic surface, and we were surprised that the configuration of the starting acid influences the final product-forming step. Apparently the departure of the freshly formed carbonium ion from the anodic surface is not so much in advance of its combination with solvent water that the surface has no effect on the regioselectivity of alcohol production.

Chlorinolysis of Arenesulfenates.—The most widely accepted description of carbonium ion reactions is that of Winstein and coworkers.[15] It includes different kinds of ionic intermediates, any or all of which may form products. The extent and nature of the solvent

$$RX \rightleftharpoons \underset{\text{intimate ion pair}}{R^+X^-} \rightleftharpoons \underset{\text{solvent-separated ion pair}}{R^+ \| X^-} \rightleftharpoons \underset{\text{dissociated ions}}{R^+ + X^-}$$

environment of a carbonium ion strongly influences the stereochemical behavior of that ion. The ion-pairing behavior of the intermediates involved in the chlorinolysis in acetic acid of alkyl 2,4-dinitrobenzenesulfenates has been extensively characterized by means of the lithium perchlorate effect criterion.[16] Generally, the arenesulfenate is chlorinated to form an intimate sulfoxonium ion pair, which may lose a sulfinyl chloride fragment, before or after solvent reorganization, to form the corresponding carbonium ion pair. These carbonium ion pairs are "born in an inherited solvent environment;"[16a] that is, the solvent structure organized about the intimate and solvent-separated sulfoxonium ion pairs is transferred to the corresponding carbonium ion pairs, which do not interconvert.[16b,c] The effect of lithium perchlorate on the product mixtures of systems studied has led to the conclusion that acetate products arise principally from solvent-separated carbonium ion pairs and chloride products from intimate carbonium ion pairs.[16b] Thus, the stereochemistry of product formation from both kinds of ion pairs is subject to investigation.

Isomerically pure *cis*- and *trans*-4-*tert*-butylcyclohexyl 2,4-dinitrobenzenesulfenates were prepared from the isomerically pure alcohols[17] and freshly recrystallized 2,4-dinitrobenzenesulfenyl chloride. Chlorinolysis in acetic acid of each sulfenate was effected at 20° with a 2:1 molar ratio of chlorine to sulfenate, both without and with added lithium perchlorate. The products were identified by comparison of their gc retention times with those of authentic samples, and the yield of each product was calculated from the gc data and the relative response factor for that component. The results are summarized in Tables I and II.

Chlorinolysis of the trans sulfenate, Ie-OSAr, gives predominantly 4-*tert*-butylcyclohexyl acetate; 4-*tert*-butylcyclohexene and 4-*tert*-butylcyclohexyl chloride are formed in lesser amounts. In the presence of lithium perchlorate, the olefin becomes the predominant product. Although the absolute amount of acetate decreases, the ratio of acetate to chloride increases almost twofold; thus, the olefin is formed at greater expense of the chloride than of the acetate. This unequal effect of lithium perchlorate on the acetate and chloride products indicates that substantial amounts of these products arise from different intermediates. Earlier workers[16] have shown for other alkyl systems that chloride product comes predominantly or exclusively from intimate ion pairs and acetate and olefin products come from other intermediates. The decrease in yield of acetate with added lithium perchlorate in the present system (an effect not reported for previously studied systems) indicates either that a substantial amount of the acetate must arise from intimate ion pairs or that, with lithium perchlorate present, another ionic intermediate (*e.g.*, completely separated ions) becomes important and gives rise to acetate and olefin in different proportions than do the solvent-separated ion pairs.[18] The latter interpretation is the more consistent with

(15) S. Winstein, P. E. Klinedinst, Jr., and G. C. Robinson, *J. Amer. Chem. Soc.*, **83**, 885 (1961).

(16) (a) H. Kwart and J. L. Irvine, *ibid.*, **91**, 5541 (1969); (b) H. Kwart, E. N. Givens, and C. J. Collins, *ibid.*, **91**, 5532 (1969); (c) J. G. Traynham and A. W. Foster, *ibid.*, **93**, 6216 (1971).

(17) An initial attempt to prepare isomerically pure *cis*- and *trans*-4-*tert*-butylcyclohexanols by the fractional crystallization of their phthalate derivatives[5a] proved tedious. Spinning-band distillation of the corresponding acetates, followed by hydrolysis, gave a convenient pathway to large amounts of the isomerically pure alcohols.

(18) Independent studies (H. Kwart and J. W. Boghosian, private communications, 1971) of this system have shown that added lithium chloride has little effect on the product distributions from I-OSAr without lithium perchlorate present but has a substantial effect on those from I-OSAr with lithium perchlorate present. These results strongly imply that completely separated ions are important in the reaction sequence when lithium perchlorate is present but unimportant when it is absent.

all other data reported for chlorinolyses of sulfenates.[16,18] The great increase in proportion of olefin when lithium perchlorate is included in the reaction mixture suggests that olefin is formed mainly from intermediates other than intimate ion pairs.

Chlorinolysis of the cis sulfenate, Ia-OSAr, yields predominantly 4-*tert*-butylcyclohexene, both in the presence and in the absence of lithium perchlorate. This result is harmonious with those obtained for other systems having axial reactant groups. The nitrous acid deamination of *cis*-4-*tert*-butylcyclohexylamine also gives olefin in high yield;[5g] in fact, axial cyclohexylamines generally give high yields of olefin.[19a] The solvolysis of each 4-*tert*-butylcyclohexyl arene- or methanesulfonate gives predominantly elimination rather than substitution product, but the axial sulfonates give about 10% more olefin than do the equatorial sulfonates.[5b,c] The stereochemistry of an axial substituent normally favors elimination over substitution, probably because the solvating molecule equatorially associated with the developing carbonium ion center is favorably located to assist in the removal of the vicinal axial hydrogen. (An axially associated solvent molecule is not so located.)

The effect of lithium perchlorate on the chloride:acetate product ratio from the cis sulfenate (Ia-OSAr) is dramatic. The chloride yield is reduced by a factor of >6, while the yield of acetate is only slightly reduced. This effect strongly implies that the chlorides are intimate ion pair products, and that the acetate must arise predominantly from solvent-separated ion pairs. The increase in olefin with lithium perchlorate addition implies that olefin is also a product of solvent-separated ion pairs.

Although lithium perchlorate addition reduces the absolute amount of chloride products from both Ia-OSAr and Ie-OSAr, the isomeric distribution from each reactant remains unchanged, supporting the conclusion that the chlorides are formed only from intimate ion pairs. Since the stereochemistry of each chloride mixture is directly related to that of the sulfenate from which it is obtained (36–43% retention, 64–57% inversion[20]), these results are of little value in elucidating the preferred stereochemistry of product formation from cyclohexyl cations.

Predominant inversion could be taken to imply a substantial amount of S_N2-like displacement by chloride on the $ROS(Cl)Ar^+$ ion, but the extensive amount of retention requires another process as well. It seems unlikely to us that partitioning between S_N2 and ionizing processes leading to RCl would be about the same with both axial and equatorial reactants. The orientation between cation and chloride in the intimate ion pair is not inflexible; transannular rearrangement is as extensive in the chloride product as in the acetate one from cyclooctyl arenesulfenate.[16c] Therefore both retention and inversion could occur in the RCl formation from carbonium chloride intimate ion pairs.

Four isomeric acetates are formed in the chlorinolysis reactions: *cis*- and *trans*-4-*tert*-butylcyclohexyl acetate (Ia-OAc and Ie-OAc) and *cis*- and *trans*-3-*tert*-butylcyclohexyl acetate (IIe-OAc and IIa-OAc). The trans sulfenate gives a very small amount of IIa-OAc, whereas this is the major acetate from the cis sulfenate. Both rearrangement (1,2-hydride shift) and elimination processes are more extensive with the cis sulfenate than with the trans sulfenate.

Substantial amounts of hydride-shift products are also obtained from solvolysis of cyclohexyl arenesulfonates, usually more so from axial than from equatorial reactants.[5a-e] These products have led to the suggestion that one or more hydrogen-bridged species intervene.[5a,b] Such species conveniently account for the preferred formation of IIa-X[21] and for the formation of large amounts of olefin from Ia-X. Alternatively, a twist–boat conformation for the rearranged ion may be the important precursor to IIa-OAc,[18] since a single hydrogen-bridged species will not account for the preferred axial stereochemistry of II-OAc from both isomers of I-OSAr. The absence of rearranged chloride products in the sulfenate product mixtures implies that hydrogen bridging is unimportant in the intimate ion pairs in this system and contrasts sharply with data from the cyclooctyl system.[16c] Although the extents of transannular hydride shifts are the same in the intimate and solvent-separated carbonium ion pairs generated by chlorinolysis of cyclooctyl arenesulfenate,[16c] 1,2-hydride shift occurs far more extensively in the separated ion pairs of the cyclohexyl system than in the intimate ones.

The difference in the ratio of stereoisomers of I-Cl and of I-OAc and the insignificant effect of lithium perchlorate on the distribution of the isomeric acetates derived from cis sulfenate together demonstrate that little, if any, of these acetates is formed from intimate ion pairs. In contrast to these results with cis sulfenate, lithium perchlorate does bring about a significant change in the Ie-OAc:Ia-OAc ratio (from about 2:1 to about 1:1) obtained from trans sulfenate. This change, coupled with the accompanying reduction in yield of acetate, strongly implies that, with lithium perchlorate present, a substantial portion of the acetate-forming process from trans sulfenate is shifted from solvent-separated ion pairs to completely separated ions.[18] The chloride product is formed mainly with inversion of configuration from each sulfenate, but the ionic intermediates derived from cis sulfenate and from trans sulfenate exhibit different stereochemistry of formation of acetate products. Those from cis sulfenate (with or without added lithium perchlorate) form equatorial acetate (inverted configuration) preferentially (4:1), those from trans sulfenate without added lithium perchlorate also form equatorial acetate (retention of configuration) preferentially (2:1); but those from trans sulfenate with added lithium perchlorate form axial and equatorial products in an approximately 1:1 ratio, just as we observed in the lead tetraacetate oxidation of Ie-COOH and Ia-COOH. These results reveal that carbonium ions free from the stereochemical influence of the leaving group (or other associated

(19) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., pp 89–91; (b) pp 99–100.

(20) The yield of chloride from Ia-OSAr with added lithium perchlorate was too small for us to determine the cis:trans chloride ratio accurately, but the inverted chloride was clearly the major isomer.

(21) Covalent return from the rearranged ion pair intermediates generated from substituted cyclohexyl tosylates has been suggested to account for the predominant stereochemistry of the ultimate products;[5b,c] for example, axial tosylate rearranges mainly to equatorial tosylate, which gives axial acetate. A parallel process, however, for the carbonium acetate ion pairs generated from arenesulfenates would produce mainly equatorial acetate (IIe-OAc) from axial sulfenate, while the actual result is mainly axial acetate (IIa-OAc).

anion) are seldom, if ever, involved in these sulfenate reactions. We have speculated about a variety of competing product-forming processes, each with its own stereochemical consequences, occurring with the several ionic intermediates. Our data do not, we believe, permit us to make firm choices to account exactly for the observed stereochemical results.

We investigated brominolysis of the arenesulfenates, Ia-OSAr and Ie-OSAr, using the same procedure as we did for chlorinolysis. No monobromides were present in the product mixtures, I-OAc was the major product, and it was formed with about 96% retention of configuration from each sulfenate. Addition of lithium perchlorate to the initial reaction mixtures increased slightly the yields of both olefin and rearranged acetate (II-OAc) products at the expense of the major acetate product, but the changes were not extensive enough to be the basis for meaningful interpretations. The data do imply that intimate ion pairs are far less important for product formation in brominolysis than in chlorinolysis of the arenesulfenates.

Thermolysis of Chlorocarbonates.—The rate-determining step in the thermal decomposition of chlorocarbonates appears to involve a carbonium ion,[22] but the nature of this ion has not been fully defined. The decomposition has recently been described by an ion pair mechanism.[23] We thought it of interest to compare the stereochemistry of product formation from this reaction with that observed from the different kinds of ion pairs in the arenesulfenate chlorinolysis. Thermal decomposition of both *cis*- and *trans*-4-*tert*-butylcyclohexyl chlorocarbonates, obtained from the reaction of phosgene with the isomeric 4-*tert*-butylcyclohexanols, yields as the major chloride product the isomer with retained configuration. This result suggests an Sni mechanism for the decomposition. However, since chloride with retained configuration is only the predominant and not the exclusive product, an unmodified Sni process can account only for the major part of the reaction mixture. It is clear that if an ion-pair mechanism is involved in this reaction, the ion pairs are different from both the intimate and the solvent-separated ion pairs of the sulfenate chlorinolysis reaction.

Tertiary Carbonium Ions.—We have compared some reactions of tertiary cyclohexyl cations with the reactions of secondary ones described above. We have used acidic conditions with both tertiary alcohols and olefins to generate the tertiary carbonium ions.

A 1:1 ratio of the *cis*- and *trans*-1-methyl-4-*tert*-butylcyclohexanols, obtained from a Grignard reaction of 4-*tert*-butylcyclohexanone, was converted to a mixture of the isomeric acetates, which were separated by spinning band distillation and then hydrolyzed to the isomerically pure alcohols. Anhydrous hydrogen chloride reacted with each alcohol to give chloride products, III-Cl, arising from a tertiary carbonium ion. Identical product mixtures, rich in axial chloride (80%), were obtained from both isomers. The chlorides were identified by their nmr spectra (see Experimental Section for details). Hydrochlorination of the olefins IV and V would presumably go through the same tertiary cyclohexyl cation as is produced from the alcohols. Addition of hydrogen chloride gas to a methylene chloride solution of IV gave III-Cl as the only products, with an axial:equatorial chloride ratio of 65:35.[24] A similar treatment of V gave 70% axial chloride and 30% equatorial chloride as the only products. The high preference for attack which results in axial bond formation can be explained by torsional interactions, as has been done for the same preference in attack on cyclohexyl radicals.[3a] Attack on the essentially planar cationic center from a direction leading to equatorial bond formation will increase torsional interaction, since the methyl group (on C-1) must eclipse the equatorial hydrogens on C-2 and C-6 at some stage in the reaction; no such interaction would occur with attack leading to axial bond formation. To the degree that bond formation is substantial at the transition state, the rate of axial attack will exceed that of equatorial attack. If hydrogen rather than methyl is on C-1, the torsional interaction should be much smaller, and therefore, the preference for axial product formation should be much less. This expectation corresponds exactly to the observation in the case of lead tetraacetate oxidative decarboxylation (change in a-X:e-X from 80:20 for III-Cl from III-OH to 53:47 for I-OAc from I-COOH).

In a previous investigation of the chlorodehydroxylation of mixtures of IIIa-OH and IIIe-OH, the ratio of IIIa-Cl:IIIe-Cl was found to be 5.9:1.[26] The stereochemical assignments were made on the basis of the infrared spectra of the products and the selective dehydrochlorination of IIIa-Cl. We made our stereochemical assignments on the basis of the nmr line width of the methyl adsorption in each isomer (see Experimental Section for details). The axial methyl adsorption is broadened because of "W" coupling with the axial protons at the two adjacent ring positions.[27] The measured line-width values fall well within the predicted range for each isomer,[28] and the stereochemical assignments agree with those made on the basis of infrared data.[26]

Conclusions

Most carbonium ion processes with cyclohexyl systems, even those which involve solvent-separated ion

(22) (a) K. B. Wiberg and T. M. Shryne, *J. Amer. Chem. Soc.*, **77**, 2774 (1955); (b) K. L. Oliver and W. G. Young, *ibid.*, **81**, 5811 (1959).

(23) J. L. Kice and G. C. Hanson, *Tetrahedron Lett.*, 2927 (1970).

(24) The axial chloride might have been expected to be the major product from the hydrochlorination of IV, since most additions to double bonds proceed by a diaxial pathway,[19b] but deuterium chloride reacts with 3-methyl-2-cholestene to give the diequatorial adduct.[25]

(25) (a) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956); (b) D. H. R. Barton, *Experientia, Suppl.*, II, 121 (1955).

(26) N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967).

(27) (a) C. W. Shoppee, F. P. Johnson, R. E. Lack, J. S. Shannon, and S. Sternhell, *Tetrahedron, Suppl.*, **8**, Part II, 421 (1966). (b) The minor isomer, IIIe-Cl, is difficult to obtain completely free of IIIa-Cl by preparative gc, apparently because of some isomerization on the metal surfaces of the splitter or exit port. The chemical shifts of CH_3CCl in the two isomers are so close together that contamination of IIIe-Cl by IIIa-Cl raised some doubts about the dependability of the differentiation based on nmr line widths. After extensive experimentation in these laboratories, Dr. E. E. Green confirmed our nmr differentiation of the isomers. Dr. Green also found that the compositions of various mixtures of IIIa-Cl and IIIe-Cl were not changed by heating at 110° in sealed glass ampoules, with and without solvent, with and without added hydrogen chloride. These experiments strongly support our view, implied in the discussion, that the isomer mixture obtained results from kinetic rather than thermodynamic control, even though its composition is close to that of the equilibrium mixture.[26] We acknowledge with appreciation Dr. Green's contribution to this investigation.

(28) D. N. Kirk and P. M. Shaw, *J. Chem. Soc. C*, 182 (1970), found no difference in the line widths of the methyl adsorptions of the isomers IIIa-Cl and IIIe-Cl. These authors, apparently misinterpreting the nomenclature used by Allinger and Liang,[26] assign axial-Cl stereochemistry to the minor isomer.

pairs, are so strongly influenced by the stereochemistry of the reactant that they offer little information about the preferred stereochemistry of product formation from cyclohexyl cations. Secondary carbonium ions generated by lead tetraacetate oxidative decarboxylation and tertiary ones derived from alcohols, however, are apparently free so far as the stereochemical influence of the leaving group is concerned. For cyclohexyl cationic reactions in which the stereochemistry of the leaving group is not influential, and in which there is substantial bond making in the transition state, the preferred reaction path will lead to axial bond formation. The degree of preference is small for secondary cations, but substantial for tertiary ones.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates Model A-60A spectrometer unless otherwise stated. Carbon tetrachloride (CCl_4) and deuteriochloroform ($CDCl_3$) were normally used as solvents with tetramethylsilane as the internal standard. Gas chromatographic (gc) analyses were obtained with either a Beckman GC-5 or a Hewlett-Packard Model 700 gas chromatograph, each equipped with a flame ionization detector and 0.125-in. columns. Spinning-band distillations were carried out on a Nester/Faust Teflon annular spinning band column, Model NFT-50. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Element microanalyses were done by Mr. Ralph Seab of these laboratories.

Preparation of *cis*- and *trans*-4-*tert*-Butylcyclohexanecarboxylic Acids.—Hydrogenation of 30 g of 4-*tert*-butylbenzoic acid in 150 ml of acetic acid with 2 g of platinum oxide and 50 psig of hydrogen pressure was complete in 1 hr. The resulting isomeric mixture was separated by the use of thiourea, which preferentially entraps Ie-COOH when crystallized from methanol solution.[9] Isolated were Ie-COOH, mp 173.5–174.5° (lit.[9] mp 175–176°), and Ia-COOH, mp 116–117° (lit.[9] mp 118–118.5°).

Preparation of Ia-OH and Ie-OH.—A commercial mixture of Ia-OAc and Ie-OAc was conveniently separated by distillation through a spinning band column, and saponification of each acetate gave the isomerically pure alcohol. From the trans acetate[29] we obtained Ie-OH, mp 79–79.8° (lit.[5a] mp 81–82°), and from the cis acetate,[29] Ia-OH, mp 78–79° (lit.[5a] mp 80–81°).

Preparation of IIa-OAc and IIe-OAc.—4-*tert*-Butyl-1-cyclohexene[5a] [bp 50° (10 mm), nmr (CCl_4) δ 5.6 (m, 2, C=CH)], prepared by dehydration of a mixture of I-OH with thionyl chloride in refluxing benzene solution, was converted to a mixture of four alcohols in 70% yield by hydroboration.[30] A mixture of the alcohols (20.4 g), sodium acetate (20 g), and acetic anhydride (100 ml) was refluxed for 3 hr, cooled, poured into ice water, and extracted with ethyl ether. The ether solution was dried and concentrated. Gc analysis of the product residue on four different columns (9.5 ft Carbowax 20M, 6 ft UC-W98, and 9.25 and 12 ft XF-1150) showed four clearly separated peaks of approximately equal intensity.[31] By use of authentic samples, the second and fourth peaks were assigned to Ia-OAc and Ie-OAc, respectively. By distillation through a spinning-band column, the acetate mixture was substantially resolved into its four components. The component corresponding to the first gc peak gave an nmr spectrum ($DCCl_3$) indicative of IIa-OAc: δ 0.83 (s, *tert*-butyl), 2.05 (s, $OCOCH_3$), 0.8–2.1 (21 total, ring protons, *tert*-butyl, $OCOCH_3$ superimposed), 5.14 (1, CHOAc, shape indicative of equatorial H). The distillate corresponding to the third gc peak gave an nmr spectrum ($DCCl_3$) indicative of IIe-OAc: δ 0.83 (s, *tert*-butyl), 2.02 (s, $OCOCH_3$), ~4.65 (m, broad shape indicative of axial H, CHOAc).

Partial saponification of the mixture of four acetates with 0.5 molar equiv of sodium hydroxide in 95% ethanol confirmed the nmr stereochemical assignments. The third and fourth gc peaks were greatly diminished, relative to the first and second ones, by the partial hydrolysis. Equatorial acetates undergo hydrolysis more rapidly than do axial acetates,[29] and a control experiment with a mixture of Ia-OAc and Ie-OAc confirmed the expected difference in rates for this system.

TABLE III
SUMMARY OF HCX NMR CHEMICAL SHIFTS

Compd	δ[a] Axial H	δ[a] Equatorial H
I-OAc	4.52	4.95
	4.60[b]	5.01[b]
	4.53[c]	4.90[c]
	4.70[d]	5.09[d]
	4.70[e]	5.10[e]
I-OH	3.37	3.98
I-Cl	3.72	4.46
	3.75[b]	4.44[b]
I-Br	4.18	4.67
I-OSAr[f]	3.58	3.96
I-OCOCl	4.70	5.12
I-OSOCl	5.08	5.51
II-OAc	~4.65[b,g]	5.14[b]

[a] 60-MHz spectra, relative to internal TMS reference, 10% solutions, CCl_4 solvent except where indicated; axial H absorption broader than equatorial H absorption in all cases. [b] $DCCl_3$ solvent. [c] DMSO-d_6 solvent. [d] Pyridine solvent. [e] Benzene solvent. [f] Ar = 2,4-dinitrophenyl. [g] Some uncertainty in precise location because of overlapping absorptions by Ia-OAc present.

Lead Tetraacetate Oxidative Decarboxylation of Ia-COOH and Ie-COOH.—The method used is essentially that described by Corey and Casanova.[10a] All reactions were carried out under nitrogen in a flame-dried apparatus. In a typical experiment a solution of 5 g (0.03 mol) of cis acid, 2.8 g (0.035 mol) of dry pyridine, 100 ml of freshly distilled benzene, and 17.7 g (0.04 mol) of lead tetraacetate was refluxed for 8 hr. After work-up, gc analysis (10 ft Carbowax 20M column at 130°) of the products by comparison with authentic samples showed 38% (mol %) 4-*tert*-butylcyclohexene, 30% Ia-OAc, 27% Ie-OAc, and about 5% other products arising from Ia-COOH. Similar analysis of the products from Ie-COOH showed 30% (mol %) 4-*tert*-butylcyclohexene, 34% Ia-OAc, 29% Ie-OAc, and about 6% other products. The "other products" in both cases corresponded in retention times to Ia-OH, Ie-OH, IIa-OAc, and IIe-OAc, in approximately equal amounts. Nmr spectra (100 MHz) of the product mixtures supported the gc assignments, but the "other products" were not detected by nmr.

Halodecarboxylation of *cis*- and *trans*-4-*tert*-Butylcyclohexanecarboxylic Acids.[11]—The same mixture of Ia-Cl and Ie-Cl was isolated in 50–70% yield from a reaction mixture of either Ia-COOH or Ie-COOH (1.0 g, 5.4 mmol), dry benzene (10 ml), lead tetraacetate (2.4 g, 5.4 mmol), acetic acid (1.2 g, 19 mmol), and lithium chloride (0.23 g, 5.4 mmol) heated at 80° for 0.5 hr. Gc analysis did not reveal any other products, and the Ia-Cl:Ie-Cl gc ratio of 2:1 was confirmed by nmr data (relative intensities of the two CHCl absorptions).

Anodic Oxidations[14d] **of Ia-COOH and Ie-COOH.**—A large, flat-bottomed glass tube was fitted with a nitrogen inlet, thermometer, disc-shaped copper cathode, carbon anode, and stirring bar. The reaction temperature was regulated by a water bath. Current was supplied by a direct current power supply that allowed variation of the voltage applied across the electrolysis cell. In a typical experiment, 5.0 g (0.03 mol) of I-COOH, 1.2 g (0.03 mol) of sodium hydroxide, and 60 ml of water (for a 0.5 *M* solution) were placed in the electrolysis cell, and current was applied. The current flow was small and decreased with reaction time; heating the reaction mixture to 80° aided current flow in most cases. The electrolysis had to be interrupted repeatedly to remove a polymer-like material from the anode which impeded current flow. The aqueous solution was filtered to remove any carbon particles, made basic with sodium hydroxide, and extracted with ether. The ethereal extract was dried (magnesium sulfate) and concentrated. The residue was then subjected to gc analysis. The aqueous portion from the work-up was made acidic with hydrochloric acid to recover any unreacted I-COOH.

(29) N. B. Chapman, R. E. Parker, and P. J. A. Smith, *J. Chem. Soc.*, 3634 (1960).

(30) H. C. Brown and M. K. Unni, *J. Amer. Chem. Soc.*, **90**, 2902 (1968).

(31) Gc analysis for the alcohol mixture on the Carbowax 20M and XF-1150 columns showed only two product peaks, and the nmr spectrum showed only three absorptions (CCl_4, δ 3.45, 4.0, and 4.1) easily assigned to CHOH.

Only small amounts of products were obtained; over 90% of the acid was recovered. The main products, identified from their gc retention times (9.5 ft Carbowax 20M and 9.25 ft XF-1150 gc columns at 160°) as Ia-OH and Ie-OH, were present in a 1.0:1.15 ratio in the mixture from Ia-COOH and in a 1.0:2.4 ratio in the one from Ie-COOH. There were several unidentified minor products.

Preparation of Ia-OSAr and Ie-OSAr.—The 2,4-dinitrobenzenesulfenates were prepared[16b] from equimolar amounts of freshly recrystallized 2,4-dinitrobenzenesulfenyl chloride, mp 96–98°, and Ia-OH or Ie-OH in ethylene chloride solution containing pyridine. The yield of bright yellow crystals was 50–60%. Prepared were Ie-OSAr [mp 143.5–146°; nmr (CCl_4) δ 0.8–2.5 (18, cyclohexane ring and *tert*-butyl), 3.58 (m, 1, CHOSAr), 8.0 (d, 1, J = 9 Hz, aromatic), 8.5 (dd, 1, J = 9 and 2.4 Hz, aromatic), 9.11 (d, 1, J = 2.4 Hz, aromatic). *Anal.* Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.2; H, 6.3. Found: C, 54.2; H, 6.5.] and Ia-OSAr [mp 161.5–162°; nmr (CCl_4) δ 0.8–2.5 (18, cyclohexane ring and *tert*-butyl), 3.96 (m, 1, CHOSAr), 7.97 (d, 1, J = 9 Hz, aromatic), 8.5 (dd, 1, J = 9 and 2.4 Hz, aromatic), 9.13 (d, 1, J = 2.4 Hz, aromatic). *Anal.* Found: C, 54.3; H, 6.2.].

Chlorinations in Acetic Acid of Ia-OSAr and Ie-OSAr.—The reactions between chlorine and each of the 2,4-dinitrobenzenesulfenates in acetic acid solution were carried out according to the published procedure.[16a,b] A typical experiment utilized 84 ml of dry acetic acid (distilled from acetic anhydride), 2.0 g (5.7 mmol) of Ia-OSAr or Ie-OSAr, 0.49 ml (11 mmol) of chlorine, and, if lithium perchlorate were used, 0.5 g (4.7 mmol) of lithium perchlorate. After work-up and concentration of the pentane extract of the reaction mixture,[16a] the oil obtained in each experiment was subjected to gc analyses. Separation of all components at once was difficult, but of the columns used (9.5 ft 10% Carbowax 20M, 6 ft UC-W98, and 9.5 and 12 ft 5% XF-1150, at temperatures from 110 to 160°), the XF-1150 one proved to be the most satisfactory. The products were identified by comparison of gc and nmr data with those of authentic samples. A substantial portion of each mixture was a group of olefin addition products, which gave a gc trace identical with that obtained from the product mixture formed by the addition of chlorine to 4-*tert*-butylcyclohexene but was not otherwise identified. The small peaks for Ia-OH and Ie-OH overlapped other peaks in the gc trace but quantitative analysis was effected by silylation (Regisil). The decrease in the peak area of the gc trace at the retention time of each alcohol resulting from silylation was taken as an indication of the amount of alcohol originally present. The alcohol content measured in this way varied from 0 to 2% of the product mixture, depending upon the run. The alcohol is assumed to come from partial hydrolysis of the chloride during work-up[32] and is counted as chloride in Table II.

The area percentages obtained from the gc traces were converted to mole percentages by use of the relative response values for the chlorides, olefin, and olefin addition products. The isomeric acetates were shown to have identical responses, and the isomeric chlorides were assumed to have identical responses. In order to determine the response factor of the olefin addition products, a weighed amount of olefin containing a weighed amount of acetate was treated with chlorine in acetic acid. Since the relative molar amounts of olefin and acetate were now known, the relative gc responses could be calculated directly from the peak areas of the gc trace. In this way, the difficult process of identifying the olefin addition products was circumvented. The product distributions are summarized in Table II.

Preparation[33] and Thermolysis[23] of Chlorocarbonates (I-OCOCl).—Each alcohol, Ia-OH and Ie-OH, was esterified at −78° (Dry Ice–acetone bath) in ether solution with phosgene.[33] Addition of the alcohol solution to the phosgene solution was interrupted several times to permit resaturation of the ether solution with phosgene. The solution was stirred at −78° for 3 hr and then overnight at room temperature under a slow nitrogen flow to ensure removal of all excess phosgene and ether from the mixture, leaving crystalline product in the flask. The Ie-OCOCl product was substantially pure, nmr (CCl_4) δ 4.70 (CHOCOCl), no absorptions for Ie-OH. The Ia-OCOCl product was contaminated with unreacted Ia-OH, nmr (CCl_4) δ 5.12 (CHOCOCl) and 4.04 (CHOH), relative intensities 2:1. Both of these products were used without further purification.

Each chlorocarbonate was decomposed by refluxing a *p*-dioxane solution of it for 1.5–2 hr.[23] The mixture was then analyzed by gc (12 ft XF-1150 column at 120°). From the Ie-OCOCl mixture, the peaks for Ia-Cl and Ie-Cl were in the ratio 21:79 (a:e) and accounted for 55% of the gc trace area. Five peaks of longer retention time were not identified. From the Ia-OCOCl mixture, the peaks for Ia-Cl and Ie-Cl were in the ratio 63:37 (a:e) and accounted for 48% of the gc trace area. The alcohol Ia-OH, which contaminated the starting chlorocarbonate (33%), accounted for 27% of the gc trace area, and an unidentified peak accounted for the remaining 25%.

Preparation of 1-Methyl-4-*tert*-butylcyclohexanols.—A 1:1 mixture of IIIa-OH and IIIe-OH was obtained from the reaction of 4-*tert*-butylcyclohexanone and methylmagnesium iodide in ethyl ether solution. Separation of the isomeric alcohols on alumina[34] proved to be extremely tedious, and not well suited to obtaining large amounts of isomerically pure material. Therefore, the alcohols were esterified by refluxing with acetic anhydride and sodium acetate, and the mixture of acetates was distilled through a spinning band column. The distillation was discontinued when a solid blocked the condenser. Gc analysis showed the liquid [nmr (CCl_4) δ 0.84 (s, *tert*-butyl), 1.42 (s, 1-CH_3), and 1.92 (s, $OCOCH_3$)] and the solid [mp 47–49°; nmr (CCl_4) δ 0.85 (s, *tert*-butyl), 1.47 (s, 1-CH_3), and 1.88 (s, $OCOCH_3$)] to be the separated components of the acetate mixture. Hydrolysis of the liquid acetate[35] (IIIa-OAc) gave IIIa-OH: mp 70–71° (lit.[34,35] mp 70.5–71°); nmr ($DCCl_3$) δ 0.87 (s, *tert*-butyl), 1.20 (s, 1-CH_3). Hydrolysis of the solid acetate[35] (IIIe-OAc) gave IIIe-OH: mp 96–97.5° (lit.[34,35] mp 97.5–98°); nmr ($DCCl_3$) δ 0.87 (s, *tert*-butyl), 1.22 (s, 1-CH_3).

Chlorodehydroxylation[36] of 1-Methyl-4-*tert*-butylcyclohexanols.—Hydrogen chloride gas was passed over 1.0 g of IIIe-OH until all of the alcohol had liquefied. The water layer was removed with a pipet, excess hydrogen chloride was removed at reduced pressure, and the mixture was flushed with nitrogen. Gc analysis (12 ft XF-1150 column at 110°) of the residue showed peaks at 3.4 and 4.7 min in a ratio of 82:18. No alcohol was present. Similar treatment of IIIa-OH gave the 3.4- and 4.7-min peaks in a ratio of 78:22, and a mixture of the alcohols gave the peaks in a ratio of 82:18.

Anal. Calcd for $C_{11}H_{21}Cl$: C, 70.0; H, 11.2. Found: C, 70.4; H, 11.6.

The two chlorides were separated on a Perkin-Elmer F21 preparative gas chromatograph equipped with a 10 ft × 0.25 in. 5% Carbowax 20M column at 80°. The 100-MHz nmr spectra of the separated chlorides (≥90% isomerically pure) were examined in order to determine the line width of the absorption of the 1-methyl group, and from that the configuration of the isomer.[27] For each stereoisomer, four scans were made with at least three different rf field values[37] at a sweep width of 50 Hz. The samples were dissolved in $CDCl_3$, benzene was used for the external lock, and tetramethylsilane was added as an internal standard. The difference in line width at half height of the signals for the 1-methyl group and tetramethylsilane, ΔW_H, was calculated. The chloride comprising about 80% of the product mixture was found to have an average ΔW_H value of 0.19 ± 0.03 cps, which indicates an equatorial methyl group.[27] The chloride present as about 20% of the product mixture had an average ΔW_H value of 0.66 ± 0.10 cps, which indicates an axial methyl group[27] having long-range coupling with the axial protons of the adjacent methylene groups. The lower precision in the case of the axial methyl resulted from the shape of the methyl absorption, which made the choice of the base line less obvious than in the case of the equatorial methyl.

Hydrogen Chloride Addition to IV.—Olefin IV was prepared by the dehydration of III with phosphorus oxychloride in pyridine solution[38] and was purified by distillation through a spinning band column: bp 75° (11 mm); nmr (CCl_4) δ 0.86 (s, *tert*-butyl), 1.6 (n m, $CH_3C{=}C$), 5.33 (m, $HC{=}C$). Hydrogen chloride gas was bubbled into a solution of IV (0.5 ml) in methylene chloride (1.0 ml) during 40 min, and the system was then flushed with nitrogen to remove excess hydrogen chloride. Gc analysis (6 ft

(32) Kwart and coworkers[16a] traced the 2-phenyl-2-butanol in the product mixture from the chlorinolysis of 2-phenyl-1-methylpropyl 2,4-dinitrobenzenesulfenate to the hydrolysis of the corresponding chloride.

(33) K. L. Oliver and W. G. Young, *J. Amer. Chem. Soc.*, **81**, 5811 (1959).

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(35) C. H. DePuy and R. W. King, *J. Amer. Chem. Soc.*, **83**, 2743 (1961).

(36) (a) H. C. Brown, R. S. Fletcher, and R. B. Johannesan, *ibid.*, **73**, 212 (1951); (b) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952).

(37) L. M. Jackson and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 314.

(38) B. Cross and G. H. Whitham, *J. Chem. Soc.*, 3892 (1960).

Carbowax 20M column at 110°) of the product mixture showed 65% IIIa-Cl and 35% IIIe-Cl. In a second experiment, the relative amounts of the two chlorides were 64% IIIa-Cl and 36% IIIe-Cl.

Hydrogen Chloride Addition to V.—Olefin V was prepared by the reaction of 4-*tert*-butylcyclohexanone with methylene iodide and magnesium turnings in ethyl ether solution.[39] Distillation of the product mixture through a spinning-band column gave >99% pure V,[39] bp 78° (18 mm), nmr (CCl_4) δ 4.52 (m, 2, C=CH_2). Hydrochlorination and product analysis were carried out in the same manner as for addition to IV. In two experiments, the IIIa-Cl:IIIe-Cl isomer ratios were 70:30 and 69:31.

Registry No.—*cis*-I (X = CO_2H), 943-28-2; *trans*-I (X = CO_2H), 943-29-3; *cis*-I (X = OSDNP), 37816-62-9; *trans*-I (X = OSDNP), 37816-63-0; *cis*-I (X = OCOCl), 15595-62-7; *trans*-I (X = OCOCl), 15595-61-6; *cis*-I (X = OH), 937-05-3; *trans*-I (X = OH), 937-06-4; *cis*-I (X = OAc), 10411-92-4; *trans*-I (X = OAc), 1900-69-2; *cis*-I (X = Cl), 13131-74-3; *trans*-I (X = Cl), 13145-48-7; *cis*-II (X = OAc), 20298-72-0; *trans*-II (X = OAc), 20298-71-9; *cis*-III (X = OAc), 15807-53-1; *trans*-III (X = OAc), 15807-52-0; *cis*-III (X = OH), 16980-55-5; *trans*-III (X = OH), 16980-56-6; *cis*-III (X = Cl), 25276-09-9; *trans*-III (X = Cl), 25276-10-2; IV, 3419-74-7; V, 13294-73-0; 4-*tert*-butylbenzoic acid, 98-73-7; 4-*tert*-butyl-1-cyclohexene, 2228-98-0; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7; 4-*tert*-butylcyclohexanone, 98-53-3.

Acknowledgment.—We gratefully acknowledge the exchange of data and correspondence with Professor Harold Kwart and Mr. John Boghosian, University of Delaware, about the reactions of Ia-OSAr and Ie-OSAr before publication.

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α-Fluoro-3,3,5,5-Tetrasubstituted Cyclohexanones. I. Synthesis and Conformational Analysis[1]

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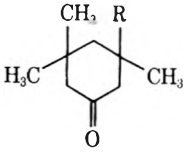
A series of new α-fluoro- and α,α-difluoro-3,3,5,5-tetrasubstituted cyclohexanones has been synthesized by the reaction of perchloryl fluoride with the α-hydroxymethylene derivatives of the following tetrasubstituted cyclohexanones: 3,3,5,5-tetramethylcyclohexanone (**1a**), 3-phenyl-3,5,5-trimethylcyclohexanone (**1b**), and 3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (**1c**). The monofluoro derivative of **1a**, the six possible mono- and difluoro derivatives of **1b**, and the three fluoroketones formed by substitution at C-6 of **1c** have been prepared and characterized. The axial or equatorial nature of the fluorine substituent has been studied as a function of solvent polarity by dipole moment measurements, infrared spectroscopy, and proton and fluorine nmr spectra. All of the results are consistent with the generalization that the fluorine of α-halocyclohexanones has a much greater preference to be equatorial in polar solvents than in nonpolar solvents. Anomalously high-field methyl resonances in the proton nmr spectra of the aryl-substituted fluoroketones furnish a sensitive indicator of the conformational equilibrium, and these lead to the conclusion that a 1,3-diaxial methyl–phenyl interaction is favored over a 1,3-diaxial dimethyl interaction by approximately 0.9 kcal/mol. The chemical shifts of the ring protons are consistent with chair conformations.

Recent work in this laboratory has been concerned with the nmr spectra and conformational analysis of highly substituted cyclohexanones and their derivatives. In these investigations[4-6] particular attention has been given to 3,3,5,5-tetrasubstituted cyclohexanones (*e.g.*, **1**), since, if these molecules are to exist in



1a, R = methyl
b, R = phenyl
c, R = 1-naphthyl

chair (or at least chairlike) conformations, a severe steric interaction between the axial substituents at C-3 and C-5 is inevitable.

The proton nmr spectrum of 3,3,5,5-tetramethylcyclohexanone (**1a**) consists of three peaks which correspond to the methyl protons, the γ-methylene protons, and the α-methylene protons. This chemical equivalence is certainly due to a rapid interconversion between conformers. Although the magnitude of a 1,3-diaxial dimethyl interaction has been shown[7] to be approximately 3.7 kcal/mol, a calculation[8] of the conformational enthalpies of **1a** by the Westheimer method indicates that the chair conformer is favored over the most stable boat form by 3.8 kcal/mol. The 2-bromo and 2,6-dibromo derivatives of **1a** have been extensively studied.[9-14] Owing to the 1,3-diaxial interaction in these compounds, Ourisson, *et al.*,[9,10] have postulated the "reflex effect" by which the cis axial methyl groups are bent outward, causing the α carbons to be pushed together. In a study[11] of the crystal structures of 2-bromo- and *cis*-2,6-dibromo-3,3,5,5-tetramethylcyclo-

(1) Taken in part from the Ph.D. dissertation submitted by M. M. Chrysam III to the Department of Chemistry, Texas A & M University, 1970; this work was initiated at the Chemistry Department of the Illinois Institute of Technology, Chicago, Ill.

(2) To whom correspondence should be addressed.

(3) National Science Foundation Graduate Fellow, 1966–1970.

(4) B. L. Shapiro, M. J. Gattuso, N. F. Hepfinger, R. L. Shone, and W. L. White, *Tetrahedron Lett.*, 219 (1971).

(5) B. L. Shapiro, M. J. Gattuso, and G. R. Sullivan, *ibid.*, 223 (1971).

(6) M. J. Gattuso, Ph.D. Dissertation, Texas A & M University, 1970.

(7) N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **83**, 2145 (1961).

(8) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **91**, 337 (1969).

(9) C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1524 (1958).

(10) B. Waegell and G. Ourisson, *ibid.*, 496 (1963).

(11) L. C. G. Goaman and D. F. Grant, *Tetrahedron*, **19**, 1531 (1963).

(12) M. Anteunis, N. Shamp, and H. De Pooter, *Bull. Soc. Chim. Belg.*, **76**, 541 (1967).

(13) C. W. Jefford and B. Waegell, *ibid.*, **79**, 427 (1970).

(14) M. Anteunis and N. Shamp, *ibid.*, **79**, 437 (1970).

hexanone by X-ray analysis, the cis diaxial methyl carbon atoms were found to be separated by 3.4 Å (the distance between 3,5-diaxial substituents in an ideal cyclohexanone ring), and the ring angles were found to deviate markedly from the values in cyclohexanone itself, with the C_2–C_1–C_6 angle decreasing to 108° and the C_3–C_4–C_5 angle increasing to 121° for the monobromo derivative. The proton nmr spectra of 2-bromo- and 2-chloro-3,3,5,5-tetramethylcyclohexanone have been interpreted in terms of chairlike conformations.[12-14]

A detailed study[4,6] of 3-aryl-3,5,5-trimethylcyclohexanones (*e.g.*, **1b** and **1c**) by nmr spectroscopy demonstrated that these molecules exist in chairlike conformations and that the conformer having an axial aryl group is heavily favored, contrary to previous conclusions.[15,16] The most interesting and informative aspect of the proton nmr spectra of these compounds is the occurrence of a very high-field resonance for one of the methyl groups at C-5 (δ 0.15–0.4 ppm). These high-field shifts are considered to arise from the C-5 methyl group which is cis to an axial aryl substituent, since in this conformation the methyl protons spend a considerable portion of time in the shielding region of the aromatic ring. The equatorial C-5 methyl shift is quite normal (δ 1.0), while the C-3 methyl protons are deshielded (δ 1.3 to 1.8) because they lie near the edge of the aromatic substituent. The high-field methyl resonance appears only in the spectra of 1,1,3,3-tetrasubstituted cyclohexanoid systems having at least one aryl substituent, and it is not dependent on the presence of an sp^2-hybridized carbon in the ring.[4,6] Although this study established that one conformer is predominant, a reliable estimate of the amount by which a 1,3-diaxial aryl–methyl interaction is favored over the alternative 1,3-diaxial dimethyl interaction was not obtained.

We therefore felt that these systems could be made more amenable to study by the addition of a substituent which could provide a "handle" into the molecular conformation, *i.e.*, a means by which the conformational equilibrium could be altered in a known way. The conformations of mobile α-haloketones in solution have been shown to be dependent on the polarity of the solvent, since a solvent of high dielectric constant tends to stabilize the conformation having the higher dipole moment, *i.e.*, that with carbon–oxygen and carbon–halogen dipoles coplanar, relative to a solvent of low dielectric constant. For this reason α-haloketones have been the subject of considerable conformational study by numerous physical methods including dipole moments, optical rotatory dispersion, and nmr, infrared, and ultraviolet spectroscopy.[17]

The α-fluoro derivatives of ketones **1** are particularly appropriate choices for the present study. Since the size of the fluorine atom approximates that of the hydrogen atom more closely than that of the other halogens, the conformations of the fluoroketones are not expected to differ greatly from those of the parent ketones. Also, the presence of fluorine in the molecule increases the suitability for study by nmr spectroscopy, since measurement of fluorine chemical shifts which are very sensitive to stereochemical environment of the fluorine nucleus and the presence of ^{19}F–H and ^{13}C–^{19}F couplings in the proton and carbon-13 nmr spectra give useful aids in spectral interpretation and chemical shift assignments. In addition, these α-fluoro-3,3,5,5-tetrasubstituted cyclohexanones provide excellent substrates for the study of the geometric dependence of long-range H–H and H–F coupling constants, since the ring proton resonances are usually well separated and since there are no vicinal H–H couplings. Regrettably, in many previous nmr studies of cyclohexanoid systems such as 2-fluorocyclohexanone,[18] most of the long-range couplings and many of the ring proton chemical shifts were not reported, being obscured by the complexity of the spectra.

This paper, then, presents the details of the synthesis of the α-fluoro derivatives of **1**, their identification, the conformational conclusions which can be made in light of dipole moment measurements, and infrared and nmr spectra, all determined as a function of solvent polarity. Although the proton and fluorine nmr spectral parameters, directly related to stereochemical conclusions, are presented here, the complete tabulation of proton, fluorine, and carbon-13 parameters, together with a full discussion of the interpretation and significance of the spectral data, will be given elsewhere.[19]

Synthetic.—The α-fluoroketones were synthesized from the intermediate α-hydroxymethylene ketones by treating the sodium salt with perchloryl fluoride, using the method of Kende,[20] followed by alkaline hydrolysis to ensure cleavage of the α-formyl group.[21] Attempts to prepare 2-fluoro-3,3,5,5-tetramethylcyclohexanone from the corresponding 2-bromoketone by fluoride ion exchange failed,[22] and it was found that perchloryl fluoride does not react with the pyrrolidylenamine of **1a**.[23]

When 2-hydroxymethylene-3,3,5,5-tetramethylcyclohexanone was fluorinated, only 2-fluoro-3,3,5,5-tetramethylcyclohexanone (hereafter, TMF[24]) was obtained; however, in addition to the two isomeric monofluoroketones, a small amount of the corresponding α,α-difluoroketone forms upon fluorinating 2- and 6-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone and 6-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone. Since the 2-hydroxymethylene derivative of **1c** was formed in very low yield (*ca.* 2%), this compound was not fluorinated.

The syntheses of the α-fluoro derivatives of **1b** are illustrated in Chart I. Isomers were separated by means of fractional crystallization and chromatography on silica gel. The isomers with the fluorine predom-

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(16) M. Balasubramanian and A. D'Souza, *ibid.*, **25**, 2973 (1969).
(17) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 460–469.
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(20) A. S. Kende, *Tetrahedron Lett.*, 13 (1959).
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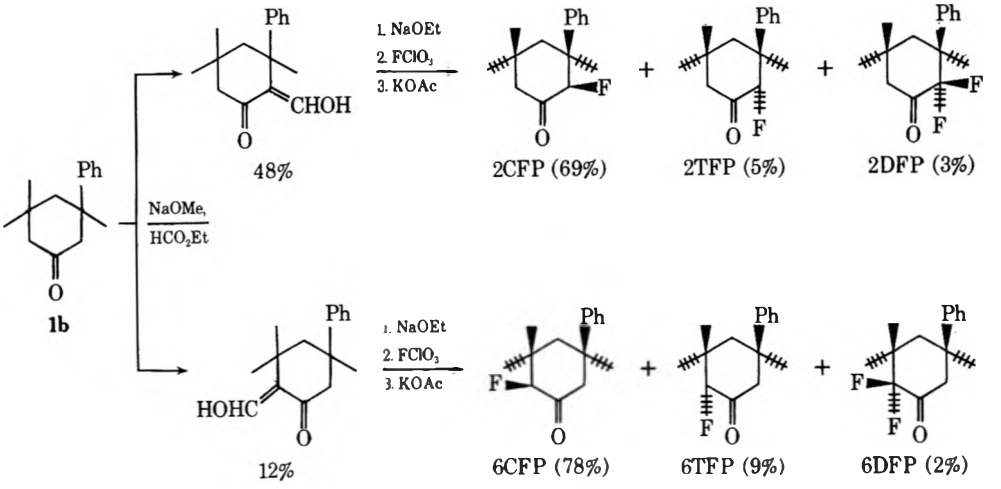
(22) This work; see Experimental Section.
(23) B. L. Shapiro and W. A. Thomas, unpublished results.
(24) The aryl-substituted fluoroketones are named according to whether the α fluorine is at C-2 or C-6 and cis or trans to the aryl group, always taken to be at C-3. In order to ensure clarity and brevity, and to avoid constant referrals to Roman numerals, the following abbreviations are used for the fluoroketones discussed in this work: 2-fluoro-3,3,5,5-tetramethylcyclohexanone, TMF; *cis*-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 6CFP; *trans*-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 6TFP; 6,6-difluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 6DFP; *cis*-2-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 2CFP; *trans*-2-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 2TFP; 2,2-difluoro-3-phenyl-3,5,5-trimethylcyclohexanone, 2DFP; *cis*-6-fluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 6CFN; *trans*-6-fluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 6TFN; 6,6-difluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 6CFN.

CHART I

PREPARATION AND YIELDS OF α-FLUORO-3-PHENYL-3,5,5-TRIMETHYLCYCLOHEXANONES



inantly equatorial, *viz.*, 6CFP and 2CFP, are shown to be formed in much greater yield by dipole moment measurements (*vide infra*), in agreement with the results of earlier work.[21,25]

Several deuterated compounds were also prepared for use in spectroscopic studies. Base-catalyzed deuterium exchange was used to prepare 2,2,6,6-tetradeuterio-3,3,5,5-tetramethylcyclohexanone, 2-fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone, and 6-fluoro-2,2,6-trideuterio-3-phenyl-3,5,5-trimethylcyclohexanone. Finally, a mixture of four isomers of α-fluoro-4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone (2) was prepared by the sequence of reactions shown in Chart II.

Identification of Compounds.—Because of ambiguity in the proton nmr spectral data of the intermediate α-hydroxymethylene ketones,[19] identification of these compounds was accomplished by means of their fluorination products rather than vice versa. In the proton nmr spectra of the isomers designated 2CFP, 2TFP, and 2DFP, only the C-3 methyl (low field) is coupled to fluorine, indicating that these isomers are indeed derived from 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone. Similarly, the proton nmr spectra of 6CFP, 6TFP, 6DFP, 6CFN, 6TFN, and 6DFN reveal that fluorine is coupled only to one or both of the *C-5* methyl groups (the "normal" and the "high-field" methyl resonances), indicating that these fluoroketones are derived from the corresponding 6 hydroxymethylene ketones. Similarly, in the carbon-13 spectrum of the 2 isomers, the fluorine is coupled to C-3, the tertiary carbon bearing the aryl substituent, ($^2J_{^{13}C-^{19}F}$ = 18 Hz) but not to C-5, while in the 6 isomers the fluorine is coupled to C-5, but not to C-3.

The *cis*- and *trans*-monofluoroketones can be distinguished by means of their dipole moments and proton nmr spectra. As an example, the highest field methyl resonances of the compounds designated 6CFP and 6TFP in dilute solution in carbon tetrachloride occur at δ 0.29 and 0.43, respectively, which indicates that in nonpolar solvents the phenyl group is predominantly axial in both of these isomers. The dipole moments of 6CFP (4.09 D) and 6TFP (3.01 D) in cyclohexane are very similar to the observed dipole moments of *cis*- and *trans*-2-fluoro-4-*tert*-butylcyclohexanone (4.35 and 2.95 D).[25] Since the latter compounds exist exclusively in those conformations with equatorial and axial fluorine, respectively, the fluorine of 6CFP is predominantly equatorial and that of 6TFP is predominantly axial. Thus, if chair conformations are assumed, the isomer formed in greater yield, designated 6CFP, must be the cis isomer and 6TFP must be the trans isomer. From previous studies of 3,3,5,5-tetrasubstituted cyclohexanones and several α-bromo derivatives mentioned in the introduction, it should be expected that these fluoroketones exist in chair-like conformations, and there is evidence from the proton nmr spectra that this is indeed the case (*vide infra*).

Dipole Moments.—Dipole moments of the monofluoroketones, except for 2TFP, which was not obtained pure, were determined by the Guggenheim method in both cyclohexane and benzene. The results are given in Table I.

The greater dipole moments found in benzene than in cyclohexane indicate that these fluoroketones are conformationally mobile.[26] By comparing these dipole moments with those of *cis*- and *trans*-2-fluoro-4-*tert*-butylcyclohexanone (*vide supra*), is is obvious that, in cyclohexane solution, the fluorine is predominantly equatorial in 6CFP, 6CFN, and 2CFP and predominantly axial in 6TFP and 6TFN, while there appears to be a substantial amount of both conformers of TMF present at equilibrium.

The dependence of the observed dipole moments on the position of the conformational equilibria is given by the relation

$$\mu_{obsd}^2 = N_e\mu_e^2 + N_a\mu_a^2$$

(25) N. L. Allinger and H. M. Blatter, *J. Org. Chem.*, **27**, 1523 (1962).

(26) Although the dielectric constant of benzene (ε 2.28) is not appreciably greater than that of cyclohexane (ε 2.03), the effect of benzene on α-halocyclohexanones is greater than its bulk dielectric constant would suggest. For example, Allinger and Blatter[25] found that the dipole moments of 2-fluorocyclohexanone in heptane and benzene are 3.76 and 4.09 D, respectively, while the corresponding dipole moments of the rigid molecule, *cis*-2-fluoro-4-*tert*-butylcyclohexanone, are 4.37 and 4.35 D. The reason for this effect on mobile 2-halocyclohexanones is quite possibly the stability of the "collision complex"[27] between the considerably polarizable benzene and the equatorial conformer relative to that between benzene and the axial conformer.

(27) For an excellent discussion of benzene collision complexes, see J. Ronayne and D. H. Williams, "Annual Review of NMR Spectroscopy," Vol. 2, E. F. Mooney, Ed., Academic Press, New York, N. Y., 1969, pp 97–106.

Chart II

Preparation of α-Fluoro-4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone

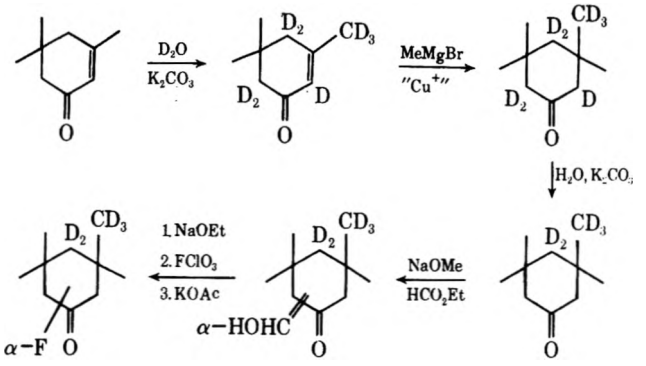


Table I

Experimental Dipole Moments of α-Fluoro-3,3,5,5-tetrasubstituted Cyclohexanones

Compd	Dipole moments[a] Cyclohexane	Benzene	Δ(μ²)[b]
TMF	3.62 ± 0.01	3.93 ± 0.01	2.3
6CFP	4.09 ± 0.01	4.18 ± 0.01	0.8
6TFP	3.01 ± 0.01	3.31 ± 0.01	1.9
2CFP	3.94 ± 0.01	4.08 ± 0.01	1.2
6CFN	4.04 ± 0.02	4.12 ± 0.02	0.7
6TFN	3.04 ± 0.01	3.27 ± 0.02	1.5

[a] In Debye units, at 20°. [b] Δ(μ²) is the dipole moment in benzene squared minus the dipole moment in cyclohexane squared.

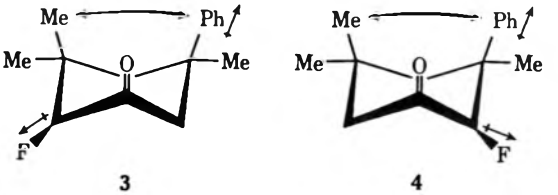
where N is the fraction, μ is the dipole moment, and e and a refer to the conformers having equatorial and axial fluorine, respectively. Of course, N_e and N_a could be calculated exactly if the dipole moments of the pure conformers were known, but no attempt was made to calculate these values because the molecular dipole moments are a sensitive function of inductive effects and geometry. So many assumptions regarding induced dipole effects and bond angles would be necessary as to make the results of any such calculation unreliable.

However, using the above equation, it can easily be shown that

$$N_B - N_C = \Delta(\mu^2)/(\mu_e^2 - \mu_a^2)$$

where N_B and N_C are the fractions of the conformer with equatorial fluorine in benzene and cyclohexane, respectively, $\Delta(\mu^2)$ is the difference of the squares of the experimentally observed dipole moments in benzene and cyclohexane, and μ_e and μ_a are the dipole moments of the axial and equatorial conformers. If the quantity $(\mu_e^2 - \mu_a^2)$ can be considered constant throughout this series (probably only approximately true owing to the small dipole moment of the aryl substituents), the change in mole fraction of the equatorial conformer on going from cyclohexane to benzene solution is proportional to $\Delta(\mu^2)$. In short, the value of $\Delta(\mu^2)$ is indicative of the "conformational purity" of the compound: the lower the $\Delta(\mu^2)$ value, the greater the energy difference between the conformers [*cf.* *trans*-2-fluoro-4-*tert*-butylcyclohexanone,[26] for which the value of $\Delta(\mu^2)$ is 0.0 within experimental error]. Thus, from the values in Table I, it can be said that for a given solvent the equilibrium amount of the conformer with equatorial fluorine increases in the series TMF < 2CFP < 6CFP < 6CFN, and decreases in the series TMF > 6TFP > 6TFN.

The dipole moment of the conformer with fluorine equatorial is expected to be greater in the case of 6CFP than for 2CFP, since in the 6 isomer the C–F bond dipole is slightly opposed to that of the phenyl group (see **3**), while in the 2 isomer these dipoles are



3 **4**

much more nearly coplanar (**4**), assuming that the 3,5-diaxial substituents are twisted outward (*vide supra*). However, since 2CFP has the lower dipole moment of the two isomers, it appears that the conformer having an axial fluorine is present to a greater extent than in 6CFP. The $\Delta(\mu^2)$ values support this conclusion.

Infrared Spectra.—It is well known that substitution of an α-halogen atom affects the carbonyl stretching frequency to an extent which depends on the relative orientation of the two dipoles.[17] For six-membered rings, axial and equatorial fluorine atoms have been reported[25,28-31] to cause C=O stretching frequency increases of 12–20 and 22–29 cm^{-1}, respectively.

Although the carbonyl bands of the parent ketones (**1**) are very broad, the C=O absorptions of the fluoroketones are sharp enough to show the presence of two conformations in many instances. As the dielectric constant of the solvent increases, the low-frequency band (axial F) is seen to disappear. The spectrum of TMF-d_3 also shows two absorptions of the same relative heights as TMF; therefore it is probable that Fermi resonance, shown[32] to cause doubling of the carbonyl resonance of some α-haloketones, is not involved in this case.

The carbonyl frequencies of the fluoroketones in CCl_4 solutions are listed in Table II. The high-frequency band (equatorial fluorine) is stronger for TMF, 6CFP, 2CFP, and 6CFN, whereas the low-frequency absorption is predominant for 6TFP and 6TFN with, finally, the two carbonyl resonances of 2TFP being comparable. The spectrum of 6CFN indicates that it is the most "conformationally pure" of the monofluoroketones, while 2CFP and 2TFP are more ambiguous in the sense that they are less "conformationally pure" than the corresponding 6 isomers. The $\Delta\nu$ values throughout the table are remarkably consistent and additive, the $\Delta\nu$ values of the difluoroketones being approximately equal to the sum of the values of the corresponding monofluoroketones. The use of the carbonyl absorption for anything more than a very crude quantitative estimate of conformational equilibrium is prohibited by the large amount of overlap, the fact that the extinction coefficients are unknown, and the possibility of hidden overtones of other resonances.

(28) J. Cantacuzene and D. Richard, *Bull. Soc. Chim. Fr.*, 2950 (1968).
(29) L. Mion, A. Casadevall, and E. Casadevall, *ibid.*, 2950 (1968).
(30) L. Mion, A. Casadevall, and E. Casadevall, *ibid.*, 3199 (1969).
(31) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).
(32) J. P. Bervelt, R. Ottinger, P. A. Peters, J. Reisse, and G. Chiurodoglu, *Can. J. Chem.*, **45**, 81 (1967).

TABLE II

CARBONYL ABSORPTION FREQUENCIES OF α-FLUORO-3,3,5,5-TETRASUBSTITUTED CYCLOHEXANONES IN CCl_4

Compd	$W_{1/2}$,[a] Hz	ν_{max}, cm^{-1}	$\Delta\nu_{max}$,[b] cm^{-1}	Shoulder,[c] cm^{-1}	$\Delta\nu_S$,[b] cm^{-1}
Ia	14	1718			
TMF	19	1743	25	1732 (s)	14
Ia-d_4[d]	15	1714			
TMF-d_3[e]	22	1740	26	1726 (s)	12
Ib	16	1721			
6CFP	12	1744	23	1734 (vw)	13
6TFP	17	1737	16	1745	24
6DFP	10	1757	36		
2CFP	13	1744	23	1734 (w)	13
2TFP	23	1738	17	1743 (vs)	22
2DFP	10	1757	36		
Ic	16	1720			
6CFN	13	1744	24	None	
6TFN	19	1735	15	1744	24
6DFN	10	1758	38		

[a] Approximate width at half-height; includes shoulder except where shoulder is weak. [b] $\Delta\nu = \nu_{C=O}$(fluoroketone) − $\nu_{C=O}$(ketone). [c] s = strong, w = weak, v = very. [d] 2,2,6,6-Tetradeuterio-3,3,5,5-tetramethylcyclohexanone. [e] 2-Fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone.

The C=O absorptions of the fluoroketones in acetonitrile (Table III) appear to indicate that only one conformer is present to any large extent; however, the bands are much broader for the trans fluoroketones than for the corresponding cis isomers, the width increasing in the order 2TFP < 6TFP < 6TFN. In particular, 6TFN exhibits a broad, fairly flat maximum possibly caused by a large percentage of the axial fluorine conformer. If this be the case, the shifts due to axial and equatorial fluorine are closer in magnitude in acetonitrile than they are in carbon tetrachloride.

TABLE III

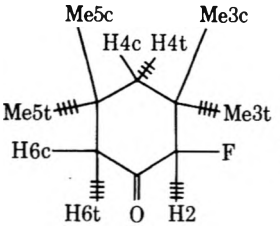
CARBONYL ABSORPTION FREQUENCIES OF α-FLUORO-3,3,5,5-TETRASUBSTITUTED CYCLOHEXANONES IN CH_3CN

Compd	$W_{1/2}$,[a] Hz	ν_{max}, cm^{-1}	$\Delta\nu_{max}$,[b] cm^{-1}
Ia	15	1712	
TMF	12	1736	24
Ia-d_4[c]	(26)[d]	(1705)[d]	
TMF-d_3[e]	12	1734	(29)
Ib	22	1715	
6CFP	10	1738	23
6TFP	15	1738	23
6DFP	9	1754	39
2CFP	11	1738	23
2TFP	13	1738	23
2DFP	8	1754	39
Ic	15	1715	
6CFN	10	1737	22
6TFN	16	1737	22
6DFN	9	1753	38

[a] Approximate width at half-height. [b] $\Delta\nu = \nu_{C=O}$(fluoroketone) − $\nu_{C=O}$(ketone). [c] 2,2,6,6-Tetradeuterio-3,3,5,5-tetramethylcyclohexanone. [d] Partially obscured by solvent. [e] 2-fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone.

The C–F stretching vibrations were not extensively studied in this work. However, in the spectrum of TMF in carbon tetrachloride the vibrations at 1034 and 1083 cm^{-1} are tentatively assigned to the axial and equatorial C–F bonds, respectively. The presence of a large number of bands in the 1000–1100-cm^{-1} region of the ir spectra of the α-fluoro derivatives of the aryl-substituted cyclohexanones precluded assignments of the C–F stretching vibrations.

Nmr Spectra. —The nomenclature used in discussing spectral data is shown in **5** and **6**. The protons of



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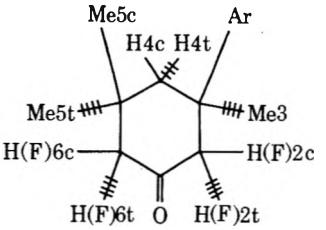

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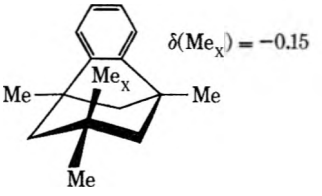
TMF are designated cis or trans with respect to the C-2 fluorine, while substituents in the other mono- and difluoroketones are labeled according to whether they are cis or trans to the aryl substituent at C-3.

Methyl Proton Chemical Shifts.—The effect of an aryl substituent on methyl resonances has already been discussed (*vide supra*). Further support for the interpretation that an axial aryl substituent causes the anomalous high-field resonance is demonstrated by the observation[5] of the high-field methyl signal of the bicyclic hydrocarbon **7**, locked in the conformation



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shown. It may be noted that the high-field resonance of 6CFP, for which free rotation of the phenyl group occurs,[33] appears at δ 0.29, more than halfway between the resonance of **7** and that of a normal methyl resonance at $\delta \approx 1$.

The methyl chemical shifts of the aryl-substituted fluoroketones are given in Table IV. An examination of the chemical shifts in carbon tetrachloride reveals that all of these compounds exist predominantly in the conformation with an axial aryl substituent, since in each case Me5c appears at high field ($\delta \approx 0.5 \pm 0.1$). The more polar solvent acetonitrile-d_3 tends to minimize dipolar repulsion, stabilizing the conformation containing equatorial fluorine. Assuming an equilibrium between chairlike conformations, this stabilization should increase the population of the conformation with an axial aryl substituent in those compounds in which the fluorine is cis to the aromatic ring, leading to positive Δδ(Me5c) values, and vice versa for those compounds with trans. These predicted trends are observed experimentally. Even the small Δδ(Me5c) value of 6CFP being due to conformational change is fully supported by and consistent with the observed coupling constant variations discussed below.

It is necessary to evaluate the effect of fluorine on the chemical shift before the high-field methyl shifts can be

(33) This assumption is based on the observation that the aryl proton absorptions of 6CFP appear to be those of a not-uncommon type of tightly coupled AA'BB'C system,[34] rather than an ABCDE system which would be the case if free rotation were not possible.

(34) S. M. Castellano, private communication.

Table IV

The Methyl Chemical Shifts of 3-Aryl-3,5,5-trimethylcyclohexanones (1b and 1c) and the Derived Mono- and Difluorocyclohexanones

Compd	Solvent[a]	δ(Me3)	δ(Me5t)	δ(Me5c)	δΔ(Me5c)[b]
Ib[c]	CCl_4	1.333	1.011	0.353	
					0.04
Ib[c]	CD_3CN	1.316	1.005	0.317	
6CFP	CCl_4	1.342	1.099	0.291	
					0.11
6CFP	CD_3CN	1.306	1.088	0.177	
6TFP	CCl_4	1.360	1.051	0.434	
					−0.44
6TFP	CD_3CN	1.329	1.065	0.871	
2CFP	CCl_4	1.485	1.025	0.416	
					0.16
2CFP	CD_3CN	1.500	0.988	0.256	
2TFP	CCl_4	1.378	1.091	0.628	
					−0.33
2TFP	CD_3CN	1.379	1.106	0.961	
6DFP	CCl_4	1.372	1.090	0.394	
					0.05
6DFP	CD_3CN	1.348	1.093	0.342	
2DFP	CCl_4	1.474	1.057	0.427	
					−0.09
2DFP	CD_3CN	1.405	1.062	0.515	
Ic[c]	CCl_4	1.724	0.995	0.138	
					0.06
Ic[c]	CD_3CN	1.718	1.010	0.082	
6CFN	CCl_4	1.736	1.074	0.072	
					0.13
6CFN	CD_3CN	1.687	1.034	−0.064	
6TFN	CCl_4	1.757	1.044	0.256	
					−0.53
6TFN	CD_3CN	1.688	1.137	0.788	
6DFN	CCl_4	1.770	1.070	0.160	
					0.05
6DFN	CD_3CN	1.730	1.050	0.110	

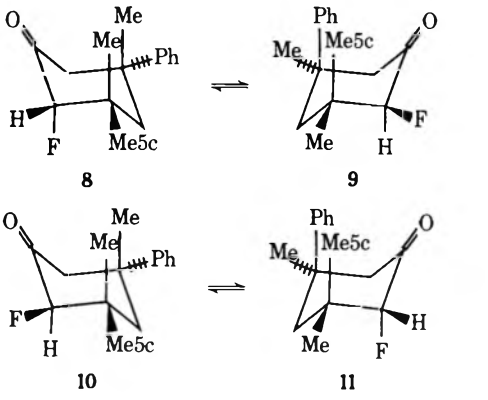
[a] Concentrations of the fluoroketones are approximately 3 mol %; concentrations of 1b and 1c are 5% (w/w). [b] Δ(Me5c) is the chemical shift of Me5c in CCl_4 minus the chemical shift of Me5c in CD_3CN. [c] From ref 6.

employed to give a quantitative estimate of the percentage of each conformer present at equilibrium. In TMF, the chemical shift differences between Me3c and Me5c (δ 0.97 and 1.02) and Me3t and Me5t (δ 1.12 and 1.04) in acetonitrile should be indicative of the effect of an equatorial fluorine on the chemical shift of a vicinal methyl group, resulting in an upfield shift of 0.05 ppm for an axial methyl group and a downfield shift of 0.08 ppm for an equatorial methyl group. The effect of an equatorial fluorine on the chemical shift of a vicinal equatorial methyl group is demonstrated by a comparison of the Me5c resonance of 2CFP (δ 0.99) and 6CFP (δ 1.09), while the effect of the additional fluorine (axial) in 6DFP (δ 1.09) appears to be slight.[35] In a study of a series of 11 5α-fluoro steroids, Jacquesy and Levisalles[36] found that the presence of an axial fluorine at C-5 causes the vicinal axial C-19 methyl resonance to move downfield by 0.14 ± 0.03 ppm. Thus, although the effect of fluorine on methyl resonances is small in comparison with the effect of an aryl substituent, it is certainly not negligible.

In order to calculate the fractions of each conformation present in equilibrium, it is necessary to know the chemical shift of Me5c in each of the pure conformers. Although model compounds are not available, it is possible to make reasonable estimates of these chemical shifts in order to gain some insight into the conformational free energies, although values so calculated must be regarded as approximate, because of the dangers inherent in using estimated chemical shifts rather than observed limiting values (here, unavailable). For this calculation the conformational equilibria of 6CFP and 6TFP in both carbon tetrachloride and acetonitrile-d_3 are considered in Chart III. The following

Chart III

Conformational Equilibria of 6CFP and 6TFP



values were estimated for δ(Me5c) in the conformers indicated.

Conformer	δ(Me5c)
8	1.10
9	0.14
10	1.19
11	0.24

The estimate for 9 is based on an extrapolation of the low-temperature chemical-shift data for Me5c in acetone (*vide infra*). The value of 1.10 for conformer 8 seems reasonable in view of the observed chemical shifts of 3-phenyl-5,5-dimethylcyclohexanone[6] and the 3,5-methyl-substituted cyclohexanones studied by Laszlo, *et al.*[37] In the latter case the effect of axial fluorine on the equatorial methyl resonance was assumed negligible. However, for 6TFP (10 and 11), these values were modified, since the equatorial–equatorial and axial–axial relationships of the fluorine and Me5c in conformers 10 and 11 were expected to result in downfield shifts of the order of 0.1 ppm (*vide supra*). By substituting these values into the equation $\delta_{obsd} = N_1\delta_1 + N_2\delta_2$, the equilibrium constants, K, and the difference in free energy between the conformers can be calculated and the results are given in Table V.

Two primary factors influence the overall conformational preferences: (1) a conformational energy difference (ΔG_x) between the 1,3-diaxial methyl–phenyl interaction and a 1,3-diaxial dimethyl interaction, assumed to be solvent independent; and (2) a conformational energy difference between equatorial and axial fluorine, which is solvent dependent and designated as

(35) The values for CD_3CN solutions are compared since the compounds are expected to be more conformationally pure in this solvent.

(36) R. Jacquesy and J. Levisalles, *Bull. Soc. Chim. Fr.*, 1884 (1966).

(37) M. Fetizon, J. Gore, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

TABLE V

CALCULATED CONFORMATIONAL FREE ENERGIES OF 6CFP AND 6TFP IN CARBON TETRACHLORIDE AND ACETONITRILE-d_3

Compd	Solvent	Equilibrium constant[a]	Conformational free energy difference, kcal/mol
6CFP	CCl_4	5.41	−1.03
6CFP	CD_3CN	26.0	−1.98
6TFP	CCl_4	3.96	−0.83
6TFP	CD_3CN	0.55	+0.36

[a] For the equilibria as written in Chart III.

ΔG_y in CCl_4 and ΔG_z in CD_3CN. Using the values in Table V, the following equations can be written.

$$-1.03 = \Delta G_x + \Delta G_y \text{ (6CFP in } CCl_4)$$
$$-1.98 = \Delta G_x + \Delta G_z \text{ (6CFP in } CD_3CN)$$
$$-0.83 = \Delta G_x - \Delta G_y \text{ (6TFP in } CCl_4)$$
$$+0.36 = \Delta G_x - \Delta G_z \text{ (6TFP in } CD_3CN)$$

The three values which best fit[38] these four equations are $\Delta G_x = -0.87$, $\Delta G_y = -0.10$, and $\Delta G_z = -1.17$ kcal/mol. The fit is reasonably good considering the assumptions on which this calculation is based and is in good agreement with the values found by Stothers and Pan[18] for the conformational energies of 2-fluorocyclohexanone in these solvents (−0.35 and −1.17 kcal/mol, respectively). It has been observed that, for the ketone **1b**, δ(Me5c) = 0.30 in CS_2 at room temperature and δ(Me5c) = 0.08 at very low temperature.[6] Although this shift has been ascribed to a decrease in the rate of phenyl rotation at low temperature,[6] it is interesting to note that, if it is assumed that δ(Me5c) = 0.08 for the axial conformer, ΔG_x for **1b** is calculated to be −0.8 kcal/mol, in excellent agreement with the value found above.

The high-field methyl resonances of 2CFP and 2TFP are somewhat anomalous. Since the fluorine is across the ring from Me5c, there should be very little, if any, effect of fluorine on the methyl chemical shift. However, Me5c of 2CFP appears at lower field in CCl_4 than the corresponding resonance of 6CFP or even the parent ketone **1b**. Similarly, the Me5c resonance of 2TFP in CD_3CN is at lower field than that of 6TFP, even though in the latter compound an additional downfield effect due to the influence of vicinal equatorial fluorine on the equatorial methyl is expected (*vide supra*). If δ(Me5c) is assumed to be 0.08 and 1.10 in the pure conformers of 2CFP and 2TFP (*vide infra*), one obtains $\Delta G_x = -0.1$, $\Delta G_y = -0.4$, and $\Delta G_z = -0.9$. Thus it appears that the 1,3-diaxial methyl–phenyl interaction is barely favored over the 1,3-diaxial methyl–methyl interaction. The discrepancy between the free-energy values obtained for the 6 isomers and those calculated for the 2 isomers is possibly the result of an electrostatic interaction between the fluorine and the adjacent phenyl group.

Because of the difficulty in making accurate estimates for the limiting values of δ(Me5c) in the conformers 6CFN and 6TFN, the ΔG values were not calculated. However, inspection of the chemical shifts indicates that these values are probably not appreciably different from those calculated for the corresponding phenyl compounds.

(38) Each of the four possible combinations of these equations was solved for ΔG_x, ΔG_y, and ΔG_z. The best values are considered to be the averages of the four solutions obtained.

The high-field methyl resonances of the two 6,6-difluoroketones are at slightly lower field (0.03 ppm) than the resonances of the parent ketones. Therefore, since these resonances are expected to be at lower field by at least 0.10 ppm from the influence of adjacent fluorine, these difluoroketones probably exist in the conformation in which the aromatic substituent is axial to a slightly greater extent than in the ketones from which they were derived. Coupling-constant variations in the spectrum of 6DFP on going from CCl_4 to CD_3CN (given below) indicate that the upfield shift of Me5c which accompanies the solvent change is conformational in origin. Again, the high-field methyl shift of 2DFP is anomalous in the sense that it appears downfield of the corresponding resonance of **1b** in CCl_4, and also because it moves *downfield* on going to CD_3CN as the solvent. The coupling constants of 2CFP were not thoroughly investigated.

Coupling Constants.—Although it is not the purpose of this paper to discuss all of the couplings observed in these compounds, the couplings on which the assignments of the methylene proton resonances are based are worthy of note here. Four-bond coupling between protons is expected to be largest for an all-trans or "W" arrangement of sp^3-hybridized bonds, which corresponds to equatorial–equatorial coupling in cyclohexanoid systems.[39] There is also evidence that a similar geometric dependence obtains for four-bond coupling between protons and fluorine.[40]

The four-bond couplings between the protons of the α-methylene protons and the fluorine nucleus with the C-4 methylene protons of some of the monofluoroketones are given in Table VI. Trans couplings

TABLE VI

FOUR-BOND COUPLINGS OF FLUORINE AND THE α-METHYLENE PROTONS WITH THE C-4 PROTONS

		^4J, Hz			
Compd	Solvent[a]	Hα[c]–H4c	Hα[b]–H4t	F-H4c	F-H4t
TMF	CCl_4	1.76	±0.3	4.59	0
TMF	CD_3CN	2.75	0	6.66	0
6CFP	CCl_4	3.22	0	6.50	0
6CFP	CD_3CN	3.54	0	7.23	0
6TFP	CCl_4	1.8	0	0	3.00
6TFP	CD_3CN	0	1.98	0	4.65
6TFN	CD_3CN	0	2.28	0	5.15

[a] Concentrations are 2–4 mol %. [b] Hα = H6 of TMF, H2 of 6CFP, 6TFP and 6TFN.

(axial–equatorial) between these nuclei were not observed. The coupling assignments are based on the assumptions that the largest observed couplings are between equatorial nuclei and that the molecules exist in chairlike conformations. The corresponding couplings in the unlisted monofluoroketones are qualitatively consistent with those given in Table VI; however, the exact parameters were not determined.[41]

The couplings of TMF and 6CFP are observed to increase as the dielectric constant of the solvent increases, since the conformer in which the coupled nuclei are

(39) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

(40) A. B. Foster, R. Hems, L. D. Hall, and J. F. Manville, *Chem. Commun.*, 158 (1968).

(41) It was found that the observable splittings do not correspond exactly to the true coupling constants, which had to be determined by computer simulation of the spectra as *six*-spin systems.

equatorial becomes more predominant, with TMF undergoing the largest increase, as expected (*vide supra*). However the large coupling between H2c and H4c of 6TFP in carbon tetrachloride is found to diminish as the dielectric constant of the medium is gradually increased by adding acetonitrile. This decrease of $^4J_{H2c-H4c}$ is paralleled by an increase in $^4J_{H2t-H4t}$ and $^4J_{F-H4t}$ as these nuclei become equatorial. In 6DFP, the only difluoroketone whose nmr spectra were thoroughly analyzed, $^4J_{H2c-H4c}$ increases from 2.46 to 2.69 Hz and $^4J_{F6c-H4c}$ increases from 4.41 to 4.81 Hz on going from carbon tetrachloride to acetonitrile-d_3 solution.

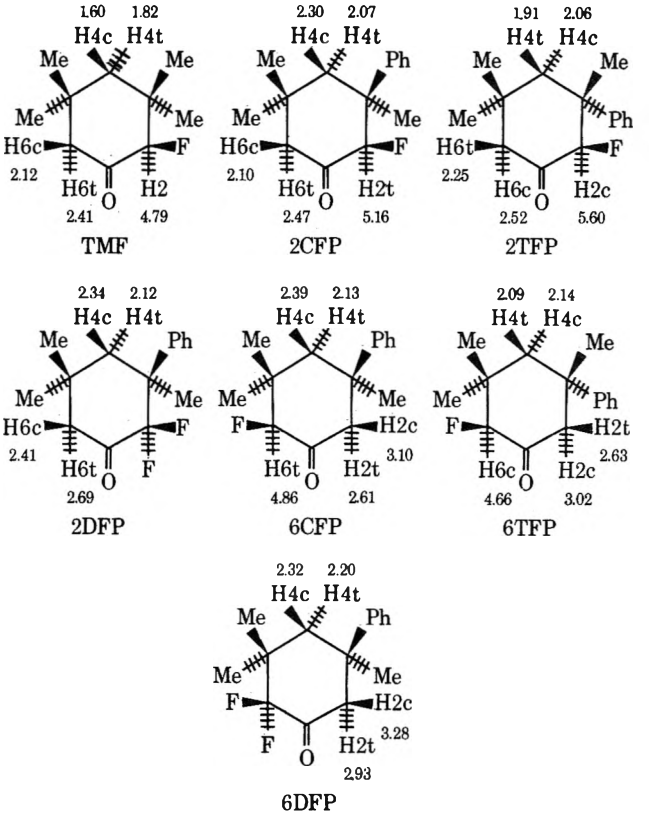
These assignments based on coupling constants are strongly supported by the fact that the observed benzene-induced solvent shifts of the α-methylene and methine protons of the monofluoroketones are in excellent agreement with predicted[27] trends if the effect of the dielectric constant of the solvent on the conformational equilibrium is taken into account.[19]

Chemical Shifts of the Ring Protons.—In order to demonstrate that these compounds exist in chair or chairlike conformations, it is necessary to show that the chemical shifts of the ring protons are consistent with the proposed geometry. In the following discussion, the chemical shifts in acetonitrile-d_3 are compared because most of the monofluoroketones exhibit a greater degree of conformational purity in this solvent than in the other solvents studied [however, 6TFP is expected to be the least "pure," with the conformer having equatorial fluorine favored by only slightly more than 2:1 (*vide supra*)]. Also, by comparing only solutions in the same solvent, solvent effects other than those which are conformational in origin can be minimized.

The chemical shifts of the ring protons of TMF and the α-fluoro-3-phenyl-3,5,5-trimethylcyclohexanones and the chair conformers which are expected, in light of the previous discussion, to predominate are illustrated in Chart IV. In this chart the fluorine of each of the monofluoroketones is equatorial, and the phenyl groups of 2DFP and 6DFP are axial. The axial methylene protons of TMF (H4t and H6t) resonate at lower field than their equatorial counterparts [as does the methine proton, which shifts to much higher field as the dielectric constant of the solvent decreases, δ(H2) 4.31 in CCl_4].

The chemical shifts of the α protons at C-6 should be little affected by the presence of an axial phenyl group and slightly deshielded by an equatorial phenyl group at C-3, since these protons are fairly remote but still in the ring plane of an equatorial C-3 aryl substituent. These trends are observed. The C-6 protons of 2CFP appear at approximately the same δ value as the corresponding protons of TMF, while the equatorial and axial protons of 2TFP are both deshielded to a small extent by the equatorial phenyl group. Also H6t of 6CFP is more axial and hence resonates slightly downfield of H2 of TMF. In the spectrum of 6TFP, H6c appears at higher field than H2 of TMF, even in the presence of the equatorial aryl substituent; however this is understandable in view of the large amount of the other conformer of 6TFP (*vide supra*). The fact that the C-6 protons of 2DFP resonate about 0.3 ppm to low field of the C-6 protons of TMF may be attributable to a combination of inductive and anisotropic effects of the additional fluorine.

Chart IV
Ring Proton Chemical Shifts of TMF and the α-Fluoro-3-phenyl-3,5,5-trimethylcyclohexanones in Acetonitrile-d_3 Solution



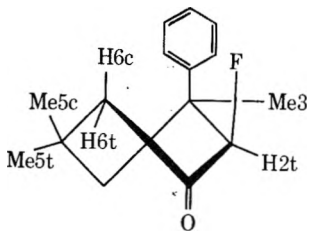
A *vicinal* phenyl group should have considerable influence on the ring-proton chemical shifts. Models indicate that, if the phenyl group is axial and facing the C-5 methyl, the equatorial C-2 proton is very close to the edge of the aromatic ring. This effect is particularly noticeable in the spectrum of 6CFP, where the H2c signal appears 1 ppm downfield of the corresponding resonance of TMF, and the axial proton is shifted downfield by 0.2 ppm. The C-2 protons of 6DFP exhibit the same trends but the shifts are slightly greater owing to the additional fluorine, as was observed for the C-6 protons of 2DFP (*vide supra*). The observation that the effect on the equatorial proton is diminished and more nearly equal to the effect on the axial proton in the trans isomers may be attributed to the fact that an equatorial aryl substituent is almost equidistant from the adjacent α protons and has greater rotational freedom, so that neither H2c nor H2t spends as much time near the edge of the aromatic ring as does the H2c proton when the phenyl group is axial.

The effect of a phenyl group on the resonances of γ protons is very similar to the effect on the adjacent α protons. In the spectra of 6DFP, 2CFP, 6DFP, and 2DFP, the axial phenyl group causes a downfield shift of *ca.* 0.7 ppm for the equatorial C-4 proton while the axial proton is deshielded by only 0.3 ppm relative to TMF. In the trans isomers the equatorial and the axial protons occur 0.3–0.5 ppm to lower field.

The same conformational conclusions are apparent from the ring proton shifts when the aryl substituent is

a 1-naphthyl group. However, when the naphthyl group is axial (6CFN and 6DFN), the H4c and H2c resonances are shifted downfield by *ca.* 1.5 and 1.1 ppm, respectively, relative to the corresponding resonances of TMF.[19] The H2c shift is close to that experienced by H2c of 6CFP, but the H4c difference is much larger, which probably indicates that the B ring of the 1-naphthyl group spends considerably more time near C-4 than C-2.

In summary, it is found that the chemical shifts of the ring protons of the aryl-substituted fluoroketones are consistent with the corresponding values of TMF if the effects of the aryl substituent are considered. These results strongly support the assumption that these compounds exist as an equilibrium mixture of chair conformations. Indeed, models indicate that, if these molecules existed in a twist-boat (flexible) conformation (*e.g.*, **12**), the aryl substituent would have a



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significant shielding influence on the chemical shift of a cis proton at C-6, which was not observed.

Effect of Temperature on Chemical Shifts.—There are at least four temperature-dependent factors which can alter the conformational equilibrium of the fluoroketones: (a) the equilibrium constant increases if ΔG is negative, and decreases if ΔG is positive, as the temperature is lowered; (b) the dielectric constant of the solvent increases as the temperature decreases, thereby stabilizing dipolar interactions in the more polar conformer; (c) solute–solute association may increase with decreasing temperature, causing an increase in the effective dielectric constant in the vicinity of the solute; and (d) increased solute–solvent association may also increase the apparent dielectric constant.

Several preliminary low-temperature proton nmr spectra were obtained in the course of this work. In acetone-d_6 6CFP, TMF, and 6TFP are all expected to exist predominantly in that conformation with fluorine equatorial. Therefore each of the factors mentioned above has the same effect on the equilibrium, *i.e.*, to increase the percentage of the conformer in which the C=O and C–F dipoles are aligned. The data in Table VII show that, as the temperature is lowered, the axial methine protons of TMF, 6CFP, and 6TFP move to lower field while the equatorial methylene protons of TMF are shifted upfield. In addition, the Me5c resonances of 6CFP and 6TFP move to higher and lower fields, respectively. All of these observations indicate that the fluorine is becoming more equatorial. The magnitudes of the shift changes of the methine proton resonances (these resonances should be directly comparable, since in each case this proton is remote from the aryl substituent) show that the conformational change of 6TFP is greater than that of TMF, which in turn is greater than that of 6CFP, as expected if the aryl substituent prefers to be axial.

TABLE VII
VARIATION OF SELECTED PROTON CHEMICAL SHIFTS WITH TEMPERATURE

Compd	Solvent[a]	Temp, °C	δ(CHF)	δ(Me5c)
TMF	$(CD_3)_2CO$	31	4.83	*b*
TMF	$(CD_3)_2CO$	−43	5.02	
TMF	$(CD_3)_2CO$	−95	5.14	
6CFP	$(CD_3)_2CO$	31	4.94	0.22
6CFP	$(CD_3)_2CO$	−43	5.08	0.15
6CFP	$(CD_3)_2CO$	−95	5.15	0.14
6TFP	$(CD_3)_2CO$	31	4.64	0.82
6TFP	$(CD_3)_2CO$	−43	4.87	0.89
6TFP	$(CD_3)_2CO$	−95	5.08	1.00
TMF	CS_2	31	4.27	
TMF	CS_2	−43	4.40	
TMF	CS_2	−60	4.45	
6TFP	CS_2	31	4.03	0.434
6TFP	CS_2	−43	4.03	0.372
6TFP	CS_2	−60	4.04	0.377

[a] Concentrations are *ca.* 2% by weight. [b] Assignment uncertain.

The methine proton chemical shift of TMF in carbon disulfide indicates that the relative amount of the most stable conformer (equatorial fluorine) becomes greater as the temperature is decreased. The Me5c resonance of 6TFP in carbon disulfide indicates that at room temperature the aryl substituent is predominantly axial, and therefore that the fluorine is also predominantly axial. As the temperature is lowered, the equilibrium constant should change in favor of the more stable conformer, and consequently both the Me5c and H6c resonances should move upfield. However, when the temperature is lowered from 31° to −43°, δ(H6c) is constant, while Me5c absorbs only 0.06 ppm to higher field. Lowering the temperature to −60° leads to a very small (0.01 ppm) downfield shift of both of these resonances. These shifts indicate that the effect of temperature on the equilibrium is opposed and approximately equal to the effect of increasing effective dielectric constant at low temperature.

Experimental Section

General Synthetic Remarks.—All solvents and common reagents used for synthesis were reagent grade. The 2-bromo-3,3,5,5-tetramethylcyclohexanone, mp 48.5–49.5° (lit.[9] mp 50–51°), was prepared and purified by W. A. Thomas. Ethyl formate and isophorone (practical grades, Eastman) were dried and distilled before use. Commercial *n*-pentane and *n*-hexane were washed with concentrated sulfuric acid, aqueous potassium carbonate, and water, dried with sodium and magnesium sulfate, and distilled, discarding the first and final 10% of the distillate. The 3,3,5,5-tetramethylcyclohexanone, bp 101° (30 Torr), was prepared and purified by B. C. Mikuska. Tetramethylene sulfone (Aldrich) was stored over molecular sieves. The following materials were used as received: aluminum oxide, neutral, and silica gel (Woelm, activity grade I, Alupharm Chemicals); cuprous chloride (reagent, Fisher Scientific); deuterium oxide (99.7%, Merck Sharp and Dohme of Canada); methyl bromide (gas, Matheson Co.); molecular sieves, Linde type 3A (Matheson Coleman and Bell); perchloryl fluoride (gas, Pennsalt Chemicals); and sodium methoxide (Olin Chemicals).

Boiling points are uncorrected. Capillary melting points are corrected and were determined using a Mel-Temp melting point apparatus (Laboratory Devices, Cambridge, Mass.). Refractive indices were measured on a Bausch and Lomb Abbe-3L refractometer, temperature controlled at 20.0°. Infrared spectra were measured on a Beckman IR-12 spectrophotometer using internal calibration, or a Beckman IR-8 spectrophotometer calibrated by means of the 1603-cm^{-1} absorption of a polystyrene film. Nuclear magnetic resonance spectra were recorded on Varian A-60 or HA-100 spectrometers. Mass spectral data were

obtained by Professor Ronald D. Grigsby of the Department of Biochemistry and Biophysics of Texas A & M University, using a Consolidated Electrodynamics Model 21-110B mass spectrometer. Microcombustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Micro-Tech Laboratories, Skokie, Ill.

2,4,4,6,6-Pentadeuterio-3-trideuteriomethyl-5,5-dimethyl-2-cyclohexen-1-one (Isophorone-d_8).—This is an adaptation of the procedure of Anet.[42] A mixture of 55.2 g (0.40 mol) of isophorone, 5.4 g (0.039 mol) of potassium carbonate, and 160 g (8.0 mol) of deuterium oxide was refluxed with stirring for 48 hr. At this time, the lower layer (D_2O) was drawn off and another 5.4 g of potassium carbonate and 160 g of fresh D_2O were added. After refluxing for 48 hr, the process was repeated once more. The final mixture was extracted twice with ether and the ether solutions were combined, washed twice with water, and dried over magnesium sulfate. The ether was evaporated and the remaining brown liquid was distilled on a spinning band column to yield 47.5 g (0.326 mol, 81%) of colorless product: bp 88.5–89.5° (15 Torr); ir (CCl_4) 1660 cm^{-1} (C=O); nmr (neat) δ (methyls) 0.97; $n^{20}D$ 1.4757; mass spectrum molecular ion m/e 146, abundant fragment peaks m/e 131, 103, 88, 60, 42. *Anal.* Calcd for $C_9H_6D_8O$: mol wt, 146.1547. Found: mol wt, 146.1557 (mass spectrum). The nmr spectrum indicated that, overall except for the *gem*-dimethyl protons, the isophorone was greater than 98% deuterated.

2,4,4,6,6-Pentadeuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone.—This reaction was run using the cuprous iodide–tri-*n*-butylphosphine complex which is described by House, *et al.*,[43] and which was prepared according to the method of Kaufman and Teter.[44] Into a 1000-ml flask equipped with a stirrer, an addition funnel, and a gas inlet was placed 11.0 g (0.455 mol of magnesium turnings and 500 ml of anhydrous ether. The system was flushed with dry nitrogen, and methyl bromide was bubbled into the solution at a moderate rate with stirring until all of the magnesium was dissolved. Then the excess methyl bromide was displaced with dry nitrogen as the flask was cooled with a Dry Ice–carbon tetrachloride mixture. A solution of 1.8 g (0.0045 mol) of tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] and 36.5 g (0.25 mol) of isophorone-d_8 in 100 ml of anhydrous ether was added over a period of 0.5 hr. After the addition, the mixture was stirred with cooling for 10 min. The reaction mixture was then added to 500 ml of 1 *M* ammonium chloride solution. The ether layer was separated and the aqueous layer was washed with ether. The ether extracts were combined, washed once with water, and dried over magnesium sulfate. The ether was evaporated and the resulting pale yellow liquid was distilled on a spinning band column to yield 31.8 g (0.197 mol, 78%) of colorless product: bp 106–108° (50 Torr); ir (neat) 1712 cm^{-1} (C=O); nmr (neat) δ (methyls) 1.01.

4,4-Dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone.—The procedure used for the deuteration of isophorone (*vide supra*) was employed, starting with 31.0 g (0.191 mol) of 2,4,4,6,6-pentadeuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone, 1.34 g of potassium carbonate, and 40 ml of H_2O. The ketone was refluxed for three 48-hr periods. Extraction yielded a colorless liquid (27.1 g, 89%) which was not purified: nmr (neat) δ (methyls) 1.02; $n^{20}D$ 1.4524; mass spectrum molecular ion m/e 159, abundant fragment peaks m/e 144, 128, 101, 86, 83, 72, 57. *Anal.* Calcd for $C_{10}H_{13}D_5O$: mol wt, 159.1668. Found: mol wt, 159.1678.

2,2,6,6-Tetradeuterio-3,3,5,5-tetramethylcyclohexanone.—A procedure similar to that employed above was used starting with 14.3 g (0.093 mol) of 3,3,5,5-tetramethylcyclohexanone, 20 g (1.0 mol) of deuterium oxide, and 0.67 g of anhydrous potassium carbonate. The ketone was refluxed for two 20-hr periods. An nmr spectrum of the crude product indicated that it was very pure and that the ketone was more than 97% deuterated in the α positions. This reaction afforded 11.55 g (0.073 mol, 79%) of colorless product which was not subjected to further purification: ir (CCl_4) 1715 cm^{-1} (C=O); nmr δ (methyls) 1.04; $n^{20}D$ 1.4519; mass spectrum molecular ion m/e 158, abundant fragment peaks m/e 143, 128, 97, 85, 84, 72, 57. *Anal.* Calcd for $C_{10}H_{14}D_4O$: mol wt, 158.1605. Found: mol wt, 158.1604.

3-Phenyl-3,5,5-trimethylcyclohexanone (1b).—This compound was prepared according to established procedures[6,15,45] starting with 317.9 g (2.3 mol) of isophorone, 313 g (2.0 mol) of bromobenzene, 48.5 g (2.0 g-atoms) of magnesium, and 6.0 g (0.061 mol) of cuprous chloride. The isophorone was added to the Grignard reagent with ice-bath cooling, over a period of 2 hr. The mixture was then allowed to return to room temperature and was stirred for an additional 8 hr. Then, using the procedure of Skattebøl, *et al.*,[46] just enough of a saturated ammonium chloride solution was added to the reaction mixture to cause the inorganic salts to precipitate (about 250 ml). The resultant clear solution was filtered, and the precipitate was washed twice with 100-ml portions of anhydrous ether. The ether solutions were combined and the ether was evaporated. The crude product was distilled through a vertical condenser from a trace of *p*-toluenesulfonic acid in order to remove some of the dienes and unreacted isophorone. The fractions boiling at 90–104° (0.5 Torr) were redistilled on a spinning band column to afford 186 g (0.86 mol, 43%) of the colorless ketone: bp 100–101° (1 Torr); ir (CCl_4) 1721 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 0.35, 1.01, 1.34; $n^{20}D$ 1.5291.

3-(1-Naphthyl)-3,5,5-trimethylcyclohexanone (1c).—This compound was prepared by an established procedure,[6] starting with 38.9 g (1.60 g-atoms) of magnesium, 331.2 g (1.6 mol) of 1-bromonaphthalene, 221 g (1.6 mol) of isophorone, and 5 g (0.051 mol) of cuprous chloride. A short-path distillation afforded the ketone **1c**, bp 148–158° (0.5 Torr), which was recrystallized twice from hexane: yield 162 g (0.61 mol, 38%); mp 64–66°; nmr (CCl_4) δ (methyls) 0.15, 1.01, and 1.73.

2- and 6-Hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone (*Caution!*).[47]—The following procedure is adapted from the method of Johnson and Posvic.[48] To a dry, nitrogen-filled, 3-l. flask provided with a mechanical stirrer, a nitrogen inlet, and a dropping funnel was added 1250 ml of benzene (dried over molecular sieves) and 109.0 g (2.02 mol) of sodium methoxide. A very slow stream of nitrogen was passed over the stirred suspension, which was cooled with an ice bath while a mixture of 150 g (2.03 mol) of ethyl formate and 218.0 g (1.01 mol) of 3-phenyl-3,5,5-trimethylcyclohexanone (**1b**) was added dropwise over a period of 2 hr. After the addition, the mixture was allowed to return slowly to room temperature and stirred vigorously for 18 hr. The resulting brown mixture was then extracted with 750 ml of water followed by three 200-ml portions of 1 *M* sodium hydroxide solution. The aqueous extracts were combined, washed once with ether (the wash ether was added to the benzene layer above), and acidified with concentrated hydrochloric acid. The milky suspension was then saturated with sodium chloride and extracted thoroughly with ether. The ether solution was washed with three 150-ml portions of saturated sodium chloride solution and dried with anhydrous sodium sulfate. After the ether was evaporated, 141.2 g (58%) of an oily solid remained. Since the crude yield was less than what was expected on the basis of the results of previous experiments, the benzene–ether solution was evaporated to give 75 g (35%) of almost pure 3-phenyl-3,5,5-trimethylcyclohexanone. This recovered starting material (0.35 mole) was condensed with 51.9 g (0.7 mol) of ethyl formate and 37.8 g (0.7 mol) of sodium methoxide as above. This reaction yielded an additional 54.1 g (72%) of crude product, and 20 g of starting material was recovered. The nmr spectrum of the combined crude products (195.3 g total, 79%) showed that the two isomers were formed in an approximate ratio of 4:1 (6 isomer predominant), and that the mixture was free of substantial impurities.

The crude product was dissolved in 400 ml of boiling hexane, and the solution was allowed to deposit crystals at room temperature. After 10 hr, 111 g (A) of 6 isomer, mp 87–92°, was collected. The filtrate was evaporated to two-thirds of its volume and an additional 8.0 g (B) was collected, mp 89–92°. The process was repeated to give 0.9 g (C), mp 89–91°. The remaining solution was put in a refrigerator overnight. A large crystalline mass formed in which two types of crystals were apparent, one small and white and the other large and yellow. The crystals

(42) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

(43) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(44) G. B. Kaufman and L. A. Teter, *Inorg. Syn.*, **7**, 9 (1963).

(45) M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941).

(46) L. Skattebøl, E. R. H. Jones, and M. C. Whiting, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 792.

(47) *Note:* Care should be taken not to allow 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone to come into contact with the skin, since it may cause a severe rash, followed by blistering and cracking of the skin. These symptoms disappear approximately one week after last contact, leaving no scars.

(48) W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, **69**, 1361 (1947).

were decanted from the liquid (D) and were dissolved in 100 ml of hexane and seeded with the 6 isomer. After 8 hr, 2.1 g (E) of 6 isomer, mp 85–89°, was removed from the solution (F).

Filtrate D was evaporated to two-thirds of its volume, seeded with a small chip of one of the large yellow crystals formed above, and placed in the refrigerator. After 8 hr, 5.2 g (G) of yellow crystals was collected, mp 56–75° (*ca.* 90% 2 isomer by nmr). When the filtrate was evaporated, 8.1 g (H) of a red oil remained (*ca.* 60% 2 isomer many impurities present.) Filtrate F was evaporated to three-fourths of its volume and seeded with G to yield 45.5 g (I) of crystals, mp 56–60°, *ca.* 70% 2 isomer. The filtrate was evaporated, leaving 5.6 g (J) of a yellow oil which was combined with H. After several hours an additional 2 g (K) of impure 2 isomer was collected and washed with hexane. The remaining oil was chromatographed on a 2.5 × 40 cm silica gel column in order to remove the impurities which prevent crystallization. The chromatogram was developed with 350 ml of hexane, 200 ml of 4% (v/v) ether–hexane, and 200 ml of 7% ether–hexane. Nothing was eluted in these fractions. This was followed by five 150-ml portions of 8% ether–hexane. The first four of these fractions contained both isomers with the 2 isomer predominant and decreasing [11.0 g (L), combined total]. The last fraction (0.3 g) contained mostly 6 isomer and impurities, and was discarded. The isomeric mixtures G, I, K, and L were combined and chromatographed on a 500-g silica gel column. The column was developed with 1200 ml of hexane and 800 ml of 4% ether–hexane. Nothing was eluted in these fractions. This was followed by six 300-ml portions of 5% ether–hexane. The first three of these fractions deposited crystals which were recrystallized from hexane to give 20.0 g (M) of pure 2 isomer, mp 66–67°. The second three fractions deposited 9.1 g of crystals which were recrystallized twice from hexane to give 8.2 g (N) of pure 6 isomer, mp 89–91°. The filtrates from all of the fractions were combined (25.1 g) and again chromatographed on silica gel to yield an additional 9.5 g (P) of pure 2 isomer, mp 66–67°.

The fractions A, B, C, E, and N were combined and recrystallized twice from 250 ml of hexane. This afforded 119.0 g (48%) of pure 6 isomer, mp 89.5–91.0°. Two grams of these white crystals was sublimed [(bath temperature 80° (0.5 Torr)] for analysis and spectroscopic measurements: mp 89.5–91.0°; ir (CCl_4) 1639, 1598 cm^{-1} (C=C–C=O); nmr (CCl_4) δ (methyls) 0.58, 1.20, 1.33.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.73, 78.52; H, 8.26, 8.27.

The fractions M and P were combined as pure 2 isomer, 29.5 g (12%), mp 66–67°. Two grams of this white crystalline solid was recrystallized from hexane with cooling and sublimed [bath temperature 60° (0.5 Torr)]; mp 66–67°; ir (CCl_4) 1640, 1590 cm^{-1} (C=C–C=O); nmr (CCl_4) δ (methyls) 0.71, 1.02, 1.62.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.53, 78.37; H, 8.13, 8.07.

2-Hydroxymethylene-3,3,5,5-tetramethylcyclohexanone.—The same procedure that was used to prepare the hydroxymethylene derivatives of the phenyltrimethyl ketone was followed, starting with 30.8 g (0.200 mol) of 3,3,5,5-tetramethylcyclohexanone, 29.6 g (0.40 mol) of ethyl formate, and 23.0 g (0.43 mol) of sodium methoxide in 200 ml of dry benzene. After evaporation of the final ether solution, there remained 31.4 g of a colorless liquid (pure by nmr) which turned an intense violet on addition to alcoholic ferric chloride solution. Distillation on a spinning band column afforded 27.8 g (76%) of product: bp 55.0 ± 0.5° (0.45 Torr); ir (CCl_4) 1637, 1593 cm^{-1} (C=C–C=O); nmr (neat) δ (methyls) 0.99, 1.24; $n^{20}D$ 1.4926.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.50, 72.47; H, 10.02, 9.97.

2- and 6-Hydroxymethylene-4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone.—The same procedure as above was employed using 22.3 g (0.140 mol) of 4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone, 20.7 g (0.28 mol) of ethyl formate, and 16.1 g (0.30 mol) of sodium methoxide. The crude product, 21.2 g (81%) of a pale yellow liquid, was shown by nmr to be a pure mixture of equal quantities of the two isomers, and this was used without further purification, nmr (CCl_4) δ (methyls) 0.97, 1.21.

2- and 6-Hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone.—The same procedure (above) was employed using 71.0 g (0.265 mol) of 3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (1c), 42.9 g (0.58 mol) of ethyl formate, and 29.0 g (0.53 mol) of sodium methoxide. The methoxide was suspended in 250 ml of dry benzene, and the formate and the ketone were added as a solution in 200 ml of dry benzene. The product was isolated as usual except that after the aqueous solution of the sodium salts of the products was acidified, the solution was saturated with sodium chloride and the crude hydroxymethylenes were removed by filtration. The solid was recrystallized twice from hot carbon tetrachloride. This product, the 6 isomer, was obtained as colorless cubic crystals, 58 g (74%), mp 164–166°. A small amount of this substance was sublimed [bath temperature 50° (0.5 Torr)] for analysis and spectroscopic measurements: mp 164–166°; ir (CCl_4) 1639, 1596 cm^{-1} (C=C–C=O); nmr (CCl_4) δ (methyls) 0.28, 1.21, 1.70; mass spectrum molecular ion *m/e* 294, abundant fragment peaks *m/e* 279, 261, 233, 223, 220, 193. *Anal.* Calcd for $C_{20}H_{22}O_2$: mol wt, 294.1614. Found: mol wt, 294.1634.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found C, 81.69, 81.54; H, 7.43, 7.25.

The filtrates from the above recrystallizations were evaporated to a brown oil. This oil was dissolved in ether and placed in a refrigerator for 2 days. A small quantity of 6 isomer precipitated, leaving a red gum. The gum was kneaded in a small amount of hexane, giving a yellow solid which was recrystallized twice from hexane. The 2 isomer was obtained as 1.5 g (1.9%) of an impure yellow powder: mp 89–114°; nmr (CCl_4) δ (methyls) 0.87, 1.16, 1.87; ir (CCl_4) 1635, 1592 cm^{-1} (C=C–C=O); mass spectrum molecular ion *m/e* 294, abundant fragment peaks *m/e* 279, 261, 247, 223, 195. *Anal.* Calcd. for $C_{20}H_{22}O_2$: mol wt, 294.1614. Found: mol wt, 294.1617.

***cis*- and *trans*-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone (6CFP and 6TFP), and 6,6-Difluoro-3-phenyl-3,5,5-trimethylcyclohexanone (6DFP).**—This reaction was carried out in a 3-l. flask equipped with a magnetic stirrer, a nitrogen inlet above the reaction mixture, an inlet for perchloryl fluoride (HOOD!)[49] which extended almost to the bottom of the flask, and a gas outlet which was connected (Tygon tubing) to a 50-ml bubbler filled with absolute ethanol. The system was connected to the perchloryl fluoride cylinder through an empty 500-ml gas-washing bottle in order to eliminate the possibility that the reaction mixture might be drawn suddenly into the cylinder. To an ice bath cooled solution of 12.5 g (0.5 g-atom) of sodium in 1100 ml of absolute ethanol was added (in one portion) 108 g (0.44 mol) of powdered 6-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone. The solution turned bright yellow. A slow stream of nitrogen was passed through the system as gaseous perchloryl fluoride was bubbled vigorously into the stirred solution for 1 hr. Nitrogen was bubbled through the solution for 1 hr, after which 30 g of potassium acetate was added and the solution was heated just to boiling. Then 1600 ml of water was added and the solution was stirred until it cooled to room temperature. The mixture was extracted with eight 100-ml portions of ether. The ether layers were combined and washed with three 100-ml portions of 1 *M* sodium hydroxide solution, three 100-ml portions of water, and 100 ml of a saturated sodium chloride solution. The ether solution was dried with anhydrous sodium sulfate and evaporated. The remaining mass (100.5 g) was dissolved in 120 ml of boiling hexane and left to stand overnight. The next day 79.2 g of crystals were collected and these were recrystallized to give 75.3 g (A) of 6CFP, mp 85.7–86.5°. The filtrate was evaporated to give 20.5 g (B) of a viscous, pale yellow liquid which nmr showed to contain 6TFP and 6CFP in a 3:2 ratio. Five grams of mixture B was chromatographed on a 2.8 × 58 cm column of silica gel. The chromatogram was developed with 400 ml of hexane, 300 ml of a 1.5% (v/v) ether–hexane solution, and 850 ml of 2% ether–hexane.[50] The column was then eluted with 3% ether–hexane. The first 300 ml contained 160 mg (C) of 6DFP and a small amount of impurity. The next 200 ml of eluent contained 730 mg (D) of a mixture of 6TFP and 6DFP. The following six fractions (*ca.* 200 ml each) afforded a total of 2.1 g (E) of slightly impure (by nmr) 6TFP. The column was

(49) *Caution:* Perchloryl fluoride is moderately toxic and a powerful oxidizing agent. All perchloryl fluoride reactions should be run, using safety shields, in a hood.

(50) Elution with benzene–hexane was subsequently shown to be much more effective in separating 6DFP and 6TFP. However, using this eluent, 6TFP and 6CFP are not well separated and a second chromatography using ether–hexane is necessary. It was found that, when 6.5 g of a 6TFP–6CFP mixture (6:1) was allowed to stand on a silica gel column for several weeks, the ratio of isomers in the 5.8 g of material collected was 48:1, with 6CFP favored. Therefore the chromatography of mixtures of the fluoro isomers should be carried out as rapidly as possible without sacrificing separation.

then washed with ether to obtain 1.6 g of yellow solid, which was recrystallized to yield 1.3 g (F) of 6CFP, mp 83–84°. Fraction E was rechromatographed on silica gel, using 3% ether–hexane. The first 400 ml contained nothing, and the next 300 ml afforded 1.9 g (G) of pure colorless 6TFP. The last 100 ml contained *ca.* 0.2 g of impure 6TFP which was added to the remainder of mixture B, as was fraction D from the first chromatography. The combined mixture was chromatographed three times as above yielding an additional 3.9 g (H) of 6CFP, 7.1 g (I) of 6TFP, and 1.9 g (J + K) of 6DFP.

Fractions A, F, and H were combined as pure 6CFP, giving a total yield of 80.5 g (0.343 mol, 78%) of white crystals. Some of this material was sublimed [bath temperature 45° (0.5 Torr)] for nmr and dipole moment studies: mp 85.7–86.5°; ir (CCl_4) 1744 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.34, 1.10, 0.29.

Anal. Calcd for $C_{15}H_{19}OF$: C, 76.89; H, 8.17; F, 8.11. Found: C, 76.78, 77.04; H, 8.19, 8.16; F, 7.41, 7.48.

Fractions G and I were combined as pure (by nmr) 6TFP for a total yield of 9.0 g (0.0385 mol, 8.7%) of this colorless liquid: ir (CCl_4) 1737 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.37, 1.05, 0.43; mass spectrum molecular ion *m/e* 234, abundant fragment peaks, *m/e* 219, 214, 199, 171, 159, 145. *Anal.* Calcd for $C_{15}H_{19}OF$: mol wt, 234.1415. Found: mol wt, 234.1436.

Fraction J (1.0 g) was combined with C (0.16 g) since, in addition to 6DFP, both of these contained significant impurities (*ca.* 5–10% by nmr). This mixture was used for obtaining carbon-13 nmr spectra. Fraction K, a colorless liquid (0.9 g), was pure 6DFP by nmr and this was used for proton spectra and ir studies. Therefore the yield was approximately 2.0 g (0.008 mol, 1.8%): ir (CCl_4) 1757 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.37, 1.09, 0.39; mass spectrum molecular ion *m/e* 252, abundant fragment peaks *m/e* 237, 189, 175, 159, 145. *Anal.* Calcd. for $C_{15}H_{18}OF_2$: mol wt, 252.1323. Found: mol wt, 252.1335.

Summary.—6-Hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone (108 g, 0.44 mol) gives 80.5 g (0.343 mol, 78%) of 6CFP, mp 85.7–86.5°; 9.0 g (0.038 mol, 8.7%) of 6TFP, a colorless liquid; and approximately 2 g (0.008 mol, 1.8%) of 6DFP, also a colorless liquid.

2,2,6-Trideuterio-6-fluoro-3-phenyl-3,5,5-trimethylcyclohexanone.—Approximately 1 g of 6CFP was placed in a bottle with 30 ml of D_2O and 1 g of anhydrous potassium carbonate. The bottle was capped and heated on a steam bath, with stirring for 24 hr. After this time, an nmr spectrum of the crude product indicated that sufficient deuterium incorporation had taken place, and that the reaction had been accompanied by considerable decomposition. The product was extracted with ether. The ether solution was washed with water and a saturated salt solution, and dried with sodium sulfate. Evaporation of the ether left an oil which was dissolved in a few milliliters of pentane and seeded with 6CFP. The resultant oily crystals were almost completely deuterated at C-6 and greater than 60% deuterated at C-2. This impure product was used to differentiate between C-2 and C-4 in the carbon-13 nmr spectrum[19] without further purification, nmr (CCl_4) δ (methyls) 1.33, 1.10, 0.29.

***cis*- and *trans*-2-Fluoro-3-phenyl-3,5,5-trimethylcyclohexanone (2CFP and 2TFP), and 2,2-Difluoro-3-phenyl-3,5,5-trimethylcyclohexanone (2DFP).**—The fluorination of 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone was carried out in the same manner as the fluorination of the 6 isomer starting with 3.0 g (0.13 g-atom) of sodium and 27.6 g (0.113 mol) of the 2-hydroxymethylene ketone in 250 ml of absolute ethanol. Perchloryl fluoride was bubbled into the solution for 30 min. The crude product was isolated as 25.0 g of a viscous yellow liquid, which was dissolved in 50 ml of hexane and refrigerated overnight. The next day 19.8 g of oily white crystals were collected. The crystals were recrystallized from 45 ml of hexane to give 17.8 g (B) of large white crystals, mp 79–80°. The filtrate was evaporated leaving 6.0 g (A) of a yellow oil. An examination of the methyl resonances in the nmr spectrum of liquid A indicated that the relative proportions of 2TFP/2CFP/2DFP/starting material were approximately 1.9:1.0:1.0:1.0.

This mixture was chromatographed on a 3 × 60 cm silica gel column,[51] eluting first with a benzene–hexane mixture (gradually increasing from 20 to 60% benzene). Nothing was eluted in the first 800 ml. The next 350 ml contained 1.09 g (C) of impure 2DFP, while the following fraction contained nothing. At this point the eluent was changed to ether–hexane, gradually increasing from 0 to 2.5% (v/v). Nothing was eluted in the next 2200 ml. Then, using 3% ether–hexane, 0.96 g of starting material was collected. This was closely followed by a number of impurities and then impure 2TFP and 2CFP with the proportion of 2CFP increasing on elution.[52] All of the last fractions were combined, dissolved in a small amount of hexane, seeded with 2CFP, and refrigerated. In this way, an additional 0.5 g (D) of 2CFP was collected, mp 76–77°. The filtrate was evaporated to 2.5 g of liquid (E) which an nmr spectrum showed to be *ca.* 70% 2TFP.

The total yield of isolated 2CFP (B and D) was 18.3 g (0.078 mol, 69%): mp 79–80°; ir (CCl_4) 1744 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.49, 1.03, 0.42; mass spectrum molecular ion *m/e* 234, abundant fragment peaks, *m/e* 219, 188, 159, 136, 83.

Anal. Calcd for $C_{15}H_{19}OF$: C, 76.89; H, 8.17; F, 8.11; mol wt, 234.1415. Found: C, 76.84, 77.05; H, 8.35, 8.52; F, 7.70, 7.68; mol wt, 234.1422.

The impure 2DFP (C) was recrystallized from pentane, yielding 0.85 g (0.0034 mol, 3%): mp 50–52°; ir (CCl_4), 1757 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.49, 1.07, 0.44; mass spectrum molecular ion *m/e* 252, abundant fragment peaks *m/e* 237, 196, 159, 154, 133.

Anal. Calcd for $C_{15}H_{18}OF_2$: C, 71.41; H, 7.19; F, 15.06; mol wt, 252.1323. Found: C, 70.40, 70.56; H, 7.38, 7.40; F, 15.53, 15.42; mol wt, 252.1325.

The mixture E was again chromatographed on silica gel using ether–hexane as the eluent. The resulting fractions were combined into three mixtures: (1) slightly impure 2TFP (0.33 g, does not contain 2CFP) (this colorless liquid was used for proton nmr studies and mass spectral analysis); (2) a mixture of 2TFP and 2CFP (0.93 g, 4:1 ratio); and (3) a mixture of 2TFP and 2CFP (0.53 g, 1:1 ratio). The total yield of 2TFP in the above mixtures is approximately 1.4 g (0.006 mol, 5.3%): ir (CCl_4) 1738 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.38, 1.10, 0.64; mass spectrum molecular ion *m/e* 234, abundant fragment peaks *m/e* 219, 188, 159, 136, 83. *Anal.* Calcd for $C_{15}H_{19}OF$: mol wt, 234.1415. Found: mol wt, 234.1420.

Summary.—2-Hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone (27.6 g, 0.113 mol) gives 18.3 g (0.078 mol, 69%) of 2CFP, mp 79–80°; approximately 1.4 g (0.006 mol, 5.3%) of 2TFP (impure liquid); and 0.85 g (0.0034 mol, 3%) of 2DFP, mp 50–52°.

***cis*- and *trans*-6-Fluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (6CFN and 6TFN), and 6,6-Difluoro-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (6DFN).**—This fluorination was accomplished by the same procedure (*vide supra*) starting with 4.0 g (0.17 g-atom) of sodium and 50.0 g (0.170 mol) of 6-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone in 350 ml of absolute ethanol. Perchloryl fluoride was bubbled into the solution for 30 min. The crude reaction product, a yellow solid, was recrystallized from 200 ml of absolute ethanol, yielding 36.0 g of 6CFN (A), mp 123°. The filtrate was evaporated, leaving 6 g of a yellow liquid which was chromatographed on a column of 100 g of silica gel. The chromatogram was developed with 500 ml of ether–hexane (0–8%). The next five 100-ml fractions (10% ether–hexane) contained mixtures of all three compounds and were combined (B).

The following four fractions contained a total of 1.4 g of almost pure 6CFN which was combined with A and recrystallized from 75 ml of boiling hexane by adding just enough acetone to dissolve the materials, yield 34.9 g (0.123 mol, 72.5%), mp 126–128°. A few grams of these white crystals (6CFN) was sublimed [bath temperature 100° (0.5 Torr)] for spectroscopic and dipole moment studies: mp 126.5–128°; ir (CCl_4) 1743 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.73, 1.08, 0.07.

Anal. Calcd for $C_{19}H_{21}OF$: C, 80.25; H, 7.44; F, 6.68. Found: C, 80.11, 80.30; H, 7.30, 7.48; F, 6.66, 6.75.

Mixture B was again chromatographed on silica gel. The chromatogram was developed with 200 ml of hexane and 100 ml of 3% ether–hexane and then eluted with 100-ml portions of 5% ether–hexane. The first two fractions afforded 0.93 g of a colorless, viscous liquid (C) and the next four fractions yielded 2.6 g of a white, crystalline solid (D). The liquid C was identified by nmr as impure (80%) 6DFN: yield *ca.* 0.9 g (0.003 mol, 1.8%); ir (CCl_4) 1757 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.77, 1.07,

(51) An attempt to chromatograph a mixture of 2TFP and 2CFP on alumina resulted in total decomposition of both compounds. The decomposition products were not identified.

(52) It was found that, if benzene–hexane is used to elute these monofluoroketones, 2CFP is eluted first; however, the separation is still very poor.

0.16; mass spectrum molecular ion m/e 302, abundant fragment peaks m/e 287, 209, 195, 167, 165, 153. *Anal.* Calcd for $C_{19}H_{20}OF_2$: mol wt, 302.1477. Found: mol wt, 302.1464.

The crystals D were recrystallized from 50 ml of hexane, affording 2.16 g (0.0076 mol, 4.5%) of 6TFN: mp 122.5–123.5°; ir (CCl_4) 1735 cm^{-1} (C=O); nmr (CCl_4) δ (methyls) 1.77, 1.05, 0.26.

Anal. Calcd for $C_{19}H_{21}OF$: C, 80.25; H, 7.44; F, 6.68. Found: C, 79.79, 79.98; H, 7.41, 7.27; F, 6.69.

Summary.—6-Hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone (50 g, 0.17 mol) gives 34.9 g (0.123 mol, 72.5%) of 6CFN, mp 126–128°; 2.16 g (0.0076 mol, 4.5%) of 6TFN, mp 122.5–123.5°; and approximately 0.9 g (0.003 mol, 1.8%) of 6DFN (an impure, colorless liquid).

2-Fluoro-3,3,5,5-tetramethylcyclohexanone (TMF).—The usual procedure (*vide supra*) was used employing 4.83 g (0.21 g-atom) of sodium and 37.4 g (0.21 mol) of 2-hydroxymethylene-3,3,5,5-tetramethylcyclohexanone. The crude product was recrystallized three times from pentane (with cooling), yielding 21.0 g (0.122 mol, 58%) of crystalline TMF, mp 34–36°. This compound was then sublimed [25° (0.5 Torr)]: mp 36.0–36.5°; bp 37° (0.15 Torr); ir (CCl_4) 1743 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{17}OF$: C, 69.73; H, 9.95; F, 11.03. Found: C, 69.98, 69.88; H, 9.82, 9.69; F, 11.40, 11.68.

α-Fluoro-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone.—The same procedure (*vide supra*) was used to fluorinate α-hydroxymethylene-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone. The product consists of four isomers which were not separated and the yield was only 30% owing to accidental losses, mp 33.5–34°.

2-Fluoro-2,6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone.—A mixture of 4.62 g (0.0268 mol) of 2-fluoro-3,3,5,5-tetramethylcyclohexanone, 30 g (1.5 mol) of deuterium oxide, 1.05 g of anhydrous potassium carbonate, and a trace of sodium methoxide was vigorously stirred in an air bath at 55°. After 7 days, the reaction mixture was extracted with methylene chloride. Since the deuteration was incomplete, the process was repeated. The product was then extracted with methylene chloride and recrystallized three times from pentane. This reaction afforded 2.1 g (0.012 mol, 45%) of the deuterated fluoroketone, mp 34–35°, ir (CCl_4) 1740 cm^{-1} (C=O).

Attempted Preparations of 2-Fluoro-3,3,5,5-tetramethylcyclohexanone from the Corresponding 2-Bromoketone. A.—Approximately 0.8 g of 2-bromo-3,3,5,5-tetramethylcyclohexanone, 6 ml of acetonitrile, and 2 g of potassium fluoride (dried at 150° for 12 hr) were refluxed for 24 hr. An nmr spectrum of the crude product indicated that no reaction had taken place.

B.—Three grams of the bromoketone was refluxed with 5 g of potassium bifluoride in 50 ml of ethylene glycol for 5 hr. Again, none of the desired product was apparent in the nmr spectrum of the product.

C.—Into a flask equipped with a Dean–Stark trap was placed 5.8 g of 2-bromo-3,5,5-tetramethylcyclohexanone, 15 g of potassium fluoride, 50 ml of tetramethylene sulfone, and 10 ml of benzene. The flask was heated and 10 ml of benzene and 2 ml of water were collected in the trap. The mixture was then stirred at 200° for 36 hr. The contents were allowed to cool, mixed with an equal quantity of water, and extracted with pentane. An nmr spectrum showed considerable decomposition and none of the desired product.

Dipole Moments.—A WTW Dipolemeter, type DM01 (Kahl Scientific Instrument Corp., El Cajon, Calif.), was used for all of the dielectric constant measurements. The following materials were used to calibrate the measuring scale of the Dipolemeter. Gaseous nitrogen, prepurified, was dried with concentrated sulfuric acid and then with Drierite (ϵ 1.0005[53]). Reagent cyclohexane (J. T. Baker Chemical Co.) was washed with concentrated sulfuric acid and then water, dried with magnesium sulfate, and distilled, discarding the first and final 15%, bp 81–82° (ϵ 2.0228[54]). Benzene (spectroquality, Matheson Coleman and Bell) (ϵ 2.2825[54]) and carbon tetrachloride (Spectrograde, Eastman) (ϵ 2.2363[54]) were used without further purification. Each of the liquids was stored overnight with one-half of its volume of molecular sieves (Linde type 4A, Allied Chemical) which had been washed five times with cyclohexane and dried *in vacuo* at 100°. The number of scale divisions per dielectric constant unit is given by the least squares slope of a plot of dielectric constant *vs.* scale reading. The four points were found to give an excellent linear relationship. Before each determination the calibration was checked using nitrogen and the solvent being used for that particular determination.

A Bausch and Lomb Model 33-45-03-01 precision refractometer was used to measure refractive indices. An adjustment of the absolute accuracy of the instrument was made only coarsely using water; however, this does not affect the relative accuracy to any appreciable extent. The precision attainable assuming a sharp dividing line is approximately ±0.00003. Sodium light was used for all measurements.

The dielectric cell and this refractometer were connected in series to a Haake Model F constant-temperature circulator. The temperature of the circulating water was maintained at 20.0 ± 0.02°.

The samples of 6TFP and 6TFN were placed in a vacuum (0.5 Torr) for 2 hr, and all of the other fluoroketones were sublimed prior to measurement. Cyclohexane, purified as above, and benzene were stored over molecular sieves. Solutions were prepared in a cool, dry room, and care was taken to ensure that all solutions were unstoppered for the same short length of time. The sample of pure solvent was treated in the same manner as the solutions. The measurements were made in the following manner. The cell was flushed with dry nitrogen and the scale reading corresponding to nitrogen was determined. Approximately 20 ml of the first solution was then transferred to the cell by pipette and the solution was covered and allowed to come to thermal equilibrium for 15 min, during which time the refractive index of the solution was measured three times. After the dielectric constant was determined, the cell was rinsed thoroughly with the solvent and dried with nitrogen until the previously determined reading for nitrogen was obtained. The remaining solutions were treated similarly. As a trial measurement, the dipole moment of *m*-nitroaniline was determined to be 4.85 ± 0.02 D (lit.[55] 4.89 D).

Dipole moments, which were determined using the method developed by Guggenheim[56] and subsequently modified by Smith,[57] were calculated for the relation

$$\mu^2 = \frac{27kTM_2(\alpha_\epsilon - \alpha_n)}{4\pi N_L d_1(\epsilon_1 + 2)^2}$$

where μ is the molecular dipole moment, k is the Boltzmann constant, T is the absolute temperature, N is Avogadro's number, M_2 is the molecular weight of the solute, and d_1 and ϵ_1 are density and the dielectric constant of the solvent, respectively. The quantities α_ϵ and α_n are the slopes of the dielectric constant, ϵ_{12}, and refractive index, n_{12}, of the solution as a function of the weight fraction of solute, W_2, respectively. The values of the dipole moments and the experimental data from which they were calculated are given in Table VIII.

Infrared Spectra.—The concentration of samples was 0.5 to 1.5% by weight in spectroquality carbon tetrachloride, acetonitrile, or benzene (Matheson Coleman and Bell). The spectra were recorded on a Beckman IR-12 infrared spectrophotometer employing prism-grating optics. The carbonyl absorptions of the fluoroketones were measured on an expanded scale of 10 cm^{-1}/in. at a scan rate of 3.2 cm^{-1}/min, and all spectra were recorded in double-beam operation using 0.2-mm KBr cells. The slit width was sufficiently narrow to allow a resolution of 1.5 cm^{-1} to be attained. The positions of the shoulders were estimated visually.

Nmr Spectra.—Proton nmr spectra were recorded several times on the 50-Hz scale of a Varian HA-100 spectrometer at a sweep rate of 1000 sec. The chemical shifts of the methyl protons and some of the ring protons were determined directly from the measured peak frequencies. Most of the ring proton chemical shifts and all H–H and H–F coupling constants were determined by spectrum simulation and iterative fitting using LAOCN3, a computer program developed by Castellano and Bothner-By.[58] A detailed description of instrumental techniques and spectral interpretation will be published later.[19]

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Table VIII
Dipole Moment Data (20°)

W_2	ϵ_{12}	n_{12}
TMF in Cyclohexane		
0.000000	2.0234	1.42532
0.001116	2.0310	1.42532
0.001899	2.0359	1.42526
0.003043	2.0431	1.42523
0.004368	2.0522	1.42520
0.004987	2.0563	1.42520
0.007241	2.0710	1.42520
0.010387	2.0917	
M_2 = 172.24, d_1 = 0.7791, α_ϵ = 6.57, α_n = −0.06, μ = 3.62 ± 0.01 D		
TMF in Benzene		
0.000000	2.2829	1.50065
0.001328	2.2959	1.50057
0.002357	2.3062	1.50053
0.003247	2.3146	1.50045
0.004063	2.3230	1.50041
0.005037	2.3325	1.50036
0.006234	2.3441	1.50031
0.007703	2.3591	1.50026
M_2 = 172.24, d_1 = 0.879, α_ϵ = 9.87, α_n = −0.16, μ = 3.93 ± 0.01 D		
6CFP in Cyclohexane		
0.000000	2.0228	1.42532
0.001598	2.0326	1.42543
0.003197	2.0432	1.42552
0.004596	2.0519	1.42564
0.006693	2.0658	1.42578
0.007647	2.0713	1.42584
0.009176	2.0816	1.42593
0.010818	2.0923	1.42599
M_2 = 234.32, d_1 = 0.7791, α_ϵ = 6.42, α_n = 0.18, μ = 4.09 ± 0.01 D		
6CFP in Benzene		
0.000000	2.2831	1.50069
0.001450	2.2950	1.50072
0.002788	2.3056	1.50074
0.004047	2.3163	1.50076
0.005518	2.3292	1.50079
0.006978	2.3417	1.50081
0.008132	2.3513	1.50084
0.009616	2.3629	1.50089
M_2 = 234.32, d_1 = 0.879, α_ϵ = 8.38, α_n = 0.06, μ = 4.18 ± 0.02 D		
6TFP in Cyclohexane		
0.000000	2.0228	1.42572
0.001701	2.0289	1.42580
0.003655	2.0356	1.42596
0.005345	2.0418	1.42607
0.007506	2.0496	1.42618
0.009393	2.0562	1.42629
0.011344	2.0632	1.42641
M_2 = 234.32, d_1 = 0.7791, α_ϵ = 3.56, α_n = 0.17, μ = 3.01 ± 0.01 D		
6TFP in Benzene		
0.000000	2.2825	1.50045
0.002113	2.2935	1.50053
0.003299	2.2995	1.50055
0.004584	2.3062	1.50057
0.007011	2.3195	1.50065
0.007647	2.3231	1.50065
0.009095	2.3304	1.50069
M_2 = 234.32, d_1 = 0.879, α_ϵ = 5.29, α_n = 0.08, μ = 3.31 ± 0.01 D		
2CFP in Cyclohexane		
0.000000	2.0242	1.42578
0.001707	2.0341	1.42590
0.003678	2.0459	1.42601
0.005540	2.0564	1.42612
0.007136	2.0667	1.42620
0.008672	2.0758	1.42629
0.010219	2.0849	1.42641
M_2 = 234.32, d_1 = 0.7791, α_ϵ = 5.96, α_n = 0.17, μ = 3.94 ± 0.01 D		
2CFP in Benzene		
0.000000	2.2825	1.50065
0.001605	2.2953	1.50069
0.003311	2.3088	1.50072
0.004389	2.3174	1.50074
0.004642	2.3196	1.50074
0.005863	2.3295	1.50077
0.007288	2.3408	1.50079
M_2 = 234.32, d_1 = 0.879, α_ϵ = 8.01, α_n = 0.06, μ = 4.08 ± 0.01 D		
6CFN in Cyclohexane		
0.000000	2.0254	1.42575
0.001752	2.0341	1.42595
0.003240	2.0425	1.42612
0.004466	2.0489	1.42623
0.006337	2.0586	1.42643
0.007857	2.0672	1.42663
0.009365	2.0749	1.42679
0.010996	2.0842	1.42698
M_2 = 284.38, d_1 = 0.7791, α_ϵ = 5.35, α_n = 0.32, μ = 4.04 ± 0.02 D		
6CFN in Benzene		
0.000000	2.2825	1.50069
0.001514	2.2926	1.50079
0.002624	2.2999	1.50089
0.004147	2.3100	1.50098
0.005462	2.3197	1.50108
0.007128	2.3312	1.50120
0.009002	2.3436	1.50133
0.010176	2.3529	1.50142
M_2 = 284.38, d_1 = 0.879, α_ϵ = 6.89, α_n = 0.21, μ = 4.12 ± 0.02 D		
6TFN in Cyclohexane		
0.000000	2.0252	1.42572
0.001813	2.0309	1.42593
0.003829	2.0378	1.42612
0.005250	2.0417	1.42629
0.006689	2.0461	1.42644
0.008225	2.0512	1.42661
0.009729	2.0557	1.42676
M_2 = 284.38, d_1 = 0.7791, α_ϵ = 3.15, α_n = 0.30, μ = 3.04 ± 0.01 D		
6TFN in Benzene		
0.000000	2.2825	1.50069
0.002003	2.2911	1.50081
0.003207	2.2964	1.50089
0.004693	2.3023	1.50098
0.005901	2.3085	1.50108
0.007125	2.3137	1.50115
0.009283	2.3232	1.50133
M_2 = 284.38, d_1 = 0.879, α_ϵ = 4.40, α_n = 0.21, μ = 3.27 ± 0.02 D		

Registry No.—**1a**, 14376-79-5; **1b**, 25109-54-0; **1c**, 33044-58-5; 6CFP, 37781-16-1; 6TFP, 37781-17-2; 6DFP, 37781-18-3; 2CFP, 37781-19-4; 2TFP, 37781-20-7; 2DFP, 37781-12-7; 6CFN, 37781-13-8; 6TFN, 37781-14-9; 6DFN, 37781-15-0; TMF, 37783-39-4; isophorone-d_8, 14397-59-2; isophorone, 78-59-1; 2,4,4,-6,6-pentadeuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone, 37783-42-9; 4,4-dideuterio-3-trideuteriomethyl-3,5,5-trimethylcyclohexanone, 37783-43-0; 6-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone, 37783-44-1; 2-hydroxymethylene-3-phenyl-3,5,5-trimethylcyclohexanone, 37786-75-7; 2-hydroxymethylene-3,3,5,5-tetramethylcyclohexanone, 37786-76-8; 6-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 37786-77-9; 2-hydroxymethylene-3-(1-naphthyl)-3,5,5-trimethylcyclohexanone, 37818-68-1; α-fluoro-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone, 37786-78-0; α-hydroxymethylene-4,4-dideuterio-3-(trideuteriomethyl)-3,5,5-trimethylcyclohexanone, 37786-79-1; 2-fluoro-2,-6,6-trideuterio-3,3,5,5-tetramethylcyclohexanone, 37786-80-4.

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Acid-Catalyzed Cyclization of (*E*)- and (*Z*)-4,8-Dimethylnona-3,7-dien-2-one

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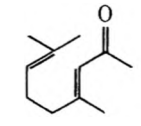
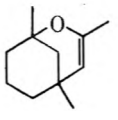
Cyclization of (*E*)- and (*Z*)-4,8-dimethylnona-3,7-dien-2-one (**1**) with 75% aqueous sulfuric acid gave 1,3,5-trimethyl-2-oxabicyclo[3.3.1]non-3-ene (**2**), the tertiary alcohol **4**, and only minor amounts of 1,1,3-trimethyl-2-acetylcyclohex-3-ene (**3**). The major product **2** results from a hypothetical dienone **10** formed prior to cyclization. The mechanism of these cyclizations is discussed briefly.

Both the overall structural and stereochemical course of acid-catalyzed polyene cyclizations are fairly well known today.[1] These reactions are of great importance, not only because of their close relationship with enzymic cyclizations leading to polycyclic terpenes and steroids in nature but also because of their synthetic value in the *in vitro* synthesis of such substances. In the vast majority of cases the products of cyclization result directly from the starting polyolefin and there is no need to consider movements of double bonds prior to cyclization. In the course of a study aimed at preparing ketones related to damascenone[2] we found that acid-catalyzed cyclization of the dienone **1** leads to a



1



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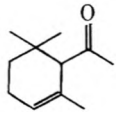

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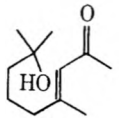

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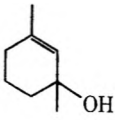

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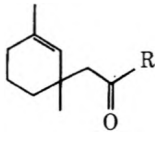


6, R = OC_2H_5
7, R = OH
8, R = CH_3

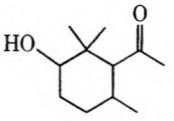
major product not derived from the starting material directly.

Cyclization of 4,8-dimethylnona-3,7-dien-2-one (**1**) (mixture of *E* and *Z* isomers) prepared from citral as described[3] with cold aqueous sulfuric acid gave three principal products separable by vapor phase or column chromatography. Examination of the spectral properties of the major product led to the conclusion that it is the vinyl ether **2** rather than a ketone. Further evidence in favor of structure **2** was provided by synthesis. Condensation of 1,3-dimethyl-2-cyclohexen-1-ol (**5**) with triethyl orthoacetate[4] followed by saponification of the ester **6** and condensation of the resulting acid **7** with methyllithium afforded the monocyclic ketone **8**. As anticipated, when submitted to the action of sulfuric acid the unsaturated ketone **8** was cyclized to the bicyclic vinyl ether **2**.

Spectral properties and elemental composition of the second product indicated that it had structure **4** resulting from hydration of the nonconjugated double bond. This was verified by an alternative synthesis from **1** using the oxymercuration–demercuration sequence[5] and by cyclization to a 4:1 mixture of **2** and **3** in the presence of sulfuric acid.

The least abundant product formed in the acid-catalyzed cyclization of the dienone **1** was the anticipated monocyclic ketone **3** identical with the product prepared from α-cyclogeranic acid and methyllithium.

The sulfuric acid catalyzed cyclization of dienone **1** was explored previously by Walls and coworkers.[3] They did not investigate the "nonpolar" fraction of the reaction mixture and consequently did not identify the three major products **2**, **3**, and **4**. The only product reported was isolated from the "polar" fraction in 2.5% yield and assigned structure **9**. After receiving an



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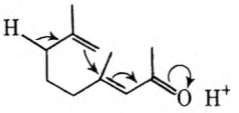

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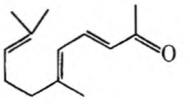

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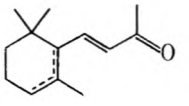


12

authentic sample of the hydroxy ketone **9** from Professor Walls[6] we were able to detect it in trace amounts in our crude reaction mixtures but did not accumulate enough material to substantiate its structure.

A few comments on the mechanism of these cyclizations seem justified. In analogy with the highly efficient cyclization of ψ-ionone (**11**) to the ionones **12** in the presence of acid (*e.g.*, sulfuric or formic acid) the formation of **3** is initiated by Markovnikov protonation of the nucleophilic isopropylidene double bond. Cyclization within the carbonium ion followed by loss of a proton affords the thermodynamically more stable β,γ-unsaturated ketone **3**. The major product **2**, on the other hand, originates from cyclization of the isomeric diene **10**. Protonation of the carbonyl oxygen atom, cyclization (arrows in **10**), deprotonation, and proton transfer leads to the monocyclic ketone **8**. Molecular models reveal the transition state for this cyclization to be much less crowded than that leading from **1** to the monocyclic ketone **3**. In support of the intermediacy of the hypo-

(1) For summaries see W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968); A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Connor, Ed., J. and A. Churchill, London, 1959.

(2) E. Demole, P. Enggist, U. Säuberli, M. Stoll, and E. sz. Kovats, *Helv. Chim. Acta*, **53**, 541 (1970).

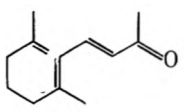
(3) C. Aguilar, M. Salmón, and F. Walls, *Bol. Inst. Quim. Univ. Nacl. Autón. Méx.*, **21**, 226 (1969).

(4) Method of W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(5) H. C. Brown and P. Geoghean, *ibid.*, **89**, 1522 (1967).

(6) We wish to thank Professor F. Walls, University of Mexico, for a sample of his hydroxy ketone. He has verified his earlier experiments but reported in a letter of August 25, 1970, that the actual yield of this compound is in the order of 1%.

thetical compound **10** we cite the formic acid catalyzed cyclization of 6,10-dimethyl-3,5,10-undecatrien-2-one (**13**) to a mixture of ketones **14**.[7] Interestingly, cycliza-



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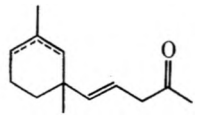

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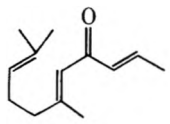

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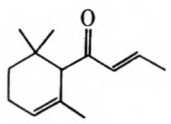

16

tion of **13** in concentrated sulfuric acid is set off by protonation of the weakly basic isopropenyl double bond and gives β-ionone (**12**) in 85% yield.[7] Finally, the behavior of dienone **1** in aqueous sulfuric acid should be contrasted with that of the structurally related ψ-damascone (**15**) in benzene containing stannic chloride. No double-bond isomerization prior to cyclization was observed in the latter case and α-damascone (**16**) was formed in good yield.[8] We attribute the difference to the catalyst and the medium. Proton transfers leading to double-bond isomerizations are faster in protic solvents than in hydrocarbon solvents containing a Lewis acid.

Experimental Section

Microanalyses were performed by the M. I. T. Microanalytical Laboratory. Infrared (ir) spectra were taken in chloroform solution on a Perkin-Elmer Model 247 grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were measured on a Varian Associates T-60 instrument and chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane standard. The abbreviations s, t, q, and m refer to singlet, triplet, quartet, and multiplet, respectively. Vpc analyses were carried out on a F & M gas chromatograph Model 720 on columns having silicon rubber as the liquid phase. Merck silica gel, 0.2–0.05 mm, was used for column chromatography. All solutions were dried over anhydrous sodium sulfate.

Cyclization of (E)- and (Z)-4,8-Dimethylnona-3,7-dien-2-one (1).—To a solution of 20 ml of 75% aqueous sulfuric acid which was kept below 0° with an ice–salt bath was added 4.6 g of **1**. After the addition was complete (10 min) the mixture was stirred for 4 hr at −5 to 0°, poured into 50 g of ice, and extracted four times with 50 ml of ether. The combined ether extracts were washed with sodium bicarbonate and sodium chloride solutions, dried, and concentrated *in vacuo* to yield 4.5 g of a yellow oil which was shown by vpc analysis to consist of three compounds. Four grams of the mixture was chromatographed on 150 g of silica gel. Elution with hexane–ethyl acetate (8:2) gave 1.500 g of **2**: ir ($CHCl_3$) 1670 cm^{-1} (sharp); nmr (CCl_4) δ 0.95 (s, 3 H), 1.18 (s, 3 H), 1.68 (s, 3 H), 4.0 (s, 1 H), broad pattern of signals from 1.35 to 1.80 (8 H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (40), 151 (55), 123 (100), 108 (33), 93 (34), 83 (45), 43 (81).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.42; H, 11.15.

Further elution gave 0.35 g of **3**: ir ($CHCl_3$) 1705 cm^{-1}; nmr (CCl_4) δ 0.90 (s, 6 H), 2.06 (s, 3 H), 2.60 (broad s, 1 H), 5.45 (s, 1 H), broad pattern of signals from 1.02 to 2.10 (7 H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (25), 123 (100), 81 (62), 32 (45).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.46; H, 11.21.

The last fractions of the chromatogram contained 1.040 g of **4**: ir ($CHCl_3$) 3640, 3470, 1685, 1615 cm^{-1}; nmr (CCl_4) δ 1.15 (s, 6 H), 1.35–1.45 (m, 3 H), 1.85 (s, 1 H), 1.90 (s, 1 H) (OH), 2.08 (s, 6 H), 2.30–2.55 (m, 2 H), 5.95 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 169 (6.5), 166 (7), 151 (13), 123 (30), 109 (53), 95 (37), 83 (43), 43 (100).

Ethyl 1,3-Dimethylcyclohex-2-en-1-ylacetate (6).—A solution of 1.26 g (0.01 mol) of **5**, 11 g (0.07 mol) of triethyl orthoacetate, and 0.045 ml of propionic acid was stirred for 5 hr at 138° until no more starting alcohol was detectable by thin layer chromatography. After excess triethyl orthoacetate was distilled off at 50° (20 mm), the residue was washed with sodium bicarbonate and sodium chloride solutions, dried, and distilled to give 0.38 g (20%) of a colorless oil: bp 45–48° (1 mm); ir ($CHCl_3$) 1720 cm^{-1}; nmr (CCl_4) δ 1.02 (s, 3 H), 1.12 (t, J = 8 Hz, 3 H), 1.60 (s, 3 H), 1.50–1.85 (m, 6 H), 2.12 (s, 2 H), 4.05 (q, J = 8 Hz, 2 H), 5.16 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 196 (4), 181 (1.7), 150 (5), 109 (100), 108 (54), 107 (17), 93 (26), 81 (9), 79 (10), 77 (9), 67 (20), 55 (10), 43 (8), 41 (16), 29 (16).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.10; H, 10.52.

1,3-Dimethylcyclohex-2-en-1-ylacetic Acid (7).—A solution of 0.090 g (0.54 mmol) of **6** in 2 ml of 1.2% sodium hydroxide in methanol was refluxed for 40 min. After the methanol was removed *in vacuo*, the residue was poured into 3 ml of water and was washed three times with ether. The aqueous phase was acidified with 2 *N* hydrochloric acid and extracted four times with ether. The combined ether solutions were dried and the solvent was removed *in vacuo* to yield a brown oil which was distilled at 1 mm (bath 140°) to give 0.061 g (75%) of a colorless, viscous oil: ir ($CHCl_3$) 2950 (broad), 1700 cm^{-1}; nmr (CCl_4) δ 1.12 (s, 3 H), 1.62 (s, 3 H), 1.40–1.90 (m, 6 H), 2.12 (s, 2 H), 5.15 (s, 1 H), 11.60 (broad s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (7), 153 (5), 122 (4), 109 (100), 108 (36), 93 (37), 77 (17), 67 (28), 55 (12), 41 (22).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.81.

1,3-Dimethylcyclohex-2-en-1-ylacetone (8).—A solution of 0.62 g (0.0037 mol) of **7** and 10 ml of anhydrous ether was added dropwise to 5.2 ml of 1.6 *M* methyllithium in ether at −78°. After the addition was complete (20 min) the reaction mixture was stirred for 1 hr at this temperature and was then poured into 5 g of ice and extracted four times with ether. The combined ether solutions were washed with sodium chloride solution and dried, and the solvent was removed *in vacuo*. The residue was distilled at 28 mm (130° bath temperature) to give 0.565 g of a colorless liquid which showed two peaks in the vpc in the ratio of 88:12. The compounds were chromatographed on 15 g of silica gel with hexane–ethyl acetate (95:5) to give after distillation 0.402 g of pure **8**: ir ($CHCl_3$) 1700 cm^{-1}; nmr (CCl_4) δ 1.02 (s, 3 H), 1.62 (s, 3 H), 1.40–1.92 (m, 6 H), 2.00 (s, 3 H), 2.30 (s, 2 H), 5.20 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 166 (0.7), 151 (1.3), 123 (3.5), 109 (100), 108 (70), 93 (30), 81 (17), 67 (30), 55 (14), 43 (67), 41 (19).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.37; H, 11.08.

1,3,5-Trimethyl-2-oxabicyclo[3.3.1]non-3-ene (2).—To 1.0 ml of 75% aqueous sulfuric acid at 0° was added dropwise 0.180 g of **8**. After stirring for 4 hr in an ice bath, the mixture was poured onto 3 g of ice and extracted four times with ether. The organic phase was washed with sodium bicarbonate and sodium chloride solutions and dried, and the solvent was removed *in vacuo*. The residue was distilled at 25 mm (bath 90°) to give 0.146 g (81%) of a colorless liquid which had ir, nmr, mass spectrum, and vpc retention time identical with those of an authentic sample of **2**.

1,1,3-Trimethyl-2-acetylcyclohex-3-ene (3).—To 10 ml of 1.6 *M* methyllithium solution in ether was added 0.100 g (0.55 mmol) of α-cyclogeranic acid methyl ester and the mixture was heated at reflux for 12 hr. The reaction mixture was poured onto 5 g of ice and extracted five times with ether, the combined organic extract was washed with sodium chloride solution and dried, and the solvent was evaporated *in vacuo*. The residue was distilled at 20 mm (bath 120°) to give 0.060 g (66%) of a colorless liquid, which had ir, nmr, mass spectrum, and vpc retention time identical with those of an authentic sample of **3**.

Hydration of 4,8-Dimethylnona-3,7-dien-2-one (1).—To a suspension of 3.5 g of mercuric acetate in 22 ml of water–tetrahydrofuran (1:1) was added 1.66 g (0.01 mol) of **1**. The temperature was kept below 20° with an ice bath. The yellow precipitate disappeared after 20 sec and the clear solution was stirred for 10 min at 25°. After cooling in an ice bath, 11 ml of 3 *N* sodium hydroxide and 11 ml of 0.5 *M* sodium borohydride in 3 *N* sodium

(7) W. Hoffmann, H. Pasedach, H. Pommer, and W. Reif, *Justus Liebigs Ann. Chem.*, **747**, 60 (1971).

(8) K. H. Schulte-Elte, H. Strickler, and G. Ohloff, *Helv. Chim. Acta*, in preparation.

hydroxide were added. The liquid phase was decanted from the precipitated mercury and extracted with ether. The organic extract was washed with sodium chloride solution and dried, and the solvent was removed *in vacuo* to yield 1.80 g of a yellow liquid which showed four spots on tlc. Chromatography on 30 g of silica gel eluting with hexane–ethyl acetate (2:1) gave 0.300 g of a compound which had ir, nmr, mass spectrum, and tlc identical with those of **4**.

Cyclization of **4**.—To a solution of 0.40 ml of 75% aqueous sulfuric acid was added 0.10 g of **4**. After stirring for 4 hr at 10°, the mixture was poured onto 2 g of ice and extracted four times with ether. The organic phases were washed with sodium bicarbonate and sodium chloride solutions and dried. The residue, after evaporation of the solvent *in vacuo*, showed by vpc analysis **2** and **3** in the ratio of 81:19 as the only reaction products.

Registry No.—(*E*)-**1**, 27539-94-2; (*Z*)-**1**, 27575-61-7; **2**, 37709-65-2; **3**, 37709-66-3; **4**, 27243-05-6; **5**, 29481-98-9; **6**, 37709-69-6; **7**, 37709-70-9; **8**, 37709-71-0.

Acknowledgment.—We are indebted to Firmenich et Cie., Geneva, for generous financial support.

Synthesis of *C*-Methyl Derivatives of 1-Phenyl-1,3,5-hexanetrione[1]

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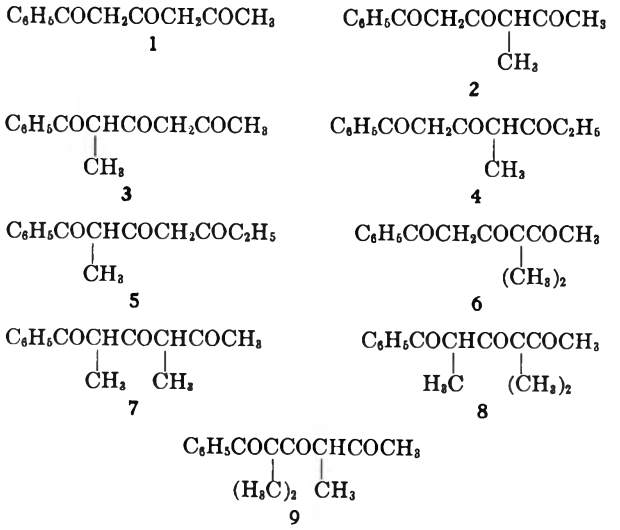
Received September 27, 1972

Eight *C*-methyl derivatives of 1-phenyl-1,3,5-hexanetrione (**1**) have been prepared using two basic techniques: acylation of substituted diketones with esters using lithium amide or sodium hydride as the base, and alkylation of triketone **1** with methyl iodide using sodium hydride or potassium carbonate as the base. The lithium amide method compliments the sodium hydride method in the acylation of diketones, since the former gives good yields when aliphatic esters are employed and the latter is convenient for, but limited to, aromatic esters. The reaction of triketone **1** with sodium hydride and methyl iodide gave the 2- and 4-mono- and 2,2- and 4,4-dimethylation products, the 4 position being the preferred site of reaction. Proton transfer reactions played a major role in the formation of the dialkylation products. Under conditions suppressing proton transfer reaction, the disodium salt of triketone **1** reacted with methyl iodide to give the 2,4-dimethyl derivative. The 2,2,4- and 2,4,4-trimethyl derivatives were prepared by treatment of **1** with excess methyl iodide and potassium carbonate in acetone; both of the trimethylation products cyclized spontaneously to give cyclic hemiketals.

The cyclization reactions of 3,5,7-triketo acids have been studied intensively because they are possible models of the pathways by which resorcylic acids, acylphloroglucinols, and related compounds are formed in nature.[2] Often these metabolites are found having methyl or other alkyl groups present at one or more of the unsubstituted positions, and it has been proposed[3] and, in some cases, demonstrated[4] that these substituents can be introduced prior to cyclization of the triketo acids. For this reason we sought to study the cyclization reactions of 2-, 4-, and 6-*C*-methyl derivatives of 7-phenyl-3,5,7-trioxoheptanoic acid, the synthesis of which required the corresponding methyl derivatives of 1-phenyl-1,3,5-hexanetrione (**1**). Numerous triketones have been prepared previously, but most of those required for this study have not. This paper, therefore, describes synthetic approaches to methyl derivatives **2**–**9**, employing either acylation reactions of β diketones or methylation reactions of anions of **1**. Although the alkylation reactions of β-dicarbonyl compounds have been studied extensively,[5] the reactions of β triketones have received only limited attention.[6,7]



Results

Acylation Reactions.—Hauser and coworkers developed several closely related procedures for the preparation of 1,3,5 triketones by acylation of β diketones with esters in the presence of strong bases. The use of sodium amide or potassium amide in liquid ammonia gave satisfactory results with aromatic esters, but aliphatic esters required the use of lithium amide.[8] These reactions involve formation and acylation of 1,3 dianions of the β diketones; the metallic cation effect results from rapid proton abstraction from aliphatic esters by disodio and dipotassio diketones but relatively slow abstraction by the dilithium derivatives. With aromatic esters, an attractive alternative to the amide methods is the use of sodium hy-

(1) We gratefully acknowledge the generous support by the U. S. Public Health Service through Research Grant GM-12848 and Career Development Grant (to T. M. H.) GM-27013.

(2) T. T. Howarth and T. M. Harris, *J. Amer. Chem. Soc.*, **93**, 2506 (1971), and references cited therein.

(3) A. J. Birch, *Proc. Chem. Soc.*, 3 (1962).

(4) For example, see A. I. Scott, H. Guilford, and E. Lee, *J. Amer. Chem. Soc.*, **93**, 3534 (1971).

(5) See H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9.

(6) K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965).

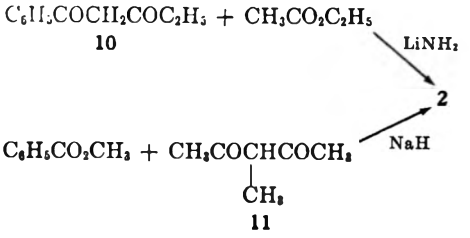
(7) J. Carnduff, J. A. Miller, B. R. Stockdale, J. Larkin, D. C. Nonhebel, and H. C. S. Wood, *J. Chem. Soc., Perkin Trans. 1*, 692 (1972).

(8) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958); R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960); S. D. Work and C. R. Hauser, *ibid.*, **28**, 725 (1963); F. B. Kirby, T. M. Harris, and C. R. Hauser, *ibid.*, **28**, 2266 (1963).

dride in ethereal solvents.[6,9] Here the reaction mechanism is far from clear. Sodium hydride converts diketones into their monoanions but not their dianions; yet the monosodio diketones in the presence of excess sodium hydride react at the terminal position with aromatic esters to give 1,3,5 triketones.

Either the acetylation of diketone **10** or the benzoylation of diketone **11** should be satisfactory for the preparation of diketone **2** (Scheme I). Because of the

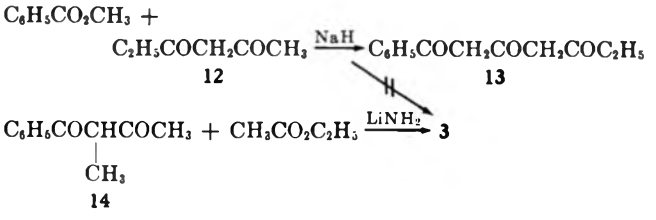
SCHEME I



simplicity of the sodium hydride method, the latter was chosen and gave diketone **2** in 43% yield.

For the preparation of **3** the sodium hydride method would not have been satisfactory, since methyl–methylene type unsymmetrical diketones undergo aroylation at the methyl position.[6] Consequently, benzoylation of diketone **12** would have given the isomeric triketone **13**. However, triketone **3** was formed in 46% yield by acetylation of diketone **14** using the lithium amide method (Scheme II).

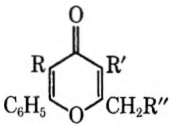
SCHEME II



In contrast, the sodium hydride method was the method of choice for the preparation of **4**; benzoylation of unsymmetrical diketone **15** occurred preferentially at the acetyl methyl group to give **4** in 65% yield. Similarly, triketone **5** was prepared in 52% yield by the benzoylation of symmetrical diketone **16**.

The structures of triketones **2–5** were consistent with physical data (see Experimental Section), the mass spectra being of particular value. These showed α cleavage on one and sometimes both sides of each of the carbonyl groups, along with some McLafferty-type cleavages. The structures were confirmed by the conversion of **2–5** into the corresponding 4-pyrones (**17–20**) by treatment with cold, concentrated sulfuric acid. It is noteworthy that **2–5** undergo pyrone formation much more readily than **1**; indeed, pyrone formation was observed during distillation of the compounds and sometimes on storage.

(9) (a) M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965); (b) D. M. von Schriltz, M. L. Miles, and C. R. Hauser, *ibid.*, **32**, 1774 (1967).

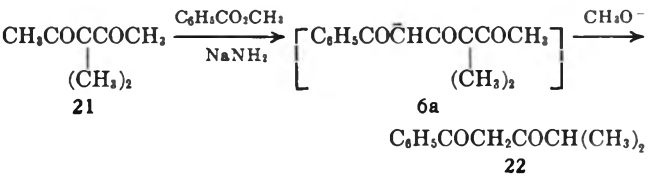


17, R = R'' = H; R' = CH_3
18, R = CH_3; R' = R'' = H
19, R = H; R' = R'' = CH_3
20, R = R'' = CH_3; R' = H

It should be mentioned that the successful benzoylations of diketones **11**, **15**, and **16** provide a useful extension of the sodium hydride method. Previous examples have been limited to aroylations of acetyl methyl groups of diketones, yielding triketones lacking substituents at the central methylene positions.

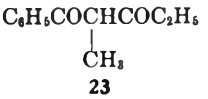
For the preparation of triketone **6**, benzoylation of diketone **21** was investigated, sodium amide being employed as the condensing agent (Scheme III). The

SCHEME III



method was unsatisfactory; the only product isolated was diketone **22**, which presumably arises by cleavage of the triketone. Cleavage occurs at the 4 bond because the uncharged 5-carbonyl group of **6a** is prone to attack by methoxide ion. The same problem exists with the sodium hydride method; in fact, the higher temperatures required for sodium hydride reactions increase the risk of this type of cleavage. The prospects for assembly of **6** by acetylation of **22** are poor; acylation of dianions of isobutyryl-type diketones has never been observed and alkylation occurs only in low yield.[10]

For the preparation of **7**, the best method appeared to be acetylation of the dilithium salt of diketone **23**, but the reaction was unsuccessful and unaltered diketone **23** was recovered. It is not known whether the dianion of **23** failed to form or failed to be acylated, but the successful acetylation of the dilithium salt of **14** suggests the former.



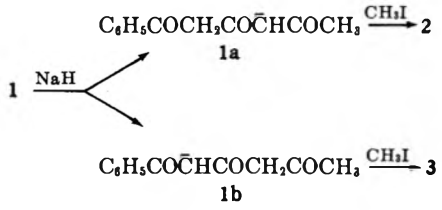
In view of these failures, the synthesis of **8** and **9** by anionic acylation procedures appeared unlikely and alkylation methods were next investigated as possible routes to the 2- and 4-di- and -trimethylated triketones **6–9**.

Methylation Reactions.—Triketone **1** reacts with 1 equiv of sodium hydride to form monoanions **1a** and **1b**. By monitoring the evolution of hydrogen, ionization was found to be essentially complete after 1–2 min. Treatment of the mixture of **1a** and **1b** with 1 equiv of methyl iodide gave a product mixture composed mainly of **1**, **2**, and **3** in the ratios 56:26:18

(10) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **31**, 1035 (1966).

(Scheme IV). The analysis was made by comparison of the nmr spectrum of the unfractionated product

SCHEME IV



mixture with spectra of authentic samples of **1**–**3**. We would expect the acidities of **1a** and **1b** to be similar since the pK_a values (determined in hydroxylic solvents) of acetylacetone and benzolacetone are, respectively, 9.01 and 8.73.[11] The 4-methylation to 2-methylation ratio of 1.4 suggests that **1a** might be slightly more nucleophilic than **1b**.

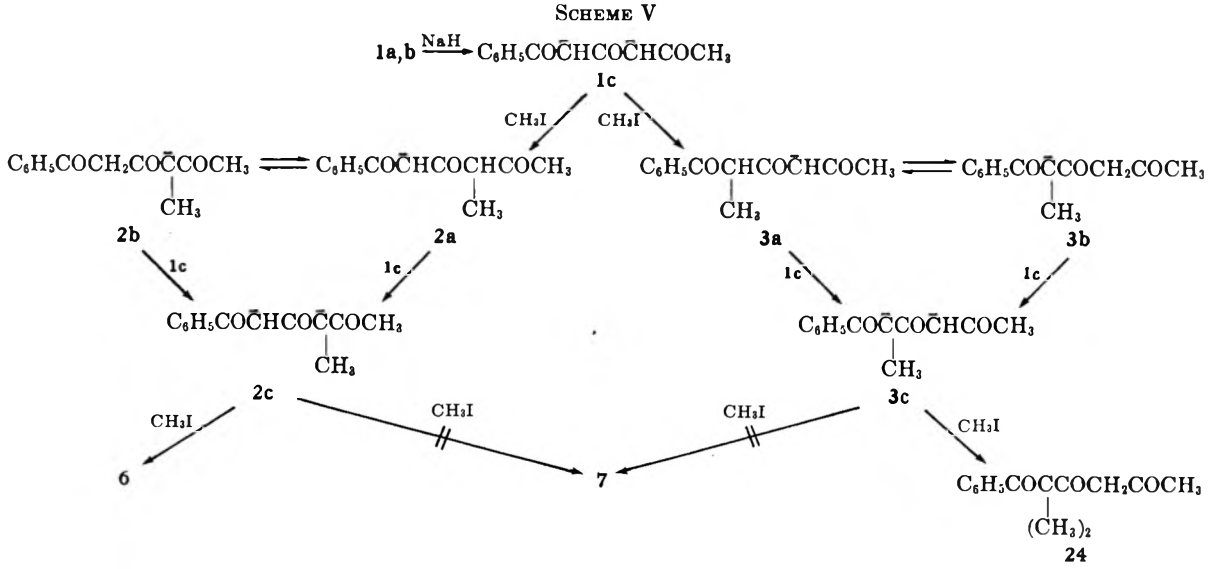
An additional equivalent of hydrogen was evolved when the mixture of **1a** and **1b** was treated with excess sodium hydride, the ionization process to form dianion **1c** requiring as much as 2 hr to go to completion. No significant additional amount of hydrogen was evolved during a subsequent 24-hr period. A crude comparison of alkylation rates showed **1c** to be at least ten times more reactive than **1a,b**. When **1c** was treated with 1 equiv of methyl iodide, nmr analysis of the product mixture indicated **1**, **2**, **3**, and **6** to be present in the approximate ratios 18:46:24:12 (Scheme V).

In view of the lower reactivity of monoanions **1a,b** compared with **1c**, it seems likely that **6** arose primarily from **2c**, which was formed by reionization of **2a,b** by **1c**. This hypothesis for formation of **6** requires that **2c** not be appreciably more basic than **1c** and that **2c** show high selectivity for methylation at the 4 position. The pK_a of diketone **11**, measured in an aqueous medium, has been reported to be 10.88,[13] which by comparison with that for benzoylacetone[11] suggests that **2c** should be about 100 times more basic than **1c**. However, recent studies of the acidities of aliphatic monoketones by House and coworkers have shown that with lithium salts in an ethereal solvent alkyl branching at the α position tends to stabilize enolate anions.[14] A similar effect in the present case would diminish the difference in the basicities of **1c** and **2c** and would facilitate formation of **2c**.

The selectivity of **2c** for methylation at the 4 position was demonstrated by forming **2c** from **2** and treating it with 1 equiv of methyl iodide. The reaction afforded 43% of triketone **6**; most of the remainder of the product mixture was starting triketone **2** and the related pyrone **18**. Less than 3% of triketone **7** was present, emphasizing the greater nucleophilicity of the 4 position of **2c** compared to the 2 position.

In the alkylation of **1c**, the failure of product **3** to undergo further methylation under the reaction conditions would appear to stem from failure of **3a,b** to be reionized by **1c**. Steric inhibition of resonance in **3c**, resulting from interaction between the phenyl and

SCHEME V



Complete interpretation of the nmr spectrum was not possible until after the synthesis of **6** and **7** had been achieved and a sample of **24** had been prepared by the method of Pinder and Robinson.[12] Little evidence was found for the presence of triketones **7** and **24**, indicating that, if present, they made up less than 3% of the product mixture. Combining the yields of **2** and **6** to obtain the total amount of initial attack at the 4 position, the ratio of 4- to 2-methylation was 2.1, reflecting again a preference for the initial attack to occur at the 4 position.

the 2-methyl groups, makes **3c** substantially more basic than **1c**.

From the above considerations, it is clear that, for the synthesis of **6**, the use of 3 equiv of sodium hydride (as well as 2 equiv of methyl iodide) would be advantageous. The third equivalent would replace **1c** in the ionization of **2a,b** to form **2c** (see Scheme V). Another way to view this is that, irrespective of the mechanism of formation of **6**, as much as 3 equiv of base will be consumed in the formation of **6**, since the com-

(11) L. Laloi and P. Rumpf, *Bull. Soc. Chim. Fr.*, 2461 (1964).
(12) A. R. Pinder and R. Robinson, *J. Chem. Soc.*, 3341 (1955).
(13) L. Laloi and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1645 (1961).
(14) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); H. O. House and B. M. Trost, *ibid.*, **30**, 1341 (1965).

pound will probably be present in the final reaction mixture as its monoanion. These expectations were borne out when a reaction employing 3 equiv of sodium hydride and 2 of methyl iodide produced triketones **2**, **3**, **6**, and **24** in the ratios 1:12:81:6. Triketone **6** was isolated from the mixture by column chromatography in 52% yield. The course of this reaction was followed by taking aliquots from the reaction mixture periodically and estimating their composition by nmr. The results are shown in Table I.

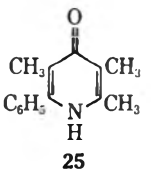
TABLE I

ALKYLATION OF TRIKETONE 1 EMPLOYING 3 EQUIV OF SODIUM HYDRIDE AND 2 EQUIV OF METHYL IODIDE IN TETRAHYDROFURAN

Reaction period, hr	Triketones, %					
	1	2	3	6	7	24
0.1	80	12	6	2	0	0
0.5	52	24	11	10	0	3
3	3	4	12	75	0	6
18	0	5	7	80	0	8
21	0	1	12	81	0	6

Initially, the main products were monomethylated triketones **2** and **3**, with the former predominating, the concentration of **2** peaking after 0.5 hr and then falling as further alkylation occurred to give **6**. This second alkylation was rapid and **6** made up 75% of the mixture after 3 hr, the reaction being essentially complete at that point. The presence of **24** in the reaction mixture reflects the fact that sodium hydride, in contrast to **1c**, is able to convert **3a,b** to **3c** (see Scheme V). It is interesting that **3c**, like **2c**, methylates at the site of initial methylation. Thus, **24**, not **7**, was the product formed.

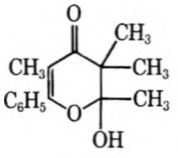
In order to prepare triketone **7** from **1**, conditions were required under which the alkylation of both of the anions of **1c** would proceed faster than proton transfer reactions. This would avoid the formation of **6** and **24** and was achieved using methyl iodide as the solvent, following a procedure for the monoalkylation of a benzoylacetone by Hindley.[15] The disodium salt of **1c** was formed in tetrahydrofuran, isolated, and resuspended in methyl iodide. After refluxing for 3 hr, **7** was isolated in 24% yield by column chromatography. Longer reaction periods gave higher yields of **7** but the isolation was complicated by the presence of additional products. The structure of **7** was confirmed spectroscopically and by transformation into pyridone **25**. Triketone **7** might also have been prepared by use



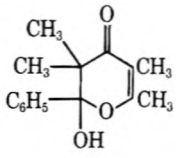
25

of the thallium salt of **1c**.[16] However, the present method avoids the toxicity hazards associated with the handling of thallium compounds.

Triketones **8** and **9** were prepared by treatment of **1** with excess methyl iodide and potassium carbonate in refluxing acetone. The reaction yielded 20% of a mixture of the two trimethylated compounds with **8** predominating and no indication of the tetramethylation product. Triketones **8** and **9** exist as cyclic hemiketals **26** and **27** with dissymmetry of the molecules



26



27

evident in the nmr spectra, the geminal methyl groups being nonequivalent in both cases. The hemiketals were distinguished from each other by their ultraviolet spectra, the more highly conjugated **26** exhibiting λ_{max} at 296 nm compared with 243 nm for **27**. Similar structures could not be detected in the tautomer mixtures of **1**–**6**, although it is likely that they are intermediates in the formation of 4-pyrones from triketones lacking geminal substituents. Triketone **7** possibly has small amounts of hemiketal epimers in equilibrium with the acyclic tautomers. A more useful preparative synthesis of **26** is treatment of triketone **6** with methyl iodide and potassium carbonate in refluxing acetone. Cyclic hemiketal **26**, identical in all respects with the sample prepared above, was isolated in 57% yield.

Experimental Section

Silicar CC-4 (100–200 mesh) silicic acid, obtained from Mallinckrodt Chemical Works, was used for column chromatography. The products were eluted with hexane containing increasing amounts of ether. Melting points were taken in open capillaries and are corrected. Infrared spectra were obtained using either liquid films or potassium bromide discs with a Beckman IR-10 spectrophotometer. Ultraviolet spectra were recorded with a Beckman DB spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a Varian A-60 or an XL-100 spectrometer with tetramethylsilane as the internal standard. With triketones, which can exist as a mixture of several keto–enol tautomers, data are given for the dominant form. Mass spectra were recorded using the direct inlet of an LKB-9000 gas chromatograph–mass spectrometer at 70 eV. Only molecular ions and important α-cleavage and McLafferty-type fragments are reported. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

4-Methyl-1-phenyl-1,3,5-hexanetrione (2).—A solution of 3-methyl-2,4-pentanedione[17] (11, 19.4 g, 0.17 mol) in 20 ml of tetrahydrofuran (THF) was added to a cooled (ice bath) suspension of sodium hydride (16.8 g, 0.7 mol, from a sodium hydride suspension in oil) in THF (600 ml). When hydrogen evolution from the mixture had ceased, methyl benzoate (46 g, 0.34 mol) in THF (50 ml) was added dropwise over 2 hr. After an additional 7 hr at reflux, the solvent was removed *in vacuo*, ether (250 ml) was added to the cooled residue, and excess base was destroyed with the cautious addition of ice. The mixture was extracted with water and the extract was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with 5% sodium bicarbonate and with water, dried with magnesium sulfate, and evaporated *in vacuo* to leave a brown oil. Distillation afforded **2** (14.0 g, 38%) as a pale yellow oil: bp 115–120° (0.2 mm); ir (neat oil) 1720, 1601, 1450 cm^{-1}; uv (EtOH) 310 nm (ϵ 15,700), 247 (5400), 222 (6200); nmr (CCl_4) δ (2-enol tautomer), 1.39 (3, d, J = 7 Hz, 4-$CHCH_3$), 2.23 (3, s, 6-CH_3), 3.57 (1, q, J = 7 Hz, 4-$CHCH_3$), 6.24 (1, s, 2-CH=), 7.25–8.00 (5, m, 1-C_6H_5), 12.0–13.5 ppm (1, s, enol); mass spectrum m/e (rel intensity) 218 ($M^{\cdot+}$, 21), 176 (46), 147 (100), 120 (4), 105 (87), 99 (5), 43 (52).

(15) K. B. Hindley, Ph.D. Thesis, Liverpool University, England, 1970, p 30.

(16) E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

(17) A. W. Johnson, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 4254 (1958).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.57; H, 6.52.

2-Methyl-1-phenyl-1,3,5-hexanetrione (3).—To a suspension of 0.5 mol of lithium amide (prepared from 3.5 g of lithium) in anhydrous, liquid ammonia (750 ml) was added 2-methyl-1-phenyl-1,3-butanedione[18] (**14**, 16.3 g, 0.0925 mol) in ether (15 ml). After 2 hr, 35.2 g (0.4 mol) of ethyl acetate was added and, after an additional 10 hr, the ammonia was evaporated. Ether (300 ml), ice, and then dilute hydrochloric acid were added; the ethereal layer was separated, washed with water and with 5% sodium bicarbonate, dried over magnesium sulfate, and evaporated *in vacuo* to leave a dark red-brown oil. Chromatography afforded **3** (9.0 g, 45%) as a pale yellow oil which solidified below 0°: bp 115–118° (0.2 mm); mp 25–30°; ir (neat) 1690, 1600, 1455 cm^{-1}; uv (EtOH) 281 nm (ϵ 11,500), 249 (11,900); nmr (CCl_4) δ (4-enol tautomer) 1.41 (3, d, J = 7 Hz, 2-$CHCH_3$), 1.93 (3, s, 6-CH_2), 4.25 (1, q, J = 7 Hz, 2-$CHCH_3$), 5.43 (1, s, 4-CH=), 7.3–8.1 (5, m, 1-C_6H_5), 15–17 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 218 ($M\cdot^+$, 3), 134 (3), 105 (100), 85 (5), 43 (16).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.80; H, 6.60.

4-Methyl-1-phenyl-1,3,5-heptanetrione (4).—Following the general procedure outlined for triketone **2**, the reaction of 3-methyl-2,4-hexanedione[19] (**15**, 12.8 g, 0.1 mol), methyl benzoate (34 g, 0.25 mol), and sodium hydride (7.2 g, 0.3 mol) afforded **4** (15 g, 65%) as a pale yellow oil: bp 118–125° (0.18 mm); ir (neat) 1720, 1605, 1455 cm^{-1}; uv (EtOH) 314 nm (ϵ 15,300), 248 (5550), 222 (5700); nmr (CCl_4) δ (2-enol tautomer) 1.02 (3, t, J = 7 Hz, 7-CH_3), 1.35 (3, d, J = 7 Hz, 4-$CHCH_3$), 2.46 (2, q, J = 7 Hz, 6-CH_2), 3.52 (1, q, J = 7 Hz, 4-$CHCH_3$), 6.20 (1, s, 2-CH=), 7.25–8.00 (5, m, 1-C_6H_5), 13.7–15.5 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 232 ($M\cdot^+$, 9), 203 (5), 176 (57), 147 (71), 105 (100), 57 (52).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.26; H, 6.95.

2-Methyl-1-phenyl-1,3,5-heptanetrione (5).—Following the general procedure outlined for triketone **2**, the reaction of dipropionylmethane[19] (**16**, 12.8 g, 0.1 mol), methyl benzoate (27.2 g, 0.2 mol), and sodium hydride (7.2 g, 0.3 mol) afforded **5** (12.0 g, 52%) as a pale yellow oil: bp 110–113° (0.08 mm); ir (neat) 1685, 1600, 1452 cm^{-1}; uv (EtOH) 282 nm (ϵ 11,000), 249 (11,300); nmr (CCl_4) δ (4-enol tautomer) 1.05 (3, t, J = 7 Hz, 7-CH_3), 1.42 (3, d, J = 7 Hz, 2-$CHCH_3$), 2.22 (2, q, J = 7 Hz, 6-CH_2), 4.27 (1, q, J = 7 Hz, 2-$CHCH_3$), 5.47 (1, s, 4-CH=), 7.25–8.10 (5, m, 1-C_6H_5), 12.6–14.0 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 232 ($M\cdot^+$, 3), 176 (4), 134 (5), 105 (100), 99 (5), 57 (8).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.49; H, 6.96.

4,4-Dimethyl-1-phenyl-1,3,5-hexanetrione (6).—This compound was synthesized by two routes.

(1) A solution of 1-phenyl-1,3,5-hexanetrione[9a] (**1**, 10.2 g, 0.08 mol) in THF (100 ml) was added with stirring to an ice–salt cooled suspension of sodium hydride (6.0 g, 0.25 mol) in THF (100 ml). The mixture was stirred at −20° for 2 hr and then methyl iodide (15 g, 0.17 mol) was added in one batch. The mixture was stirred for 6 hr at −20° and 20 hr at room temperature. The solvent was removed *in vacuo*, the excess base was destroyed by cautious addition of ice, and the mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to give a red-brown oil. Chromatography on silicic acid afforded **6** (6.05 g, 52%) as a pale yellow oil: ir (neat) 1710, 1600, 1565, 1455, and 1350 cm^{-1}; uv (EtOH) 306 nm (ϵ 15,900), 244 (5500), 229 (sh, 6400), 223 (7100); nmr ($CDCl_3$) δ (2-enol tautomer) 1.35 [6, s, 4-$C(CH_3)_2$], 2.08 (3, s, 6-CH_3), 6.11 (1, s, 2-CH=), 7.25–7.94 (5, m, 1-C_6H_5), 13.7–15.7 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 232 ($M\cdot^+$, 11), 190 (60), 147 (100), 105 (80), 86 (31), 43 (47).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.60; H, 7.04.

(2) Triketone **2** was added to a suspension of sodium hydride (0.286 g, 0.012 mol) in THF (100 ml). After the evolution of hydrogen had slowed, the mixture was warmed at 40° until evolution ceased. The mixture was cooled and methyl iodide (1.5 g, 0.011 mol) was added. After 0.5 hr at room temperature and 1 hr at 45°, the solvent was removed *in vacuo* and the excess base was destroyed with the cautious addition of ice. The mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water, dried with magnesium sulfate, and evaporated *in vacuo* to yield a brown oil. Chromatography afforded **6** (1.0 g, 43%) as a pale yellow oil, identical in all respects with the sample prepared above.

2,4-Dimethyl-1-phenyl-1,3,5-hexanetrione (7).—Triketone **1** (25.5 g, 0.125 mol) in THF (120 ml) was added to a slurry of sodium hydride (6.0 g, 0.25 mol) in THF (500 ml) over 1 hr. The mixture was stirred at room temperature for 18 hr, concentrated to 200 ml *in vacuo*, and cooled in an ice bath. The precipitate was collected by filtration and recrystallized from THF (100 ml) to yield fine crystals of disodium salt **1c** (9.8 g, 39%).

A mixture of disodium salt **1c** (2.00 g, 0.0115 mol) and methyl iodide (80 ml) was refluxed for 3 hr, cooled to room temperature, and filtered. The filtrate was evaporated *in vacuo* to yield a yellow oil which was taken up in ether. The solution was washed with water, dried with magnesium sulfate, and evaporated *in vacuo*. Chromatography of the residue furnished **7** (0.445 g, 24%) as a pale yellow oil: ir (neat) 1692, 1600, 1454 cm^{-1}; uv (EtOH) 290 nm (ϵ 9620), 220 (8030); nmr ($CDCl_3$) δ (triketo tautomer) 1.15–1.55 (2- and 4-$CHCH_3$ not resolved from signals of enol tautomers), 2.1 (3, s, 6-CH_3), 3.83 (1, q, J = 7 Hz, 4-$CHCH_3$), 4.8 (1, q, J = 7 Hz, 2-$CHCH_3$), 7.25–8.1 ppm (m, 1-C_6H_5); mass spectrum (rel intensity) 232 (1.1, $M\cdot^+$), 190 (6.1), 161 (9.1), 134 (10), 105 (100), 43 (25). The material, although substantially free of impurities, was not analytically pure; purification was hampered by decomposition that occurred during chromatography and other manipulation. A satisfactory analysis was obtained on the pyridone derivative **25** described below.

2,3-Dihydro-2-hydroxy-2,3,3,5-tetramethyl-6-phenyl-4*H*-pyran-4-one (26) and 5,6-Dihydro-6-hydroxy-2,3,5,5-tetramethyl-6-phenyl-4*H*-pyran-4-one (27) by Methylation of 1.—A mixture of triketone **1** (10.2 g, 0.05 mol), methyl iodide (18.2 g, 0.128 mol), anhydrous potassium carbonate (17.0 g, 0.123 mol), and acetone (150 ml) was refluxed for 7 hr, cooled, and filtered. The filtrate was evaporated *in vacuo;* recrystallization of the residue from chloroform–hexane gave **26** (3.0 g, 20%), containing a small amount of **27**. Chromatography gave **26** as colorless crystals: mp 120–140° after recrystallization from chloroform–hexane; ir (KBr pellet) 1640, 1600, 1455, 1375 cm^{-1}; uv (EtOH) 296 nm (ϵ 13,800), 227 (6700); nmr ($CDCl_3$) δ 1.20 (3, s, 3-CH_3), 1.26 (3, s, 3-CH_3), 1.62 (3, s, 2- or 5-CH_3), 1.83 (3, s, 5- or 2-CH_3), 3.61 (1, s, 2-OH, exchangeable with D_2O), 7.1–7.8 ppm (5, m, 6-C_6H_5); mass spectrum *m/e* (rel intensity) 246 ($M\cdot^+$, 10), 204 (14), 161 (100), 134 (6), 105 (97), 86 (20), 43 (37).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.17; H, 7.48.

A later fraction from the column was recrystallized from chloroform–hexane to give **27**: mp 136–148°; ir (KBr pellet) 1600, 1440, 1385, 1342 cm^{-1}; uv (EtOH) 273 nm (ϵ 10,300); nmr ($CDCl_3$) δ 0.93 (3, s, 5-CH_3), 1.11 (3, s, 5-CH_3), 1.80 (3, s, 2- or 3-CH_3), 2.08 (3, s, 3- or 2-CH_3), 3.1 (1, s, 6-OH, exchangeable with D_2O), 7.1–7.8 ppm (5, m, 6-C_6H_5); mass spectrum *m/e* (rel intensity) 46 ($M\cdot^+$, 6), 204 (3), 148 (21), 105 (100), 99 (6), 43 (21).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15, H, 7.37. Found: C, 73.33; H, 7.53.

Pyran 26 by Methylation of 6.—A mixture of triketone **6** (1.0 g, 0.0043 mol), methyl iodide (1.4 g, 0.0106 mol), anhydrous potassium carbonate (3.0 g, 0.0217 mol), and acetone (60 ml) was refluxed for 5 hr, cooled, and filtered. The filtrate was evaporated *in vacuo*, the residue was dissolved in ether, and the ethereal solution was washed with water, dried with magnesium sulfate, and evaporated *in vacuo*. Recrystallization of the residue from chloroform–hexane gave **26** (0.6 g, 57%) as colorless cubes, mp 120–140°, identical in all respects with the specimen prepared above.

General Procedure for Preparation of Pyran-4-ones 17–21.—Approximately 1.5 g of the appropriate triketone was combined with sulfuric acid (20 ml) at 0°. After 2 hr, the mixture was neutralized by the addition of ice and solid sodium bicarbonate and was extracted with ether. The extract was washed with 2 *M* sodium hydroxide and with water, dried with magnesium sulfate, and evaporated *in vacuo*. Solid products were re-

(18) Diketone **14**, bp 90° (0.2 mm), was prepared in 88% yield by the procedure described by Johnson, *et al.*, for the preparation of **11**.[17]

(19) F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 1352 (1950).

crystallized from chloroform–hexane; liquids were purified by column chromatography. Yields and physical data are given for each compound.

2,3-Dimethyl-6-phenyl-4*H*-pyran-4-one (17) was obtained (62%) as tan needles: mp 103–105°; ir (KBr pellet) 1650, 1605, 1445, 1415, 1370 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (3, s, 3-CH_3), 2.39 (3, s, 2-CH_3), 6.70 (1, s, 5-CH=), 7.3–7.9 ppm (5, m, 6-C_6H_5).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.17; H, 6.18.

2,5-Dimethyl-6-phenyl-4*H*-pyran-4-one (18) was obtained (87%) as a pale yellow oil: ir (neat) 1660, 1620, 1445, 1405 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (3, s, 2-CH_3), 2.22 (3, s, 5-CH_3), 6.15 (1, s, 3-CH=), 7.3–7.7 ppm (5, m, 6-C_6H_5).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.75; H, 6.02.

2-Ethyl-3-methyl-6-phenyl-4*H*-pyran-4-one (19) was obtained (98%) as tan needles: mp 62–63°; ir (KBr pellet) 1640, 1600, 1450, 1410, 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.34 (3, t, J = 7 Hz, 2-CH_3), 2.01 (3, s, 3-CH_3), 2.74 (2, q, J = 7 Hz, 2-CH_2), 6.70 (1, s, 5-CH=), 7.3–7.9 ppm (5, m, 6-C_6H_5).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.45; H, 6.58.

2-Ethyl-5-methyl-6-phenyl-4*H*-pyran-4-one (20) was obtained (98%) as a pale yellow liquid: ir (neat) 1660, 1650, 1620, 1445, 1405, 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (3, t, J = 7 Hz, 2-CH_3), 2.06 (3, s, 5-CH_3), 2.57 (2, q, J = 7 Hz, 2-CH_2), 6.20 (1, s, 3-CH=), 7.51 ppm (5, s, 6-C_6H_5).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.26; H, 6.69.

2,3,5-Trimethyl-6-phenyl-4-(1*H*)-pyridone (25).—Liquid ammonia (10 ml) was added to a solution of triketone **7** (1.0 g, 0.0045 mol) in absolute ethanol (300 ml) and the mixture was warmed gently for 10 min and then boiled to dryness on the steam bath. The remaining oil was triturated with acetone to form crude **25** (0.83 g, 86%) as a pale yellow solid. Recrystallization from acetone–absolute ethanol and then from chloroform gave colorless needles: mp 270°; ir (KBr pellet) 1614, 1598, 1490, 1371 cm^{-1}; nmr ($CDCl_3$) δ 2.33 (3, s, 2-CH_3), 2.45 (3, s, 5-CH_3), 2.75 (3, s, 3-CH_3), 7.3–7.7 (5, m, 6-C_6H_5), the 2- and 3-CH_3 signals are broadened by long-range coupling.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.73; H, 6.99; N, 6.45.

Registry No.— **1**, 1469-95-0; **1c**, 37676-25-8; **2**, 37676-26-9; **3**, 37676-27-0; **4**, 37676-28-1; **5**, 37676-29-2; **6**, 37676-30-5; **7**, 37676-31-6; **11**, 815-57-6; **14**, 6668-24-2; **15**, 4220-52-4; **16**, 7424-54-6; **17**, 37676-33-8; **18**, 37676-34-9; **19**, 37735-76-5; **20**, 37676-35-0; **25**, 37676-36-1; **26**, 37676-37-2; **27**, 37735-77-6; methyl benzoate, 93-58-3; ethyl acetate, 141-78-6.

Synthesis of 1,4 and 1,5 Diketones from *N,N,N′,N′*-Tetramethyldiamides and Organolithium Reagents

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A new, one-step synthesis of 1,4 and 1,5 diketones from a variety of organolithium compounds and *N,N,N′,N′*-tetramethylsuccinamide and *N,N,N′,N′*-tetramethylglutaramide is described. Yields vary from 4 to 76%. Yields of 1,5 diketones are generally higher than those of 1,4 diketones. *N,N,N′,N′*-Tetraethylsuccinamide did not give 1,4 diketones with phenyllithium, 2-pyridyllithium, or 6-bromo-2-pyridyllithium.

During the course of some studies on the synthesis and properties of a number of heterocyclic systems, we needed a series of 1,4 and 1,5 diketones as intermediates. In the case of a bis-2-pyridyl diketone, no ready one-step synthesis of these compounds was available. The pyridine substitution pattern dictated the use of a 2-pyridyl Grignard reagent or 2-pyridyllithium compound.

Both aldehydes and ketones have been prepared from *N,N*-dialkylamides and either Grignard reagents[1] or organolithium compounds.[2] Furthermore, it has been reported that diketones are produced in low yield by the reaction of 2 equiv of a Grignard reagent with an *N,N,N′,N′*-tetraalkyldiamide.[3] Repeated failures to prepare any ketone from the Grignard reagent of 2,6-dibromopyridine led us to investigate the organolithium compound.[4] Owing to our initial success, we decided to study the scope of the reaction. To our knowledge, no reaction of 2 equiv of an organolithium compound with *N,N,N′,N′*-tetraalkyldiamides has been reported.

(1) (a) L. Bouveault, *Bull. Soc. Chim. Fr.*, **31**, 1322 (1904); (b) G. Gilbert and B. F. Aycock, *J. Org. Chem.*, **22**, 1013 (1957).

(2) (a) J. Sicé, *J. Amer. Chem. Soc.*, **75**, 3697 (1953); (b) J. Sicé, *J. Org. Chem.*, **19**, 70 (1954); (c) E. A. Evans, *J. Chem. Soc.*, 4691 (1956); (d) E. A. Braude and E. A. Evans, *ibid.*, 3334 (1955); (e) E. Jones and I. M. Moodie, *J. Chem. Soc. C*, 1195 (1967).

(3) (a) E. E. Blaise, *C. R. Acad. Sci.*, **173**, 313 (1921); (b) E. E. Blaise and M. Montague, *ibid.*, **180**, 1345 (1925).

(4) J. E. Parks, B. E. Wagner, and R. H. Holm, *Inorg. Chem.*, **10**, 2477 (1971).

Results and Discussion

The results of our study of the reaction of a variety of organolithium reagents with either *N,N,N′,N′*-tetramethylsuccinamide or *N,N,N′,N′*-tetramethylglutaramide are summarized in Table I. With the exception of 2-thienyllithium, no attempts were made to optimize yields. Butyllithium gave a very complex mixture with *N,N,N′,N′*-tetramethylsuccinamide. In general, the yields of 1,5 diketones were higher than those of the 1,4 diketones.

TABLE I

YIELDS OF PRODUCTS FROM THE REACTION

$$2RLi + Me_2NCO(CH_2)_nCONMe_2 \xrightarrow{-78^\circ} RCO(CH_2)_nCOR$$

R	n	Yield,[a] %	Solvent	Reaction time, hr
Phenyl	2	4	Ether	24
6-Bromo-2-pyridyl	2	71	Ether	3
2-Pyridyl	2	20	Ether	3–4
2-Thienyl[b]	2	33	THF	24
Phenyl	3	50	Ether	24
6-Bromo-2-pyridyl	3	76	Ether	3
2-Pyridyl	3	20	Ether	3–4
2-Thienyl[b]	3	24	THF	24
n-Butyl	3	19	Ether	2

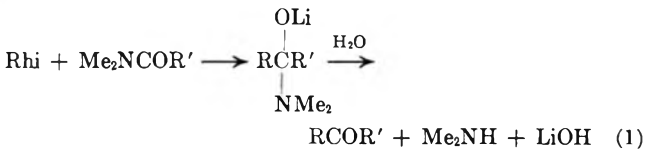
[a] Yields based on purified product. [b] Run with 4 equiv of 2-thienyllithium.

The reactions were monitored by glc. Immediately after mixing of the organolithium reagent with amide, glc showed that all of the starting amide had disappeared and was replaced by diketone and another component which had a shorter retention time. As the reactions proceeded, the shorter retention time peak slowly disappeared as more diketone was formed. In all reactions, this intermediate compound was never completely consumed. The nmr spectra of the crude products showed that an amide was present.

Apparently the short retention time by-products of the reactions are keto amides. These materials were oils which were difficult to purify and were not characterized further. The ease of separation of diketone from these by-products is one of the advantages of the synthetic method.

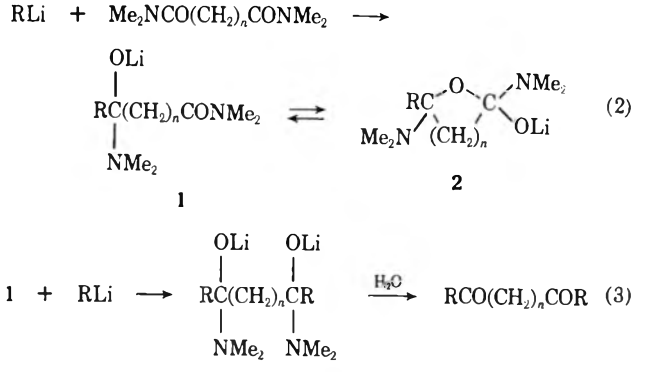
A monoadduct of organolithium compound and an *N,N,N′,N′*-tetraalkyldiamide is implicated as an intermediate in these reactions on the basis of the glc data and in the reaction of 6-bromo-2-pyridyllithium with *N,N,N′,N′*-tetramethylglutaramide. This reaction gives only a 21% yield of diketone when it is hydrolyzed after 5-min reaction time (all of the starting amide was completely consumed in this time). After 3 hr, a 76% yield of diketone was obtained. In our studies, glc also indicated that very little polyalkylation occurred except in the reactions of *n*-butyllithium. The violence of some of the hydrolyses indicated that organolithium reagent remained in some of the reactions.

It is thought that the intermediate formed in the reaction of an organolithium reagent with an *N,N*-dialkylamide does not lose amine until hydrolysis (eq 1).[2d,e] Thus, this appears to be the reason why very



$$\mathrm{RCOR' + Me_2NH + LiOH} \quad (1)$$

little polyalkylation is observed. However, this does not explain why the intermediate (**1**) which leads to keto amide reacts so slowly with additional organolithium reagent. We believe that our data indicate an interaction between the amide and alkoxide groups in **1** (**2**, eq 2, 3). The possibility of an interaction such as in



2 stabilizing **1** toward the attack of additional organolithium reagent is most markedly seen in the reaction of 2-thienyllithium with either *N,N,N′,N′*-tetramethylsuccinamide or *N,N,N′,N′*-tetramethylglutaramide. These reactions, which were the only ones in which product optimization studies were carried out, gave the best yields of 1,4 and 1,5 diketones when 4 equiv of 2-thienyllithium was utilized. In some attempts to hinder the possible formation of **2** sterically, 2-pyridyllithium, 6-bromo-2-pyridyllithium, and phenyllithium were treated with *N,N,N′,N′*-tetraethylsuccinamide. These reactions failed to produce any 1,4 diketone. An attempt to trap **1** or **2** with chlorotrimethylsilane also failed.

We believe that our data indicate that it may be possible to prepare any 1,*n* diketone (where $n = 2, 3, 4 \ldots$) from *N,N,N′,N′*-tetraalkyldiamides and organolithium reagents (except in the case of acidic amides such as malondiamides or monoalkylmalondiamides). If **2** is a factor which inhibits the formation of diketones from **1**, then the yields of diketones from diamides should increase with increasing chain length because of decreased intramolecular interactions as the ring size of **2** is increased.

Experimental Section

All nmr spectra were recorded on a Varian Associates T-60 nmr spectrometer. Ir spectra were obtained on a Beckman IR-8. Mass spectra were run on a Varian MAT CH-7 instrument. Gas chromatography was carried out on a Varian-Aerograph 1200 instrument using a 10 ft × 0.125 in. stainless steel 1% OV-17 on Chromosorb G column programmed from 70 to 260° at 10°/min. Microanalyses were obtained by Alfred Bernhardt Mikroanalytisches Laboratorium.

Materials.—*n*-Butyllithium (Foote Mineral Co.) in hexane was standardized before use.[5] 2,6-Dibromopyridine (Aldrich) was used without further purification. Thiophene (Fisher), bromobenzene (Baker and Adamson), and 2-bromopyridine (Eastman) were distilled from calcium hydride before use. Ether (Mallinckrodt Anhydrous Reagent) was used directly from the can. Tetrahydrofuran (THF) (Taylor Chemical) was distilled from benzophenone ketyl. Dimethylamine (Eastman) was used without further purification. 6-Bromo-2-pyridyllithium was prepared from 2,6-dibromopyridine and *n*-butyllithium.[4] 2-Pyridyllithium was prepared from 2-bromopyridine and *n*-butyllithium[6] at −78°. Phenyllithium[7] and 2-thienyllithium[8] were prepared according to "Organic Syntheses" procedures.

***N,N,N′,N′*-Tetramethylsuccinamide.**—To a Parr 650-ml stainless steel split ring bomb equipped with magnetic stirrer was added 1 g of sodium methoxide and 174.2 g (1 mol) of diethyl succinate. To this mixture, cooled in an ice bath, was added 200 g (4.44 mol) of anhydrous dimethylamine. The sealed bomb was heated at 100° for 24 hr. The cooled reaction mixture, consisting of a solid and a liquid, was dissolved in THF and filtered. The filtrate was concentrated *in vacuo* to produce a solid which was recrystallized from THF–ether to yield 130 g (0.76 mol, 76%) of *N,N,N′,N′*-tetramethylsuccinamide, mp 81–82° (lit.[9] mp 84.5–85.5°).

***N,N,N′,N′*-Tetramethylglutaramide.**—Potassium *tert*-butoxide (1 g) and 240 g (1.5 mol) of dimethyl glutarate were placed in the 650 ml split ring bomb. The mixture was cooled and 250 g of anhydrous dimethylamine was added. The bomb was sealed and heated at 100° for 24 hr. At the end of this period some of the methanol which had formed was evaporated *in vacuo*. More dimethylamine (100 g) was added and the mixture was heated at 100° for 3 days. The cooled reaction mixture was filtered, concentrated *in vacuo*, and distilled at 117–120° (0.1 mm) to yield 215 g (1.16 mol, 77%) of *N,N,N′,N′*-tetramethylglutaramide, mp 48–49° (lit.[10] 49–51°).

Preparation of Diketones.—The general procedure for the preparation of the diketones is illustrated for 1,5-diphenylpentane-1,5-dione and 1,4-bis(6-bromo-2-pyridyl)butane-1,4-dione.

(5) H. Gilman and F. K. Carteledge, *J. Organometal. Chem.*, **2**, 447 (1964).
(6) (a) D. W. Adamson and J. W. Billinghurst, *J. Chem. Soc.*, 1039 (1950); (b) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).
(7) L. A. Walters, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 757.
(8) E. Jones and I. M. Moodie, *Org. Syn.*, **50**, 104 (1970).
(9) J. K. Lawson, Jr., and J. T. Croom, *J. Org. Chem.*, **28**, 232 (1963).
(10) P. A. Meerburg, *Recl. Trav. Chim. Pays-Bas*, **18**, 365 (1899).

TABLE II[c]

PHYSICAL MEASUREMENTS ON DIKETONES

$$RC(CH_2)_nCR \quad (O \text{ at each end})$$

Registry No.	R	Mp, °C	Recrystn solvent	Ir,[a] cm^{-1}	Nmr,[b] ppm
		$n = 2$			
	Phenyl	144–146° (lit.[d] 145–147°)	Petroleum ether–ether–benzene	1680	3.43 (s, 4 H) 7.53 (m, 6 H) 8.00 (m, 4 H)
37709-52-7	6-Bromo-2-pyridyl	200–201°	Ethanol–ethyl acetate	1700	3.63 (s, 4 H) 7.60–8.22 (2 m, 6 H)
37709-53-8	2-Pyridyl	140–141°	Ethanol	1700	3.70 (s, 4 H) 7.2–8.8 (2 m, 6 H)
13669-05-1	2-Thienyl	131–132°	Chloroform–ethanol	1660	3.37 (s, 4 H) 7.13 (m, 2 H) 7.57 (dd, 2 H) 7.73 (dd, 2 H)
		$n = 3$			
	Phenyl	65–66° (lit.[e] 65°)	Petroleum ether–ether	1680	2.22 (q, 2 H) 3.13 (t, 4 H) 7.25 (m, 6 H) 7.98 (m, 4 H)
37709-55-0	6-Bromo-2-pyridyl	121–122°	Ethanol–water	1700	2.17 (q, 2 H) 3.32 (t, 4 H) 7.53–8.13 (2 m, 6 H)
37709-56-1	2-Pyridyl	79–81°	Ethanol	1700	2.20 (q, 2 H) 3.37 (t, 4 H) 7.27–8.17 (m, 6 H) 8.67 (d, 2 H)
37709-57-2	2-Thienyl	88–89°	Ethanol	1660	2.17 (q, 2 H) 3.03 (t, 4 H) 7.17 (m, 2 H) 7.57 (m, 4 H)
37709-58-3	*n*-Butyl	61–62°	Ethanol–water	1710	2.32[f] (t, 8 H) 0.66–2.02 (m, 16 H)

[a] $CHCl_3$ solution. [b] $CDCl_3$ solution, parts per million downfield from TMS internal standard. [c] Satisfactory analytical and molecular weight data were reported for all new compounds listed in the table. [d] P. S. Bailey and A. E. Lutz, *J. Amer. Chem. Soc.*, **70**, 2412 (1948). [e] L. A. Wiles and E. C. Baughan, *J. Chem. Soc.*, 933 (1953). [f] CCl_4 solution (TMS internal standard).

1,5-Diphenylpentane-1,5-dione.—A solution of 0.2 mol of phenyllithium[7] was prepared from lithium wire and bromobenzene under argon in 160 ml of ether in a 250-ml round-bottomed flask equipped with mechanical stirrer, addition funnel, condenser, and thermometer. The phenyllithium solution was cooled to −78° with a Dry Ice–acetone bath and 18.6 g (0.1 mol) of solid *N,N,N′,N′*-tetramethylglutaramide was added. The reaction was stirred for 24 hr at −78° and was then hydrolyzed with 75–150 ml of water. The hydrolysate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted twice more with 100 ml of ether. The ether was dried over sodium sulfate and concentrated *in vacuo* to yield a semisolid. Recrystallization from petroleum ether (bp 30–60°)–ether gave 12.1 g (0.05 mol, 50%) of 1,5-diphenylpentane-1,5-dione.

1,4-Bis(6-bromo-2-pyridyl)butane-1,4-dione.—To a 250-ml, three-necked, round-bottomed flask equipped with mechanical stirrer and addition funnel was added under argon 10.0 g (0.042 mol) of 2,6-dibromopyridine and 100 ml of ether. As soon as all of the dibromopyridine was dissolved, the reaction flask was quickly cooled with constant stirring to −78° with a Dry Ice–acetone bath. The suspension of microcrystalline solid[4] was stirred for a few minutes and 0.042 mol of *n*-butyllithium in hexane was added in one portion. The solid dissolved to give a pale yellow solution. As soon as the solid dissolved, 3.6 g (0.021 mol) of *N,N,N′,N′*-tetramethylsuccinamide was added. The mixture was stirred for 3 hr at −78°, allowed to warm to room temperature, hydrolyzed with 50 ml of water, and then concentrated *in vacuo* to give a solid which was recrystallized from ethanol–ethyl acetate or dichloromethane to yield 5.8 g (0.015 mol, 71%) of 1,4-bis(6-bromo-2-pyridyl)butane-1,4-dione.

Table II gives the pertinent physical data on all the compounds prepared in this study.

Registry No.—*N,N,N′,N′*-Tetramethylsuccinamide, 7334-51-2; *N,N,N′,N′*-tetramethylglutaramide, 13424-80-1; 6-bromo-2-pyridyllithium, 37709-60-7; 2-pyridyllithium, 17624-36-1; 2-thienyllithium, 2786-07-4; *n*-butyllithium, 109-72-8.

Reaction of Lithium Alkyls with Aldehydes and Ketones. A General Study

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The maximum yield of addition product from *n*-butyllithium and representative aldehydes and ketones is obtained by adding a hexane or ether solution of the carbonyl compound to the lithium reagent at −78°. In most cases under these conditions, products resulting from reduction or condensation of the aldehyde or ketone are insignificant, while enolization gives rise to moderate amounts of the starting carbonyl reagent upon hydrolysis. In the case of nonenolizable aldehydes and ketones, quantitative yields of alcohols are obtained. *tert*-Butyllithium reacts similarly to *n*-butyllithium, but because of increased amounts of enolization, somewhat lower yields of secondary and tertiary alcohols are obtained.

In connection with work in progress in this laboratory dealing with the preparation of organolithium reagents from trialkylboranes *via* organomercurials,[2] the feasibility of analyzing for LiR by treating the lithium alkyls with a carbonyl compound and analyzing the resulting secondary or tertiary alcohol was considered. This would require a quantitative reaction between the lithium reagent and the ketone or aldehyde in order to be useful. However, a search of the literature proved fruitless in finding data on such a reaction. No general study of alkyllithium additions to carbonyl reagents could be found which reported all products and yields. Nearly all examples in the literature involved only specific compounds and usually reported only isolated yields of the major product. This was somewhat surprising, not only because of the wide use of lithium alkyls in organic synthesis, but also because of the large number of similar studies reported on the corresponding Grignard reactions. For this reason, a brief study of the reaction of *n*-butyl- and *tert*-butyllithium with various aldehydes and ketones was undertaken, being careful to determine all products and their yields. Efforts were made to determine the conditions which would maximize the yield of the desired addition product.

Results

The lithium alkyls used were *n*-butyl- and *tert*-butyllithium. They were chosen because they are frequently used, they are commercially available, and they represent extreme examples of various lithium reagents (*i.e.*, primary *vs.* tertiary, unhindered *vs.* sterically hindered). Various typical aldehydes and ketones were used. The reaction products resulting from addition, reduction, and enolization were determined (Chart I).

The first efforts were aimed at maximizing the yields of the addition product. For this purpose, *n*-butyllithium and 3-pentanone were chosen as typical examples. The results of this study are given in Table I.

Once the optimum reaction conditions were determined, *n*-butyllithium was treated with various aldehydes and ketones using three standard sets of conditions. The results of these reactions are given in Table II.

Finally, *tert*-butyllithium was treated under the same conditions (1.0 *M* hexane solution of carbonyl added to *t*-BuLi at −78°) with several of the same aldehydes and ketones, and the results were compared with those from *n*-butyllithium. These results are given in Table III.

(1) Procter and Gamble Fellow, 1971–1972.
(2) J. D. Buhler and H. C. Brown, *J. Organometal. Chem.*, **40**, 265 (1972).

CHART I

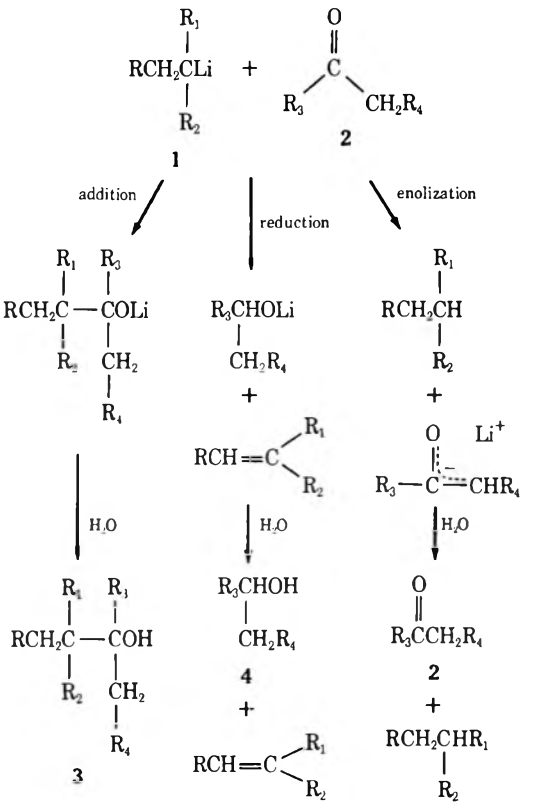

TABLE I

REACTION OF *n*-BUTYLLITHIUM WITH 3-PENTANONE

Solvent	Addition temp, °C	Ketone form[a]	Yield,[b] % Et₂C-(Bu)OH (addn)	Et₂CHOH (redn)	Et₂C=O (enol)	Mass balance
Hexane	0	Neat	82	Tr	18	100
Hexane	0	Neat[c]	66	0	30	96
THF[d]	0	Neat	73	0	16	89
Et_2O	0	Neat	83	0	12	95
Hexane	−30	Neat	82	Tr	15	97
Hexane	RT → 50°	Neat	81	Tr	18	99
Hexane	0	Neat[e]	83	Tr	14	97
Hexane	0	2.0 *M* Hexane soln	85	Tr	12	97
Hexane	−78	2.0 *M* Hexane soln	84	0	14	98

[a] Ketone added to *n*-BuLi in all cases except as noted. [b] Determined by glc analysis. [c] Inverse addition, *n*-BuLi to ketone. [d] Tetrahydrofuran. [e] 100% excess *n*-BuLi used.

Discussion

Table I shows that, in the reaction of *n*-butyllithium with 3-pentanone, the greatest possible yield of addition product is obtained by adding a solution of the

TABLE II
REACTION OF *n*-BUTYLLITHIUM WITH REPRESENTATIVE ALDEHYDES AND KETONES

Ketone	Conditions[a]	Yield,[b] % RR'C-(Bu)OH (addn)	RR'CHOH (redn)	RCOR' (enol)	Mass balance
Acetone	A	53	0	28	81
Acetone	B	67	0	19	86
Acetone	C	80	0	16	96
3-Pentanone	A	82	Tr	18	100
3-Pentanone	B	85	Tr	12	97
3-Pentanone	C	84	0	14	98
Cyclohexanone	A	75	Tr	19	94
Cyclohexanone	B	82	Tr	13	95
Cyclohexanone	C	89	0	9	98
Cyclopentanone	A	44	0	27	71
Cyclopentanone	B	63	0	18	81
Cyclopentanone	C	75	0	18	93
Norcamphor[c]	B	76	Tr	12	88
Norcamphor	C	81	Tr	9	90
Acetophenone	A	67	2–3	27	97
Acetophenone	B	73	2	22	97
Acetophenone	C	81	1–2	20	102
Benzophenone	B[d]	64	23	Tr	87
Benzophenone	C[d]	73	26	Tr	99
Di-*tert*-butyl ketone	C	101	0	Tr	101
Camphenilone[e]	C	98	0	0	98
Nortricyclanone	C	95	0	0	95
Benzaldehyde	C	100	0	0	100

[a] Conditions: A, neat carbonyl reagent added to *n*-BuLi at 0°; B, 1.0 *M* hexane solution of carbonyl compound added to *n*-BuLi at 0°; C, as in B, except at −78°. [b] Determined by glc analysis. [c] 2-Norbornanone. [d] 0.40 *M* hexane solution. [e] 3,3-Dimethyl-2-norbornanone.

TABLE III
REACTION OF *tert*-BUTYLLITHIUM WITH REPRESENTATIVE ALDEHYDES AND KETONES

Ketone	Yield,[a] % RR'C-(*t*-Bu)OH (addn)	RR'CHOH (redn)	RCOR' (enol)	Mass balance
3-Pentanone	66	3	27	96
3-Pentanone[b]	70	3	27	100
3-Pentanone[c]	61	3	35	99
Cyclohexanone	53	0	44	97
Norcamphor[d]	40	0	38	78
Nortricyclanone	102	0	0	102
Acetophenone	52	7	31	90
Benzaldehyde	63	2	3	68

[a] Determined by glc analysis. [b] 10% excess *t*-BuLi used [c] Inverse addition, *t*-BuLi added to ketone. [d] 2-Norbornanone.

carbonyl compound (preferably in hexane or ether) to the alkyllithium at −78°, then stirring at room temperature. [Although 3-pentanone does not show any difference between reaction at 0 and −78°, other ketones (Table II) do show a considerable variation with −78° being significantly preferred in all cases.]

That the residual ketone found in all cases was not due to incomplete reaction is shown in the two reactions (entries 6 and 7, Table I) in which the reaction temperature was increased to 50° and 100% excess *n*-BuLi was used, respectively. No increase in yields or decrease in the amount of remaining 3-pentanone occurred in either case. Further, experiments in which several reaction mixtures were methanolized after various reaction times at −78° showed that the reaction of *t*-BuLi with 3-pentanone was over in less than 5 min at −78° and gave essentially the same product distribution as that given in entry 1, Table III. This data indicates that enolization is taking place. That is, a rapid metalation reaction leading to the enolate anion of the carbonyl compound along with butane appears to compete with addition, even at −78°. Hydrolysis then regenerates the carbonyl compound. Finally, enolization is also indicated by the fact that quantitative yields of addition product were obtained when *n*-BuLi was treated with nonenolizable aldehydes and ketones such as benzaldehyde, nortricyclanone, di-*tert*-butyl ketone, and camphenilone (Table II).

Table II confirms the results of Table I in that −78° is the preferred reaction temperature in nearly all cases. At this temperature, reduction and enolization are minimized, thus giving rise to higher yields of addition product. Condensation reactions also appear to be minimized, since the highest mass balances are obtained at −78°. The outstanding feature revealed by this data is the clean reactions observed. In all cases except acetophenone and benzophenone, the addition product was contaminated only with the starting carbonyl reagent (resulting from enolization to the enolate anion prior to hydrolysis), with no significant reduction or condensation products observed. Even in the case of acetophenone, less than 3% of the reduction product was found. Thus, when nonenolizable ketones were used, the one competing side reaction (enolization) was no longer possible and quantitative yields of addition products were obtained, except with benzophenone.

Benzophenone was the only case in which significant amounts of reduction were observed. This is possibly due to the slower reaction of this ketone, since it was observed in a separate experiment that the reaction was only 75% complete in 5 min at −78° while the previously mentioned *t*-BuLi addition to diethyl ketone was complete in less than 5 min at the same temperature.

Thus, in reactions with *n*-butyllithium at −78°, aldehydes and ketones which can enolize can be expected to give rise to alcohol yields of 75–90% with the sole impurity being in nearly all cases the starting carbonyl reagent. With nonenolizable ketones and aldehydes, quantitative yields of alcohols can be obtained. (The aromatic carbonyls appear to be the exceptions to this statement.) Remarkably, this is true of even highly hindered ketones such as di-*tert*-butyl ketone and camphenilone, both of which gave quantitative yields of addition product. These carbonyls can thus serve as reagents for the analysis of this type of lithium reagent.

With *tert*-butyllithium yields of addition products are somewhat lower (Table III), but still quite impressive. For example, a 53% yield of 1-*tert*-butyl-1-cyclohexanol from cyclohexanone is quite respectable when compared with the poor yield of addition product obtained with *tert*-butylmagnesium chloride[3] and the 7% obtained with *tert*-butylsodium.[4] With nonenolizable ketones, such as nortricyclanone, quantitative yields were obtained as with *n*-alkyllithiums. However, benzaldehyde gave only a 63% yield of addition product with a correspondingly low mass balance. The reason for this is not known at the present; again the aromatic carbonyl reagents give anomalous behavior. Thus, even

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TABLE IV

PHYSICAL PROPERTIES OF ALCOHOL PRODUCTS[r]

Alcohol	Bp, °C (mm)	n^{20}D or mp, °C
2-Methyl-2-hexanol	67–68.5 (35)	1.4175
	[68.5 (35)][a]	(1.4176)[b]
3-Ethyl-3-heptanol	72 (9.8)	1.4364
	[70–72 (11)][c]	(1.4360)[c]
1-Butyl-1-cyclohexanol	89–92 (8.2)	1.4648
	[88–91 (7)][d]	(1.4648)[d]
1-Butyl-1-cyclopentanol	95–98 (15)	1.4576
	[99 (20)][e]	(n^{19}D 1.4562)[f]
2-Butyl-2-norbornanol[s]	76 (19)	1.4820
2-Phenyl-2-hexanol	100–104 (4)	1.5112
	[120 (10)][g]	(1.5091)[h]
1,1-Diphenyl-1-pentanol	136–138 (0.08)	1.5673
	[134–135 (1.5)][i]	(1.5680)[j]
2,2-Dimethyl-3-(2-methyl-2-propyl)-3-heptanol	103–104 (8.1)	1.4548
	[121.5–123 (24)][k]	(1.4540)[k]
3,3-Dimethyl-2-butyl-2-norbornanol[t]	89 (1.8)	1.4843
1-Phenyl-1-pentanol	82–84 (0.95)	1.5095
	[100–104 (3)][l]	(1.5078)[l]
3-Butyl-3-nortricyclanol[u]	83–84 (3.0)	1.4866
2,2-Dimethyl-3-ethyl-3-pentanol	76–77 (28)	1.4429
	[84 (40)][m]	(1.4429)[m]
1-(2-Methyl-2-propyl)-1-cyclohexanol	93–94 (18)	44–49
	[80 (13)][n]	(49–50)[n]
2-(2-Methyl-2-propyl)-2-norbornanol[v]		66–67
3-(2-Methyl-2-propyl)-3-nortricyclanol[w]		61.0–61.5
3,3-Dimethyl-2-phenyl-2-butanol	82–84 (2.1)	1.5145
	[95.5 (4.5)][o]	(n^{25}D 1.5142)[p]
2,2-Dimethyl-1-phenyl-1-propanol	93 (5.0)	1.5122
	[97 (7)][q]	

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sterically hindered *tert*-butyllithium gives reasonable yields of addition products with carbonyl compounds with no significant reduction or condensation. In most cases, alkyllithiums appear to be the preferred reagents for alkylation of a carbonyl group with a tertiary alkyl group.

Experimental Section

Materials.—THF was distilled from $LiAlH_4$ under nitrogen. Et_2O was Mallinckrodt anhydrous grade used directly. Hexane was stirred for several days over concentrated H_2SO_4, washed with aqueous K_2CO_3 and water, dried over CaH_2, and distilled under nitrogen.

n-Butyllithium in hexane and *tert*-butyllithium in pentane were purchased from Alfa Inorganics, stored at 0°, and standardized in benzene by the method of Watson and Eastham[5] using 2-butanol in xylene as titrant with 2,2′-biquinoline as indicator (2.24 and 1.11 *M*, respectively). Total base was determined by hydrolysis with 5 *M* H_2O in THF followed by titration with standard H_2SO_4 to a bromothymol blue end point (2.34 and 1.13 *M*, respectively).

Acetone (Mallinckrodt Spectral Grade), cyclopentanone (Matheson Coleman and Bell Reagent Grade), norcamphor (Aldrich Reagent Grade), acetophenone (Baker Reagent Grade), and di-*tert*-butyl ketone (Chemical Samples, 98%) were commercial products and were used without further purification. 3-Pentanone, cyclohexanone, benzophenone, camphenilone (98% pure), and benzaldehyde were commercial products which were purified by distillation under nitrogen. Nortricyclanone was prepared by the method of Hall:[6] bp 78.5–79.5 (24 mm); n^{25}D 1.4873; 98% pure by glc analysis [lit.[6] bp 78–79° (24 mm); n^{25}D 1.4878]. All ketones and aldehydes were shown to be 100% pure by glc analysis except in the cases stated otherwise above.

General.—All glassware was dried in an oven at 140° and flushed with dry nitrogen during cooling. Glc analyses were performed on a 6 ft × 0.25 in. Carbowax 20M column with Chromosorb W as stationary phase. Various straight-chain saturated hydrocarbons (Phillips, 99%) were used as internal standards.

General Procedure for Alkyllithium Reactions.—In a standard reaction, 4.45 ml of 2.24 *M* *n*-BuLi (10.0 mmol) and 5.0 ml of hexane (or 9.0 ml of 1.11 *M* *t*-BuLi in pentane) were syringed into a 25-ml flask at −78°, followed by the appropriate internal standard; 10.0 ml of 1.0 *M* ketone or aldehyde in hexane was then syringed in dropwise at −78°. After addition, the reaction was allowed to warm to room temperature and stirred for 1 hr, after which it was hydrolyzed with aqueous K_2CO_3, and the organic layer was dried ($MgSO_4$) and analyzed by glc.

All products were isolated from larger scale reactions (50 mmol) and compared with literature data. Consistent ir and nmr spectra were obtained in all cases. Satisfactory combustion analyses (±0.3%, C, H) were obtained for all new compounds. Table IV gives the physical properties of all alcohols prepared.

Registry No.—*n*-Butyllithium, 109-72-8; 3-pentanone, 96-22-0; acetone, 67-64-1; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; norcamphor, 497-38-1; acetophenone, 98-86-2; benzophenone, 119-61-9; di-*tert*-butyl ketone, 815-24-7; camphenilone, 13211-15-9; nortricyclanone, 695-04-5; benzaldehyde, 100-52-7.

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The Electrical Discharge Reactions of $CF_2=CF_2/Br_2$, $CF_2=CF_2/BrCF_2CF_2Br$, and $BrCF_2CF_2Br$

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The electrical discharge reactions of $CF_2=CF_2/Br_2$, $CF_2=CF_2/BrCF_2CF_2Br$, and $BrCF_2CF_2Br$ were studied. In the $CF_2=CF_2/Br_2$ system, the major products (63%) were identified as perfluoro-α,ω-dibromoalkanes. Minor amounts of perfluoroalkanes, 1-bromoperfluoroalkanes, and an essentially linear bromine-containing polymeric material were also present. From the $CF_2=CF_2/BrCF_2CF_2Br$ system, similar products were obtained; however, a greater proportion of monobromides and polymeric material was formed. A radical mechanism was suggested for these two systems, in which $CF_2=CF_2$, $:CF_2$, $\cdot Br$, and $\cdot F$ were considered active species. The electrical discharge reaction of $BrCF_2CF_2Br$ was slow and gave only small yields of $CFBr_3$, $BrCF_2CFBr_2$, $Br(CF_2)_4Br$, and a complicated olefinic mixture.

It has previously been reported[2-7] that electrical discharge reactions of fluoro olefins could be utilized to produce a variety of saturated and unsaturated fluorocarbons. The product mixtures obtained with this process were complex and the mechanisms involved in these reactions were not clear. It was thought that the introduction of another halogen to such systems would minimize the olefinic products and consequently simplify the identification of the discharge products. The present investigation describes the electrical discharge reactions of the following systems: $CF_2=CF_2/Br_2$, $CF_2=CF_2/BrCF_2CF_2Br$, and $BrCF_2CF_2Br$.

Results and Discussion

The electrical discharge reactions of $CF_2=CF_2/Br_2$ and $CF_2=CF_2/BrCF_2CF_2Br$ gave good yields of liquid bromofluorocarbons. ^{19}F nmr analysis indicated that both discharge products were essentially linear. Infrared analysis showed the presence of terminal and internal olefinic structures. The amount of unsaturation, however, was less than that present in the tetrafluoroethylene (TFE)[8] or hexafluoropropene[2] discharge products. Gas chromatography indicated that there were significant differences between the distribution of monobromides and dibromides in the two systems.

In the TFE/Br_2 system, the higher bromine concentration favored formation of dibromides (see Table I). It also suppressed the "polymerization" of TFE, as shown by the lesser amount of nonvolatile residue present in this system. The formation of $Br(CF_2)_nBr$, where n = 1–8, indicated that TFE was not only a monomer but also a source of difluorocarbene ($:CF_2$). The presence of monobromoalkanes substantiated the evidence of free fluorine in this discharge. The major reactions in the system can be represented by the following equations.

In the $TFE/BrCF_2CF_2Br$ system, the discharge product contained more of the monobromides and the polymeric fraction (see Table I). $BrCF_2CF_2Br$ reacted more like a telogen than a monomer (see below).

TABLE I
MAJOR COMPONENTS IDENTIFIED FROM THE ELECTRICAL DISCHARGE PRODUCTS OF TFE/Br_2 AND $TFE/BrCF_2CF_2Br$

Structure	Registry no.	TFE/Br_2, %[a]	$TFE/BrCF_2CF_2Br$, %[a]
C_6F_{14}	355-42-0	1.43	4.53
n-C_4F_9Br	375-48-4	2.56	6.91
n-$C_5F_{11}Br$	558-91-8	2.47	5.75
n-$C_6F_{13}Br$	335-56-8	2.74	3.52
n-$C_7F_{15}Br$	375-88-2	1.66	2.20
$BrCF_2Br$	75-61-6	0.40	
$Br(CF_2)_2Br$	124-73-2	24.00	9.21
$Br(CF_2)_3Br$	4259-29-4	2.33	1.27
$Br(CF_2)_4Br$	335-48-8	20.50	8.64
$Br(CF_2)_5Br$	24331-48-4	6.70	3.30
$Br(CF_2)_6Br$	918-22-9	5.43	1.74
$Br(CF_2)_7Br$	37819-18-4	2.48	0.67
$Br(CF_2)_8Br$	812-58-8	1.53	0.27
Unidentified (many peaks)		7.77	5.99
Nonvolatile residue[b]		12.00	40.00
Gaseous components[c]		6.00	6.00

[a] Area measurement by gas chromatographic analysis of the distillate. [b] Weight per cent of nonvolatile residue left after fractional distillation. [c] Weight per cent lost during fractional distillation.

$$CF_2=CF_2 \longrightarrow 2{:}CF_2$$

$$CF_2=CF_2 \longrightarrow CF_2=CF\cdot + \cdot F$$

$$Br_2 \longrightarrow 2Br\cdot$$

$$\cdot Br + nCF_2=CF_2 + m{:}CF_2 \longrightarrow Br(CF_2CF_2)_n(CF_2)_m\cdot \quad n,m \geq 0$$

$$\downarrow \cdot F \qquad \downarrow \cdot Br \text{ or dimerize}$$

monobromides dibromides

$$\cdot F + CF_2=CF_2 \longrightarrow$$

$$CF_3\dot{C}F_2 + nCF_2=CF_2 + m{:}CF_2 + \cdot Br \longrightarrow \text{monobromides}$$

The larger amount of monobromoalkanes also indicated that more free fluorine was present during the discharge.

The electrical discharge reaction of $BrCF_2CF_2Br$ was slow. The small amount of liquid collected after prolonged discharge was essentially the starting dibromide (84%). Other products identified were $Br(CF_2)_4Br$, $CFBr_3$, $BrCF_2CFBr_2$, and a few complicated olefins. These results were in accordance with previous findings[2,3,5,6] that alkanes were more stable than olefins under similar discharge conditions. The experiment also indicated that the discharge reaction of $BrCF_2CF_2Br$ occurred to a negligible extent in the TFE/Br_2 and $TFE/BrCF_2CF_2Br$ systems.

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Experimental Section

The Electrical Discharge Cell.—The cell used was similar to that reported in the literature.[2,7] A small modification described below was necessary to introduce Br_2 (or $BrCF_2CF_2Br$) to the system. A flask fitted with a gas inlet tube and an exit tube was placed between the TFE source and the gas inlet tube of the quartz discharge cell.

Spectra.—^{19}F nmr spectra were obtained with a 56.4 MHz/sec Varian DP-60 spectrometer (shifts *vs.* $CFCl_3$ as internal standard). A Bendix time-of-flight mass spectrometer was employed to record the mass spectra at 70 eV. Infrared spectra were obtained with a Beckman IR-2 spectrophotometer.

Glpc Analyses.—Analytical chromatograms were obtained with an Aerograph (202B) using a column (0.25 in. × 24 ft) packed with 10% UC-W 98 Chromosorb G, AW, DMCS 60–80 mesh. The column temperature was programmed from 70° to 250° by setting the Variac initially at 20 V and then at 80 V immediately after sample injection. Preparative glpc was accomplished by using a Nester-Faust "Prepkro" unit equipped with a column (0.25 in. × 24 ft) packed with 30% SF-96 on Chromosorb P.

Discharge Reactions of TFE/Br_2 and TFE/$BrCF_2CF_2Br$.—Liquid bromine (or $BrCF_2CF_2Br$) was placed in a flask fitted with an inlet tube just above the liquid surface and an exit tube connected to the gas inlet tube of the discharge cell. The inlet tube of the flask was connected to a pressure-regulated (by Solenoid valve) TFE line. Bromine (or $BrCF_2CF_2Br$) was kept frozen in a Dry Ice bath until the whole system was evacuated. The Dry Ice bath was then removed and the scrubbed TFE was allowed to pass through the flask carrying a small amount of bromine vapor into the discharge cell. High-voltage electric power was then applied to the reactor. The discharge was initiated between concentric quartz electrodes of 1.5–2.0 mm gaseous gap. Pressure of the reaction was maintained by the automatically controlled valve which fed TFE to the system on demand at 260 Torr. The temperature of the halogen solution was allowed to reach 45° in order that a maximum amount of bromine be allowed to enter the discharge area. However, there seemed to be an upper limit for the bromine concentration, above which the discharge would be quenched. The electrical conditions and the results of the two reactions are summarized in Table II.

TABLE II

	TFE/Br_2	TFE/$BrCF_2CF_2Br$
TFE monomer pressure, Torr	260	260
Liquid bromine charged, g	60	
$BrCF_2CF_2Br$ charged, g		50
Operating voltage kV, rms	18.0	18.0
Frequency, kc/sec	1.4	1.4
Power, W	398	396
Time, hr	1.25	1.5
Wt of product, g	96	124
TFE consumed, g	78	77
Bromine consumed, g	42	
$BrCF_2CF_2Br$ consumed, g		50
kW-hr/lb	2.35	2.18
Br_2 content in product, %	32.63	24.29

The pale yellow liquid (50 g) from the electrical discharge of TFE/Br_2 was carefully fractionated. Gas chromatographic analysis was used to follow the components present. There were many overlapping peaks in eight fractions collected [bp 50° (760 Torr) to 68° (0.7 Torr), 41 g, 82%]. Three selected fractions [bp 50–59°, 60–75° (9 Torr), and 40–64° (0.7 Torr)] covering most of the major peaks present were further separated into individual components by preparative gas chromatography and identified by mass spectroscopy, ^{19}F nmr, and infrared (see below).

The residue, a semisolid (6 g, 12%) containing 22% Br, was shown to have terminal and internal unsaturation by ir analysis. Some branching was also observed by ^{19}F nmr analysis.

The product from the electrical discharge of TFE/$BrCF_2CF_2Br$ showed similar peaks in the gas chromatographic analysis (see Table I). Fractional distillation of the product showed the following: gaseous components, 6%; distillable fluorocarbon bromides, 54%; and residue, 40%. The residue contained 13.5% Br. Instrumental analyses indicated the presence of internal and terminal double bonds and some branching.

Monobromides.—Perfluoro-1-bromobutane had ^{19}F nmr CF_2Br ϕ 64.0, CF_2CF_2Br 118.6, CF_2CF_2 126.0, CF_3 81.9; mass spectrum *m/e* (rel intensity) 300, 298 (0.9, 0.6) $C_4F_9Br^+$ (parent ion), 219 (10.0) $C_4F_9^+$, 131, 129 (10.0, 7.0) CF_2Br, 100 (16.0) $C_2F_4^+$, 81, 79 (1.3, 0.9) Br^+, 69 (100.0) CF_3, 31 (38.5) CF^+.

Perfluoro-1-bromopentane had ^{19}F nmr CF_2Br ϕ 63.9, CF_2-CF_2Br 118.0, $CF_2CF_2CF_2$ 122.4, $CF_2CF_2CF_2$ 126.9, CF_3 81.6; mass spectrum *m/e* (rel intensity) 350, 348 (tr) $C_5F_{11}Br^+$ (parent ion), 269 (8.0) $C_5F_{11}^+$, 131 (48.0) $C_3F_5^+$, 100 (12.0) $C_2F_4^+$, 81, 79 (2.0, 1.4) Br^+, 69 (100.0) CF_3^+, 31 (52.0) CF^+.

Perfluoro-1-bromohexane had ^{19}F nmr CF_2Br ϕ 64.1, CF_2-CF_2Br 118.0, $CF_2CF_2CF_2Br$ 122.1, $CF_2CF_2CF_2$ 124.1, CF_2CF_2 126.9, CF_3 81.6; mass spectrum *m/e* (rel intensity) 319 (2.0) $C_6F_{13}^+$, 131 (15.0) $C_3F_5^+$, 119 (10.0) $C_2F_5^+$, 100 (3.5) $C_2F_4^+$, 81, 79 (0.4, 0.3) Br^+, 69 (100.0) CF_3^+, 31 (27.0) CF^+.

Perfluoro-1-bromoheptane had ^{19}F nmr CF_2Br ϕ 63.8, CF_2-CF_2Br 118.2, $CF_2CF_2CF_2Br$ 122.2, $CF_2CF_2CF_2CF_2Br$ 123.1, CF_2CF_2 127.2, CF_3 81.9.

Dibromides.—Perfluoro-1,1-dibromomethane[9] had ^{19}F nmr CF_2 ϕ −6.6; mass spectrum *m/e* (rel intensity) 131, 129 (65.0, 40.0) CF_2Br^+, 81, 79 (15.0, 10.0) Br^+, 69 (100.0) CF_3^+, 50 (30.0) CF_2^+, 31 (83.0) CF^+.

Perfluoro-1,2-dibromoethane[9] had ^{19}F nmr CF_2CF_2 ϕ 64.0; mass spectrum *m/e* (rel intensity) 260 (9.5) $BrCF_2CF_2Br$ (parent ion), 181, 179 (100.0, 71.0) $CF_2CF_2Br^+$, 131, 129 (33.0, 27.0) CF_2Br^+, 100.0 (12.0) $C_2F_4^+$, 81, 79 (25.0, 20.0) Br^+, 69 (18.0) CF_3^+, 50 (51.0) CF_2^+, 31 (56.0) CF^+.

Perfluoro-1,3-dibromopropane had mass spectrum *m/e* (rel intensity) 310 (tr) $C_3F_6Br_2^+$ (parent ion), 231, 229 (24.0, 18.0) $C_3F_6Br^+$, 131, 129 (25.0, 18.0) CF_2Br^+, 100 (17.0) $C_2F_4^+$, 81, 79 (3.0, 2.3) Br^+, 69 (40.0) CF_3^+, 50 (7.0) CF_2^+, 31 (100.0) CF^+.

Perfluoro-1,4-dibromobutane had ^{19}F nmr CF_2Br ϕ 64.0, CF_2CF_2 118.1; mass spectrum *m/e* (rel intensity) 360 (tr) $C_4F_8Br^+$ (parent ion), 281, 279 (30.0, 22.0) $C_4F_8Br^+$, 131, 129 (47.0, 31.0) CF_2Br^+, 119 (10.0) $C_2F_5^+$, 100 (37.0) $C_2F_4^+$, 81, 79 (11.0, 8.0) Br^+, 69 (89.0) CF_3^+, 50 (28.0) CF_2^+.

Other dibromides were assigned structures on the basis of gas chromatogram retention time and ^{19}F nmr analysis (see Table III).

TABLE III

^{19}F NMR DATA OF PERFLUORODIBROMIDES

Assigned structure	CF_2Br	CF_2CF_2Br	$-CF_2-$	Gc[b] retention time, min
$Br(CF_2)_5Br$	64.0 (1)[a]	118.4 (1)	121.7 (0.5)	2.7
$Br(CF_2)_6Br$	63.9 (1)[a]	118.1 (1)	121.8 (1)	3.4
$Br(CF_2)_7Br$	64.1 (1)[a]	118.2 (1)	122.2 (1.5)	4.25
$Br(CF_2)_8Br$	64.0 (1)[a]	118.2 (1)	122.4 (2.0)	5.0

[a] Relative area ratios. [b] Gas chromatogram.

The retention times for other dibromides follow: $BrCF_2Br$, 1.1 min; $Br(CF_2)_2Br$, 1.3 min; $Br(CF_2)_3Br$, 1.7 min; and Br-$(CF_2)_4Br$, 2.1 min.

Perfluorohexane[10] had ^{19}F nmr CF_3 ϕ 82.0, CF_3CF_2 128.3, $-CF_2-$ 124.3; mass spectrum *m/e* (rel intensity) 300 (3.3) $C_6F_{12}^+$ (parent ion), 250 (19.0) $C_5F_{10}^+$, 231 (54.0) $C_5F_9^+$, 169 (46.0) $C_3F_7^+$, 131 (64.8) $C_3F_5^+$, 119 (28.1) $C_2F_5^+$, 100 (38.0) $C_2F_4^+$, 69 (100.0) CF_3^+, 50 (39.8) CF_2^+.

Discharge Reaction of $BrCF_2CF_2Br$.—Forty grams of $BrCF_2$-CF_2Br was placed in a precooled flask as described previously. It was kept frozen in a Dry Ice bath until the discharge system was evacuated. The Dry Ice bath was then replaced by a hot water bath. When the vapor pressure of $BrCF_2CF_2Br$ reached 170 Torr, high voltage electric power was applied. The discharge was initiated at the operating voltage of 18 kV and at the frequency of 1.4 kcps. There was a gradual pressure buildup (170–750 Torr), which was not observed with the other two systems. After 3.5 hr of discharge, a small amount (17 g) of light brown, clear liquid was collected. Gas chromatographic analysis indicated that 84% of the liquid was the original di-

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bromide. The liquid was carefully fractionated at reduced pressure. A fraction, bp 70–100° (18 Torr), 2 g, containing the major peaks of this discharge reaction was further separated by preparative gas chromatography. Some of the peaks were identified as follows.

Perfluoro-1,4-dibromobutane (0.7%) was identified as above.

Fluorotribromomethane[9] (0.5%) had ^{19}F nmr CF ϕ −7.5.

1,1,2-Trifluoro-1,2,2-tribromoethane[11-13] (6%) had ^{19}F nmr CF_2Br ϕ 58.7 (d, J = 17.9 Hz), $CFBr_2$ 69.6 (t); ir 8.42 (s), 8.65 (m), 9.05 (m), 9.15 (s), 9.95, 10.05 (s), 12.0 (s), 13.85 (s), 14.6 μ.

Three other peaks (area ratios 0.8, 0.4, and 1.5%) were unsaturated as shown by ^{19}F nmr (ϕ 56.8 and 59.7) and ir (5.85 and 5.89 μ). These structures were complicated. Other small peaks (total 6.1%) were not identified.

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Registry No.—TFE, 116-14-3; Br_2, 7726-95-6; fluorotribromomethane, 353-54-8; 1,1,2-trifluoro-1,2,2-tribromoethane, 354-49-4.

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Oxidation of *n*-Butane with Cobalt Salts and Oxygen *via* Electron Transfer

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Low-temperature Co(III) ion promoted oxidation of *n*-butane affords acetic acid selectively. Yields of the C_2 acid around 84%, assuming 2 mol of acid/mol of butane, require predominant cleavage of the 2–3 bond. In view of the dependence of rate on Co(III) ion concentration, the ineffectiveness of Mn(III) ions in this reaction, and other general characteristics which were also observed with alkylbenzenes, results are rationalized in terms of an electron transfer pathway in which cobalt ions function as chain carriers.

A new system for reacting alkylbenzenes with oxygen in the presence of large concentrations of cobaltic acetate was reported in 1960.[1] Later papers in this area dealt mostly with toluene oxidations.[2-5] To account for the vastly different parameters of this system compared to those of conventional free radical processes, an electron transfer concept was advanced.[6,7] While oxidation of alkylbenzenes *via* electron transfer was thought to depend on the presence of a π system,[6,7] satisfactory evidence to justify this postulate was not presented. Since side chains are the entities undergoing chemical change in alkylbenzene oxidations, it was of interest to investigate oxidation of purely aliphatic substrate in this system. With *n*-butane as the model, oxidation of this purely aliphatic substrate was found to depend on the same parameters that are critical in the oxidation of alkylbenzenes. Butane oxidation is an example of electron transfer from C–H σ bond to Co(III) ion. Electron transfer, therefore, is a general phenomenon operating on C–H σ bonds and not limited to π systems.

Results

Products of the low-temperature Co(III) ion promoted oxidation of *n*-butane are acetic acid (83.5% yield, average of three experiments, Table I), propionic acid (5.4%), *n*-butyric acid (3.5%), and methyl ethyl ketone (MEK)(4.4%). Butane conversions were around 78%. Minor products (<2%) include varying amounts of methyl and ethyl formates, methyl, ethyl, and propyl acetates, traces of acetaldehyde as well as biacetyl, but no formaldehyde or formic acid. Identical results were obtained in both flow and closed systems. Experimental conditions, products obtained, and other data are summarized in Table I. In the oxidation of butane a considerable amount of water is formed during the first few minutes, much more than could be accounted for by the liquid products formed. We have attributed this to total combustion of MEK during initiation. To test this assumption, small amounts of water, known to inhibit MEK oxidation, were added. It was found that, with *ca.* 4.5% of water in the charge, combustion of MEK to CO_2 and H_2O was virtually eliminated. With 9% of water in the acetic acid phase, oxygen absorption diminished substantially. To determine what proportion of MEK was initially converted into CO_2 and H_2O, a control experiment was carried out with MEK alone in the concentration employed for initiation. Of the MEK charged, about 45% was consumed by total combustion. Calculations in Table I were made on a loss free basis assuming that MEK found in the reaction mixture was produced from butane, and that only 55% of MEK added for promotion was converted into acetic acid. At a pressure of 20 atm, highest rates and best acetic acid yields were obtained at temperatures ranging from 100 to 125°. At 80°, oxidation was very slow. Above 130°, rates decreased due to a lower partial pressure of oxygen in the system.

Oxidation of *n*-pentane (104°, 17 atm, 4 hr, ~45% conversion) gave acetic acid and propionic acid in yields of 48 and 27%, respectively. *n*-Butyric acid, *n*-valeric acid, and 2- and 3-pentanones were also formed in smaller amounts. Formic acid was not observed under our conditions.

Oxidation of isobutane (80 g) under conditions of expt 3 afforded 2.5 g of acetone, 6.6 g of *tert*-butyl alcohol, and 3.1 g of methanol (~10% conversion). The lower reactivity of isobutane compared to the *n*-butane is attributed to steric hindrance with the

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TABLE I
OXIDATION OF *n*-BUTANE[a]

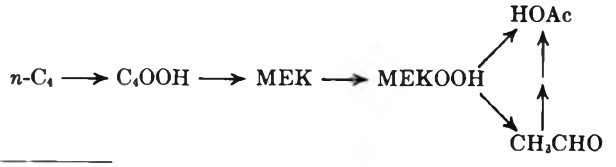
	Expt no. 1[b]	2[c]	3[c]	4[i]
Charge data, g				
n-C_4H_{10}	185	157	157	70
HOAc	345	280	280	100
$Co(OAc)_2 \cdot 4H_2O$	25	20	20	0.12
MEK[d]	28	20	20	
Conditions				
Pressure, atm[e]	17	21.6	24	20[j] (155°)
Reaction time, hr	4	4	2	3.5
Products, g (% selectivity)				
HOAc[f]	245.7 (83.3)	207.0 (82.8)	220.0 (84.6)	106.8 (41.0)[k]
C_3 acid	8.9 (4.9)	9.1 (5.9)	8.5 (5.3)	2.0 (1.2)
C_4 acid	4.3 (2.0)	7.3 (4.0)	8.5 (4.4)	
MEK[g]	5.5 (3.1)	7.3 (4.9)	8.5 (5.4)	18.8 (12.0)
Misc oxygend products[h]	4.4	2.1	2.0	120.8 (45.8)[l]
Water	59.0	48.2	51.1	
Total	327.8	281.0	298.6	248.4
Conversion data				
C_4 conversion g (%)	142.5 (77)	120.9 (77)	125.6 (80)	125.6 (24)
C_4 lost on venting	16.6 (9)	13.6 (8.7)	5.0 (3.2)	
C_4 recovered	25.9 (14)	22.5 (14.3)	26.4 (16.8)	
Efficiency to total acids, %	90.2	92.7	94.3	~42

[a] 110°. [b] Flow system; exit gases withdrawn at *ca.* 1 l./hr. [c] Closed system. [d] Assumed all reacted during initiation period: *ca.* 55% going to HOAc, and *ca.* 45% to carbon dioxide and water; yield of HOAc was corrected accordingly. [e] Total pressure (mostly partial pressures of C_4 and oxygen). [f] Acid formed from C_4, assuming 2 mol of HOAc/mol of C_4. [g] Formed from butane. [h] Includes varying amounts of methyl and ethyl formates, methyl, ethyl, and propyl acetates, and traces of acetaldehyde, biacetyl, and acetone. Acetone is thought to come mostly from isobutane impurity in the feed. [i] Experiment taken from Table III, 4th run, of ref 16 for comparison purposes. [j] Partial pressure of oxygen. [k] Products are corrected to correspond to 125.6 g of C_4 reacted as in expt 3. [l] Distribution of oxygenated products by wt % was as follows: ethyl acetate (41.5), methyl acetate (18.8), methanol (1.6), 1-butanol (1.1), *n*-butyl acetate (1.3), acetone (6.5), ethanol (2.4), carbon dioxide (26.4), and formic acid (2.4).

bulky liganded metal ion. Whatever reaction occurred under conditions employed probably proceeded *via* the normal free radical pathway which is therefore not a significant contributor in the cobalt system. In a competitive oxidation *n*-butane was at least three times as reactive as isobutane.

Discussion

Low-temperature oxidation of *n*-butane with large concentrations of cobaltic ion distinguishes itself by its high selectivity (>83%). Radicals are generated by electron transfer from substrate to metal ion with high rates at 100°. Temperatures up to 170°[8] and higher, on the other hand, are required for thermal formation of radicals in classical free radical processes which employ small amounts of metal salt solely for initiation.[9-11] Noncatalytic butane oxidation of this latter type affords acetic acid in about 40% efficiency as only one component in a complex mixture of oxygenated species. The preceding general pathway has been proposed.[11-14]



These reactions could also occur under electron transfer conditions, but should be negligible at low temperatures. For electron transfer the sequence n-$C_4 \rightarrow$ MEK $\rightarrow Ac_2 \rightarrow$ 2HOAc is favored in which butane reacts with Co(III) in the initiation step. Propagation again involves oxidation of butane by Co(III), as well as reduction of C_4 and MEK peroxy radicals by Co(II). While a thorough study has not been completed, the presence of biacetyl (Ac_2) in all reaction mixtures allows some speculation as to the mechanism involved. Biacetyl was found to be more reactive than MEK under the oxidation conditions, producing acetic acid in high selectivity. Formation of the symmetrical intermediate is consistent with high selectivity to acetic acid, requiring predominant cleavage of the 2–3 butane bond.

Conversion of Co(II) into Co(III) precedes the maximum oxidation rate. Shortening and final elimination of induction periods with increasing Co(III) ion concentration is further evidence for the interaction of substrate with cobaltic ion. This rate dependence is shown in Table II. Requirements for large amounts of metal salt is in contrast to commercial butane oxidations which are dependent on direct oxygen trans-

(8) The patent literature alone dealing with the liquid phase oxidation of C_4–C_8 paraffins runs into hundreds of patents; therefore, no attempt was made to provide a comprehensive review.

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TABLE II

EFFECT OF CATALYST CONCENTRATION ON BUTANE CONVERSION[a]

$Co(OAc)\cdot 4H_2O$, mol	Butane, mol	HOAc/Butane (molar ratio)	Butane/ $Co(OAc)_2\cdot 4H_2O$ (molar ratio)	Log (butane/ $Co(OAc)_2\cdot 4H_2O$)	Butane conversion, %[b]
0.00120	2.90	1.74	2417	3.382	~6.7 (1.0)[d]
0.00683	3.22	1.78	471	2.672	31.5 (4.7)
0.02010	3.07	1.88	153	2.184	40.8 (6.1)
0.100[c,e,g]	3.19	1.81	32	1.505[f]	74.0 (11.1)

[a] 100°, 17 atm, 3 hr. [b] Based on products. [c] Corresponds to *ca.* maximum solubility (~0.3 *M*) in HOAc at room temperature. [d] Estimate of relative rate. [e] Final concentration was 35 mol % Co(III) and 65 mol % Co(II). [f] Plot against conversion gives a straight line. [g] Induction times in this system varied between 15 and 45 min; induction times increased with a decrease in catalyst concentration.

TABLE III

REACTIVITY OF SELECTED HYDROCARBONS TOWARD Co(III) IONS AND SOME RADICALS[a]

Hydrocarbon	Registry no.	Co(III), 78°	Co(III) + O_2, 100°, 20 atm	*t*-BuO·,[b] 40°	Ph·,[b] 60°	$RO_2\cdot$,[d] 100°
Toluene	108-88-3	1.00[c]	1.00	1.00	1.00	
Cyclohexane	110-82-7	0.5	0.5	6.0	3.6	
Methylcyclohexane	108-87-2	0.2	0.2	6.6	4.6	
Cumene	98-82-8	0.3	0.2	2.3	2.9	
n-Butane	106-97-8		(≥3)[e]	1.8	1.6	1
Isobutane	75-28-5		(1)	1.8	1.9	4

[a] Relative reactivities per molecule; chlorobenzene used as internal standard. [b] Predicted reactivities; calculated from data of Table IV of W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Amer. Chem. Soc.*, **94**, 1632 (1972). [c] Assumed standard, reactivity = 1.00. [d] *t*-$BuO_2\cdot$, or *sec*-$BuO_2\cdot$, ref 13. [e] Not related to toluene.

fer to the substrate,[15] and not on the intermediacy of metal ions. The function of small amounts of metal salt in this case is to decompose hydroperoxides into radicals. No rate changes were observed varying cobalt concentrations at 155°.[16] Rate dependence on metal salt concentration has also been observed in the Teijin TPA process, also proceeding by electron transfer.[17] Facile oxidation of cyclohexane with cobaltic salts and added cupric acetate in the absence of oxygen is additional evidence that the new system is not dependent on hydrogen abstraction by free radicals as cupric ion are effective free radical terminators.[18,19]

Unlike high-temperature (155°)[16] butane oxidation, which prefers manganese catalysts to those of cobalt, low-temperature oxidation of butane by electron transfer has so far been limited to cobalt salts as the effective oxidants. This is attributed to the lower oxidation potential of the Mn(III)–Mn(II) couple compared to that of Co(III)–Co(II) (1.51 *vs.* 1.82 eV).[20] It implies that Mn(III) ions are not sufficiently strong oxidants to abstract electrons from C–H σ bonds. Electron transfer with Mn(III) was successful only with substrates having ionization potentials below 8.0 eV, which excludes simple paraffins and alkylbenzenes.[21] Free radical reactions with manganese salts, *via* $Mn(OAc)_3 \rightarrow \cdot CH_2COOH + Mn(OAc)_2$, occur at higher temperatures.[21]

An interesting phenomenon was found in both the oxidation of paraffins and alkylbenzenes in the cobalt system. Surprisingly, substrates with tertiary hydrogen showed poor reactivity. Isobutane was less reactive than *n*-butane, methylcyclohexane less reactive than cyclohexane, just as cumene was much less reactive than toluene. In a series of normal paraffins, *n*-butane was found to react faster than *n*-pentane, while *n*-undecane was unreactive. This is inconsistent with a normal free radical pathway which predicts increasing reactivity with increasing number of methylene groups in the substrate.[22,23]

Oxidation of paraffins and alkylbenzenes are analogous in the following respects: (1) good rates of oxidation are observed at low temperature, (2) oxidations show unusual selectivity, (3) reactions are limited to Co(III) as the effective oxidants, (4) rates are dependent on Co(III) ion concentration, (5) reactions are not inhibited by cupric ions, and (6) substrates with tertiary hydrogen atoms are the least reactive (Table III). Electron transfer, clearly in evidence, is therefore not limited to π systems. It represents a more general phenomenon operating on C–H σ bonds, the common feature in both hydrocarbon types. In support of this postulate, oxidations of toluene and cyclohexane by cobaltic ions were found to proceed at comparable rates in aqueous methyl cyanide. Reactions were first order with respect to both substrates and Co(III) ions.[4]

The interaction of Co(III) with aliphatic substrates is now under investigation with a number of cycloaliphatic substrates. This work may provide a new avenue towards selective hydrocarbon oxidation.

Experimental Section

Experiments were carried out in a 1-l., 316 stainless steel, magnetically stirred autoclave (Autoclave Engineers, Inc., Erie,

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Pa.), equipped with a Dispersomax stirrer, a heating mantle, and cooling coils. Instruments for measuring oxygen absorption and formation of carbon dioxide and carbon monoxide were employed to monitor the reaction. Molecular oxygen was used as the oxidant, introduced into the autoclave through a medium porosity, 2-in. o.d. stainless steel sparger. In the closed system, oxygen was supplied at the rate at which it was consumed. In the continuous system, exit gases were removed at about 1 l./hr.

In a typical experiment (expt 3, Table I), 157 g of *n*-butane was charged into the autoclave together with a solution of 20 g of cobaltous acetate tetrahydrate in 280 g of glacial acetic acid as well as 20 g of MEK. This mixture was agitated for 2 hr at 110° and 24 atm of total pressure. The autoclave was then cooled and depressured through a series of Dry Ice–acetone traps, and the product was withdrawn. A total of 615.7 g of material was recovered from the autoclave and an additional 20.3 g of butane from the traps. Analysis was carried out employing standard procedures such as vpc, titration, and distillation. Water of reaction and nonacidic oxygenated products were determined by vpc on a 4-ft Porapak Q column, programmed from 75 to 250° at 10°/min using acetone as the internal standard. Propionic and *n*-butyric acids were chromatographed on a 10-ft 20% sebacic acid column at 135° using isobutyric acid as internal standard. Total acidity was obtained by titration, obtaining the yield of acetic acid by difference. Results were verified by actual isolation of products by distillation. Approximately 5 g of butane was unaccounted for and was assumed to be lost during the venting operation.

Registry No.—Co(III), 22541-63-5; acetic acid, 64-19-7.

Selective Reductions. XVIII. The Fast Reaction of Primary, Secondary, and Tertiary Amides with Diborane. A Simple, Convenient Procedure for the Conversion of Amides to the Corresponding Amines

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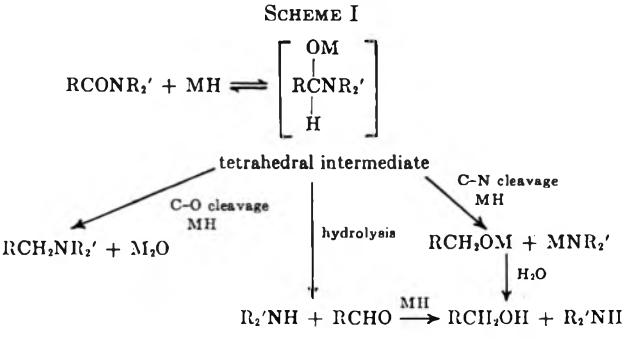
Primary, secondary, and tertiary amide derivatives of both aliphatic and aromatic carboxylic acids were reduced rapidly and quantitatively into the corresponding amines by excess diborane in refluxing tetrahydrofuran. Highly reactive tertiary amides, such as *N*,*N*-dimethylpivalamide, were reduced at moderate rates even at room temperature. The ease of reduction of the different amide functions, as revealed by the rate studies, follows the order tertiary amide ≥ secondary amide ≫ primary amide. Primary aliphatic amides are reduced at faster rates than primary aromatic amides. Unlike lithium aluminum hydride reductions, the tendency for C–N bond cleavage to yield alcohol is completely absent. The mildness of the reagent, diborane, permits the presence of other substituents less susceptible to the reducing action of the reagent, such as nitro, ester groups, halogen, etc. This reaction provides a convenient synthetic procedure for the selective reduction of amides where this is required in synthetic operations.

Reduction of carboxylic acid amides to the corresponding amines has been examined with a variety of complex metal hydrides and metal hydrides such as lithium aluminum hydride, lithium trimethoxyaluminohydride, aluminum hydride, etc.[2] The most common reagent, lithium aluminum hydride, has been widely applied to such reductions. However, it is very well known that the reaction of lithium aluminum hydride with primary amides is extraordinarily slow and incomplete,[2c] whereas with hindered tertiary amides the yield of the corresponding amine is always quite low owing to side reactions. The tetrahedral intermediate formed initially (Scheme I) undergoes both carbon–oxygen bond rupture leading to the amine, and carbon–nitrogen bond rupture leading to the alcohol. The relative importance of these two pathways depend on (a) steric and electronic characteristics of the amide structure, (b) nature of the reducing agent. Finally, lithium aluminum hydride, lithium trimethoxyaluminohydride, and, to a certain extent, aluminum hydride are exceedingly powerful reducing agents, capable of reducing almost all of the functional groups in an organic molecule. Consequently, this introduces severe limitation in the utility of these reagents for the selective reduction of amides to amines in the presence of other reducible functional groups in a multifunctional substrate.

SCHEME I



We recently reported an extensive investigation of the approximate rates and stoichiometry of the reaction of diborane with organic compounds containing representative functional groups in tetrahydrofuran at 0°.[3] During the course of that investigation, it was observed that primary, secondary, and especially tertiary amides (both aliphatic and aromatic) are reduced by diborane to the corresponding amines rapidly and quantitatively under relatively mild conditions[4] (eq 1).

(1) Postdoctorate Research Associate, 1962–1964, on research grants supported by the Atomic Energy Commission, AT(11-1)-70, and the National Institutes of Health, GM 10937.

(2) (a) For a summary of the literature, see N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp 544–592. (b) For a recent review, see J. Zabicky, "The Chemistry of Amides," Interscience, New York, N. Y., 1970, pp 795–801. (c) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966); H. Uffer and E. Schlitter, *Helv. Chim. Acta*, **31**, 1397 (1948); V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953). (d) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965). (e) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966). (f) N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968).

(3) H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 1637 (1970).

(4) For a preliminary communication on this reaction, see H. C. Brown and P. Heim, *ibid.*, **86**, 3566 (1964).

$$RCNR_2' \xrightarrow[THF]{BH_3} RCH_2NR_2' \quad 83\text{-}97\% \qquad (1)$$

R = alkyl or aryl
R′ = alkyl or hydrogen

The unique reduction characteristics of diborane permit the reduction of tertiary amides to amines in the presence of a variety of other less reactive functional groups. Encouraged by the results of our preliminary exploratory studies, we undertook a detailed study of the scope of the reaction and the influence of the electronic and steric characteristics of the amide structure on the rate of reaction. The results of these investigations are reported in the present paper.

Results and Discussion

Stoichiometry.—Primary amides, such as hexanamide, would require a total of seven "active hydrides"[5] for the reduction to amine, two hydrides for the reaction with "active hydrogen" present on the nitrogen, two hydrides for the reduction, and three hydrides (1 mol of borane) tied down to the resulting amine as the amine–borane complex.

In the case of secondary amides, such as *N*-methylpivalamide, a total of six "active hydrides" (one for reaction with active hydrogen present in the molecule, two for the reduction, and the remaining three for the complex formation with the resulting amine) would be required for the smooth reduction.

Finally, tertiary amides, such as *N*,*N*-dimethylpivalamide, where there is no active hydrogen present, would need a total of five "active hydrides" (two for reduction and three for the complex formation) for complete reduction.

General Procedure for Rate and Stoichiometry Studies.—In order to understand the influence of the amide structure on the rate of this reaction, a series of tertiary amides was prepared and their reactivity toward diborane was measured. Tertiary amides were the substrate of choice because of the absence of any complication due to active hydrogen present on nitrogen as in primary and secondary amides.

The general procedure adopted was to add 20 mmol of N,N-disubstituted amide to 20 mmol of borane solution in sufficient tetrahydrofuran (THF) to give 20 ml of solution. This makes the reaction mixture 1.0 *M* in BH_3 and 1.0 *M* in substrate.[6] The solutions were maintained at constant temperature (*ca.* 25°) and aliquots were removed at appropriate intervals of time and analyzed for "residual hydride" by hydrolysis in a mixture of concentrated hydrochloric acid–THF.

Effect of Structure of the Amide on the Reactivity.—

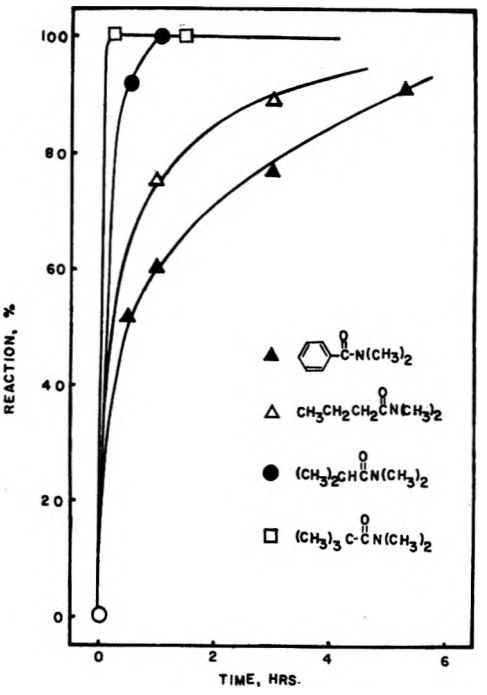
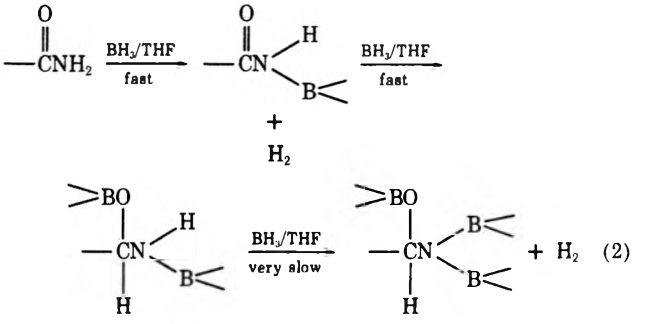


Figure 1.—Rates of reduction of the *N*,*N*-dimethylamides with borane in tetrahydrofuran at 25° (both reagents 1.0 *M*).

Primary amides react relatively rapidly to evolve their active hydrogen, but such hydrogen evolution stops well before 2 mol are realized (1.1 mmol of hydrogen per mmol of compound was observed for hexanamide and 1.4 mmol for benzamide at room temperature). The incomplete hydrogen evolution in the case of primary amides might be due to a simultaneous attack by the diborane on the carbonyl group. The adduct would resemble an amine and would cease to evolve hydrogen further with diborane (eq 2).



(2)

They are also reduced very slowly, far slower than secondary and tertiary amides. Secondary amides, such as *N*-methylpivalamide, liberate 1 mol of hydrogen per mol of substance, as expected, and are also reduced faster than primary amides. Tertiary amides evolve no hydrogen and are reduced rapidly and quantitatively even at room temperature. A series of N,N-disubstituted tertiary amides were examined toward diborane to understand the influence of electronic and steric characteristics of amide group on the rate of reaction.

Increasing the branching on α carbon to the carbonyl group increases the rate of reduction, as revealed by the rates of reduction of *N*,*N*-dimethylamide derivatives of *n*-butyric, isobutyric, and pivalic acid. Aliphatic amides, such as *N*,*N*-dimethylbutyramide, are reduced faster than aromatic amides, such as *N*,*N*-dimethylbenzamide (Figure 1).

(5) It is convenient to discuss the utilization of the reagent in terms of moles of hydride taken up per mole of amide. However, it should not be confused that free "hydride" ion is the active species. An "active hydride" refers to one B–H bond.

(6) During the course of this investigation, it was realized that, in scaling up this reaction for preparative purposes, the yield of amines decreased, especially for the more reactive amides, such as *N*,*N*-dimethylpivalamide. However, the analysis of the resulting mixture indicated the presence of unreacted amide and the absence of any alcohol, indicating that the lower yield is not the result of any side reaction.

It was concluded that the tertiary amine first formed reacts with diborane to form an amine–borane complex of much lower reactivity. Alkylamine–borane reduces acyl halides, aldehydes, and ketones, but is inert to esters, carboxylic acids, and amides; see H. Nöth and H. Beyer, *Ber.*, **93**, 1078 (1960). However, this difficulty can be overcome by using additional diborane, 2 mol of borane per mol of amide.

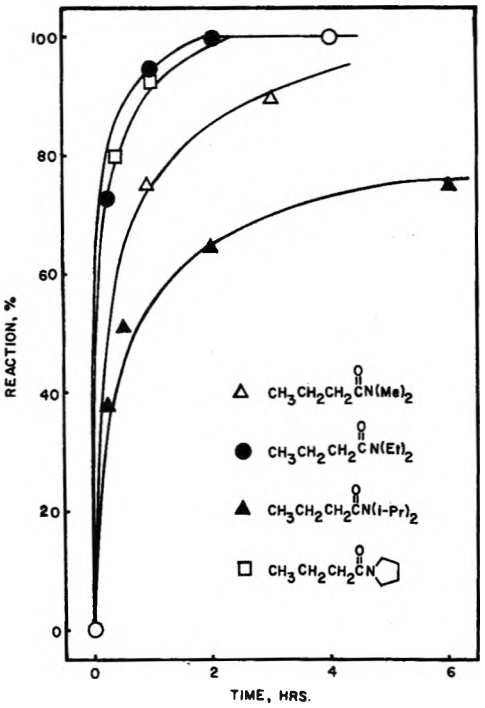


Figure 2.—Rates of reduction of the *N*,*N*-dialkylbutyramides with borane in tetrahydrofuran at 25° (both reagents 1.0 *M*).

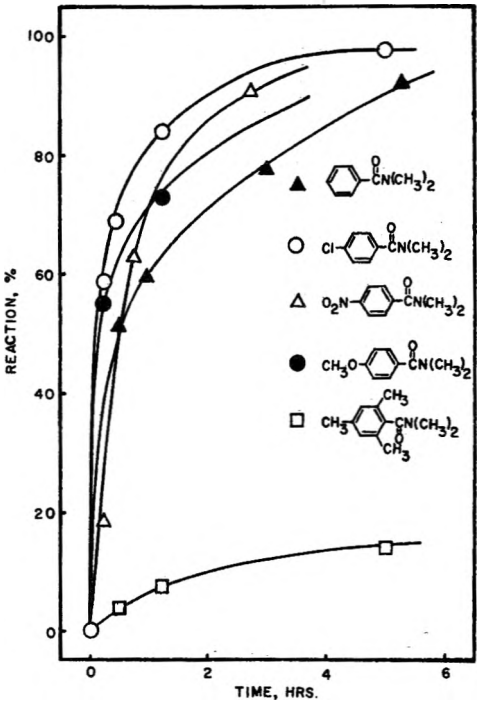


Figure 3.—Rates of reduction of the *N*,*N*-dimethylbenzamides with borane in tetrahydrofuran at 25° (both reagents 1.0 *M*).

The reaction is also sensitive to the nature of the substituent present on the nitrogen. Thus, *N*,*N*-diethylbutyramide and *N*-butyrylpyrrolidine are reduced at a faster rate than *N*,*N*-dimethylbutyramide. However, *N*,*N*-diisopropylbutyramide is reduced at a slower rate than the above-mentioned amides. This clearly indicates that the reaction is sensitive to both electronic and steric effects (Figure 2).

Introduction of polar substituents in *N*,*N*-dimethylbenzamide (both electron releasing and electron withdrawing), such as *p*-nitro, *p*-chloro, *p*-methoxy, and *p*-methyl, does not influence the rate of reduction to any appreciable extent, revealing insensitiveness of the reaction to electronic effects. However, substituents in the ortho position greatly retard the reaction, which should be attributed to the steric hindrance to the formation of the tetrahedral intermediate. Thus, *N*,*N*-dimethylmesitoic acid amide is reduced at a far slower rate than *N*,*N*-dimethylbenzamide (Figure 3).

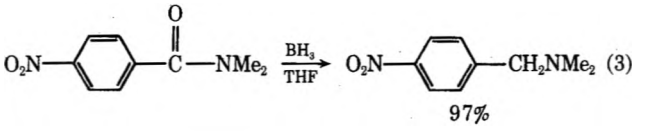
Synthetic Utility.—The rate and stoichiometric studies previously discussed indicated that for optimum rate of reduction it is desirable to use at least $1^2/_3$ mol of borane per mol of tertiary amide. In extending this procedure to primary and secondary amides, the amount of borane used was increased by $^1/_3$ for each equivalent of active hydrogen present in the amide. The amide in THF was added to borane solution at 0°. With tertiary and secondary amides, the resulting mixture was brought to reflux and maintained there for 1 hr to drive the reaction essentially to completion. In the cases of primary amides, it was found desirable to increase the reaction time at reflux to 2 hr for primary alphatic amides and to 8 hr for primary aromatic amides. Accordingly, we adopted these conditions for examining the synthetic applicability of the procedure. A critical step in the reaction is the hydrolysis of the excess hydride and the liberation of amine from amine–borane complex. A series of exploratory experiments indicated the necessity of refluxing the resulting mixture with concentrated hydrochloric acid with simultaneous distillation of the THF.

Simple primary amides, such as hexanamide and benzamide, were converted into *n*-hexylamine and benzylamine, respectively, in 87% yield.

Secondary amides, such as *N*-methylhexanamide and *N*-methylpivalamide, were converted into their corresponding secondary amines in 98 and 83% yield, respectively.

N,*N*-Diethylpivalamide was converted into diethylneopentylamine in 94% yield. Similarly, *N*,*N*-diisopropylbenzamide was converted into diisopropylbenzylamine in a yield of 98%.

Finally, *N*,*N*-dimethyl-*p*-nitrobenzamide was examined to test the utility of this procedure for selective reductions. The product, *N*,*N*-dimethyl-*p*-nitrobenzylamine, was obtained in 97% yield, confirming the value of this procedure for selective reductions (eq 3). The results are summarized in Table I.



Scope and Applicability.—It was previously established that diborane is a highly selective reducing agent. Being a Lewis acid by itself, it exhibits many unique reduction characteristics which are absent in other complex metal hydrides, such as lithium aluminum hydride. For achieving amide to amine conversion, diborane has two major advantages over the conventional reagents, such as lithium aluminum hydride: (a) the reaction is rapid, quantitative, and very clean, even in the case of tertiary amides; (b) the reaction can tolerate many functional groups such as nitro, halogen, ester, sulfone, carbamate, etc. The remarkable utility

TABLE I

REDUCTION OF REPRESENTATIVE AMIDES TO AMINES BY DIBORANE IN TETRAHYDROFURAN

Registry no.	Acid amide	Product	Yield, % Anal.[a]	Yield, % Isolated
628-02-4	Hexanoic[d]	*n*-Hexylamine	87	
3418-05-1	*N*-Methylhexanoic[c]	Methyl-*n*-hexylamine	98	
5830-30-8	*N,N*-Dimethylhexanoic[b]	Dimethyl-*n*-hexylamine	95	
754-10-9	Pivalic[d]	Neopentylamine	83	
6830-83-7	*N*-Methylpivalic[c]	Methylneopentylamine	83	
24331-71-3	*N,N*-Dimethylpivalic[b]	Dimethylneopentylamine	92	79
55-21-0	Benzoic[e]	Benzylamine	87	
611-74-5	*N,N*-Dimethylbenzoic[b]	Dimethylbenzylamine	98	
7291-01-2	*N,N*-Dimethyl-*p*-nitrobenzoic[b]	Dimethyl-*p*-nitrobenzylamine	97	84
24331-72-4	*N,N*-Diethylpivalic[b]	Diethylneopentylamine	94	81
20383-28-2	*N,N*-Diisopropylbenzoic	Diisopropylbenzylamine	98	

[a] Determined by gas chromatographic analysis, isolation as the picrate, or by titration. [b] $1^2/_3$ mol of BH_3 per mol of amide, heated under reflux in tetrahydrofuran for 1 hr. [c] 2 mol of BH_3 per mol of amide, heated under reflux for 1 hr. [d] $2^1/_3$ mol of BH_3 per mol of amide, heated under reflux for 2 hr. [e] $2^1/_3$ mol of BH_3 per mol of amide, heated under reflux for 8 hr.

of this procedure over other methods is evidenced by numerous applications of this procedure in medicinal, pharmaceutical, and biological chemistry since our preliminary communication on this reaction.

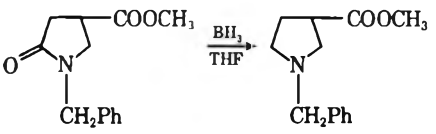
There are quite a large number of instances where the use of conventional lithium aluminum hydride has failed to achieve conversion of amide to amine in any appreciable yield. The failure has been attributed to two factors, the incomplete and slow reaction and the side reaction of C–N bond cleavage resulting in the corresponding alcohol. However, in such cases, the difficulty has often been overcome by using diborane in place of lithium aluminum hydride, resulting in rapid and essentially quantitative conversion to the desired amine.[7]

Recently diborane has been applied to the reduction of 1,2-diacylhydrazines to 1,2-dialkylhydrazines without the rupture of the nitrogen–nitrogen bond,[8] and of ketoxime acetate or tosylate to the corresponding amine.[9]

Diborane, unlike lithium aluminum hydride and its derivatives, being a mild and selective reducing agent, makes possible the presence of many other substituents less susceptible to the reducing action of the reagent.

Thus, diborane has been successfully utilized for the reduction of halogen-substituted amide derivatives to the corresponding halo-substituted amine, in excellent yield,[10] where lithium aluminum hydride causes extensive hydrogenolysis of the carbon–halogen bonds in both aromatic and aliphatic substrates.[11]

The utility of diborane for such amide reductions is further evidenced by the successful selective reduction of the amide function in the presence of carbamate, ester,[12] and sulfone[13] groups, applications where lithium aluminum hydride had failed. Thus, 1-benzyl-3-methoxycarbonyl-5-pyrolidinone was selectively reduced to methyl 1-benzyl-3-pyrolidinecarboxylate in 54% yield (eq 4). The utility of this method can be



(4)

realized by the previous three-step procedure for the preparation of this compound[14] in an overall yield of 28%.

A disadvantage of diborane for such reductions occurs with unsaturated derivatives, such as *N,N*-dimethylcinnamamide, since diborane rapidly adds to the double bonds. However, for such reductions, aluminum hydride can often be successfully applied.[15]

Experimental Section

Materials.—Tetrahydrofuran was dried with excess lithium aluminum hydride and distilled under nitrogen. Diborane solution in tetrahydrofuran was prepared from sodium borohydride and boron trifluoride etherate.[16] The borane–THF solution was standardized by hydrolyzing a known aliquot of the solution with a glycerine–water–THF mixture and measuring the hydrogen evolved. For most experiments, the concentration was approximately 2 *M* in BH_3.

Primary amides used were the commercial products of the highest purity. Secondary and tertiary amides were prepared by the method of Brown and Taukamoto.[17] In all of the cases physical constants agreed satisfactorily with constants in the literature. For further details, the thesis should be referred to.

All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.

Rates of Reduction of N,N-Disubstituted Acid Amides.—Reduction of *N,N*-dimethylisobutyramide is representative. A 100-ml flask was dried in an oven and cooled down in a dry nitrogen atmosphere. The flask was equipped with a rubber syringe cap and a magnetic stirring bar, and a reflux condenser was connected to an inverted gas buret *via* a Dry Ice trap. The flask was immersed in a water bath at room temperature (*ca.* 25°), and 9.7 ml (20 mmol) of 2.1 *M* borane solution in THF was introduced into the reaction flask, followed by 0.3 ml of THF. Then 20 mmol of *N,N*-dimethylbutyramide in 10 ml of THF was introduced. Now the reaction mixture was 1.0 *M* in BH_3 and amide.

At the end of 20 min, a 2.0-ml aliquot of the reaction mixture was removed with a hypodermic syringe and injected into a hydrolyzing mixture of 10 ml of concentrated hydrochloric acid and 5 ml of THF. The hydrogen evolved was measured with a gas buret. This indicated that 1.86 mmol of hydride has reacted per mmol of the amide, indicating the completion of 93% of the reduction. The reaction was monitored at 1 hr, 3 hr, etc. Reaction was essentially complete in 1 hr.

(7) W. G. Duncan and D. W. Henry, *J. Med. Chem.*, **12**, 711 (1969); A. J. Birch and J. J. Wright, *Tetrahedron*, **26**, 2329 (1970); M. P. Mertes and A. J. Lin, *J. Med. Chem.*, **13**, 77 (1970); P. L. Warner, Jr., and T. J. Bardos, *ibid.*, **13**, 407 (1970); P. S. Portoghese and J. G. Turcotte, *ibid.*, **14**, 288 (1971); R. Kuttan, A. N. Radhakrishnan, T. Spande, and B. Witkop, *Biochemistry*, **10**, 361 (1971); K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968); R. J. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3207 (1968); R. D. Schuetz, G. P. Nilles, and R. L. Titus, *ibid.*, **33**, 1556 (1968); K. E. Wiesner, Z. Valenta, D. E. Orr, V. Liede, and G. Kohan, *Can. J. Chem.*, **46**, 3617 (1968).

(8) H. Feuer and F. Brown, Jr., *J. Org. Chem.*, **35**, 1468 (1970).

(9) A. Hassner and P. Catsoulacos, *Chem. Commun.*, 590 (1967).

(10) Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, **29**, 2870 (1964); J. B. Hester, Jr., A. D. Rudzik, and W. Veldkamp, *J. Med. Chem.*, **13**, 827 (1970); G. Schüll, *Justus Liebigs Ann. Chem.*, **750**, 76 (1971); J. W. McFarland and H. L. Howes, Jr., *J. Med. Chem.*, **13**, 109 (1970); H. J. Brabander and W. B. Wright, Jr., *J. Org. Chem.*, **32**, 4053 (1967); N. B. Chapman, R. M. Scrowston, and R. Westwood, *J. Chem. Soc.*, 528 (1967); J. I. DeGraw and W. A. Skinner, *Can. J. Chem.*, **45**, 63 (1967).

(11) H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969); H. C. Brown and S. Krishnamurthy, manuscript in preparation.

(12) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **31**, 3867 (1966); M. J. Kornet, P. A. Thio, and S. I. Tan, *ibid.*, **33**, 3637 (1968).

(13) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **5**, 875 (1968).

(14) J. F. Cavalla, *J. Chem. Soc.*, 851 (1959).

(15) N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 2927 (1968).

(16) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963); H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **90**, 2915 (1968).

(17) H. C. Brown and A. Tsukamoto, *ibid.*, **86**, 1089 (1964); A. Tsukamoto, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1959.

The results for other amides are summarized graphically in Figures 1, 2, and 3.

Procedure for Product Analysis.—For analyzing reduction products separate experiments on a 20-mmol scale were carried out. The yields were determined by titration with 1.0 *N* HCl, isolation as the picrate, or by glpc analysis on a 10% Porimene JM-T on Fluoropak. Reduction of *N,N*-diisopropylbenzamide to *N,N*-diisopropylbenzylamine is representative. The experimental setup is as in the previous experiment. A typical reaction setup was assembled. Then 33.3 mmol of borane solution (20 ml of a 1.67 *M* solution in THF) was placed in the reaction flask maintained at *ca.* 25°. To this 4.1 g (20 mmol) of *N,N*-diisopropylbenzamide in 20 ml of THF was added and the mixture was stirred well. The resulting mixture was refluxed for 1 hr. The flask was allowed to cool to room temperature and 8 ml of 6 *M* HCl was added. The tetrahydrofuran was removed by distillation at atmospheric pressure as hydrogen was evolved (1.5 l., 60 mmol) from hydrolysis of excess borane. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted three times with a total of 25 ml of ether. Titration of a known aliquot of this reaction mixture with a standardized HCl solution revealed the presence of amine in 98% yield.

To 2.5 ml (1 mmol) of the ether extract of the amine, a saturated solution of picric acid in 95% ethanol was added and heated. Water was added drop by drop until the solution turned slightly milky. After cooling, yellow needles of picrate crystallized out in 98% yield, mp 134–135°. *Anal.* Calcd for $C_{19}H_{24}N_4O_7$: C, 54.27; H, 5.75; N, 13.32. Found: C, 54.42; H, 5.82; N, 13.32.

General Preparative Procedure for the Reduction of Amides to Amines.—The following general procedure illustrated for the reduction of *N,N*-dimethylpivalamide to dimethylpivalamine is suggested for the reduction of amides. (Depending upon the nature of the amide and the substituents present, the hydride to compound ratio and the time required may require an increase or decrease.)

To a solution of 200 ml (334 mmol) of 1.67 *M* borane in THF in a 500-ml flask equipped with a reflux condenser, dropping funnel, and a magnetic stirring bar maintained under nitrogen was added 25.8 g (200 mmol) of *N,N*-dimethylpivalamide in 100 ml of THF over 15 min. The temperature was maintained approximately at 0° during the addition. The colorless solution was then brought to reflux and maintained there for 1 hr. The flask was permitted to cool to room temperature and 50 ml of 6 *M* hydrochloric acid was added slowly through a dropping funnel. The THF was removed by distillation at atmospheric pressure as hydrogen was evolved (15.5 l., 0.6 mol) from the hydrolysis of the amine–borane complex. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted three times with a total of 100 ml of ether. After drying with sodium sulfate, distillation yielded 18.2 g (79% yield) of dimethylneopentylamine, bp 95–96°, $n^{20}D$ 1.3982.

Similarly, *N,N*-diethylpivalamide was converted into isolated diethylneopentylamine in an isolated yield of 81%.

Selective Reduction of *N,N*-Dimethyl-*p*-nitrobenzamide to Dimethyl-*p*-nitrobenzylamine.—To a solution of 50 ml (83.3 mmol) of a 1.67 *M* solution of borane in THF in a 200-ml flask maintained at 0° under nitrogen was added 9.76 g (50 mmol) of *N,N*-dimethyl-*p*-nitrobenzamide in 4.0 ml of THF over a period of 10 min. After the addition was completed, the resulting mixture was refluxed for 1 hr. After the reaction flask was cooled, the reaction mixture was worked up as in the previous experiment and the combined ether extracts were dried over sodium sulfate. Distillation yielded 7.6 g (84%) of dimethyl-*p*-nitrobenzylamine, bp 96–98° (1.5 mm), $n^{20}D$ 1.5421.

Registry No.—Diborane, 19287-45-7.

Formation of Mercaptomethylamine as an Intermediate[1]

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Bis(aminomethyl) disulfide dihydrochloride (**2**) was hydrogenated to yield bis(aminomethyl) sulfide dihydrochloride (**3**) and hydrogen sulfide. Similarly, reaction of phthalimidomethyl aminomethyl disulfide hydrochloride (**4**) with hydrogen and palladium gave *N*-(mercaptomethyl)phthalimide (**5**), **3**, and hydrogen sulfide. These reactions indicate the formation of mercaptomethylamine hydrochloride (**1**) as an intermediate which undergoes self-condensation to yield **3** and hydrogen sulfide. Compounds **2** and **4** were prepared by the acid hydrolysis of bis(*o*-carboxybenzoylaminomethyl) disulfide (**8**), which was obtained by partial alkaline hydrolysis of bis(phthalimidomethyl) disulfide (**7**). Hydrazinolysis of **7** in liquid ammonia gave **2** directly in low yield. The sulfide **3** was independently synthesized from bis(phthalimidomethyl) sulfide (**10**) by saponification to bis(*o*-carboxybenzoylaminomethyl) sulfide (**11**) followed by acid hydrolysis. Treatment of β-mercaptoethylamine hydrochloride (**12**) with sulfur trioxide–pyridine afforded *S*-2-aminoethanethiosulfuric acid (**13**).

Chemical protection of mammals against ionizing radiation was demonstrated in 1949.[3] It was soon established that compounds showing radiation protection possessed both the amino and mercapto groups,[4] and β-mercaptoethylamine (MEA) is one of the most active of the more than 3000 compounds tested.[5]

The protective action of aminothiols has been shown to decrease with increasing separation of the functional groups.[5,6] We were therefore led to examine the synthesis and properties of the hydrochloride of mercaptomethylamine (**1**), the parent *N,S*-acetal of formaldehyde. Two *N,S*-hemiacetals of **1** containing tertiary nitrogens have been reported, 1-piperidinemethanethiol and 4-morpholinemethanethiol.[7]

In general, Bunte salts (*e.g.*, **13**) are less toxic than the corresponding thiols, and *S*-2-aminoethanethiosulfuric acid (**13**) and MEA (**12**) are equally protective at their maximum tolerated doses.[6] A new synthesis of **13** is reported and an attempt was made to extend the reaction to the preparation of *S*-aminomethanethiosulfuric acid (**14**).

Results and Discussion

Hydrogenation of Disulfides 2 and 4.—This communication reports evidence for the formation of mercaptomethylamine hydrochloride (**1**) as an inter-

(1) Presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, I23.

(2) Taken in part from the dissertation submitted by S. Abdou-Sabet in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Maryland, 1966; *Diss. Abstr. B*, **27**, 3028 (1967).

(3) (a) A. Herve and Z. M. Bacq, *C. R. Soc. Biol.*, **143**, 881 (1949); (b) H. M. Patt, E. B. Tyree, R. L. Straube, and D. E. Smith, *Science*, **110**, 213 (1949).

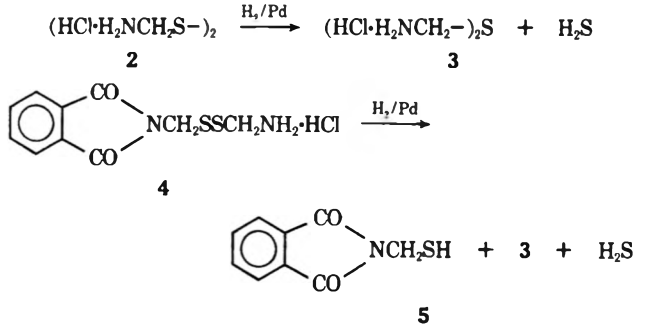
(4) Z. M. Bacq and A. Herve, *Schweiz. Med. Wochenschr.*, **82**, 1018 (1952).

(5) Z. M. Bacq, "Chemical Protection against Ionizing Radiation," Charles C Thomas, Springfield, Ill., 1965, p 12.

(6) D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 510 (1969).

(7) A. Binz and L. H. Pence, *J. Amer. Chem. Soc.*, **61**, 3134 (1939).

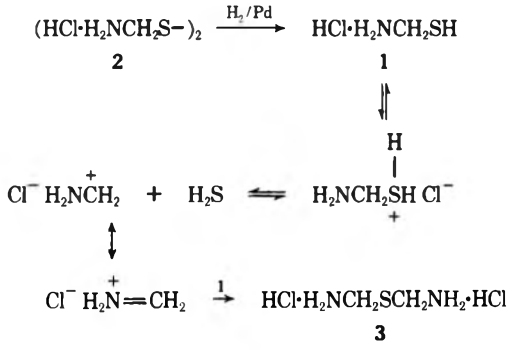
mediate in two related reactions. The reaction of bis(aminomethyl) disulfide dihydrochloride (2) with



hydrogen in the presence of palladium black afforded crystalline bis(aminomethyl) sulfide dihydrochloride (3) and hydrogen sulfide. In a similar reaction, hydrogenation of phthalimidomethyl aminomethyl disulfide hydrochloride (4) gave *N*-(mercaptomethyl)phthalimide (5), 3, and hydrogen sulfide.

Catalytic reduction of disulfides is known to produce mercaptans,[8] and the primary products from the hydrogenation of the disulfides 2 and 4 were very likely the corresponding mercaptans 1 and 5. The mercaptan 5 was isolated and its structuree was confirmed by an independent synthesis. Two molecules of mercaptan 1 are considered to have undergone condensation with elimination of hydrogen sulfide and formation of the sulfide dihydrochloride 3. The mechanism proposed in Scheme I suggests the forma-

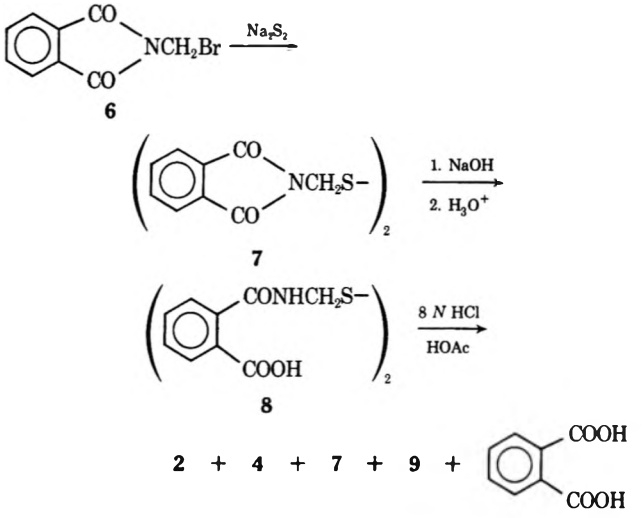
SCHEME I
PROPOSED MECHANISM FOR CONVERSION OF DISULFIDE 2 INTO SULFIDE 3



tion of protonated methyleneimine[9] as an intermediate. A similar intermediate, *N*,*N*-dimethylbenzaliminium ion, has been presented to explain the kinetics observed in the SN1 cleavage of alkyl α-dimethylaminobenzyl sulfides in aqueous acidic media.[10]

Synthesis of Disulfides 2 and 4.—The route leading to the disulfides 2 and 4 is outlined in Scheme II. Utilization of a thiol ester as a single protective group was not attempted, since α-aminothio esters were prepared successfully only with tertiary amino groups.[11] The synthesis of monoalkylaminomethanethiol esters is not practical (3% yield) owing to the predominance of polymer formation.[11]

SCHEME II
SYNTHESIS OF DISULFIDES 2 AND 4



The synthesis of the known *N*-(bromomethyl)phthalimide (6) from *N*-(hydroxymethyl)phthalimide was carried out by a modification of the literature procedure.[12] A purer and more stable product was obtained in higher yield (85%) by substitution of 62% for 48% hydrobromic acid and by the use of glacial acetic acid as the solvent in place of concentrated sulfuric acid.

The reaction of 6 with sodium disulfide in 0.1 *M* quantities following the general literature procedure[13] gave variable and low yields (1–29%) of bis(phthalimidomethyl) disulfide (7). No product, however, was isolated with larger scale reactions. With acetone–water as the solvent system and using freshly prepared sodium disulfide, compound 7 was reproducibly obtained in 70–80% yield.

Cleavage of the phthalimido group of 7 with hydrazine in dioxane–water, methyl alcohol, carbon tetrachloride, chloroform, or benzene gave phthalhydrazide but 2 could not be isolated; however, it was later found that a very low yield of the disulfide 2 could be obtained using liquid ammonia as the solvent. An improved method was the two-step hydrolysis which afforded 2 and 4 simultaneously. Treatment of 7 with 2 equiv of sodium hydroxide followed by acidification with hydrochloric acid gave analytically pure bis(*o*-carboxybenzoylaminomethyl) disulfide (8) in 80% yield. Hydrolysis of 8 was effected using 8 *N* hydrochloric acid in acetic acid at room temperature to give five products, 2 (13–20%), 4 (41%), 7 (39%), phthalic acid, and a small amount of compound 9 whose structure was not determined. Attempted hydrolysis of 8 using 12 *N* hydrochloric acid in acetic acid resulted in dehydration and cyclization of the phthalamic acid to 7, whereas 4 *N* hydrochloric acid in acetic acid gave phthalic acid, ammonium chloride, and uncharacterized polymers, possibly derived from thioformaldehyde. The disulfide dihydrochloride 2 is unstable in moist air and when dissolved in water it decomposes with the evolution of hydrogen sulfide and formation of a white polymeric precipitate.

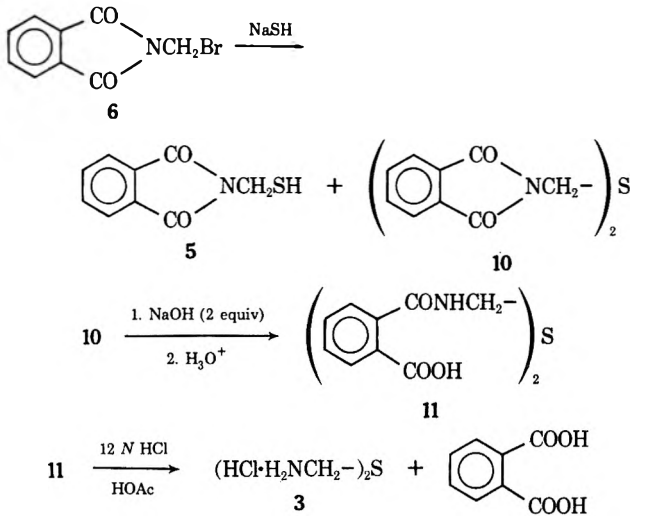
Syntheses of Bis(aminomethyl) Sulfide Dihydro-

(8) C. Berse, R. Boucher, and L. Piche, *J. Org. Chem.*, **22**, 805 (1957).
(9) F. Cacace and A. P. Wolf, *J. Amer. Chem. Soc.*, **87**, 5301 (1965).
(10) W. M. Schubert and Y. Motoyama, *ibid.*, **87**, 5507 (1965).
(11) S. Searles, Jr., S. Nukina, and E. R. Magnuson, *J. Org. Chem.*, **30**, 1920 (1965).
(12) G. W. Pucher and T. B. Johnson, *J. Amer. Chem. Soc.*, **44**, 820 (1922).
(13) F. I. Rachinskii, N. M. Slavacheskaia, and D. V. Iofee, *Zh. Obshch. Khim.*, **28**, 2998, 3027 (1958).

chloride (3) and Phthalimidomethyl Mercaptan (5).—The structures of **3** and **5** were confirmed by independent syntheses, as shown in Scheme III. The

SCHEME III

SYNTHESIS OF SULFIDE 3 AND MERCAPTAN 5



reaction of sodium hydrosulfide with **6** at 0° in a tetrahydrofuran–water medium gave mainly the mercaptan **5** and very little **10**; at room temperature, however, the predominant product was the sulfide **10**. The phthaloyl protecting group of **10** was removed in two steps. The initial saponification gave the phthalamic acid **11** in good yield. The subsequent hydrolysis of **11** using 12 *N* hydrochloric acid in glacial acetic acid afforded the sulfide dihydrochloride **3** in moderate (41%) yield.

***S*-2-Aminoethanethiosulfuric Acid (13).**—Aminoalkanethiosulfuric acids, an important class of zwitterionic Bunte salts, are usually prepared by the reaction of the corresponding bromoalkylamine hydrobromide with sodium thiosulfate.[6] Thiophenols react with sulfur trioxide–pyridine to give the corresponding phenylthiosulfuric acids,[14] and later workers[15] have prepared aliphatic and aromatic thiosulfuric acids by reaction of the corresponding mercaptan with sulfur trioxide. This reaction was extended to an aminoalkanethiol; the reaction of β-mercaptoethylamine hydrochloride (**12**) with sulfur trioxide–pyridine afforded a new route to **13**.

$$\underset{\mathbf{12}}{HCl\cdot H_2NCH_2CH_2SH} + SO_3\text{–}Py \xrightarrow{DMF} \underset{\mathbf{13}}{H_2NCH_2CH_2S_2O_3H} + Py\cdot HCl$$

An unsuccessful attempt was made to trap **1** as a Bunte salt by hydrogenation of **2** in the presence of

$$\underset{\mathbf{2}}{(HCl\cdot H_2NCH_2S)_2} \xrightarrow[SO_3\text{-}Py]{H_2/Pd} \underset{\mathbf{14}}{H_2NCH_2S_2O_3H}$$

sulfur trioxide–pyridine. The reaction mixture turned black immediately and no pure products could be isolated.

(14) P. Baumgarten, *Ber.*, **63**, 1330 (1930).
(15) M. Schmidt and G. Talsky, *Chem. Ber.*, **94**, 1352 (1961).

Experimental Section[16]

N-(Bromomethyl)phthalimide (**6**).—Major modifications were made in the Pucher and Johnson[12] procedure. To a mixture of 17.7 g (0.1 mol) of *N*-(hydroxymethyl)phthalimide[12] in 35 ml of glacial acetic acid was added, with stirring, 27.5 ml of 62% hydrobromic acid (Michigan Chemical Co., New York, N. Y.). The mixture was heated and kept at 48–52° for 20 hr. After cooling overnight at 0–5°, the colorless solid was collected by filtration and washed with water, then with dilute ammonium hydroxide solution, and again with water. The dry solid (22.1 g) was crystallized from benzene and gave 18.5 g (85%) of **6**, mp 152° (lit. mp 148°,[12] 150°[17]).

Anal. Calcd for $C_9H_6BrNO_2$: C, 45.03; H, 2.51; N, 5.84; Br, 33.29. Found: C, 44.94; H, 2.51; N, 5.98; Br, 33.11.

Bis(phthalimidomethyl) Disulfide (7).—This compound was prepared using a modification of the general literature procedure.[12] A 2-g portion (0.0625 mol) of sublimed sulfur was dissolved in a solution of 15 g (0.0625 mol) of $Na_2S\cdot 9H_2O$ in 20 ml of water with heating; then an additional 30 ml of water was added. After cooling to room temperature, the Na_2S_2 solution was added to a solution of 24 g (0.1 mol) of **6** in 200 ml of acetone with vigorous stirring and ice-bath cooling over a period of 2 min. The suspension was stirred for an additional 5 min, then 200 ml of water was added, the mixture was cooled, and 16.5 g of crude product was collected by filtration. Crystallization from chloroform–*n*-hexane afforded 14.65 g (76%) of the analytically pure disulfide **7**: mp 194°; ir 5.63 and 5.85 (phthalimido carbonyls), 6.23, 6.83, 7.10, 7.15, 7.30, 7.70, 7.88, 8.40, 8.55, 9.25, 10.95, 12.40, 12.65, 13.50, and 14.80 μ.

Anal. Calcd for $C_{18}H_{12}N_2O_4S_2$: C, 56.23; H, 3.15; N, 7.29; S, 16.68. Found: C, 56.43; H, 3.29; N, 7.08; S, 16.63.

Bis(*o*-carboxybenzoylaminomethyl) Disulfide (8).—To a suspension of 7.68 g (0.02 mol) of **7** in 600 ml of 95% ethyl alcohol at 42–45° was added 40 ml (0.02 mol) of 1.00 *N* NaOH dropwise over a period of 30 min to give a homogeneous solution which was evaporated *in vacuo* at 35°. Crystallization of the residue from water–ethanol gave 8.5 g of crystalline solid, mp 143°, which on recrystallization afforded 7.52 g (81%) of needle-shaped crystals of the hydrate of the disodium salt of **8**: mp 175° dec; ir 3.00 (NH), 6.06 (sh), 6.17 (sh), 6.35, 6.95, 7.30, 7.52, 7.90, 8.60, 9.15, 9.65, 10.60, 11.85, and 13.70 μ.

Anal. Calcd for $C_{18}H_{14}O_6N_2S_2Na_2\cdot H_2O$: C, 44.82; H, 3.34; N, 5.81; S, 13.29. Found: C, 44.76, 45.30; H, 3.30, 3.52; N, 5.93; S, 13.53.

To a solution of 5.36 g (0.0115 mol) of the disodium salt hydrate of **8** in 50 ml of water was added 23 ml of 1.0 *N* HCl dropwise with stirring and ice bath cooling. After cooling at 0° for 2 hr, 4.20 g (80% based on **7**) of analytically pure **8** was collected by filtration: mp 142° dec; ir 3.00, 3.35, 3.40, 5.90 (COOH), 6.08 (CONH), 6.20, 6.30, 6.50, 6.60, 6.80, 7.30, 7.60, 7.95, 8.20, 8.75, and 9.25 μ.

Anal. Calcd for $C_{18}H_{16}O_6N_2S_2$: C, 51.44; H, 3.84; N, 6.66; S, 15.22. Found: C, 51.40; H, 4.05; N, 6.62; S, 15.27.

Hydrolysis of 8.—A suspension of 5.3 g (0.0125 mol) of **8** in 150 ml of glacial acetic acid and 6.25 ml of 8 *N* HCl was stirred for 24 hr. The suspension was lyophilized and the dry white solid residue was extracted with a 100-ml portion of refluxing $CHCl_3$ and washed with four 25-ml portions of hot $CHCl_3$. The combined chloroform extract was concentrated to give a white solid (0.2 g) that was crystallized three times from chloroform–ether to afford compound **9**: mp 163–165°; ir 2.95, 5.65, 5.82, 5.88 6.20, 7.05, 7.20, 7.62, 7.72, 9.05, 9.35, 10.35, 10.80, 12.50, 13.65, and 13.90 μ.

Anal. Found: C, 44.66; H, 4.50; Cl, 15.22; N, 11.53; S, 12.30. Compound **9** was not characterized further.

The chloroform filtrate was evaporated to dryness and the residue was crystallized from chloroform–*n*-hexane to afford 1.9 g (39%) of disulfide **7**, mp 194°; the infrared spectrum was identical with that of an authentic sample.

The solid insoluble in the original chloroform extract was extracted in a Soxhlet apparatus with anhydrous ether for 12 hr. The ether extract afforded 2.1 g (51%) of phthalic acid, mp 191–192° dec.

(16) All melting points are uncorrected. Infrared spectra were determined in KBr on a Beckman IR-5 instrument (reported in μ) or on a Perkin-Elmer Model 337 spectrophotometer (reported in cm^{-1}). Elemental analyses were performed by Dr. Franz J. Kasler.
(17) O. Mancera and O. Lemberger, *J. Org. Chem.*, **15**, 1253 (1950).

The residue remaining after the ether extraction was digested with 60 ml of anhydrous dimethylformamide–ether (5:1) mixture. The extract was evaporated at low pressure to give 1.5 g (41%) of solid that was purified by crystallization from 12 ml of benzyl alcohol–ether (5:1) to afford pure disulfide hydrochloride **4**: mp 114°; ir 2.95, 3.90 (sh), 5.60, 5.80, and 6.30 μ.

Anal. Calcd for $C_{10}H_{11}ClN_2O_2S_2$: C, 41.26; H, 3.81; N, 9.65. Found: C, 41.48; H, 4.03; N, 9.70.

The residue remaining after the dimethylformamide–ether extraction, 0.52 g, showed no absorption for the carbonyls of the phthalimido in the ir spectrum. The solid was dissolved in 15–20 ml of glacial acetic acid by heating and adding concentrated HCl dropwise. Cooling afforded 0.34 g (14%) of crystalline, analytically pure disulfide dihydrochloride **2**: shrinking at 145°, obvious decomposition at 210°, and extensive decomposition with strong, unpleasant odor above 235°; ir 2.94 (m), 3.36 (vs), 3.42 (vs), 3.51 (vs), 3.91 (m), 6.28 (m), 6.32 (m), 6.67 (s), 7.05 (m), 7.60 (w), 8.92 (vw), 9.25 (w), 10.24 (m), 11.85 (m), and 14.6–15.0 μ (broad and weak).

Anal. Calcd for $C_2H_{10}Cl_2N_2S_2$: C, 12.18; H, 5.07; Cl, 35.99; N, 14.21; S, 32.55. Found: C, 12.29; H, 5.30; Cl, 36.23; N, 14.11; S, 32.35.

Preparation of Bis(aminomethyl) Disulfide Dihydrochloride (2) by the Hydrazinolysis of Bis(phthalimidomethyl) Disulfide (7).—To about 250 ml of liquid ammonia, 5.51 g (0.01435 mol) of **7** and 1.0 ml of 97+% anhydrous hydrazine were added. The mixture was stirred at −36° for 25 hr. The ammonia was then allowed to evaporate under anhydrous conditions to give a yellow solid, which was dissolved in 50 ml of glacial acetic acid, followed by the addition of 10 ml of 36% hydrochloric acid during which H_2S gas was evolved and a white solid precipitated. The mixture was digested for 2 hr, heated to 50–60°, and then filtered to give 2.0 g (86%) of phthalhydrazide. The filtrate upon standing afforded a crystalline solid, 1.1 g, which was collected by filtration. This solid was then extracted with dimethylformamide to afford 0.7 g of white solid that was suspended in 17 ml of glacial acetic acid and 3 ml of concentrated hydrochloric acid, heated to 70°, and filtered hot; the residue was found to be ammonium chloride, mp 330° dec. The filtrate upon cooling in the ice box afforded a crystalline solid that was recrystallized from acetic acid–concentrated hydrochloric acid to give 0.2 g (7%) of pure **2**. The melting point, the infrared spectrum, and the chemical analyses were identical with those obtained for an authentic sample prepared by the two-step hydrolysis.

Hydrogenation of Bis(aminomethyl) Disulfide Dihydrochloride (2).—Hydrogen gas was bubbled for 5 hr at room temperature through a solution of 0.148 g (0.75 mmol) of **2** in 75 ml of glacial acetic acid–concentrated hydrochloric acid (2:1) to which had been added 0.452 g of purified palladium black (Fisher Scientific); the exiting gas had the odor of H_2S and when bubbled through a 10% lead acetate solution a black precipitate of lead sulfide was obtained. After the catalyst was removed by filtration, the filtrate was lyophilized to give a white solid, which was dissolved in about 20 ml of glacial acetic acid containing a few drops of concentrated hydrochloric acid by heating to 70–80°. The solution was cooled to 30°, then ethyl ether was added, and on further cooling to 5° crystallization occurred. Collection of the crystals by filtration afforded 0.105 g (85%) of analytically pure bis(aminomethyl) sulfide dihydrochloride (**3**): the melting point and mixture melting point were identical with the melting point of an authentic sample of **3**, prepared by an independent route (*vide infra*), and the infrared spectrum was identical with that of the authentic sample.

Anal. Calcd for $C_2H_{10}Cl_2N_2S$: C, 14.55; H, 6.10; Cl, 42.95; N, 16.97; S, 19.42. Found: C, 14.98; H, 6.14; Cl, 43.73; N, 16.58; S, 19.72.

Hydrogenation of Phthalimidomethyl Aminomethyl Disulfide Hydrochloride (4).—Hydrogen gas was bubbled for a period of 5 hr at room temperature through a solution of 0.1 g (0.346 mmol) of **4** in 50 ml of glacial acetic acid–concentrated hydrochloric acid (9:1), containing 0.3 g of purified palladium black; H_2S was detected in the exiting gases. After the catalyst was removed by filtration, the filtrate was lyophilized to a white solid which was extracted with ethyl acetate. The residue, 0.056 g (85%), was crystallized and the needle-shaped crystals obtained were found to be identical with an authentic sample of **3**. The ethyl acetate extract was concentrated to a white solid, which was crystallized from ethyl acetate–*n*-hexane to afford 0.06 g (90%) of *N*-(mercaptomethyl)phthalimide (**5**), mp 135–137°, identical with an authentic sample (*vide infra*) by melting point, mixture melting point, and comparison of infrared spectra.

***N*-(Mercaptomethyl)phthalimide (5) and Bis(phthalimidomethyl) Sulfide (10).**—To a cooled (0°) solution of 12 g (0.05 mol) of pure *N*-(bromomethyl)phthalimide (**6**) in 100 ml of reagent-grade tetrahydrofuran was added, over a period of 1–2 min with vigorous stirring and ice-bath cooling, a cooled (0°) solution of 2.8 g (0.05 mol) of NaSH[18] in 15 ml of water; the stirring was continued for an additional 5–10 min. The two liquid phases were separated and the organic layer was evaporated *in vacuo* to give an amorphous solid that was extracted with a 50-ml portion of refluxing ethyl acetate. Cooling the filtrate afforded crystalline mercaptan which on recrystallization gave 6.7 g (79%) of analytically pure **5**: mp 138–139°; ir 3.40, 3.95 (SH), 5.68 and 5.87 (C=O), 6.25, 6.89, 7.10, 7.30, 7.60, 7.74, 7.85, 8.45, 9.00, 9.40, 10.15, 10.38, 11.00, 11.45, 12.55, and 13.90 μ.

Anal. Calcd for $C_9H_7NO_2S$: C, 55.96; H, 3.65; N, 7.25; S, 16.60. Found: C, 55.98; H, 3.64; N, 7.45; S, 16.32.

The ethyl acetate insoluble solid was crystallized from 99% ethanol and gave 0.9 g (10%) of the sulfide **10**: mp 241–242°; the ir spectrum was very similar to that of the disulfide **7** except for the appearance of doublets at 9.08 and 9.32 and at 10.80 and 10.92 instead of singlets in **7** at 9.28 and 10.92 μ.

Anal. Calcd for $C_{18}H_{12}N_2O_4S$: C, 61.37; H, 3.43; N, 7.95; S, 9.08. Found: C, 61.24; H, 3.45; N, 8.10; S, 9.30.

Bis(*o*-carboxybenzoylaminomethyl) Sulfide (11).—To a stirred suspension of 14.08 g (0.04 mol) of **10** in 800 ml of 95% ethanol was added dropwise a solution of 3.3 g (0.08 mol) of 97% NaOH in 200 ml of water while heating at 65–70°. The resulting clear solution was stirred for an additional 1 hr at 65–70°. The solution was concentrated *in vacuo* to a volume of 150 ml and then 6.7 ml of 36% HCl in 50 ml of water was added with stirring; an oil began to separate halfway through the addition and again near the end of the addition, and enough dioxane was added in each case to restore homogeneity. Upon standing, solid began to precipitate from the clear solution and after storage at 5° overnight, 14 g of colorless solid was collected by filtration, mp 110° dec. Crystallization from methanol–water gave 10 g (63%) of the crystalline monohydrate of **11**: mp 116° dec; the ir spectrum showed absence of the phthalimido carbonyls and the appearance of new carbonyl bands at 1700 and 1640 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}N_2O_6S \cdot H_2O$: C, 53.21; H, 4.46; N, 6.89; S, 7.86. Found: C, 53.18; H, 4.28; N, 6.40; S, 7.98.

Bis(aminomethyl) Sulfide Dihydrochloride (3).—To a suspension of 2.1 g (5.2 mmol) o fthe hydrate of **11** in 50 ml of glacial acetic acid was added with stirring 2 ml of 36% HCl; the resulting clear solution was heated at 40° for 29 hr, during which time a precipitate formed. Lyophilization gave a solid which was extracted with a 50-ml portion of refluxing $CHCl_3$ and then washed with three 25-ml portions of hot $CHCl_3$. The residue was extracted in a Soxhlet apparatus with anhydrous ether for 12 hr. Concentration of the ether extract afforded 0.8 g (39%) of phthalic acid, mp 194–195°. The residue was digested with 25 ml of anhydrous benzyl alcohol–ether (4:1); a solid was collected by filtration and washed with 2 ml of benzyl alcohol and then with anhydrous ether. The dry solid was dissolved in acetic acid by adding a few drops of 36% HCl. After addition of ether and storage at 5°, 0.17 g (41%) of needles of pure **3** was obtained: slight yellowing at 175° and extensive decomposition at 225–230°; ir 3.33 (vs), 3.48 (vs), 3.88 (s), 6.23 (s), 6.32 (m), 6.70 (vs), 7.00 (m), 7.56 (s), 8.97 (m), 9.19 (m), 9.38 (m), 10.21 (s), 10.32 (s), 11.34 (s), 12.38 (m), 13.85 (w), and 14.85 μ (w).

Anal. Calcd for $C_2H_{10}Cl_2N_2S$: C, 14.55; H, 6.10; Cl, 42.95; N, 16.97. Found: C, 14.82; H, 6.23; Cl, 42.68; N, 17.26.

***S*-2-Aminoethanethiosulfuric Acid (13).**—To a solution of 2.26 g (0.02 mol) of dry β-mercaptoethylamine hydrochloride in 40 ml of anhydrous dimethylformamide in a nitrogen atmosphere was added with stirring 3.2 g (0.02 mol) of sulfur trioxide–pyridine,[19] and stirring was continued for 24 hr at room temperature. The dimethylformamide was removed *in vacuo* at room temperature and then a 50-ml portion of 95% EtOH was added and the mixture was stored at 5° overnight to afford 1.8 g (57%) of crystalline **13**: mp 185° dec (lit.[20] mp 183–185°); the mixture melting

(18) A. Rule, *J. Chem. Soc.*, **99**, 558 (1911).

(19) H. H. Sisler and L. F. Audrieth in "Inorganic Synthesis," Vol. II, W. C. Fernelius, Ed., McGraw-Hill, New York, N. Y., 1946, p 173.

(20) D. L. Klayman, W. F. Gilmore, and T. R. Sweeney, *Chem. Ind. (London)*, 1632 (1965).

point with an authentic sample was undepressed; the infrared spectrum was identical with that of an authentic sample. Conditions were not developed to obtain an optimum yield.

Registry No.—**1**, 16627-75-1; **2**, 37709-20-9; **3**, 37710-01-3; **4**, 37710-02-4; **5**, 32280-93-6; **6**, 5332-26-3; **7**, 37710-05-7; **8**, 37710-06-8; **8** disodium salt, 37710-07-9; **10**, 37710-08-0; **11**, 37710-09-1; **12**, 156-57-0; **13**, 2937-53-3; *N*-(hydroxymethyl)phthalimide, 118-29-6.

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Acid Decomposition of Tosylazocyclohex-1-ene and 3-Tosylazocholesta-3,5-diene

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The decomposition in acetic acid of tosylazocyclohex-1-ene and 3-tosylazocholesta-3,5-diene is described. The first furnishes a mixture of 1,2-cyclohexanediol diacetate (**3**), 1-tosylcyclohex-2-ene (**4**), *cis*-2-tosylbicyclo[3.1.0]hexane (**5**), *trans*-2-tosyl-1-acetoxycyclohexane (**6**), (*Z*)-2-tosylcyclohexan-1-one tosylhydrazone (**7**), and (*E*)-2-tosylcyclohexan-1-one tosylhydrazone (**8**); the second furnishes practically the sole 3-acetoxy-6β-tosylcholest-4-ene (**9**).

The chemical properties of azoalkenes have been of interest to us recently. Tosylazoalkenes in particular showed dual behaviour in their transformations; either they kept the original sequence of CNS bonds during a reaction, or exhibited extensive rearrangement with loss of nitrogen.[1]

Some new reactions of tosylazocyclohex-1-ene (**1**)[2] and 3-tosylazocholesta-3,5-diene (**2**)[3] are reported.

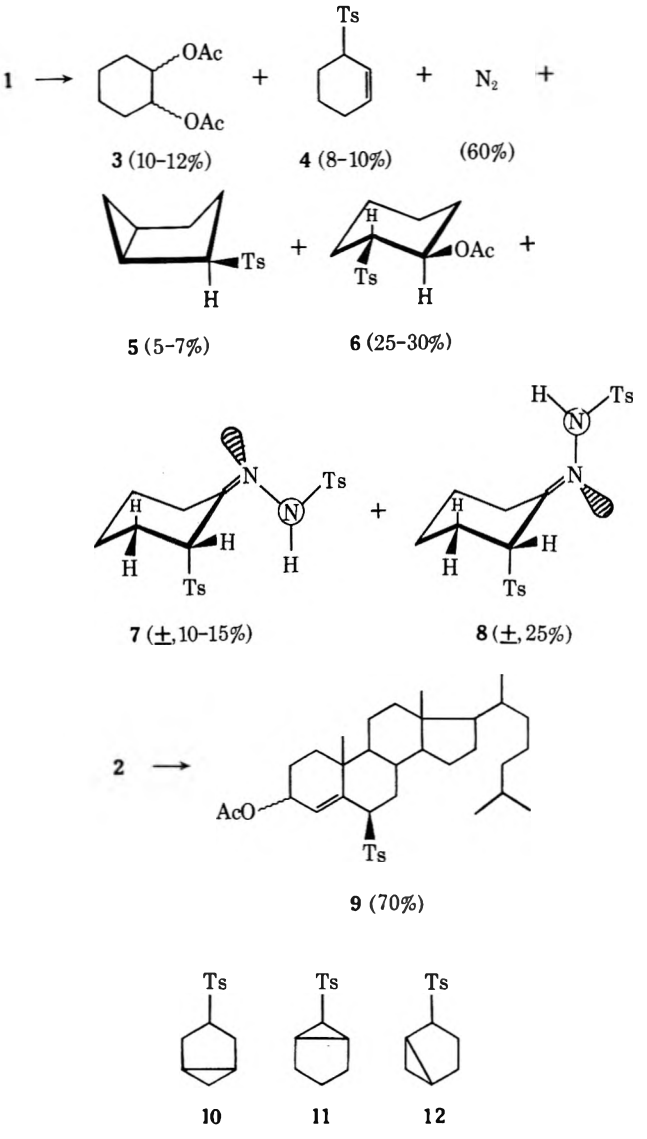
Results

Treatment of **1** and **2** with acetic acid in chloroform at room temperature resulted in the evolution of nitrogen accompanied by the disappearance of the yellow color of the solutions. By absorption chromatography, compounds **3**–**8** were isolated starting from **1** and compound **9** from **2**.

Structures **3** and **4** were determined by direct comparison with specimens prepared by independent routes (ir, pmr, mass spectra).[4] The ir spectrum of **5** revealed the presence of the sulfone function, para-substituted phenyl group, and aliphatic hydrogens. The analytical data indicated the molecular formula $C_{13}H_{16}SO_2$. Osmotic determination of the molecular weight (235.6) and the highest *m/e* peak in the mass spectrum (236) confirmed the monomeric nature of **5**.

The high-resolution pmr spectrum at 100 MHz of compound **5** is reported in Table I.

On the ground of the absence of vinyl hydrogens and as a tetrasubstituted ethane structure is impossible the bicyclic structures **10**, **11**, or **12** are proposed.



(1) L. Caglioti and G. Rosini, *Chem. Ind. (London)*, 1093 (1969).

(2) (a) L. Caglioti, P. Grasselli, F. Morlacchi, and G. Rosini, *ibid.*, 25 (1968); (b) A. Dondoni, G. Rosini, G. Mossa, and L. Caglioti, *J. Chem. Soc. B*, 1404 (1968).

(3) L. Caglioti, M. Poloni, and G. Rosini, *Chim. Ind. (Milan)*, 156 (1970).

(4) K. B. Wiberg and K. A. Saegebart, *J. Amer. Chem. Soc.*, **79**, 6256 (1957).

TABLE I

Compd	Solvent	δ	
	C_6D_6	H_A	0.20
		H_B	0.74
		$H_X + H_Y$	0.85–1.15
		$2CH_2$	1.15–1.70
		CH_3Ar	2.0
		H_M	3.31
		Aromatic (4 H, q, J = 8 Hz)	6.88–7.82
	$CDCl_3$	H_A	0.44
		H_B	0.69
		$H_X + H_Y$	1.25–1.45
		$2CH_2$	1.45–2.10
		CH_3Ar	2.4
		H_M	3.58
		Aromatic (4 H, q, J = 8 Hz)	7.3–7.8

Irradiation of H_X and H_Y caused H_A and H_B to give an AB system (J_{AB} = 5.5 Hz), while H_M is singly decoupled (J_{MX} = 4.0 Hz), giving rise to a pseudo-triplet. The value of the latter coupling constant is in agreement with a dihedral angle H_X–H_M of *ca.* 30°, and the absence of appreciable long-range couplings between the methylene of the cyclopropane ring and H_M infers a cis configuration for the tosyl group relative to the CH_2 bridge.[5]

The boat conformation of the cyclohexane ring would account for the relatively large separation (~8 Hz) of H_M caused by the C_3 hydrogens (no right angles).

On irradiation of H_M the signals of H_A and H_B become narrower, thus indicating some long-range coupling. This type of coupling was observed in an analogous system.[6] The other possible isomer (**10**) would give a J_{MX} value too large to be interpreted as a long-range coupling and has never been observed in similar structures; furthermore, it should exhibit a long-range coupling through four nonplanar bonds. Structure **11** must be ruled out, since it would not show the cyclopropane methylene at high field of the AB system. Structure **12** is therefore proved. Use of pmr was also useful in establishing the conformation of compound **6**; the signals at δ 5.05 and 3.3 with a half-width of 20 Hz suggest the structure of *trans*-2-tosyl-1-acetoxycyclohexane in a diequatorial configuration. It is known that the width of the resonance peak due to the ring protons is considerably larger in the conformer with the diequatorial conformation.[7]

Analytical and spectroscopic data suggest that **7** and **8** structures of which have been established from analytical and spectroscopic data reported in the Experimental Section, are geometric isomers. The broad signal centered at δ 4.75 for **7** and at 3.92 for **8** is assigned to CHTs; the low value of $W_{1/2}$ = 7.5 Hz for both compounds indicates that the protons are equatorial (axial tosyl group), and therefore **7** and **8** are syn and anti isomers.

On the basis of the work of Karabatsos and Taller[8] we have assigned the syn structure to isomer **7** with the α-methine proton resonating at lower magnetic fields and the anti structure **8** to the other.

When **2** was treated with acetic acid the main product was **9**, the structure of which was assigned on the grounds of the analytical and spectroscopic data reported in the Experimental Section. As for the configuration of the sulfonyl group at C_6, the pmr spectrum showed a double doublet centered at δ 3.5 (J_a^{app} = 1.5 and 7.0 Hz) assigned to C_6 H. These values agree with the data available in the case of bulky 6β substituents (Cl, Br, J_{AX}^{app} = 1.8 and J_{BX}^{app} = 3.6 Hz) but very different from the values reported for 6α substituents (J_{AX}^{app} = 12.5 and J_{BX}^{app} = 4.5 Hz). This suggest a 6β configuration for the tosyl group; the slight difference in J should be ascribed to distortion of ring B due to interaction between the 6β tosyl and the C-19 methyl group.[9,10] The pmr spectrum of **9** obtained by decomposition of **2** with CH_3COOD in chloroform showed signals at δ 5.3 (1 H, vinylic proton) and 3.5 (m, 1 H, CHTs), and the disappearance of the signals at 5.0 assigned to CHOAc; the other signals were identical with those of the spectrum of undeuterated **9** (see Experimental Section).

Moreover, if the C_6–H bond is not broken, no isotopic exchange is observed at this position. Therefore, according to the mechanism now proposed, the deuterium enters position 3. It can be deduced from the pmr results reported above that the –OAc group is also in position 3 and thus the tosyl is in position 6.

Discussion

The compounds isolated from the decomposition of **1** with acetic acid in chloroform and the relative yields suggest mechanism 1.

p-Toluenesulfinate anion and acetate anion may add to the β position of C to give the substituted diazoalkanes D and F, which then react with a proton to form the products **3** and **6**.

Alternatively, D and F may be formed by rearrangement of **1** *via* ion pairs A and B.

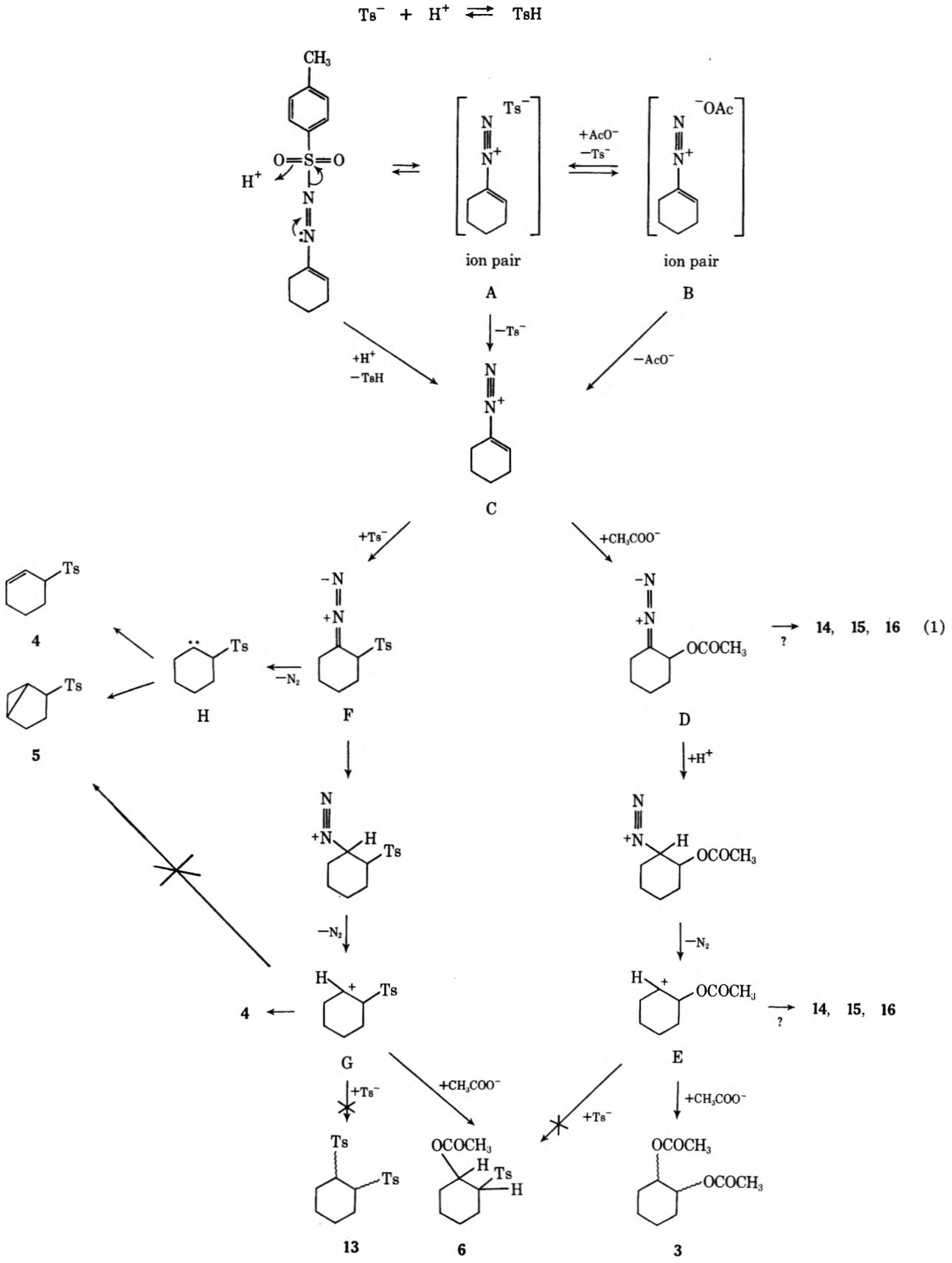
When the reaction was carried out in CH_3COOD, there was deuterium exchange in compound **6** in the position α to the acetoxy group, but none on the α carbon attached to the tosyl group. This indicates that the neutralization of the carbonium ion G with acetate anion in the scheme was the main route to **6**.

All efforts to isolate compound **13** were unsuccessful. The fact that the intermediate E was not converted into compound **6** and that compound **13** was not appreciably formed can be tentatively rationalized by assuming the high reactivity of intermediates E and G and the relatively high concentration of acetic acid in the mixture.

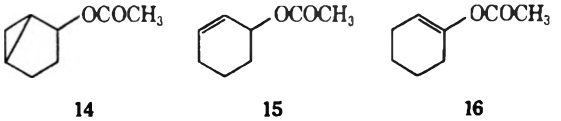
Alternatively, the α-tosyldiazocyclohexane F could undergo thermal decomposition to form *cis*-2-tosylbicyclo[3.1.0]hexane (**5**) and 1-tosylcyclohex-2-ene (**4**), possibly through the divalent carbon intermediate H.

Compound **5** could be formed by internal rearrangement of the carbonium ion G, but the total absence of deuterium in **5** when the decomposition of **1** is performed with CH_3COOD indicates that the carbene H is the true precursor of **5**.

(5) A. Dieffenbacher and W. von Philipsborn, *Helv. Chim. Acta*, **49**, 897 (1966).
(6) R. J. Abraham and G. Gatti, *Org. Magn. Res.*, **2**, 173 (1970).
(7) S. Browstein and R. Miller, *J. Org. Chem.*, **24**, 1866 (1959).
(8) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3923 (1968).
(9) M. S. Bhacca and D. M. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 108 and 148.
(10) K. Tori and K. Kuriyama, *Chem. Ind. (London)*, 1525 (1963).



The formation of compounds **7** and **8** can be explained as a 1,4 addition of *p*-toluenesulfinate anion or *p*-toluenesulfinic acid to the azoenic system of compound **1**. The addition of acetate anion or acetic acid would give the α-acetoxycyclohexanone tosylhydrazone, which undergoes a 1,4 elimination to form compound **1**. We have not been able to detect compounds **14**, **15**, or **16**, which could arise from D or E, but the possibility that such compounds are formed during the



reaction cannot be ruled out. The decomposition of tosylazocyclohex-1-ene in methanol[1,2a] and the thermal decomposition of tosylazostilbene[11] are explained in terms of the dissociation of S–N bonds as indicated in the scheme; the data now collected on the acidic decomposition of tosylazocyclohex-1-ene fit the general reactivity patterns of this system well.

Experimental Section

All melting points and boilings points are uncorrected. Spectra were recorded on Beckman IR-5A, Unicam SP 800, Jeol 60-HL, and Varian 100-XL spectrometers. Pmr spectra were recorded using TMS as internal standard. Molecular weights were determined with a Hewlett-Packard Macrolab vapor phase osmometer. Microanalyses were performed using a Hewlett-Packard C, H, N analyzer, Model 185. Gas chromatographic analyses were performed on a Varian Aerograph Model 1440 using SE-30 on Chromosorb W and FFAP (10%) with Chromosorb W columns (2 m).

Reagents.—All reagents were commercial materials. Analytical grade solvents were purified by standard methods.

Apparatus.—Nitrogen evolution was measured by attaching a series of burets through a Dry Ice trap to the outlet of the condenser.

Tosylazocyclohex-1-ene (1).—This was synthesized as previously described.[1,2b] Further purification was achieved by dissolving 1.0 g of 1 in ether (50 ml) and a few drops of benzene. The yellow solution was rapidly filtered and *n*-hexane was added to turbidity; then the solution was allowed to stand in an ice bath (5–10 min). Yellow crystals were collected and dried under reduced pressure, mp 59–61° dec.

Decomposition of Tosylazocyclohex-1-ene (1) **with Acetic Acid.**—1 (8.00 g, 3.00×10^{-2} mol) was added to a solution of 8.65 ml (0.152 mol) of acetic acid in 240 ml of chloroform under magnetic stirring at room temperature. The acidic decomposition of 1 resulted in the evolution of nitrogen and the disappearance of the yellow color of the solution.

The evolved nitrogen, collected and measured at STP, gave a 60% mol yield with respect to 1.

The colorless solution was allowed to stand for 10 hr, placed in a separating funnel and shaken with a saturated aqueous solution of Na_2CO_3, washed several times with water, dried (Na_2SO_4), and evaporated under reduced pressure.

The mixture obtained was dissolved in ethyl acetate (8 ml), and *n*-hexane (12 ml) was added; a white compound was collected and recrystallized. This compound was identified as (*E*)-2-tosylcyclohexanone tosylhydrazone (**8**).

The filtrate was evaporated under reduced pressure and then a chromatographic separation was performed on a silica gel column using *n*-hexane–ethyl acetate (75:25) as eluent. The first fraction consisted of a mixture of 1,2-cyclohexanediol diacetate (**3**) and 1-tosylcyclohex-2-ene (**4**), successively separated by distillation under vacuum; the other fraction consisted of *cis*-2-tosylbicyclo[3.1.0]hexane (**5**), *trans*-2-tosyl-1-acetoxycyclohexane (**6**), and (*Z*)-2-tosylcyclohexanone tosylhydrazone (**7**).

1,2-Cyclohexanediol diacetate (**3**) was a colorless oil, yield 10–12%; ir and mass spectra are in good agreement with the data reported in the literature[4] for a mixture of *cis*- and *trans*-1,2-cyclohexanediol diacetate.

1-Tosylcyclohex-2-ene (**4**) was white crystals, mp 59°, yield 8–10%. Ir (KBr) shows peaks at 1280–1140 (SO_2), 725–705 (cis CH=CH–), and 812 cm^{-1} (para-substituted phenyl). Pmr (DMSO-d_6) signals are at δ 7.75 and 7.45 (AA'BB' pattern, 4 H, J = 8.5 Hz, *p*-C_6H_4), 6.08 and 5.6 (AB pattern, J_{AB} = 10.5 Hz, cis vinylic protons), 3.96 (m, 1 H, C**H**Ts), 2.4 (s, 3 H, *p*-CH_3-C_6H_4), 1.5–2.0 (m, 6 H, other aliphatic protons).

Anal. Calcd for $C_{13}H_{18}SO_2$: C, 66.08; H, 6.82. Found: C, 66.21; H, 6.68.

***cis*-2-Tosylbicyclo[3.1.0]hexane** (**5**) was white crystals, mp 69–70° (AcOEt–*n*-hexane), yield 5–7%. Ir (KBr) shows peaks at 1280–1140 (SO_2), 812 cm^{-1} (para-substituted phenyl). Pmr ($CDCl_3$) signals are reported in the Discussion. The molecular weight (vapor pressure osmometer, $C_2H_4Cl_2$) was 235.6; mol wt (mass spectrum, 80 eV) 236 m/e (molecular ion).

Anal. Calcd. for $C_{13}H_{16}SO_2$: C, 66.08; H, 6.83. Found: C, 65.85; H, 6.79.

***trans*-2-Tosyl-1-acetoxycyclohexane** (**6**) was white crystals, mp 105–106° (AcOEt–*n*-hexane), yield 25–30%. Ir (KBr) shows peaks at 1740 (–C=O) 1280–1140 (SO_2), 812 cm^{-1} (para-substituted phenyl). Pmr ($CDCl_3$) signals are at δ 7.78 and 7.35 (AA'BB' pattern, 4 H, J = 8 Hz, *p*-C_6H_4), 5.05 (m, $W_{1/2}$ 2.0 Hz, 1 H, C**H**OCOCH$_3$), 3.3 (m, $W_{1/2}$ 2.0 Hz, 1 H, C**H**Ts), 2.45 (s, 3 H, C**H**$_3$C$_6$H$_4$), 1.68 (s, 3 H, –OCOC**H**$_3$), 1.0–2.2 (m, 8 H, other aliphatic protons).

Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.80; H, 6.80. Found: C, 60.72; H, 6.70.

(*Z*)-2-Tosylcyclohexan-1-one tosylhydrazone (**7**) was white crystals, mp 146–147° (AcOEt–*n*-hexane), yield 10–15%. Ir (KBr) shows peaks at 3150 (–NH), 1280–1140 (SO_2), 812 cm^{-1} (para-substituted phenyl); pmr (DMSO-d_6) δ 10.4 (s, 1 H, –SO_2NH–), 7.2–7.8 (m, 8 H, two para-substituted phenyls), 4.75 (m, $W_{1/2}$ = 7.5 Hz, 1 H, C**H**Ts), 2.4 (s, 3 H, C**H**$_3$C$_6$H$_4$–), 2.35 (s, 3 H, C**H**$_3$C$_6$H$_4$–), 1.3–2.2 (m, 8 H, other aliphatic protons).

Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.34; H, 5.94; N, 6.59.

(*E*)-2-Tosylcyclohexane-1-one tosylhydrazone (**8**) was white crystals, mp 160–162° (AcOEt–*n*-hexane), yield 25%. Ir (KBr) shows peaks at 3230 (–NH), 1280 and 1140 (–SO_2), 812 cm^{-1} (para-substituted phenyl); pmr (DMSO-d_6) δ 1.05 (s, 1 H, –SO_2NH–), 7.7-7.0 (m, 8 H, two para-substituted phenyls), 3.92 ($W_{1/2}$ = 7.5 Hz, C**H**Ts), 2.4 (s, 3 H, C**H**$_3$C$_6$H$_4$–), 2.35 (s, 3 H, C**H**$_3$C$_6$H$_4$–), 1.4–2.7 (m, 8 H, other aliphatic protons).

Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 57.13; H, 5.75; N, 6.66. Found: C. 57.11; H, 5.58; N, 6.87.

Decomposition of 3-Tosylazocholesta-3,5-diene (**2**).—2[3] (4.24 g, 7.7×10^{-1} mol) was added to a solution of 8.0 ml (0.140 mol) of acetic acid in 130 ml of chloroform under magnetic stirring at room temperature. The evolved nitrogen, collected and measured at STP, gave 85% yield with respect to 2.

The pale yellow colored solution was treated as given for the decomposition of 1. Chromatographic separation on a silica gel column (0.05–0.20) using a mixture of cyclohexane–AcOEt (80:20) as eluent gave 3-acetoxy-6-β-tosylcholest-4-ene (**9**) as the main product (yield 70%).

3-Acetoxy-6β-tosylcholest-4-ene (**9**) was white crystals, mp 147–148°. Ir (KBr) shows peaks at 1748 (ether C=O), 1600 (phenyl), 1280–1140 (SO_2), 820 cm^{-1} (para-substituted phenyl). Pmr (CCl_4) showed signals at δ 7.68 and 7.29 (AA'BB' pattern, 4 H, J = 8 Hz; aromatic protons), 5.3 (d, 1 H, J = 5 Hz, vinylic proton), 5.0 (m, 1 H, –C**H**OAc), 3.5 (m, 1 H, –C**H**Ts), 2.43 (s, 3 H, C**H**$_3$C$_6$H$_4$–), 0.8–2.2 (other aliphatic protons).

Anal. Calcd for $C_{36}H_{54}SO_4$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.20.

Registry No.—**1**, 17344-06-8; **2**, 26152-91-0; **4**, 37488-68-9; **5**, 37500-26-8; **6**, 37500-27-9; **7**, 37500-28-0; **8**, 37500-29-1; **9**, 37500-30-4.

Acknowledgment.—We wish to thank Miss Bruna Bonfiglioli and R. Di Marino for their collaboration to this work. This work was done with financial support from the Italian National Research Council (C. N. R.).

(11) G. Rosini and R. Ranza, *J. Org. Chem.*, **36**, 1915 (1971); G. Rosini and S. Cacchi, *ibid.*, **37**, 1865 (1972).

Photocyclizations. III. Synthesis of 3,6-Dimethyl-8-hydroxy-3,4,5,6-tetrahydro-3-benzazocin-2(1*H*)-one

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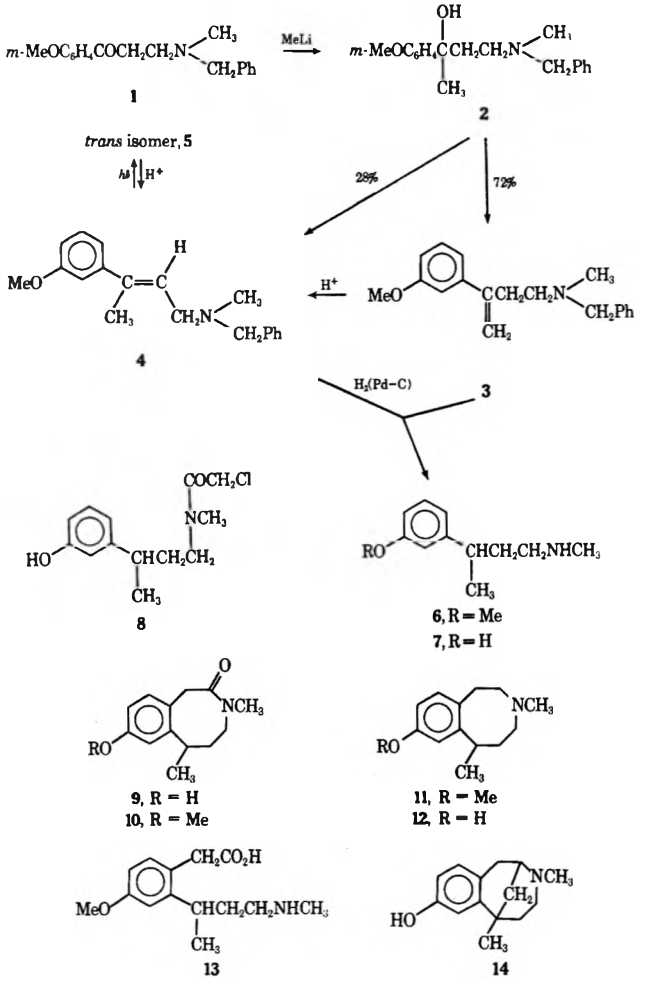
Photolysis of *N*-chloroacetyl-3-*m*-hydroxyphenyl-*N*-methylbutylamine (**8**) has given a 30% yield of benzazocinone **9**, convertible to benzazocine **12**, a demethano analog of benzomorphan **14**. The structure **9** was confirmed by conversion to amino acid **13** and by spectral data. Compound **6** was prepared from "Mannich" ketone **1** *via* carbinol **2**, dehydration of which gave vinylic compounds **3** and **4** in a ratio of 2.5:1. Irradiation of **4** produced stereoisomer **5**, which, like **3**, was isomerized to **4** by H^+. Nmr measurements served to distinguish **3**, **4**, and **5**.

(−)-2,5-Dimethyl-2′-hydroxy-6,7-benzomorphan (3,6-dimethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3-benzazocine, **14**) is a strong analgesic agent displaying other interesting pharmacological properties.[1] Compound **12**, 3,6-dimethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-3-benzazocine, lacking the methano bridge of **14**, was desired for comparison. Recently,[2] photolytic ring closure of appropriate *N*-chloroacetyl compounds has given seven- and eight-membered nitrogen heterocycles. We now wish to report a similar success in the synthesis of benzazocinone **9**, and ultimately **12**.



Photolysis of *N*-chloroacetyl derivative **8** in aqueous methanol[3] produced major product **9** (30% yield), assigned the formula $C_{13}H_{17}NO_2$ from its mass spectrum and elemental analysis. A broad, relatively low-frequency (1615 cm^{-1}) amide I band suggested hydrogen bonding with the phenolic proton. The cite of cyclization was established as para to the phenolic hydroxyl by a 100-MHz nmr spectrum of **9** showing clearly three remaining 1,2,4-distributed aromatic protons. Two of these, H_a at δ 6.55 and H_b at 7.04, were ortho coupled to each other (J_{ab} = 8.0 Hz). H_b was further split into a quartet by the third proton, H_c (J_{bc} = 2.2 Hz), located meta to H_b; H_c appeared as a doublet at δ 6.64. Signals for the alicyclic protons were not well resolved, probably a reflection of an incomplete averaging process in the (large) benzazocine system (slow rate of inversion).[4] Further proof of the structure of **9** was provided by acid hydrolysis of the methyl derivative **10**[5] to a crystalline amino acid hydrochloride whose ir and nmr spectra were consistent with **13**. Reduction ($LiAlH_4$) of the acetate of **9** gave **12**. Diborane reduction of **10** followed by *O*-demethylation with pyridine hydrochloride also afforded **12**.[6]

Amide **8** was synthesized from Mannich ketone **1** (obtained in 75% yield)[7] *via* carbinol **2** (dehydration of which with methanesulfonyl chloride[8] gave olefins **3** and **4**), debenzylated amine **6** (by Pd/C reduction of the **3**–**4** mixture), and phenol **7**, obtained by HI hydrolysis of **6**. Preparation of **8** was best achieved by O,N-bischloroacetylation of **7** followed by partial hydrolysis as described previously.[2]

The nmr spectrum of **8** (at 25°) was complex; two sets of signals were seen, corresponding to the two conformers **8a** and **8b**, interchanging slowly owing to the partial bond character of the C–N linkage.[9,10]

(1) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969).

(2) H. H. Ong and E. L. May, *J. Org. Chem.*, **37**, 712 (1972); **35**, 2544 (1970).

(3) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Amer. Chem. Soc.*, **88**, 3941 (1966).

(4) F. A. L. Anet and M. A. Brown, *Tetrahedron Lett.*, 4881 (1967).

(5) Acid hydrolysis of **9** gave an unstable, hygroscopic compound, difficult to purify.

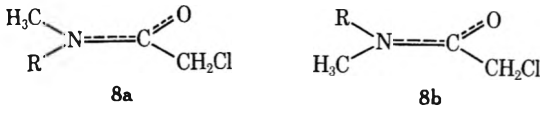
(6) Y. Sawa, T. Kato, and T. Masuda (Third International Congress of Heterocyclic Chemistry, Sendai, Japan, August 23–27, 1971) photocyclized *m*-$MeOC_6H_4C(Me)_2CH_2CH_2NHCOCH_2Cl$ to the 6,8-dimethyl homolog of **9**; B. Pecherer, F. Humiec and A. Brossi, *Helv. Chim. Acta*, **54**, 743 (1971), prepared the 6-demethyl analog of **12** by a nonphotolytic sequence. While this manuscript was in preparation, Dr. A. Brossi informed us that **12** has been prepared in the laboratories of Hoffmann-La Roche, Inc., Nutley, N. J., in continuation of their benzazocine program.

(7) Our original plan was to use *N*-chloroacetyl-3-*m*-methoxyphenylbutylamine for the photocyclization reaction, but dibenzylamine was totally inert in the Mannich reaction.

(8) A modification of the procedure of G. G. Hazen and D. W. Rosenburg, *J. Org. Chem.*, **29**, 1930 (1964), was used after numerous trials with other reagents.

(9) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955).

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 361.



8a 8b

R = *m*-$HOC_6H_4CHMeCH_2CH_2$

Coalescence of the signals was observed at 80°.[11] The averaged chemical shifts for the two singlets due to chloromethyl and *N*-methyl protons were δ 4.08 and 2.80, respectively.[11]

The crude product obtained in the dehydration of **2** was shown by vpc (before acid treatment) to be a 2.5:1 mixture of olefins corresponding to the formula $C_{19}H_{23}NO$ (mass spectrum, elemental analyses). Both compounds gave *m/e* 281 (M^+) with different fragmentation patterns by combined vpc–mass spectrometry (LKB 9000). Conventional efforts to separate the two olefins were unsuccessful, and, in an attempt to prepare hydrobromide salts, the predominant olefin was isomerized quantitatively to the lesser one, unambiguously assigned structure **4** from nmr data (Figure 1b).

Thus at 100 MHz in $CDCl_3$, the allylic methyl protons of **4** appeared as double triplets[12] centered at δ 2.03 ($^4J_{allylic}$ = 1.3 and $^5J_{homoallylic}$ = 0.8 Hz) due to long-range coupling with the vinylic and allylic methylene protons. The three singlets at δ 2.24, 3.54, and 3.77 can be assigned to NCH_3, benzylic methylene, and OCH_3, respectively. The doublet at 3.18 (J = 6.8 Hz) is due to the allylic methylene protons,[13] and the lone vinyl proton, as expected, gave rise to a triplet of quartets (centered at δ 5.96) indicative of vicinal and long-range (allylic) coupling.

On brief irradiation (>280 mμ) of **4** in a nonpolar solvent with the aid of a photosensitizer (PhCOPh), a new isomer, **5** (readily HCl-catalyzed to **4**), was detected; vpc analysis showed a 9:1 ratio of **5** to **4** which equilibrated to 2:1 after 2 days at 0°.[14] The mass spectrum of **5** (mol wt 281) and its nmr spectrum (deduced by subtracting signals assigned to **4** from a spectrum taken on the photoisomerization mixture, Figure 1c) were consistent with structure **5**.[15,16] These assignments would suggest that **4**, with its bulkiest substituents trans to each other, should be the thermodynamically favored configuration; indeed, this is verified by experimental observation.

The structure of **3** is also based on nmr data ($CDCl_3$, 100 Mz), deduced by subtracting those signals assigned to **4** from a spectrum taken on a 2.5:1 mixture of **3** and **4** (Figure 1a). The three singlets due to NCH_3, NCH_2, and OCH_3 are similar to those of **4**; protons

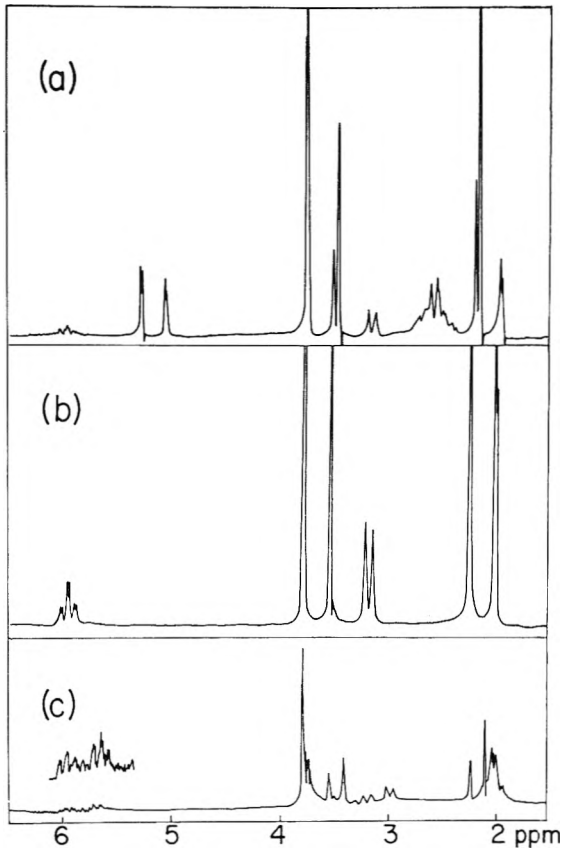


Figure 1.—Nmr spectra measured in $CDCl_3$ at 100 MHz: (a) a 2.5:1 mixture of **3** and **4**; (b) pure **4**; (c) a 1:2 mixture of **4** and **5**.

from the adjacent methylene groups gave an AA'BB' multiplet centered at δ 2.61 and the two geminal vinyl protons appeared as a double doublet[17] at 5.07 and 5.29 (J_{gem} = 1.8 Hz). The signal at lower field is assigned to the proton cis to the *m*-methoxyphenyl radical.[15,16]

Experimental Section

General Comments.—Melting points, determined on a Kofler hot stage, are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 257 unless otherwise stated. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E double-focusing spectrometer at 70 eV. Nmr spectra were obtained either with a Varian HA-100 or an A-60 instrument (TMS, δ 0). Vpc analyses were made isothermally using an F & M instrument (Model 1609, flame-ionization detector).

γ-(*N*-Benzyl-*N*-methyl)amino-*m*-methoxypropiophenone (1) Hydrochloride.—*m*-Methoxyacetophenone (3.0 g, 20 mmol), 1.2 g (10 mmol) of $C_6H_5CH_2NHCH_3$, 1 ml of 12 *M* HCl, 1.7 ml of formalin, and 50 ml of EtOH were refluxed for 48 hr and evaporated *in vacuo*, leaving a residue which, upon trituration in Me_2CO, gave 2.4 g of hydrochloride: mp 135–138°; irregular plates from Me_2CO–EtOAc, mp 142–145°; *m/e* 283 (M^+), 268, 192 (base); ir (Nujol) 1685 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}ClNO_2$: C, 67.6; H, 6.9; N, 4.4. Found: C, 67.4; H, 7.2; N, 4.4.

Attempts to distil the free base at 0.05 mm resulted in complete polymerization above 120° (bath temperature).

4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-2-butanol (2).—To freshly prepared MeLi (1.4 g of Li wire, 15 g of MeI, and 100 ml of Et_2O) was added dropwise 28.3 g (0.1 mol) of **1** in 100 ml of dry C_6H_6. After 24 hr of reflux (stirring), the mixture was poured into 200 g of ice. The organic layer was dried ($MgSO_4$) and fractionated to give 22 g (73%) of viscous oil, bp

(11) At room temperature using DMSO-d_6 the chloromethyl protons appeared as an uneven doublet at δ 4.20 and 4.04 (relative population 2:1 in favor of the conformer resonating at lower field); the NCH_3 protons were similarly split into a 2:1 doublet at δ 2.85 and 2.71. In $CDCl_3$ the two conformers were about equal in population.

(12) The double triplets were evident only when the spectrum was expanded 20-fold (sweep width 50 Hz); otherwise, a doublet was observed.

(13) Long-range coupling was not seen, however, because of a slight broadening of lines caused by electric quadrupole relaxation of the adiacent ^{14}N: F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 21.

(14) Similar, photoinduced cis–trans isomerization has been observed for stilbene as well as for a large number of other olefins: D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold, New York, N. Y., 1967, p 198.

(15) The difference in chemical shifts observed for the two β-vinyl protons in α-methylstyrene was 0.31 ppm. The downfield signal was assigned to the proton cis to the phenyl group. See ref 10, p 224.

(16) S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

(17) Long-range coupling between the two vinyl and the allylic methylene protons was not closely examined.

165–168° (0.05 mm). Ir and nmr data are consistent with structure **2**.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.2; H, 8.4; N, 4.7. Found: C, 76.5; H, 8.5; N, 4.6.

Dehydration of 2. 4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-1-butene (3) and 4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-*cis*-2-butene (4).—Pyridine (50 ml), 20 ml of DMF, and 6.4 g (21.4 mmol) of **2** were cooled to 0° and treated dropwise with 2.4 ml of $MeSO_2Cl$ during 30 min. The mixture was left at room temperature overnight, heated (under N_2) on a steam bath for 2 hr, poured into 200 g of ice, and made basic with 40% NaOH. The slowly liberated amine was extracted exhaustively with Et_2O. The extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue gave 3.1 g (51%) of oil, bp 146–148° (0.05 mm), *m/e* 281 (M^+), 266.

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.1; H, 8.3; N, 5.0. Found: C, 80.7; H, 8.0; N, 4.9.

Although tlc of the distilled oil showed only one spot,[18] vpc analysis[19] revealed two components, **3** and **4** (2.5:1 ratio, retention times 5.5 and 7.8 min, respectively). Individual mass spectra of **3** and **4** were obtained with an LKB 9000 spectrometer[20] fitted with a vpc column.[19] Major peaks for **3** were at 281 (M^+), 266, and 136 (base) and for **4**, 281 (M^+), 266 (base), 190, 161, 160, and 146. The nmr spectrum of the distillate also indicated approximately a 7:3 mixture of **3** to **4**.

Isomerization of 3 to 4.—Ether (50 ml) and 200 mg of the distillate above (2.5:1 mixture of **3** and **4**) were treated with ethereal HBr to strong congo red acidity. The precipitate was separated by decantation and warmed (steam bath) with 10 ml of EtOAc for 30 min to give 178 mg of crystals: mp 146–148° (from Me_2CO–Et_2O); mass spectrum *m/e* 281 (M^+), 266, 190, 161, 160, 146; nmr (DMSO-d_6, 100 MHz) δ 2.08 (s, 3, $CH_3C{=}C$),[21] 2.71 (s, 3, $-NCH_3^+$), 3.80 (s, 3, OCH_3), 4.00 (d, $C{=}CHCH_2-$, J = 7.8 Hz), 4.45 (broad s, 2, $ArCH_2N-^+$), 6.04 (t, 1, $-C{=}CH-$, J = 7.8 Hz), 6.85–7.80 (m, 9, aromatic H).

Anal. Calcd for $C_{19}H_{23}NO \cdot HBr$: C, 63.0; H, 6.7; N, 3.9. Found: C, 62.9; H, 6.7; N, 3.6.

Treatment of this hydrobromide with 1 *N* NaOH and ether gave, after distillation at 10^{-3} mm, 110 mg of oil which proved (vpc analysis) to be pure **4**. The combined filtrates above gave an additional 45 mg of pure **4** base.

Photoisomerization of 4 to 4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-*trans*-2-butene (5).—EtOAc (100 ml), 50 mg of **4**, and 10 mg of PhCOPh were irradiated under N_2 for 1 hr with a 200-W, high-pressure Hg lamp and a Pyrex filter. Immediate vpc analysis[19] of the solution revealed a new compound, **5**, retention time 3.6 min, and a 9:1 ratio of **5** to **4**; at 0° and 48 hr later, this ratio was 2:1. The mass spectrum of **5** (LKB 9000 combined with gas chromatography as described before)[19,20] gave *m/e* 281 (M^+), 280, 266, 161, 146; the nmr spectrum of **5** was determined from the 2:1 photoisomerization solution of **5** and **4** (*cf.* Figure 1c). Assignments were consistent with structure **5**, especially that for the vinyl proton as stated before. Conversion of **5** to **4** was easily effected with HCl.

3-*m*-Methoxy-*N*-methylbutylamine (6).—The 2.5:1 mixture of **3** and **4** (9 g, 32 mmol), 100 ml of glacial HOAc, 3 ml of 12 *N* HCl, and 3 g of 10% Pd/C were hydrogenated at room temperature and pressure to absorption of *ca.* 0.1 mol of H_2 to give, after the usual work-up, 6.2 g (82%) of chromatographically pure **6**, *m/e* 193 (M^+), 163 (base).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.5; H, 9.9; N, 7.2. Found: C, 74.4; H, 9.9; N, 7.4.

3-*m*-Hydroxyphenyl-*N*-methylbutylamine (7).—Compound **6** (6.2 g, 32 mmol) and 5 ml of 47–50% HI were refluxed together for 2 hr and evaporated to dryness *in vacuo*, and the residue was made basic with dilute NH_4OH. The liberated base was dried in CH_2Cl_2, evaporation of which left 4.5 g (79%) of an oil which solidified on cooling. Recrystallization from ether–ligroin (bp 30–60°) gave prisms, mp 103–104°, *m/e* 179 (M^+). Nmr data ($CDCl_3$–D_2O, 100 MHz) were consistent with structure **7**.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.6; N, 7.8. Found: C, 73.8; H, 9.3; N, 7.7.

***N*-Chloroacetyl Derivative (8) of 7.**—To a mixture of 0.6 g (3.3 mmol) of **7**, 100 ml of CH_2Cl_2, and 0.25 g of $NaHCO_3$ was added dropwise during 30 min (stirring) (1.1 g (10 mmol) of $ClCH_2COCl$. After 2 hr the mixture was poured into 100 g of ice water; the organic layer was separated and evaporated to dryness *in vacuo*. After addition of 20 ml of 1 *N* NaOH to the residue, a clear solution was gradually obtained. Acidification with 12 *M* HCl and extraction with CH_2Cl_2 afforded, after drying and evaporation of solvent, 0.69 g (82%) of oily **8** as prisms from ether–ligroin, mp 77–79°, *m/e* 255 (M^+), 220, 206. Nmr and ir spectral data were consistent with structure **8**.

Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.0; H, 7.1; 5.5. Found: C, 60.8; H, 7.4; N, 5.3.

3,6-Dimethyl-8-hydroxy-3,4,5,6-tetrahydro-3-benzazocin-2-(1*H*)-one (9).—Nitrogen was "bubbled" through a solution of 1.0 g (4 mmol) of **8** in 600 ml of 50% MeOH while the solution was irradiated[3] with a 200-W, high pressure, Hg-immersion lamp equipped with a Vycor[22] filter (water cooling of the quartz well). After 6 hr,[23] the solution was lyophilized or evaporated to dryness at 35°. Trituration of the residue in 2 ml of Me_2CO, then cooling overnight at 0° gave 192 mg of **9**, mp 223–225°. Thick layer chromatography of the filtrate (2-mm Brinkman plates, 95:5 $CHCl_3$–MeOH) gave an additional 67 mg (total yield 30%) of **9**: R_f 0.43; ir (KBr) 3250, 1615 cm^{-1} (broad);[24] *m/e* 219 (M^+), 204 (base); nmr (DMSO-d_6–D_2O, 100 MHz) δ 1.29 (d, 3, CH_3CH-, J = 7.0 Hz), 2.70 (broad s, 3, NCH_3) (*cf.* text for aromatic proton signals).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.1; H, 7.8; N, 6.4. Found: C, 71.2; H, 7.5; N, 6.5.

Methyl Ether 10 of 9.—Methanol (20 ml), **9** (910 mg, 4.1 mmol), and excess ethereal diazomethane (from 10 g of *N*-methyl-*N'*-nitrosoguanidine) were left overnight. Molecular distillation (10^{-4} mm, 150°) of the product gave 920 mg (95%) of a viscous, chromatographically pure oil,[24] *m/e* 233 (M^+), 218, 190, 176, 175.

Anal. Calcd for $C_{14}H_{19}NO_2$: N, 6.1. Found: N, 5.7.

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-8-methoxy-3-benzazocine (11) Hydrobromide.—Borane (25 ml of 1 *M*, THF) was added to 920 mg (3.8 mmol) of **10** in 50 ml of THF. The solution was refluxed overnight, cooled slightly, and refluxed with 50 ml of 6 *N* HCl for 2 hr. Evaporation *in vacuo* left a semisolid which was made basic with 1 *N* NaOH. The liberated base was dried (K_2CO_3) in Et_2O and converted to 1.0 g (90%) of **11** HBr (ethereal HBr) as irregular prisms from Me_2CO–Et_2O, mp 169–170°, *m/e* 219 (M^+), 204, 176, 162.

Anal. Calcd for $C_{14}H_{22}BrNO$: C, 56.0; H, 7.4; N, 4.7. Found: C, 56.0; H, 7.7; N, 4.5.

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-3-benzazocine (12). A. From 9.—Ac_2O (2 ml) and 500 mg (2.3 mmol) of **9** were warmed to homogeneity (2 hr) on the steam bath, and reagent was evaporated *in vacuo*. The residue was dissolved in ether, washed with dilute $NaHCO_3$, dried ($MgSO_4$), and reduced with 1.0 g of $LiAlH_4$ in 50 ml of THF (4-hr reflux). After the usual work-up, 390 mg (83%) of **12** crystallized from Me_2CO in needles, mp 206–207.5°, *m/e* 205 (M^+), 190, 162.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.0; H, 9.3; N, 6.8. Found: C, 75.8; H, 9.4; N, 6.7.

The hydrobromide crystallized from EtOH–Et_2O as prisms, mp 205° dec.

Anal. Calcd for $C_{13}H_{20}BrNO$: C, 54.6; H, 7.0; N, 4.9. Found: C, 54.5; H, 7.3; N, 4.8.

B. From 11.—Pyridine HCl[25] (1.5 g) and 150 mg (0.7 mmol) of **11** were fused at 200–210° under N_2 for 30 min and treated with 20 ml of H_2O. Basification (aqueous K_2CO_3), extraction with CH_2Cl_2, and evaporation of the extract *in vacuo* gave a brown oil which was molecularly distilled (10^{-4} mm, bath temperature 150°). Trituration of the distillate in cold Et_2O gave 82 mg (57%) of **12**, mp 205–207°, identical with that obtained by procedure A.

3-(2-Carboxymethyl-5-methoxyphenyl)-*N*-methylbutylamine (13) Hydrochloride.—Refluxing **10** (100 mg) and 10 ml of 4 *N* HCl for 3 hr, vacuum distillation to dryness, and trituration of the residue in 1 ml of EtOAc afforded 92 mg (72%), of prisms: mp 157–159° (from EtOH–Et_2O); ir (Nujol) 1715 cm^-; nmr

(18) Silica gel plates: system I, BuOH–HOAc–H_2O (4:1:1), R_f 0.72; system II, $CHCl_3$–MeOH (40:1), R_f 0.51.

(19) On a 6-ft, 1% ECNSS-S (on Gas-Chrom Q) column, 160°.

(20) Electron energy 70 eV, separation temperature 285°, ion source 295°.

(21) Long-range couplings were too small to be measured.

(22) When a Corex filter was used, no **9** was formed.

(23) Optimal time because of competitive cleavage and/or polymerization of **9**.

(24) Perkin-Elmer 421. This amide I band was shifted to 1650 cm^{-1} (Nujol) and sharpened in the methyl ether **10**.

(25) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).

(D_2O, 60 MHz)[26] δ 1.26 (d, 3, CH_3CH, J = 7.0 Hz), 1.84–2.48 (m, 2, $ArCHCH_2$), 2.70 (s, 3, NCH_3), 2.77–3.22 (m, 3, ArCH and CH_2N), 3.74 (s, 2, CH_2CO_2H), 3.88 (s, 3, OCH_3), 6.89 (1, 1, aromatic H, J_{ortho} = 8.5 and J_{meta} = 2.5 Hz), 7.01 (d, 1, aromatic H, J_{meta} = 2.5 Hz), 7.26 (d, 1, aromatic H, J_{ortho} = 8.5 Hz).

Anal. Calcd for $C_{14}H_{22}ClNO_3$: C, 58.4; H, 7.7; N, 4.9. Found: C, 58.6; H, 7.7; N, 4.6.

Registry No.—**1**, 37436-85-4; **1** HCl, 37436-86-5; **2**, 37436-87-6; **3**, 37436-88-7; **4**, 37440-18-9; **4** HBr, 37440-19-0; **5**, 37440-20-3; **6**, 37436-89-8; **7**, 37436-90-1; **8**, 37436-91-2; **9**, 37436-79-6; **10**, 37436-80-9; **11**, 37436-81-0; **11** HBr, 37436-82-1; **12**, 37436-83-2; **12** HBr, 37567-13-8; **13** HCl, 37436-84-3; *m*-methoxyacetophenone, 586-37-8; *N*-methylbenzylamine, 103-67-3.

(26) 3-(Trimethylsilyl)propanesulfonic acid sodium salt was the internal standard.

Acknowledgments.—The nmr measurements and some interpretations are due to Dr. Herman Yeh and most of the mass spectra were performed by Mr. William Landis, both of this laboratory. Dr. H. M. Fales of the National Heart and Lung Institute, NIH, made available the LKB-9000 instrument for combined gas chromatography–mass fragmentography.

Reaction of Aromatic Amine Oxides with Acid Halides, Sulfonyl Halides, and Phosphorus Oxychloride. Stereochemical Configuration of Substituents in the 1 Position of 12,13-Benzo-16-chloro[10](2,4)pyridinophanes[1]

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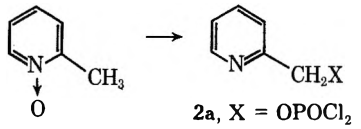
The reaction of 12,13-benzo-16-chloro[10](2,4)pyridinophane *N*-oxide (**3**) with benzoyl chloride, *p*-toluenesulfonyl chloride, phosphorus oxychloride, phosphorus thiotrichloride, and one hydrazidic bromide are described. Reactions of **3** with organic anhydrides or acid chlorides give mixtures of syn and anti esters; reaction with *p*-toluenesulfonyl chloride gives exclusively the syn tosylate **4d**. Reaction of **3** with phosphorus oxychloride is the first example in which a stable phosphate ester is formed; evidence is presented that alkyl chlorides, usually formed when alkylpyridine *N*-oxides react with *p*-toluenesulfonyl chloride or phosphorus oxychloride, are secondary products derived from intermediate esters. A new procedure has been developed to determine whether derivatives of type **4** or **5** have the syn or anti configuration at C-1 which is based on the chemical shifts observed for the methinyl proton when **4** or **5** is converted into the corresponding *N*-oxide.

Reactions of heterocyclic amine oxides with reagents such as acid anhydrides, sulfonyl halides, and acid chlorides have been intensively investigated and reviewed.[3–5] While there is a great deal known about these synthetically useful reactions, a number of points remain obscure. Among these, and of particular interest to us, is the question as to whether chlorides such as **2c**[6,7] (Scheme I), generally formed from appropriately

SCHEME I

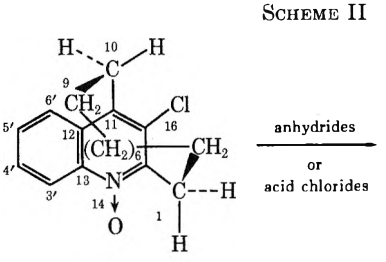


1 **2a**, X = $OPOCl_2$; **b**, X = OSO_2Ar; **c**, X = Cl

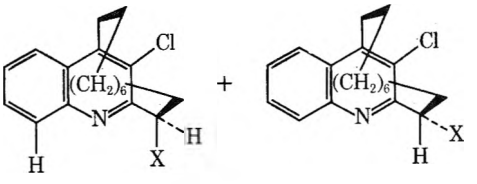
substituted *N*-oxides such as **1** by reaction with *p*-toluenesulfonyl chloride or phosphorus oxychloride, are primary products or whether they are derived in secondary reactions involving intermediate phosphate (**2a**) or sulfonate (**2b**) esters with the hydrogen chloride liberated.

The availability of metacyclophanes of type **3** (Scheme II) is of particular interest in this regard, since

SCHEME II



3



4a, X = $OCOCH_3$; **b**, X = OH; **c**, X = $OCOC_6H_5$; **d**, X = $OSO_2C_6H_4CH_3$; **e**, X = $OPOCl_2$; **f**, X = $OPO(OC_2H_5)_2$; **g**, X = Cl; **h**, X = Br; **j**, X = OCH_2CH_3; **k**, X = H

5a, X = $OCOCH_3$; **b**, X = OH; **c**, X = $OCOC_6H_5$; **d**, X = $OSO_2C_5H_4CH_3$; **j**, X = OCH_2CH_3

(1) This work was supported by the National Science Foundation, Grant No. GP-11918.

(2) Correspondence should be addressed to Department of Chemistry, Duke University, Durham, N. C. 27706.

(3) E. Ochiai, "Aromatic Amine Oxides," transl. by D. V. Mizoguchi, Elsvier, Amsterdam, 1967.

(4) V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1969, pp 1–42.

(5) A. R. Katritsky and J. M. Lagowsky, "Chemistry of Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971, pp 349–367.

(6) T. Kato, *Yakugaku Zasshi*, **75**, 1239 (1955); ref 3, p 264.

(7) E. Matsumura, *Nippon Kagaku Zasshi*, **74**, 363 (1953); ref 3, p 278.

data accumulated[8-10] suggest that functional groups on the methylene bridge (specifically at the benzylic methylene group at position 1) in such compounds are resistant to both SN1 and SN2 type reactions.

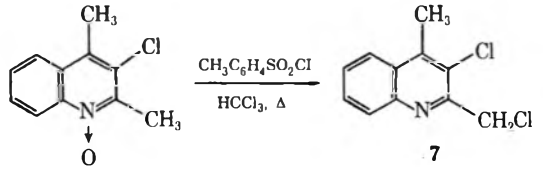
The reaction of **3** with acetic anhydride has been reported[8] and the structures of the derived syn and anti alcohols (**4b** and **5b**, respectively) have been established. We have now investigated the reactions of **3** with benzoyl chloride,[11] *p*-toluenesulfonyl chloride, and phosphorus oxychloride, and the results constitute the major subject of this report.

The reaction of **3** with benzoyl chloride in hot chlorobenzene proceeded in a manner analogous to that reported for **3** with acetic anhydride[8] and gave both the syn benzoate **4c** (21% pure) and the anti benzoate **5c** (62% crude, 46% pure). There was no evidence for the formation of the chloro derivative **4g**. Stereochemical assignments were made by analysis of the nmr spectral data (see subsequent discussion) and by hydrolysis of **4c** to **4b** (76% yield) and **5c** to **5b** (91% yield) by action of potassium hydroxide in methanol.

The reaction of **3** with *p*-toluenesulfonyl chloride in hot chloroform gave almost exclusively a single product (73% yield, pure) which was shown to be syn tosylate **4d** by its independent synthesis from **4b** (by treatment with *n*-butyllithium and *p*-toluenesulfonyl chloride). The anti isomer **5d** was similarly prepared from anti alcohol **5b**; nmr studies (see subsequent discussion) provided additional support for the assigned structures **4d** and **5d**.

It is of significance to note that the reaction of the model compound **6** with *p*-toluenesulfonyl chloride and chloroform, under identical conditions used for **3**, gave only the chloride **7** (74% yield, Scheme III).

SCHEME III



6 **7**

The reaction of **3** with excess phosphorus oxychloride at 100° gave a mixture, presumably containing **4e**, which was processed by the addition of ethanol; two products were isolated, the syn phosphate **4f** (30% yield) and the deoxygenated derivative of **3** (**4k**, 13% yield). The yield of **4f** was improved somewhat (40%) when the reaction was carried out in hot chloroform; a small amount (1–2%) of *syn*-1-chloro-12,13-benzo-16-chloro[10](2,4)pyridinophane (**4g**) was also isolated from this reaction. The stereochemical assignment of **4f** was tentatively made on the basis of its hydrolysis with potassium hydroxide in methanol to syn alcohol **4b** (64% yield). The stereochemical assignment of **4g** was made by nmr studies (see subsequent discussion).

(8) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).

(9) W. E. Parham, K. B. Sloan, and J. B. Biasotti, *Tetrahedron*, **27**, 5767 (1971).

(10) Additional evidence on this point will be presented in a subsequent communication.

(11) I. J. Pachter, *J. Amer. Chem. Soc.*, **75**, 3026 (1953); J. Vozza, *J. Org. Chem.*, **27**, 3856 (1962).

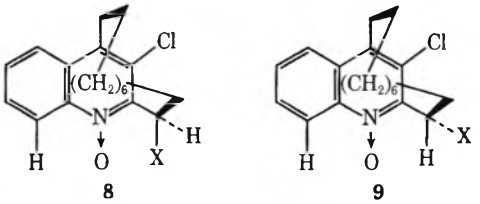
Similar results were obtained with 12,13-(5′-chlorobenzo)-14-oxo-16-chloro[10](2,4)pyridinophane,[12] the 5′-chloro analog of **3**; the phosphate, obtained in 30% yield, was assumed by analogy to **4f** to have the 1-syn configuration corresponding to the 5′-chloro analog of **4f**. The formation of **4f** and the 5′-chloro analog of **4f** are the first instances, to our knowledge, where stable phosphate esters have been obtained by reaction of an *N*-oxide with phosphoric acid derivatives.

While we are not at present able to define the reasons for the difference in stereochemistry observed for the products of reaction of **3** with acetic anhydride and benzoyl chloride (mixture of syn and anti isomers) as opposed to that obtained by reaction of **3** with *p*-toluenesulfonyl chloride where only the syn isomer (**4d**) was formed, the results are of mechanistic interest and constitute the subject of further studies in our laboratory. The observations described here suggest that chlorides of type **2c**, usually formed when *N*-oxides of type **1** are treated with sulfonyl halides or phosphorus oxychloride, are indeed secondary products derived from the intermediate esters of type **2a** and **2b**.

A number of reactions of **3** with other acid halides (as shown in Scheme II) were run. Reaction of **3** with phosphorus thiochloride ($PSCl_3$) gave only the reduced product, 12,13-benzo-16-chloro[10](2,4)pyridinophane (**4k**, isolated in 53% yield as the hydrochloride). Similarly, reaction of **3** with *N*-(2-bromo-4-nitrophenyl)benzhydrazidic bromide[13] gave only **4k** (48% isolated yield).

It was recognized that further studies of reactions on derivatives of 1-substituted pyridinophanes of type **4** and **5** would require a convenient and accurate method of determining the stereochemistry of the substituent at the 1 position (syn or anti).

It was anticipated that the chemical shift of a methinyl proton at C-1 in the nmr spectrum of an appropriately substituted pyridinophane *N*-oxide, in which the methinyl proton is rigidly held in or near the plane of the *N*-oxide group, should be quite informative concerning the anisotropic effect of the *N*-oxide group. The *N*-oxides **8** and **9**, respectively, of the pyridinophane derivatives of type **4** and **5** were of particular interest in this regard.



8 **9**

In **8** (syn orientation of the substituent) the methinyl proton is held away from the *N*-oxide group, and no anisotropic effect due to the *N*-oxide group on the methinyl hydrogen is expected. In **9** (anti orientation of the substituent) the methinyl proton is held in or near the plane of the *N*-oxide group, and one would expect the methinyl proton to experience the anisotropic effect of the *N*-oxide group. Therefore, no appreciable shift would be expected in the nmr absorption of the methinyl proton in **4** in going to the *N*-oxide **8**. On the other hand, in the corresponding *N*-

(12) W. E. Parham and K. B. Sloan, *Tetrahedron Lett.*, 1947 (1971).

(13) J. M. Burgess and M. S. Gibson, *Tetrahedron*, **18**, 1001 (1962).

oxide **9** of the anti isomer **5**, the methinyl proton should be deshielded by the *N*-oxide bond, and a large downfield shift in the nmr signal for the methinyl proton should be observed in going from the free base **5** to its *N*-oxide **9**.

The *N*-oxides of the 1-substituted derivatives of the 12,13-benzo-16-chloro[10](2,3)pyridinophane were prepared by oxidation of the corresponding derivative **4** or **5** with *m*-chloroperbenzoic acid or with hydrogen peroxide in glacial acetic acid, and the products were characterized by nmr, mp and elementary analysis. The nmr spectrum of the *N*-oxides in both syn and anti series showed a characteristic downfield shift of the peri proton at C-3′ (**3**) by as much as 1.5 ppm.

As expected, there was only a slight shift (0.01–0.09 ppm) in the methinyl proton in going from *syn*-pyridinophanes to the *N*-oxides (**4** → **8**). On the other hand, the corresponding protons in the anti series are deshielded by the *N*-oxide, and there is a shift of 1.42–1.73 ppm in going from the *anti*-pyridinophane derivative to the corresponding *N*-oxide (compare **5** and **9**).

The structures of syn and anti alcohols **4b** and **5b** (from ir data),[8] syn and anti ethers **4j** and **5j** (synthesis from the corresponding alcohols),[9] syn and anti tosylates **4d** and **5d** (synthesis from the corresponding alcohols), and syn and anti benzoates **4c** and **5c** (hydrolysis to corresponding alcohols) are known. The nmr signal data therefore provide confirmation of their structures and permit the assignment of the chloride **4g** and the previously reported bromide **4h**[8] as syn on the basis of no appreciable shift of the methinyl proton in the *N*-oxide when compared to the free base.

This procedure of comparing the nmr spectra of the free base to that of the corresponding *N*-oxide constitutes a convenient method of assigning the stereochemistry of syn and anti derivatives in the 12,13-benzo-16-chloro[10](2,4)pyridinophane system.

Experimental Section

The Reaction of 12-13-Benzo-14-oxo-16-chloro[10](2,3)pyridinophane (3) with Benzoyl Chloride.—A solution of **3** (1.5 g, 4.8 mmol) and benzoyl chloride (0.80 g, 5.7 mmol) in chlorobenzene (30 ml) was heated at the reflux temperature for 24 hr. Tlc (silica gel, petroleum ether[14]–diethyl ether, 50:50) showed only two spots, R_f 0.55, 0.45, and the absence of *syn*-1-chloro-12,13-benzo-16-chloro[10](2,4)pyridinophane (**4g**). The reaction mixture was diluted with chloroform (50 ml) and was extracted with 100 ml of 20% sodium hydroxide. The chloroform solution was dried ($MgSO_4$) and was chromatographed on alumina (375 g) using petroleum ether[14]–diethyl ether (50:50) as solvent to afford the following products in order of elution.

1. *syn*-1-**Benzoyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane** (**4c**): 425 mg, mp 131–134° from ethyl acetate–petroleum ether,[14] 21% yield. Tlc (as above) and nmr showed the absence of **5c** (anti isomer). Pure **4c** melted at 147–148° (from ethyl acetate): ir (Nujol) 1720 (C=O) and 1275 cm^{-1} (C–O); nmr[15] ($CDCl_3$) δ 8.4–7.3 (m, 9 aromatic H), 6.90–6.60 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX}$ = 14 Hz), 1, CHOC=O], and 3.8–3.2 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 326 (3.52), 312 (3.54), 236 (4.67), 216 (4.52), and 200 (4.39).

Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.68; N, 3.32. Found: C, 74.26; H, 6.77; N, 3.28.

2. *anti*-1-**Benzoyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane** (**5c**): 905 mg; 46% yield; mp 116–118° from ethyl acetate–petroleum ether;[14] ir (Nujol) 1730 (sh) and 1720 (C=O) and 1270 cm^{-1} (C–O); nmr[15] ($CDCl_3$) δ 8.4–7.25 (m, 9, aromatic H), 6.48–6.21 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz), 1, CHOC=O], and 3.8–3.2 (m, 2 benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 325 (3.46), 311 (3.51), 236 (4.77), 216 (4.48), and 200 (4.40).

Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.68; N, 3.32. Found: C, 73.76; H, 6.66; N, 3.12.

Traces (less than 1%) of *syn*-1-chloro-12,13-benzo-16-chloro-[10](2,4)pyridinophane (**4g**) were detected when the reaction was run in excess benzoyl chloride as solvent.

The Hydrolysis of *syn*-1-Benzoyloxy-12,13-benzo-16-chloro[10]-(2,4)pyridinophane (4c).—The benzoate **4c** (126 mg, 0.3 mmol) was treated with KOH (0.5 g) in methanol (50 ml) at 90° for 20 hr and was then cooled and diluted to 100 ml with water. The solution was filtered and the residue was air-dried to give 95 mg (mp 157–159°, 100% yield) of syn alcohol (**4b**) which showed only one spot on tlc analysis (silica gel, petroleum ether[14]–diethyl ether, 50:50). The product was recrystallized from chloroform–petroleum ether[14] to give 72 mg (mp 160–161.5°, mmp 158.5–160.5°, 76% yield) of syn alcohol **4b**.

The Hydrolysis of *anti*-1-Benzoyloxy-12,13-benzo-16-chloro-[10](2,4)pyridinophane (5c).—The benzoate **5c** (0.3 g, 0.7 mmol) was dissolved in hot methanol (30 ml) and allowed to react with 5 ml of 20% potassium hydroxide at reflux for 24 hr. The methanol was evaporated and the residue was dissolved in chloroform (40 ml). The chloroform was washed with water (100 ml) and evaporated to afford 0.2 g (mp 197–202°) of a white solid which showed only one spot on tlc analysis. Recrystallization of the solid gave 0.15 g (mp 204.5–206.5°, from petroleum ether[14]–diethyl ether, mmp 205–207°, 66% yield) of anti alcohol **5b**.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with *p*-Toluenesulfonyl Chloride.—A solution of **3** (1.352 g, 4.3 mmol) and *p*-toluenesulfonyl chloride (1.349 g, 7.1 mmol) in chlorobenzene (10 ml) was heated at 100° for 44 hr. The cooled reaction mixture was diluted with chloroform (50 ml) and extracted with 100 ml of 20% sodium hydroxide. Analysis of the organic extract by tlc (silica gel, petroleum ether[14]–diethyl ether, 50:50) showed one major spot (R_f 0.50) and a minor spot (R_f 0.75). The solution was chromatographed on alumina (200 g) using petroleum ether[14]–diethyl ether as eluent to give 2.05 g of a light oil (R_f 0.50). The oil was crystallized from chloroform–petroleum ether[14] to give 1.481 g (mp 105–107°, 73% yield) of *syn*-1-*p*-toluenesulfonyloxy-12,13-benzo-16-chloro-[10](2,4)pyridinophane (**4d**): nmr[15] ($CDCl_3$) δ 7.33 [q (AB, J_{AB} = 8 Hz, $\Delta\nu_{AB}$ = 41 Hz), 4, tosyl aromatic H], 8.1–7.3 (m, 4, aromatic H), 6.53–6.26 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz), 1, $CHOSO_2$], 3.6–3.3 (m, 2, benzylic CH_2), and 2.16 (s, 3, CH_3); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 326 (3.42), 312 (3.50), 233 (4.65), 229 (4.63), and 215 (4.53).

Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 66.15; H, 6.41; N, 2.97; S, 6.79. Found: C, 66.15; H, 6.56; N, 2.90; S, 6.93.

When chloroform (20 ml) was used as the solvent for reaction of **3** (1.6, g, 5.1 mmol) with *p*-toluenesulfonyl chloride (1.1 g, 5.8 mmol) at a pot temperature of 80° (48 hr), the yield of **4d** was 55–58%; unchanged **3** was recovered as the hydrochloride (mp 172–180°) from petroleum ether[14]–chloroform.

Anal. Calcd for $C_{19}H_{25}Cl_2NO$: C, 64.41; H, 7.11; N, 3.96; Cl, 20.01. Found: C, 64.26; H, 7.7; N, 3.88; Cl, 20.12.

Reaction of 3-Chloro-2,4-dimethylquinoline *N*-Oxide (6) with *p*-Toluenesulfonyl Chloride.—The reaction of **6** (500 mg, 2.4 mmol) with *p*-toluenesulfonyl chloride was carried out in chloroform solvent as described for **3**. The reaction mixture was cooled, extracted with 50 ml of 20% potassium hydroxide, and concentrated to give 0.7 g of greenish solid. The solid was chromatographed on alumina (40 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give 402 mg (mp 97–99°, 75% yield) of 3-chloro-2-chloromethyl-4-methylquinoline (**7**) as a white solid. The solid was recrystallized from petroleum ether[14] to give a pure sample of **7**: 341 mg; mp 101–103°; 63% yield; ir (Nujol) 1580 and 1500 cm^{-1} (w) (aromatic); nmr[15] ($CDCl_3$) δ 8.26–7.40 (m, 4, aromatic H), 5.00 (s, 2, CH_2Cl), and 2.76 (s, 3, CH_3); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 325 (3.40), 311 (3.48), 282 (3.65), 235 (4.76), and 215 (4.15).

Anal. Calcd for $C_{11}H_9Cl_2N$: C, 58.43; H, 4.01; N, 6.20. Found: C, 58.47; H, 4.01; N, 6.17.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with Phosphorus Oxychloride.—A mixture of **3** (1.1 g, 3.48 mmol) and phosphorus oxychloride (1.0 g, 6.5 mmol)

(14) Petroleum ether of bp 60–70°.

(15) In addition to the benzylic protons, which are given in the Experimental Section, a broad complex absorption weighted ~16 protons at δ 2.6–0.0 (±0.2) is characteristic for the 12,13-benzo-16-chloro[10](2,4)pyridinophane system and their *N*-oxides (*cf.* ref 8).

was heated at 100° for 0.5 hr [reflux condenser equipped with drying tube ($CaCl_2$)]. The mixture was cooled; nmr analysis showed an absorption at δ 6.53–6.13 (CHOP=O) which when integrated corresponded to 50% conversion into the substitution product. The mixture was heated for an additional 17 hr at 100°, then absolute ethanol (1.5 ml) and *N*,*N*-dimethylaniline (2.4 g) was added to the hot solution. The mixture was stirred at 30° for 1 hr and then diluted with benzene (50 ml). The benzene solution was extracted with aqueous hydrochloric acid (0.6 *N*, 20 ml) and concentrated. Analysis of the concentrate on tlc (silica gel, petroleum ether[14]–diethyl ether, 50:50) showed products with R_f 0.0, 0.32, and 0.87. The concentrate was chromatographed on silica gel (100 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give the following.

(a) The fraction with R_f 0.87 was a yellow oil (0.35 g) which crystallized from ethyl acetate to give 142 mg (mp 77–80°, mmp 78–81°, 13.5% yield) of 12,13-benzo-16-chloro[10](2,4)-pyridinophane (**4k**).

(b) The fraction with R_f 0.32 was isolated as a dark yellow oil (1.00 g) which crystallized from petroleum ether[14] to give 474 mg (mp 83–85°, 30% yield) of *syn*-diethyl 12,13-benzo-16-chloro[10](2,4)pyridinophane-1-phosphate (**4f**): mp 84.5–86.5° from petroleum ether;[14] ir (Nujol) 1575 and 1505 (w) (aromatic), 1275 (s) (P=O), and 1040, 1030, 980, and 970 cm^{-1} (s) (COP=O); nmr[15] ($CDCl_3$) δ 8.30–7.53 (m, 4, aromatic H), 6.53–6.11 (m, 1, CHOP=O), 4.40–3.80 (m, 4, $POCH_2CH_3$), and 3.63–3.53 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 235 (4.71) and 213 (4.49); mass spectrum (70 eV) *m*/*e* (rel intensity) 453 (100 M^+), 455 (37), 300 and 299 (23), 264 (96), 233 (M^*, M_1 = 300, M_2 = 264) and 198 (M^*, M_1 = 453, M_2 = 300).

Anal. Calcd for $C_{23}H_{33}ClNO_4P$: C, 60.95; H, 7.52; N, 2.91; Cl, 8.39. Found: C, 61.17; H, 7.52; N, 3.00, Cl, 8.08.

(c) *syn*-1-Chloro-12,13-benzo-16-chloro[10](2,4)pyridinophane (**4g**) [mp 144–145° (from petroleum ether[16])] was isolated (1.2–2.4% yields, two runs) from the chromatogram: nmr[15] ($CDCl_3$) δ 8.33–7.53 (m, 4, aromatic H), 6.13–5.85 (apparent t, 1, *J* = 8 Hz, CHCl) and 3.66–3.33 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 215 (4.42), 238 (4.62), 314 (3.52), and 328 (3.43).

Anal. Calcd for $C_{19}H_{23}Cl_2N$: C, 67.86; H, 6.89; N, 4.17; Cl, 21.08. Found: C, 68.09; H, 6.99; N, 4.03; Cl, 21.10.

Hydrolysis of *syn*-Diethyl 12,13-Benzo-16-chloro[10](2,4)pyridinophane-1-phosphate (4f).—The phosphate (**4f**) (800 mg, 1.77 mmol) was dissolved in 100 ml of methanol and treated with 6 ml of 20% potassium hydroxide (21.0 mmol) at reflux for 3 hr. The methanol was evaporated and the residue was suspended in 500 ml of water and extracted with chloroform (2 × 200 ml). The combined chloroform extracts were washed with water (200 ml), dried ($MgSO_4$), and evaporated to give 0.65 g of a wax. Nmr analysis of the wax showed only syn alcohol **4b** (CHO absorption at δ 5.60–5.30); no anti alcohol **5b** (δ 5.33–4.80) was present. Tlc (alumina, petroleum ether[14]–diethyl ether, 75:25, as eluent) showed one spot with R_f 0.65 corresponding to syn alcohol **4b** (anti alcohol under these conditions had R_f 0.13). The residue was crystallized from chloroform–petroleum ether[14] to give 360 mg (mp 159–161°, mmp 159–161°, 64% yield) of the syn alcohol **4b**.

Reaction of 12,13-(5′-Chlorobenzo)-14-oxo-16-chloro[10](2,4)-pyridinophane with Phosphorus Oxychloride.—A sample of the pyridinophane *N*-oxide[12] (800 mg, 2.27 mmol) in chloroform (50 ml) was treated with phosphorus oxychloride (0.7 g, 4.5 mmol) at the reflux for 12 hr. Absolute ethanol (1 ml) was added and after 1 hr of additional reflux the mixture was chromatographed on alumina (200 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give diethyl 12,13-(5′-chlorobenzo)-16-chloro[10]-(2,4)pyridinophane-1-phosphate as a white solid: 405 mg; 30% yield; mp 114–116° from petroleum ether[14]; ir (Nujol) 1240 (s) (P=O), 1495, 1570, and 1610 (w) (aromatic), and 1030 and 970 cm^{-1} (broad s) (COPO=O); nmr[15] ($CDCl_3$) δ 6.46–6.10 (m, 1, CHOP=O), 8.01 [d (X portion of ABX, J_{BX} = 2 Hz), 1, 6′-H), 7.86 [q (AB portion of ABX, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 28 Hz), 2, 3′- and 4′-H], 4.36–3.76 (m, 4, $POCH_2CH_3$) and 3.60–3.26 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) 332 (3.55), 317 (3.50), 238 (4.72), and 220 (4.46).

Anal. Calcd for $C_{23}H_{32}Cl_2NO_4P$: C, 56.56; H, 6.61; N, 2.87; Cl, 14.52. Found: C, 56.76; H, 6.74; N, 2.80; Cl, 14.37.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with Phosphorus Thiochloride.—A solution of *N*-oxide **3** (1.0 g, 3.16 mmol) in chloroform (20 ml) was treated with phosphorus thiochloride (800 mg, 4.7 mmol) as described above. To the mixture was added absolute ethanol (0.2 ml, 3.5 mmol) and the reaction mixture was heated at reflux for 36 hr. A calcium chloride drying tube was employed to protect the reaction from atmospheric moisture. More absolute ethanol (5 ml) was added to the solution, and it was refluxed for 8 hr. The solution was chromatographed on silica gel (100 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give 1.0 g of a light yellow oil which was dissolved in dry ether and treated with dry ether saturated with hydrogen chloride. The light yellow solid that precipitated (557 mg, mp 178–186°, 52.5% yield) was recrystallized from chloroform–diethyl ether to give 420 mg (mp 191–199°, 38% yield) of 12,13-benzo-16-chloro[10](2,4)-pyridinophane hydrochloride: ir (Nujol) 2300 and 1960 (broad, s) (^+NH), 1640, 1580 and 1490 (m) (aromatic), and 1520 cm^{-1} (broad, w) (aromatic); nmr[15] ($CDCl_3$) δ 9.25–9.06 (m, 1, 3′-H), 8.45–7.86 (m, 3, 4′-, 5′-, and 6′-H), and 4.36–3.20 (m, 4, benzylic CH_2).

Anal. Calcd for $C_{19}H_{25}NCl_2$: C, 67.45; H, 7.45; N, 4.14. Found: C, 67.32; H, 7.46; N, 3.92.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with *N*-(2-Bromo-4-nitrophenyl)benzyhydrazidic Bromide.[13]—A solution of **3** (1.0 g, 3.16 mmol) and the benzhydrazidic bromide[13] (1.3 g, 3.26 mmol) was heated at a pot temperature of 90° for 18 hr, protected from atmospheric moisture by a calcium chloride drying tube. The solution was chromatographed on alumina (180 g) using petroleum ether[14]–diethyl ether (50:50) as eluent. In addition to some recovered *N*-oxide **3** there was obtained 450 mg (mp 76–78.5°, mmp 76–80°, 48% yield) of 12,13-benzo-16-chloro[10](2,4)pyridinophane (**4k**).

***syn*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)-pyridinophane (4d).**—*n*-Butyllithium (0.81 ml, 2.1 *M* solution in hexane, 1.7 mmol) was added to a solution of syn alcohol **4b** (500 mg, 1.56 mmol) in tetrahydrofuran (10 ml, distilled from lithium aluminium hydride) maintained under nitrogen atmosphere. *p*-Toluenesulfonyl chloride (315 mg, 1.65 mmol) was then rapidly added. After 1 hr the reaction mixture had developed a white suspension. The suspension was filtered and the solvent was removed (*in vacuo*) to yield a pasty light yellow oil (1.1 g). The oil was dissolved in chloroform. The chloroform layer was washed with water, dried ($MgSO_4$), and concentrated (*in vacuo*) to give an oil, which was crystallized from chloroform–petroleum ether[14] to give crystals of pure **4d** (305.5 mg, 41.5% yield, mp 117.5–118°, mmp 116–119° with sample prepared by the reaction of the *N*-oxide **3** with *p*-toluenesulfonyl chloride).

***anti*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)-pyridinophane (5d)** was prepared from anti alcohol **5b** (1.164 g, 3.67 mmol) essentially as described above for **4d**. The crude oil was crystallized from chloroform–petroleum ether[14] to give anti tosylate **5d** (mp 121–123°, 1.22 g, 70.5% yield): ir (KBr) 1370 (s), 1180 cm^{-1} (COS); nmr[15] ($CDCl_3$) δ 8.1–6.8 (m, 8, aromatic H) and 5.83–5.60 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz), 1, $CHOSO_2$].

Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 66.15; H, 6.41; N, 2.97. Found: C, 66.04; H, 6.43; N, 2.86.

Preparation of the *N*-Oxides of the Syn- and Anti Derivatives (8 and 9).—The *N*-oxides of 1-substituted derivatives of the 12,13-benzo-16-chloro[10](2,4)pyridinophanes were prepared by oxidation of the corresponding bases (**4** or **5**) with *m*-chloroperbenzoic acid in chloroform at room temperature (method 1) or by treatment with hydrogen peroxide in glacial acetic acid at 90° (method 2). The products were characterized by nmr, mp, and elementary analysis.

***syn*-1-Hydroxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8b).**—A chloroform (10 ml) solution of syn alcohol **4b** (390 mg, 1.23 mmol) was treated with 85% *m*-chloroperbenzoic acid (290 mg, 1.68 mmol). The mixture was warmed slightly to ensure solution and was kept at room temperature for 12 hr. Analysis of the mixture by tlc showed the presence of trace quantities of unreacted starting material. Therefore, 100 mg (0.58 mmol) of *m*-chloroperbenzoic acid was added, and the reaction was continued for four more hr. The reaction mixture was washed with a solution of potassium carbonate, followed by water. The chloroform layer was concentrated (*in vacuo*) to give a residue which on crystallization from diethyl ether gave pale yellow crystals (250 mg, 61% yield, mp 174–175°) of the *N*-oxide (**8b**): nmr[15] ($CDCl_3$) δ 9.03–8.70 (m, 1 peri 3′-H), 8.33–7.56 (m, 3, 4′-, 5′-, and 6′-H), 7.46–7.00 (m, 1, OH, dis-

(16) Petroleum ether of bp 30–60°.

appears on adding D_2O), 5.76–5.40 (m, 1, CHOH) and 3.90–3.16 (m, 2, benzylic H).

Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.05; H, 7.19; N, 4.19. Found: C, 67.96; H, 7.32; N, 4.19.

anti-1-Hydroxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (9b).—Oxidation of 5b (530 mg) was carried out essentially as described for 4b. The *N*-oxide 9b (400 mg from chloroform–petroleum ether,[14] 72% yield) showed mp 220–230° dec; nmr[15] ($CDCl_3$) δ 8.68 (d, 1, peri 3′-H), 7.88–7.48 (m, 3, aromatic H), 6.64–6.34 [doublet of doublets (X portion of ABX system, $J_{AX} + J_{BX} = 16$ Hz), 1, CHOH], 3.35 (m, 1, CHOH), and 3.10–2.48 (m, 2, benzylic H).

Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.05; H, 7.19; N, 4.19. Found: C, 67.91; H, 7.33; N, 3.87.

syn-1-*p*-Toluenesulfonyloxy-12,13-benzo-14-oxo-16-chloro[10]-(2,4)pyridinophane (8d) was prepared from 4d as described for 8b: mp 145° from petroleum ether[14]–chloroform; 68% yield; nmr[15] ($CDCl_3$) δ 8.83–8.40 (m, 1, peri 3′-H), 6.57–6.30 (m, 1, $CHOSO_2$), 8.3–6.8 (m, 7, aromatic H), and 4.00–2.76 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

Anal. Calcd for $C_{26}H_{20}ClNO_3S$: C, 64.01; H, 5.54; N, 2.88. Found: C, 63.90; H, 5.73; N, 2.83.

anti-1-*p*-Toluenesulfonyloxy-12,13-benzo-14-oxo-16-chloro[10]-(2,4)pyridinophane (9d) was prepared from 5d (59 mg) as described for 8b. The crude product was dissolved in ether and washed with aqueous potassium hydroxide; the solid obtained from the dry ether was recrystallized from chloroform–petroleum ether[14] to give pure 9d: hygroscopic; mp 166–167°; 41% yield; nmr[15] ($CDCl_3$) δ 8.9–8.6 (1, m, peri 3′-H), 8.40–6.94 [m, 8, 7 aromatic H and a clear quartet centered at 7.28–7.08 (doublet of doublets) (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz, 1, $CHOSO_2$)], 3.80–2.68 (m, 3, benzylic CH_2 and 1 H from bridge methylene), 2.10 (s, 3, CH_3).

Anal. Calcd for $C_{26}H_{20}ClNO_3S$: C, 64.01; H, 5.54; N, 2.88. Found: C, 63.80; H, 5.89; N, 2.71.

anti-1-Ethoxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (9j) was prepared from 5j (380 mg) as described for 8b: mp 160° from diethyl ether; nmr[15] ($CDCl_3$) δ 9.10–8.66 (m, 1, peri 3′-H), 8.23–7.43 (m, 3, aromatic H), 6.46–6.13 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 15$ Hz), 1, $CHOC_2H_5$] and 4.0–3.2 (m, 4, benzylic H and OCH_2).

Anal. Calcd for $C_{21}H_{21}ClNO_2$: C, 69.72; H, 7.75; N, 3.87. Found: C, 69.9; H, 7.86; N, 3.76.

syn-1-Ethoxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8j) was prepared from 4j (100 mg) as described for 8b. The *N*-oxide was purified by preparative tlc (silica gel, petroleum ether[14]–10% diethyl ether as eluent) to give 59 mg (59% yield) of 8j as an oil: nmr[15] ($CDCl_3$) δ 9.10–8.65 (m, ~1, peri 3′-H), 8.35–7.35 (m, ~3, aromatic H), 5.65–5.35 [doublet of doublets (X portion of ABX $J_{AX} + J_{BX} \cong 15$ Hz), 1, $CHOC_2H_5$], 4.0–3.2 (m, 4, benzylic CH_2 and OCH_2CH_3). The oil was hygroscopic and satisfactory C and H analyses were not obtained.

syn-1-Benzoyloxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8c) was prepared from 4c (227 mg) essentially as described for 8b. The *N*-oxide 4c was obtained as an oil which resisted crystallization: nmr[15] ($CDCl_3$) δ 8.96–8.68 (m, 1, peri 3′-H), 8.33–7.23 (m, 8, aromatic H), 7.00–6.60 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz), 1, CHO], 3.80–2.80 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

The hydrochloride of 8c was prepared in diethyl ether saturated with dry hydrogen chloride: mp 146–150° from chloroform–diethyl ether, 56% yield pure from 4c; nmr[15] ($CDCl_3$) δ 11.73 (broad s, 1, ^+NH), 9.10–8.86 (m, 1, peri 3′-H), 8.38–7.33 (X, 3, aromatic), 7.00–6.66 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz), 1, CHO], and 4.00–2.90 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

Anal. Calcd for $C_{26}H_{29}Cl_2O_3N$: C, 65.82; H, 6.17; N, 2.95 Found: C, 65.58; H, 6.08; N, 2.96.

anti-1-Benzoyloxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (9c).—A solution of anti benzoate 5c (198 mg, 0.47 mmol), glacial acetic acid (10 ml), and 30% hydrogen peroxide (0.5 ml) was heated at 85° for 24 hr. More hydrogen peroxide (0.5 ml) was added, and the reaction mixture was maintained at 85° for additional 24 hr. The reaction mixture was cooled and diluted with chloroform (50 ml), and water (500 ml) was added. The chloroform layer was removed and the water layer was extracted with chloroform. The solution was chromatographed on silica gel (40 g) using diethyl ether as eluent to give an oily wax. The oily wax was crystallized from chloroform–petroleum ether[15] to give the *anti*-benzoyloxy *N*-oxide 9c (37 mg, 18% yield, mp 175–178°). The product was recrystallized from chloroform–petroleum ether[14] to give a pure sample: 25 mg; mp 176–178°; nmr[15] ($CDCl_3$) δ 9.06–8.86 (m, 1, peri 3′-H) and 8.30–7.43 (m, 9, aromatic H and CHO).

Anal. Calcd for $C_{26}H_{28}ClNO_3$: C, 71.30; H, 6.45; N, 3.20. Found: C, 71.05; H, 6.58; N, 3.09.

syn-1-Chloro-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8g) was prepared from 4g (90 mg) essentially as described for 8b and showed mp 189.5–191° from chloroform–petroleum ether;[14] 58% yield; nmr[15] ($CDCl_3$) δ 8.63–8.33 (m, 1, peri 3′-H), 8.16–7.46 (m, 3, aromatic H), 6.16–5.88 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 15$ Hz), 1, CHCl], and 3.70–3.00 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

Anal. Calcd for $C_{19}H_{23}Cl_2NO$: C, 64.77; H, 6.57; N, 3.98; Cl, 20.12. Found: C, 64.81; H, 6.57; N, 3.84; Cl, 20.14.

Registry No.—**3**, 25907-81-7; **3** HCl, 37781-22-9; **4b**, 25866-36-8; **4c**, 37781-24-1; **4d**, 37781-25-2; **4f**, 37781-26-3; **4g**, 37781-27-4; **4k**, 22200-39-1; **5b**, 25907-82-8; **5c**, 37781-30-9; **5d**, 37781-31-0; **6**, 37781-32-1; **7**, 37781-33-2; **8b**, 37781-34-3; **8c**, 37781-35-4; **8c** HCl, 37781-36-5; **8d**, 37781-37-6; **8g**, 37781-38-7; **8j**, 37781-39-8; **9b**, 37781-40-1; **9c**, 37781-41-2; **9d**, 37781-42-3; **9j**, 37781-43-4; 12,13-(5′-chlorobenzo)-14-oxo-16-chloro[10](2,4)pyridinophane, 37781-44-5; diethyl 12,13-(5′-chlorobenzo)-16-chloro[10](2,4)pyridinophane-1-phosphate, 37781-45-6; 12,13-benzo-16-chloro[10](2,4)pyridinophane hydrochloride, 25866-34-6.

Desulfurization of Episulfides. A Sulfurane Reaction

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The desulfurization of *cis*- and *trans*-2-butene episulfides with *n*-butyllithium, diiron nonacarbonyl, and triiron dodecacarbonyl to the corresponding butenes was studied. These reactions proceed with complete stereospecificity, the 2–6% crossover in the cases of the iron carbonyls being attributable to subsequent olefin isomerization. The intermediacy of 2-lithio-3-alkylthiobutanes for the *n*-butyllithium reaction can be excluded. Independent generation of these species demonstrates considerable loss of stereochemistry under the conditions of episulfide desulfurizations. The loss of stereochemistry is a function of the thioether leaving group, the loss being considerably less for thiophenoxide than for ethyl thiolate. A consequence of these studies also demonstrates that metal–halogen exchange between an alkyl halide and an organolithium proceeds with at least 95% retention of configuration.

The question of the role of pentacoordinate sulfur compounds, sulfuranes, in the reaction of sulfonium salts with nucleophiles has caused discussion and debate. While there are no known cases of stable sulfuranes[3,4] in which sulfur is bound only to carbon ligands, their existence has been implicated in many reactions by spectral[3,5] and product analysis.[6] Most of these reactions have been carried out on partially or fully aromatic substituted sulfonium species. While a sulfurane mechanism has been advanced to explain the observed products, other mechanisms, such as aryne formation, radical formation, or nucleophilic aromatic substitution, have also been put forth.[6]

In order to learn more about the intermediacy of sulfuranes, without the problems associated with aromatic species, we decided to investigate nonaromatic cases. Anticipating that small rings stabilize the predicted trigonal bipyramid geometry of a sulfurane compared to tetrahedral geometry, a study of the stereochemistry of organolithium-induced fragmentation of small sulfur heterocycles was undertaken.[7]

Approximately 15 years ago, Bordwell reported that reaction of aryl- or alkyllithium with episulfides produced olefins and the corresponding aryl or alkyl mercaptides.[8,9] Further study of the stereochemistry of the reaction with *cis*- and *trans*-2-butene episulfides revealed that, in each case, the olefin formation proceeded with greater than 97% stereospecific retention of configuration.[9] Bordwell presented two mechanisms for this reaction (Scheme I). In the first, the concerted process, fragmentation occurs *via* a sulfurane **1**. The second, the carbanion mechanism, requires that elimination must be 30–60 times faster than inversion and bond rotation rates. Since this report represents the first potential example of an aliphatic sulfurane, we reinvestigated this reaction to attempt to differentiate between the two proposed mechanisms.

Preparation and Reaction of Episulfides.—The *cis*- and *trans*-2-butene episulfides needed for our study were synthesized in the following manner. The *erythro*- and *threo*-2-bromo-3-hydroxybutanes were prepared from the corresponding *cis*- and *trans*-2-butenes by the method of Lucas and Winstein.[10] Conversion to the cis and trans epoxides was achieved by dehydrobromination with strong aqueous base.[11] The epoxides were converted to their respective episulfides by reaction with an aqueous thiourea solution.[12] The purity of each of the episulfides was determined by vpc and, while the trans material was free of the cis, the cis contained 0.6% of the trans isomer.

We carried out the reactions of the cis and trans episulfides with *n*-butyllithium at −78° for 1 hr. The reaction was then slowly warmed to 40° and held at that temperature for 1 hr. During the entire reaction, a stream of nitrogen was blown over the reaction mixture and into a series of bromine–carbon tetrachloride traps. The butenes were analyzed as their dibromide adducts.

Preparation and Reactions of *erythro*- and *threo*-2-Bromo-3-ethylthiobutane and 2-Bromo-3-phenylthiobutane.—The *erythro*- and *threo*-2-bromo-3-ethylthiobutanes **3a** and **4a**, which would serve as the precursors to the carbanion intermediates, were synthesized by the addition of ethylsulfenyl bromide, to excess *trans*- or *cis*-2-butene, respectively.[13] Each isomer was shown to be free of the other by nmr analysis of the expanded methine region. In a similar manner, addition of *cis*- or *trans*-2-butene to a hexane solution of phenylsulfenyl bromide gave the corresponding *threo*- and *erythro*-2-bromo-3-phenylthiobutanes, **3b** and **4b** (Scheme II).

The reactions of **3a** or **3b** and **4a** or **4b** with *n*-butyllithium were carried out at −78°, approximating the conditions of the episulfide decomposition reaction. In addition, the reactions were also run at −5°. The resultant 2-butenes were analyzed as the *meso*- and *dl*-2,3-dibromides. In some of the runs, the reaction was quenched with a proton source such as methanol or water, and *sec*-butylethyl sulfide was isolated, indicating that the reaction proceeded through a discrete carbanion intermediate.

Results and Discussion

Our results verified those of Bordwell. The trans isomer produced only *trans*-2-butene in 93% yield.

(1) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient.

(2) National Institutes of Health Predoctoral Fellow.

(3) For an example in which there seems to be good evidence by nmr, see W. Sheppard, *J. Amer. Chem. Soc.*, **93**, 5597 (1971).

(4) For a case in which two of the ligands are alkoxy groups, see I. C. Paul, J. C. Martin, and E. F. Perozzi, *ibid.*, **93**, 6674 (1971); J. C. Martin and R. J. Ashart, *ibid.*, **93**, 2339, 2341 (1971).

(5) (a) D. C. Owsley and G. K. Helmkamp, *ibid.*, **91**, 5239 (1969); (b) C. R. Johnson and J. J. Rigau, *ibid.*, **91**, 5398 (1969).

(6) B. M. Trost and R. W. LaRochelle, *ibid.*, **93**, 6077 (1971), and references cited therein.

(7) Also see J. I. Musher, *Advan. Chem. Ser.*, in press. We are grateful to Professor Musher for making a preprint of this paper available to us.

(8) F. G. Bordwell, H. M. Andersen, and B. M. Pitts, *J. Amer. Chem. Soc.*, **76**, 1082 (1954).

(9) N. P. Neureiter and F. G. Bordwell, *ibid.*, **81**, 578 (1959).

(10) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1580 (1939).

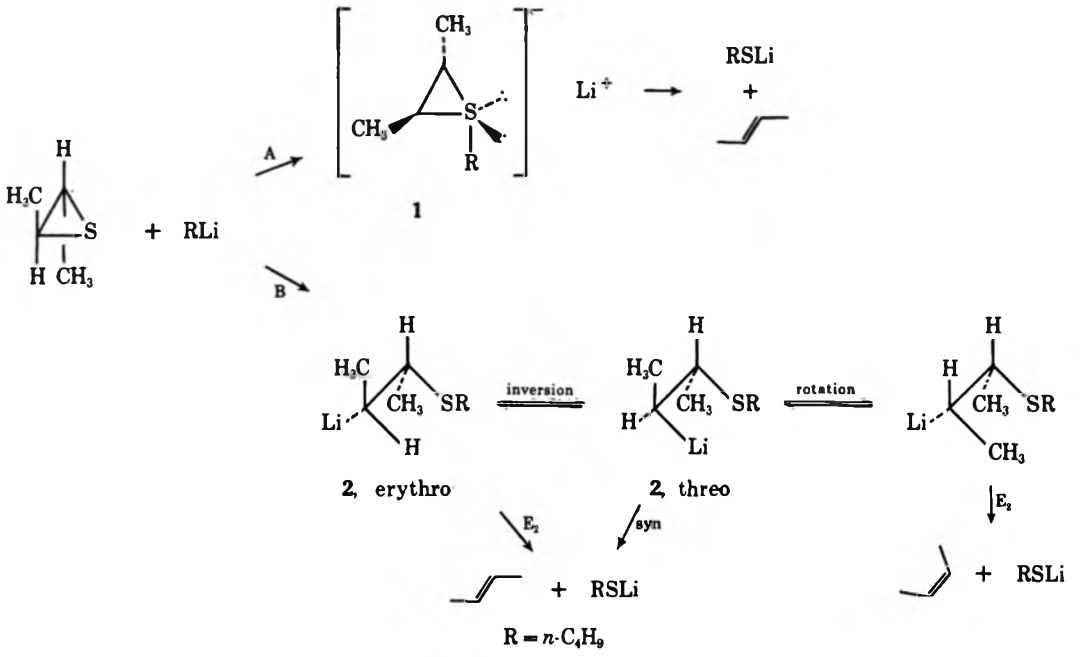
(11) C. W. Wilson and H. J. Lucas, *ibid.*, **58**, 2396 (1936).

(12) F. G. Bordwell and A. M. Andersen, *ibid.*, **75**, 4959 (1953).

(13) G. K. Helmkamp and D. J. Pettitt, *J. Org. Chem.*, **29**, 3258 (1964).

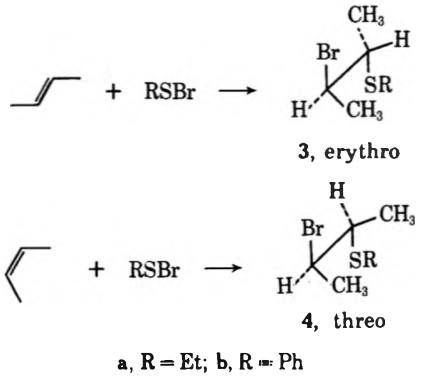
SCHEME I

REACTION OF EPISULFIDE WITH *n*-BUTYLLITHIUM



SCHEME II

PREPARATION OF 2-BROMO-3-ALKYL(ARYL)THIOBUTANES



a, R = Et; b, R = Ph

The cis isomer produced 98.8% *cis*-2-butene in 78% yield.[14] In the two mechanisms presented in Scheme I, the first, path A, assumes that the *n*-butyllithium will act as a nucleophile and attack at sulfur to form a trigonal bipyrimidal structure, **1**. It would be expected that the three-membered ring would assume a distorted apical basal orientation; the two lone pairs would be bisbasal, and the attacking group would be in the other apical position. A concerted disrotatory fragmentation of the two weakest bonds, those of the episulfide, would lead to the observed products. In a slight variation of the sequence of events (the idea actually put forth by Bordwell) the bond-making and bond-breaking process proceeds simultaneously. However, a transition state of this type seems less likely in terms of entropy considerations.

In the second mechanism, path B, SN2 displacement at sulfur could occur with either retention or inversion of configuration at carbon, leading respectively to either the threo or the erythro carbanions, **2t** or **2e**. Alternatively, sulfurane intermediate **1** could also lead to either of these conformers by heterolysis of one bond. The product observed could arise from either trans elimination of the erythro isomer or syn elimination of the threo isomer. As little was known about the stereospecificity of β-carbanion elimination in sulfides, a study was undertaken to examine this reaction.

From the results of the series of reactions, summarized in Tables I and II, it is apparent that both the ethyl and phenyl compounds **3** and **4** showed some degree of stereospecificity, however, considerably less specificity than in the episulfide cases.

TABLE I

REACTION OF *erythro*-[e] AND *threo*-2-BROMO-3-ETHYLTHIOBUTANE[f] WITH *n*-BUTYLLITHIUM

Isomer	Total yield, %	2-Butenes[a] % trans	2-Butenes[a] % cis	Temp, °C
Threo	80	44.0	56.0	−78[b]
Erythro	92.5	79.5	20.5	−78[b]
Threo	52	40.5	59.5	−78[c]
Erythro	74	89.0	11.0	−78[c]
Threo	58	43.2	56.8	−5[d]
Erythro	94	73.7	26.3	−5[d]

[a] Analyzed as *meso*- and *dl*-2,3-dibromobutanes. [b] Reaction mixture was allowed to warm to 40° before addition of water. [c] Water was added to the reaction mixture at −78° and it was then allowed to warm to 40°. [d] Water was added to the reaction mixture at −5° and it was then allowed to warm to 40°. [e] Registry no., 23289-26-1. [f] Registry no., 23289-25-0.

TABLE II

REACTION OF *erythro*-[d] AND *threo*-2-BROMO-3-PHENYLTHIOBUTANE[e] WITH *n*-BUTYLLITHIUM

Isomer	Total yield, %	2-Butenes[a] % trans	2-Butenes[a] % cis	Temp, °C
Threo	66	43.3	56.7	−5[c]
Erythro	82	88.0	12.0	−5[c]
Threo	54	11.3	88.7	−78[b]
Erythro	78	94.8	5.2	−78[b]

[a] Analyzed as *meso*- and *dl*-2,3-dibromobutanes. [b] Water was added to the reaction mixture at −78° and it was then allowed to warm to 40°. [c] Water was added to the reaction mixture at −5° and it was then allowed to warm to 40°. [d] Registry no., 37434-63-2. [e] Registry no., 37434-62-1.

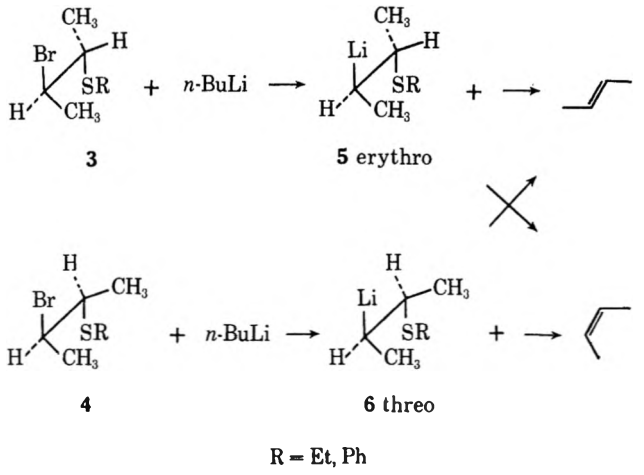
(14) The difference is well within the limits of experimental error. It may also be due to different rates of reaction of the cis and trans compounds.

There are two aspects to the reaction—metal halogen exchange and elimination. It has been demonstrated by Letsinger that metal halogen exchange occurs with a high degree of retention of configuration.[15] The fact that the overall elimination reaction in our cases can proceed with 95% stereospecificity indicates that metal–halogen exchange occurred with at least that degree of specificity.

Thus, the results suggest that either there is conversion between the erythro and threo isomers **5** or **6**, or competition between syn and anti elimination, or both (see Scheme III). In an analogous study by Sicher on

SCHEME III

n-BUTYLLITHIUM INDUCED ELIMINATIONS OF 2-BROMO-3-ALKYL(ARYL)THIOBUTANES



metal-induced olefin formation of vicinal dibromides, it was established that syn elimination plays a minor role compared to that of anti elimination in the acyclic cases.[16] Furthermore, House established the trans elimination in a series of metal-induced eliminations of 2-bromo-3-X-butanes where X was bromo, methoxyl, or acetoxyl.[17] He also established that the degree of stereospecificity was a function of the leaving group—the better the leaving group, the higher the stereospecificity.[18]

A similar interpretation appears most reasonable in these cases as well. At −78°, *erythro*- and *threo*-2-bromo-3-ethylthiobutanes eliminate with 50 ± 5 and 16 ± 2% stereospecificities, respectively.[19] Raising the temperature to −5° allows the interconversion of carbanion isomers to compete a little more effectively with elimination and causes a slight diminishment in stereospecificity. These effects are magnified in the case of 2-bromo-3-phenylthiobutane. Using thiophenoxide as the leaving group rather than ethylthiolate dramatically increases the stereospecificities[19] to 90 and 78% for the erythro and threo cases, respectively, at −78°. Thus, the rate of elimination is enhanced at the expense of loss of configuration of the carbanion. Raising the temperature to −5° makes the slower reaction, loss of carbanion configuration, more competitive with elimination with the consequence of diminished stereospecificity (to 66 and 14%). In both cases, the threo organolithium exhibits greater loss of configuration. This fact undoubtedly arises from the higher energy content of the conformation required for the anti elimination in this isomer in which there is maximal eclipsing of large groups. These results clearly eliminate the carbanion route, path B, for episulfide desulfurizations, thereby suggesting the sulfurane mechanism.

In an ancillary study, the stereochemistry of desulfurization of episulfides with diiron nonacarbonyl or triiron dodecacarbonyl in refluxing benzene was investigated. Such a reaction, originally reported by King,[20] may be envisioned as proceeding through metal π sulfuranes.[21] Table III lists the pertinent data for

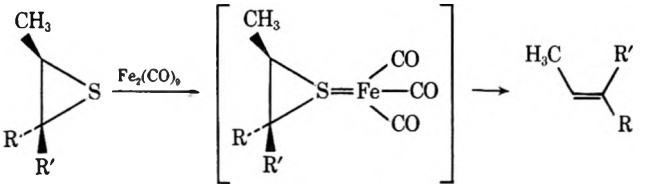


TABLE III

DECOMPOSITION OF *cis*-[c] AND *trans*-2-BUTENE EPISULFIDES[d] WITH IRON CARBONYLS

Episulfide	Iron carbonyl	Total yield, %	2-Butene[a] % trans	2-Butene[a] % cis
Cis	$Fe_2(CO)_9$[e]	80.5	6.4	93.6
Trans	$Fe_2(CO)_9$	81.9	97.5	2.5
Cis	$Fe_3(CO)_{12}$[f]	*b*	5.0	95.0
Trans	$Fe_3(CO)_{12}$	*b*	97.3	2.7

[a] Analyzed as *meso*- and *dl*-2,3-dibromobutane. [b] Yields not determined. [c] Registry no., 5954-71-2. [d] Registry no., 5955-98-6. [e] Registry no., 15321-51-4. [f] Registry no., 33727-76-3.

the desulfurizations of *cis*- and *trans*-2-butene episulfides. Like the organolithium induced decompositions, these reactions also proceed with a very high degree of stereospecificity. Control experiments demonstrated that the olefins are somewhat unstable to the reaction conditions. Thus, bubbling *trans*-2-butene through a benzene solution of diiron nonacarbonyl between 40° and 80° caused isomerization to *cis*-2-butene to the extent of 12–15% depending on contact times. Thus, partial isomerization of the initially formed olefins readily accounts for the 2–6% crossover observed. While a concerted disrotatory fragmentation of the π sulfurane can explain the results, alternative explanations exist and the mechanism must be considered an open question.

The results of organolithium and iron carbonyl induced desulfurizations may be compared to other desulfurizations of three-member sulfur heterocycles. The direct thermal decomposition of *cis*- and *trans*-2-butene episulfides,[22] as well as the thermal decomposi-

(15) (a) R. Letsinger, *J. Amer. Chem. Soc.*, **72**, 4842 (1950); (b) D. Y. Curtin and W. J. Koehl, Jr., *ibid.*, **84**, 1967 (1962).

(16) J. Sicher, M. Haval, and M. Svoboda, *Tetrahedron Lett.*, 4269 (1968).

(17) H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 182 (1958). Also see W. Adam and J. Arce, *J. Org. Chem.*, **37**, 507 (1972).

(18) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, pp 182–185.

(19) The per cent stereospecificity is defined as the relative per cent of expected product arising from a stereospecific anti elimination in excess of 50%.

(20) R. B. King, *Inorg. Chem.*, **2**, 326 (1963).

(21) In order to differentiate between a decet sulfur species which is pentacoordinate and tetracoordinate (counting the lone pair as a ligand), we refer to the former as σ and the latter as π sulfuranes. In a σ sulfurane, sulfur possesses four σ bonds and a lone pair, whereas in a π sulfurane sulfur possesses two σ bonds, one π bond, and a lone pair. Thus, in the latter case, valence-shell expansion of sulfur occurs only to the extent that back electron donation from the ligand to empty orbitals on sulfur is important. The sulfur ylides are members of such a class.

(22) E. M. Lown, H. S. Sandhu, H. E. Gunning, and O. P. Strausz, *J. Amer. Chem. Soc.*, **90**, 7164 (1968).

tion of episulfones,[23] has been reported to proceed stereospecifically. In contrast to these cases, episulfoxide decomposition has been reported to proceed nonstereospecifically.[24] Equation of stereospecificity to concertedness presents a dilemma in terms of orbital symmetry, since all these chelotropic processes are orbital symmetry forbidden for the least motion pathway. Furthermore, these diverse results make it difficult to claim that those cases of stereospecific decomposition involve a change in the correlation diagram because of the involvement of d orbitals of sulfur.

Experimental Section[25]

Preparation of *cis*-2-Butene Episulfide.—*threo*-3-Bromo-2-butanol was prepared from 110 g (0.62 mol) of *N*-bromosuccinimide and 34.6 g (0.62 mol) of *cis*-2-butene as previously described.[10] There was obtained 78.1 g (82% yield) of a colorless oil distilling at 52° (13 mm) [lit.[10] bp 49–51° (13 mm)] with n^{25}D 1.4753 (lit.[10] n^{25}D 1.4756). With 29.1 g (0.32 mol) of potassium hydroxide, 57 g (0.375 mol) of *threo*-3-bromo-2-butanol was converted into 24.5 g (90%) of *cis*-2-butene epoxide, bp 59° (lit.[18] bp 59–60°), as described.[18] Subsequent treatment of 49.7 g (0.68 mol) of epoxide with 52.2 g (0.68 mol) of thiourea in aqueous sulfuric acid as described in the literature[12] generated 27.5 g (46%) of *cis*-2-butene episulfide as a colorless liquid, bp 99° (lit.[12] bp 98°). Vpc analysis[26] showed the cis isomer to contain 0.6% trans.

Preparation of *trans*-2-Butene Episulfide.—*erythro*-3-Bromo-2-butanol was prepared by the literature procedure from 173 g (1.0 mol) of *N*-bromosuccinimide and 56 g (1.0 mol) of *trans*-2-butene in 700 ml of water and 20 ml of acetic acid.[10] Distillation of the product at 56° (13 mm) [lit.[10] bp 53° (13 mm)] gave 80.1 g (52%) of the erythro compound, n^{25}D 1.4763 (lit.[10] n^{25}D 1.4767). Treatment[11] of this bromohydrin with 41 g (0.72 mol) of potassium hydroxide converted it into 33.0 g (88%) of *trans*-2-butene epoxide which distilled at 56° (lit.[11] bp 54°). Dissolution in an aqueous sulfuric acid solution of 34.8 g (0.45 mol) of thiourea produced 12.7 g (43%) of a colorless liquid, bp 89° (lit.[12] bp 89°). Vpc analysis[26] of the *trans*-2-butene episulfide revealed no detectable amount of cis isomer.

Preparation of *threo*-2-Bromo-3-ethylthiobutane.[13]—A solution of ethyl disulfide (13.5 g, 0.11 mol) in 250 ml of dry methylene chloride was cooled to −17° with a carbon tetrachloride–Dry Ice bath and wrapped with aluminum foil to shield it from light. Bromine (16.0 g, 0.10 mol) in 75 ml of dry methylene chloride was added to the stirred, cooled solution at a rate which kept the temperature below −10° throughout the addition. At the end of addition, the solution was clear red. Excess *cis*-2-butene was bubbled through the red solution while the temperature was kept below −10° until the color disappeared. Methylene chloride was removed by evaporation *in vacuo* and the product was distilled to give 31.5 g (80% yield) of the threo material: bp 30° (0.4 mm); nmr ($CDCl_3$) τ 5.63 (qd, J = 7, 3 Hz, 1 H), 6.88 (qd, J = 7, 3 Hz, 1 H), 7.43 (q, J = 7.5 Hz, 2 H), 8.35 (d, J = 7.0 Hz, 3 H), 8.67 (d, J = 7.0 Hz, 3 H), 8.80 (t, J = 7.5 Hz, 3 H); mass spectrum m/e (rel intensity) 198 (3), 196 (3), 154 (7), 152 (12), 137 (9), 135 (12), 122 (39), 117 (15), 116 (36), 94 (30), 89 (100), 87 (27). *Anal.* Calcd for $C_6H_{13}BrS$: 195.9922. Found: 195.9983. Analysis of the methine and methyl region by nmr on an expanded scale showed the threo to be free of the erythro within the detectable limits of nmr (1%).

Preparation of *erythro*-2-Bromo-3-ethylthiobutane.—In a similar manner, 13.5 g (0.11 mol) of ethyl disulfide in 250 ml of dry methylene chloride was treated with 16.1 g (0.10 mol) of bromine to give the bromoethyl sulfide intermediate. This was treated with excess *trans*-2-butene to give 19.9 g (50% yield) of the erythro material: bp 31° (0.1 mm); nmr ($CDCl_3$) τ 5.85 (quintet, J = 6.5 Hz, 1 H), 7.21 (quintet, J = 6 Hz, 1 H), 7.40 (quintet, J = 7 Hz, 2 H), 8.21 (d, J = 6.5 Hz, 3 H), 8.62 (d, J = 6 Hz, 3 H), 8.73 (t, J = 7 Hz, 3 H); mass spectrum m/e (rel intensity) 198 (6), 196 (6), 137 (14), 135 (14), 123 (34), 122 (10), 117 (20), 116 (10), 94 (28), 91 (14), 89 (100). *Anal.* Calcd for $C_6H_{13}BrS$: 195.9922. Found: 195.9898. Analysis of the erythro compound by nmr on an expanded scale (methine and methyl regions) showed it to be free of the threo within the detectable limits of nmr (1%).

Preparation of *threo*-2-Bromo-3-phenylthiobutane.—In a manner similar to the preparation of *erythro*- and *threo*-2-bromo-3-ethylthiobutane, 24.0 g (0.11 mol) of phenyl disulfide was treated with 16.0 g (0.10 mol) of bromine to give the intermediate phenylsulfenyl bromide. The intermediate was not isolated, but was treated with excess *cis*-2-butene to give 22.9 g (47% yield) of the threo isomer: bp 102° (0.4 mm); nmr ($CDCl_3$) τ 2.83 (m, 5 H), 5.80 (qd, J = 7, 3 Hz, 1 H), 6.40 (qd, J = 7, 3 Hz, 1 H), 8.35 (d, J = 7 Hz, 3 H); mass spectrum m/e (rel intensity) 246 (25), 244 (25), 190 (30), 188 (30), 165 (45), 137 (60), 110 (43), 109 (49), 93 (50), 69 (100).

Anal. Calcd for $C_{10}H_{13}BrS$: C, 49.02; H, 5.30; Br, 32.62; S, 13.06. Found: C, 49.11; H, 5.22; Br, 32.55; S, 13.11.

Analysis of the threo methine and methyl region by nmr on an expanded scale showed it to be free of the erythro isomer within the limits of detection by nmr (1%).

Preparation of *erythro*-2-Bromo-3-phenylthiobutane.—In a manner similar to the preparation of the *erythro*- and *threo*-2-bromo-3-ethylthiobutane, 13.0 g (0.082 mol) of phenyl disulfide was treated with 12.0 g (0.075 mol) of bromine. The resultant bromophenyl sulfide intermediate was treated with excess *trans*-2-butene to give 2.49 g (7% yield) of the erythro compound: bp 88° (0.2 mm); nmr ($CDCl_3$) τ 2.75 (bm, 5 H), 5.92 (bq, J = 7 Hz, 1 H), 6.75 (bq, J = 7 Hz, 1 H), 8.22 (d, J = 7 Hz, 3 H), 8.60 (d, J = 7 Hz, 2 H).

Anal. Calcd for $C_{10}H_{13}BrS$: C, 49.02; H, 5.30; Br, 32.62; S, 13.06. Found: C, 49.16; H, 5.29; Br, 32.70; S, 13.21.

Analysis of the erythro methine and methyl regions by nmr on an expanded scale showed it to be free of the threo compound within the detectable limits (1%).

General Procedure for *n*-Butyllithium Decomposition Reactions.—The apparatus used for the decomposition reactions consisted of a 50-ml three-neck flask with stirrer, condenser, a rubber septum, and a nitrogen inlet tube. The condenser was connected by tygon tubing to two carbon tetrachloride–bromine traps, followed by an aqueous thiosulfate trap. The system, excluding the trap, was dried rigorously in a 120° oven for 12 hr.

The material to be decomposed was placed in the flask in 3 ml of dry tetrahydrofuran and cooled to −78°. An equivalent amount of 1.6 *M* *n*-butyllithium in hexane was added all at once *via* syringe and the solution was stirred for 1 hr at −78°. A steady stream of nitrogen was blown across the solution and through the traps. In some of the experiments, the solution was

TABLE IV

DECOMPOSITION OF *cis*- AND *trans*-2-BUTENE EPISULFIDES WITH *n*-BUTYLLITHIUM

Episulfide	Mmol	Mmol episulfide / mmol n-butyllithium	Total yield, %	% meso	% dl
Cis[a]	11.3	1.1	6	<1	>99
Cis[a]	11.3	1.1	78	0.5	99.5
Trans	0.20	1.1	6	100	0
Trans	11.3	1.1	93	100	0

[a] Corrected for starting material impurity.

(23) N. P. Neureiter and F. G. Bordwell, *ibid.*, **85**, 1209 (1963); N. P. Neureiter, *ibid.*, **88**, 558 (1966); L. A. Carpino and L. V. McAdams, III, *ibid.*, **87**, 5804 (1965); N. Tokura, T. Najai, and S. Matsumura, *J. Org. Chem.*, **31**, 349 (1966).

(24) G. E. Hartzell and J. N. Paige, *ibid.*, **32**, 459 (1967); K. Kondo, M. Matsumoto, and A. Negishi, *Tetrahedron Lett.*, 2131 (1972).

(25) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer, and ultraviolet spectra were recorded on Cary Model 11 and Model 15 spectrophotometers. Nmr spectra were determined on a Varian Associates Model A-60A spectrometer fitted with a variable temperature probe. Chemical shifts are given in parts per million relative to TMS as an internal standard. Mass spectra were taken on a CEC 103 C or a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 V. Analyses were performed by Spang Microanalytical Laboratory and Micro-Tech Laboratories, Inc. Unless otherwise indicated, extractions were performed with chloroform and magnesium sulfate was employed as a drying agent. Vpc analyses were performed on an Aerograph Model 90P instrument.

(26) A 10 ft × 0.25 in. column of 20% Dow silicone oil 710 on Chromosorb P was employed.

TABLE V

DECOMPOSITION OF *erythro*- AND *threo*-2-BROMO-3-ETHYLTHIOBUTANE WITH *n*-BUTYLLITHIUM

Compd	Mmol	Mmol compd / mmol RLi	Yield, %	% meso	% *dl*	Temp range °C	Quenched with H_2O	% *sec*-Butyl ethyl sulfide recovered
Threo	11.3	1.1	80	44.0	56.0	−78–40	No	
Erythro	11.3	1.1	92.5	79.5	20.5	−78–40	No	
Threo	5.7	1.1	52	40.5	59.5		Yes	2.4
Erythro	5.7	1.1	74	89.0	11.0	−78	Yes	2.9
Threo	5.7	1.1	58	43.2	56.8	−5	Yes	2.2
Erythro	5.7	1.1	94	73.7	26.3	−5	Yes	17.0

TABLE VI

DECOMPOSITION OF *erythro*- AND *threo*-2-BROMO-3-PHENYLTHIOBUTANE WITH *n*-BUTYLLITHIUM

Compd	Mmol	Mmol compd / mmol *n*-butyllithium	Yield, %	% meso	% *dl*	Temp range °C	Quenched with H_2O	% *sec*-Butyl phenyl sulfide recovered
Threo	5.0	1.1	66	43.3	56.7	−5	Yes	None
Erythro	1.0	1.2	82	88.0	12.0	−5	Yes	None
Threo	5.0	1.1	59	11.3	88.7	−78	Yes	1.4
Erythro	1.0	1.2	78	94.8	5.2	−78	Yes	.1

quenched with water, which served as a proton source to trap any carbanions present. This was done by addition of 1 ml of water *via* syringe to the cold solution.

The reaction was allowed to warm to room temperature by removal of the −78° bath and it was then held at 40° for 1 hr to ensure that all volatile products would be swept along to the traps by the nitrogen. The carbon tetrachloride solutions were combined and the excess bromine was reduced with a saturated sodium thiosulfate solution. The carbon tetrachloride was washed with 5 × 50 ml of water and dried ($MgSO_4$), and the solvent was removed by evaporation. The *meso*- and *dl*-2,3-dibromobutanes were analyzed by vpc[27] utilizing 1,2-dibromoethane as an internal standard.

Analysis of the sulfide components (*sec*-butylethyl sulfide or *sec*-butylphenyl sulfide) in the quenching experiments with *threo*- and *erythro*-2-bromo-3-ethylthiobutane and 2-bromo-3-phenylthiobutane was carried out in the following manner. The tetrahydrofuran solution was mixed with 50 ml of a 10% sodium hydroxide solution and the combined solution was extracted with 5 ml of pentane. The pentane was washed with 5 × 5 ml of water and dried ($MgSO_4$), and analysis was carried out by vpc[28] using decalin as an internal standard. The results for the various runs with the episulfides and the bromo thioethers are summarized in Tables IV, V, and VI.

Decomposition of *cis*- and *trans*-2-Butene Episulfide with Iron Carbonyl.[17]—The equipment used in these reactions is the same as that used in the organolithium reactions. In a typical reaction, *cis*- or *trans*-2-butene episulfide (0.176 g, 2.0 mmol) in 5 ml of thiophene-free benzene was placed in the 50-ml flask. To this was added 0.504 g (2.0 mmol) of diiron nonacarbonyl and the mixture was heated to reflux. After refluxing for 4 hr, the reaction was stopped and the carbon tetrachloride–bromine traps were combined and worked up as described in the previous experiments. Analysis by vpc with an internal standard was carried out (Table VII).

TABLE VII

REACTION OF *cis*- AND *trans*-2-BUTENE EPISULFIDES WITH DIIRON NONACARBONYL OR TRIIRON DODECACARBONYL AT 80°

Episulfide	Mmol	Iron carbonyl	Mmol	Total yield, %	% meso	% *dl*
Trans	2.0	$Fe_3(CO)_{12}$	2.0	*a*	97.3	2.7
Trans	2.0	$Fe_2(CO)_9$	2.0	80.5	97.5	2.5
Cis	2.0	$Fe_3(CO)_{12}$	2.0	*a*	5.0	95.0
Cis	2.0	$Fe_2(CO)_9$	2.0	81.9	6.4	93.6

[a] Qualitative run.

Registry No.—Ethyl disulfide, 110-81-6; bromine, 7726-95-6; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; phenyl disulfide, 882-33-7; *n*-butyllithium, 109-72-8.

Acknowledgment.—We wish to thank the National Institutes of Health and the National Science Foundation for their generous support of our programs.

(27) A 20 ft × 0.25 in. column of 20% Dow silicone oil 710 on Chromosorb P was employed.

(28) An 8 ft × 0.25 in. column of 20% SE-30 on Chromosorb W was employed.

Large-Ring Cyclic Disulfide Diamides[1]

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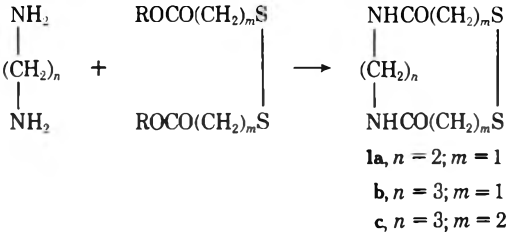
Unsubstituted 10-, 11-, and 13-membered ring cyclic disulfide diamides result in good to excellent yields from reaction of ethylenediamine and trimethylenediamine with esters of dithiodiacetic and 3,3′-dithiodipropionic acid in the absence of solvent. The procedure fails to give the desired products even from very simple substituted diamines and dithio diesters, however. Oxidation of the appropriate dithiols proved to be a satisfactory alternative route, good yields of ethylenedithiodiacetamide, its 2-methyl derivative, and what is probably its *N*,*N*′-dimethyl derivative being obtained. Ethylenedithiodiacetamide appears to exist in two diastereoisomeric forms, interconversion of which is precluded by steric hindrance.

Cyclic disulfides with more than five or six ring atoms are formed rather more readily than are their carbocyclic congeners. As long ago as 1887, Fasbender[2] reported that cautious oxidation of ethane-1,2-dithiol with bromine or iodine gave mainly the cyclic bisdisulfide. 1,1-Dithiols give linear polymers.[3] Both Calvin, *et al.*,[4] and Schoberl and Grafje[5] have shown that higher α,ω-dithiols [$HS(CH_2)_nSH$, n = 3–8, 10, 13] give monomeric cyclic disulfides under mild conditions and in dilute solution but when n = 3 or 4 these readily dimerize to give bisdisulfides. Similarly, the predominant product of X-radiolysis of lipoic acid (n = 3) in aqueous solution is thought to be the cyclic dimer.[6] The most striking case, however, appears to be the formation of *N*,*N*′-ethylenedithiodiacetamide (ethylenedithiodiglycolamide, perhydro-1,2,5,8-dithiadiazecine-4,9-dione, **1a**) in almost quantitative yield when ethylenediamine is mixed with a dithiodiacetate ester in the absence of solvent.[7] Plausibly, major controlling factors are the preferred cis dihedral configuration about the disulfide group and the lack of freedom of rotation within the amide group of the intermediate acyclic monoamide. We now report the preparation of further large-ring disulfide diamides of the same sort.

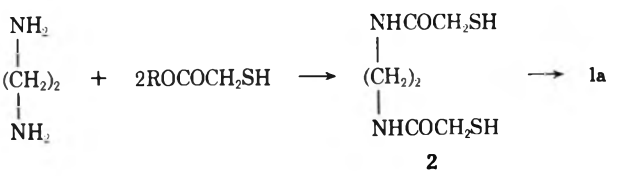


1a, $n = 2; m = 1$
b, $n = 3; m = 1$
c, $n = 3; m = 2$

The simple 11- and 13-membered ring disulfides (**1b**, **1c**) were obtained just as was **1a** by mixing equimolar amounts of trimethylenediamine with dimethyl dithiodiacetate or dimethyl 3,3′-dithiodipropionate in the absence of solvent. Each reaction was moderately exothermic, each reaction mixture set solid in due course, and yields of recrystallized products were good (60–70%). Low-resolution mass spectra of the dithiodiacetamides (**1a**,**1b**) showed no masses (other than ^{34}S isotope peaks) above those expected for the molecular ions at 206 and 220 daltons. The dithiodipropionamide (**1c**) however, gave additional small peaks up to M + 32. A high-resolution spectrum of **1c** showed conclusively that the M + 32 peak at 280 daltons contained an additional atom of sulfur. Presumably it corresponds to the cyclic trisulfide present as impurity. Repeated crystallization failed to remove this impurity completely, although a satisfactory elemental analysis was obtained. The trisulfide (if such it be) does not result from trisulfide impurity in the dithiodipropionate starting material, since this methyl ester analyzed satisfactorily and exhibited no M + 32 peak in the mass spectrum. It must arise from some relatively deep-seated reorganization of the disulfide group. A product analogous to **1c**, presumed to be largely the 12-membered ring compound (**1**, n = 2; m = 2) resulted from reaction of ethylenediamine with dimethyl dithiodipropionate. This also exhibited a marked M + 32 peak.

Attempts to extend the above procedure to substituted diamines and disulfide diesters revealed that cyclic diamide formation is most sensitive to slight steric hindrance. Neither reaction of dimethyl 2,2′-dithiodipropionate with ethylenediamine nor even of propylenediamine with dimethyl dithiodiacetate gave the desired products. In the latter case, a modest amount of a 2-substituted imidazoline may have been formed. Both *N*,*N*′-dimethyl- and *N*,*N*′-diethylethylenediamines with 3,3′-dithiodipropionate esters gave brown tars, a foul stench, and no desired product. The disulfide bond is known to be reactive toward primary and secondary amines, and it seems that cyclic amide formation depends upon a nice balance of steric and electronic factors.

An alternative route to the desired disulfides is oxidation of the corresponding dithiols (**2**). While the control afforded by the cisoid disulfide dihedral is lacking in this approach, the two amide groups present in the dithiol would seem to offer a good measure of conformational restriction. In any event, reaction of ethylenediamine with methyl mercaptoacetate (2 mol) readily afforded the dithiol **2** (82% yield, characterized as its bis-*S*-dinitrophenyl derivative, mp 245°), which, upon oxidation with iodine solution, gave, immediately



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(1) Financial support from the National Institute of General Medical Sciences, Public Health Service, Research Grant GM 16477, is gratefully acknowledged.

(2) H. Fasbender, *Ber.*, **20**, 460 (1887).

(3) T. L. Cairns, G. L. Evans, A. W. Larchar, and B. C. McKusick, *J. Amer. Chem. Soc.*, **74**, 3982 (1952).

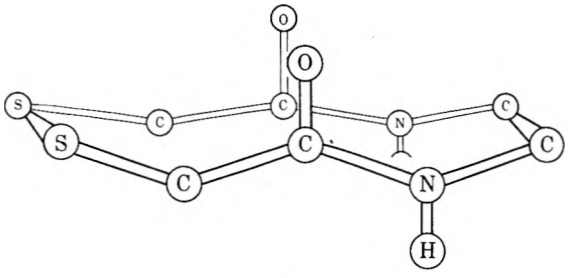
(4) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954).

(5) A. Schoberl and H. Grafje, *Justus Liebigs Ann. Chem.*, **614**, 66 (1958).

(6) T. C. Owen and A. C. Wilbraham, *J. Amer. Chem. Soc.*, **91**, 3365 (1969).

(7) T. C. Owen and J. M. Fayadh, *J. Org. Chem.*, **35**, 3198 (1970).

and in excellent yield (80%), disulfide **1a** identical in melting point, mixture melting point, and mass spectrum with material prepared by the earlier procedure. The dithiol **2** proved to be unusually sensitive to air oxidation also. However, to our consternation, the product of aerial oxidation melted at 245°, in sharp contrast to the melting point (215°) of the earlier products. A mixture of the two substances, from which the lower melting one was selectively extracted by warm dimethylformamide, resulted when the dithiol was oxidized with aqueous hydrogen peroxide. The higher melting product analyzed satisfactorily for cyclic disulfide. Its mass spectrum was essentially identical with that of the lower melting one, showing, in particular, no masses above the 206–208 isotopic pair, so that it is unlikely to be a dimer or oligomer. Yet its melting point, its solubility (it is much less soluble even than **1a**, dissolves only in boiling DMF or DMSO, and could not be recrystallized owing to polymerization under such vigorous conditions), and its X-ray powder pattern all show it to be quite different from the earlier product. Both gave back the dithiol (characterized as the DNP derivative) upon reduction with mercaptoethanol. The two may perhaps be just different crystalline modifications of the same substance or, despite the mass spectral data, one may be a polymer. However, models show that the ten-membered ring is a trapezoid in which the amide planes occupy the long, nonparallel sides and that these planes are sterically precluded from rotating through the plane of the trapezoid. Thus, two diastereoisomeric structures (**3**, **4**) are possible, in one of which (**3**) the amide carbonyl groups are cis and in the other (**4**) trans to each other.



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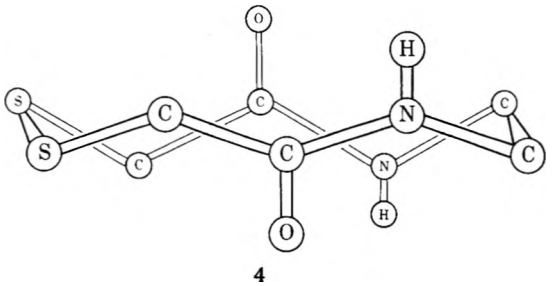

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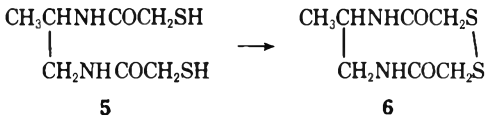
We suggest that our two products may well be such isomers. For the present, we refer to the lower melting form as α-ethylenedithiodiacetamide and to the higher melting as the β form.

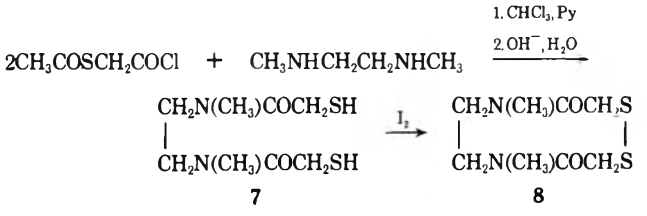
Propylenediamine reacted much more sluggishly with methyl mercaptoacetate than did ethylenediamine. Nevertheless, the desired dithiol **5** was obtained as a yellow oil [consistent nmr spectrum, bis-*S*-dinitrophenyl derivative mp 214–219°, uv λ_{max} 337 nm (ϵ_{max} 25,350)] which, upon oxidation with iodine or with hydrogen peroxide, gave the desired cyclic disulfide **6** in good yield.



5 **6**

Elemental analysis, mass spectrum, and nmr and ir spectra were entirely consistent with the cyclic monomer structure. In contrast with the unsubstituted compounds **1a–1c**, **6** proved to be quite soluble in water and the common polar solvents. No evidence for different forms of **6** has been observed, although the product from iodine oxidation did appear to have a slightly higher melting point than did that from oxidation with peroxide.

Attempts to prepare *N*,*N*′-dialkyl derivatives of ethylene dithiodiacetamide in the same manner failed completely. Only partial diminution of ester carbonyl and development of amide carbonyl bands in the infrared spectrum occurred when appropriate diamines were heated for prolonged periods with methyl mercaptoacetate. The reaction of acetylthioacetyl chloride with *N*,*N*′-dimethylethylenediamine proceeded smoothly, however, to give, after alkaline hydrolysis of thioester groups, a liquid product exhibiting properties consistent with its being the desired dithiol **7**.



7 **8**

This, upon oxidation with iodine followed by continuous extraction with chloroform, afforded a colorless oil. The product, which may be the disulfide **8**, has stubbornly refused to crystallize and has not given acceptable elemental analytical data, presumably because of persistent retention of solvent. Its nmr spectrum is consistent with structure **8**, however, and its mass spectrum shows the expected isotopic molecular ion pair (*m*/*e* 234, 236) and no significant higher masses.

Experimental Section[8]

Materials. Dimethyl Dithiodiacetate.—A mixture of *p*-toluenesulfonic acid (1.0 g), dithiodiacetic acid (31 g, 0.170 mol), and methanol (110 ml) was heated under reflux for 4 hr. Methanol was removed under reduced pressure, chloroform (200 ml) was added to the oily residue, the solution was washed with aqueous $NaHCO_3$ (5%, 75 ml × 3) and water, dried ($MgSO_4$), and evaporated, and the residue was distilled under vacuum to give dimethyl dithiodiacetate as a colorless liquid: 24.3 g (68%); bp 109–114° (1.5 mm);[9] nmr ($CDCl_3$) τ 6.38 (s, 4 H, 2 SCH_2) and 6.24 (s, 6 H, 2 $COOCH_3$).

Dimethyl 3,3′-dithiodipropionate was similarly prepared: 63% yield; bp 148–152° (1.2 mm); nmr (CCl_4) τ 7.18 (symmetrical octet, 8 H, SCH_2CH_2CO) and 6.30 (s, 6 H, 2 $COOCH_3$).

***N*,*N*′-Ethylenebismercaptoacetamide (2).**—Ethylenediamine

(8) Melting points are uncorrected. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Mass spectra were by Florida State University, Tallahassee, Fla. A Perkin-Elmer Model 137 G spectrophotometer was used for ir spectra. Proton magnetic resonance spectra were determined with Varian A-60 and JEOL 100 instruments using tetramethylsilane as an internal standard.

(9) T. S. Price and D. F. Twiss, *J. Chem. Soc.*, 1645 (1908).

(3.6 g, 60 mmol) was added slowly to stirred, ice-cooled methyl mercaptoacetate (12.8 g, 120 mmol) and the mixture then was heated at 100° for 1.5 hr. Overnight, the product solidified. Trituration with cold EtOH gave crude **2** (10.25 g, 82%, mp 135–139°). Pure **2**, white needles from hot EtOH, had mp 138–139°; nmr (D_2O) τ 6.41 (s, 4 H, 2 $COCH_2$), 6.55 (s, 4 H, 2 NCH_2). *Anal.* Calcd for $C_6H_{12}O_2S_2N_2$: C, 34.59; H, 5.82. Found: C, 34.72; H, 5.94.

Bis-*S*-dinitrophenyl Derivative of 2.—Crude **2** (0.62 g), $NaHCO_3$ (1 g), and fluoro-2,4-dinitrobenzene (1.3 g) in water (20 ml) were stirred for 2 hr and filtered, and the product was washed with ethanol, gave a yellow solid (1.32 g, 76%). Recrystallization from EtOH gave pale yellow crystals, mp 245–247°. *Anal.* Calcd for $C_{18}H_{16}N_6O_{10}S_2$: C, 40.00; H, 2.96. Found: C, 39.84; H, 3.17.

***N,N'*-Ethylenedithiodiacetamide (1a), α Form. A. From Ethylenediamine and Dimethyl Dithiodiacetate.**—The melting point of the product prepared by the published procedure[7] was raised to 213–215° (72% yield) by careful recrystallization from fairly hot (90–95°) dimethylformamide.

B. From *N,N'*-Ethylenebismercaptoacetamide.—The dithiol **2** (2.0 g) was stirred with water (75 ml) for 1 hr. The solution was separated from a moderate amount (0.38 g, 18%) of insoluble white solid (β form, mp 244.5–246°) and treated with I_2–KI solution (0.1 *N*) until a faint yellow color persisted. The precipitate (1.39 g, 69%), recrystallized from dimethylformamide, had mp 214–216, undepressed upon admixture with material from procedure A. Spectra (ir, mass) and elemental analysis were as previously reported.[7]

***N,N'*-Ethylenedithiodiacetamide (1a), β Form.**—A brisk stream of air was blown over a solution of the dithiol **2** (0.9 g) in EtOH (10 ml) containing ethylenediamine (1 drop) until the solvent had evaporated. The residue, washed with water, hot EtOH, and hot (90°) dimethylformamide, afforded the β form of **1a** as a white powder (0.75 g, 83%), mp 245–246.5°, identical in all respects with the initial precipitate in procedure B above and with the less soluble product from peroxide oxidation (below). *Anal.* Calcd for $C_6H_{10}N_2O_2S_2$: C, 34.95; H, 4.85. Found: C, 34.87; H, 4.95. The mass spectrum (50 eV) was very similar indeed to that of the α form.[7] Oxidation (overnight) of an aqueous solution of dithiol **2** with the requisite amount of 3% H_2O_2 gave, in 50% yield, a white precipitate which, after washing with hot EtOH, had mp 220–227°. Repeated extraction of this solid with hot (90°) dimethylformamide left a residue having mp 242–245°. Crystalline powder, mp 213–215° after recrystallization, was deposited by the first dimethylformamide extract.

Characterization of α- and β-Ethylenedithiodiacetamides by Reduction.—Either disulfide (0.2 g), heated with mercaptoethanol (0.5 ml) on the steam bath overnight, dissolved in part. Dilution of the mixtures with warm EtOH (2–3 ml), filtration, partial evaporation, and chilling afforded the crude solid dithiol **2**, which was converted directly into its bis-*S*-dinitrophenyl derivative as described above. The overall yield from the α disulfide was 0.23 g (43%); from the β form, 0.18 g (34%). The melting points were undepressed upon admixture with authentic material.

***N,N'*-Trimethylenedithiodiacetamide (1b).**—The exothermic reaction between trimethylenediamine (1.41 g, 19 mmol) and dimethyl dithiodiacetate (4.00 g, 19 mmol) was moderated by means of an ice–water bath. The resulting oil, kept at 25° for 2 hr and then heated at 100° for 1.5 hr, solidified upon cooling. Trituration with ethanol followed by recrystallization from EtOH–dimethylformamide mixture gave a pale yellow solid (2.5 g, 62%), mp 164–165°. *Anal.* Calcd for $C_7H_{12}N_2O_2S_2$: C, 38.18; H, 5.45. Found: C, 38.37; H, 5.47. The mass spectrum (70 eV) showed *m/e* 220 (^{32}S ion) with minor peaks (~8%) at 222 (^{34}S ion) and 221 (^{32}S, ^{13}C–^{2}H ion); ir (Nujol) 1640 cm^{-1}.

***N,N'*-Trimethylene-3,3'-dithiodipropionamide (1c).**—Addition of trimethylenediamine (0.64 g, 8.6 mmol) to dimethyl 3,3'-dithiodipropionate (2.00 g, 8.4 mmol) gave a light brown, viscous oil which, after standing for 1.5 hr at 25° and refrigeration overnight, solidified. Trituration with EtOH gave a pale yellow solid (1.77 g, 85%). Recrystallization from hot (90°) dimethylformamide gave a white product (1.39 g, 67%), mp 181–183°. *Anal.* Calcd for $C_9H_{16}O_2N_2S_2$: C, 43.52; H, 6.51. Found: C, 43.31; H, 6.66. The mass spectrum (70 eV) showed *m/e* 248 (^{32}S ion) with additional peaks (10, 10, 15, and 5% intensity, respectively) at 249 (^{32}S, ^{13}C–^{2}H ion), 250 (^{34}S ion), 280 (M + 32 ^{32}S ion), and 284; high-resolution mass spectrum, measured masses *m/e* 248.0656 and 280.0373; calcd mass for $C_9H_{16}O_2N_2S_2$, 248.0652; and for $C_9H_{16}O_2N_2S_3$, 280.0373; ir (Nujol) 1635 cm^{-1}.

***N,N'*-Propylenebismercaptoacetamide (5) and *N,N'*-Propylenedithiodiacetamide (6).**—Methyl mercaptoacetate (8.0 g, 75 mmol) was heated with propylenediamine (2.8 g, 37.5 mmol) at 100° for 5 hr, the disappearance of ester (1735 cm^{-1}) and development of amide (1640 cm^{-1}) carbonyl bands being followed by ir. Removal of a trace of volatile matter under reduced pressure gave the dithiol **5** as a yellow oil [6.88 g (82%), ir 2510 (SH), 1635 cm^{-1}], a portion (0.46 g, 2.0 mmol) of which was converted into its bis-*S*-dinitrophenyl derivative by stirring a solution in water (20 ml) containing $NaHCO_3$ (0.53 g, 6.3 mmol) with fluoro 2,4-dinitrobenzene (0.82 g, 4.4 mmol) for 2 hr at 25°. The yellow precipitate, crystallized from EtOH (20 ml), had mp 227–229°; uv (acetone) λ_{max} 337 nm (ϵ_{max} 25,350). Oxidation of the dithiol **5** (3.25 g, 14 mmol) in water (75 ml) with hydrogen peroxide (3%, 18 ml, 16 mmol), overnight, followed by continuous extraction with $CHCl_3$, gave the disulfide **6** as a white solid (2.24 g, 69%), recrystallized from $CHCl_3$, mp 189–191°. Oxidation of another portion (2.88 g, 12.5 mmol) with I_2–KI solution (0.1 *N*, 130 ml, 13 mmol) followed by continuous extraction with $CHCl_3$ gave pale yellow solid (2.10 g, 73%), recrystallized from $CHCl_3$, mp 188–189°. *Anal.* Calcd for $C_7H_{12}N_2O_2S_2$: C, 38.18; H, 5.45. Found: C, 38.01; H, 5.56. The mass spectrum (70 eV) showed *m/e* 220 (^{32}S ion) with minor peaks (~8%) at 222 (^{34}S ion) and 221 (^{32}S, ^{13}C–^{2}H ion); ir (Nujol) 1635 cm^{-1}. It is noteworthy that **6**, in sharp contrast to the unsubstituted cyclic disulfide diamides, is moderately soluble in water and the common solvents.[10]

***N,N'*-Dimethyl-*N*-*N'*-ethylenebismercaptoacetamide (7) and Presumed *N,N'*-Dimethyl-*N,N'*-ethylenedithiodiacetamide (8).**—A solution of *N,N'*-dimethylethylenediamine (1.35 g, 15 mmol) in pyridine (2.70 g, 34 mmol) was added slowly to an ice-cooled solution of acetylthioacetyl chloride (5.16 g, 33 mmol) in $CHCl_3$ (15 ml). The milky solution was heated under reflux for 2 hr, kept at 5° overnight, and filtered, and the filtrate was washed successively with 3 *N* HCl, water, and 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude bisacetylthioacetamide as a colorless oil (4.10 g, 85%), ir 1690 (–COS–), 1640 cm^{-1} (–CONH–). Selective hydrolysis of thiolester groups was effected with NaOH (1.02 g) in water (7.2 ml) at 65° during 4.5 hr with stirring. Extraction with $CHCl_3$ followed by evaporation gave crude *N,N'*-dimethyl-*N,N'*-ethylenebismercaptoacetamide (**7**) as a colorless oil (2.2 g, 62% overall), ir 1640 (–CONH–), 2530 cm^{-1} (–SH). The bis-*S*-dinitrophenyl derivative, prepared as usual and recrystallized from EtOH, had mp 195–197°, uv (acetone) λ_{max} 335 nm (ϵ_{max} 21,700). *Anal.* Calcd for $C_{20}H_{20}N_8O_{10}S_2$: C, 42.25; H, 3.52. Found: C, 42.38; H, 3.63. The crude dithiol (2.00 g, 8.5 mmol), dissolved in water (60 ml), was treated with 0.1 *N* I_2–KI until a faint yellow color persisted. Continuous extraction with $CHCl_3$ followed by evaporation gave presumed *N,N'*-dimethyl-*N,N'*-ethylenedithiodiacetamide as a colorless oil (1.50 g, 74%) which did not crystallize. The mass spectrum (70 eV) showed *m/e* 234 (^{32}S ion) with minor peaks (~8%) at 236 (^{34}S ion) and 235 (^{32}S, ^{13}C–^{2}H ion); nmr ($CDCl_3$) τ 6.86 (s, 6 H, 2 CH_3N)), 6.41 (s, 4 H), and 6.20 (s, 4 H).

Registry No.—**1a**, 25286-76-4; **1b**, 37709-50-5; **1c**, 37818-76-1; **2**, 692-93-3; **2** (bis-*S*-dinitrophenyl), 37709-97-0; **5**, 37709-98-1; **5** (bis-*S*-dinitrophenyl), 37709-99-2; **6**, 37710-00-2; **7**, 37709-09-4; **7** (bis-*S*-dinitrophenyl), 37709-10-7; **8**, 37709-11-8; dimethyl dithiodiacetate, 1665-64-1; dimethyl 3,3'-dithiodipropionate, 15441-06-2; ethylenediamine, 107-15-3; methyl mercaptoacetate, 2365-48-2; trimethylenediamine, 109-76-1; acetylthioacetyl chloride, 10553-78-3; *N,N'*-dimethylethylenediamine, 108-00-9; bisacetylthioacetamide, 37709-13-0.

Acknowledgment.—We thank Dr. R. G. Stevenson, Jr., of the Department of Geology, University of South Florida, for providing X-ray powder patterns of α- and β-ethylenedithiodiacetamides.

(10) NOTE ADDED IN PROOF.—Mol wt (osmometric in DMF) 240 (calcd 220) confirms the monomeric nature of this disulfide.

The Removal and Displacement of the Thiazolidine Ring of Penicillin. I. 3-Acylaminoazetidinone and 3-Acylamino-4-phenylthioazetidinone[1]

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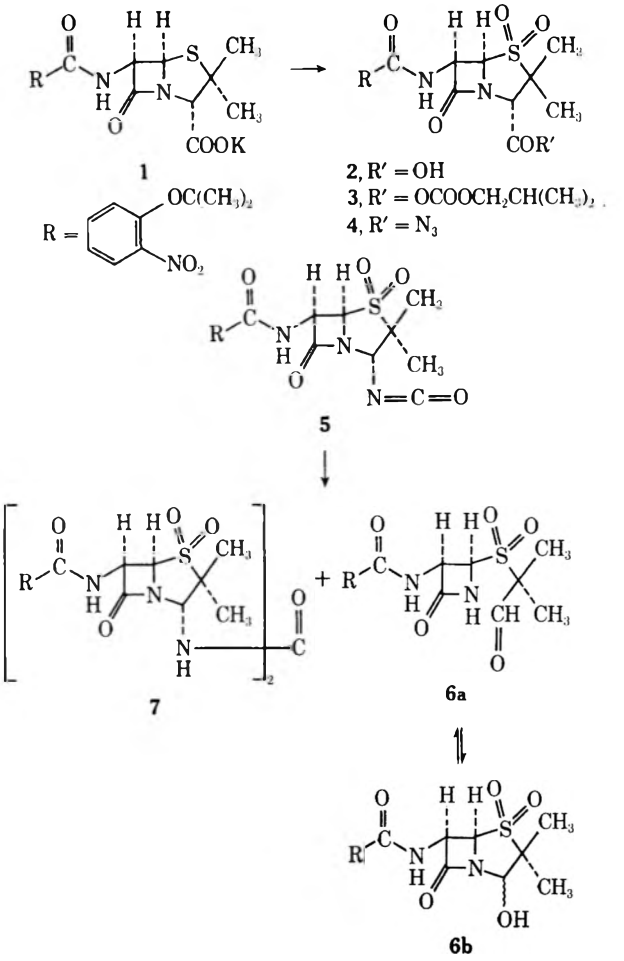
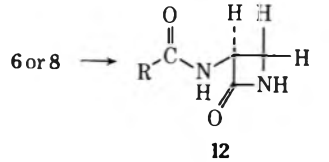
The thiazolidine ring in the penicillin **1** has been removed completely without opening or otherwise affecting the labile β-lactam ring. The key reaction is the removal of the sulfonyl side chain in the "aldehyde" **6** with excess potassium borohydride to afford **12**. Subsequently, the thiazolidine ring has been replaced by the phenylthio group (**9**).

A novel reaction of 4-sulfonyl-2-azetidinones derived from a penicillin has been discovered. Using this reaction, we have replaced and have removed completely the thiazolidine ring of a penicillin while the relatively more labile β-lactam ring was left intact. So far, this is one of the first reported examples of such a transformation. The thiazolidine ring in penicillins has been opened,[2] rearranged,[3] expanded,[4] and replaced.[5] However there appears to be no report of the complete removal of this ring.

Potassium 6-[2-methyl-2-(*o*-nitrophenoxy)propionamido]penicillanate[6] (**1**) was oxidized with potassium permanganate in neutral aqueous solution[7] to the corresponding sulfone, **2**. Compound **2** was then converted to the penamyl isocyanate **5** *via* the mixed anhydride **3** and the acid azide **4**, according to a modification of the method of Perron, *et al.*[8] Following the procedure of Sheehan and Brandt[2b] for the preparation of the 6-phthalimido analog, the acid hydrolysis of the isocyanate afforded 3-(2-methyl-2-(*o*-nitrophenoxy)-propionamido)-4-(1′-formyl-1′-methylethylsulfonyl)-2-azetidinone (**6**). This compound crystallized as a benzene solvate and appeared to exist mainly as the ring-closed form **6b**. Compound **6** slowly formed a 2,4-dinitrophenylhydrazone in aqueous alcoholic sulfuric acid. However, the infrared spectrum of a methylene chloride solution of **6** showed a hydroxyl stretching absorption and the nmr spectrum of a solution in deuteriochloroform contained a peak for the tertiary thiazolidine hydrogen at C-3 in **6b**. The urea **7** was obtained as a by-product in both the preparation of the isocyanate **5** and of the cyclic product (**6**). In contrast to the observations of Sheehan and Brandt[2b] and Heusler,[2h] the tautomeric aldehyde form of **6** (**6a**) was not detected by nmr and infrared analysis.



The remnant of the original thiazolidine ring in **6** was removed completely by the action of a large excess of potassium borohydride in cold aqueous 2-propanol. The crystalline product was shown to be 3-[2-methyl-2-(*o*-nitrophenoxy)propionamido]-2-azetidinone (**12**) by



the following data. Lassaigne's test disclosed that there was no sulfur in the unknown compound. Secondly, the disappearance of the 1310-cm^{-1} sulfone band

(1) This work was assisted financially by Bristol Laboratories, Division of Bristol Myers Co., Syracuse, N. Y.

(2) (a) "The Chemistry of Penicillin," H. T. Clarke, T. R. Johnson, and R. R. Robonson, Ed., Princeton University Press, Princeton, N. J., 1949, p 243; (b) J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, **87**, 5468 (1965); (c) J. C. Sheehan, U. S. Patent 3,487,079 (1969); *Chem. Abstr.*, **72**, 100688k (1969); (d) D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Commun.*, 1683 (1970); (e) R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, **92**, 2575 (1970); (f) K. Heusler and R. B. Woodward, German Patent 1,935,640 (1970); *Chem. Abstr.*, **72**, 100689m (1970); (g) S. Kukolja, *J. Amer. Chem. Soc.*, **93**, 6267 (1971); (h) K. Heusler, *Helv. Chim. Acta*, **55**, 388 (1972).

(3) S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *J. Amer. Chem. Soc.*, **85**, 643 (1963); J. P. Clayton, *J. Chem. Soc. C*, 2123 (1969).

(4) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1856 (1963); **91**, 1401 (1969); R. B. Morin and B. G. Jackson, U. S. Patent 3,275,626 (1966); *Chem. Abstr.*, **65**, 20133d (1966); D. O. Spry, *J. Amer. Chem. Soc.*, **92**, 5006 (1970).

(5) J. C. Sheehan, U. S. Patent 3,487,074 (1969); *Chem. Abstr.*, **72**, 66933z (1969); I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *Chem. Commun.*, 601 (1972).

(6) D. A. Johnson, C. A. Panetta, and R. R. Smith, *J. Org. Chem.*, **31**, 2560 (1966).

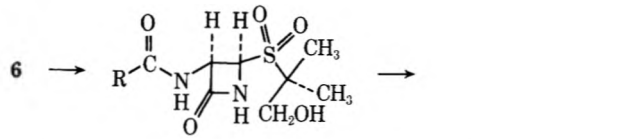
(7) D. A. Johnson, C. A. Panetta, and D. E. Cooper, *ibid.*, **28**, 1927 (1963).

(8) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964).

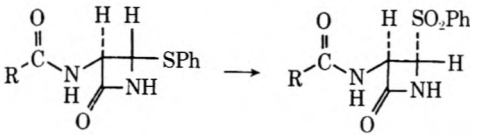
in the infrared spectrum and the shift of the β-lactam carbonyl absorption to a lower wavenumber added to the evidence that the 1-formyl-1-methylethylsulfonyl moiety had been cleaved from the β-lactam ring. Oxidation of the sulfur atom in penicillins to a sulfone has been reported to shift the β-lactam carbonyl absorption in the infrared region to higher wavenumbers.[7] Finally, elemental analyses and a molecular weight determination established the molecular formula and the nmr spectrum confirmed the structure assignment.

The desthioazetidinone **12** has also been prepared by the treatment of **6** with a large excess of lithium tri-*tert*-butoxyaluminum hydride in anhydrous tetrahydrofuran.

When compound **6** was treated with a smaller excess of potassium borohydride than was used in the preparation of **12** and the reaction time was limited to 2 min, the corresponding alcohol, **8**, was produced in quantitative yield. 3-[2-Methyl-2-(*o*-nitrophenoxy)-propionamido]-4-(2′-hydroxy-1′,1′-dimethylethylsulfonyl)-2-azetidinone (**8**) was easily characterized from elemental analysis and spectroscopic data.



8



9, α-SPh, β-H
11, α-H, β-SPh

10

The reaction of **6** with a large excess of potassium borohydride was examined using 20-cm long silica gel-coated glass plates. Starting at zero time and at 5-min intervals thereafter, aliquots of the reaction solution were acidified and spotted on the plates. The resultant chromatograms showed the alcohol **8** to be essentially the sole product during the first 5 min. Thereafter, the concentration of **12** increased while that of the alcohol decreased until 45 min, at which time it disappeared completely. These results have been interpreted to indicate that the alcohol **8** is an intermediate in the transformation of **6** to **12**.

We have replaced successfully the 2-hydroxy-1,1-dimethylethylsulfonyl side chain with the phenylthio group by the reaction of **8** with benzenethiol in aqueous ethanol for 25 min at pH 9.0 and room temperature. The product, 3-[2-methyl-2-(*o*-nitrophenoxy)propionamido]-4-phenylthio-2-azetidinone (**9**), was consonant with the observed elemental analysis and spectral properties. The β-lactam carbonyl absorption in the infrared spectrum shifted to a lower wavenumber than that observed for the alcohol **8**, and the sulfonyl band was absent. The nmr spectrum confirmed the presence of a benzene solvate in the crystalline structure of **9**. The coupling constants of the signals centered at 4.95 and 4.70 ppm indicate that the β-lactam hydrogens are cis in the alcohol **8**[9] and trans in the phenylthioazetidinone **9**.[10]

(9) G. F. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 1595 (1965).

The replacement of the sulfonyl side chain with the phenylthio group also occurred when **6** was treated with sodium thiophenoxide in *N*,*N*-dimethylformamide. However, the reaction was slower and the yield lower than when the alcohol **8** was employed under similar conditions. The product obtained from either precursor was the same (**9**) in all respects.

The filtrates from **9** always contained, in low yield, a second reaction product which had a smaller R_f value on silica gel coated plates. This product was never obtained completely free of **9**, but it was assumed to be the 4 epimer of **9**, **11**.

The phenylthioazetidinone **9** was easily oxidized to 3-[2-methyl-2-(*o*-nitrophenoxy)pripionamido]-4-phenylsulfonyl-2-azetidinone (**10**) by treatment with potassium permanganate in aqueous acetic acid. The coupling constants of the β-lactam hydrogens (2.0 cps) of **10** indicate that it retains the same trans configuration of the unoxidized precursor, **9**.

The phenylsulfonyl group was replaced by the phenylthio group on the β-lactam ring in a reversal of the above oxidation experiment. The *trans*-phenylsulfonylazetidinone **10** was treated with benzenethiol in a manner similar to that used with the alcohol **8**. The product consisted of two components according to thin layer chromatography. Only one of these was isolated in a pure form and crystallized. It was identical with the phenylthioazetidinone **9** with respect to melting point and R_f value.

Experimental Section[11]

6-[2-Methyl-2-(*o*-nitrophenoxy)propionamido]penicillanic Acid Sulfone (2).—A stirred solution of 111 g (0.24 mol) of potassium 6-[2-methyl-2-*o*-nitrophenoxy)propionamido]penicillanate[6] in 1200 ml of cold water was treated with the dropwise addition of a solution of 79.0 g (0.5 mol) of potassium permanganate, 25.9 ml of 85% phosphoric acid, and 2 l. of water until the permanganate color persisted (required about 20 min and about ½ of the permanganate solution). During the above addition, the pH was maintained at 6.0–6.5 by the addition of 10% sodium hydroxide or 10% phosphoric acid. Sodium bisulfite was added in order to destroy excess permanganate and the mixture was filtered through a layer of Standard Super-Cel. Ethyl acetate (1 l.) was added to the filtrate and the resultant mixture was chilled in an ice bath while the pH was adjusted to 2.0 with 6 *N* hydrochloric acid. Two more extractions were made with ethyl acetate (700 and 300 ml) and the combined extracts were washed with water and with aqueous sodium chloride solution. The organic solution was dried over anhydrous magnesium sulfate and concentrated to a volume of 300 ml under reduced pressure. The sulfone **2** crystallized from the concentrate. The mixture was diluted with 2 l. of petroleum ether (bp 37–50°) and stirred for 30 min. The crystalline product was collected by filtration and washed with petroleum ether to yield 96.5 g (88.3%) of a homogeneous solid: tlc R_f 0.3 (benzene/acetone/acetic acid, 60:35:5); mp 153.0–154.0°; ir (CH_2Cl_2) 3370 (NH), 1815 (β-lactam), 1755 (carboxyl), 1690

(10) (a) E. J. Corey and A. M. Felix, *J. Amer. Chem. Soc.*, **87**, 2518 (1965); (b) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 3325 (1965); (c) H. B. Kagan, J. Basselier, and J. Luche, *ibid.*, 941 (1964); (d) I. McMillan and R. J. Stoodley, *ibid.*, 1205 (1966).

(11) Melting points were determined with a Kofler hot-stage microscope. Infrared spectra were recorded on a Perkin-Elmer Model 237 recording spectrophotometer. The nmr spectra were recorded on a Varian A-60. Microanalytical data were supplied by Dr. S. M. Nagy and his associates and by Midwest Microlab, Inc., Indianapolis, Ind. The thin layer chromatograms were run on silica gel G coated (250 μ) glass microscope slides (25 × 75 mm) except where exact R_f values are given, in which case 20-cm plates were used. The zones were detected as yellow areas on a purple background after spraying with a 0.5% aqueous potassium permanganate solution. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 mass spectrometer at 70 eV.

(amide I), 1525 (amide II), 1505 and 1340 (nitro), and 1310 cm^{-1} (sulfone); nmr (acetone-d_6) δ 8.06 (d, 1, NH), m centered at 7.32 (4, aromatic), 6.01 (dd, 1, $J_1 = 4$, $J_2 = 10$ Hz, H-6), 4.84 (d, 1, $J = 4$ Hz, H-5), 4.46 (s, 1, H-3), 1.52, 1.37 (singlets, 12, methyl).

Anal. Calcd for $C_{18}H_{21}N_3O_9S$: C, 47.45; H, 4.64; N, 9.23; S, 7.04. Found: C, 47.65; H, 4.83; N, 9.69; S, 7.65.

2,2-Dimethyl-6-[2-methyl-2-(*o*-nitrophenoxy)propionamido]-1,1-dioxo-3-penamyl Isocyanate (5).—A molecular sieve (type 4A) dried solution of 2.15 g (4.71 mmol) of the penicillin sulfone **2** in 12 ml of tetrahydrofuran was cooled to −5°, and 0.66 ml (0.48 g, 4.71 mmol) of triethylamine and 0.618 ml (0.644 g, 4.71 mmol) of isobutyl chloroformate were added consecutively. After stirring for 50 min at −5°, a cold solution of 0.31 g (4.71 mmol) of sodium azide in 5 ml of water was added dropwise during a 5–15-min period. Cold water (40 ml) was added and the resultant mixture was extracted with three portions (40, 15, and 5 ml) of benzene. The benzene solution was dried over molecular sieves (type 4A) and anhydrous magnesium sulfate and the filtrate was heated to reflux for 20 min. The solvent was removed under reduced pressure, leaving 1.28 g (60%) of a yellow glass. Crystallization from benzene gave a solvated solid with a diffuse melting point. Recrystallization from chloroform–benzene gave a sharp melting point (131–133°): $[\alpha]^{25}D$ 12.7° (*c* 1, $CHCl_3$); ir (Nujol) 3570 (water), 3395 (NH), 2260 (thiocyanate), 1810 (β-lactam), 1695 (amide I), 1520 (amide II), 1510 and 1360 (nitro), 1320 (sulfone), and 1250 cm^{-1} (phenoxy); nmr (acetone-d_6) δ 8.25 (d, 1, NH), m centered at 7.5 (4, aromatic), 6.10 (dd, 1, $J_1 = 4.5$, $J_2 = 11$ Hz, H-6), 5.37 (s, 1, H-3), 5.9 (d, 1, $J = 5$ Hz, H-5), 1.63, 1.50, 1.45 (singlets, 12, CH_3).

Anal. Calcd for $(C_{18}H_{20}N_4O_8S)_2 \cdot H_2O$: C, 46.90; H, 4.58; N, 12.12; S, 6.95. Found: C, 46.73; H, 4.37; N, 11.85; S, 7.02.

***N,N'*-Bis[2,2-dimethyl-6-[2-methyl-2-(*o*-nitrophenoxy)propionamido]-1,1-dioxo-3-penamyl]urea (7).**—In some preparations of the penamyl isocyanate **5**, the glassy yellow product did not completely dissolve in hot benzene. When this happened, the insoluble material was separated and crystallized from ethyl acetate: mp 198–200°; ir (Nujol) 3620 and 3540 (water), 3360 and 3390 (NH), 1810 (β-lactam), 1700–1865 (amide I and urea), 1550 (amide II), 1510 and 1350 (nitro), 1330 (sulfone), and 1255 cm^{-1} (phenoxy).

Anal. Calcd for $C_{35}H_{42}N_8O_{15}S_2 \cdot H_2O$: C, 46.90; H, 4.94; N, 12.50; S, 7.14. Found: C, 46.98; H, 4.72; N, 12.31; S, 6.83.

3-[2-Methyl-2-(*o*-nitrophenoxy)propionamido]-4-(1'-formyl-1'-methylethylsulfonyl)-2-azetidinone (6).—A solution of 13.9 g (0.0292 mol) of the penamyl isocyanate **5** in 370 ml of tetrahydrofuran was added dropwise during a 3.5-hr period to a stirred solution of 29.2 ml of 1 *N* hydrochloric acid in 300 ml of water and 300 ml of tetrahydrofuran. The resultant solution was stirred for 40 min and extracted with 3 × 370 ml of methylene chloride. The extract was washed with 2 × 250 ml of water and dried. Removal of the solvent under reduced pressure afforded a yellow glass, which crystallized from 70 ml of benzene. The total yield of two crystalline fractions was 12.8 g (86.4%). Two recrystallizations from chloroform–benzene gave an analytical sample: mp 87°, resolidified and melted again at 125–127°; $[\alpha]^{25}D$ 77.8° (*c* 1, $CHCl_3$); tlc R_f 0.5 (benzene–ethyl acetate, 1:1); ir (Nujol) 3370 (NH), 1800 (β-lactam), 1680 (amide II), 1525 (amide II), 1510 and 1360 (nitro), 1310 (sulfone), and 1245 cm^{-1} (phenoxy); ir (CH_2Cl_2) 3525 cm^{-1} (OH); nmr ($CDCl_3$) δ 8.30 (d, 1, NH), m centered at 7.35 (10, aromatic and solvate), 6.05 (dd, 1, $J_1 = 4.5$, $J_2 = 10$ Hz, H-6), 4.90 (d, 1, $J = 4$ Hz, H-5), 5.32 (d, 1, $J = 5.5$ Hz, H-3), 4.65 (d, 1, $J = 5.5$ Hz, OH), 1.60, 1.40 (singlets, 12, methyl); mass spectrum *m/e* 292 [M − $SO_2C(CH_3)_2CHO$].

Anal. Calcd for $C_{17}H_{21}N_3O_8S \cdot C_6H_6$: C, 54.65; H, 5.38; N, 8.31; S, 6.34. Found: C, 54.59; H, 5.35; N, 8.38; S, 6.23.

A sample of **6** was treated with 2,4-dinitrophenylhydrazine in aqueous, alcoholic sulfuric acid for 2 hr at room temperature. Yellow crystals separated and were collected, mp 197–200°, tlc R_f 0.4 (benzene–ethyl acetate, 1:1). The infrared spectrum showed bands in the proper region for NH stretching, β-lactam, amide, nitro, and sulfone absorptions.

3-[2-Methyl-2-(*o*-nitrophenoxy)propionamido]-2-azetidinone (12). A. Using Potassium Borohydride.—A cold solution of 0.10 g (0.198 mmol) of **6** in 6.0 ml of 2-propanol was added in two or three portions to a stirred solution of 0.056 g (1.04 mmol) of potassium borohydride[12] in 5.0 ml of 2-propanol and 5.0 ml of water at 5°. The solution was stirred in an ice bath for 25 min, the pH was adjusted to 7, and 25 ml of water was added. The resultant solution was extracted with 3 × 20 ml of methylene chloride and the extracts were combined, washed with 2 × 15 ml of water, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a colorless glass (62.7 mg) which slowly crystallized from a mixture of benzene and petroleum ether, 8.6 mg. Two recrystallizations of another sample afforded material suitable for analysis: mp 151.5–152.5°; $[\alpha]^{25}D$ −34.0° (c 0.7, $CHCl_3$); tlc R_f 0.34–0.35 (ethyl acetate); qualitative tests following sodium fusion[13] showed no sulfur present; ir (Nujol) 3325 and 3250 (NH), 1770 (β-lactam), 1670 (amide I), 1545 (amide II), and 1515 and 1340 cm^{-1} (nitro); nmr (acetone-d_6) δ 8.5–7.1 (m, 5, aromatic and NH), 5.1 (broad m, 1, H-3), 3.4 (m, 2, H-4), 1.65, 1.58 (singlets, 6, CH_3); mass spectrum *m/e* 264 (M − CH_2NH_2), 250 (M − CONH).

Anal. Calcd for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.16; N, 14.33; mol wt, 293. Found: C, 52.98; H, 5.14; N, 14.03; mol wt (in dioxane freezing), 285, 289.

B. Using Lithium Tri-*tert*-butoxyaluminum Hydride.—A solution of 0.20 g (0.396 mmol) of **6** in 10 ml of dry tetrahydrofuran was stirred at −5° while a solution of 1.02 g (4.0 mmol) of lithium tri-*tert*-butoxyaluminum hydride[12] in 20 ml of dry tetrahydrofuran was added in two portions. After the solution was stirred cold for 30 min, 1.0 ml of ethanol was added. Almost all of the tetrahydrofuran was evaporated and the residue was treated with 20 ml of benzene and anhydrous magnesium sulfate. The mixture was filtered through Standard Super-Cel and the filtrate was concentrated *in vacuo* to a yellow solid, 49.7 mg. Crystallization from benzene and petroleum ether gave 5.2 mg. The infrared spectrum of this substance was identical with that of the desthioazetidinone **12**.

3-[2-Methyl-2-(*o*-nitrophenoxy)propionamido]-4-(2'-hydroxyl-1',1'-dimethylethylsulfonyl)-2-azetidinone (8).—A cold (5°) solution of 0.117 g (2.16 mmol) of potassium borohydride[12] in 100 ml of water and 100 ml of methanol was added in one portion to a stirred and cooled (5°) solution of 2.19 g (4.34 mmol) of **6** in 100 ml of methanol. After exactly 2.0 min, the pH was adjusted to 2.0 (6 *N* hydrochloric acid) and 450 ml of water was added. The mixture was extracted with 3 × 120 ml of methylene chloride and the organic solution was washed with 2 × 90 ml of water and dried. The methylene chloride was evaporated and the residual glass, which was entirely the alcohol **8** according to thin layer chromatography, was obtained in almost quantitative yield, 1.86 g (99.6%). Recrystallization from benzene gave an analytical sample: mp 176.0–176.5°; $[\alpha]^{25}D$ 54.1° (*c* 1, $CHCl_3$); tlc R_f 0.21–0.23 (ethyl acetate); ir (CH_2Cl_2) 3560 (OH), 3365 (NH), 1810 (β-lactam), 1695 (amide I), 1525 (amide II), 1515 and 1345 (nitro), and 1290 cm^{-1} (sulfone); nmr ($CDCl_3$) δ 6.9–8.1 (m, 6, NH and aromatic), 5.9 (dd, 1, $J_1 = 5$, $J_2 = 10$ Hz, H-6), 5.15 (d, 1, $J = 5$ Hz, H-5), 3.75 (d, 2, $J = 7$ Hz, CH_2), 3.5 (broad s, 1, OH), 1.65, 1.57, 1.39, 1.31 (singlets, 12, methyl); mass spectrum *m/e* 292 [M − $SO_2C(CH_3)_2CH_2OH$].

Anal. Calcd for $C_{17}H_{23}N_3O_8S$: C, 47.50; H, 5.39; N, 9.78; S, 7.47. Found: C, 47.64; H, 5.49; N, 9.60; S, 7.38.

3-[2-Methyl-2-(*o*-nitrophenoxy)propionamido]-4-phenylthio-2-azetidinone (9). A. From the Alcohol 8.—A solution of 0.22 g (0.50 mmol) of the alcohol **8** in 20 ml of ethanol and 10 ml of water was treated with 0.051 ml (0.055 g, 0.50 mmol) of benzenethiol and the pH was adjusted to and maintained at 9.0–9.5 (1 *N* sodium hydroxide). Nitrogen was bubbled through the solution. After 26 min, 65 ml of water was added and the resultant mixture was extracted with 3 × 40 ml of methylene chloride. The organic solution was washed with 2 × 25 ml of water and dried. The solvent was evaporated and the residual oil was crystallized from 5 ml of benzene to yield 0.102 g (51%) of product. Recrystallization from benzene gave a solvated solid with diffuse melting point. Recrystallization from chloroform–benzene gave a sharp melting point (81.5–83°); $[\alpha]^{25}D$ −98.3° (c 1, $CHCl_3$); ir (CH_2Cl_2) 3395 (NH), 1795 (β-lactam), 1695 (amide I), 1530 (amide II), and 1515 and 1345 cm^{-1} (nitro); nmr ($CDCl_3$) δ 6.8–7.9 (m, benzene solvate, aromatic and NH), 4.95 (d, 1, $J = 2$ Hz, H-5), 4.7 (dd, 1, $J_1 = 2$, $J_2 = 8$ Hz, H-6), 1.54, 1.58 (singlets, 6, methyl); mass spectrum *m/e* 401 (M^+).

(12) Obtained from Metal Hydrides, Inc., Beverly, Mass.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, pp 57–58.

Anal. Calcd for $C_{19}H_{19}N_3O_5S \cdot 0.5C_6H_6$: C, 60.00; H, 5.03; N, 9.54; S, 7.28. Found: C, 60.22; H, 4.92; N, 9.33; S, 7.20.

B. From the Aldehyde 6.—A solution of 0.51 g (1.0 mmol) of **6**, 0.13 g (1.0 mmol) of sodium thiophenoxide,[14] and 1.0 ml of *N*,*N*-dimethylformamide was stirred for 40 min. Water (25 ml) was added and the resulting mixture was extracted with 3 × 10 ml of methylene chloride. The methylene chloride solution was washed with 2 × 7 ml of water and dried. The solvent was evaporated and residual oil was chromatographed on a silicic acid (100 mesh) column with ethyl acetate. The effluent was separated into a homogeneous fraction which crystallized from a mixture of benzene and petroleum ether after a seed of the phenylthioazetidinone **9** was added, 87.6 mg (19.9%), tlc R_f was identical with that of **9** in ethyl acetate.

C. From the *trans*-Phenylsulfonylazetidinone 10.—A stirred solution of 0.284 g (0.656 mmol) of *trans*-phenylsulfonylazetidinone **10** (see below for preparation), 0.067 ml (0.072 g, 0.66 mmol) of benzenethiol, 20 ml of ethanol, and 10 ml of water was prepared under nitrogen. The pH was held at 9.0 (1 *N* sodium hydroxide) for 40 min. Water (65 ml) was added and the mixture was extracted with 3 × 40 ml of methylene chloride. The organic solution was washed with 2 × 25 ml of water, dried, and evaporated under reduced pressure. The residue (85.3 mg) contained two components according to thin layer chromatography (benzene–ethyl acetate, 1:1). Only one of these was obtained pure by chromatography on a 2-mm thick silica gel coated plate (Brinkmann Instruments) (same solvent as above). Crystallization from benzene gave 8.9 mg, mp 76.0–78.5°; tlc R_f was the same as that of the phenylthioazetidinone **9**.

trans-**3-[2-Methyl-2-(*o*-nitrophenoxy)propionamido]-4-phenylsulfonyl-2-azetidinone (10).**—A solution of 0.88 g (5.6 mmol) of potassium permanganate in 8.4 ml of water was added dropwise over a 10-min period to a solution of 1.23 g (2.8 mmol) of phenylthioazetidinone **9** in 20 ml of 80% acetic acid. The resultant mixture was stirred for 45 min, and 30% hydrogen peroxide was added until all color was discharged. Water (100 ml) was added and the mixture was extracted with three portions (80, 40, 40 ml) of methylene chloride. The organic solution was washed with 2 × 20 ml of water and dried. The methylene chloride was removed and the residual oil was slowly crystallized from benzene. This was recrystallized from benzene–ethanol (4:1) to yield the pure trans isomer, **10**: 0.33 g; mp 158.0–159.0°; $[\alpha]^{25}D$ −32.5° (c 1, $CHCl_3$); tlc R_f 0.59 (benzene–ethyl acetate, 1:1); ir (CH_2Cl_2) 3395 (NH), 1815 (β-lactam), 1695 (amide I), 1525 (amide II), 1150 and 1335 (nitro), and 1300 cm^{-1} (sulfone); nmr (acetone-d_6) δ 6.9–8.7 (m, 11, aromatic and amide), 5.0–5.4 (dd overlapped by d, 2, J_1 of dd = 2 Hz, H-5 and H-6), 1.52, 1.49 (singlets, 6, methyl).

Anal. Calcd for $C_{10}H_{10}N_3O_7S$: C, 52.65; H, 4.42; N, 9.70; S, 7.37. Found: C, 52.41; H, 4.47; N, 9.56; S, 7.43.

Registry No.—**1**, 10514-63-3; **2**, 37696-07-4; **5**, 37696-08-5; **6b**, 37696-09-6; **6** 2,4-DNPH, 37696-10-9; **7**, 37818-75-0; **8**, 37696-11-0; **9**, 37755-01-4; **10**, 37755-02-5; **12**, 37696-12-1.

(14) Prepared from benzenethiol and sodium methoxide in anhydrous methanol. Addition of ether caused separation of the product.

Synthesis of 6-Methylthiopenicillins and 7-Heteroatom-Substituted Cephalosporins

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A number of 6α-methylthiopenicillins and 7α-methylthiocephalosporins have been prepared from intermediates obtained by methylthiolation of Schiff bases of 6-aminopenicillanic acid esters and 7-aminocephalosporanic acid esters. Fluorination with perchloryl fluoride gave a 7α-fluorocephalosporin Schiff base that could be solvolyzed to 7α-methoxy- and 7α-methylthiocephalosporin intermediates. The same 7α-methoxycephalosporin Schiff base intermediate could be obtained by mercuric acetate catalyzed methanolysis of the corresponding 7α-methylthio Schiff base. Reaction of a 7α-methylthiocephalosporin with mercuric acetate in methanol gave a mixture of 7α- and 7β-methoxycephalosporins from which pure 7β-methoxy epimer could be isolated. The same reaction with methanol replaced by dimethoxyethane or acetic acid yielded a 7α-acetoxycephalosporin. Nuclear Overhauser studies performed on the 7-substituted cephalosporins led to assignments of configuration at C-7, which were supported by single-crystal X-ray analysis of 7α-methylthio-7-phenylacetamidodeacetoxycephalosporanic acid *tert*-butyl ester.

Previous investigations have shown that neither the introduction of a 7α-methyl group into a cephalosporin nor of a 6α-methyl group into a penicillin results in improved antimicrobial activity.[1,2] Similar results were found when the 7(6)-α-methyl substituents were replaced by α-acetyl groups.[3] As part of the biological study of cephalosporins and penicillins possessing substituents at the C-7(6) position, it seemed reasonable for us to examine the effects of electron-withdrawing substituents other than acetyl. Heteroatom substituents were an obvious choice; thus, we report now our synthesis of 7-acetoxy-, 7-methoxy-, and 7-methylthiocephalosporins and 6-methylthiopenicillins.[4] Key compounds and the general synthetic schemes are outlined below (1).

The methylthio group was introduced stereospecifically into the 7 position of the Δ^3-cephem nucleus by two routes. Using a one-step method, the anion of the benzaldehyde Schiff base (I) of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester, prepared by using 1 equiv of KO-*t*-Bu in dimethoxyethane at −20°, was methylthiolated with methyl methanethiolsulfonate ($CH_3SSO_2CH_3$)[5] or methylsulfenyl chloride (CH_3SCl)[5] to give the crystalline 7α-methylthio Schiff base II in 40% yield. In an alternative procedure, the anion of the Schiff base I was fluorinated, using perchloryl fluoride, to give the 7α-fluoro Schiff base III, which could be solvolyzed with methanethiol under acidic conditions to the 7α-methylthio Schiff base II. Schiff bases ob-

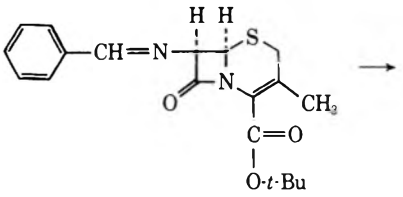
(1) E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).

(2) R. A. Firestone, N. Scheleehow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

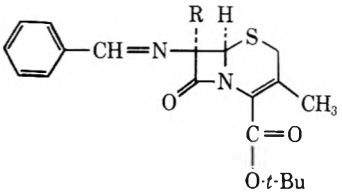
(3) E. H. W. Bohme, H. E. Applegate, J. B. Ewing, P. T. Funke, M. S. Puar, and J. E. Dolfini, *J. Org. Chem.*, **38**, 230 (1973).

(4) During these studies, there appeared reports of 7-methoxycephalosporins obtained from fermentations[4a,b] and by an elegant synthesis[4c] of these and related analogs: (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971); (b) S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *ibid.*, **94**, 1410 (1972); (c) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *ibid.*, **94**, 1408 (1972).

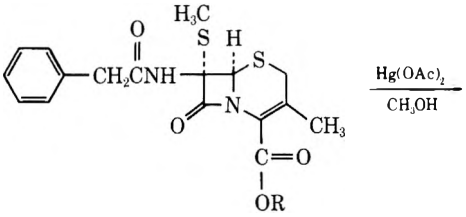
(5) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959).



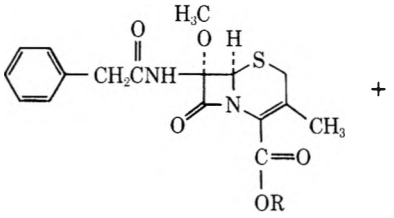
I



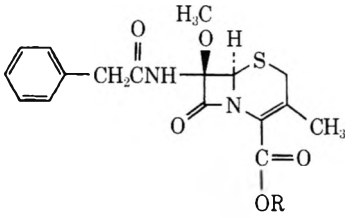
II, R = SCH_3
III, R = F
IV, R = OCH_3



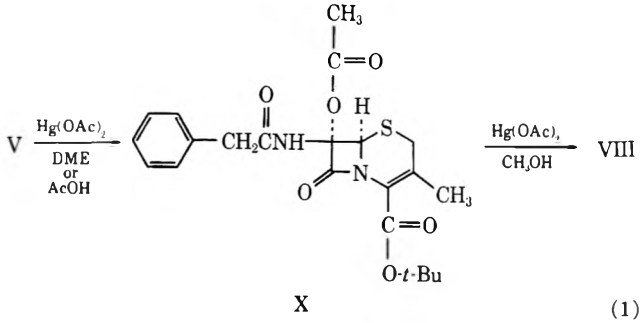
V, R = $C(CH_3)_3$
VI, R = H



VII, R = $C(CH_3)_3$



VIII, R = $C(CH_3)_3$
IX, R = H



X (1)

tained by either method were found to be identical by pmr, ir, and tlc comparisons. Direct acylation of the Schiff base II, using phenylacetyl chloride and water in dichloromethane, provided the amide V; subsequent removal of the *tert*-butyl protecting group with trifluoroacetic acid afforded 7α-methylthio-7-phenylacetamidodeacetoxycephalosporanic acid (VI).

Evidence that the methylthio group was introduced from the less hindered side of the Schiff base I, the α side, and that the methylthio group is as shown in II was obtained by single-crystal X-ray analysis of the 7-methylthio-7-phenylacetamido-Δ^3-cephem V. The X-ray determination indicated that the methylthio group is cis to the C-6 proton in the Δ^3-cephem V and, since the conversion of the methylthio Schiff base II to the Δ^3-cephem V involves no reaction at the 7 position, the methylthio group must also be cis to the C-6 proton in the Schiff base II.

In addition to the X-ray analysis, nuclear Overhauser effect (NOE) studies[6] were performed on the Δ^3-cephem V. Double irradiation of the methylthio protons showed a 5% NOE for the C-6 proton, whereas double irradiation of the amide NH gave a 0% NOE for the C-6 proton. These findings were consistent with those of the X-ray determination; nuclear Overhauser effect studies were used to assign structures to other new C-7 substituted cephalosporins (Table II).

In one approach to 7α-methoxy-7-phenylacetamidodeacetoxycephalosporanic acid, the 7α-methylthio cephem V was solvolyzed with methanol in the presence of 1 equiv of mercuric acetate, yielding essentially a quantitative conversion to a mixture of 7-methoxy epimers, VII and VIII. On the basis of nuclear Overhauser effect studies, the epimer obtained in yields of 10–30% was assigned structure VII, having the 7α-methoxy substituent, whereas the epimer obtained in 70–90% yield was assigned structure VIII, possessing the 7β-methoxy configuration. The 7β-methoxy epimer VIII could be isolated readily in yields of 50% or more by fractional crystallization. The 7α-methoxy epimer VII, however, was not obtained as a single component, but as a mixture consisting of 7α-methoxy epimer (75%) and 7β-methoxy epimer (25%), after partial removal of 7β-methoxy epimer, either by repeated preparative tlc on silica gel or by crystallization. When silver tetrafluoroborate was substituted for mercuric acetate, only the 7β-methoxy epimer VIII was isolated (44% yield). Treatment of the 7β-methoxy epimer VIII with trifluoroacetic acid gave the Δ^3-cephem acid IX, in 90% acid yield, which could be isolated from acetone–hexane as a crystalline product containing one acetone per equivalent of acid.

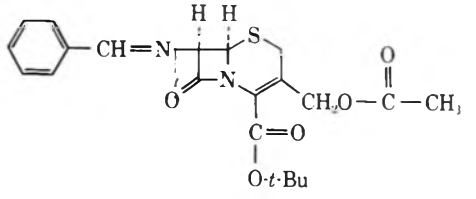
In a second approach to the 7α-methoxy-7-phenylacetamidodeacetoxycephalosporanic acid, the 7α-fluoro Schiff base III was solvolyzed with methanol to give the Schiff base IV, which was assigned the 7α-methoxy configuration by analogy with the methanethiol solvolysis of the fluoro Schiff base III, which yielded the 7α-methylthio Schiff base II. The 7α-methoxy Schiff base IV was obtained alternatively in 74% yield from the 7α-methylthio Schiff base II by methanolysis in the presence of mercuric acetate.

As mentioned previously, methanolysis of the 7α-methylthiocephem V in the presence of mercuric acetate leads to a mixture of 7-methoxy epimers VII and VIII. However, treatment of the Δ^3-cephem V with 1 equiv of mercuric acetate not in the presence of methanol, but in the presence of dimethoxyethane or acetic acid, for 20 min at room temperature, afforded a quantitative conversion to an acetoxy compound that was assigned structure X. Although the oily acetoxy com-

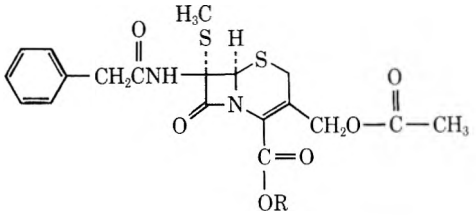
(6) R. A. Bell and J. K. Saunders, *Chem. Rev.*, **71**, 617 (1971).

pound could not be crystallized, its spectral properties (pmr and ir) were consistent with structure X, and the results of nuclear Overhauser effect studies were in agreement with the 7α-acetoxy configuration. Attempted removal of the *tert*-butyl protecting group from the acetoxy compound, using trifluoroacetic acid at 0°, gave a complex mixture of acidic components that could not be readily separated. Treatment of the acetoxy compound with methanol and 1 equiv of mercuric acetate at room temperature, however, gave the 7β-methoxy cephem VIII in quantitative yield. Spectral (pmr and ir) and mixture melting point comparisons of this product with the 7β-methoxycephem VIII, obtained by mercuric acetate methanolysis of 7α-methylthio cephem V, revealed no differences between the samples.

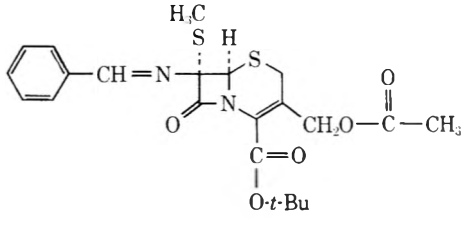
The 7α-methylthiocephalosporanic acid XIV was prepared by procedures similar to those described for the synthesis of the 7α-methylthiodeacetoxycephalosporanic acid VI. Treatment of the Schiff base XI with potassium *tert*-butoxide and methyl methanethiolsulfonate gave the expected methylthio Schiff base XII, whose configuration at C-7 is assigned, as shown, by analogy with the direction of methylthiolation of the deacetoxycephalosporin Schiff base I. Direct acylation of XII, using phenylacetyl chloride–water (10% excess) in dichloromethane and subsequent removal of the *tert*-butyl protecting group with trifluoroacetic acid gave, finally, the 7α-methylthiocephalosporanic acid (XIV).



XI

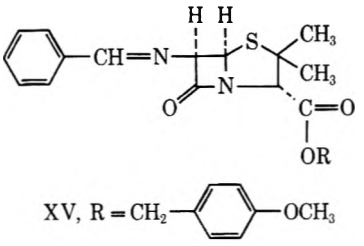


XIII, R = $C(CH_3)_3$
XIV, R = H

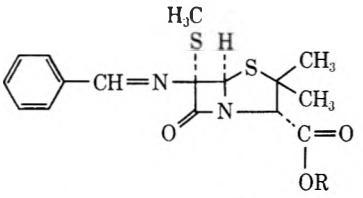


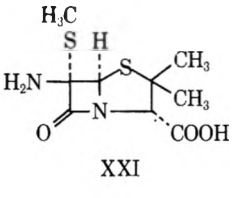
XII

In an initial approach to the synthesis of 6-methylthiopenicillins, the Schiff base XV of 6-aminopenicillanic acid *p*-methoxybenzyl ester was methylthiolated with potassium *tert*-butoxide and methyl methanethiolsulfonate to give, in 95% yield, the 6α-methylthio Schiff base XVIII, whose configuration at C-6 is assigned by analogy with alkylation and acylation reactions of penicillin Schiff bases that have been shown to occur



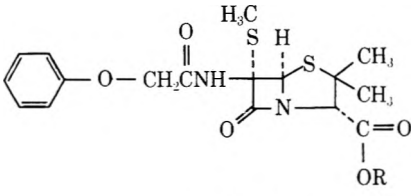
XV, R = CH_2—OCH_3
XVI, R = $Si(CH_3)_3$
XVII, R = H



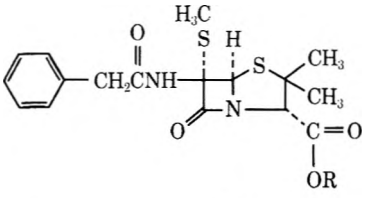


XXI

XVIII, R = CH_2—OCH_3
XIX, R = $Si(CH_3)_3$
XX, R = H



XXII, R = CH_2—OCH_3
XXIII, R = H
XXIV, R = $Si(CH_3)_3$



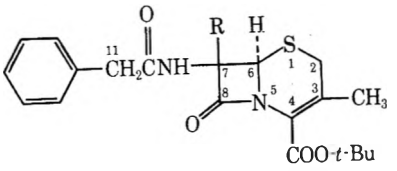
XXV, R = CH_2—OCH_3
XXVI, R = H
XXVII, R = $Si(CH_3)_3$

from the α side. Direct acylation of XVIII with phenoxyacetyl chloride or phenylacetyl chloride gave the amides XXII and XXV, respectively, which could not be readily hydrogenolyzed to the corresponding free acids.

The 6α-methylthiopenicillanic acids XXIII and XXVI were prepared by an alternative approach, utilizing the trimethylsilyl group as a protecting agent. Treatment of the Schiff base XVII of 6-aminopenicillanic acid, sequentially, with equimolar amounts of potassium *tert*-butoxide, trimethylsilyl chloride, potassium *tert*-butoxide, and methyl methanethiolsulfonate gave 6α-methylthio-6-aminopenicillanic acid (XXI) in 23% yield, along with the 6α-methylthio Schiff base XX in 19% yield. Acylation of the *N*,*O*-bistrimethylsilyl derivative of XXI with phenoxyacetyl chloride or phenylacetyl chloride gave after hydrolysis and acidification the corresponding 6α-methylthiopenicillanic acids XXIII and XXVI in yields of 38 and 78%, re-

TABLE I

NMR DATA ($CDCl_3$, τ) FOR CEPHALOSPORIN *tert*-BUTYL ESTERS[a]



Compd	R Group	H-6	R-7	H-2[b]	H-11	NH	C-3 Methyl
V	SCH_3	5.08	7.75	6.82, 6.72	6.34	3.64	7.87
VII	OCH_3	4.86	6.58	6.86, 6.68	6.37	~2.77[c]	7.92
VIII	OCH_3	4.98	6.55	6.90, 6.72	6.32	3.40	7.89
X	$OCOCH_3$	4.90	7.93	7.04, 6.92	6.34	~2.9[c]	7.88

[a] Measurements were made using a Varian XL-100 nmr spectrometer; tetramethylsilane was used as an internal standard. [b] AB quartet (J = 18.0 Hz). [c] NH signal is under phenyl resonance.

spectively. Although the acids XXIII and XXVI and the Schiff base acid XX were amorphous and, therefore, difficult to analyze, their spectral properties (pmr and ir) and the mass spectra of their trimethylsilyl esters were consistent with the assigned structures.

Assignment of Configurations.—Single-crystal X-ray analysis of needles of 7-methylthio-7-phenylacetamidodeacetoxycephalosporanic acid *tert*-butyl ester that had been recrystallized from methanol indicated that they were of the monoclinic space group $P2_1$, having unit cell parameters a = 10.18 Å, b = 5.84 Å, c = 18.54 Å, β = 95°27′, two molecules per unit cell. A Patterson map was used to locate the two sulfur atoms, and Fourier maps were used to locate other atoms. An R factor of 0.20 for the 1600 nonzero reflections was obtained without any refinement, thereby establishing the absolute configuration of the molecule that verified the suspected cis relationship for the methylthio group at C-7 and the proton at C-6.

In addition to the X-ray study of the 7-methylthiocephem V, nuclear magnetic resonance measurements were used to determine the stereochemical relationships at C-6 and C-7 in the Δ^3-cephems synthesized. Pmr assignments for the Δ^3-cephems V, VII, VIII and X are shown in Table I; corresponding nuclear Overhauser effect data are given in Table II. Nuclear Overhauser effects for the C-6 proton in the methylthiocephem V after double irradiation of the methylthio protons and the amide protons have already been discussed. The assignment of the cis relationship to the 7-acetoxy and the C-6 proton, as shown in structure X, is based on findings similar to those found for the methylthiocephem V. Double irradiation of the acetoxy protons gave a 13% NOE for the C-6 proton, which is consistent with the acetoxy group being cis to the C-6 proton; yet, in the case of a group such as acetoxy, this finding does not exclude entirely the possibility of a trans acetoxy C-6 proton relationship. Double irradiation of the amide proton, on the other hand, showed a 0% NOE for the C-6 proton, which is consistent only with the amido group being trans to the C-6 proton and the acetoxy group, therefore, being cis.

TABLE II

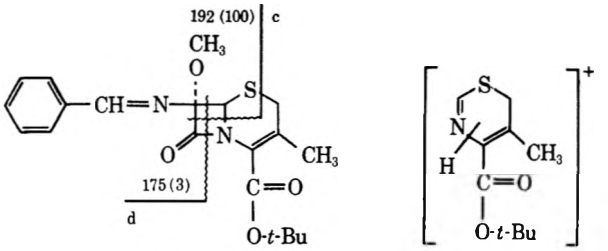
NUCLEAR OVERHAUSER EFFECT DATA[a]

Compd	R Group	Group irradiated	% Enhancement of C-6 proton	Stereochemical assignment of C-6 H and C-7 R
V	SCH_3	SCH_3 at 7.75	5	α cis
V	SCH_3	NH at 3.64	0	β trans
VII[b]	OCH_3	OCH_3 at 6.58	14	α cis
VII[b]	OCH_3	NH at 2.77	1	β trans
VIII	OCH_3	OCH_3 at 6.55	5	β trans
VIII	OCH_3	NH at 3.40	10	α cis
X	$OCOCH_3$	$OCOCH_3$ at 7.93	13	α cis
X	$OCOCH_3$	NH at 2.90	0	β trans

[a] The nuclear Overhauser effect measurements were carried out on deoxygenated, sealed $CDCl_3$ solutions containing tetramethylsilane as an internal standard. The nmr spectrometer (Varian XL-100-15) was internally locked to ^2H of the solvent. The C-6 protons of the cephalosporins were integrated at least ten times with maximum irradiation of the C-7 substituent protons or the amido protons. The irradiating frequency was moved 30 Hz off resonance and the procedure was repeated.[6] [b] This data was obtained on a mixture (60:40) of VII and VIII.

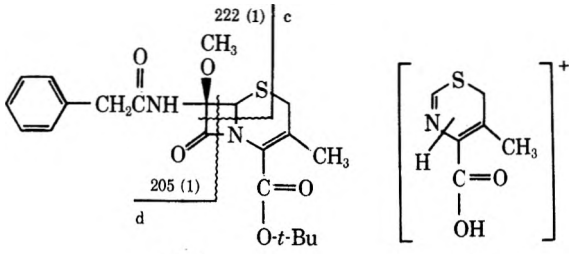
The stereochemical assignments of the 7-methoxy epimers VII and VIII were made by comparison of the respective NOEs obtained for the C-6 protons after saturation of the methoxy proton and amide proton resonances. Two samples of 7-methoxy epimers were examined. One contained the more adundant epimer, the crystalline one, and the other contained both the noncrystalline and crystalline epimers (noncrystalline: crystalline 60:40). As shown in Table II, the crystalline epimer gave 5 and 10% NOEs for the methoxy–C-6 proton and amide proton–C-6 proton interactions, respectively, whereas the noncrystalline epimer gave 14 and 1% NOEs for the same interactions, respectively. A 10% NOE for the amide proton–C-6 proton interaction in the crystalline epimer strongly suggests that the methoxy group is trans to the C-6 proton in this epimer. A 0% NOE should be expected for the amide proton–C-6 proton interaction in the epimer where the methoxy group is cis to the C-6 proton; however, errors of ±3% in the determination of NOEs are quoted in the literature, and, in the measurement of NOEs for the noncrystalline epimer using the 60:40 mixture, the error might be even higher because of difficulties inherent in the integration. The order of the NOEs is consistent, however, with assignment of the trans methoxy structure VIII for the crystalline epimer and the cis methoxy structure VII for the noncrystalline epimer.

The mass spectral fragmentation patterns of the 7-heteroatom-substituted Schiff bases were found to differ considerably from those of the corresponding 7-substituted 7-phenylacetamido compounds, as illustrated by differences in intensities for molecular ions and for frag-



IV a

M^+ 388 (20)
a 214 (1)
b 158 (4)



VIII b

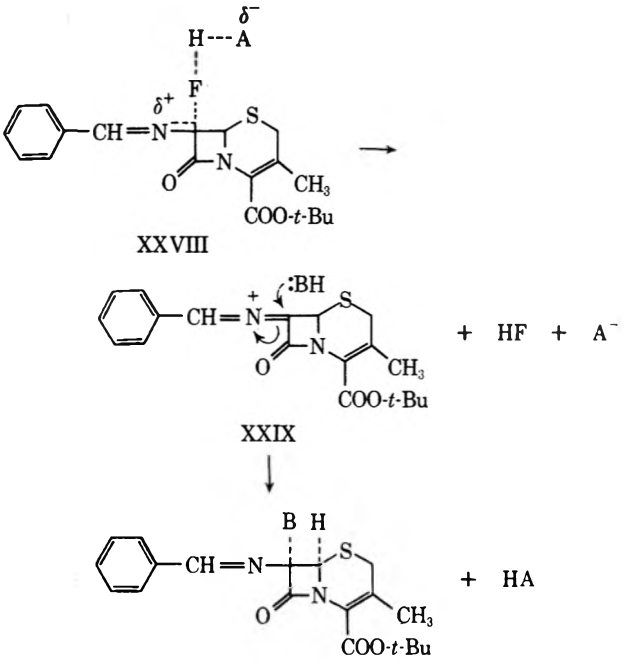
M^+ 418 (2)
a 214 (29)
b 158 (100)

ments a, b, and c derived from the 7-methoxy *tert*-butyl esters IV and VIII. Similar differences were found for the 7-fluoro- and 7-methylthiocephems and the 6-methylthiopenicillins.

The mechanism for the solvolysis of the fluoro Schiff base III appears to proceed by acid catalysis, since reaction occurred only under acidic conditions. No reaction occurred at room temperature when methanol and triethylamine in deuteriochloroform, methanethiol in dimethoxyethane, or water in acetone-d_6 were used, whereas reaction with each of these mixtures did occur after the addition of trifluoroacetic acid. Methanolysis of III proceeded readily in a chloroform–methanol mixture (4:1); however, it is believed that the small amount of acid present in commercially available chloroform was sufficient to catalyze the reaction.

Acid catalysis of the solvolysis reaction should be expected, since incipient fluoride ions are known to form strong hydrogen bonds, and since acid catalysis has been demonstrated for many fluorides, including benzyl fluoride and methyl fluoroacetate.[7] A possible mechanism for the solvolysis is one in which an acid (HA) hydrogen bonds with III to give an intermediate XXVIII; the developing charge at C-7 could be stabilized by the imine nitrogen, leading to the planar intermediate XXIX and, finally, attack by solvent (BH) (methanethiol or methanol) would then be expected to occur from the less hindered exo face (α side). Attack from the exo face was established in the case of solvolysis of the fluoro compound III with methanethiol, which gave material that was identical with 7α-methylthiocephem II, that had been prepared by methylthiolation of the anion of I with methyl methanethiolsulfonate or methylsulfenyl chloride. Presumably, solvolysis of the fluoro compound III with methanol proceeds in an analogous manner to give the 7-methoxy Schiff base IV whose methoxy group is considered to be α. It is possible that mercuric acetate–methanol solvolysis of the methylthio Schiff base II proceeds in a similar fashion, since only one 7-methoxy product is formed, the presumed 7α-methoxy epimer.

(7) M. Stacey, J. C. Tatlow, and A. G. Sharpe, *Advan. Fluorine Chem.*, 3, 63 (1963).



The mechanism of the mercuric acetate solvolysis of the 7α-methylthio-7-phenylacetamido-Δ^3-cephem V remains obscure. It has been shown that (1) treatment of 7α-methylthiocephem V with mercuric acetate in methanol at room temperature for 30 min or at reflux for 10 min yields a mixture of 7α-methoxy and 7β-methoxy epimers (ratio 1:4); (2) treatment of 7α-methylthiocephem V with mercuric acetate in dimethoxyethane at room temperature for 15 min yields, exclusively, 7α-acetoxycephem X; (3) treatment of 7α-acetoxycephem X with mercuric acetate in methanol for 30 min gives, exclusively, 7β-methoxy VIII, whereas treatment of X with methanol or methanol–acetic acid for several hours at room temperature results in no reaction; (4) treatment of 7α-methylthiocephem V with mercuric acetate in methanol for 15 min at 0°, followed by immediate work-up, leads, as shown by pmr examination, to the presence of a large amount of 7α-acetoxycephem X and lesser amounts of the methoxy epimers VII and VIII; (5) treatment of the 7β-methoxycephem VIII with mercuric acetate and methanol yields no 7α-methoxy cephem VII.

These data suggest that more than one mechanism is in operation in the mercuric acetate methanolysis of 7α-methylthiocephem V to the mixture of 7-methoxy epimers VII and VIII. Formation of a major portion of the 7β-methoxycephem VIII probably proceeds through the intermediate, 7α-acetoxycephem X; by what mechanism the 7α-methoxycephem VII is formed remains unclear.

The substituted penicillins and cephalosporins described here were tested for antimicrobial activity *in vitro*. The 6α-methylthio penicillins XXIII and XXVI and the 7α-methylthiocephalosporins VI and XIV had activities considerably less than those found for corresponding compounds that are unsubstituted at C-6 or C-7. The 7β-methoxycephalsoprin IX, at a concen-

tration of 100 μg/ml, showed no activity against any gram-positive and gram-negative microorganism tested.

Experimental Section

The pmr spectra were determined on Varian nuclear magnetic resonance spectrometers (Models T-60 and XL-100-15) using tetramethylsilane as an internal standard, and chemical shifts are reported on the τ scale. Infrared spectra were recorded on Perkin-Elmer spectrometers (Models 257 and 621), and the mass spectra were obtained on an AEI-MS-902 mass spectrometer. Melting points are uncorrected.

Methylsulfenyl Chloride and Methyl Methanethiolsulfonate.—Methyl methanethiosulfonate was prepared by a modification of the procedure of Douglas.[5] Liquid chlorine (50.3 g, 0.71 mol) at Dry Ice–acetone temperature was allowed to warm carefully and distil into dimethyl sulfide (61 g, 0.647 mol), and was then stirred at −20° and protected from moisture to give methylsulfenyl chloride sufficiently pure for methylthiolations or for conversion to methyl methanesthiolsulfonate. Water (23.3 ml, 1.29 mol) was slowly added dropwise to the methylsulfenyl chloride; the temperature was maintained at −20° for 30 min and then allowed to rise to room temperature. The mixture was stirred overnight, during which time HCl was evolved and the color turned from orange to yellow. Distillation of the mixture gave an initial fraction of water–dimethyl sulfide and, finally, one of methyl methanethiolsulfonate (32.4 g), bp 96–97° (4.5 mm). Ir and pmr spectra were consistent with the desired product.

7α-Methylthio-7-benzalimmodeacetoxycephalosporanic Acid *tert*-Butyl Ester (II) from Methylthiolation of Schiff Base I. Method A. Methyl Methanethiolsulfonate Procedure.—To a stirred solution of Schiff base I (13.5 g, 0.377 mmol) in 200 ml of dimethoxyethane at −20° under N_2 was added potassium *tert*-butoxide (4.22 g, 0.377 mmol). The deep-red solution was stirred for 1.5 min and methyl methanethiolsulfonate (4.75 g, 0.377 mmol) was added. As soon as the color of the solution had turned from deep red to yellow, the reaction mixture was poured into pH 6.5 buffer (300 ml). The mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to a residue. Recrystallization of the residue from acetone–hexane gave 5.38 g (35% yield) of 7α-methylthio Schiff base II: ir ($CHCl_3$) 1764 (β-lactam C=O), 1715 (conjugated ester C=O), 1628 (C=N), and 1130 cm^{-1} (SCH_3); pmr ($DCCl_3$) τ 8.45 (9 H, s, *tert*-butyl), 7.93 (3 H, s, $C=CCH_3$), 7.70 (C-6), 2.0–2.8 (5 H, m, aromatics), 1.91 (1 H, s, CH=N); mass spectrum molecular ion at 404.1206 (calcd for $C_{20}H_{24}N_2O_3S_2$: 404.1226). An analytical sample that was recrystallized from CH_2Cl_2–petroleum ether (bp 30–60°) had mp 165°. *Anal.* Calcd for $C_{20}H_{24}N_2O_3S_2$: C, 59.38; H, 5.98; N, 6.93; S, 15.85. Found: C, 59.48; H, 6.08; N, 6.90; S, 15.69.

Method B. Methylsulfenyl Chloride Procedure.—The procedure in part A was followed, with methylsulfenyl chloride used in place of methyl methanethiolsulfonate. From 20.3 g (56.5 mmol) of Schiff base I. 6.33 g (56.5 mmol) of potassium *tert*-butoxide, 4.6 g (56.5 mmol) of methylsulfenyl chloride, and 250 ml of dimethoxyethane was obtained 7.70 g (34% yield) of crystalline Schiff base. The 7α-methylthio Schiff bases prepared by methods A and B were found to be identical by ir, pmr, melting point, and mixture melting point comparisons.

7-Benzalimino-7-fluorodeacetoxycephalosporanic Acid *tert*-Butyl Ester (III).—To a stirred solution of the Schiff base I (218 mg, 0.611 mmol) in anhydrous dimethoxyethane (40 ml) at −50° under nitrogen was added sublimed potassium *tert*-butoxide (67 mg, 0.611 mmol), yielding a dark red mixture. Perchloryl fluoride, diluted in a stream of nitrogen, was passed slowly through the solution until the red color was discharged. Nitrogen was bubbled through the solution as it was warmed to room temperature. The mixture was cooled to −20°, diluted with an equal volume of $CHCl_3$, and passed rapidly through silica gel. Removal of solvent under reduced pressure gave the ester III as a yellow oil (259 mg): ir (neat) 1780 (β-lactam C=O), 1720 (*tert*-butyl ester C=O), 1640 cm^{-1} (C=N); pmr ($DCCl_3$) τ 8.35 (9 H, *tert*-butyl CH_3), 7.87 (3 H, s, CH_3), 6.68 (2 H, m, C-2), 4.80 (1 H, s, J_{H-F} = 8.0 Hz, C-6), 2.03–2.63 (5 H, m, aromatic); M^+, *m/e* 376.1209 ($C_{19}H_{21}N_2O_3SF$, 346.1255). A diagnostic peak at *m/e* 180.0261 (C_9H_7NSF, 180.0283) is consistent with $PhCH=NCF=CHS^+$.

7-Benzalimino-7-methylthiodeacetoxycephalosporanic Acid *tert*-Butyl Ester (II) from Solvolysis of the Fluoro Schiff Base III.—To a solution of the fluoro Schiff base III (110 mg. 0.293 mmol) in anhydrous dimethoxyethane at 0° was added a solution of methanethiol (0.2 g) in dry dimethoxyethane (5 ml) and trifluoroacetic acid (0.023 ml, 0.30 mmol). The mixture was stirred at 0° for 1 hr and allowed to warm to room temperature for another hour. After being purged with nitrogen, the solution was diluted with benzene and washed with saturated aqueous sodium bicarbonate and water. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to a yellow oil (101 mg), which was purified by silica gel tlc with $CHCl_3$:hexane (3:1). The resulting solid (46 mg) had spectral (pmr and ir) and R_f values identical with those of a sample of II obtained by methylthiolation of I.

7-Benzalimino-7-methoxydeacetoxycephalosporanic Acid *tert*-Butyl Ester (IV). Procedure A.—A mixture of mercuric acetate (431 mg, 1.35 mmol) and the methylthio Schiff base II (500 mg, 1.24 mmol) in anhydrous methanol (15 ml) was stirred at room temperature for 1 hr. Dilution with anhydrous ether (75 ml) and filtration through Celite removed insoluble material. After solvent had been stripped under reduced pressure, the residue was taken up in ether and washed with 5% bicarbonate solution and water. The organic layer was treated with Norit, and the volume of solvent was reduced, yielding IV as colorless crystals, 305 mg, mp 141–142°. A second crop of IV was obtained from the filtrate, 520 mg, mp 137.5–139° (total yield 74%). Recrystallization from methanol yielded analytically pure material: mp 142–143°; ir ($CHCl_3$) 1770 (β-lactam C=O), 1715 (*tert*-butyl ester C=O), 1635 cm^{-1} (C=N); pmr ($DCCl_3$) τ 8.47 (9 H, s, *tert*-butyl C=O), 7.78, (3 H, s, CH_3), 6.98 (1 H, d, J_{gem} = 17 Hz, C-2), 6.55 (1 H, d, J_{gem} = 17 Hz, C-2), 6.39 (3 H, s, OCH_3), 4.92 (1 H, s, C-6), 1.97–2.75 (5 H, complex m, aromatic), 1.30 (1 H, s, azomethine CH). *Anal.* Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.60; H, 6.18; N, 7.24.

Procedure B.—A solution of the fluoro Schiff base III (297 mg) in chloroform (6 ml) and anhydrous methanol (2 ml) was stirred at room temperatue for 10 min. Solvent was removed *in vacuo*, and residual methanol was azeotropically distilled with benzene under reduced pressure. The pmr and ir spectra of the yellow oily residue were identical with those obtained for material prepared by procedure A. The mass spectrum exhibited a parent peak at *m/e* 388 ($C_{20}H_{24}N_2O_4S$, 388).

7α-Methylthio-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (V).—To a stirred solution of 7α-methylthio Schiff base II (2.54 g, 6.28 mmol) in 30 ml of CH_2Cl_2 at room temperature under N_2 was added phenylacetyl chloride (0.84 ml, 6.28 mmol) and water (0.15 ml, 8.34 mmol). The mixture was stirred for 18 hr, diluted with CH_2Cl_2, and poured into water. The pH was adjusted to 7.5, and the CH_2Cl_2 layer was washed successively with water, dilute aqueous $NaHSO_3$, and water. The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated *in vacuo* to a residue that crystallized from Et_2O–CH_2Cl_2 to give 1.18 g (43% yield) of V: ir ($CHCl_3$) 1775 (β-lactam C=O), 1712 (conjugated C=O), 1675 (amide C=O), 1480 ("amide II" band), and 1130 cm^{-1} (SCH_3); pmr ($DCCl_3$) τ 8.50 (9 H, s, *tert*-butyl), 7.92 (3 H, s, $C=CCH_3$), 7.75 (3 H, s, $-SCH_3$), 6.82 (2 H, broad singlet, C-2), 6.36 (2 H, broad singlet, $ARCH_2C=O$), 5.09 (1 H, s, NH). An analytical sample that was recrystallized from Et_2O–$CHCl_3$ had mp 174–175°. *Anal.* Calcd for $C_{21}H_{26}N_2O_4S_2$: C, 58.04; H, 6.03; N, 6.45; S, 14.76. Found: C, 58.03; H, 5.86; N, 6.41; S, 14.56.

7α-Methylthio-7-phenylacetamidodeacetoxycephalosporanic Acid (VI).—To 7α-methylthio amide V (652 mg, 1.5 mmol) cooled in an ice–water bath was added 2 ml of trifluoroacetic acid. The stoppered mixture was removed from the cooling bath and left at room temperature for 20 min. The mixture was evaporated *in vacuo* to a residue that was taken up in $CHCl_3$–H_2O. The pH was adjusted to 7.5 with 0.5 *N* NaOH, and the $CHCl_3$ was removed. The aqueous portion was layered with $CHCl_3$ and adjusted to pH 2.0 with 1 *N* HCl. Sodium chloride was added, and the mixture was extracted repeatedly with $CHCl_3$. Evaporation of the dried (Na_2SO_4) $CHCl_3$ extract gave 459 mg of acid VI (81% yield) as a colorless residue: ir ($CHCl_3$) 3500–3100 and 2700–2400 (acid OH), 1774 (β-lactam C=O), 1715 (conjugated C=O), and 1680 cm^{-1} (amide C=O); pmr ($DCCl_3$) τ 7.77 (6 H, s, $-SCH_3$ and $C=CCH_3$), 6.77 (2 H, s, C-2), 6.32 (2 H, s, $ArCH_2C=O$), 5.07 (1, H, s, C-6), 3.07 (1 H, s, NH), 2.68 (5, H, s, aromatic), 1.04 (1 H, s, COOH). Recrystallization from acetone–hexane gave an analytical sample, mp 105–116°

dec, containing 1 equiv of acetone, which was verified by its pmr spectrum ($DCCl_3$): τ, 7.83 [6 H, s, $(CH_3)_2C{=}O$ and $C{=}CCH_3$], 7.7 (6 H, s, SCH_3 and $C{=}CCH_3$). *Anal.* Calcd for $C_{17}H_{18}N_2O_4S_2 \cdot C_3H_6O$: C, 55.02; H, 5.54; N, 6.42; S, 14.69. Found: C, 54.66; H, 5.73; N, 6.44; S, 14.51.

7α-Methoxy-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (VII) and 7β-Methoxy-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (VIII).—To a suspension of methylthioamide V (652 mg, 1.5 mmol) in 5 ml of refluxing CH_3OH under N_2 was added mercuric acetate (478 mg, 1.5 mmol). The mixture was stirred under reflux for 10 min, cooled to room temperature, and evaporated *in vacuo* to a residue. The residue was taken up in benzene–water, and the benzene layer was washed three times with water, dried (Na_2SO_4), and evaporated to a residue. The residue was subjected to slow fractional crystallization from small amounts of CH_3OH, which yielded 420 mg of pale-yellow crystalline β-methoxy epimer (VIII), a residue from crystal washings, and 130 mg of mother liquor whose pmr spectrum indicated a 60:40 mixture of α-methoxy and β-methoxy epimers, respectively. Slow crystallization of this mixture of epimers gave additional crystalline β-methoxy epimer and 76 mg of mother liquor whose pmr spectrum indicated a 70:30 mixture of α-methoxy and β-methoxy epimers.

The crystalline β-methoxy epimer VIII, on recrystallization from CH_3OH, had mp 175–176°; ir spectrum ($CHCl_3$) 1770 (β-lactam C=O), 1710 (conjugated C=O), 1690 (amide C=O), 1158, 1134, 1106, and 1086 cm^{-1} (COC and CSC); pmr ($DCCl_3$, 60 MHz) τ 8.50 (9 H, s, *tert*-butyl), 7.90 (3 H, s, $C{=}CCH_3$), 6.55 (3 H, s, OCH_3), 6.75, 6.95 (2 H, q, J = 17 Hz, C-2), 6.33 (3 H, s, $-CH_2C{=}O$), 4.98 (1 H, s, C-6), 3.32 (1 H, b, NH), 2.67 (5, H, s, aromatics); mass spectrum molecular ion at m/e 418.1584 (calcd, for $C_{21}H_{26}N_2O_5S$, 418.1560).

The mother liquor containing 70% of α-methoxy epimer showed ir ($CHCl_3$) 1770 (β-lactam C=O), 1710 (conjugated C=O), 1690 (amide C=O), and 1155, 1138, 1100, and 1090 cm^{-1}; pmr ($DCCl_3$) τ 8.50 (9, H, s, *tert*-butyl), 7.93 (3 H, s, $C{=}CCH_3$), 6.68 and 6.88 (2 H, q, J = 17 Hz, C-2), 6.58 (3 H, s, $-OCH_3$), 6.37 (2 H, s, $-CH_2C{=}O$), 4.83 (1 H, s, C-6), 2.67 (5 H, s, aromatics).

7β-Methoxy-7-phenylacetamidodeacetoxycephalosporanic Acid (IX).—To the 7β-methoxy *tert*-butyl ester VIII (145 mg, 0.346 mmol) cooled in an ice bath was added 2 ml of trifluoroacetic acid. The stoppered mixture was stirred for several seconds, removed from the bath, and left at room temperature for 20 min. Excess trifluoroacetic acid was removed *in vacuo*, and the residue was taken up in $CHCl_3$–H_2O and adjusted to pH 7.5 with 0.5 *N* NaOH. The $CHCl_3$ layer was removed, discarded, and replaced with fresh $CHCl_3$. The pH was adjusted to 2.0 with 1 *N* HCl and, after the addition of NaCl, the mixture was extracted repeatedly with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and evaporated to give the acid IX (113 mg, 90% yield) as a colorless residue: ir ($CHCl_3$) 1774 (β-lactam C=O), 1710 (sh) (conjugated C=O), and 1690 cm^{-1} (amide C=O), in addition to absorptions at 3500–3100 and 2700–2400 cm^{-1} (NH and acidic OH); pmr ($DCCl_3$) τ 7.80 (3, H, s, $C{=}CCH_3$), 6.87 (2 H, s, C-2), 6.55 (3 H, s, OCH_3), 6.30 (2 H, s, $-CH_2C{=}O$), 4.95 (1 H, s, C-6), 2.67 (5 H, s, aromatics), 0.02 (1 H, s, COOH). Recrystallization of the residue from acetone–hexane gave colorless crystals, mp 92–94°, containing one acetone of crystallization, as evidenced by its pmr spectrum and elemental analysis. *Anal.* Calcd for $C_{17}H_{18}N_2O_5S \cdot C_3H_6O$: C, 57.13; H, 5.75; N, 6.66; S, 7.63. Found: C, 57.25; H, 5.55; N, 6.44; S, 7.62.

7α-Acetoxy-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (X).—To a suspension of the 7α-methylthio ester V (651 mg, 1.5 mmol) in 5 ml of dimethoxyethane was added mercuric acetate (478.5 mg, 1.5 mmol). The mixture was stirred under nitrogen for 20 min at room temperature. The precipitate was filtered and washed with dimethoxyethane, yielding 413 mg of pale-yellow powder. The filtrate was evaporated to a residue, which was taken up in benzene–water. The benzene layer was washed with water, dried (Na_2SO_4), and evaporated to give 620 mg (93% yield) of 7α-acetoxy-*tert*-butyl ester X, as an almost colorless oil: ir ($CHCl_3$) 1785 (β-lactam C=O), 1750 (sh) (ester C=O), 1720–1685 (broad band, conjugated C=O and amide C=O), and 1480 cm^{-1} (amide II band); pmr ($DCCl_3$) τ 8.48 (9 H, s, *tert*-butyl), 7.90 [3 H, s, $-OC(=O)CH_3$], 7.87 (3, H, s, $C{=}CCH_3$), 6.98 (2 H, s, C-2), 6.32 (2 H, s, $-CH_2C{=}O$), 4.87 (1 H, s, C-6), 2.85 (1 H, s, NH), 2.67 (5 H, s, aromatics); mass spectrum, no molecular ion, but m/e 344 ($M - CH_3COOH$).

Stereospecific Conversion of 7α-Acetoxy Ester X to 7β-Methoxy Ester VIII.—To a solution of 7α-acetoxy ester X (81 mg, 0.182 mmol) in 2 ml of anhydrous methanol was added mercuric acetate (58 mg, 0.182 mmol). The mixture was stirred under nitrogen for 30 min at room temperature. The methanol was removed under reduced pressure, and the residue was taken up in benzene–water. The benzene layer was washed with water, dried (Na_2SO_4), and evaporated, leaving 75 mg of 7β-methoxy ester VIII as a colorless residue having pmr and ir spectra like those of pure 7β-methoxy ester VIII. Recrystallization from Et_2O–CH_2Cl_2 gave colorless crystals, mp 175–176°.

7α-Methylthio-7-benzaliminocephalosporanic Acid *tert*-Butyl Ester (XII).—To a stirred solution of Schiff base XI (2.43 g, 5.84 mmol) in 50 ml of dry dimethoxyethane at −5° under N_2 was added potassium *tert*-butoxide (655 mg, 5.84 mmol). The solution was stirred for 1 min, and methyl methanethiolsulfonate (7.37 g, 5.84 mmol) was added. After being stirred for 5 min, the solution was poured into pH 6.5 buffer. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to a residue. Chromatography of the residue on a column of silica gel (200 g) using hexane–$CHCl_3$ (60:40) and subsequent purification by silica gel tlc in the system 1,2-dichloroethane–benzene–acetone (75:25:1) afforded 570 mg of XII (21% yield) as a crystalline product: ir ($CHCl_3$) 1770 (β-lactam C=O), 1720 (ester C=O), 1625 (C=N), and 1125 cm^{-1} (SCH_3); pmr ($DCCl_3$) τ 8.43 (9 H, s, *tert*-butyl), 7.93 (3 H, s, *O*-acetyl), 7.72 (3 H, s, SCH_3), 6.47, 6.67 (2 H, AB quartet, J = 18 Hz, C-2), 4.98, 5.15 (2 H, AB quartet, J = 13 Hz, CCH_2O), 4.93 (1 H, s, C-6), 2.66–2.92 (5 H, m, aromatics), and 1.14 (1 H, s, CH=N). An analytical sample that was recrystallized from hexane–acetone had mp 124–125°. *Anal.* Calcd for $C_{22}H_{26}N_2O_5S_2$: C, 57.12; H, 5.67; N, 6.06; S, 13.86. Found: C, 56.91; H, 5.50; N, 6.31; S, 13.70.

7α-Methylthio-7-phenylacetamidocephalosporanic Acid *tert*-Butyl Ester (XIII).—To a stirred solution of Schiff base XII (262 mg, 0.566 mmol) in 10 ml of CH_2Cl_2 at room temperature under N_2 was added phenylacetyl chloride (94 mg, 0.566 mmol) followed by water (11.5 mg, 0.624 mmol). The mixture was stirred for 18 hr, diluted with CH_2Cl_2, and poured into water. The CH_2Cl_2 layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to a residue that was fractionated by silica gel tlc in the system $CHCl_3$–hexane (9:1), yielding 184 mg of XIII (66% yield) as a residue: pmr ($DCCl_3$) τ 7.92 (3 H, s, *O*-acetyl), 7.77 (3 H, s, SCH_3), 6.60 (2 H, broad singlet, C-2), 6.34 (2 H, s, $ArCH_2$), and 5.07 (1 H, s, C-6).

7α-Methylthio-7-phenylacetamidocephalosporanic Acid (XIV).—To 7α-methylthioamide XIII (184 mg, 0.374 mmol) cooled in an ice–water bath was added 2 ml of trifluoroacetic acid. The stoppered mixture was removed from the bath and stirred at room temperature for 15 min. The mixture was evaporated *in vacuo* to a residue that was taken up in EtOAc–H_2O. The pH was adjusted to 7.5 with 0.5 *N* NaOH, and the EtOAc was removed. Sodium chloride was added, and the mixture was extracted repeatedly with EtOAc. Evaporation of the dried (Na_2SO_4) EtOAc extract gave a residue that was taken up in $CHCl_3$–MeOH. Evaporation of the solvent gave 101 mg (62% yield) of crystalline XIV: ir (KBr) 1775 (β-lactam C=O), 1730 (ester C=O), 1700 (acid C=O), and 1640 cm^{-1} (amide C=O); pmr ($DCCl_3$–D_3COD) τ 7.92 (3 H, s, *O*-acetyl), 7.73 (3 H, s, SCH_3), 6.60 (2 H, broad singlet, C-2), 6.37 (2 H, s, $ArCH_2$), 5.08 (1 H, s, C-6), 5.00 (2 H, AB quartet, J = 14 Hz, $-CH_2OAc$), and 2.67 (5 H, s, aromatics). Recrystallization from acetone–hexane gave an analytical sample, mp 156–157°. *Anal.* Calcd for $C_{19}H_{20}N_2O_6S_2$: C, 52.28; H, 4.62; N, 6.42. Found: C, 52.50; H, 4.83; N, 6.43.

6α-Methylthio-6-benzaliminopenicillanic Acid *p*-Methoxybenzyl Ester (XVIII).—To a stirred solution of Schiff base XV (1.04 g, 2.43 mmol) in dimethoxyethane (150 ml) at −10° was added potassium *tert*-butoxide (272 mg, 2.43 mmol). The orange solution was stirred for 2 min, and methyl methanethiolsulfonate (306 mg, 2.43 mmol) was added. After stirring for 1 hr at −10°, the mixture was poured into pH 6.6 buffer (300 ml) and extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) extract gave 1.10 g of XVII (95% yield) as a yellow oil: ir ($CHCl_3$) 1765 (β-lactam C=O), 1740 (ester C=O), and 1610 cm^{-1} C=N); pmr ($DCCl_3$) τ 8.67 (3 H, s, $-CH_3$), 8.57 (3 H, s, $-CH_3$), 7.83 (3 H, s, $-SCH_3$), 6.37 (3 H, s, $-OCH_3$), 5.57 (1 H, s, C-3), 4.93 (2 H, s, $-OCH_2$), 4.43 (1 H, s, C-5), 2.93 (9 H, m, aromatic), and 1.33 (1 H, s, CH=N); mass spectrum molecular ion at m/e 470, base peak at m/e 121.

6α-Methylthio-6-phenoxyacetamidopenicillanic Acid *p*-Methoxybenzyl Ester (XXII).—To a solution of methylthio Schiff base XVII (104 mg, 2.45 mmol) in 4 ml of dimethoxyethane was added phenoxyacetyl chloride (33.5 μl, 2.45 mmol), followed by water (4 μl, 2.45 mmol). The mixture was stirred for 40 min at room temperature and poured into water. Extraction with ethyl acetate gave a yellow oil (61 mg) that was purified by tlc on Quantum PQIF silica gel in the system hexane–ethyl acetate (4:1), to give 32 mg (25% yield of XXII as a colorless oil: ir ($CHCl_3$) 1780 (β-lactam C=O), 1745 (ester C=O), and 1692 cm^{-1} (amide C=O); pmr ($DCCl_3$) τ 8.67 (3, H, s,$-CH_3$), 8.53 (3 H, s, $-CH_3$), 7.73 (3 H, s, $-SCH_3$), 6.20 (3 H, s, $-OCH_3$), 5.63 (1 H, s, C-3), 5.50 (2 H, s, $-CH_2C$=O), 4.90 (2 H, s, $-OCH_2$), 4.45 (1 H, s, C-5), 3.00 (9 H, s, aromatic), and 1.93 (1 H, m, NH).

The amide XXII was also prepared in 20% yield by treating XVIII with equivalent amounts of *p*-toluenesulfonic acid monohydrate, triethylamine, and phenoxyacetyl chloride in EtOAc.

6α-Methylthio-6-phenylacetamidopenicillanic Acid *p*-Methoxybenzyl Ester (XXV).—The 6α-methylthioamide XXV was obtained in 14% yield by the procedure described for the preparation of amide XXII: ir ($CHCl_3$) 1775 (β-lactam C=O), 1740 (ester C=O), and 1680 cm^{-1} (amide C=O); pmr ($DCCl_3$) τ 8.70 (3 H, s, $-SCH_3$), 7.83 (3 H, s, $-SCH_3$), 6.32 (2 H, s, $-CH_2C$=O), 6.18 (3 H, s, $-OCH_3$), 5.63 (1 H, s, C-2), 4.88 (2 H, s, $-OCH_2$), 4.45 (1 H, s, C-5), and 3.30–2.57 (10 H, m, NH and aromatics).

6α-Methylthio-6-benzaliminopenicillanic Acid (XX) and 6α-Methylthio-6-aminopenicillanic Acid (XXI).—To a slurry of 6-benzaliminopenicillanic acid (XVII) (5.11 g, 16.9 mmol) in dry dimethoxyethane (200 ml) at room temperature was added potassium *tert*-butoxide (1.89 g, 16.9 mmol). The mixture turned orange, and complete solution occurred after 3 min. Trimethylsilyl chloride (1.83 g, 16.9 mmol) was added, and the mixture was stirred for 12 min as it cooled to −10°. Potassium *tert*-butoxide (1.89 g, 16.9 mmol) was added, and the solution turned red. After 15 min, methyl methanethiolsulfonate (2.12 g, 16.9 mmol) was added, and stirring was continued for 30 min at −10°. The dimethoxyethane was removed *in vacuo*, and the residue was taken up in pH 7.8 phosphate buffer and EtOAc. The EtOAc layer was discarded, and the aqueous layer was washed repeatedly with EtOAc. The EtOAc washings were discarded, and the aqueous part was layered with EtOAc and adjusted to pH 4.0 with dilute HCl. Extraction with $CHCl_3$ and EtOAc gave a residue, after drying ($MgSO_4$) and concentration. Trituration of the residue with $CHCl_3$ gave 240 mg of amino acid XXI as a solid, and a supernate. Evaporation of the supernate gave 650 mg of Schiff base XX (19% yield) as an oil. Adjustment of the pH 4 aqueous solution to pH 1.9 and extraction with EtOAc gave a further quantity of XXI (800 mg), for a total yield of 23%.

The amorphous amino acid XXI could not be recrystallized: ir (Nujol) 1755 (β-lactam C=O) and 1715 cm^{-1} (acid C=O); mp 172–176° dec; pmr (DMSO-d_6) τ 8.60 (3 H, s, $-CH_3$), 8.53 (3, H, s, $-CH_3$), 7.85 (3 H, s, $-SCH_3$), 5.82 (1 H, s, C-5), and 3.90 (3 H, broad, NH_3^+); mass spectrum, molecular ion *m/e* 262, base peak *m/e* 160. *Anal. Calcd* for $C_{19}H_{14}N_2O_3S_2$: C, 41.22; H, 5.38; N, 10.68. Found: C, 41.88; H, 5.78; N, 10.00.

The Schiff base XX had ir ($CHCl_3$) 1760 (β-lactam C=O), 1720 (COOH), and 1622 cm^{-1} (C=N); pmr ($DCCl_3$) τ 8.43 (6 H, s, 2-CH_3), 7.73 (3, H, s, SCH_3), 5.60 (1 H, s, C-3), 4.45 (1 H, s, C-5) 4.60 (5 H, m, aromatics), 1.57 (1 H, broad, COOH); mass spectrum of trimethylsilyl ester, molecular ion at *m/e* 422.

6α-Methylthio-6-phenoxyacetamidopenicillanic Acid (XXIII).—To a stirred suspension of the methylthioamino acid XXI (127 mg, 0.485 mmol) in dimethoxyethane (12 ml) was added *N,O*-bistrimethylsilylacetamide (100 μl, 0.485 mmol). Solution occurred after 15 min of stirring. Triethylamine (68 μl, 0.485 mmol) and phenoxyacetyl chloride (67 μl, 0.485 mmol) were added sequentially, and the mixture was stirred for 1.5 hr at room temperature and concentrated under vacuum to a residue. The residue was taken up in EtOAc–H_2O, and the water layer was discarded. Water was added to the EtOAc layer, and the pH was adjusted to 7.5. The EtOAc layer was discarded, and the aqueous solution was covered with EtOAc and adjusted to pH 3.2 with dilute HCl. The resulting EtOAc extract was dried (Na_2SO_4) and evaporated to a residue. Trituration with hexane–benzene gave 72 mg of amorphous XXIII (38% yield): ir ($CHCl_3$) 1780 (β-lactam C=O), 1730 (COOH), and 1690 cm^{-1} (amide C=O); pmr ($DCCl_3$) τ 8.47 (6 H, s, 2 CH_3), 7.70 (3 H, s, $-SCH_3$), 5.50 (1 H, s, C-3), 5.33 (2 s, OCH_2), 4.35 (1 H, s, C-5), 2.83 (5 H, m, aromatics), and 2.30 (1 H, s, NH); mass spectrum of trimethylsilyl ester, molecular ion at *m/e* 468.

6-Methylthio-6-phenylacetamidopenicillanic Acid (XXVI).—The acid XXVI was obtained in 78% yield by the method described for the preparation of the acid XXIII. The amorphous acid XXVI had ir ($CHCl_3$) 1777 (β-lactam C=O), 1725 (COOH), and 1680 cm^{-1} (amide C=O); pmr ($DCCl_3$) τ 8.57 (6 H, m, 2 CH_3), 7.83 (3 H, s, $-SCH_3$), 6.38 (2 H, s, $-CH_2C$=O), 5.67 (1 H, s, C-3), 4.48 (1 H, s, C-5), 2.67 (5 H, m, aromatics), 2.17 (1 H, m, NH); mass spectrum of trimethylsilyl ester, molecular ion at *m/e* 452.

Registry No.—I, 36954-81-1; II, 37786-92-8; III, 37786-93-9; IV, 37786-94-0; V, 37786-95-1; VI, 37786-96-2; VII, 37786-97-3; VIII, 37786-98-4; IX, 37786-99-5; X, 37787-00-1; XI, 36954-82-2; XII, 37787-02-3; XIII, 37787-03-4; XIV, 37787-04-5; XV, 36954-77-5; XVII, 21019-16-9; XVIII, 37787-07-8; XX, 37787-08-9; XXI, 37787-09-0; XXII, 37787-10-3; XXIII, 37787-11-4; XXV, 37787-12-5; XXVI, 37787-13-6; methylsulfenyl chloride, 5813-48-9; methyl methanethiolsulfonate, 2949-92-0.

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Prostanoic Acid Chemistry. II.[1] Hydrogenation Studies and Preparation of 11-Deoxyprostaglandins

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Selective hydrogenations, mainly by the homogeneous Wilkinson catalyst, were shown to convert PGE_2 to PGE_1, $PGF_{2\alpha}$ to $PGF_{1\alpha}$, and 5,6-*trans*-PGE_2 to PGE_1. In the same way, 11β-PGE_1, 15β-PGE_1, and 11β,15β-PGE_1 were also prepared from their 5,6-cis unsaturated precursors. Hydrogenation of PGA_1 and PGA_2 gave a number of 11-deoxyprostaglandins, including 11-deoxy-PGE_1, 11-deoxy-PGE_2, and 13,14-dihydro analogs. Sodium borohydride reduces the cyclopentenone system of PGA_1 and PGA_2 completely, to give pairs of epimeric alcohols **18, 19** and **26, 27**. Other reduction by-products and cyclization products of some prostaglandins are described.

Prostaglandins of the "2" series, *i.e.*, PGE_2 (**1**, 11α, R = R′ = H), $PGF_{2\alpha}$ (**15a**), and PGA_2 (**23**, R = R′ = H), differ from those of the "1" series, PGE_1 (**3**, 11α, R = R′ = H), $PGF_{1\alpha}$ (**15b**), PGA_1 (**20**), in having a cis double bond between carbon atoms 5 and 6. While the PG_1 series was the first studied[2] and is still of biological and clinical interest, compounds of the PG_2 series have become the most readily available *via* biosynthesis,[3] total synthesis,[4] and from the common gorgonian, *Plexaura homomalla*.[5] This led us to initiate studies on the selective hydrogenation of the 5,6 double bond of prostaglandins in order to interrelate the two series. These studies on reduction products of prostaglandins led also to a number of 11-deoxyprostaglandins. Such compounds are relatively stable to acidic or basic reagents in contrast to the β-hydroxy ketones PGE_1 and PGE_2. Since 11-deoxyprostaglandins also retain prostaglandin-like biological activity,[6] they have been the target for total synthesis dating back to the early days of prostaglandin research.[7] Most of these efforts have produced racemic products and epimeric mixtures rather than the "natural" antipodes described here. An early report of biological activities of some of the natural 11-deoxyprostaglandins or their methyl esters described below has been published.[8]

At the time of our first experiments, the only recorded selective hydrogenation of the 5,6-cis double bond was by Samuelsson,[9] who prepared 5,6-tritiated PGE_1 from PGE_2 (**1**, 11α, R = R′ = H) using tritium and 5% palladium on charcoal catalyst in ethyl acetate.[10] Using hydrogen, we found this reduction to proceed rapidly at 25° with little difference in rates of reduction of the 5,6 and 13,14 double bonds. No greater selectivity was achieved by lowering the temperature. Similar results were obtained using 5% rhodium on alumina catalyst. The less active 5% palladium–barium sulfate catalyst offered more selectivity, especially when the 15 acetate, methyl ester of PGE_2 (**1**, 11α, R = CH_3, R′ = Ac) was reduced. However, hydrogenolysis of the 15 acetate was an undesirable side reaction.

The soluble Wilkinson catalyst, tristriphenylphosphine rhodium chloride,[11] was not effective in benzene solution (no hydrogen uptake) but, in a mixture of benzene and acetone,[12] PGE_2 was reduced to PGE_1 (**3**, 11α, R = R′ = H), recrystallized yield of 50%, together with lesser amounts of 13,14-dihydro-PGE_1 (**5**, 11α) and the 15-ketoprostanoic acid **4**, 11α. These latter two materials have been previously encountered[12,13] on a microscale but are here fully characterized. Acid-catalyzed dehydration of **4**, 11α gave the cyclopentenone **7**.

The observed selectivity of the 5,6 double bond over the 13,14 bond is not entirely due to the fact that one is cis and the other trans, since a similar hydrogenation of 5,6-*trans*-PGE_2[14] (2 11α), while a little slower than that of PGE_2, also gave PGE_1 as the predominant product.

The Wilkinson catalyst was also used to reduce the 5,6 double bond of 11β,15β-PGE_2 (**12**, 11β, R = R′ = H) and the 15 acetate methyl esters of 11β-PGE_2 (**1**, 11β, R = CH_3, R′ = Ac) and 15β-PGE_2 (**12**, 11α, R = CH_3, R′ = Ac)[15] giving, after an enzymatic hydrolysis

(1) For paper I of this series, see J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

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(4) (a) W. P. Schneider, *Chem. Commun.*, 304 (1969); (b) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969), and later papers.

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(6) See, for example, ref 7b and 8.

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(8) J. E. Pike, F. P. Kupiecki, and J. R., Weeks, "Prostaglandins," Nobel Symposium 2, S. Bergstrom and B. Samuelsson, Ed., Almqvist and Wiksell, Uppsala, 1967, p 169.

(9) B. Samuelsson, *J. Biol. Chem.*, **239**, 4091 (1964).

(10) Since that time, the hydrogenation of the 11,15-bistetrahydropyranyl ether of $PGF_{1\alpha}$ and the 11,15-bisdimethylisopropylsilyl ether of PGE_2 over 5% palladium/charcoal catalyst has been reported in communication form: (a) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970); (b) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971). Selectivity of reduction of the 5,6 double bond over the 13,14 one is said to be good in these sterically hindered derivatives.

(11) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

(12) This is a procedure used by G. K. Koch and J. W. Dalenberg, *J. Label. Compounds*, VI, 395 (1970), for tritiation of PGE_2 on a microscale.

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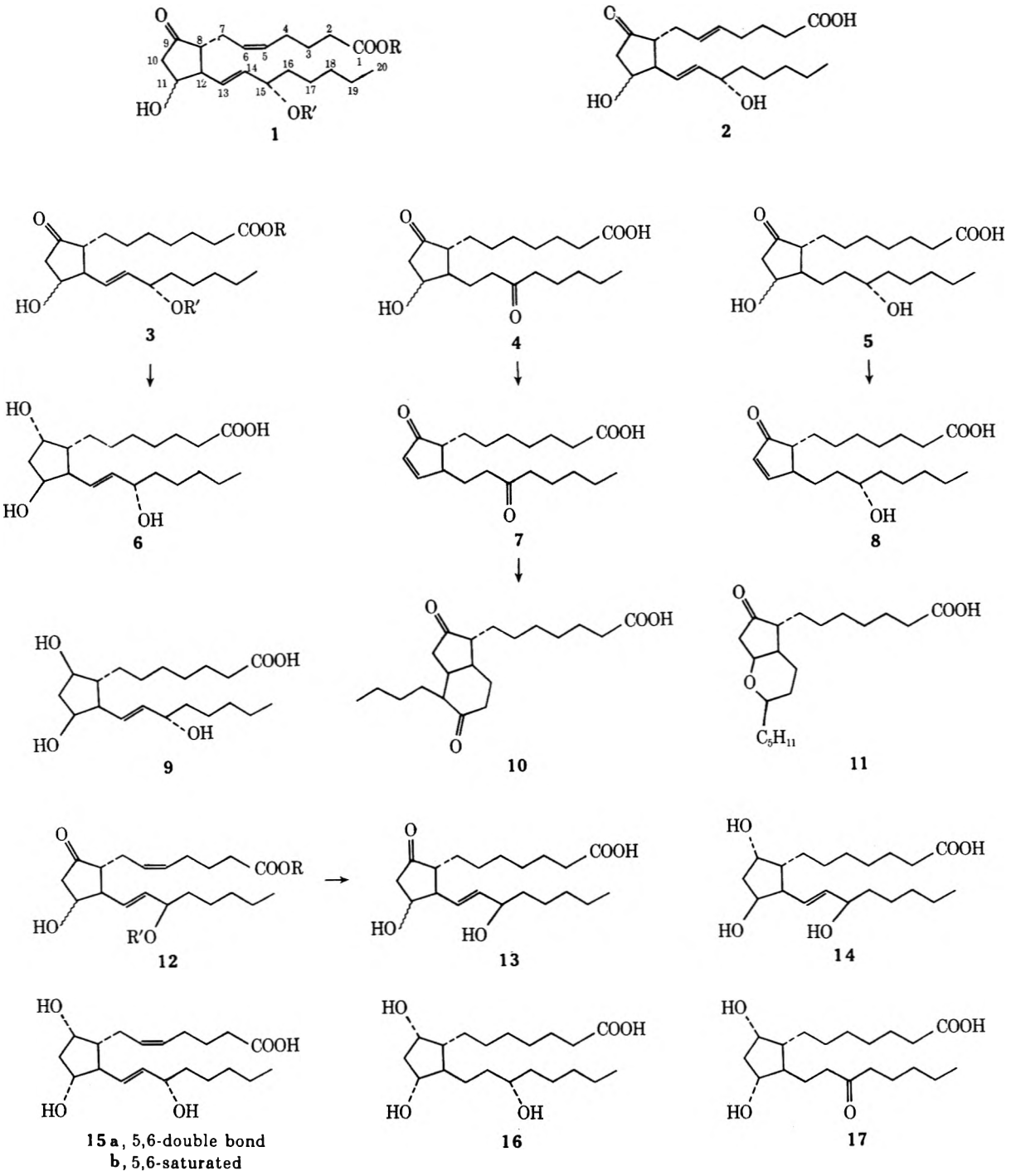
(14) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *J. Amer. Chem. Soc.*, **94**, 2124 (1972).

(15) These materials are readily available in several steps from coral-derived prostaglandins; see ref 5b.



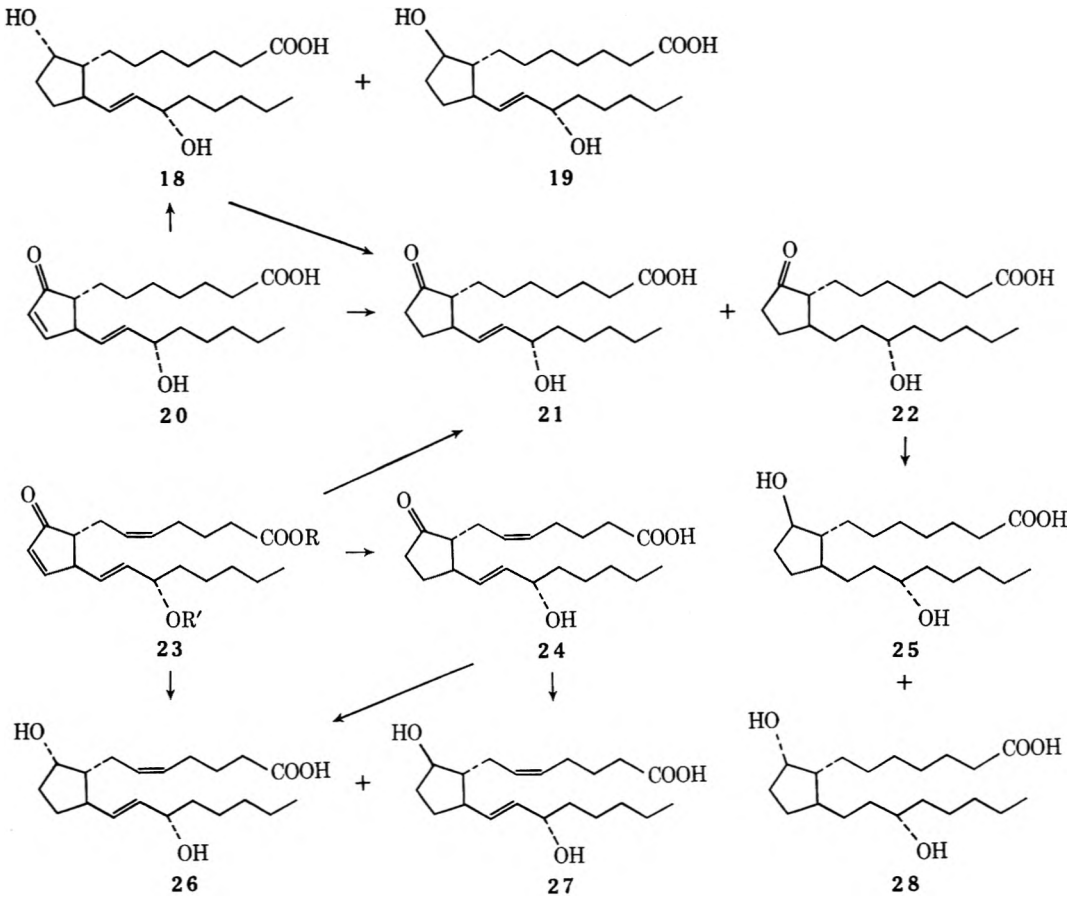
of the latter two, 11β-PGE$_1$ (**3**, 11β, R = R′ = H), 15β-PGE$_1$ (**13**, 11α), and 11β,15β-PGE$_1$ (**13**, 11β). The first of these products was also further reduced by sodium borohydride to give 11β-PGF$_1$α (**6**) and 11β-PGF$_1$β (**9**). Both were crystalline and structural assignments were made on the basis of enhancement of thin layer or column chromatographic mobility of the 1,3-cis glycol by boric acid. This could be seen either on boric acid impregnated silica gel plates[16] or with untreated silica gel developed in a methanol–chloroform–boric acid solvent system. 11β-PGE$_1$ (**3**, 11β, R = R′ = H) also serves as a source of PGA$_1$ (**20**) by virtue of acid-catalyzed dehydration.

Strangely enough, when the above hydrogenation conditions were applied to PGF$_2$α (**15a**), no uptake of hydrogen occurred. However, substitution of ethanol for the acetone in the solvent mixture[17] allowed hydrogenation to proceed as before, giving largely PGF$_1$α (**15b**) in isolated yield of about 50%, and lesser amounts of 13,14-dihydro-PGF$_1$α (**16**) and the 15 ketone (**17**).[17]

Attempts to hydrogenate PGA$_2$ (**23**, R = R′ = H) to PGA$_1$ (**20**) under these conditions were unsuccessful. With palladium and rhodium catalysts, the 10,11 double bond was the most readily reduced, and the major products were 11-deoxy-PGE$_1$ (**21**), 11-deoxy-PGE$_2$ (**24**), and the tetrahydro derivative **22**. Minor amounts of hydrogenolysis products (15 deoxy) and 15 ketones were also produced. With the Wilkinson catalyst, no uptake of hydrogen occurred in benzene or acetone–benzene. In ethanol–benzene, hydrogenation was slow and gave 11-deoxy-PGE$_1$ (**21**) as the major product. The latter was also produced by palladium-

(16) L. J. Morris, *Lipids*, **1**, 41 (1966); *J. Chromatogr.*, **12**, 321 (1963).

(17) A. S. Hussey and Y. Takiuchi, *J. Org. Chem.*, **35**, 643 (1970).



catalyzed hydrogenation of PGA_1 (**20**) at $-10°$. At higher temperatures the tetrahydro compound **22**[8] predominated. This tetrahydro-PGA_1 (**22**) was further reduced with sodium borohydride to a mixture of two epimeric 9 alcohols, **25** and **28**,[8] the less polar of which (**28**) was crystalline. A racemic mixture of epimers of the methyl esters of this structure had previously been prepared by total synthesis.[7d]

11-Deoxy-PGE_2 (**24**) could also be prepared by first reducing PGA_2 acetate methyl ester (**23**, R = CH_3, R′ = Ac) with excess sodium borohydride.[18] This results in complete 1,4 reduction of the cyclopentenone system giving a mixture of two epimeric 9 alcohols, **26** and **27**, as their 15 acetate methyl esters. Oxidation of this mixture with Jones reagent[19] followed by base hydrolysis of ester groups gave 11-deoxy-PGE_2 (**24**) in about 50% yield. Sodium borohydride reduction of either PGA_1 (**20**) or 11-deoxy-PGE_1 (**21**) gave the same mixture of 11-deoxy-$PGF_1\alpha$ (**18**) and 11-deoxy-$PGF_1\beta$ (**19**), both crystalline. Structures of these and of **25** and **28** above were assigned by comparison of nmr shifts of the 9-proton signal with analogous 9 epimers and previous work.[7c,20] In the same way, 11-deoxy-$PGF_2\alpha$ (**26**) and 11-deoxy-$PGF_2\beta$ (**27**) were also prepared.

Internal additions to the cyclopentenone system occur readily when the 13,14-trans double bond has been reduced. For example, dehydration of dihydro-PGE_1 (**5**, 11α) in dilute hydrochloric acid gave a mixture of the expected 13,14-dihydro-PGA_1 (**8**) and the 11,15-cyclic ether (**11**). This was also recently observed by other workers.[21] Also, treatment of **7** or **4** with base gave the cyclized Michael product **10**.

Experimental Section[22]

A. Hydrogenations Using Homogeneous Catalysis. 1. Preparation of PGE_1 (3, 11α, R = R′ = H), 13,14-Dihydro-PGE_1 (5, 11α), and 11α-Hydroxy-9,15-diketoprostanoic Acid (4, 11α).—Prostaglandin E_2 (containing about 15% 5,6-*trans*-PGE_2[14]), 21.2 g, in 240 ml of acetone and 160 ml of benzene was purged with nitrogen and 2 g of tris(triphenylphosphine)rhodium chloride was added. This mixture was shaken under hydrogen at 20–30-psi pressure for 7 hr, when a thin layer chromatogram (tlc) (silver nitrated impregnated silica gel plate developed twice with the AIX[23] solvent system) showed the disappearance of PGE_2. Slightly more than 1 equiv of hydrogen had been consumed. The solvents were evaporated and the dark oily residue was dissolved in 200 ml of 3A alcohol and poured into 500 ml of 0.2 *M* Na_2HPO_4 buffer solution with stirring. The mixture was extracted twice with toluene, which was back-washed with a mixture of 200 ml of the same phosphate buffer and 50 ml of 3A alcohol. The combined aqueous layers were acidified to pH 3 with 2 *M* citric acid and extracted 3–4 times with ethyl acetate. The extracts were washed with saline, dried with Na_2SO_4, and evaporated to give 19.5 g of partially crystalline residue. This was dissolved in methylene chloride and chromatographed over

(18) For other 1,4 reductions of unsaturated carbonyl compounds, see, for example, S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966). 11-Deoxy-PGE_2 was first prepared in these laboratories by a longer route by Dr. N. A. Nelson.

(19) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(20) The 9β proton of 9α-hydroxyprostaglandins is consistently observed at about δ 4.2 *vs.* 3.9 for the 9 epimer.

(21) (a) D. P. Strike and H. Smith, *Ann. N. Y. Acad. Sci.*, **180**, 91 (1971); (b) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Tetrahedron Lett.*, 4085 (1971).

(22) Ir spectra were recorded with a Perkin-Elmer Model 221 ir spectrophotometer on Nujol mulls or as neat liquids between salt plates. The nmr spectra were run on a Varian A-60A spectrophotometer using deuteriochloroform solution with tetramethylsilane as internal standard. Mass spectra were recorded on an Atlas CH-4 instrument with ionization voltage of 70 eV or on a Model LKB gas chromatograph–mass spectrograph. Uv spectra were recorded in 95% ethanol using a Carey Model 14 spectrophotometer. We are grateful to Dr. A. A. Forist and associates for much of the analytical and spectral data and to J. H. Kinner and R. A. Morge for technical assistance.

(23) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).

1 kg of acid-washed silica gel packed in ethyl acetate–Skellysolve B (33:67). The column was eluted with increasing concentration of ethyl acetate in Skellysolve B and finally with 5% CH_3OH in ethyl acetate. The first material eluted, 1.69 g, was largely 11α-hydroxy-9,15-diketoprostanoic acid (**4**, 11α), which was rechromatographed over 150 g of acid-washed silica gel. Elution with 50% ethyl acetate–Skellysolve B gave **4**, 11α, as a pale yellow oil: R_f 0.57 on silica gel, AIX system; $[\alpha]D$ −9° ($CHCl_3$); ir (neat) 3430, 3240, 2660, 1735, 1705, 1160, 1070 cm^{-1}; nmr ($CDCl_3$) δ 7.65 (2 H, OH, COOH), 4.1 (1 H, broad m, C-11 proton); mass spectrum M^+ *m/e* 354 (weak), 336, 318, 219, 208, 204, 190, 109, 95.

The second material eluted was 6.6 g of largely 13,14-dihydro-PGE_1 (**5**, 11α), which was also purified by rechromatography as above to give a pale yellow oil which solidified to a waxy solid on refrigeration: R_f 0.46 (AIX); nmr ($CDCl_3$) δ 6.3 (3 H, 2 OH + COOH), 4.12 (1 H, m) and 3.65 (1 H, m, carbinolic protons).

The third material eluted consisted of 9.89 g of crystalline PGE_1 (**3**, 11α, R = R′ = H), which was recrystallized from ethyl acetate (charcoal) to give 8.05 g (38%) of nearly colorless needles, mp 110–112.5°. One further recrystallization gave mp 112.5–115°; $[\alpha]D$ −67° (95% EtOH); equiv wt 359 (calcd 354.5); uv after base treatment 278 nm (ε 25,350).

2. **PGE_1 15 Acetate Methyl Ester (3, 11α, R = CH_3, R′ = Ac).**—In the same manner as above, 500 mg of PGE_2 15 acetate methyl ester[5b] was hydrogenated in 9 ml of acetone and 6 ml of benzene and 150 mg $(PPh_3)_3RhCl$ at 1 atm hydrogen at 25° for 2 hr. The hydrogen uptake was 28 ml (calcd for 1 equiv, 27 ml). A tlc on a $AgNO_3$-impregnated silica gel plate (50% ethyl acetate–cyclohexane) showed no starting material remaining and a major new spot slightly less polar was formed. The solvents were evaporated and the residue was chromatographed on 50 g of silica gel. Elution with 40% EtAc–Skellysolve B gave 403 mg (80%) of tlc homogeneous **3**, 11α, R = CH_3, R′ = Ac, as a nearly colorless oil: nmr (CCl_4) δ 5.5 (m, 2 H, $\Delta^{13,14}$), 5.18 (m, 1 H, CHOAc), 4.0 (m, 1 H, CHOH), 3.56 (s, 3 H, OCH_3), 1.97 (s, 3 H, Ac), 0.9 (t, terminal CH_3).

3. **Prostaglandin $F_1\alpha$ (15b).**—A solution of 1.0 g of $PGF_2\alpha$ (**15a**) in 30 ml of 95% ethanol and 20 ml of benzene containing 250 mg of $(PPh_3)_3RhCl$ was stirred under hydrogen at 25° (1 atm). After 4 hr, 1 equiv of H_2 had been absorbed and the rate of uptake slowed. After another hour, tlc [$AgNO_3$–silica gel, CH_3OH–HOAc–$HCCl_3$ (10:10:80)] showed only a trace of $PGF_2\alpha$ remaining and a heavy spot corresponding to $PGF_1\alpha$. The mixture was filtered through Celite and evaporated. The residue was partitioned between 5% NaOH and ether. The aqueous layer was acidified, extracted with ethyl acetate, dried, and evaporated to give 1 g of an oil which crystallized from ethyl acetate–Skellysolve B, 0.36 g, mp 88–95°. The filtrate was chromatographed on 33 g of acid-washed silica gel and elution with 5% methanol in ethyl acetate gave 0.18 g of additional $PGF_1\alpha$ (**15b**). Recrystallization of the combined crops gave 0.40 g (40%), mp 98–100° (reported mp 101–103°).[1]

4. **11-Deoxy-PGE_1 (21).**—On one-half the scale of the preceding experiment, 0.50 g of PGA_2 (**23**, R = R′ = H) was reduced. After work-up, the crude mixture showed on tlc [silica gel, EtAc–cyclohexane–acetic acid (40:60:2)] a major spot of 11-deoxy-PGE_1 (R_f 0.43), a medium spot like PGA_2 (R_f 0.37), and two minor, less polar spots. Chromatography over 50 g of acid-washed silica gel (20–60% EtAc–Skellysolve B elution) gave 263 mg of 11-deoxy-PGE_1 which melted at 90–92° after two recrystallizations from acetone–Skellysolve B. This material had a solution ir spectrum identical with that of 11-deoxy-PGE_1 (**21**) fully characterized below (Experiment B3). The Nujol mull ir spectrum was slightly different from that of the same material obtained below and a different crystal polymorph is indicated. The other major fraction from the column, 191 mg, by nmr was a mixture of PGA_2 and PGA_1.

5. **11β-Prostaglandin E_1 (3, 11β, R = R′ = H).**—A solution of 45 g of 11β-PGE_2 15 acetate methyl ester[5b] in 360 ml of acetone and 240 ml of benzene was purged with nitrogen and shaken in an atmosphere of hydrogen (30 psi) in the presence of 4.5 g of $(PPh_3)_3RhCl$ for 7 hr. At this time tlc [$AgNO_3$–silica gel, EtAc–cyclohexane (50:50) developed twice] showed no remaining starting material. The solvents were removed *in vacuo* and the dark residue was dissolved in 110 ml of ethyl acetate and diluted with 440 ml of Skellysolve B. The flocculent rhodium precipitate was removed by filtration and the filtrate was evaporated. The residue was dissolved in 50 ml of 3A ethanol and added to a rapidly stirred suspension of acetone-insoluble esterase-containing material prepared from frozen soft coral, *Plexaura homomalla*,[24] in 3 l. of water. The pH of the mixture was adjusted to 6.5–7.0 with phosphoric acid and the mixture was stirred for 24 hr, when tlc (silica gel, AIX system) showed no ester remaining. Acetone (6 l.) was added, and the mixture was stirred for 45 min longer and filtered. The filtrate and acetone wash was concentrated, acidified to pH 3 with citric acid, and extracted with methylene chloride. The washed and dried extracts were evaporated, the residue was equilibrated between phosphate buffer and toluene, and the acidic products were isolated as in the above experiment 1 to afford 39 g of partially crystalline residue. Crystallization from ether after decolorization with charcoal gave 13.3 g of 11β-PGE_1 (**3**, 11β, R = R′ = H), mp 90–92°. The remainder of the material was chromatographed on 1.5 kg of acid-washed silica gel to give (a) 7.0 g of PGA_1 (**20**); (b) 4.9 g of 11β-13,14-dihydro-PGE_1 (**5**, 11β); and (c) 6.7 g of additional 11β-PGE_1 which after recrystallization gave 4.6 g: mp 91–92° (total yield 46%); ir 3360, 2950, 2750, 2660, 1720, 1710 (sh), 1135, 1035, 1000, 980 cm^{-1}; uv (after base treatment) 278 nm (ε 25,850); nmr δ 5.75 (2 H, m, vinylic), 4.75 (3 H, broad, 2 OH + COOH), 4.4 (1 H, m), and 4.1 (1 H, m, carbinolic); $[\alpha]^{25}D$ 25–21° (95% EtOH). *Anal.* Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.98; H, 9.69.

Fraction b was rechromatographed to give 2.5 g of pure 11β,-13,14-dihydro-PGE_1 (**5**, 11β): R_1 0.51 (silica gel, AIX); $[\alpha]D$ +12° ($CHCl_3$); ir 3450, 3000, 2660, 1740, 1710, 1105, 1040 cm^{-1}; nmr ($CDCl_3$) δ 6.28 (3 H, OH + COOH), 4.36 (1 H, m, carbinolic), 3.66 (1 H, m, carbinolic); mass spectrum M^+ not observed, *m/e* 338 (M − 18), 249, 210, 192, 168, 119, 117, 96, 55.

6. **(15*R*)-PGE_1 (13, 11α).**—The conversion of 5.0 g of (15*R*)-PGE_2 15 acetate methyl ester[5b] to (15*R*)-PGE_1 was carried out as in experiment 5 above on a reduced scale to give 2.5 g of (15*R*)-PGE_1 (**13**, 11α) as a pale yellow oil: R_f 0.39 (silica gel, AIX system), less polar then PGE_1 (R_f 0.29); nmr δ 6.05 (3 H, 2 OH + COOH), 5.65 (2 H, m, vinylic), 4.12 and 4.0 (2 H, m, carbinolic).

7. **11β-(15*R*)-PGE_1 (13, 11β).**—A solution of 1.0 g of 11β-(15*R*)-PGE_2[5b] in 30 ml of acetone and 20 ml of benzene containing 100 mg of $(PPh_3)_3RhCl$ was hydrogenated and worked up as in experiment 1 above. After chromatography the product was obtained as a pale yellow oil, R_f 0.40 (silica gel, AIX), yield 0.49 g. The material was less polar than starting material on silver nitrate impregnated silica gel (R_f 0.32 *vs.* 0.21, AIX) and the nmr spectrum now showed only two vinylic protons at δ 5.7.

B. Heterogeneous Hydrogenations. 1. **Prostaglandin $F_1\alpha$ from $PGF_2\alpha$ 11,15-Bistetrahydropyranyl Ether.**—A solution of 7.5 g of $PGF_2\alpha$ 11,15-bistetrahydropyranyl ether[25] in 215 ml of ethyl acetate containing 2.1 g of 5% Rh/Al_2O_3 catalyst was stirred in 1 atm hydrogen at 0–5° for 7.5 hr. At this time hydrogen uptake had slowed and tlc ($AgNO_3$–silica gel, AIX) showed only a trace of $PGF_2\alpha$ diether remaining. The mixture was filtered and evaporated, and the residue was redissolved in 250 ml of HOAc, 40 ml of tetrahydrofuran, and 125 ml of water. After being heated at 40° for 4 hr, the solution was lyophilized and the residue was chromatographed on 350 g of acid-washed silica gel. Elution with 40–100% ethyl acetate–Skellysolve B and then with 5% methanol in ethyl acetate gave 2.72 g of crystalline $PGF_1\alpha$ (**15b**) as the most polar product. The less polar, ether-containing materials were retreated as above to give an additional 1.57 g of $PGF_1\alpha$. These were combined with similar fractions from another reduction of 5.22 g of starting material and recrystallized twice from ethyl acetate–Skellysolve B to give 4.63 g (54%) of $PGF_1\alpha$, mp 101–102° (reported[1] mp 101–103°), $[\alpha]D$ +28° (EtOH). *Anal.* Calcd for $C_{23}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.31; H, 9.93.

2. **$PGF_1\alpha$ (15b), 13,14-Dihydro-$PGF_1\alpha$ (16), and 9α,11α-Dihydroxy-15-ketoprostanoic Acid (17) from $PGF_2\alpha$ (15a).**—A mixture of 3.13 g of $PGF_2\alpha$, 75 ml of ethyl acetate, and 0.5 g of 5% Rh/Al_2O_3 was hydrogenated as above at 10° until slightly more than 1 equiv of hydrogen had been absorbed. The mixture was filtered and evaporated, and the residue was chromatographed on 150 g of acid-washed silica gel. Elution with ethyl acetate–Skellysolve and then 5% CH_3OH in ethyl acetate gave

(24) We are indebted to Dr. E. G. Daniels of these laboratories for this esterase-containing material and the procedure for its use in hydrolyzing prostaglandin ester.

(25) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

three fractions, the least polar, 210 mg eluted with 75% ethyl acetate, consisted of **17** as a pale yellow oil: ir 3400, 2650, 1705, 1725, 1240, 1195, 1180, 1115, 1070, 1025 cm^{-1}; nmr δ 5.6 (2 H, OH, COOH), 4.2 (1 H, m), 3.9 (1 H, m) (carbinolic protons), enhanced absorption 2.1–2.7 ($-CH_2C{=}O$); mass spectrum as tristrimethylsilyl (tris-TMS) derivative, calcd for $C_{29}H_{60}O_5Si_3$ 572.3746, found 572.3714, other major peaks at *m/e* 557, 554, 501, 482.

The second peak, eluted with ethyl acetate, contained 757 mg of 13,14-dihydro-PGF$_{1\alpha}$ (**16**) which crystallized on standing, and after recrystallization twice from EtAc–Skellysolve B gave mp 66–68°; ir 3370, 3210, 2700, 2580, 2560, 2570, 1695, 1135, 1080, 1020, 960, 845 cm^{-1}; $[\alpha]_D$ +41° ($CHCl_3$). *Anal.* Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. Found: C, 67.14; H, 11.15.

The third peak, 1.428 g, was crystalline PGF$_{1\alpha}$ (**15b**) which readily recrystallized from ethyl acetate–Skellysolve B to give material of essentially the same quality as the preceding experiment.

3. Hydrogenation of PGA$_1$. 11-Deoxy-PGE$_1$ (21) and 15α-Hydroxy-9-ketoprostanoic Acid (22).—A mixture of 1.0 g of PGA$_1$ and 150 mg of 5% Pd/C catalyst in 50 ml of ethyl acetate was stirred with H_2 at 1 atm and −18 to −10°. After 5 hr tlc indicated conversion to two slightly less polar spots [silica gel, EtAc–cyclohexane–HOAc (40:60:2)] and hydrogen uptake was 1.2 equiv. The crude products were chromatographed on 100 g of acid-washed silica gel. Elution with 40% ethyl acetate–Skellysolve B gave two main substances. The first, 207 mg, was predominately 15α-hydroxy-9-ketoprostanoic acid (**22**), which was further purified by rechromatography and obtained as a colorless oil: ir 3430, 3150, 2650, 1730, 1710, 1270, 1210, 1105, 725 cm^{-1}; nmr δ 6.68 (2 H, OH, COOH), 3.68 (1 H, broad, carbinolic, 0.9 (t, $-CH_3$); mass spectrum as trimethylsilyl derivative, M^+ *m/e* 484, 469, 413, 394, 384, 379, 355, 284.

The second material eluted was 11-deoxy-PGE$_1$ (**21**), 541 mg, which was also rechromatographed for purification and was crystallized from acetone–Skellysolve B as colorless flakes: mp 95–96°; ir 3360, 2900, 2820, 2770, 2680, 1730, 1705, 1185, 1020, 980 cm^{-1}; nmr δ 6.05 (2 H, OH, COOH), 5.6 (2 H, m, vinylic), 4.15 (1 H carbinolic), 0.9 (3 H, t, CH_3); mass spectrum *m/e* 338 (M^+), 320, 302, 292, 267, 249, 231; $[\alpha]_D$ −51° ($CHCl_3$). *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.46; H, 10.58.

4. Hydrogenation of PGA$_2$ (23, R = R′ = H).—Hydrogenation of 4.0 g of PGA$_2$ as in the preceding example gave a mixture of products which on chromatography as above gave among other things 627 mg of 15α-hydroxy-9-ketoprostanoic acid (**22**) identical with that characterized above; 1.378 g of a mixture of 11-deoxy-PGE$_1$ (**21**), isolated by crystallization from acetone–Skellysolve B, mp 88–91°; and a small amount of 11-deoxy-PGE$_2$ (**24**), separated by silver nitrate impregnated silica gel chromatography and recrystallization from ethyl acetate–Skellysolve B, mp 41–43°. This is further characterized in an alternate preparation below. Less polar fractions gave evidence (ir and nmr) of hydrogenolysis of the 15-hydroxyl group and also the presence of 15-keto compounds.

11-Deoxy-PGE$_2$ (24).—A solution of 3.4 g of PGA$_2$ acetate methyl ester[5a] (**23**, R = CH_3, R′ = Ac) in 68 ml of CH_3OH at −20° was treated with an equally cold solution of 4.7 g of $NaBH_4$ in 6.8 ml of water and 61 ml of methanol, added in portions over 5 min. After a further 15 min, 4.7 ml of HOAc and 68 ml of water were added, and the mixture was concentrated and extracted with methylene chloride. The washed and dried extract was evaporated, redissolved in 170 ml of acetone, and cooled to −5°. Then 6.8 ml of Jones chromic oxide mixture[19] was added over 5 min, and after an additional 10 min 1.4 ml of isopropyl alcohol was added. Five minutes later the solution was decanted, concentrated, and extracted with methylene chloride to give 3.5 g of residue. This was chromatographed on 300 g of silica gel and eluted with 20% ethyl acetate in Skellysolve B to give 1.90 g of tlc-homogeneous 11-deoxy-PGE$_2$ 15 acetate methyl ester. The material was treated for 1 hr under N_2 with 0.9 g of NaOH in 30 ml of methanol and 6 ml of water. After acidification and concentration, the product was isolated by methylene chloride extraction. Purification by chromatography on 170 g of acid-washed silica gel (50% ethyl acetate–Skellysolve B) gave 1.40 g of colorless **14**, R_f 0.74 (silica, AIX), which crystallized from ethyl acetate–Skellysolve B in heavy prisms: mp 42–43°; $[\alpha]_D$ −54° ($CHCl_3$); ir 3360, 2710, 2650, 1725, 1275, 1185, 1020, 980 cm^{-1}; nmr δ 7.08 (2 H, OH, COOH), 5.6 (2 H, vinylic), 5.37 (2 H, m, vinylic), 4.1 (1 H, m, carbinolic), 0.9 (3 H, t, CH_3). *Anal.* Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.77.

11-Deoxy-PGF$_{1\alpha}$ (18) and 11-Deoxy-PGF$_{1\beta}$ (19).—In the same manner as the preceding experiment, 2.0 g of PGA$_1$ was reduced with sodium borohydride in aqueous methanol. After 20 min the solution was acidified with acetic acid, concentrated, saturated with salt, and acidified to pH 3 with citric acid. Extraction with methylene chloride gave a crude product which was chromatographed on 200 g of acid-washed silica gel. From 40% EtAc–Skellysolve eluates there was obtained 270 mg of pure less polar product (**18**), determined by tlc [silica gel, EtAc–cyclohexane–acetic acid (40:60:2)]. From 50 and 60% eluates was obtained 964 mg of mixed fractions and 435 mg of pure more polar product. The mixed fractions were rechromatographed to give 186 mg of less polar, 530 mg of more polar, and 220 mg of mixed products.

The less polar product (**18**) was crystallized from ethyl acetate–Skellysolve as colorless platelets: mp 53–55°; ir 3420–3320 (OH), 2950, 2730, 2640, 1700, 1195, 1170, 1135, 1070, 1020, 970, 955, 910, 725 cm^{-1}; nmr δ 5.48 (2 H, m, vinylic), 4.75 (3 H, 2 OH + COOH), 4.25 (1 H, m), 4.1 (1 H, m, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum as the tris-TMS derivative, *m/e* 556 (M^+), 541, 485, 466, 451, 395, 376. *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.31; H, 10.81.

The more polar product (**19**) crystallized from ether–Skellysolve B and then acetone–Skellysolve B as flakes: mp 78–79°; ir 3340, 3250, 2740, 2670, 2560, 1700, 1065, 1020, 1005, 980, 970 cm^{-1}; nmr δ 5.5 (2 H, m, vinylic), 4.93 (3 H, 2 OH + COOH), 4.1 and 3.95 (2 H, m, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum as tris-TMS derivative, *m/e* 556 (M^+), 541, 485, 466, 451, 395, 305. *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.33; H, 10.71.

Borohydride Reduction of 11-Deoxy-PGE$_1$ (21).—In the same manner as the preceding experiment, 0.15 g of 11-deoxy-PGE$_1$ (**21**) was reduced in methanol with 0.4 g of sodium borohydride. The reaction was run at −15° for 15 min and then dilute HCl was added and the products were isolated by ether extraction. Chromatography gave 53 mg of **18** and 73 mg of **19**, identical in tlc mobility and ir spectra with the products of the preceding experiment.

11-Deoxy-PGF$_{2\alpha}$ (26) and 11-Deoxy-PGF$_{2\beta}$ (27).—As in the preceding experiment, 0.30 g of 11-deoxy-PGE$_2$ (**24**) was reduced with 0.8 g of sodium borohydride in methanol. After 20 min at −15°, acetic acid was added and the products were isolated by extraction with ether after concentration and acidification with dilute HCl. Chromatography on 40 g of acid-washed silica gel and elution with 20–60% ethyl acetate–Skellysolve B gave two products. The less polar, 94 mg of colorless oil, consisted of **26**: R_f 0.67 (silica gel, AIX); ir 3380, 2640, 1710, 1235, 1135, 1030, 970 cm^{-1}; nmr δ 5.53 (4 H, m, vinylic), 5.2 (3 H, 2 OH + COOH), 4.27 and 4.13 (2 H, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum *m/e* 338 (M^+, weak), 320, 302. The more polar colorless oil, 112 mg, was the 9β-hydroxy epimer **27**: R_f 0.59; ir 3350, 2640, 1710, 1305, 1235, 1075, 1020, 970 cm^{-1}; nmr same as **26**, R = R′ = H, except the carbinolic protons overlapped at δ 4.06; mass spectrum same as that of **26**, except that no M^+ was observed.

11β-PGF$_{1\alpha}$ (6) and 11β-PGF$_{1\beta}$ (9).—In the same manner as above, 2.0 g of 11β-PGE$_1$ was reduced with 5.0 g of sodium borohydride in 200 ml of methanol at −10° for 20 min. The crude product isolated was crystalline and showed two materials, R_f 0.45 and 0.52 by tlc on silica gel (AIX). Chromatography on 150 g of acid-washed silica gel and elution with 2 and 4% methanol in ethyl acetate afforded a minimum separation from which 0.28 g of **9**, mp 80–93°, and 0.20 g of **6**, mp 131–133°, were crystallized from the early and late fractions, respectively. The mixed fractions and mother liquors were dissolved in a small amount of 10% methanol in chloroform and adsorbed on a column of 40 g of acid-washed silica gel. The column was eluted with the filtrate obtained by mixing chloroform with $^1/_{10}$th its volume of methanol saturated with boric acid. Eluted fractions were washed with water to remove boric acid, and then dried before evaporating. The first 100 ml of eluate contained 561 mg of the less polar isomer **9**, followed by 60 mg of mixed fractions (next 50-ml eluate) and 235 mg of more polar isomer **6** (200 ml eluate). The combined like fractions were crystallized twice from acetone–Skellysolve B to give 0.99 g of the less polar isomer as shiny leaflets, mp 63–65° (another crystalline form, mp 94–95°, was seen once), and 0.36 g of the more polari somer as

colorless granules, mp 135–136°. The former was the less polar on both silica gel and boric acid impregnated silica gel plates and the separation was enhanced on both boric acid tlc plates and on column elution with boric acid containing solvents; so the less polar isomer is assigned the cis glycol structure, 11β-PGF$_1$β (**9**), ir 3460, 3440, 3220, 2630, 2520, 1675, 1080, 1065, 1050 and 1015 cm^{-1}. *Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.19; H, 10.08.

The more polar **6** had ir absorptions at 3270, 2710, 1750, 1130, 1120, 1085, 1025, 975 cm^{-1}. *Anal.* Found: C, 67.11; H, 10.24.

9α,15α-Dihydroxyprostanoic Acid (28) and 9β,15α-Dihydroxyprostanoic Acid (25).—A solution of 370 mg of 15α-hydroxy-9-ketoprostanoic acid (**22**) in 20 ml of isopropyl alcohol and 2 ml of water was cooled to −15° and 150 mg of sodium borohydride was added portionwise. After 25 min, tlc (silica gel, AIX) showed no starting material remaining and two new materials, R_f = 0.52 and 0.46, formed. Acetone, then 1 *N* HCl, was added, and the mixture was concentrated and extracted with ethyl acetate, giving 380 mg of crude products. These were separated by chromatography on 25 g of acid-washed silica gel, eluting with 50% ethyl acetate–Skellysolve B. The less polar isomer **28**, 138 mg, was crystalline and after two recrystallizations from ethyl acetate gave mp 89–92°; ir 3450, 2650, 2400, 1705, 1040, 1015, 960, 725 cm^{-1}; nmr δ 5.01 (3 H, 2 OH, COOH), 4.20 and 3.58 (1 H each, carbinolic), and 0.9 (3 H, t, CH_3); mass spectrum *m/e* 324 (M − 18), 306 (M − 36), 295, 280, 265, 253, 235, 208, 196, 193. *Anal.* Calcd for $C_{20}H_{35}O_4$: C, 70.13; H, 11.18. Found: C, 70.58; H, 11.31.

The more polar isomer **25**, 200 mg, was a colorless oil: ir 3400, 2700, 2600, 2350, 1705, 1220, 1155, 1050, 725 cm^{-1}; nmr δ 5.46 (3 H, 2 OH, COOH), 3.88 and 3.58 (1 H m each, carbinolic); mass spectrum *m/e* 324 (M − 18), 306 (M − 36), 265, 253, 249, 235, 208, 196, 193.

Dehydration of 11β-PGE$_1$ (3, 11β, R = R′ = H). PGA$_1$ (20).—A solution of 15.9 g of 11β-PGE$_1$ in 240 ml of tetrahydrofuran was treated under nitrogen with 160 ml of 0.5 *N* HCl at room temperature for 4 days.[26] Dilution with saturated salt and extraction with ethyl acetate gave a crude product which was purified by chromatography on 950 g of acid-washed silica gel. Elution with 30–100% ethyl acetate–Skellysolve B and 1% methanol in ethyl acetate gave 11.73 g of PGA$_1$ (**20**) and 2.03 g of recovered 11β-PGE$_1$. The PGA$_1$ fraction was crystallized from ethyl acetate–Skellysolve (1:3) to give 8.20 g of colorless crystals, mp 41–42°, and a second crop: 1.08 g; mp 40.5–41.5°; $[\alpha]_D$ +144° ($CHCl_3$); uv 217 nm (ε 10,950). *Anal.* Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.63.

Dehydration of 13,14-Dihydro-PGE$_1$ (5, 11α).—A solution of 0.50 g of 13,14-dihydro-PGE$_1$ in 10 ml of tetrahydrofuran was treated with 8 ml of 0.5 *N* HCl under nitrogen for 5 days at room temperature. Work-up as in the preceding experiment and chromatography on 50 g of acid-washed silica gel as above gave 280 mg of the cyclic compound **11**[21] as a colorless oil which solidified to a waxy mass on refrigeration: ir 2660, 1740, 1710, 1280, 1225, 1165, 1040, 735 cm^{-1}; nmr δ 8.8 (1 H, COOH), 4.35 and 3.75 (1 H each, m), 0.9 (3 H, t, CH_3); mass spectrum as the mono-TMS derivative, *m/e* 410.2821.

The next material eluted was 13,14-dihydro-PGA$_1$ (**8**), 185 mg, as a colorless oil: ir 3400, 2660, 1700, 1585, 1185, 1125, 915, 800, 735 cm^{-1}; nmr, δ 7.65 (1 H, dd, vinylic), 6.13 (1 H, dd, vinylic), 7.12 (2 H, s, OH + COOH), 3.63 (1 H, m, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum *m/e* 338 (M^+), 320, 302, 277, 267, 249, 231, 210; uv 222 nm (ε 9600).

The most polar material eluted was 40 mg of recovered 13,14-dihydro-PGE$_1$.

9,15-Diketo-Δ^{10}-prostanoic Acid (7) and Its Cyclization Product 10.—During chromatographic purification of 11α-hydroxy-9,15-diketoprostanoic acid (see first experiment) a less polar fraction was obtained which consisted of its dehydration product, 9,15-diketo-Δ^{10}-prostanoic acid (**7**), as a pale yellow oil: uv 221 nm (ε 10,050); ir 3100, 2660, 1735, 1705, 1585, 1775 cm^{-1}; nmr δ 9.0 (1 H, COOH), 7.68 (1 H, dd, vinylic), 6.15 (1 H, dd vinylic), enhanced absorption between 2.1 and 2.8, and 0.9 (3 H, t, CH_3); mass spectrum as the trimethylsilyl derivative, calcd for $C_{23}H_{40}SiO_4$ 408.2695, found 408.2694, also *m/e* 393, 337, 318, 309, 208.

To a solution of the above material (0.5 g) in 25 ml of methanol under N_2 was added 4 ml of 1 *N* NaOH. After 2 hr at 25°, the solution was concentrated, acidified, and extracted with ether. An oil was obtained which showed a heavy spot on tlc [R_f 0.43, silica gel, EtAc–cyclohexane–HOAc (40:60:2)] less polar than starting material (R_f 0.34). Purification over acid-washed silica gel (30% ethyl acetate–Skellysolve B) gave a pale yellow oil (**10**): nmr δ 10.2 (1 H, COOH), enhanced absorption between 2.1 and 3.1 and 0.9 (3 H, t, CH_3). The substance gives a crystalline bisoxime: mp 84–85° from aqueous methanol; ir 3450, 3300, 1710, 1680, 960, 945 cm^{-1}. *Anal.* Calcd for $C_{20}H_{34}O_4N_2 \cdot H_2O$: C, 62.47; H, 9.44; N, 7.28. Found: C, 62.49; H, 9.68; N, 7.29.

Registry No.—11α-**1** (R = R′ = H), 363-24-6; 11α-**1** (R = CH_3, R′ = Ac), 37785-76-5; 11β-**1** (R = CH_3, R′ = Ac), 37785-77-6; 11α-**3** (R = R′ = H), 745-65-3; 11α-**3** (R = CH_3, R′ = Ac), 37785-78-7; 11β-**3** (R = R′ = H), 24570-01-2; 11α-**4**, 5094-14-4; 11α-**5**, 19313-28-1; 11β-**5**, 25140-29-8; **6**, 37818-61-4; **7**, 20721-88-4; **7** trimethylsilyl derivative, 37785-84-5; **8**, 28834-62-0; **9**, 37785-86-7; **10**, 37818-62-5; **10** bisoxime, 37785-87-8; **11**, 34389-03-2; 11α-**12** (R = CH_3, R′ = Ac), 37785-89-0; 11β-**12** (R = R′ = H), 37785-90-3; 11α-**13**, 20897-91-0; 11β-**13**, 22468-06-0; **15a**, 551-11-1; **15a** 11,15-bistetrahydropyranyl ether, 37786-09-7; **15b**, 745-62-0; **16**, 20592-20-5; **17**, 29044-75-5; **17** tris-trimethylsilyl derivative, 37785-97-0; **18**, 37785-98-1; **19**, 37785-99-2; **20**, 14152-28-4; **21**, 37786-00-8; **22**, 37786-01-9; **23** (R = R′ = H), 37503-61-0; **23** (R = CH_3, R′ = Ac), 36323-03-2; **24**, 35536-53-9; **25**, 20592-63-6; **26**, 37786-06-4; **27**, 37786-07-5; **28**, 20592-19-2.

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Photochemistry of Nonconjugated Bichromophoric Systems. Cyclomerization of 7,7′-Polymethylenedioxycoumarins and Polymethylenedicarboxylic Acid (7-Coumarinyl) Diesters[1]

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Upon irradiation of dicoumarins with ultraviolet light, intramolecular cycloadducts with the syn configuration are formed. The structure of the isomers was proved unequivocally by nmr spectral study and dipole moment measurements. Upon irradiation of 7,7′-polymethylenedioxycoumarins with a chain length exceeding four units, the syn head-to-tail isomer is the most abundant regioisomer. On irradiation of the polymethylenedicarboxylic acid (7-coumarinyl) diesters, the syn head-to-head isomer is formed predominantly. In the former class neither the chain length nor the solvent polarity seem to exert an important influence on the ratio between the two regioisomers. In the latter this ratio is more affected by length of the link between the two chromophores. Upon increase of the concentration of the dioxycoumarins, the amount of intermolecular photoproducts increases. Upon sensitization, intermolecular reaction prevails. Steric factors such as methyl substitution on the photoreactive double bond were investigated. The photocycloadditions are reversible upon irradiation at $\lambda \sim 300$ nm.

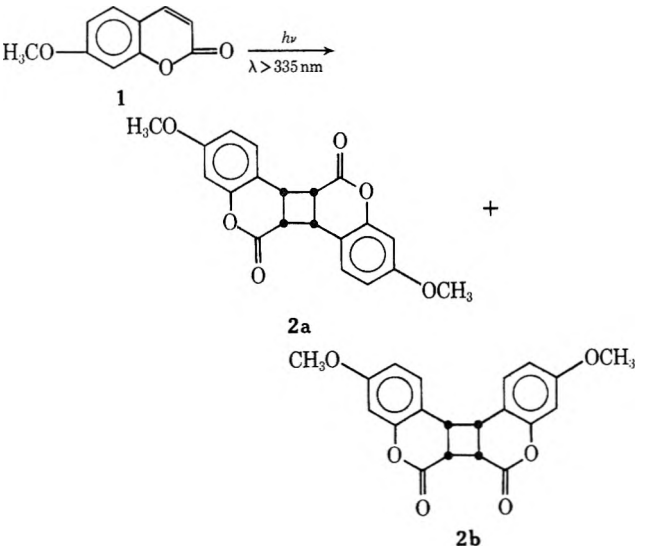
During recent years some examples of intramolecular photopolymerization between suitable chromophores, which are linked by a flexible chain, have been reported.[5] In all cases mentioned except the biscinnamates,[5h] the 1,7 dimer[5o,q] and the *N,N′*-alkylene bismaleimides,[5r] the intramolecular reaction is limited to systems in which the two functions are separated by three methylene units.

In view of the hypothesis put forward in the photocyclomerization of *N,N′*-alkylene bismaleimides[5r] and in view of the assumption that an excimer could be an intermediate in the coumarin dimerization,[6] the photochemistry of some symmetric and asymmetric dicoumarins[7] was studied. We wish here to report some synthetic aspects of this study.

Although the dimerization of coumarins is a long-known reaction,[8] only a limited number of photoreactions of substituted coumarins has been reported.[9-12] Therefore the photochemistry of the model compounds was looked into.

Results

Photochemistry of 7-Methoxycoumarin.—7-Methoxycoumarin was synthesized in analogy with the synthesis of 7,7′-methylenedioxycoumarin.[13] Although it has been reported[9] that the title compound did not photodimerize in solution, dimer **2a** was isolated in 75% yield upon irradiation of a 5×10^{-2} *M* solution in dichloromethane using light with $\lambda > 335$ nm.[14] Dimer **2b** is formed in 25% yield and its percentage is raised to 30 upon a tenfold increase in concentration of **1**. Dimer **2a** is identical with the one obtained predominantly upon direct irradiation of **1** in the solid state,[9]



(1) Abstracted in part from the Ph.D. thesis of L. H. Leenders. Presented in part at the 6th International Photochemistry Conference, Bordeaux, France, Sept 1971.

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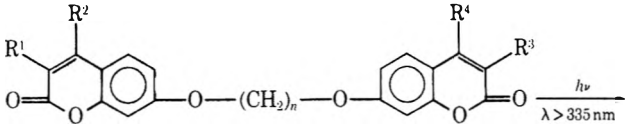
as is shown by the melting point and nmr-spectral analysis.

The structure of 2a[16] was established on the basis of nmr absorptions as compared with those of the cyclomers of the dioxycoumarins (*vide infra*) and on the basis of the dipole moment which has a value of 2.9 D in benzene, and is much lower than the value of 4.5 D for 7-methoxycoumarin itself.

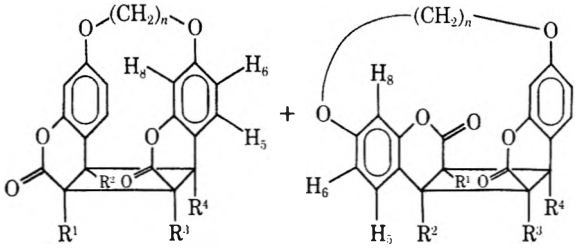
Photochemistry of 7,7′-Polymethylenedioxycoumarins.—The symmetric 7,7′-polymethylenedioxycoumarins **3** and **9** were synthesized in analogy with the synthesis of 7-methoxycoumarin. The asymmetric dioxycoumarin **6** was prepared by refluxing an acetone solution of 4-methyl-7-hydroxycoumarin and α-(7-oxycoumarinyl)-ω-bromoalkane in the presence of potassium carbonate.[17]

Bifunctional molecules can undergo an intra- or intermolecular reaction. On direct irradiation of the 7,7′-polymethylenedioxycoumarins using light with $\lambda > 335$ nm, the absorption characteristics of the –CH=CH– system in the ir and nmr spectra disappeared.

If the chain between the two coumarin chromophores is long enough, four different cis-fused isomers may theoretically be formed: the syn head-to-head, syn head-to-tail, anti head-to-head, and anti heat-to-tail configuration.



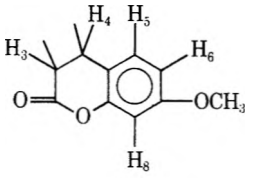
3, $R^1 = R^2 = R^3 = R^4 = H$
6, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$
9, $R^1 = R^3 = H$; $R^2 = R^4 = CH_3$



4, $R^1 = R^2 = R^3 = R^4 = H$ — **5**
7, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$ — **8**
$R^1 = R^3 = H$; $R^2 = R^4 = CH_3$ — **10**

a, **b**, **c**, **d**, **e**, **f**, **g**, **h**, **i**, **j**, $n = 2, 3, 4, 5, 6, 7, 8, 9, 10, 11$, respectively

Out of the photolysis mixtures of all the dioxycoumarins two cycloadducts have been isolated. The intramolecular nature of the reaction products was proved by mass spectroscopy. The structural proof of the cycloadducts was carried out on the two isomers of 7,7′-trimethylenedioxycoumarin (**3b**). The cyclomers formed must have a syn configuration in view of the shortness of the polymethylene linkage. However, two regioisomers are still possible: syn head-to-head **4b**[18] or syn head-to-tail **5b**.[18] The respective configuration of **4b** and **5b** was elucidated by a comparative nmr study of 3,4-dihydro-7-methoxycoumarin (**11**) and the two isomers. In deuterated chloroform, the phenyl protons of **11** appear as an ABX system: the absorption of H_5, calculated from a 100-MHz spectrum, is found at δ 7.10, H_6 at 6.67, and H_8 at 6.63, the first of these being coupled with the aliphatic protons H_4. Upon addition of EuFOD,[19] paramagnetic downfield shifts were observed: protons H_3 which are nearest to the complexing site are shifted the most; the shift of $H_3 \gg$ shift of $H_4 >$ shift of $H_8 >$ shift of $H_5 >$ shift of H_6. These 100-MHz spectra are represented in Figure 1a. In **5b**, protons H_5, H_6, and H_8 can be described as part of an AMX system. In comparison with the absorptions of the same protons in **11**, H_5 (absorption at δ 6.97) and H_6 (absorption at 6.60) are shifted slightly upfield, while H_8 is shifted over δ 0.62 to a stronger field with respect to the H_8 absorption in **11** (*cf.* Figures 1a and 1b). This effect on H_8 is caused by the diamagnetic anisotropy of a phenyl nucleus situated in front of this proton. This situation is possible only if the molecule has a syn head-to-tail configuration.



11

The 100-MHz nmr spectrum of **4b** (H_5, H_6, and H_8 absorb as a complex between δ 6.6 and 6.3) indicates that such a strong selective shift does not exist for the H_8 absorption. All the phenyl protons are shifted to a higher field in comparison with the same protons in **11**, as may be seen in Figure 1c, in agreement with a proposed syn head-to-head configuration.[20]

Strong supporting evidence for this interpretation was found upon examining the 100-MHz nmr spectra of **4b** and **5b** after adding EuFOD:[21] in **4b**, the phenyl proton which undergoes the strongest downfield shift is H_8 as was the case in **11**, the absorption of H_5 and H_6 being affected almost equally. Owing to the low solubility of **4b** in $CDCl_3$, it was impossible to determine the positions of the absorptions of the different protons accurately. Therefore we examined the spectra of **4f**. The absorptions are H_5 δ 6.62, H_6 6,45, and H_8 6.39; upon adding EuFOD,[22] the chemical shifts became H_5 6.95, H_6 6.72, and H_8 6.96. The 100-MHz nmr spectra of **4b** and **4f** prior to and after adding EuFOD are represented in Figure 1c.

On the contrary, in **5b**, H_5 undergoes the strongest downfield shift upon adding EuFOD (*cf.* Figure 1b), indicating that this proton is now nearest to the complexed C=O, which is only possible in a syn head-to-tail configuration.

(16) This dimer may be called 3,9-dimethoxy-6a*H*,6b*H*,12a*H*,12b*H*-cyclobuta[1,2-*c*;3,4-*c*′]-*syn*-biscoumarin.

(17) This synthesis was worked out simultaneously and reported by Fisons Pharmaceuticals Ltd., French Patent Specification 1,593,304.

(18) In general the *syn* head-to-head regioisomer can be called 3,10-alkylenedioxy-6a*H*,6b*H*,12b*H*,12c*H*-cyclobuta[1,2-*c*;4,3-*c*′]-*syn*-biscoumarin, while the *syn* head-to-tail isomer should be named 3,9-alkylenedioxy-6a*H*,6b*H*,12a*H*,12b*H*-cyclobuta[1,2-*c*;3,4-*c*′]-*syn*-biscoumarin.

(19) 2,2-Dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione, europium-(III) derivative.

(20) (a) The same phenomenon was observed in the syn photodimers of vitamin K_3: H. Werbin and E. T. Strom, *J. Amer. Chem. Soc.*, **90**, 7296 (1968). (b) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(21) Since the ratio between the concentrations of EuFOD and of the different compounds studied was not kept constant, we did not compare the change in chemical shifts of all these products with one another. The only comparable aspect is the relative change in chemical shift of the different protons within one compound.

(22) To 10 mg of **4f** in $CDCl_3$, 20 mg of EuFOD was added.

This interpretation was confirmed by the dipole moments of 6.7 D for **4b** and 2.0 D for **5b**[23] in dioxane. The more polar isomer can only be the one with the head-to-head configuration. These measurements agreed with the different solubilities of the two photoproducts in solvents with different polarities.

The configuration of the cyclomers of the other 7,7′-polymethylenedioxycoumarins was determined by comparison of their nmr spectra with these of **4b** and **5b**.

The nmr spectrum of the 7-methoxycoumarin photodimer **2a** resembles the spectrum of **5b**. In $CDCl_3$, the absorption of H_8 is located at δ 6.18, which in comparison with the H_8 absorption in **11** is moved to a higher field. In view of the strong spectral similarity with an isomer with the syn head-to-tail configuration together with the lower value of the dipole moment, we conclude that **2a** has a syn head-to-tail configuration.

From the nmr spectrum of a photolysis mixture of **1** in $CDCl_3$ the syn head-to-head structure of **2b** is put forward. Indeed the cyclobutane protons absorb at δ 4.15. This is at a slightly higher field than the cyclobutane of a syn head-to-tail dimer and is in agreement with the observed trend for cyclobutane proton absorption in syn head-to-head cyclomers (see Table V). The anti head-to-head dimer **13** of 7-acetoxycoumarin absorbs at higher field (δ 3.91) in $CDCl_3$ (*vide infra*). Also the absorption pattern in the phenyl region corresponds to that of a syn head-to-head cyclomer.

The percentages of the head-to-head and head-to-tail cyclomers of the nonsubstituted (**3**), monosubstituted (**6**), and disubstituted (**9**) 7,7′-polymethylenedioxycoumarins with varying numbers of methylene units are assembled in Table I.

TABLE I

PHOTOISOMERIZATION OF 7,7′-POLYMETHYLENEDIOXYCOUMARINS[a]

Starting compd	n	Head-to-head,[b,d] %	Head-to-tail,[b,d] %
3a	2	85	15
3b	3	41	59
3c	4	42	58
3d	5	40	60
3e	6	30	70
3f	7	40	60
3g	8	28	72
3h	9	33	67
3i	10	32	68
3j	11	33	67
6c	4	30	70
9d	5	3[c]	97

[a] All the dioxycoumarins were irradiated in dichloromethane at a concentration of 10^{-2} *M*, except **3a**, which was irradiated at a concentration of 2×10^{-3} *M* in the same solvent. [b] In the concentration range studied, 3% (irradiation of **3b**) up to 15% (irradiation of **3j**), intermolecular reaction occurred. [c] 3% head-to-head isomer was isolated by column chromatography. This isomer was not detected in the nmr spectrum of the photolysis mixture. [d] The ratio remains constant up to high conversions.

The non- and monosubstituted dioxycoumarins photoisomerized to both the head-to-tail and the head-to-head structures, while the dimethyl-substituted dioxycoumarin formed predominantly the head-to-tail isomer.

Upon photolysis in different solvents, no correlation was found between the dielectric constant of the solvent and the ratio between the two isomers. The irradiation of 7,7′-pentamethylenedioxycoumarin in benzene (ϵ 2), as well as in acetonitrile (ϵ 38), yielded the head-to-head (**4d**) and the head-to-tail (**5d**) isomers in the ratio of 3:7, while in dichloromethane (ϵ 8) a 2:3 ratio was found.

Upon irradiation of more concentrated solutions a larger amount of oligomeric material was formed; using a concentration of 5×10^{-2} and 10^{-1} *M*, 30 and 35% of oligomers were formed, respectively.

Upon benzophenone-sensitized irradiation of the higher 7,7′-polymethylenedioxycoumarins intermolecular adducts with an anti configuration were formed: 7,7′-deca- and 7,7′-undecamethylenedioxycoumarins yielded polymers with an intrinsic viscosity in chloroform at 25° of 0.25 and 0.38, respectively.[24] The anti configuration of this polymer was proved by the 100-MHz nmr spectrum of the polymer from **3j**. In $CDCl_3$, H_5 absorbed at δ 7.04, H_8 and H_6 as the AB part of an ABX system between 6.6 and 6.8. These absorptions correspond to these of the respective phenyl protons of **11**, excluding any interaction between adjacent phenyl nuclei.[20] At δ 3.83 and 3.75 two peaks were observed which could be attributed to cyclobutane protons absorbing considerably higher than any of the syn cyclobutane protons. This shielding effect is caused by the diamagnetic anisotropy effect of a C=O group in front of the cyclobutane proton if the molecule has an anti configuration, and such shieldings have been observed.[26]

Photochemistry of 7-Acetoxycoumarin.—7-Acetoxycoumarin (**12**) was prepared as reported in the literature[27] by the condensation reaction of acetylchloride and 7-hydroxycoumarin.

7-Acetoxycoumarin did not dimerize upon direct irradiation at 335 nm in dichloromethane, even if the concentration was increased to a value of 1 *M*.[28]

Upon benzophenone-sensitized irradiation, 7-acetoxycoumarin dimerized to form **13**, which has an anti head-to-head structure[29] as proved by the 60-MHz nmr spectrum in DMSO-d_6 and by the dipole moment. Nmr analysis showed the same results as in the case of the polymer derived from **3j**: the cyclobutane protons, absorbing as a singlet at δ 3.91, are shielded in comparison with the same protons in, *e.g.*, **4b** (4.35) and **5b** (4.08). The same explanation can be invoked. Also, the phenyl proton pattern in the nmr spectrum did not resemble that of a syn head-to-tail photocyclomer. The head-to-head arrangement of the two

(23) The dipole moments were determined by measuring the dielectric constants, the densities, and the refractive indices of isomer solutions, and using the formula of P. Huyskens and F. Cracco, *Bull. Soc. Chim. Belg.*, **69**, 422 (1960).

(24) The polymerization of these bifunctional molecules is another example of the recently defined new concept "photopolymerization."[25] Further results concerning the photopolymerization of dicoumarins will be published elsewhere.

(25) (a) F. C. De Schryver, W. J. Feast, and G. Smets, *J. Polym. Sci., Part A-1*, **8**, 1939 (1970); (b) F. C. De Schryver, N. Boens, and G. Smets, *ibid.*, **10**, 1687 (1972).

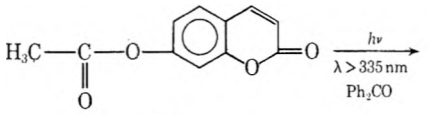
(26) (a) H. Werbin and E. T. Strom, *J. Amer. Chem. Soc.*, **90**, 7296 (1968); (b) O. L. Chapman and H. G. Smith, *ibid.*, **83**, 3914 (1961).

(27) H. Hlasiwetz, *Chem. Ber.*, **4**, 550 (1871).

(28) The only detectable change in the reaction mixture was an intense violet coloration, the cause of which is under study. It should be mentioned that the same coloration took place upon irradiation of 7-methoxycoumarin, 7,7,-polymethylenedioxycoumarins, as well as of coumarin itself in dichloromethane and in acetonitrile.

(29) Dimer **13** can be named 3,10-diacetoxy-6a*H*,6b*H*,12b*H*,12c*H*-cyclobuta[1,2-*c*:4,3-*c*′]-*anti*-biscoumarin.

coumarin units was proved by determining the dipole moments of **12** and **13** in benzene. Values of 4.8 and



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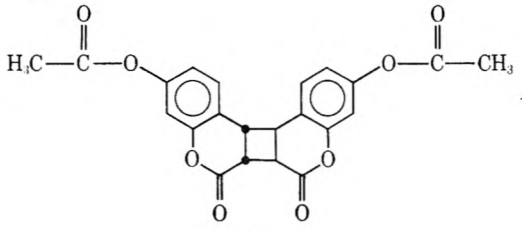


13

7.1 D, respectively, were found. Only a head-to-head position can cause this relative increase in polarity.

Photochemistry of Polymethylenedicarboxylic Acid (7-Coumarinyl) Diesters.—This class of dicoumarins (**14**) was synthetized in analogy with 7-acetoxycoumarin by the condensation of a dicarboxylic acid chloride and 7-hydroxycoumarin in benzene.

In contrast to 7-acetoxycoumarin, the analog bifunctional systems react upon direct irradiation in solution. Two cyclobutane ring containing regioisomers were formed in very divergent yields, as can be seen in Table II.

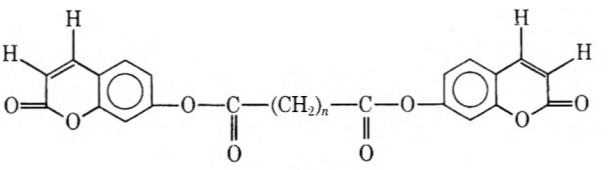
TABLE II
PHOTOISOMERIZATION OF POLYMETHYLENEDICARBOXYLIC ACID (7-COUMARINYL) DIESTERS[a]

Starting compd	n	Head-to-head **15**, %	Head-to-tail **16**, %
14c	4	90	10
14d	5	80	20
14e	6	87	13
14f	7	100	

[a] The dicoumarins **14d,e,f** were irradiated in dichloromethane at a concentration of 10^{-2} M. **14c** was irradiated in DMSO at a concentration of 5×10^{-3} M.

The structure of the photoisomer **15**[30] and **16** was established on the basis of nmr analysis. Since in **15d** and in **16d** the pentamethylene chain is too short to allow the formation of an anti isomer, these photoisomers should have the syn configuration. This was substantiated by the fact that, in the nmr spectra, the cyclobutane protons absorb at a lower field (**15d**, δ 4.24; **16d**, δ 4.20; both in DMSO-d_6) than the ones in the 7-acetoxycoumarin anti photodimer **13** (δ 3.91 in DMSO-d_6) where they are shielded by the C=O group of the opposite lactone function. The absence of a selectively shielded phenyl proton H_8 suggests a head-to-head structure for isomer **15d**. A further proof for the syn head-to-head structure follows from the comparison of the cyclobutane proton absorptions of $CDCl_3$ solutions of **4f** and **15d** in 100-MHz nmr spectra after addition of EuFOD.[21] The pattern of the AA′XX′ cyclobutane system of the syn head-to-head molecule **4f**, complexed with EuFOD, is rather complicated, as may be seen in Figure 1c. The coupling constants are

(30) In general the *syn* head-to-head regioisomer may be called 3,10-alkylenedicarboxy-6a*H*,6b*H*,12b*H*,12c*H*-cyclobuta[1,2-*c*; 4,3-*c*′]-*syn*-biscoumarin, while the *syn* head-to-tail isomer should be named 3,9-alkylenedicarboxy-6a*H*,6b*H*,12a*H*,12b*H*-cyclobuta[1,2-*c*; 3,4-*c*′]-*syn*-biscoumarin.



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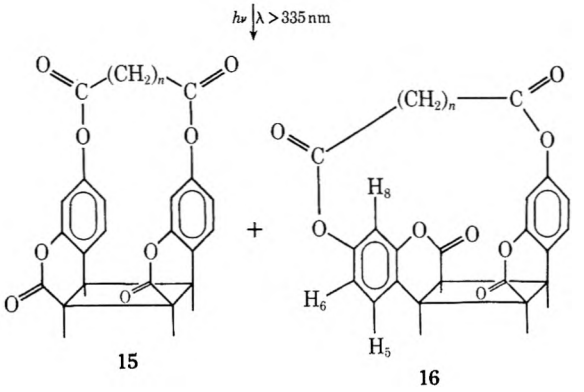


15 **16**

14,15,16c,d,e,f, n = 4,5,6,7, respectively

$J_{AA'}$ (or $J_{XX'}$) = 10, $J_{XX'}$ (or $J_{AA'}$) = 8.3, $J_{AX} + J_{AX'}$ = 10.3 cps. The cyclobutane AA′XX′ system of **15d** with EuFOD has exactly the same pattern. The minor photoisomer **16d** has a syn head-to-tail structure, since protons H_8 are shielded in comparison with the same protons in **11**. This conclusion was substantiated by the nmr spectrum in $CDCl_3$ containing EuFOD. In the syn head-to-tail molecule **5b**, the protons AA′ and XX′ of the AA′XX′ cyclobutane system absorb as two virtual triplets (Figure 1b); this is explained by the almost equal values of J_{AX} and $J_{AX'}$ (protons A and A′ are shifted the most since they are nearest to the complexed C=O; $J_{AX} + J_{AX'}$ = 15 cps. Upon addition of EuFOD to **16d**, the absorptions of protons AA′ and XX′ appear also as two virtual triplets with $J_{AX} + J_{AX'}$ = 16.2 cps.

Photoreversibility.—All the cyclomers can be cleaved upon irradiation with shorter wavelength light. Upon irradiation of a dichloromethane solution of **4b** and **5b** (5×10^{-5} M) with $\lambda \geq 300$ nm, the uv spectra of the photolyzed solutions showed the absorption characteristics of the dioxycoumarin. Upon irradiation of **5b** on a preparative scale, the nmr spectrum of the crude photolysis mixture showed the presence of 35% **3b**, 45% **4b**, and 20% **5b**.

Further work on the mechanism of the photocyclomerization and on the reverse reaction will be reported in the near future.

Conclusions

In the photolysis of the 7,7′-polymethylene dioxycoumarins containing more than two methylene units, neither the chain length between the two coumarin functions nor the solvent polarity seem to exert an important influence on the product distribution. The intramolecular syn reaction is predominant, even when the two chromophores are separated by 13 atoms (n = 11). In the case of the diesters, the syn head-to-head to syn head-to-tail ratio seems to be more strongly affected by the chain length and the former isomer is now the most abundant one.

Upon irradiation of the 7,7′-pentamethylenedi(4-methyl)oxycoumarin **9** steric factors play a role in the

determination of the reaction products. Almost no syn head-to-head isomer is formed.

Even upon irradiation of 10^{-1} M solutions the intramolecular reaction remains the most important one. Upon sensitized irradiations of the dioxycoumarins with 10 and 11 methylene units in the chain intermolecular adducts, having an anti configuration, are formed. All the photocyclomerizations are reversible.

Experimental Section

Materials.—7-Hydroxycoumarin (umbelliferon) (Fluka, pract.) was used as received. Dichloromethane (Fluka, puriss.), benzene (Merck, pro analysis), and acetonitrile (Baker Analytical Reagent) were treated with Merck 4 Å molecular sieve before use. Acetic acid (Merck, pro analysis) was used as supplied. Dimethyl sulfoxide (Carlo Erba, RP grade) was dried over sodium and distilled; it was stored over a molecular sieve. Benzophenone (Schuchardt) was distilled and recrystallized from cyclohexane. The α,ω-dibromoalkanes used were purchased from Fluka (1,8-, 1,11-dibromoalkanes), from Schuchardt (1,4-, 1,5-, 1,6-, 1,7-, 1,9-, 1,10-dibromoalkanes), from UCB (1,3-dibromopropane), and from Aldrich (1,2-dibromoethane). Methyl iodide was purchased from Merck. The 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione europium-(III) derivative was from Aldrich (Resolve-Al EuFOD).

Spectra and Physical Data.—Infrared spectra were measured in KBr pellets with a Perkin-Elmer 257 grating infrared spectrophotometer. Ultraviolet spectra were measured with a Cary Model 17 recording spectrometer. Melting points are from a Leitz Wetzlar melting point measurement microscope and are not corrected. Nmr spectral data were obtained from a Varian A-60 and a Varian XL-100 apparatus. Mass spectral data were measured with a AEI-MS902S. Molecular weights were determined with a Mechrolab 301A vapor pressure osmometer.

Irradiation Equipment.—A Rayonet photochemical reactor, type RPR 208, from the Southern New England Ultraviolet Co., was used in all the experiments. This reactor was fitted with a set of either RUL 3500-Å lamps. For the photocleavage, either RUL 3000-Å lamps were used.

Inside the reaction chamber the temperature varied between 35 and 40°. Most of the photoreactions have been carried out in double-chamber Pyrex vessels. The outer chamber contained a solution of 479 g of sodium bromide and 3 g of lead acetate of 3 g of lead nitrate[15] in 1 l. of water. A 0.5-cm layer of the solution has optical densities of 0.075, 0.44, and 1.0 at 350, 340, and 335 nm, respectively. The path length of the filter solution was 10 mm and that of the reaction solution was 24 mm.

Irradiation Procedure.—After loading, the tubes were flushed with a stream of nitrogen or argon, which was dried over $CaCl_2$. In some cases, the tubes have been degassed by three freeze–thaw cycles, sealed off, and irradiated.

Synthesis of the Model Compounds 7-Methoxycoumarin (1) and 7-Acetoxycoumarin (12).—7-Methoxycoumarin was prepared by refluxing for 8 hr 7-hydroxycoumarins (0.06 mol) with methyl iodide (0.148 mol) in dry acetone in the presence of anhydrous potassium carbonate (0.12 mol). Acetone was distilled off and the residual mixture was transferred into an excess of water. The precipitate was filtered off and washed with distilled water. The crude product was dried and sublimed at 100° under reduced pressure. Finally, the compound was recrystallized from a methanol–water mixture, mp 119–120° (lit.[31] mp 114°; lit.[9] mp 117–118°).

7-Acetoxycoumarin was prepared as described[27] and recrystallized from ethanol, mp 142–144° (lit.[31] mp 140°), yield 85%.

Synthesis of the 7,7′-Polymethylenedioxycoumarins 3, 6, and 9.—All the 7,7′-polymethylenedioxycoumarins **3** were synthesized following the same general procedure as used in the synthesis of the 7-methoxycoumarin. The precipitate contained the dioxycoumarin and a small amount of the α-(7-oxycoumarinyl),-ω-bromoalkane. It was taken up in chloroform or in acetone, treated with carbon black, and precipitated in diethyl ether or in diethyl ether–petroleum ether (bp 40–60°) (up to n = 6, no petroleum ether was used; from n = 7 on, petroleum ether must be present in the precipitating medium since the dioxycoumarins with a longer polymethylene chain are slightly soluble in diethyl ether). The precipitate was filtered off and this procedure was repeated twice, without the carbon black treatment, in order to remove the monofunctional bromo compound. The purity of the product was checked by tlc (silica gel, chloroform or chloroform–5% acetone as developing solvent). Before use, the dioxycoumarins were purified further by column chromatography on Florisil 60–100 mesh (Merck) eluting with chloroform. About 25 g of Florisil was used in a column with a diameter of 18 mm. After the solvent was evaporated off on a rotary evaporator, the residue was taken up and recrystallized several times in an appropriate solvent. The physical data concerning the polymethylenedioxycoumarins are collected in Table III.

The 7,7′-polymethylenedi(4-methyl)oxycoumarin (**9**) was prepared following the same procedure as in the synthesis of the nonsubstituted dioxycoumarins. The physical data of the 7,7′-pentamethylenedi(4-methyl)oxycoumarin are reported in Table III.

The asymmetric monomethyl-substituted dioxycoumarin **6** was synthesized by refluxing α-(7-oxycoumarinyl)-ω-bromoalkane (0.03 mol) and 7-hydroxy-4-methylcoumarin (0.03 mol) in dry acetone in the presence of 0.06 mol of dry potassium carbonate followed by the same purification procedures as for the symmetric compounds. The bromo-containing compound was obtained as a secondary product in the synthesis of the dioxycoumarins. The data concerning 1-(7-oxycoumarinyl)-4-(4-methyl-7-oxycoumarinyl) butane **6c** are given in Table III.

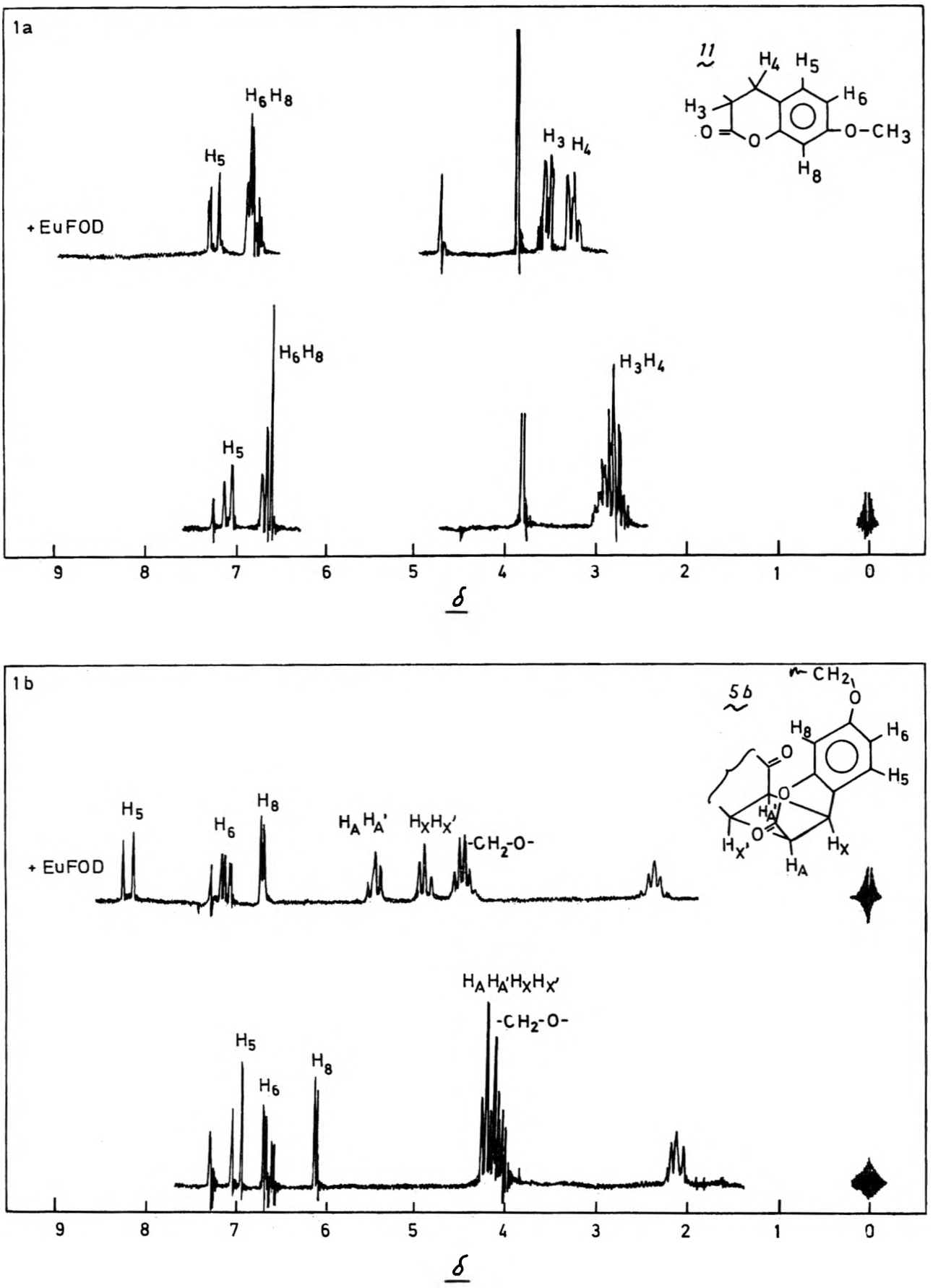
Synthesis of Polymethylenedicarboxylic acid (7-Coumarinyl) Diesters.—To a suspension of 0.06 mol of 7-hydroxycoumarin in 300 ml of dry benzene, 0.06 mol of dried and distilled pyridine was added. While the reaction mixture was warming up gently to about 40–50°, 100 ml of a benzene solution of 0.03 mol of diacid chloride was added dropwise. The reaction mixture was then warmed up until reflux. After an appropriate refluxing time, the benzene was evaporated off and the residue was transferred into a small quantity of acetone, and then into an excess of water. The precipitate was filtered off and washed several times with slightly alkaline water until fluorescence of the filtrate is no longer observed. After drying, the crude products were recrystallized several times in the appropriate solvents. Physical data concerning the diesters are given in Table IV.

Synthesis of 3,4-Dihydro-7-methoxycoumarin (11).—**11** was prepared by hydrogenation of 7-methoxycoumarin in benzene in the presence of palladium on charcoal. 7-Methoxycoumarin (2.85 g) was dissolved in 40 ml of benzene, containing 0.8 g of Pd/C catalyst. The apparatus was flushed with hydrogen prior to bubbling hydrogen through the suspension at about 50° for 4.5 hr. After the catalyst was filtered off, the solvent was evaporated. A colorless oil which solidified upon cooling was left. It was recrystallized from cyclohexane–carbon tetrachloride, yield 100%, mp 38.5–39.5°.

Direct Irradiation of 7-Methoxycoumarin in Dichloromethane.—A solution of 0.440 g of 7-methoxycoumarin in 50 ml of dichloromethane (5×10^{-2} M) was irradiated after flushing with dry argon for 1 hr, using RUL 3500-Å lamps in a Rayonet reactor and a sodium bromide–lead acetate[15] solution in the filter compartment of the reaction vessel. After a few hours, an intense violet coloration was observed which changed readily upon further irradiation to yellowish-brown. The solvent was evaporated off on a rotary evaporator under diminished pressure. The evaporation residue was dried extensively. The nmr spectrum of this crude photolysis mixture indicated that the reaction proceeded to an extend of 40%, the only detectable reaction product being one of the possible isomeric forms of the dimer of 7-methoxycoumarin. The mixture was purified by passage through a column with Florisil (60–100 mesh, Merck), using chloroform as eluent. The solvent of the slightly yellow eluents was evaporated off and the residue was taken up in ethanol. The photodimer precipitated while the starting material remained in solution. The physical data concerning this dimer are given in Table V.

Direct Irradiation of 7-Acetoxycoumarin in Dichloromethane.—Neither upon irradiation for 72 hr of a degassed solution of 0.156 g of 7-acetoxycoumarin in 7.5 ml of dichloromethane (1.02×10^{-1} M), nor upon irradiation for 184 hr of 9.1 ml of a solution containing 2.04 g of **12** (1.1 M), could dimer formation be observed. The only detectable change during the photolysis was the intense purple coloration of the solution.

(31) F. Tiemann and C. L. Reimer, *Chem. Ber.*, **12**, 993 (1879).



Figures 1a and 1b.—100-MHz nmr spectra in $CDCl_3$ of 11 (1a), **5b** (1b).

Benzophenone-Sensitized Irradiation of 7-Acetoxycoumarin in Dichloromethane.—A dichloromethane solution (19.6 ml) containing 0.621 g of **12** (1.55×10^{-1} *M*) and 0.112 g of benzophenone (3.1×10^{-2} *M*) was irradiated for 63 hr with RUL 3500-Å lamps after four freeze–thaw cycles. Benzophenone absorbed approximately 25% of the incident light [calculated on the basis of the concentrations and molar extinction coefficients at 350 nm of benzophenone (110 l. mol^{-1} cm^{-1}) and 7-acetoxy-

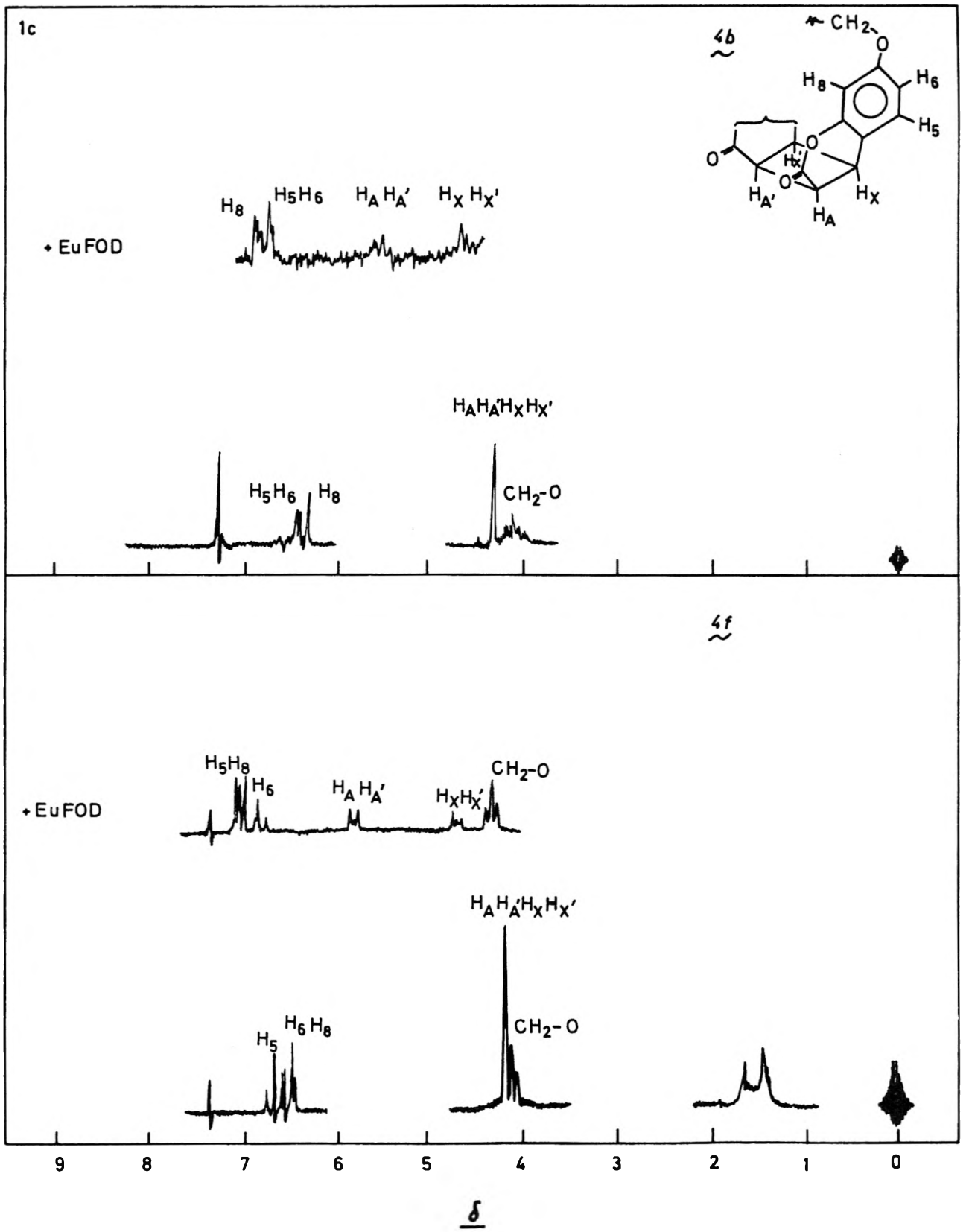


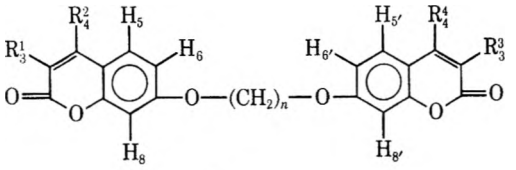
Figure 1c.—100-MHz nmr spectra in $CDCl_3$ of **4b** and **4f** (1c) prior and after addition of EuFOD.

coumarin (90 l. mol^{-1} cm^{-1}) in dichloromethane]. After reaction, the solvent was evaporated off and the residual mixture was triturated twice with ether. The ether solution contained only benzophenone, as was checked by tlc. The precipitate was dried extensively. The nmr spectrum in DMSO of this crude product showed only one signal in the cyclobutane region at δ 3.91. Apart from a weak spot due to residual starting compound, a tlc (silica gel) developed by chloroform–acetone (95:5) showed only one other spot at a higher R_f value. The crude product was taken up and recrystallized from carbon tetrachloride–chloroform (2:1). The physical data are given in Table VI.

Direct Irradiation of 7,7′-Polymethylenedioxycoumarins.—In general the two isomers in the case of shorter polymethylene chains ($n \leq 8$) were separated by taking up the evaporation residue of a photolyzed solution in dry benzene, out of which the

TABLE III

PHYSICAL DATA OF 7,7′-POLYMETHYLENEDIOXYCOUMARINS

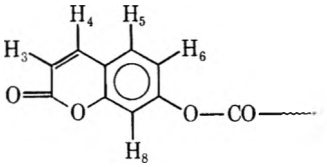


Compd	n	Reflux time, hr	Yield, %[a]	Recrystn solvent	Mp, °C[c]	Infrared spectrum, ν, cm⁻¹,[d] C=O[e,f]	Ultraviolet spectrum[g] λmax, nm	ε, M⁻¹ cm⁻¹	Nmr spectrum, δ, TMS[h,i] H8	H6H8[j]	R3	R4	Mass spectrum, M·+, m/e
3a	2	21	33	HOAc	237–238	1730	323	30,540	7.60	7.05–6.85	6.24	7.95	350
3b[b]	3	12.5	67	PhH	184–185.5	1720	324	30,960	7.55	7.0–6.75	6.22	7.88	364
3c	4	12.5	54	$CHCl_3/CCl_4$	182–183.5	1715	324	31,680	7.54	7.0–6.7	6.17	7.83	378
									7.38[k]	7.0–6.7	6.24	7.65	
3d	5	13	72	EtOH/PhH	138–138.5	1718	324	31,640	7.55	7.0–6.7	6.21	7.90	392
3e	6	18	77	PhH	163–164	1717	324	32,060	7.52	7.0–6.7	6.20	7.86	406
3f	7	14.5	64	PhH	132.5–134	1727	324	31,860	7.56	7.0–6.7	6.23	7.92	420
3g	8	13.5	67.5	PhH	148.5–149.5	1722	324	31,840	7.55	7.0–6.7	6.22	7.90	434
3h	9	13.5	63	CCl_4/CH_3CN	99–101	1727	324	32,000	7.33[k]	6.95–6.65	6.18	7.60	448
3i	10	13.5	46	PhH	135–136	1724	324	31,420	7.53	7.0–6.7	6.20	7.87	462
3j	11	17	68	PhH/hexane	117–117.5	1718	324	31,480	7.35[k]	6.95–6.65	6.21	7.60	476
6c	4	15[n]	75	$PhCH_3$	171–172.5	1715	322	31,600	7.48	6.95–6.65	R_3^1 6.11[l]	R_4^2 7.75	392
									H5, 7.42		R_3^3 6.01	R_4^4 2.33	
9d	5	34	84	CH_3CN	177–178	1742	322	31,400	7.59	7.0–6.6	6.09[m]	2.36	420

[a] Yield calculated on the basis of converted 7-hydroxycoumarin. [b] Found C, H, and O values were within 0.3% of calculated (actual results were supplied to Editor). [c] Uncorrected. [d] In KBr. [e] The C=O absorption appears as a complex structure which is centered at the given position. [f] The δ CH(cis) vibrations of 3a–j absorb as a doublet between 1390 and 1415 cm^{-1}. [g] In CH_2Cl_2. [h] In DMSO-d_6. [i] R = H. [j] H_6 and H_8 are described as the AB part of an ABX system. [k] In $CDCl_3$. [l] $R_3^1 = R_4^2 = R_3^3 = H$; $R_4^4 = CH_3$. [m] $R_3^1 = R_3^3 = H$; $R_4^2 = R_4^4 = CH_3$. [n] Refers to the reaction between 1-(7-oxycoumarinyl)-4-bromobutane and 4-methyl-7-hydroxycoumarin. Yield based on converted 4-methyl-7-hydroxycoumarin.

TABLE IV

PHYSICAL DATA OF POLYMETHYLENEDICARBOXYLIC ACID (7-COUMARINYL) DIESTERS



Compd[a]	n	Reflux time, hr	Yield, %[b]	Recrystn solvent	Mp °C[c]	Ultraviolet spectrum[d] λmax, nm	εmax, M⁻¹ cm⁻¹	Nmr spectrum, δ, TMS[e] H8	H6H8[f]	H3	H4	J34	Mass spectrum, M·+, m/e
14c	4	8	86	CH_3CN/DMSO	222–223	277	20,700						
						283	20,760	7.70	7.24–7.0	6.38	7.97	9.5	434
						313	17,200						
14d	5	6	80	EtOH/$CHCl_3$	138–139	277	20,000						
						283	20,000	7.75	7.3–7.0	6.45	8.04	9.5	448
						313	17,000						
14e	6	5	82	CH_3CN	176–178	277	20,870						
						283	20,830	7.74	7.3–7.0	6.44	8.03	9.5	462
						313	17,500						
14f	7	6	80	CH_3CN/CCl_4	123–124	277	21,250						
						283	21,330	7.72	7.3–7.0	6.42	8.01	9.5	476
						313	18,100						

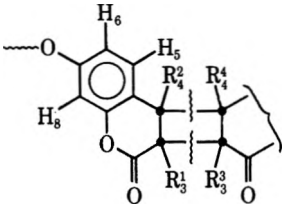
[a] In the infrared spectra, the phenyl ester carbonyl vibrations absorb at 1768 ± 2 cm^{-1}, the α,β-unsaturated lactone δ-lactone carbonyl at 1745 ± 1 and 1710 cm^{-1}, and the δ =CH (cis) vibrations absorb as a doublet between 1380 and 1405 cm^{-1}. [b] Yield based on converted 7-hydroxycoumarin. [c] Uncorrected. [d] In CH_2Cl_2. [e] In DMSO-d_6. [f] H_6 and H_8 are described as the AB part of an ABX system.

head-to-head isomer precipitates upon cooling. The irradiation products of the dioxycoumarins with a longer polymethylene chain were best separated by column chromatography.

As a typical example of the former class, a solution of 0.500 g of 7,7′-tetramethylenedioxycoumarin in 132 ml of dichloromethane (10^{-2} *M*) was degassed three times, sealed off *in vacuo*, and irradiated for 39 hr through a 1-cm filter solution.[15] After a few hours of irradiation, a violet color was observed which disappeared upon prolonged illumination. After irradiation the solvent was evaporated and the ir spectrum showed that the reaction was complete. A nmr spectrum of this crude mixture allowed the calculation of the percentages of the two isomers, based on the absorptions of the phenyl protons: 42% head-to-head and 57% head-to-tail isomer. Upon fractionated crystallization out of dry benzene, 0.173 g (34.6%) head-to-head isomer was separated. The filtrate was evaporated to dryness. A nmr spectrum of this residue showed the presence of an additional amount of about 7% of the head-to-head isomer. This mixture (0.291 g) in chloroform was brought on a column of 24-mm diameter filled with Florisil (60–100 mesh) to a height of about 10 cm.

TABLE V

PHYSICAL DATA OF THE PHOTOISOMERS OF THE DIOXYCOUMARINS



Compd	n	Recrystn solvent	Mp, °C[a]	Infrared spectrum, ν, cm⁻¹,[c] C=O	Nmr spectrum, δ, TMS[d] H6	H8	H5	R[f]	Mass spectrum, M·+, m/e
2		EtOH	205.5–207	1750	6.98	6.69	6.30	4.21	352
					7.04[e]	6.64	6.18	4.20	
4a	2	CCl_4/CH_2Cl_2	216–218	1764		6.5–6.2		4.28	350
4b	3	PhH	241–242[b]	1760		6.8–6.3		4.35	364
5b	3	$PhCH_3$	271–273[b]	1752	6.87	6.60	6.18	4.08	364
					6.97[e]	6.60	6.01	4.03	
4c	4	PhH	252–254[b]	1765		6.8–6.3		4.30	378
5c	4	$PhCH_3$	279–282[b]	1750	6.88	6.59	6.13	4.08	378
4d	5	PhH	236.5–238.5[b]	1760		6.8–6.3		4.25	392
5d	5	$PhCH_3$	291.5–294[b]	1748	6.88	6.62	6.15	4.09	392
4e	6	PhH	218	1765		6.8–6.3		4.18	406
5e	6	$PhCH_3$	*b*	1746	6.84	6.62	6.09	4.09	406
4f	7	$PhCH_3$/hexane	212–214	1768		6.7–6.3		4.13	420
						6.8–6.3		4.12	
5f	7	$PhCH_3$	286–287.5[b]	1754	6.84[e]	6.55	6.02	4.09	420
4g	8	$CCl_4/CHCl_3$	216–220	1764		6.9–6.2		4.13	434
5g	8	$PhCH_3$/hexane	246–249[b]	1752	7.00[e]	6.60	6.06	4.13	434
4h	9	CCl_4/CH_3CN	184.5–186	1767		6.7–6.2[e]		4.06	448[l]
5h	9	CCl_4	234.5–236[b]	1753	6.98[e]	6.59	6.06	4.12	448[l]
5i[k]	10	$PhCH_3$		1750	7.00[e]	6.62	6.11	4.17	462
5j[k]	11	Et_2O/hexane		1752	7.01[e]	6.62	6.11	4.16	476
7c	4	PhH	233–236	1760	6.73	6.40	6.27	*g*	392
8c	4	$PhCH_3$	215.5–217.5[b]	1757	7.09[e]	6.69	6.02	*h*	392
					H_5, 7.02	H_6, 6.66	H_7, 6.00		
10d	5	CCl_4/hexane	212–215	1757	6.88	6.57	6.04	*i*	420
					7.07[e]	6.63	6.05	*j*	

[a] Uncorrected; some of these compounds decompose to the open form upon heating. [b] These compounds sublime. [c] In KBr. [d] In DMSO-d_6. [e] In $CDCl_3$. [f] The absorption is centered at the position cited. [g] Absorptions of R_3^1 = H at δ 4.31, R_4^2 = H at 3.76, R_3^3 = H at 3.92, and R_4^4 = CH_3 at 1.76. [h] Absorptions of R_3^1 (or R_3^3) = H at δ 3.72, R_4^2 = H between 3.8 and 4.5 with $-OCH_2-$, R_3^2 (or R_3^1) = H at 3.69, and R_4^4 = CH_3 at 1.66. [i] Absorption of R_3^1 = R_3^3 = H at δ 3.50, R_4^2 = R_4^4 = CH_3 at 1.52. [j] Absorption of R_3^1 = R_3^3 = H at δ 3.37, R_4^2 = R_4^4 = CH_3 at 1.63. [k] **4i**, **5i**, **4j**, and **5j** were not isolated in pure form. [l] Tonometry (Mechrolab) in $CHCl_3$ indicated for **4h** a molecular weight of 460 and for **5h** 464.

Elution with 1 l. of chloroform yielded, after the evaporation of the solvent, 0.180 g of crude head-to-tail isomer. The column was freed of organic material by eluting with glacial acetic acid; the fraction contained a small amount of head-to-head isomer and some oligomeric species. The acid was evaporated and the residual product was extensively washed with water. The isomers were purified by recrystallization from the appropriate solvents. The photoisomers of the dioxycoumarins with a longer polymethylene chain could not be separated easily by fractionated crystallization and were isolated by column chromatography. As a typical example for this class, a degassed solution of 0.492 g of **3h** in 110 ml of dichloromethane (10^{-2} *M*) was irradiated for 115.5 hr. The head-to-tail isomer was isolated by elution of the crude photolysis mixture on a column of 24 mm diameter filled with Florisil (60–100 mesh) together with 11% of starting material (0.230 g after recrystallization from carbon tetrachloride). Subsequently acetic acid was used as eluent; the solvent was evaporated off and the residual mixture was washed extensively with water. The brown-colored residue (0.130 g) contained the head-to-head isomer and some oligomeric species, as was shown by a vapor pressure osmometric measurement of the molecular weight 627 (molecular weight of the starting material is 448). The oligomers were only slightly soluble in acetone. The acetone-soluble part was transferred into water. Upon evaporation of the acetone on a rotary evaporator, a pale yellow precipitate was formed, being the head-to-head regioisomer (0.095 g). A white crystalline precipitate was separated upon recrystallization from carbon tetrachloride–acetonitrile (15:1). Knowing the nmr absorptions of all the products present in the crude photolysis mixture, its composition was calculated to be 52% of **5h**, 26% of **4h**, 11% of **3h**, and 11% of oligomeric species.

The irradiation of the monomethyl-substituted dioxycoumarin **6c**, the analysis, and the separation of the photolysis mixture proceeded in the same way as in the latter class.

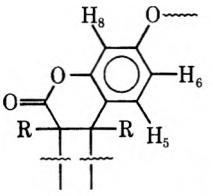
After irradiation of 7,7′-pentamethylenedi(4-methyl)oxycoumarin (**9d**), a nmr spectrum of the photolysis mixture showed that the syn head-to-tail isomer was formed predominantly (95%); 3% syn head-to-head isomer was isolated by column chromatography on Florisil with acetic acid as eluent.

The polymethylenedioxycoumarins **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, and **3j** were irradiated as 300, 132, 16.6, 100, 100, 150, 110, 100, and 100 ml, respectively, of 10^{-2} *M* solutions in tubes with a 24-mm diameter through a 1-cm filter solution layer. The irradiation times were 72, 39, 15.5, 29.75, 52.75, 91, 115.5, 160, and 142 hr, respectively. **3a** was irradiated as a 2×10^{-3} *M* solution for 216 hr. Irradiation of more concentrated solutions of **3a** resulted in the formation of insoluble polymeric material. **6c** and **9d** were irradiated as 86 and 100 ml of 10^{-2} *M* solutions for 44 and 65 hr, respectively. The physical data concerning the photoisomers of **3**, **6**, and **9** are given in Table V.

Benzophenone-Sensitized Irradiation of 7,7′-Polymethylenedioxycoumarins.—A mixture of 5×10^{-3} *M* 7,7′-decamethylenedioxycoumarin and 2.98 *M* benzophenone (50% of the light absorbed by the sensitizer) in dichloromethane was degassed and irradiated through a 1-cm filter solution[14] for 65 hr. The solvent was evaporated on a rotary evaporator and the residue

TABLE VI

PHYSICAL DATA OF THE PHOTOISOMERS OF THE POLYMETHYLENEDICARBOXYLIC ACID (7-COUMARINYL) DIESTERS



Compd	n	Recrystn solvent	Mp, °C[a]	Infrared spectrum, ν, cm⁻¹[b]	Nmr spectrum, δ, TMS[c] $H_5H_6H_8$[d]	Nmr spectrum, δ, TMS[c] R[e,f]	Mass spectrum, M·⁺, m/e
13		$CCl_4/CHCl_3$	228–231	1762	7.1–6.85	3.91	408
15c	4	$PhCH_3/CH_3CN$	215–217.5	1767	7.1–6.6	4.31	434
15d	5	PhH/CH_3CN	229–233	1762	6.8–6.3	4.24	448
					6.8–6.5[g]	4.27	
16d	5	$CCl_4/CHCl_3$	237–241	1759	H_5H_6 6.96,[f] H_8 6.06[f]	4.20	448
				1750	H_5 7.10, H_8 6.28[g] H_6 6.94	4.20	
15e	6	$PhCH_3$	229.5–232	1767	7.0–6.5	4.25	462
15f	7	$PhCH_3$	216.5–218	1787, 1756	6.9–6.5	4.22	476

[a] Uncorrected. [b] In KBr. [c] In DMSO-d_6. [d] Protons H_5, H_6, and H_8 are the constituents of an ABC system. [e] R = H. [f] The absorption is centered at the position cited. [g] In $CDCl_3$.

was triturated three times with 20 ml of diethyl ether. The residual solid was dissolved in dichloromethane and precipitated in *n*-hexane. This procedure was repeated three times. The precipitate was dried under vacuum at room temperature, yield 80%.

Direct Irradiation of the Polymethylenedicarboxylic Acid (7-Coumarinyl) Diester.—All the solutions were irradiated through a 1-cm filter solution layer.[14] Tetramethylenedicarboxylic acid (7-coumarinyl) diester (**14c**) was irradiated in dried and distilled dimethyl sulfoxide, owing to the low solubility in dichloromethane. A solution of 0.327 g in 150 ml of DMSO (5×10^{-3} *M*) was flushed with dry argon and irradiated for 187 hr. After irradiation, the solution was slightly yellow. The dimethyl sulfoxide was distilled off under reduced pressure. The residual mixture was precipitated into water. The precipitate was filtered, washed with water, and dried.

An nmr spectrum of this mixture, 0.251 g, indicated the presence of 7% starting material. This mixture (0.194 g) was recrystallized from toluene–acetonitrile (4:1); 0.128 g of the head-to-head isomer precipitated upon cooling. The second isomer has not yet been separated. Pentamethylenedicarboxylic acid (7-coumarinyl) diester (**14d**) was irradiated for 119 hr as a 10^{-2} *M* solution (0.672 g in 150 ml of dichloromethane) which was flushed with dry argon for 1 hr. The ratio of syn head-to-head to syn head-to-tail isomer was calculated from the integration of the cyclobutane proton region in the nmr spectrum. The two isomers were separated by crystallizations from benzene–acetonitrile (50:1) out of which **15d** precipitated as white needles upon cooling (0.490 g). The filtrate was evaporated off and brought on a Florisil column, which was eluted with chloroform. The first fractions contained predominantly the head-to-tail isomer **16d**, which was further purified by recrystallization from carbon tetrachloride–chloroform (30:1) (0.104 g after recrystallization).

14e and **14f** were irradiated as 10^{-2} *M* degassed solutions in dichloromethane for 69 and 88 hr, respectively. The composition of the reaction mixture was determined by nmr spectroscopy. The head-to-head isomers **15e** and **15f** were separated from the starting compound by recrystallizations from 50:1 toluene–acetonitrile and from benzene, respectively, and further purified by repeated crystallizations from toluene. The physical data of the photoisomers of **14** are given in Table VI.

Photocleavage of the Cycloadducts.—The reversibility of the photocycloaddition was checked by uv spectroscopy. A 5×10^{-5} *M* solution (10 ml) of **4b** or **5b** was irradiated in a Pyrex tube which was fitted with a uv cell. The solution was flushed with dry argon for 0.5 hr and irradiated with RUL 3000-Å lamps; 0.109 g of **5b** was irradiated in 100 ml of dichloromethane (3×10^{-3} *M*) for 139.5 hr with the same lamps. The solvent was evaporated off and the composition of the reaction mixture was calculated from the nmr spectrum.

Registry No.—**1**, 531-59-9; **2a**, 37786-10-0; **2b**, 37818-63-6; **3a**, 37786-11-1; **3b**, 34333-09-0; **3c**, 34333-10-3; **3d**, 34333-11-4; **3e**, 37818-64-7; **3f**, 37786-15-5; **3g**, 37786-16-6; **3h**, 37818-65-8; **3i**, 37818-66-9; **3j**, 37786-17-7; **4a**, 37786-18-8; **4b**, 37786-19-9; **4c**, 37782-96-0; **4d**, 37782-97-1; **4e**, 37782-98-2; **4f**, 37782-99-3; **4g**, 37783-00-9; **4h**, 37783-01-0; **5b**, 37783-02-1; **5c**, 37783-03-2; **5d**, 37783-04-3; **5e**, 37783-05-4; **5f**, 37818-67-0; **5g**, 37783-06-5; **5h**, 37783-07-6; **5i**, 37783-08-7; **5j**, 37783-09-8; **6c**, 37783-13-4; **7c**, 37783-10-1; **8c**, 37783-11-2; **9d**, 23863-89-0; **10d**, 37783-12-3; **11**, 20921-02-2; **12**, 10387-49-2; **13**, 37783-17-8; **14c**, 37783-18-9; **14d**, 37783-19-0; **14e**, 37783-20-3; **14f**, 37783-21-4; **15c**, 37783-22-5; **15d**, 37783-23-6; **15e**, 37783-24-7; **15f**, 37783-25-8; **16d**, 37783-26-9; 7-hydroxycoumarin, 93-35-6; 1,8-dibromooctane, 4549-32-0; 1,11-dibromoundecane, 16696-65-4; 1,4-dibromobutane, 110-52-1; 1,5-dibromopentane, 111-24-0; 1,6-dibromohexane, 629-03-8; 1,7-dibromoheptane, 4549-31-9; 1,9-dibromononane, 4549-33-1; 1,10-dibromodecane, 4101-68-2; α-(7-oxycoumarinyl)-ω-bromobutane, 37783-33-8; 7-hydroxy-4-methylcoumarin, 90-33-5; 1,4-butanedicarboxylic acid dichloride, 111-50-2; 1,5-pentanedicarboxylic acid dichloride, 142-79-0; 1,6-hexanedicarboxylic acid dichloride, 10027-07-3; 1,7-heplanedicarboxylic acid dichloride, 123-98-8.

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The Influence of Electron-Withdrawing Substituents on the Photochemical Behavior of Bicyclic 6/6-Fused Cross-Conjugated Cyclohexadienones[1]

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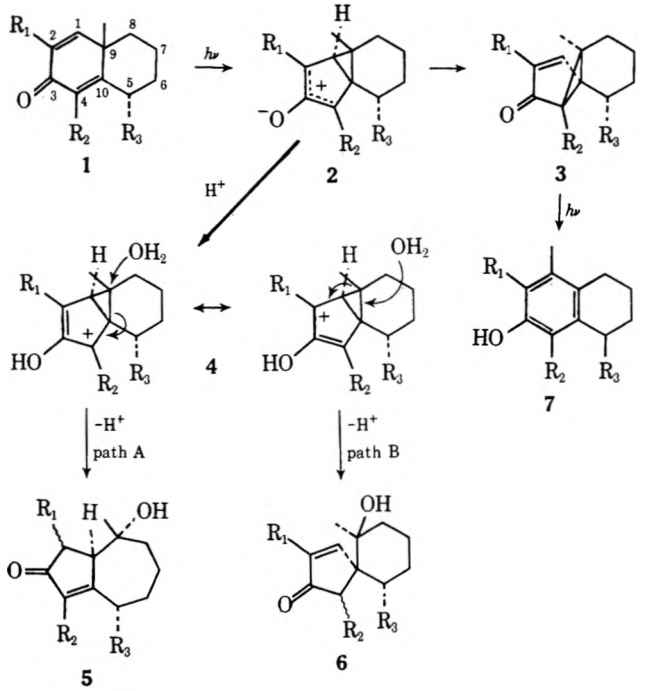
Derivatives of the bicyclic 6/6-fused cross-conjugated cyclohexadienone, 3-keto-9-methyl-$\Delta^{1,6}$-hexahydronaphthalene (**1j**), with electron-withdrawing formyl, carbonyl, and carbomethoxyl groups at positions 2 and 4 were synthesized and irradiated in aqueous acetic acid and in some cases other solvents. Each of the 2-substituted dienones was converted photochemically into a hydroazulene derivative in good yield. The 2-carboxy dienone **1e** proved to be an exceedingly useful compound for the synthesis of ring A unsubstituted hydroazulenes, as decarboxylation of the initial rearrangement products occurred spontaneously. The 4-formyl and 4-carbomethoxy dienones **1i** and **1g** failed to yield identifiable products having a rearranged carbon skeleton. In these cases it is possible that photochemical deconjugation to an enol of a β-dicarboxyl compound took place in preference to the normal cyclohexadienone rearrangement. However, the 4-carboxy dienone **1h** yielded spiro[4.5]decane derivatives on irradiation in aqueous acetic acid and in dioxane. In general, the mode of rearrangement of the substituted dienones can be intrepreted in terms of pathways generally accepted to be involved in cross-conjugated dienone rearrangements provided that the electron-withdrawing influence of the substituent and the ability of carboxyl substituents to act as internal proton donors to carbonyl groups are recognized.

The photochemical behavior of ring A unsubstituted and 2- and 4-methyl substituted cross-conjugated cyclohexadienones such as **1** (Scheme I) has been widely

SCHEME I



a, $R_1 = R_2 = H$; $R_3 = CH_3$ **d**, $R_2 = R_3 = H$; $R_1 = CHO$

b, $R_1 = R_3 = H$; $R_2 = CH_3$ **e**, $R_2 = R_3 = H$; $R_1 = CO_2H$

c, $R_2 = R_3 = H$; $R_1 = CH_3$ **f**, $R_2 = R_3 = H$; $R_1 = CO_2CH_3$

g, $R_1 = R_3 = H$; $R_2 = CO_2CH_3$

h, $R_1 = R_3 = H$; $R_2 = CO_2H$

i, $R_1 = R_3 = H$; $R_2 = CHO$

j; $R_1 = R_2 = R_3 = H$

studied.[2] The products of irradiation of dienones of this type are generally considered to arise *via* dipolar cyclopropyl intermediates such **2**, first proposed by Zimmerman and Schuster.[3a,4,5] Bicyclo[3.1.0]hex-2-en-3-one derivatives (lumiproducts) **3a–c**, which are obtained in good yield on irradiation of the corresponding dienones in neutral solvents such as dioxane,[6a–c] may be considered to arise *via* a symmetry-allowed 1,4-sigmatropic rearrangement of **2**.[7–9] However, when protic solvents such as aqueous acetic acid are employed, **2** too may be protonated to give the mesoionic species **4** which may undergo solvolytic cleavage to produce 5/7-fused or spiro hydroxy ketones. The mode of cleavage of **4** is apparently controlled by the electronic effect of methyl substituents. For example, on irradiation in aqueous acetic acid the 4-methyl dienone **1b** yielded exclusively the 5/7-fused hydroxy ketone **5b**,[10] while the 2-methyl compound **1c** yielded exclusively the spiro hydroxy ketone **6c**.[6c] Under similar conditions the unsubstituted dienone **1a** yielded an approximately 1:1 mixture of **5a** and **6a**.[6a] [In each case the hydroxy ketone products were accompanied by varying amounts of phenols (**7**), considered to arise as secondary photoproducts from the related lumiproducts.][2] Thus the location of an electron-releasing methyl group at C-4 or C-2 appears to increase the stability of the resonance form of **4** having a positive charge at that position and cleavage *via* path A or B takes place; and, when ring A of the dienone is unsubstituted, both resonance forms of **4** are approximately equal in energy so that products derived from both possible cleavage pathways are isolated.

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(2) For recent reviews see (a) P. J. Kropp, *Org. Photochem.*, **1**, 1 (1967); (b) K. Schaffner, *Advan. Photochem.*, **4**, 81 (1966).

(3) (a) H. E. Zimmerman[3b] and D. I. Schuster, *J. Amer. Chem. Soc.*, **84**, 4527 (1962); (b) H. E. Zimmerman and J. S. Swenton, *ibid.*, **86**, 947 (1964); (c) H. E. Zimmerman and J. S. Swenton, *ibid.*, **89**, 906 (1967).

(4) Zimmerman and coworkers[3a–c] have presented a detailed treatment of the mechanistic pathways by which species analogous to **2** may be formed photochemically from the parent dienone.

(5) For recent evidence for the intervention of dipolar intermediates in dienone photolysis see (a) M. H. Fisch, *Chem. Commun.*, 1472 (1969); (b) D. I. Schuster and V. Y. Abraitys, *ibid.*, 419 (1969); (c) D. I. Schuster and K. Liu, *J. Amer. Chem. Soc.*, **93**, 6711 (1971).

(6) (a) P. J. Kropp and W. F. Erman, *ibid.*, **85**, 2456 (1963); (b) P. J. Kropp, *ibid.*, **87**, 3914 (1965); (c) P. J. Kropp, *ibid.*, **86**, 4053 (1964).

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(8) T. M. Brennam and R. K. Hill, *ibid.*, **90**, 5614 (1968).

(9) R. B. Woodward and R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

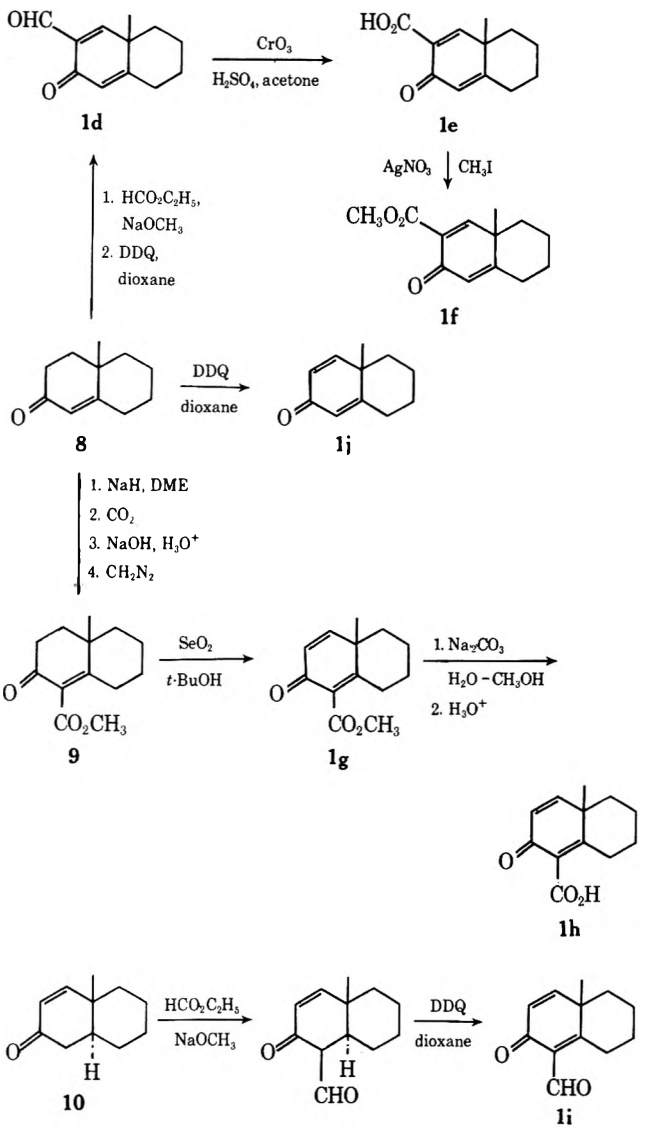
(10) (a) P. J. Kropp, *J. Org. Chem.*, **29**, 3110 (1964); (b) D. Caine and J. B. Dawson, *ibid.*, **29**, 3108 (1964).

The apparent involvement of species such as **4** in the reactions of **1a–c** suggested that substituents other than methyl groups might influence the course of cyclohexadienone photochemical rearrangements in nucleophilic solvents to produce largely or exclusively 5/7-fused or spirocyclic products. For example, electron-withdrawing groups such as formyl, carboxyl, or carbomethoxyl located at C-2 or C-4 would be expected to favor solvolytic cleavage of intermediates analogous to **4** *via* path A or path B to produce 5/7-fused or spirocyclic products, respectively. Furthermore, groups such as these should be easily removable after photolysis so that convenient routes to ring A unsubstituted products such as **5a** or **6a**, which are obtained only in poor yield from direct irradiation of **1a**,[6a] would be provided. However, it was recognized that excited-state species derived from dienones bearing chromophoric groups such as those indicated above might be capable of reactions which would prevent or compete with the formation of intermediates such as **4**. Also, even though such intermediates might be formed, the presence of functional groups on the allylic system might allow the intervention of reactions not normally encountered when simpler unsubstituted or methyl-substituted compounds are involved. The above considerations suggested that a study of the photochemical behavior of functionally substituted dienones related to **1** would be of synthetic and mechanistic interest. Thus the C-2 substituted dienones **1d–f** and the C-4 substituted compounds **1g–i** have been prepared and irradiated under various conditions. Our investigations have mainly involved a study of the photochemical behavior of compounds **1d–i** in nucleophilic solvents, but interesting results have also been obtained on irradiation of some of these compounds, particularly **1e** and **1h**, in dioxane.[11]

Results

The octalone **8**[12] served as the starting material for the synthesis of the ring A substituted dienones **1d–h** as well as the unsubstituted compound **1j**. Condensation of **8** with ethyl formate in the presence of sodium methoxide and reaction of the resulting hydroxymethylene derivative with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dry dioxane[13] gave **1d** in approximately 50% overall yield. The 2-carboxy dienone **1e** was obtained in 61% yield by oxidation of **1d** with Jones reagent.[14] This material was also prepared in low yield by condensation of 2-formyl-2-methylcyclohexanone with ethyl acetoacetate according to the procedure of Dreiding and Tomasewski.[15] The corresponding methyl ester **1f** was obtained in 88% yield by reaction of **1e** with methyl iodide in the presence of silver oxide.[15]

The 4-carbomethoxy dienone **1g** was obtained by dehydrogenation of the corresponding enone ester **9**. Enone **8** was converted into **9** by a procedure similar to that used by Wenkert and Jackson[16] for the preparation of a related compound. The $\Delta^{3,5}$-conjugated enolate of



8 [prepared from treatment of the enone with sodium hydride in 1,2-dimethoxyethane (DME)] was carbonated at C-4 by treatment with dry, gaseous carbon dioxide, and the 4-carboxy enone, obtained by brief treatment with aqueous sodium hydroxide to isomerize the β,γ double bond into conjugation and careful acidification, was esterified with diazomethane to give **9** in 63% yield. Attempted introduction of the 1,2 double bond by treatment of **9** with DDQ under a variety of conditions gave mixtures which appeared to be composed of the desired cross-conjugated dienone, the related linearly conjugated dienone, and trienone derived from further oxidation of either of the above. Attempted separation of **1g** from the other two products failed. However, the successful preparation of **1g** was carried out by oxidation of **9** with selenium dioxide in *tert*-butyl alcohol.[17] The dienone acid **1h** was obtained by mild hydroxysis of **1g** with aqueous sodium carbonate followed by acidification. The known dienone **1j**[18] was also obtained from **8** by dehydrogenation with DDQ.[19]

The 4-formyl dienone **1i** was prepared from the octalone **10**.[20] Conversion of **10** into its 4-hydroxymethylene derivative was accomplished using ethyl formate

(11) Preliminary reports which cover portions of this work have appeared: (a) D. Caine and J. F. Debardeleben, Jr., *Tetrahedron Lett.* 4585 (1965); (b) D. Caine, J. F. Debardeleben, Jr., and J. B. Dawson, *ibid.*, 3625 (1966).

(12) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

(13) J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. Cabezas Rivera, R. Urguiza, L. Carbona, J. C. Orr, and A. Bowers, *ibid.*, **29**, 3481 (1964).

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(15) A. S. Dreiding and A. J. Tomasewski, *J. Org. Chem.*, **19**, 241 (1954).

(16) E. Wenkert and G. Jackson, *J. Amer. Chem. Soc.*, **81**, 5601 (1959).

(17) A procedure similar to that described by Bloom was employed. See S. M. Bloom, *ibid.*, **81**, 4728 (1959).

(18) R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950).

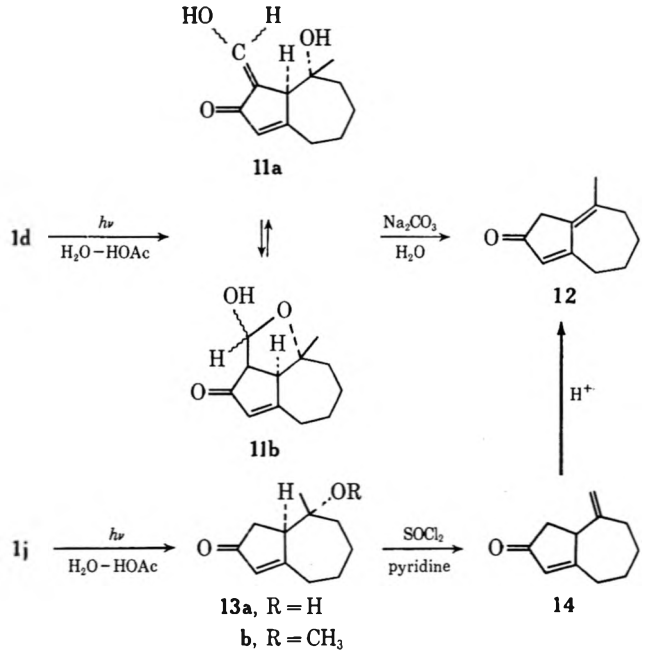
(19) D. Burn, D. M. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(20) C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.*, **80**, 3986 (1958).

and sodium methoxide in benzene in a procedure similar to that employed by Woodward and coworkers[21] for the preparation of a related compound, and this product was readily oxidized with DDQ[13] to give **1i**.

All of the new dienones exhibited the expected spectral properties (see Experimental Section). The compounds having substituents at C-4 exhibited a one-proton nmr absorption at a lower field than is normally observed for protons on saturated carbon atoms. This absorption was assigned to the C-6 equatorial proton, which is deshielded by the unsaturated substituent at C-4.[22]

The 2-formyl dienone **1d** was the first compound to be investigated. On irradiation (Pyrex)[23] of this material in 45% aqueous acetic acid for 3.5 hr at room temperature a viscous oil was obtained on removal of the solvent. The material could not be purified sufficiently to permit a positive structural assignment, but, on the basis of spectral and chemical evidence the hydroxymethylene compound **11a** and its related internal hemi-



acetal **11b** are considered to be the major components of the mixture. The crude product was soluble in dilute sodium hydroxide and it gave positive ferric chloride and Tollens' tests, indicative of an enolizable β-keto aldehyde grouping. It showed strong uv absorption at 235 nm and a weak band at 300 nm which shifted to longer wavelength (340 nm) in basic solution. The ir and nmr spectra also were consistent with the structures **11a** and **11b** (see Experimental Section). Attempts to convert the primary photoproduct to a solid derivative were unsuccessful and attempted purification of the material by chromatography on silica gel led to the isolation of the heteroannular dienone **12**, identified as described below, as the only significant product.

(21) A procedure similar to that described by Woodward and coworkers was employed. See R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952).

(22) M. Tomoeda, M. Inuzuka, T. Furuta, and T. Takahaski, *Tetrahedron Lett.*, 1233 (1964).

(23) Irradiations were carried out with a 450-W Hanovia high-pressure mercury lamp housed in a quartz or Pyrex probe. The solution was vigorously agitated with a stream of nitrogen for several minutes prior to and during the entire irradiation period.

On treatment of the crude photolysis mixture with dilute aqueous sodium carbonate, **12** was obtained in 70% yield from **1d**. This compound was readily identified on the basis of its spectral properties, which were quite similar to those reported for related 5/6-fused bicyclic[24] and steroidal[25] dienones. On catalytic hydrogenation **12** was converted into its tetrahydro derivative, which was capable of exchanging four hydrogen atoms for deuterium on equilibration with deuterium oxide in the presence of potassium carbonate.

Confirmation of the structure of **12** was obtained by its synthesis from the 5/7-fused hydroxy ketone **13a**. Using the conditions described by Kropp and Erman[10a] for the synthesis of **5a**, **13a** was obtained in *ca.* 10% yield by irradiation of **1j**. Dehydration of the hydroxy ketone with thionyl chloride in pyridine[26] gave the dienone **14** having an exocyclio double bond. This compound was readily isomerized into **12** on treatment with a catalytic amount of trifluoroacetic acid (TFA) in carbon tetrachloride.

Compound **1d** was also irradiated (quartz)[23] in dioxane solution. However, thin layer chromatography of the photolysis mixture indicated that at least four products were formed in low yield. In addition, a significant amount of polymeric material was produced. Because of these results and because Schaffner and coworkers[27] had reported that a 2-formyl steroidal dienone related to **1d** was stable to light at 2537 Å and gave a complex mixture composed of mainly phenolic products when irradiated in dioxane with a broad spectrum lamp, further studies on the photochemistry of **1d** in dioxane were not undertaken.

Irradiation (Pyrex)[23] of the 2-carboxy dienone **1e** at room temperature in several solvents gave various mixtures of products **13**, **14**, and **12**, and the enone lactone **15**. The yields of these products and the reaction conditions are shown in Table I.

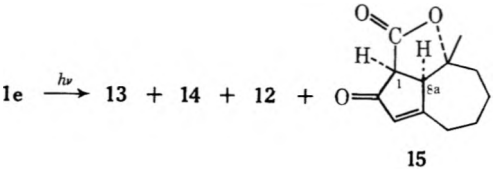


TABLE I
IRRADIATION OF
2-CARBOXY-3-KETO-9-METHYL-$\Delta^{1,4}$-HEXAHYDRONAPHTHALENE
(**1e**) UNDER VARIOUS CONDITIONS

Solvent	Time, hr	Product yield, % 13a	13b	15	12	14
45% aqueous HOAc	2.0	65		6	5	7
45% aqueous dioxane	2.0	60		12		
Anhydrous dioxane	2.0			16		67
Anhydrous methanol	2.5		48	14		13

The methoxy ketone **13b** was readily identified on the basis of its spectral properties, which were similar to those of **13a** if allowance was made for the presence of the C-8 methoxy rather than the hydroxy group. The

(24) D. Caine, A. M. Alejandre, K. Ming, and W. J. Powers, III, *J. Org. Chem.*, **37**, 706 (1972).

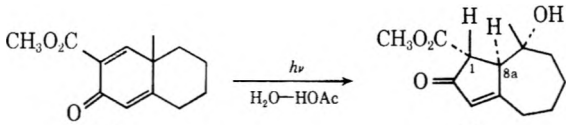
(25) G. Bozzato, H. P. Throndsen, K. Schaffner, and O. Jeger, *J. Amer. Chem. Soc.*, **86**, 2073 (1964).

(26) D. H. R. Barton, P. deMayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957).

(27) E. Alterburger, H. Wehrli, and K. Schaffner, *Helv. Chem. Acta*, **44**, 2735 (1963).

enone lactone **15** exhibited the expected ir absorptions for the γ-lactone (5.61 μ) and conjugated cyclopentenone (5.87 and 6.23 μ) groupings and its nmr spectrum showed a three-proton singlet at δ 1.05 ppm for the CH_3CO grouping, a one-proton multiplet at δ 5.81 ppm for the C-1 vinyl proton, and an AB quartet at δ 3.50 and 4.07 ppm (J = 7.4 Hz) for the C-1 and C-protons, respectively. The peaks of the doublet for the C-8a proton were slightly broadened presumably because of coupling with the C-4 proton which is allylic to it. The coupling constants for the AB quartet, indicating a dihedral angle of 15° or less,[28] are consistent with the stereochemical assignment at the 1 and 8a positions of **15**. On hydrolysis with aqueous sodium carbonate, acidification, and decarboxylation, **15** yielded a mixture of **12** and **13a**. The formation of **13a** served to verify the stereochemical assignment at C-8.

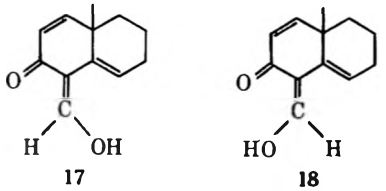
Irradiation (Pyrex)[23] of the 2-carbomethoxy dienone **1f** in 45% aqueous acetic acid at room temperature yielded the hydroazulene derivative **16** in 67% yield. The product exhibited the expected ir absorptions for the ester (5.77 μ) and conjugated cyclopentenone groupings (5.87 and 6.24 μ) and the nmr spectrum (DMSO-d_6) showed three-proton singlets at 0.82 and 3.36 ppm for the C-8 methyl and the methoxyl groups, a multiplet at 5.41 ppm for the C-4 proton, and a one-proton singlet at 3.19 ppm which probably corresponded to the C-1 or to the C-8a proton. Molecular models of **16** having the carbomethoxy group in what appears to be the more stable α configuration show that the dihedral angle between the C-8a hydrogen and the C-1 hydrogen which is trans to it is *ca.* 120°, indicating that a small coupling constant (J = 0–2 Hz) would be expected.[28] Chemical evidence for the structure of **16** was obtained by its



1f **16**

conversion into the dihydro derivative of **13a** by catalytic reduction of the carbon–carbon double bond followed by hydrolysis of the ester and decarboxylation.

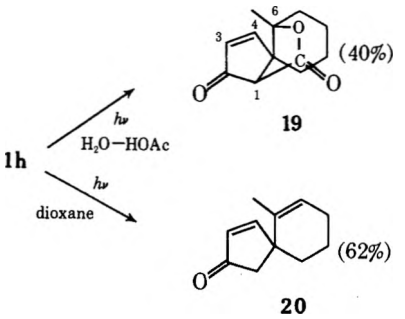
The results of irradiations of the 4-formyl dienone **1i** and the 4-carbomethoxy dienone **1g** were disappointing, since photoproducts having a rearranged carbon skeleton were not obtained. When **1i** was irradiated (Pyrex)[23] for 1.5 hr in aqueous acetic acid, examination of the nmr spectrum of the crude photolysis mixture indicated that it was composed of an approximately 4:1 mixture of the starting material and what appeared to be the enolic compounds **17** or **18**. Longer irradiation



17 **18**

periods produced no new products, and **1i** was recovered unchanged when irradiated in aqueous acetic acid using 2537-Å light source. When **1g** was irradiated (Pyrex)[23] in aqueous acetic acid for 2 hr, nmr analysis of the crude photolysis mixture indicated that a significant amount of the starting material had been consumed. However, chromatography of the photolysis mixture on silica gel failed to yield identifiable compounds other than the starting material.

Unlike dienones **1i** and **1g**, the 4-carboxy compound **1h** was smoothly converted into products having a spiro[5.4]decane carbon skeleton when irradiated in aqueous acetic acid or in anhydrous dioxane. Irradiation (quartz)[23] in the former medium for 30 min gave the lactone **19** in *ca.* 40% yield as the only isolated prod-



uct other than the starting material. Compound **19** exhibited the expected ir absorptions for a γ-lactone (5.65 μ) and cyclopentenone (5.84 and 6.05 μ), and the nmr spectrum ($CDCl_3$) showed a three-proton singlet at 1.15 ppm for the C-6 methyl group, a broad one-proton singlet at 3.38 ppm for the C-1 proton, a one-proton doublet at 6.17 ppm (J = 5.5 Hz) for the C-3 proton, and a broad doublet at 7.58 ppm (J = 5.5 Hz) for the C-4 proton. The broadening of the absorptions for the C-1 and C-4 protons presumably arises as a result of long-range interactions between the two nuclei.

When irradiated (quartz)[23] in anhydrous dioxane for 25 min, dienone **1h** gave the spiro dienone **20** in *ca.* 60% yield; a 25% recovery of starting material was obtained in this run. Compound **20** was readily identified on the basis of its spectral properties which showed close correspondence to those observed by Kropp[10b] for the related 3- and 10-methyl derivatives.

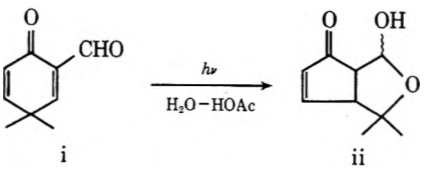
Discussion

Dienones **1d–f** were converted exclusively into hydroazulene derivatives on irradiation in aqueous acetic acid. This provides support for the premise that irradiations of cross-conjugated dienones having election-withdrawing substituents might give rise to resonance-stabilized intermediates such as **4** and that the location of these groups at C-2 would cause solvolytic cleavage of the 5,10 bond (path A) in **4** to occur preferentially.[29]

In view of the ease of preparation of 2-formyl dienones

(28) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 116.

(29) Since our initial investigation of the photochemical behavior of **1d**[11a] the conversion of 2-formyl-4,4-dimethyl-2,5-cyclohexadienone into an enone hemiacetal assumed to be ii,[30] and of 2-formyl substituted tetracyclic



i ii

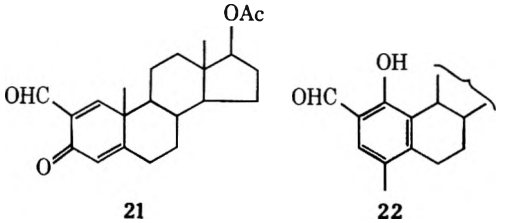
dienones into products having the Grayanotoxin carbon skeleton[31] by irradiations in aqueous acetic acid have been reported. These results are also consistent with the view that the course of solvolytic cleavage of resonance-stabilized intermediates analogous to **4** is controlled by the location of the electron-withdrawing formyl group.

(30) H. V. Secor, M. Bourlas, and J. F. DeBardeleben, *Experientia*, **27**, 18 (1971).

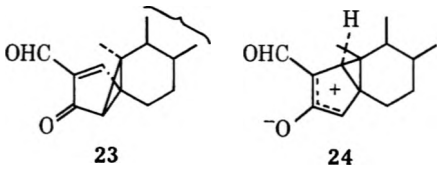
(31) M. Shiozaki, K. Mori, M. Matsui, and T. Hiraoka, *Tetrahedron Lett.*, 657 (1972).

such as **1d** from the corresponding octalone derivatives, the photochemical rearrangement of these compounds in aqueous acetic acid followed by base-catalyzed deformylation provides a convenient route to ring A unsubstituted hydroazulene derivatives. However, the synthetic value of the sequence is limited by the fact that the conditions required for the deformylation step also lead to the elimination of water. Thus **12** was the only product isolated when the crude photolysis mixture derived from irradiation of **1d** was treated with base.

The photolability of 2-formyl dienones in aqueous acetic acid contrasts strikingly with their behavior in dioxane.[27] Kropp[2a] has suggested that the phenol **22**



21 **22**

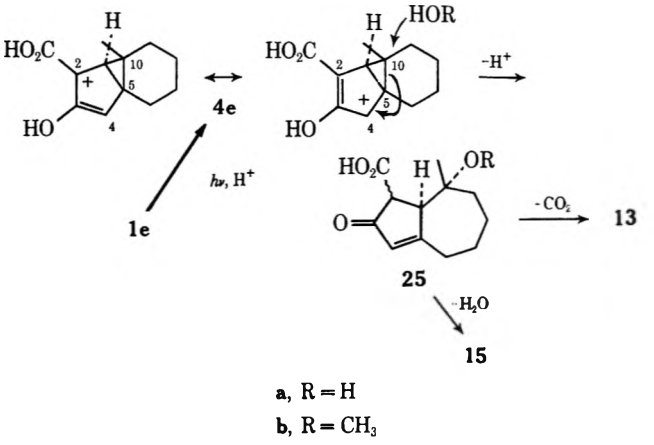


23 **24**

obtained in 9% yield by Schaffner and coworkers[27] by irradiation of the steroidal dienone **21** in dioxane arises from the lumiproduct intermediate **23**. The lumiproduct would be expected to be formed by way of the zwitterionic intermediate **24**. Because of the presence of the electron-withdrawing formyl group, **24** would be expected to be of higher energy than related unsubstituted and methyl-substituted species such as **2a–c**. Clearly charged species such as **24** might be expected to be formed more readily in polar, hydrogen bonding solvents such as aqueous acetic acid than in solvents of low polarily such as dioxane. Also, from a study of the ultraviolet spectrum of 2-formyl-$\Delta^{1,4}$-3-keto steroids in dioxane and in ethanol Edwards and coworkers[13] concluded that in ethanol reversible hemiacetal formation takes place. Thus in aqueous acetic acid it is possible that the hydrate of **1d** is formed and that excitation of this species is more efficient than that of **1d** itself. If the hydrated species were actually involved in the photochemical reaction, the *gem*-dihydroxy C-2 substituent would be expected to exert a similar influence to that of a formyl group on the course of cleavage of a species such as **4**.

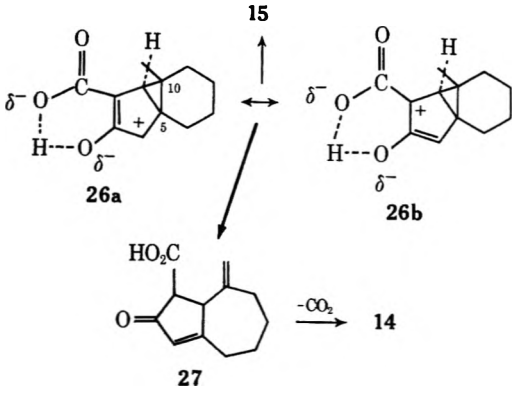
The 2-carboxy dienone **1e** proved to be a useful compound for the synthesis of ring A unsubstituted hydroazulenes. Irradiations of this compound in aqueous solvents and in methanol produced good yields of the 5/7-fused hydroxy and methoxy ketones **13a** and **13b**, respectively. The formation of these products can readily be rationalized in terms of the intervention of intermediate **4e**. In this case the structure having the positive charge at C-4 should be the major contributor to the resonance hybrid and solvolytic cleavage of the 5,10 bond would give initially the hydroxy β-keto acid **25**, which could undergo rapid decarboxylation to **13**.

Irradiation of **1c** in dioxane is likely to give rise to the dipolar intermediate **26**. The ability of the carboxyl



a, R = H
b, R = CH_3

group to internally protonate the carbonyl oxygen atom in **26** is likely to be the major factor contributing to the photolability of **1e** as compared with **1d** in dioxane. The conjugated chelate structure **26a** would be expected

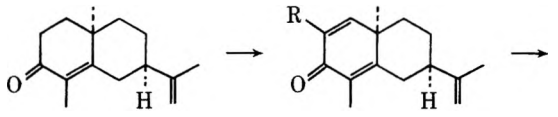


to be more stable than the unconjugated one **26b**, and cleavage of the 5,10 bond of the cyclopropane ring in **26** should again be favored. The dienone **14**, the major product of irradiation of **1e** in dioxane, may arise by the conversion of **26** into **27** followed by loss of carbon dioxide. The loss of a proton from the C-10 methyl group and the cleavage of the 5,10 bond is probably concerted, since no product derived from loss of a proton from C-9 was observed. Although we suggested earlier that the carboxyl group might internally assist in the proton abstraction reaction, it seems more likely that the proton loss to give a endocyclic double bond does not occur because neither of the C-9 protons can easily achieve a transoid-coplanar relationship with the 5,10 bond. On the other hand, free rotation readily allows such a relationship to be established between one of the methyl protons and the 5,10 bond. Dienone **14** was also obtained as a minor product of irradiation of **1e** in aqueous acetic acid and in methanol. Apparently, in these solvents proton loss competes to some degree with the nucleophilic attack of the solvent on C-10. Since dienone **13** is readily isomerized into the conjugated system **12**, it seems likely that the small amount of **12** isolated on irradiation of **1e** in aqueous acetic acid results from partial isomerization of **14** during photolysis and workup.

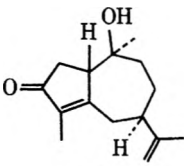
The keto lactone **15** was a minor product of irradiation of **1e** in all of the solvents studied. In the aqueous media this material probably arises as a result of competition between decarboxylation and lactonization of **25a**. Although direct conversion of **4e** into **15** cannot be excluded, the formation of **15** in anhydrous solvents

suggests that direct attack of the C-2 carboxyl group at C-10 of intermediates **4e** or **26** may be involved. Examination of models of these species shows that considerable stretching of the 5,10 bond would be required to bring the carboxyl group into the bonding distance of C-10. However, a transition state resembling the product in which breaking of the 5,10 bond is far ahead of formation of the new C–O bond would appear to satisfactorily explain the direct formation of **15**.

The photochemical rearrangement of 2-carboxy dienones such as **1e** provides a convenient method of preparation of synthetically useful hydroazulenes such as **13** and **14**. 2-Carboxy cross-conjugated dienones are relatively easily prepared from the parent octalone derivatives. Indeed, Piers and Cheng[32] have found that a better overall yield of the hydroazulene **28** is ob-



29 **30a**, R = H; **b**, R = CO_2H



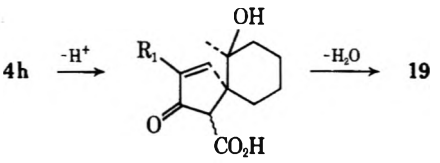
28

tained from the parent octalone **29** if the 2-carboxy dienone **30b** rather than the unsubstituted dienone **30a** is prepared and irradiated.

As expected, irradiation of the 2-carbomethoxy dienone **1f** in aqueous acetic acid produced the hydroxy keto ester **16** having the ring A substituent retained. It appears that compounds such as **16** are potentially useful intermediates for the synthesis of 1-alkyl hydroazulene derivatives, which could be obtained by base-catalyzed alkylation of **16** followed by hydrolysis and decarboxylation.

The 4-formyl and 4-carbomethoxy dienones **1i** and **1j**, respectively, failed to yield products having a rearranged carbon skeleton on irradiation under the conditions described above. This may be attributable to the fact that these compounds are capable of undergoing photochemical deconjugation of the 4,5 double bond to produce enols such as **17**.[33]

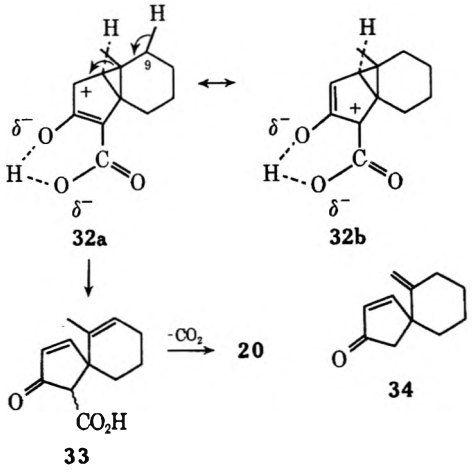
Although photochemical deconjugation of α,β-unsaturated acids has been observed,[33c,d] irradiation of the dienone acid **1h** both in aqueous acetic acid and in dioxane produced reasonably good yields of spiro[4.5]decane derivatives. The spiro lactone **19**, the product of irradiation of **1h** in aqueous acetic acid, probably arises from lactonization of the hydroxy β-keto acid **31**. Irradiation of **1h** in protic media should lead to the intermediate **4h**. The location of the electron-withdrawing group at C-4 should favor path B cleavage of **4h** and compound **31** would be the initial product of this process. Unexpectedly, no spiro hydroxy ketone derived



31

from decarboxylation of proposed intermediate **31** was obtained.

In aprotic media the spiro dienone **20** probably arises from decarboxylation of the β-keto acid **33**, which would be produced from proton loss from C-9 of the chelate intermediate **32**. Resonance structure **32a** should be



32a **32b** **33** **34**

the major contribution to the resonance hydrid **32** and this factor would be expected to favor cleavage of the 1,10 bond of the cyclopropane ring. Examination of models of **32** reveals that the C-9β proton can easily achieve a transoid-coplanar relationship with the 1,10 bond, providing a concerted pathway for the formation of **33** from **32**. No evidence for the formation of **34**, the possible product derived from proton loss from the C-10 methyl group of **32**, was obtained. Although the C-4 carboxyl group does appear to control the direction of cleavage of the cyclopropane ring in the intermediate **32** it apparently does not play a role in determining the direction of formation of the new B ring double bond. Thus, as suggested above, it seems unlikely that the presence of the C-2 carboxyl group in **26** is the primary factor responsible for the exclusive formation of the exocyclic **14** on irradition of **1e** in anhydrous dioxane. Again, the ability of the carboxyl substituent to act as an internal proton donor probably accounts for the facile rearrangement of **1h** in dioxane.

Experimental Section[34]

2-Formyl-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1d).—2-Hydroxymethylene-3-keto-9-methyl-Δ^4-octahydronaphthalene

(32) E. Piers and K. F. Cheng, *Can. J. Chem.*, **48**, 2234 (1970).

(33) (a) M. J. Jorgensen and L. Gundel, *Tetrahedron Lett.*, 4991 (1968); (b) J. A. Barltrop and J. Wills, *ibid.*, 4987 (1968); (c) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967); (d) R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968); (e) J. K. Crandall and C. F. Mayer, *ibid.*, **35**, 3049 (1970); (f) J. R. Scheffer and B. A. Boire, *J. Amer. Chem. Soc.*, **93**, 5490 (1971).

(34) Melting points and boiling points are uncorrected. Infrared spectra were taken on Perkin-Elmer Model 457 or 137 infrared spectrophotometers. Ultraviolet spectra were taken on a Cary Model 14 or a Beckman DBGT recording spectrophotometer using 1-cm matched quartz cells. Nmr spectra were determined at 60 MHz with a Varian A-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained using a Varian M-66 spectrometer. Microanalyses were obtained by Galbreath Laboratories, Inc., Knoxville, Tenn., or by Atlantic Microlab, Inc., Atlanta, Ga. Gas–liquid chromatography was carried out using a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. The following columns were used: A (6 ft × 0.125 in., 10% SE-30 on Chromosorb W); B (6 ft × 0.125 in., 10% Carbowax K-20M on Chromosorb W); C (10 ft × 0.025 in., 10% Carbowax K-20M on Chromosorb W); D (5 ft × 0.25 in., 20% SF-96 on Chromosorb W); E (10 ft × 0.25 in., 20% SE-30 on Chromosorb W); F (10 ft × 0.25 in., 10% Apiezon L on Chromosorb W).

was prepared by a method similar to that described by Edwards and coworkers.[13] A mixture of 38.2 g (0.23 mol) of 8,[12] 17.4 g (0.23 mol) of anhydrous ethyl formate (freshly distilled from P_2O_5), 500 ml of anhydrous benzene, and 21.2 g (0.4 mol) of sodium methoxide was prepared and stirred for 10 days at room temperature under nitrogen. The reaction mixture was extracted with four 25-ml portions of sodium hydroxide (5%) followed by 100 ml of water. The combined aqueous extracts were extracted with two 100-ml portions of ether. The aqueous layer was acidified with cold 1:1 hydrochloric acid and extracted with three 100-ml portions of ether. The solution was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give 31.0 g (75%) of product: bp 116–118° (0.5 mm); uv $\lambda_{max}^{95\%\ EtOH}$ 250 nm (ϵ 10,500) and 306 (5600), $\lambda_{max}^{EtOH+NaOH}$ 240 (11,700) and 360 (8000); ir $\lambda_{max}^{CHCl_3}$ 6.08 (unsaturated C=O) and 6.39 μ (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 1.14 (s, 3 H), 1.5–2.7 (broad absorption, 10 H), 5.80 (m, 1 H), and 7.43 ppm (m, 1 H). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.06; H, 8.60.

The above hydroxymethylene derivative was converted into **1d** by a method similar to that reported by Edwards and coworkers.[13] 2-Hydroxymethylene-3-keto-9-methyl-Δ^4-octahydronaphthalene, 12.0 g (0.063 mol), was dissolved in 200 ml of anhydrous dioxane cooled to 20°. Then DDQ, 21.3 g (0.094 mol), dissolved in 100 ml of anhydrous dioxane was added rapidly while the temperature was maintained at 20° by the use of an ice bath. After 3.5 min, the reaction mixture was poured into 300 ml of methylene chloride and filtered twice through alumina. The light yellow filtrate was evaporated to dryness *in vacuo* to yield an oil, which solidified on standing at room temperature for 1 hr. Recrystallization of the material from hexane gave 9.0 g (76%) of **1d**: mp 82.5–84.0°; uv $\lambda_{max}^{95\%\ EtOH}$ 220 nm (ϵ 11,900) and 244 (11,000); $\lambda_{max}^{EtOH+NaOH}$ 242 (12,000) and 347 (9600); ir $\lambda_{max}^{CHCl_3}$ 5.87 (unsaturated aldehyde), 6.00 (unsaturated ketone), 6.16 and 6.24 μ (conjugated double bonds); nmr $\delta_{TMS}^{CCl_4}$ 1.38 (s, 3 H), 1.25–2.65 (broad absorption, 8 H), 6.06 (m, 1 H), 7.40 (s, 1 H), and 10.10 ppm (s, 1 H). *Anal.* Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.54.

2-Carboxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1e).—Jones reagent[14] (15 ml) (prepared by dissolving 15.0 g of chromium trioxide in 12.01 ml of concentrated sulfuric acid, and cooling the solution to 0°) was added dropwise with stirring over 25 min to a solution of 5.0 g (0.026 mol) of **1d** in 200 ml of anhydrous acetone while the reaction mixture was maintained at 0°. The reaction mixture was allowed to stand for 5 min at 0°, 600 ml of a saturated solution of sodium chloride was added, and the mixture was extracted with five 100-ml portions of ether. The combined ether extracts were washed with 200-ml portions of a saturated solution of sodium chloride until neutral (*ca.* 1 l. required) and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Recrystallization of the residue from ether afforded 3.3 g (61%) of **1e**: mp 130–131° (lit.[15] mp 128–132°); nmr $\delta_{TMS}^{CCl_4}$ 1.40 (s, 3 H), 1.60–2.70 (broad absorption, 8 H), 6.29 (m, 1 H), and 8.13 ppm (s, 1 H). The uv and ir spectra of the sample were identical with those previously reported.[15]

The procedure of Dreiding and Tomasewski[16] was also utilized for the synthesis of **1e**. 2-Methyl-2-formylcyclohexanone,[35] 11.2 g (0.08 mol), 4.8 g of acetic acid, and 100 ml of freshly distilled ethyl acetoacetate were mixed at room temperature and 6.8 g (0.08 mol) of piperidine was added dropwise with cooling under the tap. After standing in a closed reaction vessel for 17 hr at room temperature, the mixture was heated at 55° for 80 hr using an oil bath. Ether (500 ml) was then added, and the organic layer was washed with five 100-ml portions of water, 25 ml of saturated sodium bicarbonate, and three 100-ml portions of saturated sodium chloride solution. The ether was removed *in vacuo* and the excess of ethyl acetoacetate was removed by vacuum distillation using a sand bath maintained at 100°. The residue which remained after distillation was treated overnight at room temperature with a solution of sodium ethoxide, prepared from 8.0 g of 50% of a sodium hydride mineral dispersion and 200 ml of ethanol. The alcoholic solution was heated at reflux for 30 min, 25 ml of water was added, and the alcohol was removed by distillation at atmospheric pressure. Hot water (100 ml) was added, and the reaction mixture was made acidic with 1:1 hydrochloric acid, cooled, and extracted with four 100-ml portions of ether. The combined ethereal extracts were dried over sodium sulfate and the ether was removed *in vacuo*. The residue, 9.4 g, was chromatographed on 70 g of alumina. After elution with 2 l. of benzene, elution with 1 l. of ether gave 3.0 g (18%) of **1e** having identical physical properties with those of the sample prepared above.

2-Carbomethoxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1f).—This compound was prepared according to the method reported by Dreiding and Tomasewski.[16] The dienone acid **1e**, 3.2 g (0.0155 mol), and 50 ml of freshly distilled methyl iodide were allowed to stir at room temperature for 18 hr in the presence of 3.0 g of silver oxide. The solid was removed by filtration through Celite and the filter cake was washed with three 50-ml portions of ether. The combined ether filtrates were washed with 50 ml of a saturated sodium bicarbonate solution and dried over magnesium sulfate, and the ether was removed *in vacuo*. Treatment of the resulting oil with boiling hexane gave 3.0 g (88%) of **1f**: mp 70.5–71.0; nmr $\delta_{TMS}^{CCl_4}$ 1.32 (s, (3 H), 1.5–2.7 (broad absorption, 8 H), 3.77 (s, 3 H), 5.97 (m, 1 H), and 7.29 ppm (s, 1 H). The compound showed identical infrared and ultraviolet spectral properties with those previously reported.[15] *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.66; H, 7.41.

4-Carbomethoxy-3-keto-9-methyl-Δ^4-octahydronaphthalene (9).—A 1000-ml, three-necked flask fitted with dropping funnel, variable takeoff head, mechanical stirrer, thermometer, and nitrogen inlet was charged with 11.2 g (0.25 mol) of 53.4% sodium hydride–mineral oil and 500 ml of dry DME. Compound **8** (47.0 g, 0.28 mol) was added rapidly with stirring. The solution was stirred at room temperature overnight and solvent was removed by distillation until the volume was approximately 200 ml. The solution was cooled to room temperature and 1000 ml of ether was added. Carbon dioxide which had been passed through concentrated sulfuric acid and a calcium chloride drying tube was allowed to bubble through the solution for 1.25 hr while the temperature was maintained at 0–3° by use of an ice bath. To the cold reaction mixture was added 500 ml of 10% sodium hydroxide solution and stirring was continued for 15 min. The solution was washed with three 500-ml portions of ether, acidified to pH 2–3 with 3:1 hydrochloric acid, stirred for 30 min, and extracted with three 100-ml portions of ether. The ether layers were combined and poured slowly into a stirred solution of *ca.* 10.5 g of diazomethane (the diazomethane was freshly prepared from Dupont EXR-101, *N*,*N*-dimethyl-*N*,*N*-dinitrosoterephthalamide, 70% in mineral oil, according to instructions issued by the manufacturer) in 500 ml of ether maintained at 0° with an ice bath. The cold mixture was stirred for 30 min and the excess diazomethane was destroyed by the addition of dilute hydrochloric acid. The organic layer was separated and washed with two 500-ml portions of a saturated sodium bicarbonate solution and one 100-ml portion of a saturated sodium chloride solution. The solution was dried over anhydrous sodium sulfate and the solvents were removed *in vacuo* to give 26.2 g (63%) of the crude product as a yellow oil, bp 123–127° (1.5 mm). Crystallization of the product from ether–hexane gave an analytical sample: mp 77.5–78.5°; ir λ_{max}^{KBr} 5.76 (α,β-unsaturated ester), 5.98 (α,β-unsaturated ketone), 6.19 μ (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 1.28 (s, 3 H), 1.50–2.62 (broad absorption, 12 H), 3.69 (s, 3 H, OCH_3); mass spectrum (70 eV) *m/e* 222 (M^+), EMD 222.1267 (calcd 222.1256). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 7.16; H, 8.34.

4-Carbomethoxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1g).—A 5000-ml, three-necked flask fitted with a variable takeoff distilling head and nitrogen inlet tube was flame dried and charged with 22.2 g (0.20 mol) of freshly sublimed selenium dioxide, 3000 ml of *tert*-butyl alcohol (freshly distilled over sodium *tert*-butoxide), and 10 ml of glacial acetic acid. The mixture was stirred until the selenium dioxide dissolved and a solution of 11.5 g (0.05 mol) of **9** in 500 ml of *tert*-butyl alcohol was added. The reaction mixture was then stirred at reflux for 72 hr and 3000 ml of solvent was removed by distillation. The remaining suspension was cooled to 0° and filtered using a fitted glass funnel to remove unreacted selenium dioxide. The filtrate was stirred with 200 ml of saturated sodium carbonate solution and solid sodium carbonate was added slowly with stirring until the evolution of carbon dioxide ceased. The mixture was then filtered with suction and the filter cake was washed well with ether. The layer were separated and the aqueous layer was extracted with two 100-ml portions of ether. The combined ethereal extracts were washed with water and dried over sodium sulfate, and the solvent was removed *in vacuo*. The viscous residue was fractionally distilled and *ca.* 9.0 g of material, bp 120–130° (1.5 mm), was collected which exhibited one peak on glc analysis (column A).[34] Crystallization

(35) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952).

of the product from methanol using activated carbon for decolorization gave 7.8 g (55%) of 1g: mp 53.5–54.5; uv $\lambda_{max}^{95\%\ EtOH}$ 241 nm (ε 15,400); ir λ_{max}^{KBr} 5.77 (α,β-unsaturated ester), 6.02 (α,β-unsaturated ketone), 6.22 (conjugated C=C), and 6.52 μ (conjugated C=C); nmr δ_{max}^{CCl} 1.29 (s, 3 H), 1.14–2.06 (broad absorption, 7 H), 2.18–2.58 (broad absorption, 1 H, C_5H) 3.75 (s, 3 H, OCH_3), 6.10 and 6.77 ppm (AB quartet, J_{AB} = 10 Hz, 2 H); mass spectrum (70 eV) *m/e* 220 (M^+); EMD 220.1089 (calcd 220.1099). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 70.88; J, 7.32. Found: C, 70.96; H, 7.44.

The conversion of 9 into 1g using DDQ was attempted. In a typical experiment 1.59 g (0.007 mol) of 9 and 2.01 g of DDQ were refluxed in 175 ml of dry dioxane for 48 hr. The dioxane was removed *in vacuo*, 500 ml of benzene was added, and the mixture was filtered through 50 g of alumina. After removal of the solvent *in vacuo*, a mixture which appeared on the basis of its spectral properties to be composed of about equal amounts of 1g, 4-carbomethoxy-4-keto-9-methyl-$\Delta^{1,6}$-hexahydronaphthalene, and 4-carbomethoxy-3-keto-9-methyl-$\Delta^{1,4,6}$-tetrahydronaphthalene was obtained. Attempted separation of 1g from the other components of the mixture by both fractional distillation and column chromatography was unsuccessful. Similar results were obtained when 9 was treated with DDQ in benzene or toluene under the conditions described above.

4-Carboxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1h).—A 500-ml three-necked flask fitted with a variable takeoff distilling head, nitrogen inlet tube, and magnetic stirrer was charged with 9.0 g (0.041 mol) of 1g, 200 ml of 10% aqueous sodium carbonate solution, and 200 ml of methanol. The suspension was maintained for 3 days at 50° using an oil bath, 250 ml of solvent was removed by distillation at atmospheric pressure, 200 ml of water was added, and the solvent was again removed by distillation until the remaining volume was *ca.* 200 ml. The solution was cooled and extracted with three 200-ml portions of ether, and the ethereal extracts were combined and concentrated *in vacuo* to yield 2.60 g (29%) of an oil, which exhibited the same glc (Column A)[34] and spectral properties as those of the starting material. The aqueous layer was acidified to pH 2–3 with 3:1 hydrochloric acid and extracted with three 100-ml portions of ether. The ether extracts were combined and dried over sodium sulfate, and the solvent was removed *in vacuo*. Recrystallization of the residue from ether–hexane gave 6.46 g (79%) of 1h: melting point undetermined (decomposition began at 90°); uv $\lambda_{max}^{95\%\ EtOH}$ 240 nm (ε 13,900); ir $\lambda_{max}^{CHCl_3}$ 5.78 (α,β-unsaturated acid), 6.04 (α,β-unsaturated ketone), and 6.25 μ (conjugated C=C); nmr $\delta_{TMS}^{CDCl_3}$ 1.34 (s, 3 H, 9-CH_3) 1.47–2.70 (broad absorption, 7 H, 6-, 7-, 8-CH_2 and 5-CH), 3.21–3.64 (m, 1 H, C-5 eq H), 6.33 and 7.00 (AB quartet, J_{AB} = 10 Hz, 2 H, 1-, 2-CH), and 10.02 ppm (s, 1 H, 4-CO_2H); mass spectrum (70 eV) *m/e* 162 ($M^+ - CO_2$). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.08; H, 7.01.

Compound 1h exhibited two peaks of approximately equal size on glc analysis (column C).[34] These peaks were collected separately by preparative glc (column C).[34] The first peak showed identical properties with those of 1h and the second peak showed identical spectral properties with those of a sample of 3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene prepared as described below. Thus, partial decarboxylation of 1h occurred on glc analysis.

3-Keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1j).—The octalone 8, 8.2 g (0.05 mol), was dissolved in 140 ml of dry dioxane, 13.6 g (0.06 mol) of DDQ was added, and the reaction mixture was refluxed under nitrogen for 12 hr. After being cooled to room temperature the reaction mixture was filtered through 65.0 g of alumina, the alumina was washed with two 40-ml portions of dioxane, and the solvent was removed *in vacuo* to give 5.42 g of a colorless oil. Glc analysis (column E)[34] of the oil indicated that it was composed of a *ca.* 4:1 mixture of the desired dienone and the starting material. The pure product was obtained by chromatography of the mixture on activity II alumina (100 g). Elution of the column with 1 l. of hexane and 2 l. of 5% ether–hexane removed the starting material and elution with 1 l. of 15% ether–hexane gave 1i: bp 110–114° (1.8 mm) [lit.[18] bp 123–124° (3 mm)]; ultraviolet and infrared spectra identical with those reported;[18] nmr $\delta_{TMS}^{CCl_4}$ 1.20 (s, 3 H), 1.20–2.30 (broad absorption, 8 H), 5.98 (broad absorption, 1 H), 6.06 and 6.70 ppm (AB quartet, J_{AB} = 10 Hz, 2 H).

4-Formyl-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1i).—To a stirred suspension of 3.85 g (0.16 mol) of sodium hydride in 100 ml of dry benzene under nitrogen was added dropwise 3.46 g (0.11 mol) of anhydrous methanol. The suspension was refluxed for 15 min and cooled to room temperature, and 11.8 g (0.16 mol) of ethyl formate (freshly distilled from P_2O_5) was added in a thin stream. After stirring for 30 min, the reaction mixture was cooled to 0° in an ice bath, and 10.5 g (0.064 mol) of 10^{20} in 150 ml of dry benzene was added dropwise with stirring at 0°. When the addition was complete, the cooling bath was removed and stirring was continued overnight. The reaction mixture was acidified with 100 ml of ice-cold 5% sulfuric acid and allowed to stir for 5 min. The layers were separated, and the aqueous layer was extracted with 1:1 ether–benzene. The combined organic layers were washed with four 50-ml portions of 2% potassium hydroxide, and the basic extract was washed once with ether and then acidified with dilute hydrochloric acid. The aqueous layer was then extracted thoroughly with several portions of 1:1 ether–benzene. The organic extracts were washed with saturated brine and dried over anhydrous sodium sulfate. After removal of the drying agent the volatile solvents were removed *in vacuo* to leave a viscous yellow oil. The crude product, which was not further purified, exhibited the following spectral properties: uv $\lambda_{max}^{95\%\ EtOH}$ 244 nm (ε 4900) and 305 (3900); $\lambda_{max}^{EtOH+NaOH}$ 237 (8750) and 324 (4950); ir $\lambda_{max}^{CHCl_3}$ 6.08 (α,β-unsaturated ketone) and 6.39 μ (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 0.86 (s, 3 H), 1.0–2.5 (broad absorption, 8 H), 5.75 and 6.58 (AB quartet, J_{AB} = 10 Hz, 2 H) 7.09 (d, *J* = 10 Hz, 0.9 H, =CH), 8.5 (d, 0.1 H, =CHO), and 13.9 ppm (d, *J* = 10 Hz, 0.9 H, =COH).

To a solution of 3.54 g (0.018 mol) of the 4-hydroxymethylene derivative of 8 in 100 ml of anhydrous dioxane was added 4.52 g (0.02 mol) of DDQ in 100 ml of anhydrous dioxane. The solution was swirled for 4 min and poured into 300 ml of methylene chloride, and the mixture was filtered under pressure through a column of silica gel. The column was eluted with an additional 300 ml of methylene chloride. The combined eluent was stirred with 5 g of decolorizing carbon for 10 min and the mixture was filtered through Celite. The solvents were removed *in vacuo*, 100 ml of ether was added to the residue, and the ether solution was washed with three 30-ml portions of saturated sodium bicarbonate solution and one 30-ml portion of saturated sodium chloride solution. The ether solution was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give 2.24 g (64%) of 1i, bp 110–115° (0.1 mm), which could not be induced to crystallize. The sample showed $\lambda_{max}^{95\%\ EtOH}$ 242 nm (ε 12,000); ir $\lambda_{max}^{CHCl_3}$ 3.60 (aldehyde), 6.00 (unsaturated carbonyl group), and 6.15 μ (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 1.39 (s, 3 H, 9-CH_3), 1.00–2.40 (broad absorption, 7 H), 3.80 [d (broadened), *J* = 14 Hz, 1 H, C-5 eq H], and 6.17 and 6.81 ppm (AB quartet, J_{AB} = 10 Hz, 2 H, C-1, 2 H); exact mass calcd for $C_{12}H_{14}O_2$, 190.0990; found, 190.0954.

8-Methyl-4,5,6,7,8a-hexahydro-8-hydroxy-2(1*H*)-azulenone (13a).—A solution of 2.8 g of a 4:1 mixture of 1j and the corresponding enone 8 was dissolved in 220 ml of 45% aqueous acetic acid and irradiated for 5 hr at 22° using a Pyrex probe.[23] The solution was stirred vigorously with a stream of nitrogen during the irradiation. The reaction mixture was diluted with 100 ml of toluene, evaporated to dryness *in vacuo*, and chromatographed on 100 g of silica gel. After the column had been eluted with 2000 ml of benzene and 4000 ml of 1:1 ether–benzene, elution with 1 l. of ether and 1 l. of ethanol gave colorless crystals which on three recrystallizations from 1:5 ether–hexane afforded 0.2214 g (7%) of 13a: mp 108.5–109.5°; uv λ_{max}^{EtOH} 237 nm (ε 13,000); ir $\lambda_{max}^{CHCl_3}$ 2.88 (OH), 5.97 (cyclopentenone), and 6.25 μ (conjugated C=C); nmr $\delta_{TMS}^{CDCl_3}$ 0.92 (s, 3 H, C-8 CH_3), 1.5–3.2 (broad absorption, 12 H), and 5.62 ppm (m, 1 H, C-4 H). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.45; H, 9.09.

The above alcohol, 0.78 g, was dissolved in 100 ml of absolute ethanol and 0.150 g of 10% palladium on charcoal was added. The mixture was shaken in the presence of hydrogen for 2 hr at room temperature, the catalyst was removed by filtration, and the solvent was removed *in vacuo* to give a quantitative recovery of the dihydro derivative of 13a as a colorless oil: bp 163–166° (bath temperature, 1.5 mm); ir $\lambda_{max}^{CHCl_3}$ 2.88 (OH) and 5.73 (cyclopentanone); nmr $\delta_{max}^{CDCl_3}$ 1.18 (s, 3 H, C-8 CH_3), 1.40–3.06 (broad absorption, 14 H), and 3.30 ppm (broad singlet, 1 H, C-8 OH). *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.29; H, 10.11.

Dehydration of 13a.—A solution of 0.10 g of 13a in 3 ml of pyridine was treated with 0.25 g of thionyl chloride at 0° for 10 min. Water was added slowly while the temperature was maintained below 5°, the reaction mixture was extracted with ether, and the ether solution was washed several times with water and dried over anhydrous sodium sulfate. After removal of the solvent, the

crude product exhibited an nmr spectrum (CCl_4) essentially identical with that of 14 identified below. On treatment of the nmr sample of this product with 2 drops of trifluoroacetic acid and allowing the solution to stand for 24 hr at room temperature, 14 was completely isomerized in 12 identified as described below.

Irradiation of 2-Formyl-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1d). A. In 45% Aqueous Acetic Acid.—A solution of 1.01 g of the 2-formyl dienone 1d in 220 ml of 45% aqueous acetic acid was irradiated for 3.5 hr at room temperature using a Pyrex probe.[23] Removal of the solvent by lyophilization gave a crude amber oil which was soluble in dilute sodium hydroxide and gave positive ferric chloride and Tollens' tests indicative of the presence of an enolizable β-keto aldehyde grouping. The spectral properties of the material suggested that it was likely to be composed of a mixture of the hemiactal enone **11b** and the related hydroxymethylene compound **11a**. The uv spectrum (95% EtOH) showed a strong absorption maximum at 235 nm, and a much weaker band at 300 nm. The latter band inhibited a bathochromic shift in basic solution ($\lambda_{max}^{NaOH+95\%\ EtOH}$ 340 nm). The ir spectrum ($CHCl_3$) showed bands at 2.88 (hydroxy group), 5.90 (cyclopentenone), 6.23 (broad absorption, conjugated C=C) and 6.40 μ (conjugated C=C). The nmr spectrum (CCl_4) exhibited broad singlets at *ca.* 0.9 and 6.02 ppm which could be assigned to the C-8 methyl groups and the C-3 vinyl proton of **11b** and/or **11a**. Other absorption bands ranging from 4.5 to 8.0 ppm which could not be specifically assigned but were consistent with the presence of the hemiacetal and hydroxymethylene alcohol groupings of **11b** and **11a** were also present.

Attempted purification of the crude photoproduct by chromatography on silica gel or alumina resulted in degradation and the only material that could be eluted exhibited strong uv absorption at 300 nm; the species which gives rise to this absorption is identified below. Numerous attempts to convert the photoproduct into a solid derivative which might provide further evidence for the structural assignments were unsuccessful.

In an identical run with that described above the crude photoproduct was dissolved in 70 ml of dioxane and a solution of 2.2 g of sodium carbonate in 100 ml of water was added. The mixture was heated on a steam bath for 18 hr, cooled, and extracted with five 100-ml portions of ether. After drying of the ether solution over magnesium sulfate, removal of the solvent *in vacuo* yielded 8-methyl-4,5,6,7-hexahydro-2(1*H*)-azulenone (**12**): bp 123–127° (bath temperature, 0.9 mm); uv $\lambda_{max}^{95\%\ EtOH}$ 300 nm (ϵ 10,900); ir $\lambda_{max}^{CCl_4}$ 5.99 (α,β-unsaturated ketone) and 6.40 μ (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 1.85 (s, 3 H, C-8 CH_3), 2.83 (s, 2 H, C-1 CH_2), 2.02–2.90 (broad absorption, 8 H), and 5.86 ppm (m, 1 H, C-3 H). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.62; H, 8.87.

The 2,4-dinitrophenylhydrazone derivative of **12** was prepared in the usual way, mp 174.0–175.3°. *Anal.* Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.41; H, 5.28; N, 16.24.

A solution of 1.26 g of **12** in 200 ml of 95% ethanol containing 0.1 g of 10% palladium on charcoal was shaken with hydrogen in a Parr apparatus for 2.5 hr at room temperature and the catalyst was removed by filtration. Evaporation of the solvent *in vacuo* gave the tetrahydro derivative of **12**: bp 95–102° (bath temperature, 0.7 mm); ir $\lambda_{max}^{CCl_4}$ 5.74 μ (cyclopentanone); nmr $\delta_{TMS}^{CCl_4}$ 0.92 (d, 3 H, J = 7 Hz, C-8 CH_3), 1.25–2.65 (broad absorption, 15 H). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 80.05; H, 10.99.

A mixture of 0.76 g of the saturated ketone and 30 ml of deuterium oxide containing 0.2 g of potassium carbonate was heated on a steam bath for 18 hr. After being cooled to room temperature the mixture was extracted with three 50-ml portions of ether, the ether solution was dried over magnesium sulfate, and the solvent was removed *in vacuo*. The resulting oil was shown to contain greater than 95% of one component by glc analysis (column D).[3] A sample collected by preparative glc (column D)[34] showed (direct deuterium analysis by the falling drop method)[36] atom % D calcd, 22.22; found, 18.75 (*ca.* 84% deuterium substitution based on an incorporation of four deuterium atoms). *Anal.* Calcd for $C_{11}H_{14}D_4O$: C, 77.58; weight $H_2O + D_2O$ (from 3.205-mg sample), 3.127 mg. Found: C, 78.08; weight $H_2O + D_2O$, 3.058 mg.

The mass spectrum of the sample showed peaks at m/e 166, 167, 168, 169, 170, and 171 in the region of the molecular ion. The intensity of these peaks indicated the presence of approximately 2% $C_{11}H_{18}O$, 6% $C_{11}H_{18}DO$, 21% $C_{11}H_{16}D_2O$, 40% $C_{11}H_{15}D_3O$, and 31% $C_{11}H_{14}D_4O$.

B. In Anhydrous Dioxane.—A solution of 1.76 g of 1d in 230 ml of dioxane was irradiated for 2 hr at room temperature using a quartz probe.[23] The solvent was removed *in vacuo* and the residue was subjected to thin layer chromatography. Four new compounds as well as the starting material were observed. In addition a large amount of material remained at the origin of the spot, indicating that a significant amount of polymerization had occurred. Further investigation of the products of this reaction was not carried out.

Irradiation of 2-Carboxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1e). A. In 45% Aqueous Dioxane.—A solution of 0.80 g of 1e in 220 ml of 45% aqueous dioxane was irradiated for 2 hr at room temperature using a Pyrex probe.[23] The solvents were removed *in vacuo* and the residue was chromatographed on 30 g of alumina (Merch, acid washed). Elution with 200 ml each of benzene, 20:1 benzene–ether, and 1:1 benzene–ether gave a semi solid residue shown to be composed of at least two components by thin layer chromatography. Rechromatography of this material on 30 g of alumina gave, on elution with 500 ml of benzene followed by 150 ml of 20:1 benzene–ether, 0.1 g (12%) of 1β-carboxy-8-methyl-4,5,6,7,8aα-hexahydro-8α-hydroxy-2-(1*H*)-azulenone lactone (**15**), mp 114.0–114.5. Further elution with 500 ml of 2:1 benzene–ether yielded 0.1 g of the hydroxy ketone **13a**. Further elution of the original column with 300 ml of 1:1 benzene–ether and 400 ml of 1:2 benzene–ether afforded 0.32 g of **13a**, bringing the total yield of this compound to 0.42 g (60%). The lactone **15** showed uv $\lambda_{max}^{95\%\ EtOH}$ 246 nm (ϵ 9950) and 271 (7380); ir $\lambda_{max}^{CHCl_3}$ 5.61 (γ-lactone), 5.87 (cyclopentenone), and 6.26 μ (conjugated C=C); nmr $\delta_{TMS}^{CDCl_3}$ 1.05 (s, 3 H, C-8 CH_3), 1.3–2.0 (broad absorption, 8 H), 3.50 and 4.07 (AB quartet, J_{AB} = 7.4 Hz, C-1 and C-8a H), and 5.81 ppm (s, 1 H, C-3 H). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.22; H, 6.73.

A solution of 0.037 g of **15**, 16 ml of water, 0.3 g of sodium carbonate, and 16 ml of dioxane was heated for 18 hr on a steam bath. The solution was cooled to room temperature, made acidic with 1:1 hydrochloric acid, and extracted with four 25-ml portions of ether. The ether solution was dried over magnesium sulfate, the solvent was removed *in vacuo*, and the residue was chromatographed on alumina. Elution with 5:1 benzene–ether gave a mixture which appeared to be composed of **13a** and **12** on the basis of its spectral properties. Further elution with 1:1 benzene–ether afforded 0.018 g of material which was identified as **13a** by its spectral properties and mixture melting point (107–109°) with an authentic sample.

B. In Anhydrous Dioxane.—Oxygen-free nitrogen was passed through a solution of 0.71 g of 1e in a photolysis apparatus[23] and the exhaust gases were passed through a water-cooled condenser, a Dry Ice–acetone trap, and a drying tube filled with Ascarite. After 1 hr at room temprature the Ascarite tube was weighed and the reaction mixture was irradiated for 2 hr using a Pyrex probe. At the end of the irradiation the Ascarite tube weighed an additional 0.134 g, which corresponded to 87% of carbon dioxide which could have been lost from 1e or its photolysis products. The irradiated solution was divided into two equal parts and treated as follows.

One part was evaporated *in vacuo* and distilled in a micro Hickman apparatus to yield 0.19 g (67%) of an oil, bp 95–100° (bath temperature, 0.25 mm), which solidified on standing overnight. Recrystallization from hexane afforded 8-methylene-4,5,6,7,8aα-hexahydro-2(1*H*)-azulenone (**14**): mp 61.0–61.5°; uv $\lambda_{max}^{95\%\ EtOH}$ 230 mm (ϵ 12,400); ir $\lambda_{max}^{CHCl_3}$ 5.83 and 5.90 (cyclopentenone),[10a] 6.06 (C=C), 6.19 (conjugated C=C), and 11.07 μ (=CH_2); nmr $\delta_{max}^{CDCl_3}$ 1.18–3.06 (broad absorption, 10 H), 3.56–3.82 (broad absorption, 1 H), 4.97 (s, 2 H, =CH_2), and 5.96 ppm (m, 1 H, vinyl proton). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.23; H, 8.87.

The solvent was removed from the other portion of the photolysis mixture *in vacuo* and the residue was chromatographed on 30 g of silica gel. Elution with 600 ml of 20:4 benzene–ether yielded dienone **14**, and elution with 450 ml of 2:1 benzene–ether afforded 0.057 g (16%) of crystalline material identical in all respects with the lactone **15** described above.

C. In 45% Aqueous Acetic Acid.—A solution of 1.16 g of 1e in 310 ml of 45% aqueous acetic acid was irradiated for 2 hr using a Pyrex probe.[23] The solvent was removed *in vacuo* and the residue was chromatographed on 30 g of silica gel. Elution with 300 ml of benzene, 500 ml of 7:1 benzene–ether, and 600 ml of 3:1

(36) The analysis was performed by Mr. Josef Nemeth, Urbana, Ill.

benzene–ether gave mixtures which by glc (column F)[34] and spectral analysis appeared to be composed of varying amounts of **14**, **12**, and **15**. Continued elution with 600 ml of 3:2 benzene–ether followed by 200 ml of methanol afforded, after recrystallization from ether, 0.66 g (65%) of **13a**.

The above mixture was rechromatographed on 20 g of alumina. Elution with 1200 ml of 1:1 benzene–ether gave 0.11 g of a colorless oil which by glc analysis (column D)[3] was composed of dienones **12** and **14** in a 53:47 ratio. The yield of **12** and **14** were thus *ca.* 7 and 5%, respectively. Further elution with 200 ml of methanol yielded 0.072 g (6%) of lactone **15**.

D. In Anhydrous Methanol.—A solution of 0.97 g of **1e** in 310 ml of dry methanol was irradiated for 2.5 hr using a Pyrex probe.[23] The solvent was removed *in vacuo* to afford an oily residue which was chromatographed on 45 g of alumina. Elution with 200 ml of benzene, followed by 500 ml of 100:8 benzene–ether, gave 0.10 g (14%) of **14**, and further elution with 600 ml of 100:8 benzene–ether, 600 ml of 7:3 benzene–ether, and 800 ml of 1:1 benzene–ether gave 0.45 g (50%) of 8β-methyl-8α-methoxy-4,5,6,7,8aα-hexahydro-2(1*H*)-azulenone (**13b**): mp 55.5–56.0°; uv $\lambda_{max}^{95\%\ EtOH}$ 238 nm (ϵ 12,600); ir $\lambda_{max}^{CHCl_3}$ 5.90 (cyclopentenone) and 6.23 μ (conjugated C=C); nmr $\delta_{TMS}^{CCl_4}$ 0.91 (s, 3 H), 1.5–2.9 (broad absorption, 11 H), 3.22 (s, 3 H), and 5.90 ppm (m, 1 H). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.42; H, 9.40.

Continued elution of the column with 500 ml of ether and 500 ml of methanol afforded 0.11 g (13%) of the lactone **15**.

Irradiation of 2-Carbomethoxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1f) in 45% Aqueous Acetic Acid.—A solution of 1.10 g of **1f** in 300 ml of 45% aqueous acetic acid was irradiated for 2 hr at room temperature using a Pyrex probe.[23] The solvent was removed by lyophilization to give 1.14 g of a semisolid residue which was chromatographed on 35 g of alumina (Merck, acid washed). Elution with 400 ml of 1:1 benzene–ether, 200 ml of ether, and 200 ml of methanol afforded 0.81 g (67%) of 1α-carbomethoxy-8β-methyl-8α-hydroxy-4,5,6,7,8aα-hexahydro-2-azulenone (**16**): mp 165.0–166.0°; uv $\lambda_{max}^{95\%\ EtOH}$ 240 nm (ϵ 11,100); ir $\lambda_{max}^{CHCl_3}$ 2.88 (OH), 5.77 (ester C=O), 5.87 (cyclopentenone), and 6.24 μ (conjugated C=C); nmr $\delta_{TMS}^{DMSO\text{-}d_6}$ 0.82 (s, 3 H), 0.95–2.80 (broad absorption, 10 H), 3.19 (s, 1 H), 3.36 (s, 3 H), and 5.41 ppm (m, 1 H). *Anal.* Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.35; H, 7.59.

A solution of 0.15 g of **16** in 70 ml of 95% ethanol containing 0.1 g of 10% palladium on charcoal was shaken with hydrogen for 1.5 hr in a Parr apparatus, the catalyst was removed by filtration, and the solvent was removed *in vacuo*. The residue was dissolved in 30 ml of 1:1 water–dioxane containing 0.1 g of sodium carbonate and warmed on a steam bath for 5 hr. The solvents were removed *in vacuo*, 50 ml of water was added, and the mixture was extracted with two 50-ml portions of ether. The ether layer was dried over sodium sulfate and the solvent was removed *in vacuo* to give 0.11 g of material, bp 160–165° (bath temperature, 1.5 mm), which exhibited identical spectral properties with those of the dihydro derivative of **13a** prepared as described above.

Irradiation of 4-Carboxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1h). A. In Anhydrous Dioxane.—A solution of 0.96 g of **1h** in 250 ml of anhydrous dioxane was irradiated for 25 min at room temperature using a quartz probe.[23] The solvent was removed *in vacuo*, 20 ml of ether was added to the residue, and 0.12 g of flocculent material which was insoluble in ether was removed by filtration. The ethereal filtrate was extracted with three 20-ml portions of saturated sodium bicarbonate solution and one 20-ml portion of saturated sodium chloride solution. The basic extracts were combined, acidified with 1:1 hydrochloric acid, and treated in the usual way to give 0.25 g of material whose spectral properties were identical with those of the starting dienone acid. The ether solution was concentrated *in vacuo* to yield 0.48 g (62%) of 6-methylspiro[4.5]deca-3,6-dien-2-one (**20**): bp 109–111° (bath temperature, 0.25 mm); ir λ_{max}^{film} 5.84 (cyclopentenone), 6.02 (C=C), and 6.08 μ (C=C); uv $\lambda_{max}^{95\%\ EtOH}$ 218 nm (ϵ 9200); nmr $\delta_{TMS}^{CCl_4}$ 1.54 (d, 3 H, C-6 CH_3), 1.60–2.15 (m, 6 H), 2.00 and 2.38 (AB quartet, J_{AB} = 18.5 Hz, 2 H, C-1 CH_2), 5.57 (m, 1 H C-7 H), 6.06 and 7.31 ppm (AB quartet, J_{AB} = 5.5 Hz, 2 H, C-3, 4 H). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.28; H, 8.90.

B. In 45% Aqueous Acetic Acid.—A solution of 1.02 g of **1h** in 250 ml of 45% aqueous acetic acid was irradiated for 30 min at room temperature using a quartz probe.[23] The solvent was removed by lyophilization to yield a semisolid residue. Ether (100 ml) was added and 0.28 g of flocculent material which was insoluble in ether was removed by filtration. The ether solution was washed with three 100-ml portions of saturated sodium bicarbonate solution and one 100-ml portion of saturated sodium chloride solution. The basic extracts were combined, acidified with 1:1 hydrochloric acid, and treated in the usual way to give 0.18 g of material whose spectral properties indicated that it was composed mainly of the starting dienone acid. The ether solution was dried over sodium sulfate and the solvent was removed *in vacuo* to yield a yellow oil which was crystallized from carbon tetrachloride to give 0.41 g (41%) of 1β-carboxy-6β-hydroxy-6α-methylspiro[4.5]deca-3-en-2-one lactone (**19**): mp 125.5–126.0°; uv $\lambda_{max}^{95\%\ EtOH}$ 223 nm (ϵ 8400); ir $\lambda_{max}^{CHCl_3}$ 5.65 (γ-lactone), 5.84 (cyclopentenone), and 6.06 μ (C=C); nmr $\delta_{TMS}^{CDCl_3}$ 1.15 (s, 3 H, C-6 CH_3), 1.52–2.70 (m, 8 H), 3.38 (broad s, 1 H, C-1 H), 6.17 (d, J_{AB} = 5.5 Hz, 1 H, C-3 H), and 7.58 ppm (broad d, J_{AB} = 5.5 Hz, 1 H, C-4 H). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found C, 69.94; H, 7.00.

Irradiation of 4-Formyl-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1i) in 45% Aqueous Acetic Acid.—A solution of 2.24 g of **1i** in 250 ml of 45% aqueous acetic acid was irradiated for 1.5 hr at room temperature using a Pyrex probe.[23] An equal volume of benzene was added and the solvent was removed *in vacuo*. The nmr spectrum (CCl_4) of the crude photoproduct showed absorptions characteristic of the starting material, but in addition absorptions at δ 1.36 (s), 5.32 (m), 6.07 (d, J_{AB} = 10 Hz), 6.74 (d, J_{AB} = 10 Hz), 8.20 (s), and 13.6 ppm (broad absorption) indicated that 10–20% of the enolic compounds **17** and/or **18** were also present. The formation of enolic compounds was not observed when a solution of **1i** in 45% aqueous acetic acid was allowed to stand in the dark and the solvent was removed as before.

Irradiation of 4-Carbomethoxy-3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene (1g) in 45% Aqueous Acetic Acid.—A solution of 0.88 g of **1g** in 300 ml of 45% aqueous acetic acid was irradiated for 2 hr at room temperature using a Pyrex probe.[23] The solvent was removed by lyophilization. The nmr spectrum of the residue indicated that a significant quantity of the starting material had been consumed and a large number of broad absorption bands were present. The crude photolysis mixture was subjected to chromatography on silica gel. Elution of the column with hexane–ether mixtures yielded a fraction containing 0.29 g of starting material. However, none of the other chromatography fractions yielded material having discrete nmr and ir spectral properties. Spectral evidence indicated that most of the material was polymeric in nature. Further investigation of this reaction mixture was not carried out.

Registry No.—**1d**, 5240-81-3; **1e**, 13258-46-3; **1f**, 37709-23-2; **1g**, 37709-24-3; **1h**, 37709-25-4; **1i**, 37709-26-5; **1j**, 703-02-6; **8**, 826-56-2; **9**, 37709-28-7; **10**, 22844-34-4; **12**, 6505-79-9; **12** (DNP), 5240-83-5; **12** (tetrahydro derivative), 5240-84-6; **12** (tetradeuterio derivative), 30917-38-5; **13a**, 6531-23-3; **13a** (dihydro derivative), 37709-40-3; **13b**, 13258-49-6; **14**, 13258-48-5; **15**, 13258-47-4; **16**, 37709-37-8; **19**, 37709-38-9; **20**, 37709-39-0; ethyl formate, 109-94-4; 2-hydroxymethylene-3-keto-9-methyl-Δ^4-octahydronaphthalene, 5240-82-4; 2-methyl-2-formylcyclohexanone, 37709-42-5; ethyl acetoacetate, 141-97-9; 4-hydroxymethylene-3-keto-9-methyl-Δ^1-octahydronaphthalene (trans), 37709-43-6; 4-carboxaldehyde-3-keto-9-methyl-Δ^1-octahydronaphthalene (trans), 37709-44-7.

Oligonucleotide Synthesis. III.[1] Enzymatically Removable Acyl Protecting Groups

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This work involves a study of enzymatically removable esters (acyl groups) as a means of protection for the sugar hydroxyl functions of nucleosides and nucleotides. The dihydrocinnamoyl, *o*-phenylenedioxyacetyl, and D-(+)-dihydrocoumariloyl groups were investigated to determine the relative ease of separation of the required blocked nucleoside and nucleotide intermediates and to determine the ease of removal with α-chymotrypsin. Difficulties were encountered in using the *o*-phenylenedioxyacetyl and D-(+)-dihydrocoumariloyl protecting groups in actual synthesis. The acyl chlorides were poor acylating agents, and the nucleotide esters of these acids were too alkali labile for purification of the protected oligonucleotides by column chromatography on diethylaminoethyl cellulose using triethylammonium bicarbonate buffers at pH 7.5 to 9.0. These problems were not observed with the dihydrocinnamoyl group. High yields of nucleosides, protected in the 3′ and 5′ positions, and nucleotide 5′-monophosphates, protected at the 3′ position, were obtained by reaction of the appropriate nucleoside or nucleoside 5′-monophosphate with dihydrocinnamic anhydride. The synthesis of the tetranucleotide d-pTpCpApG was achieved using the dihydrocinnamoyl group for protection of the 3′-hydroxyl functions showing that the use of this protecting group is both useful and practical. Kinetic studies on the enzymatic hydrolysis of nucleoside and nucleotide esters of the three acids showed that the *o*-phenylenedioxyacetyl and D-(+)-dihydrocoumariloyl groups were good substrates for α-chymotrypsin; complete removal of the protecting groups could be achieved in under 1 hr at 37° in neutral conditions. Removal of the dihydrocinnamoyl group was slower but could be achieved at 37° in a reasonable time (8–16 hr).

The general scheme for the synthesis of deoxyribooligonucleotides developed during the past decade is based on the sequential assembly of suitably protected monomeric building blocks.[2] The most commonly used protecting groups for hydroxyl, phosphate, and amino functions are either acid labile, such as the trityl group,[3] or alkali labile, such as the acetyl and cyanoethyl groups.[4] However, during the synthesis of a deoxyribooligonucleotide carrying a 5′-terminal phosphate, the use of these particular protecting groups is unsatisfactory, since the cyanoethyl group protecting the 5′-phosphate is generally removed under the alkaline conditions necessary to hydrolyze the 3′-hydroxyl acyl protecting group. Recently two phosphate protecting groups have been developed which circumvent this difficulty. The phosphorothioate protecting group[5] is removed by mild oxidation and the phosphoramidate group[6] by treatment with isoamyl nitrite. We have approached the problem by developing protecting groups for the 3′-hydroxyl function which are enzymatically removed under neutral conditions leaving the cyanoethyl phosphate protecting group intact.[7] In this paper we describe the use of α-chymotrypsin to hydrolyze nucleoside and nucleotide esters of three different acids, which are used as 3′-hydroxyl protecting groups. The protecting groups studied are the dihydrocinnamoyl, D-(+)-dihydrocoumariloyl, and *o*-phenylenedioxyacetyl groups. A comparison has been made of these acids as protecting groups in oligonucleotide synthesis.

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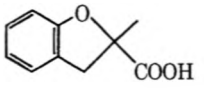
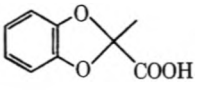
Results

(a) Synthesis of the Protecting Groups

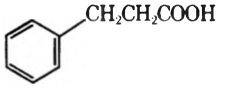
D-(+)-Dihydrocoumarilic acid (DCM acid)[8] was prepared by reduction of coumarilic acid and the resulting racemate was resolved by crystallization with d-amphetamine.[9] *o*-Phenylenedioxyacetic acid (PDA acid) was synthesized by condensation of catechol with ethyl dichloroacetate followed by hydrolysis of the resulting ester.[10] Acid chlorides were prepared without difficulty from these acids, and from dihydrocinnamic acid (DHC acid), by treatment with thionyl chloride. Dihydrocinnamic anhydride was synthesized from the acid by distillation with acetic anhydride, or by treating the acid with an equimolar amount of the acid chloride. However, synthesis of anhydrides from the other acids presented difficulties. *o*-Phenylenedioxyacetic anhydride and D-(+)-dihydrocoumarilic anhydride were prepared by both methods but in extremely low yields as the anhydrides decomposed at the temperature required for distillation (bath temperature 250° at 0.01 mm). In addition, racemization of the D-(+)-dihydrocoumariloyl group occurred at the high distillation temperature. Other milder methods of preparing the anhydrides, such as condensation with dicyclohexylcarbodiimide, were tried but only starting material was recovered. As a result, the acid chlorides



DL-dihydrocoumarilic acid



o-phenylenedioxyacetic acid



dihydrocinnammic acid

(8) DCM refers to the D-(+) enantiomer of dihydrocoumarilic acid unless otherwise stated.

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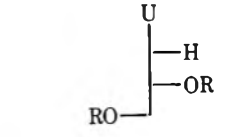
from D-(+)-dihydrocoumarilic acid and *o*-phenylenedioxyacetic acid and the anhydride of dihydrocinnamic acid were used to esterify the nucleosides and nucleotides.

(b) Synthesis of Protected Nucleosides and Nucleotides

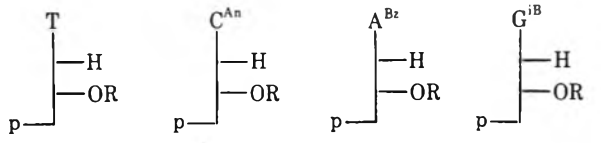
The derivatives of deoxyuridine (**1a–d**),[11] protected at the 3′ and 5′ positions, were prepared by treatment



1a, R = DHC
b, R = PDA
c, R = DCM (racemate)
d, R = DCM[(D-(+) isomer)]

with the corresponding acid chlorides or anhydrides. The yields were generally 80–95%. However, small traces of the monosubstituted nucleosides could be detected by tlc (≈2%) and so further purification was carried out by preparative tlc.

Mononucleotides protected at the 3′ position by the DHC group (**2a**, **3a**, **5**, and **6**) were prepared from the



2a, R = DHC
b, R = PDA
c, R = DCM

3a, R = DHC
b, R = PDA
c, R = DCM

5

6

corresponding mononucleotide, base protected if necessary, and DHC anhydride. Yields were almost quantitative and purification was achieved without difficulty by precipitation with ether. In contrast, the syntheses of d-pT-OR and d-pC^{An}-OR (R = DCM or PDA) using the corresponding acid chlorides were only achieved in low yields. In all cases, the main product had faster mobility on paper chromatography (solvent D) than the parent mononucleotide and was tentatively identified as the symmetrical pyrophosphate by uv spectroscopy, R_f value, and enzymatic degradation. Purification of the protected mononucleotides **2b**, **2c**, **3b**, and **3c** was achieved by preparative paper chromatography (solvent D).

(c) Kinetic Studies

Kinetic studies of the rates of hydrolysis of these esters were carried out. In a typical experiment, the substrate was dissolved or suspended in 0.1 *M* sodium chloride solution at a concentration of 10^{-2} *M* and the pH adjusted to 7.8 with dilute sodium hydroxide solution. The α-chymotrypsin was added, the amount being calculated on the basis of units per micromole of substrate (the specific activity quoted by the supplier was not checked). This gave an enzyme concentration varying from 10^{-4} to 10^{-6} *M* in these experiments. The total volume of the reaction mixture was adjusted to 2.0 ml and the mixture was incubated at 37°. The addition of the enzyme was taken as zero time. The pH of the mixture (measured on a pH meter) was maintained at 7.5 to 7.8 by titration with 0.1 *M* sodium hydroxide solution. The hydrolysis was judged to be complete when the pH of the reaction mixture had been constant for at least 2 hr and tlc showed the absence of any starting material. In addition, calculations were made of the volume of alkali required to neutralize the acid liberated by the enzymatic hydrolysis. Experiments were discounted in which the actual volume of alkali used did not correlate closely with the theoretical amount.

Control experiments excluding the enzyme were always run. Under these conditions no observable hydrolysis of the protected nucleosides or nucleotides occurred. Control experiments excluding the substrate were also run, as it is known that under certain circumstances α-chymotrypsin can function both as a catalyst and as a substrate.[12] It was found that at the high enzyme–substrate concentrations autolysis occurred, and, correspondingly, the kinetic results were corrected for this factor.

The results of the kinetic hydrolyses are summarized in Tables I and II, and some of the plots are shown in

TABLE I

TIME REQUIRED FOR FULL DEPROTECTION BY α-CHYMOTRYPSIN[a]

	Enzyme–substrate ratio expressed in units/μmol of substrate		
Compd 1	28	2.8	0.28
a, R = DHC	3 hr	8 hr	48 hr
b, R = PDA	1 hr	2 hr	8 hr
c, R = DCM (racemate)	3 hr		
d, R = DCM [D-(+) isomer]	50 min	1 hr	4 hr

[a] The reaction mixture contained 0.05 mmol of substrate (*i.e.*, 0.1 mmol of ester) suspended in 2 ml of 0.1 *M* NaCl plus the enzyme, pH maintained at 7.8 by addition of 0.1 *M* NaOH at 37°.

TABLE II

TIME REQUIRED FOR FULL DEPROTECTION BY α-CHYMOTRYPSIN[a]

	Enzyme–substrate ratio expressed in units/μmol of substrate		
Compd	30	3.0	0.30
2a, d-pT-ODHC	2 hr	5 hr	48 hr
2b, d-pT-OPDA	*b*	15 min	1 hr
2c, d-pT-ODCM	*b*	5 min	45 min
3a, d-pC^{An}-ODHC	2 hr	5.5 hr	48 hr
3b, d-pC^{An}-OPDA	*b*	15 min	1 hr
3c, d-pC^{An}-ODCM	*b*	15 min	1 hr
5, d-pA^{Bz}-ODHC	2.5 hr	5.5 hr	48 hr
6, d-pG^{iB}-ODHC	2 hr	5 hr	48 hr
17, d-CEpTpC^{An}-ODHC	30 min	2.5 hr	
19, d-CEpTpC^{An}pA^{Bz}-ODHC	30 min	4 hr	
21, d-CEpTpC^{An}pA^{Bz}pG^{iB}-ODHC	45 min	4 hr	

[a] The reaction mixture contained 0.1 mmol of substrate in 2 ml of 0.1 *M* NaCl plus the enzyme, pH maintained at 7.8 by addition of 0.1 *M* NaOH at 37°. [b] The reaction was too fast to follow.

(11) For the system of abbreviations used see H. Schaller and H. G. Khorana, *J. Amer. Chem. Soc.*, **85**, 3841 (1963). Thus, d-pT is thymidine 5′-monophosphate, d-pC^{An} is *N*-anisoyldeoxycytidine 5′-monophosphate, and d-pC^{An}pA^{Bz} is 5′-*O*-phosphoryl-*N*-anisoyldeoxycytidylyl-(3′–5′)-*N*-benzoyldeoxyadenosine. Additional abbreviations used in this paper are iB, the isobutyryl group; DHC, the dihydrocinnamoyl group; DCM, D-(+) enantiomer of the dihydrocoumariloyl group; PDA, the *o*-phenylenedioxyacetyl group.

(12) C. Niemann, *Science*, **143**, 1287 (1964); T. H. Applewhite, R. B. Martin, and C. Niemann, *J. Amer. Chem. Soc.*, **80**, 1457 (1958); A. Yapel, M. Jan, R. Lumry, A. Rosenberg, and D. F. Shiao, *ibid.*, **88**, 2573 (1966).

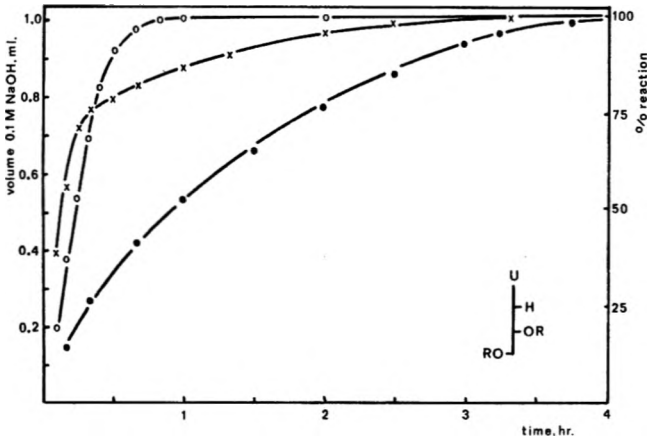


Figure 1.—Kinetics of the enzymatic hydrolysis of nucleosides. (×) R = DCM, racemate **1c**, 28 units/μmol; (○) R = DCM, D-(+) isomer **1d**, 2.8 units/μmol; (●) R = DCM, D-(+) isomer **1d**, 0.28 units/μmol. For reaction conditions see Table I.

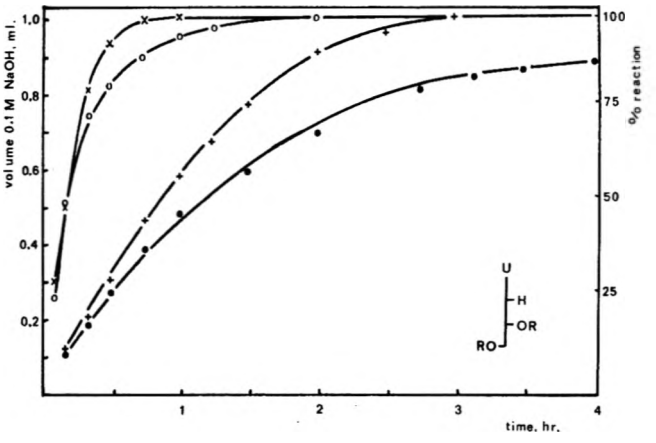


Figure 2.—Kinetics of the enzymatic hydrolysis of nucleosides. (×) R = PDA, **1b**, 28 units/μmol; (○) R = PDA, **1b**, 2.8 units/μmol; (+) R = DHC, **1a**, 28 units/μmol; (●) R = DHC, **1a**, 2.8 units/μmol. For reaction conditions see Table I.

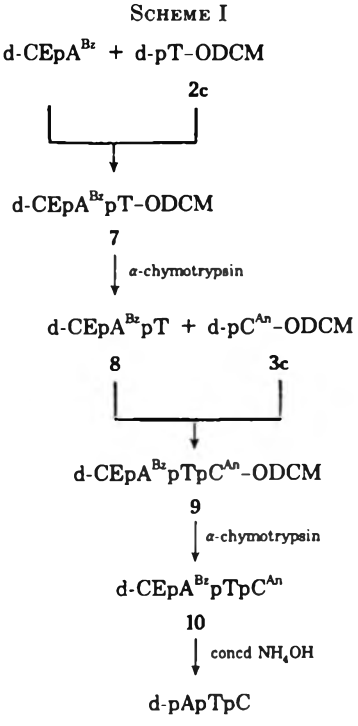
Figures 1–3. It can be seen that the best substrates for α-chymotrypsin are the DCM [D-(+) enantiomer] and PDA groups, and in fact removal of these two protecting groups from nucleotides was too fast to follow except at the lower enzyme–substrate ratios. The DCM esters were hydrolyzed more slowly.

The stability of these esters to alkaline hydrolyses was studied. Esters of DHC acid (**2a**) were stable at pH 9.5 for up to 3 days, whereas esters of the other two acids (**2b** and **2c**) were found to be extremely alkali labile. At pH 9.5 hydrolysis was complete in 4 hr in both cases and at pH 8.0 partial hydrolysis (11–13%) was observed in 24 hr.

(d) Synthesis of Oligonucleotides

The protected mononucleotides (**2a**, **2c**, **3a**, **3c**, **5**, and **6**) were used in the synthesis of various oligonucleotides. Preparation of the trinucleotide d-pApTpC was achieved as shown in Scheme I using mesitylenesulfonyl

SCHEME I



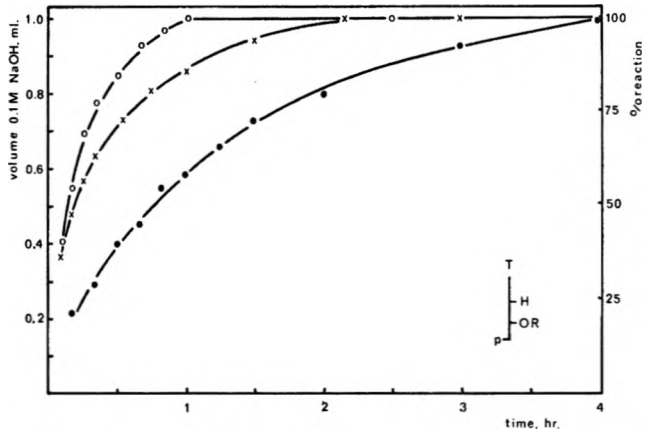


Figure 3.—Kinetics of the enzymatic hydrolysis of nucleotides. (○) R = PDA, **2b**, 0.30 unit/μmol; (×) R = DHC, **2a**, 30 units/μmol; (●) R = DHC, **2a**, 3.0 units/μmol. For reaction conditions see Table II.

chloride (MSC) as the condensing agent. In this sequence, the first condensation to give d-CEpA^{Bz}pT-ODCM (**7**) was worked up by chromatography on DEAE cellulose using a gradient of TEAB. However the R_f value of the dinucleotide isolated by this procedure seemed lower than anticipated (R_f 0.64) suggesting that the DCM protecting group had been lost during the column work-up. This was the first evidence that the DCM group was not entirely suitable for use in synthesis. Loss of the protecting group was confirmed when a second preparation was carried out but the reaction mixture was purified by preparative paper chromatography in solvent D. In this case, the pH could be maintained at 7.5 using the ammonium acetate buffer whereas when running the DEAE column using TEAB buffer at pH 7.5 it was found that after passage through the column the pH had risen to 8.5–9.0 due to loss of CO_2. Attempts to use TEAB at a lower initial pH (6.5) gave identical results. As a result of the prolonged length of time involved in running a DEAE column loss of the DCM protecting group occurred. Preparative paper chromatography at pH 7.5 proved to be a useful alternative method for isolating fully protected intermediates. Separation of materials with close R_f values was achieved by running the chromato-

grams for 24 to 36 hr giving an effective solvent front of 60–80 cm.

Treatment of the dinucleotide d-CEpA^{Bz}pT-ODCM (**7**), R_f 0.74, with α-chymotrypsin for 4 hr at 37° at an enzyme–substrate ratio of 5 units/μmol gave the partially protected dimer d-CEpA^{Bz}pT (**8**) which had R_f 0.64. The structure was also confirmed by preparation of a sample of **8** by cyanoethylation of the dimer d-pA^{Bz}pT.

Synthesis of the trinucleotide d-CEpA^{Bz}pTpC^{An}-ODCM (**9**) from d-pC^{An}-ODCM (**3c**) and **8** was achieved but the yield was extremely low (11%). Deprotection with α-chymotrypsin at a ratio of 1.5 units/μmol gave d-CEpA^{Bz}pTpC^{An} (**10**) which was isolated in 69% yield. The structure of this trimer was confirmed by degradation with snake venom phosphodiesterase after removal of all protecting groups.

Scheme II shows the synthesis of the tetranucleotide

SCHEME II

d-CEpC^{An} + d-pT-ODHC

2a

d-CEpC^{An}pT-ODHC

11

↓ α-chymotrypsin

d-CEpC^{An}pT + d-pC^{An}-ODCM

12 **3c**

d-CEpC^{An}pTpC^{An}-ODCM

13

↓ α-chymotrypsin

d-CEpC^{An}pTpC^{An} + d-pT-ODCM

14 **2c**

d-CEpC^{An}pTpC^{An}pT-ODCM

15

↓ α-chymotrypsin

d-CEpC^{An}pTpC^{An}pT

16

↓ concd NH_4OH

d-pCpTpCpT

d-pCpTpCpT using two protecting groups (DCM and DHC). Condensation of d-CEpC^{An} with d-pT-ODHC (**2a**) using dicyclohexylcarbodiimide (DCC) as the condensing agent gave the dinucleotide d-CEpC^{An}pT-ODHC (**11**) in 53% yield, which was purified by chromatography on a column of DEAE cellulose. Partial deprotection was achieved by treatment with α-chymotrypsin. Separation of the nucleotide from the protein was achieved by preparative paper chromatography.

The tri- and tetranucleotides in this series were prepared by using the DCM protecting group. The fully protected trinucleotide **13** was not isolated as separation of unreacted d-pC^{An}-ODCM and the trimer could not be achieved, but treated directly with α-chymotrypsin to give d-CEpC^{An}pTpC^{An} (**14**) which was purified by paper chromatography. Condensation of **14** with d-pT-ODCM (**2**) gave the tetramer **15** which was isolated by paper chromatography. The base composition of the tri- and tetramer were confirmed by degradation with snake venom phosphodiesterase to give the component nucleotides in the expected ratios.

The tetranucleotide d-pTpCpApG was synthesized by a stepwise procedure utilizing the DHC protecting group as shown in Scheme III. The yields at the di-,

SCHEME III

d-CEpT + d-pC^{An}-ODHC

3a

d-CEpTpC^{An}-ODHC

17

↓ α-chymotrypsin

d-CEpTpC^{An} + d-pA^{Bz}-ODHC

18 **5**

d-CEpTpC^{An}pA^{Bz}-ODHC

19

↓ α-chymotrypsin

d-CEpTpC^{An}pA^{Bz} + d-pG^{iB}-ODHC

20 **6**

d-CEpTpC^{An}pA^{Bz}pG^{iB}-ODHC

21

↓ α-chymotrypsin

d-CEpTpC^{An}pA^{Bz}pG^{iB}

22

↓ concd NH_4OH

d-pTpCpApG

tri-, and tetramer stages were 54, 46, and 36%, respectively. In all cases work-up was by paper chromatography in solvent E. Intermediate deprotection was achieved by treatment with α-chymotrypsin. Confirmation of the assigned structures was obtained by removal of all protecting groups and degradation with snake venom phosphodiesterase and also by removal of the terminal 5′-phosphate by alkaline phosphatase and subsequent degradation with spleen phosphodiesterase.

(e) Enzymatic Hydrolysis of Oligonucleotides

The kinetics of the enzymatic removal of the DHC group from the di-, tri-, and tetranucleotides was studied and compared with the corresponding rates of removal of this group from the mononucleotides (Table II). It was observed that the rate of hydrolysis was faster for the oligonucleotides than for the monomers. The hydrolysis rate was fastest for the di-

nucleotide and decreased slightly with increasing chain length.

The use of an insolubilized form of α-chymotrypsin was explored as it was hoped that column procedures could be set up for the partial deprotection step. Correspondingly, removal of the DHC group from these oligonucleotides was studied using the insolubilized form of α-chymotrypsin, Enzite-CHT. The amount of Enzite-CHT used in these experiments was calculated so as to give an equal number of units as that used with the free enzyme. The results are summarized in Table III. These show that, while the rate of hydrolysis was

TABLE III
TIME REQUIRED FOR FULL DEPROTECTION BY FREE α-CHYMOTRYPSIN[a] AND BY ENZITE-CHT[b]

Compd	Enzite-CHT, 34 units/μmol	Free α-chymotrypsin, 31 units/μmol
2a, d-pT-ODHC	8 hr	2 hr
17, d-CEpTpC^{An}-ODHC	3 hr	30 min
19, d-CEpTpC^{An}pA^{Bz}-ODHC	3 hr	30 min
21, d-CEpTpC^{An}pA^{Bz}pG^{iB}-ODHC	3 hr	45 min

[a] The reaction mixture contained 1.6 μmol of substrate in 0.05 *M* phosphate buffer, pH 7.5, plus 1 mg of α-chymotrypsin (50.4 units). [b] The reaction mixture contained 1.6 μmol of substrate in 1.0 ml of 0.05 *M* phosphate buffer, pH 7.5, plus 100 mg of Enzite-CHT (56 units).

faster for an oligonucleotide than for a mononucleotide, the hydrolysis rate in all cases was much slower than the rate obtained when using an equivalent amount of the free enzyme.

Discussion

Three different substrates of α-chymotrypsin have been used as protecting groups for the 3′-hydroxyl function of 2′-deoxynucleotides and the 3′- and 5′-hydroxyl positions of 2′-deoxynucleosides. Esters of dihydrocoumarilic acid and dihydrocinnamic acid have been studied[13,14] previously as substrates of α-chymotrypsin and compared with esters of the best synthetic substrate *N*-acetyl-L-phenylalanine. These studies showed that esters of the D-(+) enantiomer of dihydrocoumarilic acid were hydrolyzed by the enzyme at a much faster rate than those of the L-(−) form and at a rate comparable to esters of *N*-acetyl-L-phenylalanate[13] (k_{cat}/K_m, methyl *N*-acetyl-L-phenylalanate, 6.9×10^4; methyl D-dihydrocoumarilate, 1.4×10^4). Esters of dihydrocinnamic acid are not such good substrates for α-chymotrypsin[14] (k_{cat}/K_m, ethyl dihydrocinnamate, 1.5×10) and esters of *o*-phenylenedioxyacetic acid have not been studied previously as substrates for this enzyme.

The difficulties encountered in esterifying nucleotides with the acid chlorides from PDA and DCM acids are a considerable disadvantage to the use of these groups. It has been noted previously that treatment of monophosphates with low molar ratios (1–5 equiv) of an acid chloride or anhydride can result in the formation of the symmetrical pyrophosphate but use of an excess of these reagents (10–20 equiv) leads to a breakdown of the pyrophosphate bond.[15–17] However, the use of large excesses of the acid chlorides from all three acids still gave what was tentatively identified as the symmetrical pyrophosphate as the major product. The problem was solved in the case of the DHC group by use of the anhydride of this acid, which gave much cleaner reactions, but the anhydrides of the other two acids proved inaccessible. Alternative procedures involving the preparation of the mixed anhydrides with ethyl chloroformate gave no better yields of the protected mononucleotides. These results are probably due to the size and steric shape of these acylating agents, which results in an increase in the rate of pyrophosphate formation as compared to the rate of acylation.[17]

Comparison of these protecting groups as substrates for α-chymotrypsin showed that the PDA and DCM groups were very similar and both better substrates than the DHC group. The amounts of enzyme used in the kinetic experiments were measured on the basis of units per micromole of substrate so that direct comparison could be made of the results with the nucleosides carrying 2 mol of the substrate and the mono- and oligonucleotides which have only 1 mol of substrate.

In all cases hydrolysis from nucleotides was faster than from nucleosides, possibly due to the fact that the protected nucleosides are insoluble in the aqueous media and as a result the enzymatic hydrolyses were carried out on suspensions. Attempts to use a cosolvent such as acetonitrile, to increase the solubility, did not improve the results as the amounts of organic solvent required to keep the nucleoside in solution were sufficient to severely inhibit the α-chymotrypsin. Interestingly, the kinetic curve for the hydrolysis of deoxyuridine protected in the 3′ and 5′ positions by the racemate of the DCM group shows a distinct break in the curve due to the rate of hydrolysis of one enantiomer being much faster than the other.

The DHC and DCM protecting groups were used in the synthesis of several oligonucleotides. The PDA group was not used further as the kinetic results and synthetic work so far showed that no advantage could be achieved using it.

Synthesis of the trinucleotide d-pApTpC and the tetranucleotide d-pCpTpCpT revealed further disadvantages of the DCM protecting group. This group appears to be too alkali sensitive to survive passage through a DEAE cellulose column using TEAB as the eluant due to the change in pH. A more stable buffer system could have been used but this would then raise the problem of desalting the product. A suggested use for this protecting group would be as a 3′-hydroxyl protecting group which could be removed selectively by mild alkaline treatment in the presence of the cyanoethyl group. The DHC group was stable under the conditions required for column chromatography on DEAE cellulose using TEAB as the eluant.

The enzymatic conditions used to remove the protecting groups during synthesis are summarized in Table IV. Later kinetic results on the oligonucleotides **17**, **19**, and **21** showed that, in fact, much milder conditions

(13) W. B. Lawson, *J. Biol. Chem.*, **242**, 3397 (1967).
(14) S. G. Cohen, A. Milovanovic, R. M. Schyltz, and S. Y. Weinstein, *ibid.*, **244**, 2664 (1969).
(15) H. G. Khorana and J. P. Vizsolyi, *J. Amer. Chem. Soc.*, **81**, 4660 (1959).
(16) M.W. Moon and H. G. Khorana, *ibid.*, **88**, 1798 (1966).
(17) M. W. Moon and H. G. Khorana, *ibid.*, **88**, 1805 (1966).

TABLE IV

CONDITIONS USED FOR THE ENZYMATIC REMOVAL OF ACYL PROTECTING GROUPS IN SYNTHESIS

	Time, hr	Enzyme–substrate ratio, units/μmol	Yield, %
d-CEpA^{Bz}pT-ODCM → d-CEpA^{Bz}pT	4	5	90
d-CEpA^{Bz}pTpC^{An}-ODCM → d-CEpA^{Bz}pTpC^{An}	3	1.5	69
d-CEpC^{An}pT-ODHC → d-CEpC^{An}pT	16	5.4	73
d-CEpC^{An}pTpC^{An}-ODCM → d-CEpC^{An}pTpC^{An}	2	1.8	41
d-CEpC^{An}pTpC^{An}pT-ODCM → d-CEpC^{An}pTpC^{An}pT	2	8.7	75
d-CEpTpC^{An}-ODHC → d-CEpTpC^{An}	8	5.4	98
d-CEpTpC^{An}pA^{Bz}-ODHC → d-CEpTpC^{An}pA^{Bz}	24	7.3	91
d-CEpTpC^{An}pA^{Bz}pG^{iB}-ODHC → d-CEpTpC^{An}pA^{Bz}pG^{iB}	24	10.8	82

could have been used. Better results were obtained when the oligonucleotides were purified prior to treatment with α-chymotrypsin than when deprotection was carried out on the crude reaction mixture. This was due to the fact that organic solvents and other insoluble residues had to be removed before enzymatic treatment.

The separation of protein and nucleotide was achieved by preparative paper chromatography. The α-chymotrypsin used in these experiments contained several components but all were easily separated from the oligonucleotides in solvents D or E.

The tetramer d-pTpCpApG was synthesized in good yield using the DHC protecting group, demonstrating its use with all four bases. Under the conditions of enzymatic hydrolysis no loss of any base protecting group was observed. Studies of the kinetics of the enzymatic removal showed that the time required for the hydrolysis decreased considerably from monomer to dimer and then increased slightly with increasing chain length. This is in agreement with the fact that macromolecules are generally better substrates for α-chymotrypsin.

The results using the insolubilized form of α-chymotrypsin were disappointing. The insolubilized enzyme does hydrolyze esters of dihydrocinnamic acid but at a slower rate than the free enzyme when amounts containing the same number of units of activity are used. Two reasons for the decrease in rate can be put forward. One is the fact that the support used for the enzyme is carboxymethyl cellulose and as a result the negatively charged oligonucleotide will tend to be repelled by the support. Better results might be obtained if a neutral or positively charged support was used. A second reason could be the stability of the insolubilized enzyme, so that with older samples the activity was probably lower than expected, but this was not checked. It had been hoped that a column procedure could have been set up using a DEAE cellulose column with a layer of insolubilized enzyme on top so that deprotection and separation could be achieved in one step. However, the time required for hydrolysis was too great to be useful.

Conclusions

Of the three protecting groups used in this work the DCM and PDA groups are considerably better substrates for α-chymotrypsin than the DHC group. However, this advantage is offset by the difficulties encountered in synthetic work using these particular groups. Moreover, the alkali sensitivity of the resulting protected nucleotides is such that column chromatography cannot be used for purification. On the other hand the dihydrocinnamoyl group has been shown to be useful in small scale synthesis and further work involving the use of this protecting group in the large scale synthesis of an octanucleotide will be reported at a later date.

Experimental Section

Reagent grade pyridine was purified by distillation over chlorosulfonic acid and potassium hydroxide and stored over 4A molecular sieve beads (Linde Co.). All evaporations were carried out at reduced pressure below 25°. Whenever necessary, reagents and reaction mixtures were rendered anhydrous by repeated evaporation of added dry pyridine *iv vacuo*. Qualitative paper chromatography was carried out by the descending technique on Whatman No. 1 paper. Preparative paper chromatography was carried out on Whatman No. 3 MM paper. The solvent systems used were (A) *n*-BuOH–acetic acid–H_2O (5:2:3, v/v); (B) *n*-PrOH–concentrated NH_4OH–H_2O (55:10:35); (C) ethyl acetate–ethanol (9:1); (D) ethanol–1 *M* ammonium acetate (pH 7.5) (7:3), (E) ethanol–0.05 *M* ammonium acetate (pH 7.5) (7:3), (F) isobutyric acid–concentrated NH_4OH–H_2O (66:1:33). Thin layer chromatography was run on silica gel (F-254, E. Merck) and cellulose F (E. Merck). Separation of products with close R_f values was achieved by running the chromatograph for 24 to 36 hr instead of the usual 16 hr to achieve better separation of the bands. The chromatograms were dried and then soaked for 1 hr in absolute ethanol to remove ammonium acetate, washed with diethyl ether and the nucleotides eluted with water or 20% ethanol. Final traces of salts were removed by lyophilization.

The products were characterized by their uv spectra and the treatment of a sample with 1 *N* sodium hydroxide solution for 10 min at room temperature followed by neutralization with Dowex 50X-8 resin (pyridinium form) to remove any phosphate or 3′-hydroxyl protecting groups. Samples were then chromatographed on Whatman No. 1 paper in solvent D. More complete characterization was carried out by treatment with concentrated ammonia to remove all protecting groups. After separation by chromatography, the base composition was determined by enzymatic degradation with snake venom phosphodiesterase, spleen phosphodiesterase, or alkaline phosphatase as described previously.[18]

DL-Dihydrocoumarilic acid was prepared by known procedures[9] and resolved by crystallization with *d*-amphetamine to give D-(+)-dihydrocoumarilic acid, $[\alpha]^{25}D$ 22.7° (c 1.5, EtOH). *o*-Phenylenedioxyacetic acid was synthesized by published methods[10] and dihydrocinnamic acid was purchased from the Aldrich Chemical Co. The corresponding acid chlorides were prepared by standard methods using thionyl chloride and had boiling points, DHC chloride, 70–75° (0.3 mm); DCM chloride, 85–88° (0.4 mm); PDA chloride, 90–92° (0.5 mm). Dihydrocinnamic anhydride was prepared from the acid by treatment with acetic anhydride or by treatment with an equimolar amount of the acid chloride and had bp 190–200° (0.3 mm).

Adaptations of known procedures were used to synthesize the pyridinium salts of the base protected nucleotides d-pA^{Bz}, d-pC^{An}, and d-pG^{iB}.[19]

Extinction coefficients at neutral pH were as follows: d-pC^{An}, 17,700 (280 mμ); d-pC, 9,100 (273 mμ); d-pA^{Bz}, 18,300 (280

(18) H. G. Khorana, A. F. Turner, and J. P. Vizsolyi, *J. Amer. Chem. Soc.*, **83**, 686 (1961); H. G. Khorana and J. P. Vizsolyi, *ibid.*, **83**, 675 (1961); W. E. Razzel and H. G. Khorana, *J. Biol. Chem.*, **236**, 1144 (1961); M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Amer. Chem. Soc.*, **84**, 430 (1962).

(19) H. Schaller and H. G. Khorana, *ibid.*, **85**, 3828 (1963).

mμ); d-pA, 14,500 (260 mμ); d-pT, 6,400 (280 mμ) and 9,600 (267 mμ); d-pG^{iB}, 11,500 (280 mμ); d-pG, 13,600 (253 mμ).

α-Chymotrypsin was purchased from Worthington Biochemical Corporation, grades CDI and CDS. The specific activity of the different batches ranged from 47 to 54 units/mg and was not checked. Each batch was checked for lack of nuclease activity. Enzite-CHT is a product of Miles-Serovac and had a specific activity of 0.56 units/mg of dry material.

Preparation of Protected Nucleosides (1a–d). The nucleoside (1 mmol) was suspended in dry pyridine (4 ml) at 0° and the acid chloride or anhydride [dihydrocinnamic anhydride, o-phenylenedioxyacetic chloride, or D-(+)-dihydrocoumariloyl chloride (4.0 mmol)] added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 hr, then cooled to −20° and treated with water (5 ml). After stirring 1 hr the mixture was extracted with methylene chloride (3 × 5 ml) and the organic extracts were washed with water, 5% sodium bicarbonate solution, and water again, and dried over sodium sulphate. The methylene chloride solution was concentrated to 3 ml and the protected nucleoside precipitated by addition of the solution to dry ether. The yields were generally 80–90%. Further purification if necessary was by preparative tlc (silica, solvent C). Chromatographic data is summarized in Table V.

TABLE V

CHROMATOGRAPHIC DATA FOR NUCLEOSIDES AND NUCLEOTIDES

	R_f values			
Compd	Whatman No. 1, solvent A	Whatman No. 1, solvent D	Cellulose tlc, solvent D	Silica tlc, solvent C
1a, R = DHC				0.84
1b, R = PDA				0.89
1c, R = DCM (racemate)				0.85
1d, R = DCM [D-(+) isomer]				0.85
2a, R′ = DHC		0.67		
2b, R′ = PDA		0.63		
2c, R′ = DCM [D-(+)isomer]		0.61		
3a, d-pC^{An}-ODHC		0.59		
3b, d-pC^{An}-OPDA		0.62		
3c, d-pC^{An}-ODCM		0.68		
5, d-pA^{Bz}-ODHC		0.65		
6, d-pG^{iB}-ODHC		0.64		
7, d-CEpA^{Bz}pT-ODCM		0.74	0.75	
8, d-CEpA^{Bz}pT		0.64	0.61	
9, d-CEpA^{Bz}pTpC^{An}-ODCM		0.58	0.56	
10, d-CEpA^{Bz}pTpC^{An}		0.45	0.36	
11, d-CEpC^{An}pT-ODHC		0.78	0.77	
12, d-CEpC^{An}pT		0.56	0.46	
13, d-CEpC^{An}pTpC^{An}-ODCM		0.69	0.61	
14, d-CEpC^{An}pTpC^{An}		0.49	0.37	
15, d-CEpC^{An}pTpC^{An}pT-ODCM		0.27		
16, d-CEpC^{An}pTpC^{An}pT		0.20		
17, d-CEpTpC^{An}-ODHC	0.77	0.72		
18, d-CEpTpC^{An}	0.66	0.62		
19, d-CEpTpC^{An}pA^{Bz}-ODHC	0.69	0.67		
20, d-CEpTpC^{An}pA^{Bz}	0.62	0.65		
21, d-CEpTpC^{An}pA^{Bz}pG^{iB}-ODHC	0.59	0.50		
22, d-CEpTpC^{An}pA^{Bz}pG^{iB}	0.51	0.46		

Preparation of Protected Nucleotides (2a–c, 3a–c, and 4–6). The pyridinium salt of the nucleotide (1.0 mmol), base protected if necessary, was azeotroped with dry pyridine (2 × 5 ml) and dissolved in dry pyridine (5 ml). After cooling to −30° the solution was treated with the acid chloride or anhydride (10.0–20.0 mmol). The mixture was warmed to room temperature and stirred in the dark for 4–20 hr. The reaction was stopped by cooling to −30° and adding dry methanol (10 ml). After standing at room temperature for 3 hr, pyridine (10 ml) was added and the mixture stored overnight at room temperature. Solvents were removed *in vacuo*; the resulting oil was triturated with dry ether (5 × 20 ml). The residue was dissolved in dry pyridine and then added dropwise to dry ether and the resulting off-white precipitate collected. Yields of nucleotides protected by the DHC group were almost quantitative (95–100%). Mononucleotides carrying the DCM or PDA protecting groups required further purification by paper chromatography (Whatman No. 3 MM, solvent D). The band of protected nucleotide (R_f 0.60 to 0.63) was desalted by washing with absolute ethanol and then eluted with water. The yields were poor (40–45%).

Kinetic Studies. The protected nucleoside or nucleotide (0.05 mmol nucleoside or 0.1 mmol nucleotide, *i.e.*, 0.1 mmol substrate) was suspended or dissolved in 0.1 *N* NaCl solution (0.5 ml) and the pH adjusted to 7.8 (using a pH meter) with dilute NaOH solution. α-Chymotrypsin was added as a solution in 0.1 *N* NaCl and the volume of the mixture adjusted to 2.0 ml. The solution was incubated at 37° and the pH maintained at between 7.6 and 8.0 by the constant addition of 0.1 *N* NaOH solution. For the separation and identification of the reaction products silica gel plates were used for the nucleosides (solvent C) and cellulose plates for the nucleotides (solvent D). Control experiments excluding the enzyme were run in all cases; no observable hydrolysis was ever detected. Control experiments were also run excluding the substrate. It was observed that at high enzyme concentrations (5×10^{-4} *M*) autolysis occurred. Correspondingly, the results of the kinetic runs were corrected for this factor.

In order to economize on materials, enzymatic degradations of oligonucleotides were carried out on a 25-μmol scale. The volume of the mixture was adjusted to 0.5 ml. The results are summarized in Tables I and II.

Stability Studies. Samples of the protected nucleosides and nucleotides (1–5 μmol) were dissolved in 0.5 *M* TEAB solution at pH 8.0 and 9.5 (0.2 ml). The solutions were analyzed at time intervals by paper chromatography; the percentage of hydrolysis was measured by elution of the spots from the chromatograms and measurement of the absorbance at 260 mμ. The results are summarized in Table VI.

TABLE VI

STABILITY STUDIES ON THE PROTECTED NUCLEOSIDES AND NUCLEOTIDES[a]

		Hydrolysis, %	
Compd	Time, hr	pH 8.0	pH 9.5
1b	4	0	0
	24	0	2
1d	4	0	0
	24	0	3
2b	4	2	100
	24	11	100
2c	4	4	100
	24	13	100

[a] See text for experimental details. No hydrolysis was observed with **1a** and **2a**.

Degradations with Enzite-CHT. Enzite-CHT (100 mg, 56 units) was rehydrated by stirring in 0.5 *M* phosphate buffer at pH 8.0 for 1 hr and then collected by centrifugation. The Enzite-CHT was washed twice more and then suspended in 0.05 *M* phosphate buffer (pH 8.0, 0.8 ml) and incubated at 37° with a solution of the nucleotide (1.6 μmol in 0.2 ml of buffer). The reactions were followed by tlc (cellulose, solvent D).

The Enzite-CHT was recovered for reuse by centrifugation and washed with buffer. The recovered material was stored as a slurry at 0°.

Comparison degradations were run using the same amounts of nucleotides with free α-chymotrypsin (1 mg, 50.4 units) in 0.1 ml of 0.05 *M* phosphate buffer (pH 7.8). The results are summarized in Table III.

Synthesis of Oligonucleotides

d-CEpA^{Bz}pT-ODCM, 7. (a) The mononucleotides of d-CEpA^{Bz} (1.50 g, 2.64 mmol) and d-pT-ODCM (**2c**, 1.0 g, 1.60 mmol) were azeotroped with dry pyridine (3 × 10 ml), taken up in dry pyridine (15 ml), and treated with mesitylene sulfonyl chloride (MSC) (900 mg, 4.1 mmol). After 3 hr the reaction was terminated by cooling and adding water (15 ml). The solution was chromatographed on a diethylaminoethyl (DEAE) cellulose column (4 × 51 cm, gradient of triethylammonium bicarbonate (TEAB), 20% EtOH, 2 l. each 0.1 and 0.7 *M*). The main peak of dinucleotide was pooled and lyophilized. However, this product had R_f 0.64 (Whatman No. 1, solvent D) and was

thought to be d-CEpA^{Bz}pT, the D-(+)-dihydrocoumariloyl group being lost during chromatography. The yield was 830 mg, 60%.

(b) The reaction was repeated using d-CEpA^{Bz} (280 mg, 0.49 mmol) and d-pT-ODCM (200 mg, 0.32 mmol) and worked up by chromatography on 8 sheets of Whatman 3 MM paper, solvent D for 30 hr. The product, 165 mg, 51%, had R_f 0.74 (Whatman No. 1 solvent D). Starting material and d-CEpA^{Bz}pT (R_f 0.62), was also obtained (24 mg, 7.5%).

d-CEpA^{Bz}pT (8). The above dinucleotide (from b) (150 mg, 149 μmol) was dissolved in 0.05 *M* phosphate buffer pH 7.5 (10 ml) and treated with a solution of α-chymotrypsin in buffer (15 mg, 5 ml, enzyme–substrate ratio 5 units/μmol), and the mixture incubated at 37° for 4 hr. The product was isolated by preparative paper chromatography (solvent D) on 4 sheets of Whatman 3 MM paper for 28 hr. This dinucleotide, 115 mg, 90%, had R_f 0.64 (Whatman No. 1, solvent D) and was identified as d-CEpA^{Bz}pT by comparison of its R_f and uv spectrum with those of a sample prepared by cyanoethylation of d-pA^{Bz}pT (R_f 0.29, solvent D). The protecting groups were removed by treatment with concentrated ammonia to give d-pApT (R_f 0.13, solvent D; 0.31, solvent B; 0.35, solvent F). Degradation with snake venom phosphodiesterase gave dpA–dpT, 1.00:0.96.

d-CEpA^{Bz}pTpC^{An}-ODCM (9). The dinucleotide 8 (100 mg, 116 μmol) was condensed in the usual way with d-pC^{An}-ODCM (3c) (100 mg, 134 μmol) using MSC (100 mg, 460 μmol) for 3.5 hr. The product 19 mg (11%) was isolated by chromatography on 4 sheets of Whatman 3 MM paper in solvent D for 32 hr. Characterization was by removal of all the protecting groups with concentrated ammonia to give d-pApTpC (R_f 0.05, solvent D). Degradation with snake venom phosphodiesterase gave d-pA–d-pT–d-pC, 1.00:1.01:1.12.

d-CEpA^{Bz}pTpC^{An} (10). Treatment of the trinucleotide 9 (5 mg, 3.3 μmol) with α-chymotrypsin (0.1 mg, enzyme–substrate ratio 1.5 units/μmol) in 0.05 *M* phosphate buffer, pH 7.5 (0.5 ml), at 37° for 3 hr and work-up by paper chromatography gave 10 (3.1 mg, 69%).

d-CEpC^{An}pT-ODHC (11). Condensation of d-CEpC^{An} (230 mg, 0.40 mmol) and d-pT-ODHC (2a, 395 mg, 0.65 mmol) using dicyclohexylcarbodiimide (DCC) (1.60 g, 7.60 mmol) in the presence of dry Dowex 50W-X8 pyridinium form for 5 days and work-up by chromatography on a column of DEAE cellulose (4 × 34 cm), TEAB gradient (1.5 l. each of 0.05 and 0.50 *M*) gave 11 (230 mg, 53%). Treatment with ammonia gave the dinucleotide d-pCpT (R_f 0.13, solvent D; R_f 0.33, solvent B; and R_f 0.41, solvent F) which was identified by degradation with snake venom phosphodiesterase (d-pC–d-pT, 1.00:1.08).

d-CEpC^{An}pT (12). The above dinucleotide 11 (100 mg, 92 μmol) was incubated with α-chymotrypsin (10 mg, enzyme–substrate ratio 5.4 units/μmol) in 0.05 *M* phosphate buffer, pH 7.5, (10 ml) for 16 hr. Isolation was by paper chromatography (Whatman 3 MM, solvent D) (nucleotide R_f 0.56, α-chymotrypsin 0.00) and lyophilization (63 mg, 73%).

d-CEpC^{An}pTpC^{An}-ODCM (13). The dinucleotide 12, (60 mg, 63 μmol) was condensed with d-pC^{An}-ODCM (3, 120 mg, 161 μmol) using MSC (90 mg, 410 μmol) in dry pyridine (6 ml) for 7 hr. The reaction was terminated by cooling and treating with water (6 ml). Chromatography of a small sample of the reaction mixture (2 ml) on Whatman No. 3 MM paper, solvent D, gave a main band, R_f 0.69 (13.1 mg). Treatment of this band with alkali, to remove the phosphate and hydroxyl protecting groups, gave a mixture of the trinucleotide d-pC^{An}pTpC^{An} and the mononucleotide d-pC^{An} in equal amounts. This showed that separation of the excess d-pC^{An}-ODCM and d-CEpC^{An}pTpC^{An}-ODCM could not be achieved by paper chromatography. The yield of the protected trinucleotide was estimated from these results to be approximately 41%.

d-CEpC^{An}pTpC^{An} (14). The remaining solution from the above reaction (10 ml) was concentrated *in vacuo* and the residue azeotroped with water (2 × 10 ml), ethanol–water (10 ml), and water again (3 × 10 ml) to remove all traces of pyridine. The residue was dissolved in 0.05 *M* phosphate buffer, pH 7.5 (10 ml), filtered to remove some insoluble material and incubated with α-chymotrypsin (5 mg, enzyme–substrate ratio 1.8 units/μmol) at 37° for 2 hr. The partially protected trinucleotide, 14, was isolated by chromatography (Whatman 3 MM, solvent D) followed by lyophilization, 10 mg, 13%. The trinucleotide was characterized by removal of all the protecting groups with concentrated ammonia to give d-pCpTpC (R_f 0.06, solvent D; 0.27, solvent B; 0.33, solvent G). Degradation with snake venom phosphodiesterase gave d-pC–d-pT, 1.98:1.00.

d-CEpC^{An}pTpC^{An}pT-ODCM (15). The mononucleotide d-pT-ODCM (2c, 20 mg, 32 μmol) was condensed with the trinucleotide 14 (239 OD_{260}, 6.9 μmol) using MSC (20 mg, 91 μmol) in dry pyridine (1 ml) for 15 hr. The tetranucleotide 15 was isolated by paper chromatography (Whatman 3 MM, solvent D) and lyophilization, 29 OD_{260}, 10%. The product was characterized by treatment with ammonia to remove the protecting groups to give d-pCpTpCpT (R_f 0.02, solvent D; 0.20, solvent B; 0.23, solvent F). Degradation with snake venom phosphodiesterase gave d-pC–d-pT, 1.00:1.01.

d-CEpC^{An}pTpC^{An}pT (16). A sample of the tetramer 15 (10 OD_{260}, 0.23 μmol) was dissolved in 0.05 *M* phosphate buffer, pH 7.5 (0.2 ml), and heated with α-chymotrypsin (2 units, enzyme–substrate ratio 8.7 units/μmol) at 37° for 2 hr. Paper chromatography (Whatman 3 MM, solvent D) gave 16, 7.5 OD_{260}, 75%.

d-CEpTpC^{An}-ODHC (17). d-pC^{An}-ODHC (4, 1.0 g, 1.37 mmol) and d-CEpT (1.4 g, 3.1 mmol) both as pyridinium salts were condensed in dry pyridine (10 ml) using MSC (2.1 g, 9.6 mmol) as condensing agent. After 2.5 hr the reaction was stopped by the addition of water (10 ml) and after dilution the solution was chromatographed on a DEAE cellulose column (4 × 90 cm). Elution was with a gradient of TEAB containing 20% EtOH (0.05 to 0.2 *M*, 4 l. of each). The main peak was pooled and lyophilized to give the dinucleotide d-CEpTpC^{An}-ODHC, 806 mg, 54%.

d-CEpTpC^{An} (18). d-CEpTpC^{An}-ODHC (17, 11,100 OD_{280}, 0.46 mmol) was dissolved in 0.5 *M* phosphate buffer, pH 7.5 (100 ml), and treated with α-chymotrypsin (50 mg, enzyme–substrate ratio 5.4 units/μmol) for 8 hr at 37°. The solution was streaked onto 6 sheets of Whatman 3 MM paper and chromatographed in solvent E. The main band was eluted and lyophilized to give the partially protected dinucleotide 18, 10,890 OD_{280}, 98%. The recovery of 17 was 67 OD_{280}, 0.6%.

d-pTpC^{An}. A sample of d-CEpTpC^{An} (18, 3 mg) was treated with 1 *N* sodium hydroxide solution (0.5 ml) for 10 min. Chromatography on Whatman No. 1 in solvents D and A gave a single spot of d-pTpC^{An}, R_f 0.27, solvent D; R_f 0.42, solvent A.

d-pTpC. The solution from the above reaction was concentrated to dryness and the residue taken up in concentrated ammonia (1 ml) for 2 days at room temperature. The solution was streaked onto Whatman 3 MM paper and chromatographed in solvent B. A single band of d-pTpC was eluted, R_f 0.29 (R_f 0.38, solvent F). Degradation with snake venom phosphodiesterase gave d-pT–d-pC, 1.00:1.02. Treatment with bacterial alkaline phosphatase gave a single spot of d-TpC, R_f 0.59 (solvent B), which on degradation with spleen phosphodiesterase gave the monomers d-Tp and d-C in the ratio 1.00:0.95.

d-CEpTpC^{An}pA^{Bz}-ODHC (19). d-CEpTpC^{An} (10,800 OD_{280}, 0.45 mmol) and d-pA^{Bz}-ODHC (930 mg, 1.28 mmol) were dried by repeated evaporation with dry pyridine, and MSC (790 mg, 3.60 mmol) was added as a solution in dry pyridine (5 ml). After 2.5 hr at room temperature the reaction was stopped by cooling and adding water (5 ml). The solution was streaked onto Whatman 3 MM paper and chromatographed in solvent E. The main band (R_f 0.69) was eluted and lyophilized to give 19, 8,700 OD_{280}, 46%.

d-CEpTpC^{An}pA^{Bz} (20). d-CEpTpC^{An}pA^{Bz}-ODHC (7,250 OD_{280}, 170 μmol) was dissolved in 0.5 *M* phosphate buffer, pH 7.5, (90 ml) and treated with α-chymotrypsin (25 mg, enzyme–substrate ratio 7.3 units/μmol) for 24 hr. Work-up by paper chromatography on Whatman 3 MM paper, solvent E, gave the partially protected trinucleotide 20, 6,600 OD_{280}, 91%.

d-pTpC^{An}pA^{Bz}. d-CEpTpC^{An}pA^{Bz} (19, 2 mg) and also d-CEpTpC^{An}pA^{Bz}-ODHC (20, 2 mg) were each treated with 1 *N* sodium hydroxide solution (0.5 ml) for 10 min. Chromatography on Whatman No. 1 paper in solvents A (R_f 0.29) and D (R_f 0.25) gave a single spot of d-pTpC^{An}pA^{Bz}.

d-pTpCpA. The solutions from the above reactions were treated with concentrated ammonia (2 ml) for 2 days at room temperature and then chromatographed on Whatman 3 MM paper in solvent B. A single band of d-pTpCpA, R_f 0.27, was observed (R_f 0.31, solvent F). This band was eluted and part of it treated with phosphatase to give d-TpCpA (single spot, R_f 0.53 in solvent B) followed by degradation with spleen phosphodiesterase to give d-Tp, d-Cp, and d-A in the ratio 1.00:0.97:0.96. The second part of d-pTpCpA was degraded with snake venom phosphodiesterase to give d-pT, d-pC, and d-pA in the ratio 1.00:0.98:1.03.

d-CEpTpC^{An}pA^{Bz}pG^{iB}-ODHC (21). d-CEpTpC^{An}-pA^{Bz} (20, 6000 OD_{280}, 140 μmol) was condensed with d-pG^{iB}-ODHC (440

mg, 625 μmol) using MSC (330 mg, 1.50 mmol) in dry pyridine (5 ml). The reaction was stopped after 4 hr by cooling and adding water (5 ml). Work-up by paper chromatography (solvent E) gave the fully protected tetranucleotide **21**, 7500 OD_{280}, 36%.

d-CEpTpC^{An}pA^{Bz}pG^{iB} (22). Treatment of the preceding compound (1000 OD_{280}, 18.5 μmol) with α-chymotrypsin (4.0 mg, enzyme–substrate ratio 10.8 units/μmol) in phosphate buffer, pH 7.5 (40 ml), at 37° for 24 hr gave the partially protected tetranucleotide d-CEpTpC^{An}pA^{Bz}pG^{iB} (**22**), 615 OD_{280}, 82%, isolated by paper chromatography in solvent E.

d-pTpC^{An}pA^{Bz}pG^{iB}. d-CEpTpC^{An}pA^{Bz}pG^{iB} (**22**, 50 OD_{280}) was hydrolyzed with 1 *N* sodium hydroxide solution (0.5 ml) for 10 min to give d-pTpC^{An}pA^{Bz}pG^{iB}, and isolated by chromatography in solvent D, R_f 0.19.

d-pTpCpApG. Treatment of d-pTpC^{An}pA^{Bz}pG^{iB} with concentrated ammonia for 2 days gave the tetranucleotide d-pTpCpApG, R_f 0.23, solvent B (R_f 0.20, solvent F). The tetranucleotide was characterized by degradation with snake venom phosphodiesterase to give the mononucleotides in the ratio d-pT–d-pC–d-pA–d-pG, 1.00:1.01:1.01:0.96. Further characterization was by removal of the terminal phosphate to give d-TpCpApG (R_f 0.45, solvent B) followed by degradation with spleen phosphodiesterase to give d-Tp–d-Cp–d-Ap–d-G, 1.00:1.10:1.05:1.08.

Registry No.—**1a**, 23706-27-6; **1b**, 37731-23-0; **1c**, 37731-24-1; **1d**, 37731-25-2; **2a**, 37731-26-3; **2b**, 37731-27-4; **2c**, 37731-28-5; **3a**, 37731-29-6; **3b**, 37731-30-9; **3c**, 37731-31-0; **5**, 37731-32-1; **6**, 37731-33-2; **7**, 37731-34-3; **8**, 37731-35-4; **9**, 37731-36-5; **10**, 37731-37-6; **11**, 37731-38-7; **12**, 37731-39-8; **13**, 37731-40-1; **14**, 37731-41-2; **15**, 37731-42-3; **16**, 37731-43-4; **17**, 37731-44-5; **18**, 37731-45-6; **19**, 37731-46-7; **20**, 37731-47-8; **21**, 37818-77-2; **22**, 37731-48-9; D-(+)-DCM, 17332-01-3; D-(+)-DCM (acid chloride), 37731-49-0; PDA, 37731-50-3; PDA (acid chloride) 37731-51-4; DHC, 501-52-0; DHC (acid chloride), 645-45-4; DHC (anhydride), 15781-96-1; d-pC^{An}, 32909-08-3; d-pC, 1032-65-1; d-pA^{Bz}, 4546-64-9; d-pA, 653-63-4; d-pT, 365-07-1; d-pG^{iB}, 32909-09-4; d-pG, 902-04-5; d-CEpA^{Bz}, 37740-89-9; d-CEpC^{An}, 37740-90-2; d-pTpC^{An}, 37731-45-6; pTpC, 2147-10-6; d-pTpC^{An}-pA^{Bz}, 37740-92-4; d-pTpCpA, 37740-93-5; d-pTpC^{An}-pA^{Bz}pG^{iB}, 37740-94-6; d-pTpCpApG, 37740-95-7.

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Intermediates in the Ozonation of Simple Alkynes

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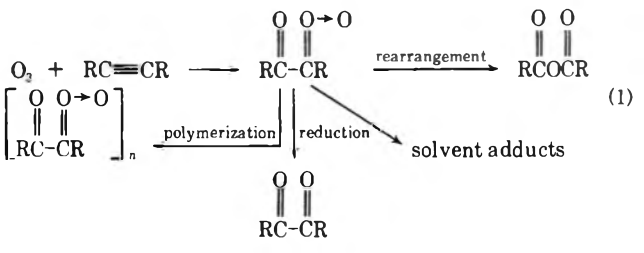
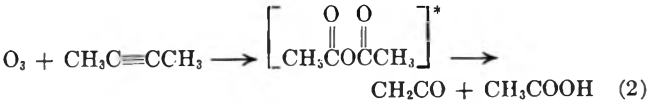
The reactions of O_3 with HC≡CH, $CH_3C{\equiv}CH$, $CH_3C{\equiv}CCH_3$, and $C_2H_5C{\equiv}CH$ have been studied in liquid CO_2 at −45°. The initial products were observed by *in situ* infrared spectroscopy, and subsequent changes occurring upon warm-up or flash vaporization of the mixture were followed by ir or gc analysis. The principal new spectral feature for all alkynes except acetylene was a strong carbonyl absorption near 1740 cm^{-1}, and all alkynes gave relatively weak absorption bands in the carbonyl region which are attributed to the corresponding acid anhydrides. The 1740-cm^{-1} band was shown to be an unstable precursor of the acid anhydrides and other products. The overall mechanism, the identity of the precursor, and factors influencing the final product distribution are discussed.

Relatively little is known about the detailed mechanism of alkyne ozonation. According to the Criegee–Lederer mechanism,[1] an acylcarbonyl oxide is produced which may react in a variety of ways.



(1)

Anhydride formation, first proposed by Paillard and Wieland[2] to explain product ratios in the ozonation of heptyne-1, has been observed only in the ozonation of diphenylacetylene.[3] For the gas-phase ozonation of simple alkynes, it has been suggested[4] that products corresponding to fission of the triple bond arise from the decomposition of an excited anhydride intermediate. For example, ketene and acetic acid produced by the gas-phase ozonation of dimethylacetylene can be explained as follows.



(2)

According to this interpretation, the excited anhydride is short-lived and decomposes completely at 1-atm pressure. However, at higher pressures or in the condensed phase the excited intermediate should be collisionally stabilized. The present work was carried out in an effort to isolate the anhydride intermediate, and to provide additional information on the anhydride precursor. The alkynes studied include acetylene, methylacetylene, dimethylacetylene, and ethylacetylene.

Apparatus and Methods

The experiments involved ozonation of the alkynes in liquid CO_2 at about −45° with *in situ* ir analysis of the products. The reaction cell (Figure 1) was a vac-

(1) R. Criegee and M. Lederer, *Justus Liebigs Ann. Chem.*, **583**, 29 (1953).
(2) H. Paillard and C. Wieland, *Helv. Chim. Acta*, **21**, 1356 (1938).
(3) E. Dallwigk, H. Paillard, and E. Briner, *ibid.*, **35**, 1377 (1952).
(4) W. B. DeMore, *Int. J. Chem. Kinet. III*, 161 (1971).

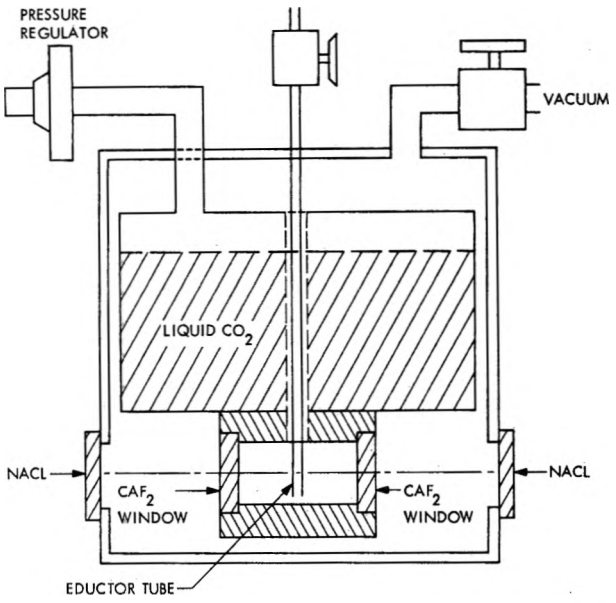


Figure 1.—Reaction cell for ozonation studies in liquid CO_2 solvent.

uum-jacketed, stainless steel cell fitted with CaF_2 windows. The cell was cooled by liquid CO_2 (separate from the reaction cell) held at about 120 psi. The ir spectra of the liquid mixtures were taken on a Model 421 Perkin-Elmer spectrometer. The combined transmission of liquid CO_2 (1 or 3 cm) and the CaF_2 windows gave good spectral observations in the carbonyl region and CH stretching region, the former being more useful for product analysis. Whenever possible product identifications were based on ir spectra of synthetic mixtures.

In addition to the *in situ* analysis, the final product distribution following warm-up of the mixture was examined in several ways. In one method, the CO_2 solution was rapidly vaporized through an eductor tube (Figure 1) into a 40-m long-path ir cell, or else into a 5-l. bulb. In the latter case the CO_2 was then separated by pumping the mixture through a U tube at $-78°$, followed by analysis of the trapped products in a conventional ir cell or by gc. The gc columns were Porapak Q (3 or 8 ft) operated at 140°. In some experiments the CO_2 was pumped away from the low-temperature cell, and the residual products were allowed to warm up in the cell and later collected for analysis.

Product yields were based on the initial ozone concentration, which was determined by uv spectrometry before addition of the alkyne. We used extinction coefficients for O_3 dissolved in other inert low-temperature solvents.[5] The yields of products following vaporization into the long-path ir cell were determined by calibration of the ir band strengths *vs.* pressure for authentic samples. The carbon monoxide yield in the liquid phase was determined by sampling the gaseous mixture above the liquid and calibrating the chromatographic peak height (8-ft molecular sieve, 40°) against standard mixtures of CO dissolved in the liquid CO_2.

The initial O_3 concentrations were usually about 5×10^{-3} M, and either equimolar or excess concentrations of alkyne were subsequently added.

(5) W. B. DeMore and O. Raper, *J. Phys. Chem.*, **68**, 412 (1964).

Results

The principal new feature upon ozonation of all the alkynes except acetylene was a strong absorption band at 1740 cm^{-1} in the liquid-phase spectrum. This band is almost certainly a carbonyl absorption. It can be distinguished in several ways from the carbonyl bands of possible products such as anhydrides, α-dicarbonyls, acids (monomeric or dimeric), or other known products. As will be shown later, this band is due to a precursor of the anhydride.

In addition to the 1740-cm^{-1} band, relatively weak carbonyl absorption bands appeared in every case, including acetylene, which we identify (see below) as the carbonyl bands of the corresponding acid anhydrides

Figure 2a shows the spectral changes occurring in the carbonyl region for the ozonation of dimethylacetylene. The anhydride bands were identified by comparison with the spectrum of an authentic sample. Unfortunately, the biacetyl band is not clearly resolved from that of the intermediate, and therefore its presence in the original product mixture is uncertain. Figure 2b shows the slow thermal rearrangement of the intermediate to give anhydride and biacetyl. When the mixture is allowed to warm to room temperature (first pumping off the CO_2) and is then redissolved in liquid CO_2, the spectrum shows strong anhydride and biacetyl bands (Figure 2c). Vaporization of the product mixture through the eductor tube into the long-path ir cell gives the spectrum shown in Figure 2d. In addition to acetic anhydride and biacetyl, ketene and acetic acid are present. The product yields, while approximate, account for a substantial portion of the ozone. It should be noted that the weak anhydride bands present in the original reaction mixture, before vaporization, are much too weak to account for the amount of anhydride present after vaporization. This proves that anhydride formation occurs during the vaporization process. Figure 3 shows a chromatographic analysis of the products following vaporization into a 5-l. bulb.

The behavior of methylacetylene was similar to that of dimethylacetylene. The initial product spectrum in liquid CO_2 (Figure 4a) shows relatively weak formic–acetic anhydride bands and a strong band due to the unstable intermediate. The anhydride bands are similar to those reported by Stevens and Van Es[6] for formic–acetic anhydride in $CHCl_3$ solution. Vaporization into the long-path ir cell gave strong bands due to the anhydride and methylglyoxal (Figure 4b). No ketene was formed, which is consistent with the fact that the gas-phase reaction[4] does not give that product.

The initial product spectrum for ethylacetylene (Figure 5) was similar to that of methylacetylene. The two features at 1775 and 1795 cm^{-1} are believed to be due to formic–propionic anhydride, based on their similarity to the formic–acetic anhydride bands.[7] On standing, these bands increased in intensity and the 1740-cm^{-1} band decreased. However, in contrast to the previous cases, vaporization of the mixture into the long-path ir cell did not produce strong anhydride absorption in the gas-phase spectrum. (As previously discussed, the small amount of anhydride corresponding to the bands in Figure 5 would not produce appreciable

(6) W. Stevens and A. Van Es, *Recl. Trav. Chim. Pays-Bas*, **83**, 863 (1964).

(7) R. Schijf and W. Stevens, *ibid.*, **85**, 627 (1966).

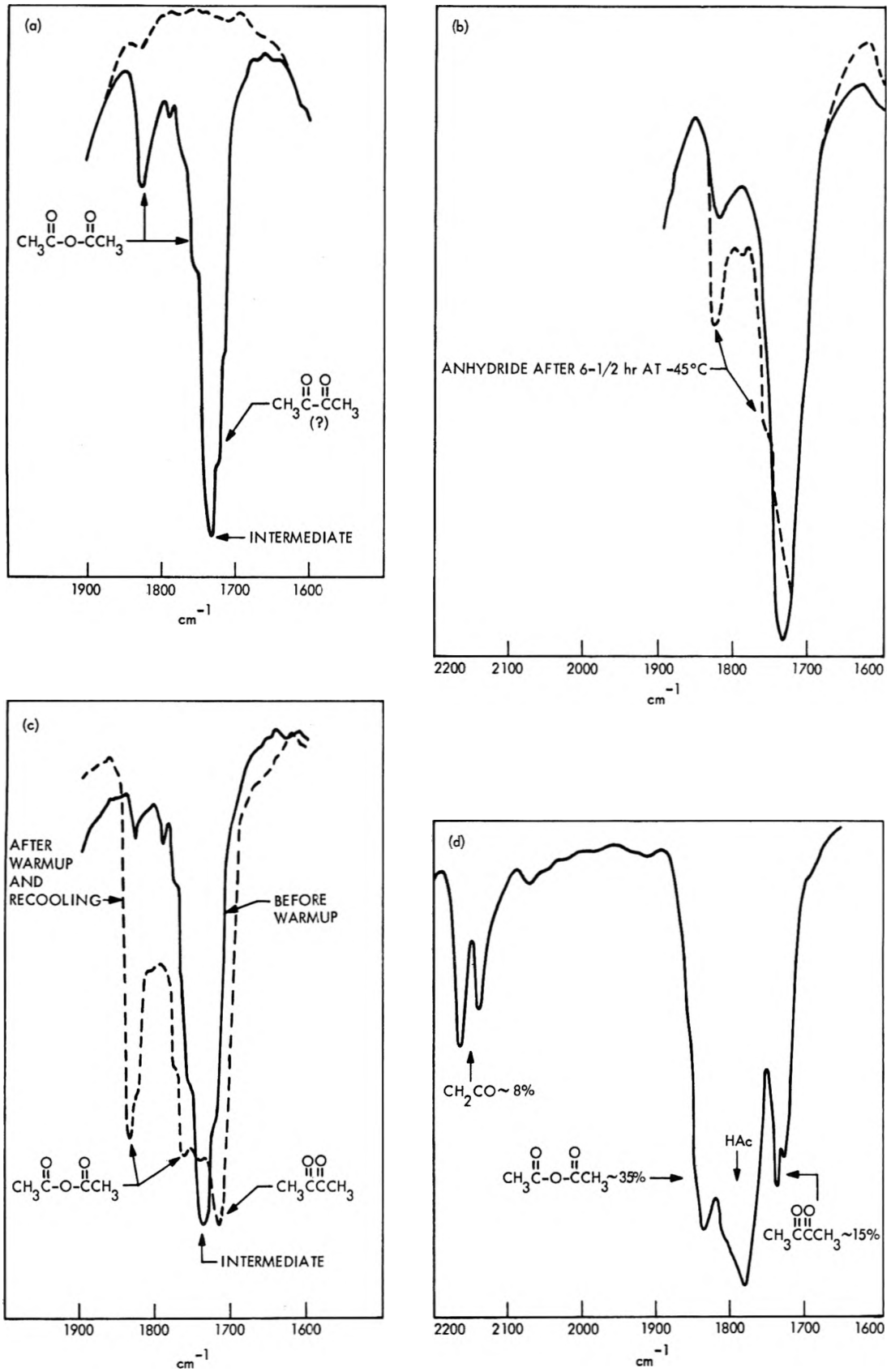


Figure 2.—Ozonation of $CH_3C{\equiv}CCH_3$ in liquid CO_2. (a) Dotted line is trace before reaction; solid line after reaction. (b) Dotted line shows spectral change after 6.5 hr at −45°. (c) Spectral changes after warm-up to room temperature followed by recooling. (d) Spectrum taken in long-path ir cell after flash vaporization of a mixture such as that of a.

absorption in the gas-phase spectrum.) No α-dicarbonyl was produced, although this product is formed when the ozonation of ethylacetylene is carried out in the gas phase. The only observable product appeared to be propionic acid.

Acetylene was the only alkyne studied which failed to give the 1740-cm^{-1} band. The strong carbonyl bands produced (Figure 6) are those of formic acid, probably in monomeric and dimeric forms. The weak band of 1810 cm^{-1} is believed to be due to formic anhydride,

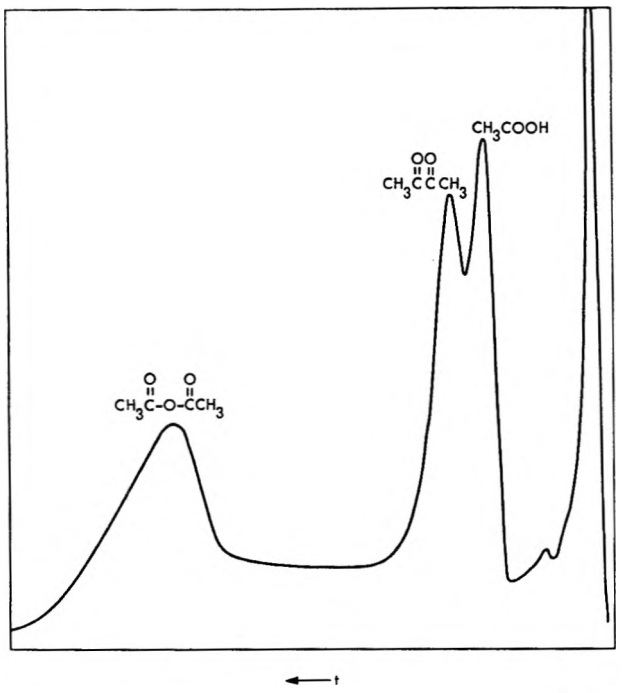


Figure 3.—Gas chromatographic analysis of $CH_3C{\equiv}CCH_3$ + O_3 reaction products after vaporization into a 5-l. bulb and separation of CO_2. Column was 3 ft Porapak Q at 140°.

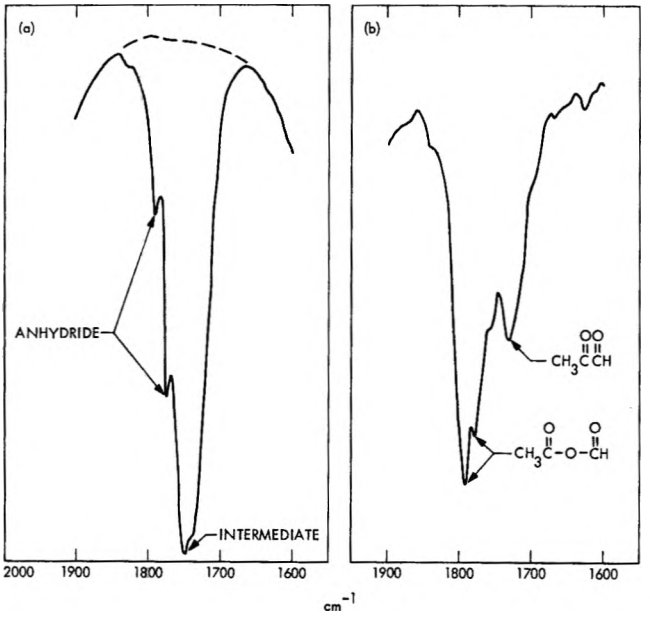


Figure 4.—Ozonation of $CH_3C{\equiv}CH$ in liquid CO_2. (a) Dotted line, before reaction; solid line, after reaction. (b) After vaporization into long-path ir cell.

although this identification is based only on the fact that the wavelength is approximately correct for a symmetric anhydride. By stoichiometry, CO should also be produced in yield equal to that of formic acid. Table I

Table I

Carbon Monoxide Yields for Ozonation of Alkynes in Liquid CO_2 at −45°

Registry no.	Alkyne	Yield, %
74-86-2	$HC{\equiv}CH$	91 ± 18
74-99-7	$CH_3C{\equiv}CH$	36 ± 7
107-00-6	$CH_3CH_2C{\equiv}CH$	12 ± 3
503-17-3	$CH_3C{\equiv}CCH_3$	3 ± 1

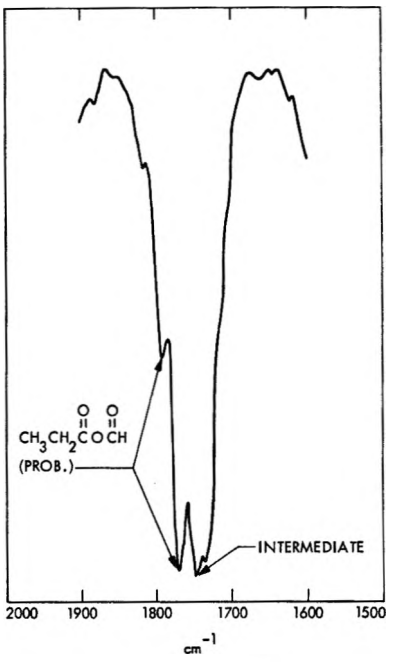
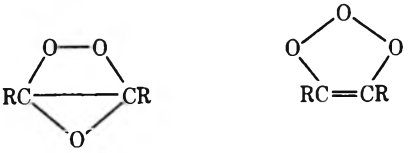


Figure 5.—Ozonation of $C_2H_5C{\equiv}CH$ in liquid CO_2.

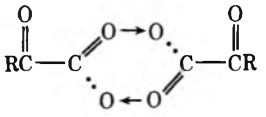
shows that such is the case, and that substantial amounts of CO are also formed in the ozonation of methyl- and ethylacetylene. Vaporization of the acetylene product mixture into the long-path ir cell gave only formic acid bands, with no more than a trace of glyoxal.

Discussion

The Anhydride Precursor.—At this time it is not possible to specify the structure of the unstable intermediate responsible for the 1740-cm^{-1} band. The evident presence of a carbonyl bond tends to rule out "ozonide" structures shown below.

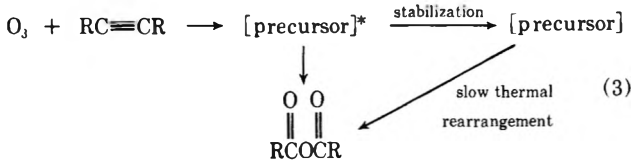


One possibility is that the presursor is the dimer (or higher polymeric form) of the acylcarbonyl oxide.



If so, the tendency of the intermediate to react in a manner characteristic of the monomer suggests that the polymerization is reversible.

Anhydride Formation.—Formation of small amounts of anhydride in the initial product mixture, before vaporization, indicates that not all of the precursor is stabilized before some rearrangement occurs (eq 3).



After thermalization at −45°, rearrangement to the anhydride is slow.

For acetylene, essentially none of the precursor could be stabilized, showing that either the precursor itself or the formic anhydride decomposes largely to HCOOH and CO before thermalization. Once equilibrated at −45°, the formic anhydride is evidently stable, assuming that our identification of the 1810-cm^{-1} band (Figure 6) is correct. Some decomposition also occurs in the cases of methyl- and ethylacetylene, as shown by the small amounts of CO present.

Absence of ketene in the liquid CO_2 in the dimethylacetylene experiments shows that the type of decomposition represented by eq 2 does not occur in the liquid. However, rearrangement of the precursor following vaporization releases sufficient energy to decompose part of the acetic anhydride (eq 4). When the ozonation

$$[\text{precursor}] \longrightarrow \left[\begin{matrix}\text{O}\ \text{O}\\ \|\ \|\\ \text{CH}_3\text{COCCH}_3\end{matrix}\right]^* \longrightarrow \text{CH}_2\text{CO} + \text{CH}_3\text{COOH} \qquad (4)$$

$$\left[\begin{matrix}\text{O}\ \text{O}\\ \|\ \|\\ \text{CH}_3\text{COCCH}_3\end{matrix}\right]^* \xrightarrow{+M} \begin{matrix}\text{O}\ \text{O}\\ \|\ \|\\ \text{CH}_3\text{COCCH}_3\end{matrix}$$

takes place in the gas phase at 1 atm, all the reaction exothermicity appears in the anhydride, and dissociation is complete. We have, in fact, carried out a few gas-phase experiments at high pressures (several hundred psi of CO_2) in which acetic anhydride was isolated as a product of the ozonation of dimethylacetylene. This shows that anhydride formation is not unique to the liquid-phase experiments.

The liquid-vaporization technique may serve as a useful synthetic method for mixed anhydrides such as formic–acetic anhydride.

Formation of α-Dicarbonyls.—More than one path may contribute to production of α-dicarbonyls, particularly when both liquid- and gas-phase reactions are considered. A probable mechanism in the gas phase is eq 5. The exact importance of reaction 5 cannot be

$$O_3 + \text{RC}{\equiv}\text{CR} \longrightarrow \left[\begin{matrix}\text{O}\ \ \text{O}{\rightarrow}\text{O}\\ \|\ \ \ \|\\ \text{RC}{-}\text{CR}\end{matrix}\right]^* \longrightarrow \begin{matrix}\text{O}\ \text{O}\\ \|\ \|\\ \text{RC}{-}\text{CR}\end{matrix} + \text{O}(^3\text{P}) \qquad (5)$$

assessed because of the possible contribution of surface reactions to α-dicarbonyl formation.[4] This reaction is considerably exothermic (87 kcal/mol for the biacetyl case) and would be expected to dominate the gas-phase mechanism were it not for the fact that it is spin forbidden. This either lowers the preexponential factor or else requires that the α-dicarbonyl be formed in an excited triplet state.

Reaction 5 is interesting in that it regenerates atomic oxygen. Occurrence of this reaction in air-pollution chemistry would have the novel effect of destruction of hydrocarbon with no attendant loss of ozone, since the ozone would be regenerated.

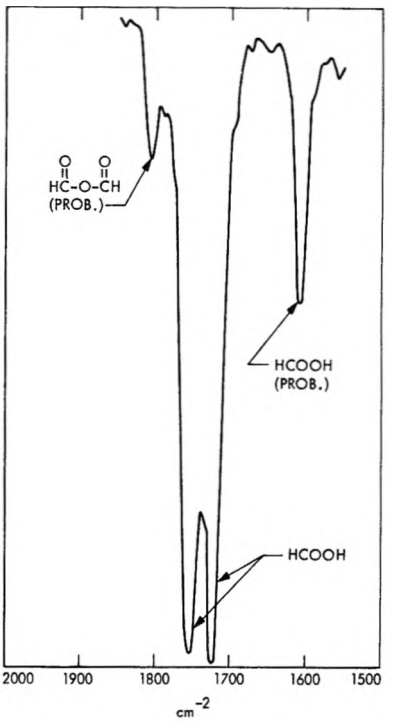


Figure 6.—Ozonation of HC≡CH in liquid CO_2.

$$O(^3P) + O_2 + M \longrightarrow O_3 + M \qquad (6)$$

For the thermalized acylcarbonyl oxide, reaction 5 is undoubtedly much slower, possibly endothermic. This serves to explain why the yields of α-dicarbonyls were lower (or zero) in the liquid-vaporization experiments than in the gas-phase experiments. Some product may be formed by a disproportionation reaction of the thermalized precursor.

$$2\text{RC}(\text{O})\text{—C}(\text{O}{\rightarrow}\text{O})\text{R} \longrightarrow 2\text{RC}(\text{O})\text{—C}(\text{O})\text{R} + O_2 \qquad (7)$$

Briner and Wunenburger[8] obtained an 81% yield of glyoxal by ozonation of acetylene in CH_2Cl_2 at Dry Ice temperature, in contrast to our yield of zero for that product. This emphasizes the strong dependence of the reaction course on experimental conditions. A possible explanation of the different results is that under their experimental conditions some stabilization of the intermediate acylcarbonyl oxide was accomplished, with subsequent glyoxal formation by reaction 7.

Acknowledgment.—This paper presents the results of one phase of research carried out at the Jet Propulsion Laboratory, California Institute of Technology, under Contract No. NAS7-100 sponsored by the National Aeronautics and Space Administration.

(8) E. Briner and R. Wunenburger, *Helv. Chim. Acta*, **12**, 786 (1929).

Nucleosides. XVI. The Synthesis of 2′,3′-Dideoxy-3′,4′-didehydro Nucleosides[1]

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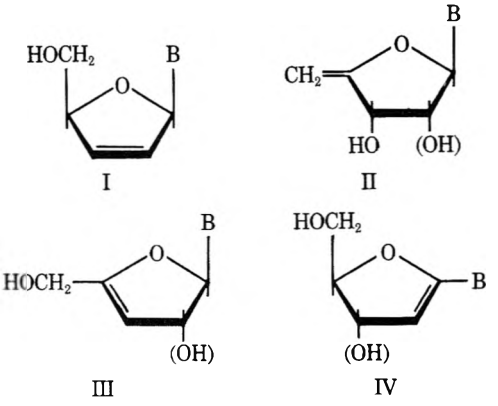
Received September 28, 1972

A general approach to 3′,4′-unsaturated nucleosides (**15a–d**) is described which proceeds from a 2′-deoxynucleoside uronic acid ester (**2a–d, 3, 8**) *via* a facile elimination reaction effected on the corresponding 2′-deoxy-3′-*O*-methylsulfonylribonucleoside uronic acid ester (**4a–e**), by the action of either triethylamine or sodium benzoate in DMF. Selective reduction of the carbalkoxy function of the intermediate 3′,4′-unsaturated nucleoside uronic esters (**5a–d, 11**) was accomplished with sodium bis(methoxyethoxy)aluminum hydride. Catalytic (Pd/C) hydrogenation of **5a** in ethanol affords a single isomer, ethyl 3′-deoxythymidine uronate (**17**), which on hydride reduction yields a product identical with 3′-deoxythymidine. Degradation of **4a** to thymine and ethyl furoate was observed on treatment with potassium *tert*-butoxide. The same course of reaction was observed in the reaction of either **2a** or **5a** with dimethylformamide dineopentyl acetal. Attempts to induce the elimination reaction in the case of **4a** with pyridine led instead to the substitution product, ethyl 3′-deoxy-3′-(*N*-pyridinium)thymidine uronate methyl sulfonate (**6**). The elements of pyridinium sulfonate are readily eliminated from **6** on treatment with sodium benzoate in DMF. Unlike pyridine, 2,6-lutidine converts **4a** to **5a**. Reaction of ethyl 2′,3′-di-*O*-methylsulfonyluridine uronate (**4e**) with $(C_2H_5)_3N$ in DMF gave ethyl 5-(uracil-1-yl)furoate (**13**) in high yield. The same product (**13**) was obtained on treatment of ethyl uridine uronate (**2d**) with diphenyl carbonate. The relationship of these elimination reactions to the conversion of uridine uronic acid (**1d**) to 5-(uracil-1-yl)furoic acid (**13**) in refluxing acetic anhydride is discussed. Moreover, the application of the latter conditions to thymidine uronic acid (**1a**) leads to 3′-deoxy-3′,4′-didehydrothymidine uronic acid (**14**), which was characterized as the ethyl ester **5a**. The nmr spectra of **5a–d, 11**, and **15a–d** are discussed.

As a result of studies conducted in this laboratory and others, methods have been developed to introduce both endo- and exocyclic unsaturation into the sugar moiety of a wide spectrum of nucleosides.[2] In point of fact, of the four possible (mono-) olefinic nucleosides (I–IV), only recently has a successful approach to 1-(2-deoxy-D-*threo*-pent-1-enofuranosyl)pyrimidines (IV) been described.[2s] However, only I and II have to date received detailed physicochemical[3] and biochemical[2k,2r,4] study.

In the last several years, synthetic avenues leading to 2′,3′-unsaturated nucleosides (I) have been the subject of several detailed studies.[2f–21] In contrast, the literature concerned with routes to corresponding 3′,4′-unsaturated derivatives (III) is limited to descriptions



B = nucleobase

of base-catalyzed decyclizations of the acetal (ketal) moiety of 2′,3′-*O*-alkylideneribonucleoside 5′-carboxaldehydes[2m,n] and a 2′,3′-*O*-alkylideneribonucleoside uronic acid ester[2o] or of the cyclic ether linkage in 5′-deoxy-5′-fluoro-2,3′-anhydrothymidine.[2q] In addition, analogous pyrimidine and purine (1- and 9-, respectively) 2,3-dideoxy-3,4-didehydro-β-D-erythrofuranosyl (2,3-dihydrofuran) derivatives have been obtained by an interesting decarboxylative elimination reaction on 2′-deoxynucleoside uronic acids.[2p] These reports comprise the principal literature on III.

The present communication describes a general approach to III *via* the facile elimination of methylsulfonic acid from 2′-deoxy-3′-*O*-methylsulfonylribonucleoside uronic acid esters (**4**). At the outset, it was anticipated that activation of $H_{4'}$ by the carbalkoxy group in **4** would facilitate proton abstraction at $C_{4'}$ over the favored $H_{2'}$ protons and thereby alter the di-

(1) (a) Presented in part at the Joint Conference of the Chemical Institute of Canada and American Chemical Society, Toronto, Canada, May 1970, Abstract No. CARBO-5. (b) Preliminary communication: J. Žemlička, R. Gasser, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **92**, 4744 (1970).

(2) (a) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, **88**, 5684 (1966); (b) J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, *ibid.*, **88**, 1549 (1966); **90**, 4993 (1968); (c) M. J. Robins, J. R. McCarthy, Jr., and R. K. Robins, *J. Heterocycl. Chem.*, **4**, 313 (1967); (d) I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 4323 (1971); (e) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972); (f) J. P. Horwitz, J. Chua, I. L. Klundt, M. A. DaRooge, and M. Noel, *J. Amer. Chem. Soc.*, **86**, 1896 (1964); (g) J. P. Horwitz, J. Chua, and M. Noel, *Tetrahedron Lett.*, 1343 (1966); (h) J. P. Horwitz, J. Chua, M. A. DaRooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, **31**, 205 (1966); (i) G. Etzold, R. Hintsche, G. Kowollik, and P. Langen, *Tetrahedron Lett.*, 2463 (1971); (j) W. V. Ruyle, T. Y. Shen, and A. A. Patchett, *J. Org. Chem.*, **30**, 4353 (1965); (k) T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **12**, 543 (1969); **10**, 1066 (1967); (l) G. Kowollik, K. Gaertner, G. Etzold, and P. Langen, *Carbohyd. Res.*, **12**, 301 (1970); (m) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969; U. S. Patent 3,457,255 (1969); *Chem. Abstr.*, **72**, 3727 (1970); (n) P. Howgate, A. S. Jones, and J. R. Tittensor, *Carbohyd. Res.*, **12**, 403 (1970); (o) K. N. Nagpal and J. P. Horwitz, *J. Org. Chem.*, **36**, 3743 (1971); (p) J. Žemlička, R. Gasser, J. Freisler, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **94**, 3213 (1972); (q) G. Kowollik, K. Gaertner, and P. Langen, *Tetrahedron Lett.*, 1737 (1971); (r) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 115; (s) V. I. Borodulina-Shvets, I. P. Rudakova, and A. M. Yurkevich, *Zh. Obshch. Khim.*, **41**, 2801 (1971).

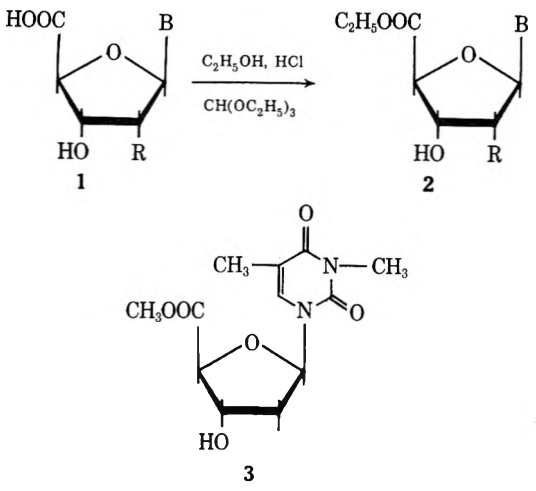
(3) (a) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967); (b) D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.*, **91**, 824 (1969); (c) D. W. Miles, W. H. Innskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *ibid.*, **92**, 3872 (1970); (d) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970); (e) D. W. Miles, M. J. Robins, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **62**, 22 (1969).

(4) (a) A. M. Doering, M. Jansen, and S. S. Cohen, *J. Bacteriol.*, **92**, 565 (1966); (b) M. R. Atkinson, M. P. Deutscher, A. Kornberg, A. F. Russell, and J. G. Moffatt, *Biochemistry*, **8**, 4897 (1969).

rection of β elimination to introduce 3′,4′ rather than 2′,3′ unsaturation.[5]

The requisite 1-(ethyl 2-deoxy-β-D-*erythro*-pentofuranosyluronate)pyrimidines (ethyl 2′-deoxynucleoside uronates[6]) were obtained by a new procedure in which esterification of the acids I[7a–c] was effected in high yield with a mixture of ethanol, triethyl orthoformate, and anhydrous hydrogen chloride (Scheme I).

SCHEME I

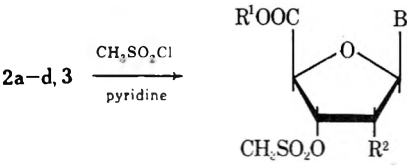


1a, 2a, B = thymine; R = H
1b, 2b, B = uracil; R = H
1c, 2c, B = 5-fluorouracil; R = H
1d, 2d, B = uracil; R = OH

It is worthy of note that the method is apparently of general application and would be valuable where the use of more conventional procedures of esterification would be precluded for a particular consideration. For example, the reaction of thymidine uronic acid (**1a**) with diazomethane leads to N_3 alkylation as well as the desired esterification[2p] to give **3**. On the other hand, diazomethane is the reagent of choice for the preparation of methyl 2′-deoxyadenosine uronate (**9**) (*cf.* Scheme VI) from the acid **8**[2p] because of the acute sensitivity of purine 2′-deoxynucleosides toward acid.

The uronic acid esters (**2a–d** and **3**), on treatment with methylsulfonyl chloride in pyridine at −20°, gave the corresponding 3′-*O*-methylsulfonates (**4a–d**) in excellent yields (Scheme II). Elimination of the methylsulfonyloxy function from **4a–d** was readily effected with triethylamine in dimethylformamide (DMF) at 100° to give the 3′,4′-unsaturated esters[8] **5a–d** in

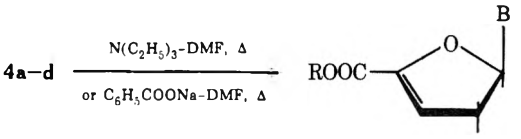
SCHEME II



4a, B = thymine; $R^1 = C_2H_5$; R^2 = H
b, B = uracil; $R^1 = C_2H_5$; R^2 = H
c, B = 5-fluorouracil; $R^1 = C_2H_5$; R^2 = H
d, B = N^3-methylthymine; $R^1 = CH_3$; R^2 = H
e, B = uracil; $R^1 = C_2H_5$; $R^2 = CH_3SO_2O$

good yields and high purity (Scheme III). The same transformation may be accomplished by substitution

SCHEME III



5a, B = thymine; R = C_2H_5
b, B = uracil; R = C_2H_5
c, B = 5-fluorouracil; R = C_2H_5
d, B = N^3-methylthymine; R = CH_3

of sodium benzoate for triethylamine, which gave, for example, **5a** in 88% yield on heating **4a** in DMF at 100°. By contrast, the unsaturated ester **5a** could not be detected after refluxing **4a** in pyridine for 10 hr. Instead, a crystalline product was obtained (46% yield) which, on the basis of spectral data and elemental analysis, was assigned the structure[9] ethyl 3′-deoxy-3′-(*N*-pyridinium)thymidine uronate methyl sulfonate (**6**). The assignment of an erythro configuration to the pyridinium moiety in **6** is not rigorous but is based on the detection of ethyl 2,3′-anhydrothymidine uronate (**7**, 27% yield) along with **6** when the same reaction is carried out at 100° for 16 hr. The salt **6** then presumably arises *via* attack of pyridine at $C_{3'}$ of **7**, leading to the introduction of the nucleophile in the ("down") erythro configuration. Apart from the configurational assignment at $C_{3'}$, it was found that elimination of pyridinium methylsulfonate from **6** readily occurred on heating with sodium benzoate in DMF to give **5a** in 70% yield.

The reaction of **4a** with 2,6-lutidine, unlike pyridine, gave the 3′,4′-unsaturated ester **5a**, though in rather low (20%) yield, instead of a substitution product. Presumably the steric requirements of the methyl groups in 2,6-lutidine simply preclude the possibility of nucleophilic displacement at $C_{3'}$ of the anhydro nucleoside **7**, but these bulk effects apparently do not deter proton abstraction at $C_{4'}$ and consequent elimination (Scheme IV). Degradation of **4a** to thymine (76% yield) occurred at room temperature on treatment with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) for 0.5 hr. A plausible reaction path leading to thy-

(5) A similar approach has recently been used for the preparation of α,β-unsaturated uronates in the carbohydrate series: (a) J. Kiss and K. Noack, *Carbohyd. Res.*, **16**, 245 (1971); (b) J. Kiss and F. Burckhardt, *Helv. Chim. Acta*, **53**, 100 (1970); (c) J. Kiss, *Carbohyd. Res.*, **10**, 328 (1969); (d) J. Kiss, *Tetrahedron Lett.*, 1983 (1970); (e) J. Kiss and F. Burckhardt, Abstracts, Joint Conference of the Chemical Institute of Canada and American Chemical Society, Toronto, Canada, May 1970, CARBO-40.

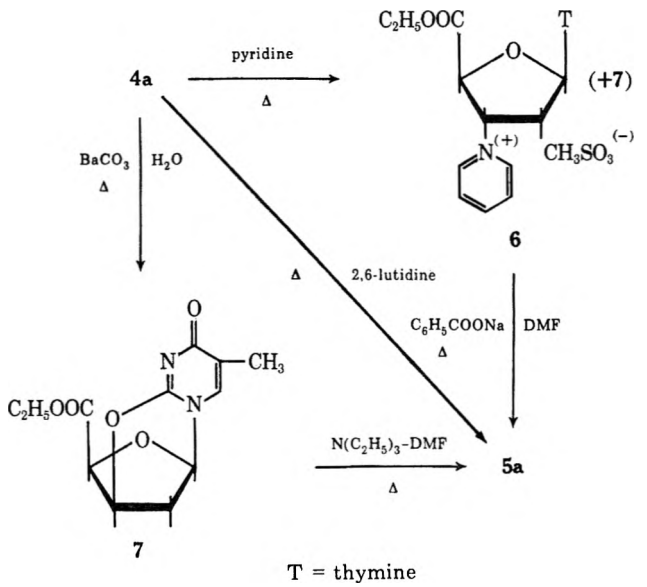
(6) According to a nomen lature devised in ref 7a an alternate name for this group of compounds would be ethyl 2′-deoxynucleoside 5′-carboxylates.

(7) (a) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro, and A. R. Todd, *J. Chem. Soc.*, 1149 (1963); (b) K. Imai and M. Honjo, *Chem. Pharm. Bull.*, **13**, 7 (1965); (c) K. C. Tsou, N. J. Santora, and E. E. Miller, *J. Med. Chem.*, **12**, 173 (1969).

(8) Application of systematic nomenclature to, *e.g.*, **5b** and **15b** leads to the names (−)-(*R*)-2,3-dihydro-2-(uracil-1-yl)-5-carbethoxyfuran and (−)-(*R*)-2,3-dihydro-2-(uracil-1-yl)-5-hydroxymethylfuran, respectively. In this paper we have adopted a nomenclature based on parent nucleosides. Thus, **5b** would be ethyl 2′,3′-dideoxy-3′,4′-didehydrouridine uronate and **15b** 2′,3′-dideoxy-3′,4′-didehydrouridine. According to the nomenclature suggested earlier[2h] for 2′,3′-unsaturated nucleosides, the name of **15b** could also be 2′,3′-dideoxy-3′-uridinene and that of **5b** ethyl 2′,3′-dideoxy-3′-uridinene uronate.

(9) A compound similar to **6**—*N*-[*trans*-2-hydroxy-*trans*-4-(1-thyminyl)-cyclopentyl]pyridinium hydroxide (inner salt and hydrochloride)—was prepared before: K. C. Murdock and R. B. Angier, *J. Amer. Chem. Soc.*, **84**, 3748 (1962).

SCHEME IV



T = thymine

mine would involve consecutive elimination reactions (Scheme V), the first of which would lead to **5a**. Abstraction of a proton from $C_{2'}$ in **5a** is obviously facilitated by transmission of the effect of the carbalkoxy group through the conjugated system and thereby a second elimination can proceed to give thymine and ethyl furoate. No attempt was made to isolate and characterize the latter. The same course of reaction was observed on heating of **5a** with sodium azide in DMF and as well from the action of dimethylformamide dineopentyl acetal on **2a** or **5a** in DMF.

The intervention of 2,3′-anhydro-2′-deoxy nucleosides in the formation of pyrimidine 2′,3′-unsaturated nucleosides from 1-(2-deoxy-3-*O*-methylsulfonyl-β-D-*erythro*-pentosyl)pyrimidines is currently accepted on the basis of earlier studies.[2h] The intermediacy of a corresponding anhydro derivative **7** in the conversion of **4a** to **5a** was presumed but could not be detected. A test of the validity of the hypothesis required the preparation of ethyl 2,3′-anhydrothymidine uronate (**7**) which was obtained (67% yield) by refluxing **4a** in aqueous barium carbonate.[10] The latter, incidentally, is the reagent of choice for the preparation of **7**. After treatment of **7** with Et_3N–DMF for 2 hr at 100°, tlc showed the reaction mixture to consist of a *ca.* 1:1 mixture of unchanged **7** and olefinic ester **5a**. The same transformation in Et_3N–DMSO-d_6 at 100° showed $t_{1/2}$ ~110 min as deduced from the rate of disappearance of the C_6 proton in the nmr spectrum of **4a**. By contrast, the conversion of **4a** to **5a** in the same base–solvent system, but at 50°, showed $t_{1/2}$ ~29 min. The findings therefore preclude the interposition of an anhydro nucleoside in the formation of **5a** from **4a**.

The possibility must be recognized that elimination in **4a–d** with triethylamine occurs *via* a two-step process of the Elcb type, involving proton abstraction at $C_{4'}$ as the initial step followed by release of the methylsulfonyloxy group in the second step. This mechanism, which is characterized by unimolecular elimination of methylsulfonate anion from the conjugate base of **4**, is considered to be dominant in reactions leading to an olefinic double bond that is conjugated with a carbonyl group. The same pathway may well apply to the formation of **5a** from the action of triethylamine on ethyl 2,3′-anhydrothymidine uronate (**7**). Indeed, the rate data probably reflect the poorer leaving group characteristics of the thyminyloxy group *vis a vis* the methylsulfonyloxy function.[11]

The scheme of reactions proceeding to **5a–d** was successfully extended to a synthesis of methyl 2′,3′-dideoxy-3′,4′-didehydroadenosine uronate (**11**). Thus, methyl *N*-dimethylaminomethylene-2′-deoxyadenosine uronate (**10**), obtained by the interaction of **9** and dimethylformamide dimethyl acetal,[12] was first treated with methylsulfonyl chloride in pyridine at −20°. The crude 3′-*O*-methylsulfonate derivative was converted to **11** by sequential refluxing in triethylamine–dioxane and methanol to effect elimination and removal of the dimethylaminomethylene[12] (protecting) group, respectively (Scheme VI).

Attempts to apply this same approach to the synthesis of a 3′-deoxy-3′,4′-didehydroribonucleoside uronic acid ester have to date been unsuccessful. Thus, the reaction of ethyl 2′,3′-di-*O*-methylsulfonyluridine uronate **4e** with either triethylamine or sodium benzoate in DMF or simply refluxing in pyridine gave instead ethyl 5-(uracil-1-yl)furoate (**12**) in high yields. The same product was obtained, albeit in lower yield (38%), on treatment of **2d** with diphenyl carbonate and sodium bicarbonate in DMF (Scheme VII). The structure of **12** follows from its nmr spectrum, which is characterized by two AB systems, one assignable to the uracil (H_5 and H_6) moiety and the other to the furan ($H_{3'}$ and $H_{4'}$) ring.

The course of the reaction is readily explained in terms of two base-catalyzed elimination reactions, the first of which affords the anticipated product ethyl 2′-*O*-methylsulfonyl-3′-deoxy-3′,4′-didehydrouridine uronate. It is likely that the latter is then converted to the corresponding 2,2′-anhydro nucleoside, which undergoes a second elimination reaction to give **12**. The presumed double-elimination sequence leading to **12** is reminiscent of the conversion of uridine uronic acid (**1d**) to furoic acid derivative **13** in refluxing acetic anhydride.[7a] A corresponding sequence of reactions can be envisioned for the latter transformation, which proceeds presumably from an intermediate 2′,3′-di-*O*-acetyluridine uronic acid. Support for the requisite initial elimination is derived from the conversion of thymidine uronic acid to 3′-deoxy-3′,4′-didehydrothymidine uronic acid (**14**) in refluxing acetic anhydride. The identity of **14** was established by esterification with triethyl orthoformate in ethanolic H_2SO_4, which produced a product identical with **5a** in all respects (Scheme VIII).

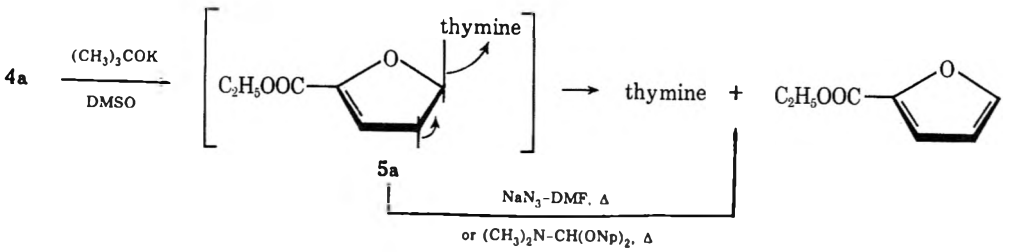
Selective reduction of **5** to the corresponding pyrimidine 2′,3′-dideoxy-3′,4′-didehydroribonucleosides (**15a–c**) was accomplished in yields ranging from 30 to 50% with sodium bis(methoxyethoxy)aluminum hydride in a mixture of benzene and tetrahydrofuran or dioxane (Scheme IX). The same reaction conditions

(10) G. Etzold, R. Hintsche, and P. Langen, German Patent 65,794 (1969); *Chem. Abstr.*, **71**, 91828 (1969).

(11) The fact that no difference between both types of leaving groups was observed in the elimination of 5′-*O*-trityl-3′-*O*-methylsulfonylthymidine and 5′-*O*-trityl-2,3′-anhydrothymidine[2h] may be explained by the "swamping effect" of a strong base (potassium *tert*-butoxide) used.

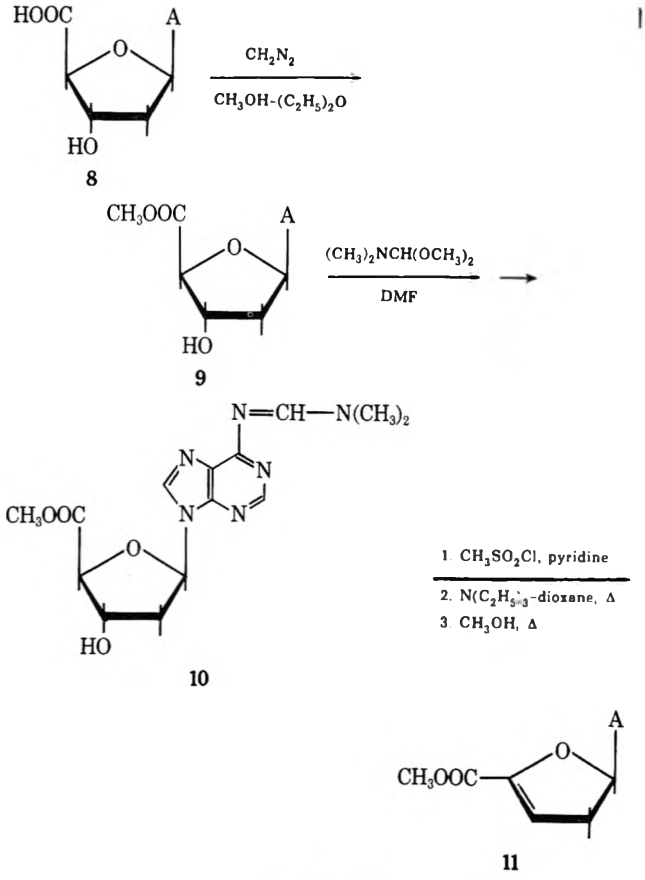
(12) (a) J. Žemlička and A. Holý, *Collect. Czech. Chem. Commun.*, **32**, 3159 (1967); (b) J. Žemlička, *ibid.*, **28**, 1060 (1963).

Scheme V

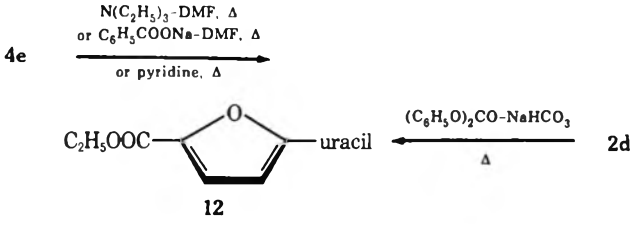


Np = $(CH_3)_3CCH_2$

Scheme VI



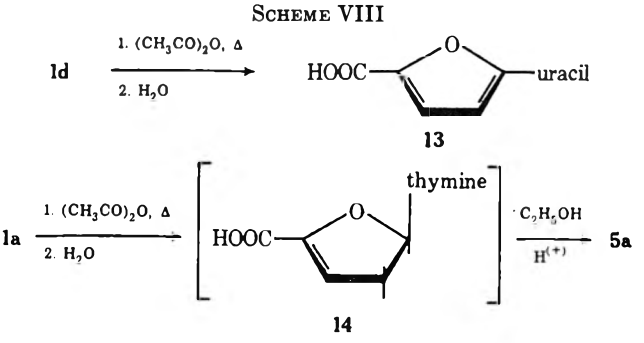
Scheme VII



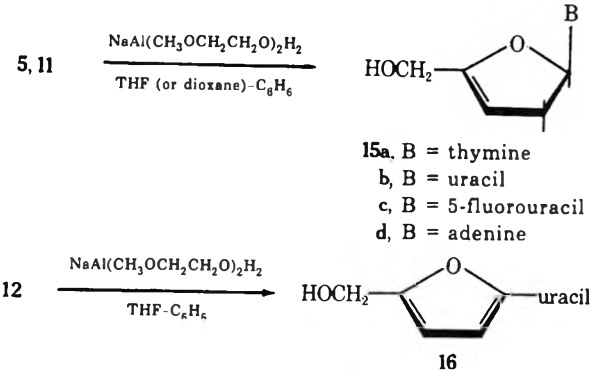
were successfully extended to the reduction of **11** and **12** to 5-(uracil-1-yl)furfuryl alcohol (**16**) and 2′,3′-dideoxy-3′,4′-didehydroadenosine (**15d**), respectively. Excess reagent in all of the reductions was destroyed with ethanol and the removal of sodium ion was accomplished with Dowex 50 (NH_4^+). The form of the resin proved to be critical to the success of the isolation procedure. Thus, the use of Dowex 50 in either the H^+ or $C_5H_5NH^+$ form led to extensive product decomposition.

Recent studies have shown that catalytic (Pd/C) hydrogenation of the olefinic double bond in pyrimidine

Scheme VIII



Scheme IX



and purine 3′-deoxy-3′,4′-didehydroribonucleosides leads to an epimeric mixture (β-D- and α-L-) of 3′-deoxy ribonucleosides.[2m,o,13] In contrast, hydrogenation (Pd/C) of **5a** in ethanol surprisingly affords a single product which has tentatively been assigned the structure ethyl 3′-deoxythymidine uronate (**17**). The ORD curve of **17** is similar to that of **2** and **4**. The chemical shift of H_6 corresponds to a nucleoside that shows preference for an anti conformation.[14] The reduction of **17** with sodium bis(methoxyethoxy)-aluminum hydride yields a product identical with 3′-deoxythymidine[15] (**18**) (Scheme X). However, this conversion cannot be offered as rigorous structure proof of **17**, since the possibility of concurrent epimerization at $C_{4'}$ under the conditions of reduction cannot be excluded. There remains, in addition, the question of the high stereoselectivity observed in the catalytic reduction of **17**, which may in some manner be related to the absence of the 2′-OH group coupled, possibly, with the influence of the aglycon.

(13) On the other hand, hydrogenation of a 4′,5′-unsaturated uridine derivative was highly stereoselective if not stereospecific.[2e]

(14) J. Žemlička and J. P. Horwitz, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., April 1971, No. CARB-35. The whole problem will be discussed separately elsewhere.

(15) (a) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955); (b) K. E. Pfitzner and J. G. Moffatt, *J. Org. Chem.*, **29**, 1508 (1964).

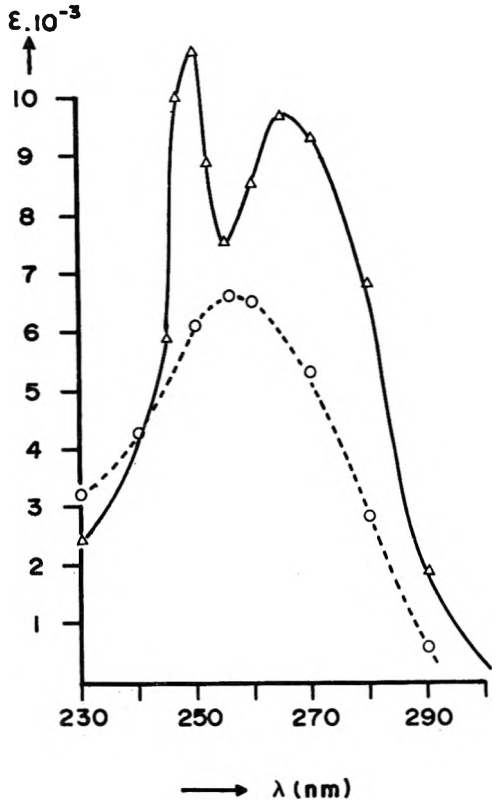


Figure 1.—Comparison of the uv spectra of thymidine, ethyl 1,2-*O*-isopropylidene-3′-deoxy-α-D-glyceropent-3-enofuranuronate[5a] and ethyl 3′-deoxy-3′,4′-didehydrothymidine uronate (**5a**): ——, superposed spectra of thymidine and 1,2-*O*-isopropylidene-3′-deoxy-α-D-glyceropent-3-enofuranuronate (the latter was taken from the literature[5a]); – – – –, spectrum of **5a**.

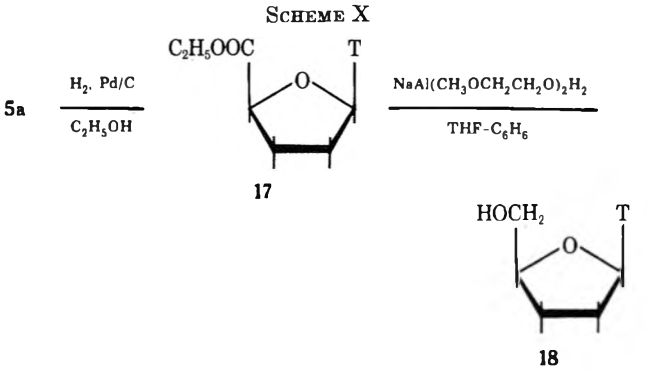
Spectral studies of **5a–d**, **11**, and **15a–d** revealed several interesting properties of this new class of nucleosides in addition to providing the requisite evidence for the location of the olefinic double bond. In accord with the assignments, infrared spectra showed the carbonyl bond of the conjugated ester at lower wavenumbers[16] than that observed for the precursory saturated derivatives. Unexpectedly, the carbonyl (ester) bonds of ethyl 2′,3′-dideoxy-3′,4′-didehydroadenosine uronate (**11**) and isopropyl 3′-deoxy-3′,4′-didehydroadenosine uronate[20] both appear at *ca.* 10 cm^{-1} higher[17] than the band assigned to the carbonyl ester of **5a**.

The introduction of 3′,4′ unsaturation into **5a–d** is accompanied by a hypsochromic shift of 5–12 nm in the ultraviolet absorption λ_{max} which reverts to the value(s) characteristic of the pyrimidine nucleosides, including the 2′,3′-unsaturated derivatives, on selective reduction of the carbethoxy group to **15c**. It was recognized that the shift in λ_{max} observed with **5a–d** might be an artifact of superposition of the chromophoric systems comprising the aglycon and unsaturated sugars. However, this possibility would appear remote in view of the fact that a composite spectrum

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 181.

(17) This phenomenon may be tentatively explained by a Michael addition type of interaction (*vide supra*) between N_3 of adenine residue in a syn-like conformation and $C_{3'}$, which would result in a decreased double-bond character of the olefinic linkage between $C_{3'}$ and $C_{4'}$ and hence an increase in wavenumber of the carbonyl group. A similar interaction between N_3 and carbonyl ester group of a purine ribonucleoside uronate has been invoked to account for the increased wave numbers of the carbonyl groups relative to 2′,3′-*O*-isopropylidene derivatives: H. J. Fritz, R. Machat, and R. R. Schmidt, *Chem. Ber.*, **105**, 642 (1972).

SCHEME X



T = thymine

(Figure 1) derived from ethyl 1,2-*O*-isopropylidene-3-deoxy-α-D-*glycero*-pent-3-enofuranuronate[5a] and thymidine shows two (independent) maxima at 265 and 250 nm. Accordingly, the observed shift in **5a–d** is real and represents an interaction of the two chromophoric systems.

Models indicate the possibility of an effective overlap of π orbitals comprising the 2-carbonyl of the aglycon and the extended conjugation of the sugar where **5a** is in a syn conformation. As a consequence of orbital overlap, an anhydro-nucleoside-like structure, tantamount to the transition state of an intramolecular Michael addition, would be approximated in an excited state and thereby account for the observed hypsochromic shifts in **5a–d**.

No comparable shift was noted with **11**, which is somewhat surprising since, in a syn conformation or an approximation thereof, an interaction between N_3 of adenine and $C_{3'}$ of the unsaturated sugar would be similarly anticipated.[17] However, the uv spectrum of **11** is different from the superimposed spectra of 2′-deoxyadenosine and ethyl 1,2-*O*-isopropylidene-3-deoxy-α-D-*glycero*-pent-3-enofuranuronate.[5a]

The nmr spectra of **5a–d**, **11**, and **15a–d** show, in accord with the infrared data, a single olefinic proton ($H_{3'}$) in the sugar moiety which appears as a triplet and, as expected, is shifted markedly upfield following reduction of the carbethoxy group to a primary alcohol. The anomeric proton in **5a–d** and **15a–c** appears as a multiplet of four having the same spacings observed for $H_{1'}$ in the 2′,3′-dideoxy-3′,4′-didehydroerythrofuranosyl nucleosides[2p] (Table IX).

In contrast to **5a–d** the anomeric proton in the adenine derivative **11**, for reasons which are not evident, appears as a triplet, though the multiplet of four reappears on reduction to **15d**. These differences point to some change in the conformation of the sugar moiety of **11** relative to **5a–d** and **15d**, but the present evidence precludes any firm conclusion. Double-resonance studies with **5b** show that both $H_{1'}$ and $H_{3'}$ are coupled with $H_{2'}$ (and/or $H_{2''}$).

Experimental Section

General Procedures.—See reference 2p. Thin layer chromatography (tlc) was performed as described previously[2p] in solvents S_1 (chloroform–methanol, 9:1) and S_2 (chloroform–methanol, 4:1) or on 2 mm thick 20 × 20 cm fixed layers of Stahl's silica gel F-254 (Merck, Darmstadt, Germany). Tetrahydrofuran (THF) and dioxane were distilled from $LiAlH_4$ and stored over sodium wire. Starting uronic acids **1a–d** and **8** were of the same quality as described previously.[2p] Yields of products,

Table I

Ethyl Nucleoside Uronates

Compd	Yield,[a] %	Mp,[b] °C	Calcd/Found C, %	Calcd/Found H, %	Calcd/Found N, %	λ_{max}, nm[c] ($\epsilon \times 10^{-3}$)	λ_{min}, nm ($\epsilon \times 10^{-3}$)	Optical rotations,[d] deg $[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	Temp, °C
2a	86	244–245	50.70	5.67	9.86	264	237	11.2	28.6	62.8	20
		(239–241)	50.78	5.64	9.65	(7.9)	(3.5)				
2b	71	242–244	48.89	5.22	10.37	261	230	25.2	64.6	134.8	24
		(238–240)	48.97	5.16	10.38	(7.9)	(1.6)				
2c	91							47.6			22
		(259–260)[e]									
2d	86	252–254	46.15	4.93	9.79	262	230	7.6	27.2	79.8	21
		(249–250)[f]	46.23	4.94	9.76	(10.3)	(1.8)				

[a] Crude product. [b] Melting point of the crude product is given in parentheses. [c] 95% ethanol. [d] c 0.5 (DMF). [e] Literature (different procedure[7c]) gives mp 258–262° (yield 32.6%). [f] Literature (different procedure[7a]) gives mp 237–239°.

Table II

Nmr Constants (DMSO-d_6) and Carbonyl Ester Frequencies of Ethyl Nucleoside Uronates

Compd	Chemical shifts, δ (number of protons, multiplicity) H_6	$H_{1'}$	H_5	$H_{4'} + H_{2'}$	CH_2 of C_2H_5O	$H_{2'}$	CH_3 of C_2H_5O	ν_{CO}, cm^{-1}
2a	7.92	6.36[a]		~4.4[b]	4.21	2.12[c]	1.27[d]	1725
	(1, d)	(1, q)		(2, m)	(2, q)	(2, m)	(3, t)	1742
2b	8.11	6.35[e]	5.73[f]	4.43[b]	4.20	2.15[c]	1.26	1724
	(1, d)	(1, t)	(1, d)	(2, s)	(2, q)	(2, m)	(3, t)	1738
								1750
2c	8.47	6.33[g]		4.43[b]	4.22	2.15[c]	1.25	
	(1, d)	(1, t)		(2, m)	(2, q)	(2, m)	(3, t)	
2d	8.00	5.97[h]	5.73[f]		~4.18[c]		1.24	1752
	(1, d)	(1, d)	(1, d)		(6, m)		(3, t)	

[a] Middle peak poorly resolved. [b] Partially overlapped with CH_2 of C_2H_5O. [c] Poorly resolved. [d] 5-CH_3: δ 1.83 (3, d). [e] Asymmetrical triplet (*cf.* ref 2p, figure 2). [f] Overlapped with OH signal(s). [g] Secondary splitting due to a long-range coupling with fluorine (*cf.* ref 2p). [h] $J_{1',2'}$ = 6 Hz.

Table III

Alkyl 3′-*O*-Methylsulfonylnucleoside Uronates

Compd	Yield,[a] %	Mp,[b] °C	Calcd/Found C, %	Calcd/Found H, %	Calcd/Found N, %	Calcd/Found S, %	λ_{max}, nm[c] ($\epsilon \times 10^{-3}$)	λ_{min}, nm ($\epsilon \times 10^{-3}$)	Optical rotations,[d] deg $[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	Temp, °C
4a	87	130–133	43.09	5.01	7.73	8.85	264	235	14.1[g]	31.7	55.6	23
		(100–101)	43.28	4.99	7.73	8.65	(11.4)	(3.0)				
4b	91						259	228				
		(103–104)					(10.5)	(2.4)				
4c	82	149–150	39.34	4.13	7.65		266	232	48			23
			39.36	4.13	7.50		(8.0)	(2.4)				
4d	86	106–108	43.09	5.01	7.73	8.85	264	235	30.2	71.6	142.8	23
		(90–95)	43.24	5.10	7.53	9.10	(7.5)	(2.5)				
4e[f]	80	188–189	35.29	4.10	6.33	14.50	259	230	46.4	109.6	210	22
		(182–184)	35.46	4.09	6.35	14.25	(11.7)	(3.2)				

[a] Crude product. [b] Melting point of the crude product is given in parentheses. [c] 95% ethanol. [d] c 0.5 (DMF, for 4d $CHCl_3$). [e] Transition point. [f] 2′,3′-Bis-*O*-methylsulfonyl derivative. [g] c 1.

melting points, and physical constants are summarized in Tables I–IX.

Ethyl Nucleoside Uronates (2a–d).—To a stirred suspension of the uronic acid (1a–d, 20 mmol) in 100 ml of ethanol was added 10 ml of triethyl orthoformate and the mixture, cooled externally by an ice bath, was saturated with hydrogen chloride. A crystalline product separated and, after *ca.* 18 hr at room temperature, dry ether (100 ml) was added and the product was collected, washed with ether, and air dried. Yields, analyses, and spectral data are summarized in Tables I and II.

Alkyl 3′-*O*-Methylsulfonylnucleoside Uronates (4a–d).—To a solution of **2a–d** or **3** (1.6 mmol) in 10 ml of pyridine chilled to −20° was added 0.14 ml (1.9 mmol) of methylsulfonyl chloride and the reaction mixture was then maintained at 0° for *ca.* 22 hr. Additional methylsulfonyl chloride (1.9 mmol) was introduced and after another 20-hr interval the reaction was judged to be complete on the basis of tlc (S_2). Pyridine hydrochloride was removed by filtration and the filter cake was washed with 5 ml of pyridine. The filtrate, diluted with 5 ml of ethanol, was evaporated to dryness and the residue was partitioned between chloroform (20 ml) and a saturated solution of sodium bicarbonate (10 ml). The chloroform layer was washed with water and the dried ($MgSO_4$) extract was evaporated to a syrup which solidified either upon evaporation from ethanol or by trituration with ethanol alone or ethanol–ether and cooling to −20°. The solid was suspended in petroleum ether and collected. For **4c** the work-up of the reaction mixture was modified as follows. After evaporation of the pyridine–ethanol mixture, the residue was applied to two plates of loose-layered silica gel GF 254, and chromatographed in solvent S_2. The major uv-absorbing band was eluted with methanol and the eluate was treated first with Norit, then filtered through a Celite bed. Evaporation of the solvent produced an amorphous material which crystallized from methanol (see Tables III and IV).

Ethyl 2′,3′-Di-*O*-methylsulfonyluridine Uronate (4e).—A solution of 0.57 g (2.0 mmol) of ethyl uridine uronate (**2d**) in 10 ml of pyridine cooled to 0° was treated with 0.31 ml (4 mmol) of methylsulfonyl chloride and the reaction mixture was maintained at this temperature overnight. A second portion of methylsulfonyl chloride (0.14 ml, 1.9 mmol) was added and the reaction was allowed to continue (0°) for an additional 24 hr. The work-up of the reaction mixture followed that described above for **4a–d** with the exception that the major portion of **4e**, because of its limited solubility, crystallized from chloroform

TABLE IV

NMR CONSTANTS ($CDCl_3$) AND CARBONYL ESTER FREQUENCIES OF ALKYL 3′-*O*-METHYLSULFONYLNUCLEOSIDE URONATES

	Chemical shifts, δ (number of protons, multiplicity)										
Compd	H_6	$H_{1'}$	H_5	$H_{4'} + H_{3'}$		CH_2 of C_2H_6O	CH_3SO_2	$H_{2'}$	5-CH_3	CH_3 of C_2H_6O	ν_{CO}, cm^{-1}
4a	7.83	6.42		5.48[a]	4.78	4.31	3.17	~2.52[a]	1.95	1.35	1755
	(1, d)	(1, q)		(1, d)	(1, s)	(2, q)	(3, s)	(2, m)	(3, d)	(3, t)	
4b	8.02	6.37	5.75	5.46	4.77	4.27	3.14	~2.55[a]		1.30	1722
	(1, d)	(1, q)	(1, d)	(1, d)	(1, s)	(2, q)	(3, s)	(2, m)		(3, t)	1735
											1742
4c[b]	8.22	6.27[c]		5.58	4.85	4.23	3.32	*d*		1.27	1743
	(1, d)	(1, t)		(1, m)	(1, s)	(2, q)	(3, s)			(3, t)	
4d	7.75	6.42		5.47	4.78	3.81[e]	3.10	~2.54[a]	1.95		1753
	(1, d)	(1, q)		(1, m)	(1, s)	(3, s)	(3, s)	(2, m)	(3, d)		
4e[b,f]	7.75	6.00[g]	5.71	5.49[h]	4.48	4.19	3.34[i]	*Cf.* $H_{4'} + H_{3'}$		1.15	1753
	(1, d)	(1, d)	(1, d)	(2, d)	(1, d)	(2, q)	(3, s)			(3, t)	

[a] Poorly resolved. [b] DMSO-d_6. [c] Secondary splitting owing to a long-range coupling with fluorine (*cf.* ref 2p). [d] Hidden under DMSO-d_5 peak. [e] CH_3O: CH_3N (3, s) at δ 3.28. [f] 2′,3′-Bis-*O*-methylsulfonyl derivative. [g] $J_{1',2'} = 3$ Hz. [h] $H_{3'} + H_{2'}$. [i] Another CH_3SO_2 (3, s) at δ 3.27.

TABLE V

ALKYL 2′,3′-DIDEOXY-3′,4′-DIDEHYDRORIBONUCLEOSIDE URONATES

						λ_{max}, nm[c] (ε × 10^{-3})	λ_{min}, nm (ε × 10^{-3})	Optical rotations,[d] deg			
Compd	Yield,[a] %	Mp,[b] °C	Calcd/Found C, %	H, %	N, %			$[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	Temp, °C
5a	75	229–231	54.13	5.30	10.52	256	230	−115.8	−258	−466.8	24
		(217–219)	54.18	5.38	10.48	(6.5)	(3.2)				
5b	71	158–160	52.38	4.80	11.11	254	226				
		(148–152)	52.68	4.78	11.10	(13.1)	(5.2)	−101.2	−227.4	−414	24
5c	54	200–201	48.89	4.10	10.37	254	228	−152.8[e]			24
			48.68	3.92	10.22						
5d	76	138–139	54.13	5.30	10.52	254	230	−105	−237.8	−433.8	22
		(135–137)	53.88	5.28	10.31	(6.8)	(3.9)				

[a] Crude tlc homogeneous product. [b] Melting point of the crude product is given in parentheses. [c] 95% ethanol. [d] $CHCl_3$ (*c* 0.5). [e] DMF (*c* 0.5).

TABLE VI

NMR CONSTANTS ($CDCl_3$) AND CARBONYL ESTER FREQUENCIES OF ALKYL 2′,3′-DIDEOXY-3′,4′-DIDEHYDRORIBONUCLEOSIDE URONATES

	Chemical shifts, δ (number of protons, multiplicity)							
Compd	H_6	$H_{1'}$	$H_{3'}$	CH_2 of C_2H_6O	$H_{2'}$	5-CH_3	CH_3 of C_2H_6O	ν_{CO}, cm^{-1}
5a	6.94[a]	6.82[b]	6.03	4.28	3.20[c]	2.34	1.32	1724
	(1, d)	(1, q)	(1, t)	(2, q)	(2, m)	(3, s)	(3, t)	
5b	7.25	6.82	6.07	4.29	3.08[c]	5.76[d]	1.32	1727
	(1, d)	(1, q)	(1, t)	(2, q)	(2, m)	(1, d)	(3, t)	
5c[e]	7.92	6.74[f]	6.15[c]	4.27	3.24[c]		1.28	1724
	(1, d)	(1, q)	(1, t)	(2, q)	(2, m)		(3, t)	
5d	6.98[a]	6.85[b]	6.03	3.30[g]	3.07[c]	1.91		1715
	(1, d)	(1, q)	(1, t)	(3, s)	(2, m)	(3, d)		1735

[a] Partially overlapped with $H_{1'}$. Both signals are perfectly separated in DMSO-d_6. [b] Partially overlapped with H_6. [c] Poorly resolved. [d] H_5. [e] DMSO-d_6. [f] Secondary splitting due to a long-range coupling with fluorine (*cf.* ref 2p). [g] CH_3O: CH_3N at δ 3.80 (3, s).

TABLE VII

2′,3′-DIDEOXY-3′,4′-DIDEHYDRO RIBONUCLEOSIDES

						λ_{max}, nm[a] (ε × 10^{-3})	λ_{min}, nm (ε × 10^{-3})	Optical rotation,[b] deg			
Compd	Yield, %	Mp, °C	Calcd/Found C, %	H, %	N, %			$[\alpha]^t_D$	$[\alpha]^t_{436}$	$[\alpha]^t_{365}$	Temp, °C
15a	53	105–110[c]	52.51[d]	5.51	12.25	267	235	−134.6	−297.4	−522.2	23
			52.32	5.29	11.99	(8.7)	(2.4)				
15b	50	125–128[e]	50.35[d]	4.93	13.05	261	231	−150.4	−326.8	−583	25
			50.18	4.82	12.77	(7.6)	(1.8)				
15c	31[f]	139–140[g]	46.44[d]	4.11	12.04	268	238				
			46.60	4.05	11.84	(7.4)	(3.1)				
15d	46	182–183	50.72[h]	4.84	29.57	260	230	−221	−489.4	−861	25
			50.38	4.81	29.83	(9.9)	(1.7)				

[a] 95% ethanol. [b] *c* 0.5 (dioxane). [c] Transition point, melting at 160–165°, decomposition above 230°. [d] Calculated for compound containing $^1/_4H_2O$. [e] Resolidifies and then decomposes above 250°. [f] Product from tlc was crystallized from methanol, mp 135–136°. [g] Product from tlc was filtered off after addition of ether and dried for analysis at 100° over P_2O_5. [h] Calculated for compound containing $^1/_6H_2O$.

Table VIII

Nmr Constants (CD_3COCD_3) of 2′,3′-Dideoxy-3′,4′-didehydro Ribonucleosides

Compd	H_8	$H_{1'}$	$H_{3'}$	$H_{4'}$	$H_{2'}$	5-CH_3
15a	7.31	6.65	5.02	4.12	3.07[a]	1.81
	(1, d)	(1, q)	(1, t)	(2, s)	(2, m)	(3, d)
15b	7.53	6.67	5.07	4.20	2.94[a]	5.70[b]
	(1, d)	(1, q)	(1, t)	(2, s)	(2, m)	(1, d)
15c	7.60	6.63[c]	5.11[a]	4.14	3.12[a]	
	(1, d)	(1, q)	(1, t)	(2, s)	(2, m)	
15d[d]	8.25[e]	6.82	5.23[a]	4.07	~3.17[a]	
	(2, s)	(1, q)	(1, t)	(2, s)	(2, m)	

[a] Poorly resolved. [b] H_5. [c] Secondary splitting due to a long-range coupling with fluorine (*cf.* ref 2p). [d] DMSO-d_6. [e] H_8 + H_2 (two poorly resolved singlets).

Table IX

Nmr Splitting Patterns of the $H_{1'}$ Proton of Some 2′,3′-Dideoxy-3′,4′-didehydro Ribonucleosides

Compd	Multiplicity	Signal width, Hz	$J_{1',2'}$ and $J_{1',2''}$, Hz	Solvent
5a	q	15.5	9.5, 6.0	DMSO-d_6
5a	q	13.0	10.0, 6.0	$CDCl_3$
5a	q	15.5	10.0, 6.0	Pyridine-d_5–D_2O
5b	q	14.5	9.5, 5.0	$CDCl_3$
5c	q[a]	15.5	9.0, 6.0	DMSO-d_6
15a	q	14.0[b]	10.0,[b] 4.5[b]	Acetone-d_6
15b	q	13.0	9.0, 4.0	Acetone-d_6
15c	q[a]	13.0	9.0, 4.0	D_2O
15d	q	12.5	8.0, 4.5	DMSO-d_6–D_2O
11	t	14.5	7.5, 7.5	DMSO-d_6

[a] Secondary splitting caused by a long-range coupling with fluorine (*cf.* ref 2p). [b] The same spacings were also observed in CD_3CN.

during the work-up. Yield, analysis, and spectral data appear in Tables III and IV.

Alkyl 2′,3′-Dideoxy-3′,4′-didehydronucleoside Uronates (5a–d).—A solution of **4a–d** (0.25 mmol) in DMF (2 ml) was heated with triethylamine (0.1 ml, 0.75 mmol) at 100° (bath temperature) for 2 hr and the reaction mixture was evaporated to dryness at 0.1 mm. The residue was either washed with ethanol (2 ml) to give a product (**5a**) homogeneous on tlc or dissolved in chloroform (in the case of **5b** and **5e**) and the solution was worked up as described for the corresponding methylsulfonyl derivatives. Compound **5c** was obtained by direct chromatography of the residue after evaporation of the DMF as described for **4c** (treatment with Norit and Celite was omitted). Analytical samples were recrystallized from ethanol (**5c** from methanol). (See Tables V and VI for corresponding physical constants.)

In a large-scale preparation of **5a** (5.25 g, 14.5 mmol of **4a**) a small amount of an unidentified by-product was isolated. According to tlc (S_1) the latter is neither identical with the ester **2a** nor the anhydro derivative **7**. Pure **5a** was obtained following silica gel (70–325 mesh, 150 g) column (51 × 2.5 cm) chromatography of the crude material. After elution with chloroform (1 l.), **5a** (2.1 g, 54%) was eluted with 2% methanol in chloroform (2 l.). Elution with 5% methanol in chloroform (3 l.) gave the by-product (0.38 g). Crystallization from ethanol gave a solid (0.3 g): mp 170–175°; homogeneous on tlc (S_1); $[\alpha]^{24}D$ −94.8°, $[\alpha]^{24}_{436}$ −221°, $[\alpha]^{24}_{365}$ −416.4° (c 0.5, DMF); uv max (95% ethanol) 261, 230 nm.

2′,3′-Dideoxy-3′,4′-didehydro Nucleosides (15a–d).—The unsaturated ester (**5a–c**, **11**) (1 mmol) was dissolved in THF (11 in dioxane) (40 ml) and to the solution was added dropwise with stirring and with an external ice-bath cooling a 70% stock solution of sodium bis(methoxyethoxy)aluminum hydride in benzene diluted to give 1 mmol of reagent in 1 ml. The progress of reduction was checked by tlc (S_1). Additional 1-mmol portions of the reagent were added at 1- and 2-hr intervals while the reaction mixture was stirred at room temperature. After 3 hr the reduction appeared to be *ca.* 90% complete. Ethanol (20 ml) was added followed by dry Dowex 50 WX (NH_4^+) 100–200 mesh (7 g, 36 mequiv). The mixture was stirred at room temperature for 30–60 min, and the resin was filtered off and washed with ethanol or with THF and methanol. The filtrate was evaporated to dryness and the residual syrup was chromatographed on two plates of silica gel in solvent S_1. The major uv-absorbing bands were eluted with solvent S_2 and evaporated to give a syrup (**15a**) which crystallized when stored at −20°. Crystallization of **15b** was effected by adding ethyl acetate–ether and cooling to −20°. The band of **15c** derived from preparative tlc afforded crystalline material directly. In the case of **15d** the crude product contained adenine (*ca.* 10%) in addition to 5–10% of starting ester (**11**). The solution in DMF was applied to preparative layers and chromatographed in solvent S_1. The band of **15d** was eluted with $CHCl_3$–methanol (1:1) to give, after evaporation, a crystalline product. Yields and constants appear in Tables VII and VIII.

Methyl 2′-Deoxyadenosine Uronate (9).—A stirred suspension of 2′-deoxyadenosine uronic acid (**8**) (1.105 g, 4.17 mmol) in methanol (70 ml) was treated portionwise with a solution of diazomethane in ether until the yellow color persisted and tlc (S_2) showed a single spot (**9**). The solution was evaporated and the residue was chromatographed on five plates of loose layers of silica gel in the solvent S_2. The major band (**9**) was eluted with a mixture of chloroform–methanol (1:1), the eluate was evaporated, and the residue was crystallized from methanol to give **9** (0.6 g, 51.5%): mp 151–152°; $[\alpha]^{25}D$ −19°, $[\alpha]^{25}_{436}$ −48.6°, $[\alpha]^{25}_{365}$ −106.6° (*c* 0.5, DMF); uv max (95% ethanol) 259 nm (ϵ 9200), min 227 (1400); nmr (DMSO-d_5) δ 8.36 (s, 1, H_8), 8.16 (s, 1, H_2), 7.17 (broad s, 2, NH_2), 6.52 (t, 1, $H_{1'}$), 3.67 (s, 3, CH_3O); ir (KBr) ν_{CO} 1770 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_5O_4 \cdot {}^3/_4H_2O$: C, 45.18; H, 5.00; N, 23.95. Found: C, 45.07; H, 5.12; N, 23.63.

Reaction of 4a with Potassium *tert*-Butoxide.—A solution of **4a** (90 mg, 0.25 mmol) and potassium *tert*-butoxide (84 mg, 0.75 mmol) in DMSO (2 ml) was stirred for 30 min at room temperature. An excess of Dry Ice was then added and the mixture was poured immediately into water (25 ml) containing carbon dioxide. The neutral (phenolphthalein) solution was extracted with chloroform (3 × 30 ml) and the dried ($MgSO_4$) extract was evaporated. The residual liquid (presumably ethyl furan-2-carboxylate) was homogeneous on tlc (S_2) and was volatile at 65° (bath temperature) and 0.1 mm. The aqueous layer was evaporated to a volume of *ca.* 10 ml, and the residue was stirred for 30 min with a mixture of excess Dowex 50 WX-4 (pyridinium form, 100–200 mesh) and Dowex 1 X2 (OH form, 200–400 mesh). The resin was filtered off and washed with 50% pyridine (50 ml). The filtrate was evaporated and the residue was coevaporated with a mixture of ethanol and ether to give thymine (24 mg, 76%) identical [tlc (S_2), melting point, and ir spectrum] with an authentic sample.

Reaction of 5a with Sodium Azide.—A mixture of **5a** (0.13 g, 0.5 mmol) and sodium azide (65 mg, 1 mmol) in DMF (5 ml) was heated for 5.5 hr at 120° (bath temperature). After cooling the reaction mixture was filtered, the insoluble portion was washed with DMF, and the filtrate was evaporated at 0.1 mm and 45° (bath temperature). The residue was washed with ethanol (3 ml) to give thymine (50 mg, 79%) identical [tlc (S_2) and melting point] with an authentic sample.

Methyl 2′,3′-Dideoxy-3′,4′-didehydroadenosine Uronate (11).—A solution of the ester **9** (0.1 g, 0.36 mmol) and dimethylformamide dimethyl acetal (0.2 ml, *ca.* 2 mmol) in 10 ml of DMF was held overnight at room temperature. Evaporation of the reaction mixture at 0.1 mm gave a solid (**10**), mp 220–222°, uv max (95% ethanol) 310 nm, min 215.

A solution of **10** (1 g, 2.99 mmol) in pyridine (100 ml) was stirred with methylsulfonyl chloride (0.77 ml, 10 mmol) for 3 hr at −20° and then kept for 16 hr at the same temperature. Methanol (25 ml) was added and the solution was evaporated at 30° (0.1 mm). The residue was dissolved in DMF (50 ml), and triethylamine (2.3 ml, 18 mmol) was added. The mixture was held for 1 hr at 0°; the triethylamine hydrochloride was filtered off and washed with a small amount of DMF. The filtrate was evaporated to near dryness, the residue was dissolved in chloroform (50 ml), and the solution was extracted with water (60 ml). The aqueous layer was extracted with chloroform (20 ml), and the combined dried ($MgSO_4$) organic layers were evaporated to a solid residue (0.9 g), which according to uv (95% ethanol), showed *ca.* 50% removal of the *N*-dimethylaminomethylene

group. This material was dissolved in dioxane (50 ml), triethylamine (0.2 ml, 1.5 mmol) was added, and the solution was heated for 2 hr at 100° (bath temperature). The reaction mixture was evaporated and the residue was refluxed for 10 hr in methanol (100 ml). Uv showed that the 6-amino group had been almost completely (94%) deblocked. Evaporation of the solvent and crystallization of the crude product from ethanol gave a solid (0.32 g, 41%), mp 228–230° dec, homogeneous on tlc (S_1). For analysis a portion of the product was chromatographed on loose layer silica gel in S_1 and then recrystallized from ethanol: mp 233° dec; $[\alpha]^{25}D$ −212.6°, $[\alpha]^{25}_{436}$ −472.8°, $[\alpha]^{25}_{365}$ −851.8° (*c* 0.5, dioxane); uv max (95% ethanol) 257 nm (ε 14,900), min 225 (4700); nmr (DMSO-d_6) δ 8.32 (s, 1, H_8), 8.21 (s, 1, H_2), 7.33 (broader s, 2, NH_2), 6.94 (t, 1, $H_{1'}$, $J_{1',2'} = J_{1',2''} = 7.5$ Hz, signal width 14.5 Hz), 6.31 (t, 1, H_3'), 3.74 (s, 3, CH_3O), 3.47 (m, 2, $H_{2'}$).

Anal. Calcd for $C_{11}H_{11}N_5O_3$: C, 50.57; H, 4.25; N, 26.81. Found: C, 50.45; H, 4.30; N, 26.72.

Reaction of Ethyl Nucleoside Uronates (2a and 5a) with Dimethylformamide Dineopentyl Acetal.—Compound **5a** (27 mg, 0.1 mmol) was heated for 7 hr at 80–90° (bath temperature) in DMF (1 ml). Tlc (S_1) showed a quantitative decomposition of **5a** to thymine and ethyl furoate. A similar result was obtained with **2a** heated with 2 equiv of dimethylformamide dineopentyl acetal for 13 hr at 90–100° (bath temperature) in DMF.

Ethyl 3'-Deoxy-3',4'-didehydrothymidine Uronate (5a). A. From Ethyl 2,3'-Anhydrothymidine Uronate (7).—A solution of **7** (2.7 mg, 10 μmol) in 0.1 ml of DMF containing 1 drop of triethylamine was heated for 2 hr at 100° (bath temperature). The mixture was then evaporated at 0.1 mm and room temperature and the residue was examined by tlc (S_1) which showed the presence of olefin **5a** and anhydro nucleoside **7** in an approximate ratio of 1:1.

B. From 4a.—The methylsulfonyl derivative (**4a**, 0.185 g, 0.51 mmol) was added to a solution of sodium benzoate (0.203 g, 1.41 mmol) in DMF, (15 ml) preheated to 100° (bath temperature), and the heating was continued for 1 hr. After cooling the solid was filtered off and washed with DMF (10 ml) and the filtrate was evaporated at 50° (bath temperature) and 0.2 mm. The resultant solid was dissolved in methanol, and the solution was applied to one layer of silica gel and developed in solvent S_1. The uv-absorbing band (R_f *ca.* 0.4) was eluted with the solvent, and the eluate was evaporated to give 0.119 g (88%) of **5a**, mp 225–226°, identical (melting point, uv spectrum) with a sample prepared by a different route (*cf.* Table V).

C. By the Action of 2,6-Lutidine on 4a.—Compound **4a** (0.1 g, 0.28 mmol) was heated in 2,6-lutidine (10 ml) at 100° (bath temperature) for 7 hr and then refluxed for 3.5 hr. After cooling the solution was decanted from a syrupy deposit and the clear solution was evaporated at 0.1 mm and 50° (bath temperature). The residue was washed with ethanol (2 ml) to give 20 mg (27%) of olefin **5a**, mp 215–219°, identical (mixture melting point, ir spectrum) with a sample obtained by an alternate method (*cf.* Table V).

D. From the Pyridinium Derivative (6).—A solution of **6** (0.11 g, 0.25 mmol) and sodium benzoate (72 mg, 0.5 mmol) in DMF (5 ml) was heated for 30 min at 90° (bath temperature). After cooling, the insoluble portion was filtered off and washed with DMF, and the filtrate was evaporated at 0.1 mm and 45° (bath temperature). The solid residue was treated with a saturated solution of sodium bicarbonate (10 ml) and the mixture was extracted with chloroform (2 × 20 ml). The organic layer was dried ($MgSO_4$) and evaporated to give **5a** (47 mg, 71%), mp 231–233°, identical [melting point, tlc (S_1), ir spectrum] with a sample prepared by another route (*cf.* Table V).

E. From 1a and Acetic Anhydride Followed by Esterification.—Compound **1a** (0.258 g, 1 mmol) in acetic anhydride (10 ml) was stirred under reflux for 30 min. After cooling, excess ice was added and the stirring was continued until the mixture was homogeneous. The solution was then evaporated and the residue was coevaporated several times with water to give a solid which was collected after addition of ether (0.165 g), melting point ill defined (decomposition above 170°). This material was dissolved in DMF (5 ml), the solution was filtered through a Celite bed, and ether (200 ml) was added to the filtrate. After filtration and cooling to −20°, a precipitate (56 mg) was obtained (mp 150–160°) containing, according to the nmr, *ca.* 42% of **1a** (or its 3' acetate) and 58% of **14**: nmr (DMSO-d_6) δ 7.94 (H_6 of **1a**), 7.32 (H_6 of **14**), 6.70 ($H_{1'}$), 6.03 ($H_{3'}$ of **14**), 2.82 [$(CH_3)_2N$ of DMF], 1.8 (CH_3 of thymine).

In another experiment, **1a** (0.5 g, 1.95 mmol) was refluxed in acetic anhydride (20 ml) for 2 hr and the reaction mixture was worked up as described above. The residue was dried by azeotropic distillation with a mixture of ethanol (30 ml) and benzene (30 ml). After removal of *ca.* one-half of the solvent mixture, ethyl orthoformate (0.63 ml, 3.75 mmol) was added at room temperature followed by ethanol (20 ml) and 1 drop of concentrated H_2SO_4. The reaction mixture was maintained for 3 days at ambient temperature. Excess sodium bicarbonate was then added and the solids were collected. The filter cake was washed with chloroform, then ethanol, and the washings were evaporated. The residue was chromatographed on one loose layer of silica gel S_1, the zone of ester (**5a**) was eluted with S_2, and the eluate was evaporated. The residue was washed with ethanol–ether to give 80 mg (15%) of **5a**, mp 227–230°, identical on the basis of ir with an authentic sample.

Kinetics of Elimination on 4a or 7.—A solution of 0.0553 mmol of **4** or **7** in DMSO-d_6 (0.25 ml) was preheated to 50° in the nmr probe. Triethylamine (0.02 ml, 0.2 mmol) was added and the decrease of the H_6 signal of the starting material was followed as a function of time for a period of 1 hr. Half-time for the conversion of **4a** to **5a** was 29 min. With anhydro derivative **7** no reaction was observed after 2 hr. Elevation of the temperature to 100° initiated elimination but the kinetic data were not readily reproducible (*ca.* $t_{1/2}$ 110 min.).

Ethyl 2,3'-Anhydrothymidine Uronate (7).—A solution of compound **4a** (0.1 g, 0.277 mmol) was heated in pyridine (5 ml) for 16 hr at 100° (bath temperature). The reaction mixture was evaporated, and the residue was washed with ethanol to give a solid which was collected. The filtrate was applied to one plate of silica gel (loose layer) which was developed in the solvent S_2. Three major uv-absorbing bands were detected (in the order of increasing mobility): compound **6** (at the origin), product **7**, and **4a** near the front. Compound **7** was eluted with a mixture of chloroform–methanol (3:1), the eluate was evaporated, and **7** (20 mg, 27%), which was homogeneous on tlc (S_2), mp 191–193°, crystallized from ethanol and was dried at 100° (10^{-3} mm): mp 227–229° (sinters at *ca.* 210°); $[\alpha]^{23}D$ −64.2° (*c* 0.5, H_2O); uv max (95% ethanol) 244 nm (ε 6200), min 219 (3700); nmr (DMSO-d_6) δ 7.65 (d, 1, H_6), 6.02 (poorly resolved d, 1, $H_{1'}$), 5.48 (poorly resolved d, 1, $H_{4'}$), 4.98 (d, 1, $H_{3'}$), 4.13 (q, 2, CH_2 of C_2H_5O), *ca.* 3.3 ($H_{2'}$ overlapped with DMSO-d_5), 1.78 (d, 3, CH_3 of thymine), 1.14 (t, 3, CH_3 of C_2H_5O); ir (KBr) ν_{CO} 1755 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.16; H, 5.32; N, 10.48.

A mixture of compound **4a** (63 mg, 0.176 mmol) and barium carbonate (17 mg, 0.088 mmol) was heated at 90° in water (5 ml) with stirring for 30 min, whereupon the solution became clear. After 15 min tlc (S_2) showed the absence of **4a** and the presence of **7**. After cooling, the solution was evaporated at 1.5 mm and room temperature. The solid residue was dissolved in methanol and applied to one layer of silica gel which was developed in the solvent S_2. The major uv-absorbing band was eluted with methanol, the eluate was evaporated, and the solid was crystallized from ethanol to give **7** (33 mg, 69%), mp 218–220°, identical in all respects with the sample of **7** prepared by the alternate route described above.

1-(5-Carbethoxyfur-2-yl)uracil (12).—A sample of **4e** (0.12 g, 0.25 mmol) was heated with triethylamine (0.1 ml, 0.75 mmol) in DMF (2 ml) for 30 min at 100° (bath temperature). The reaction mixture was then evaporated to dryness at 40° (0.1 mm) and the solid residue was washed with ethanol (2 ml) to give **12** (60 mg, 96%): mp 199° (crystallization from ethanol raised the melting point to 201–202°); uv max (95% ethanol) 264, 298 nm (ε 10,500, 11,000), min 232, 278 (4000, 9100); nmr (DMSO-d_6, poorly resolved) δ 7.8 (d, 1, H_6), 5.8 (d, 1, H_5), 7.36 (d, 1, $H_{3'}$), 5.38 (d, 1, $H_{4'}$, poorly resolved), 4.29 (q, 2, CH_2), 1.3 (t, 3, CH_3).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.89; H, 4.08; N, 11.07.

Compound **4a** (0.12 g, 0.25 mmol) was heated in pyridine (5 ml) at 100° (bath temperature) for 13 hr. The reaction mixture was evaporated as described above to give a solid (**12**, 47 mg, 70%) which after washing with a small amount of ethanol, showed mp 198–200°, and was identical according to tlc (S_1), ir, and uv spectra with a sample of **12** prepared by the above route.

Compound **2d** (0.57 g, 2 mmol), diphenyl carbonate (0.64 g, 3 mmol), and sodium hydrogen carbonate (10 mg, 0.12 mmol) were heated with stirring in DMF (2 ml) at 150° for 30 min. After cooling, the brown solution was poured into ether (40 ml), and

the tan solid was filtered off, thoroughly washed with ether, and air dried to give 0.19 g (38%) of **12**, mp 201–202°, identical according to ir and uv with a sample prepared by another method.

A mixture of **4e** (0.12 g, 0.27 mmol) and sodium benzoate (0.145 g, 1.08 mmol) was heated in DMF (5 ml) at 80–90° (bath temperature) for 30 min with stirring. After cooling, the insoluble portion was collected and washed with DMF, and the filtrate was evaporated at 45° (0.1 mm). The residue was partitioned between a saturated solution of sodium hydrogen carbonate (10 ml) and chloroform (2 × 30 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a white solid (**12**, 60 mg, 89%), mp 194–195°, homogeneous on tlc (S_1). Recrystallization from ethanol raised the melting point to 201–203°; uv and ir spectra were identical with an authentic sample of **12**.

1-(5-Carboxyfur-2-yl)uracil (13).[7a]—A sample of **1d** (0.258 g, 1 mmol) was refluxed with stirring in acetic anhydride (10 ml) for 45 min. The clear solution was allowed to cool and excess ice was added with stirring until the reaction mixture was homogeneous. After the mixture was held overnight at 0°, the solid that was deposited was filtered and washed with a small amount of water to give 0.125 g (57%) of **13**, mp 305° dec; 0.1 g was sublimed at 250–260° (0.1 mm) without decomposition[7a] to give 85 mg of **13**, mp 304–305°; ir (KBr) of the sublimate and starting material were identical; nmr (DMSO-d_6) showed δ 7.83 (d, 1, H_6), 5.87 (d, 1, H_5, $J_{5,6}$ = 8 Hz), 7.34 (d, 1, $H_{3'}$), 6.73 (d, 1, $H_{4'}$, $J_{3',4'}$ = 3 Hz).

Ethyl 3′-Deoxy-3′-(*N*-pyridinium)thymidine Uronate Methyl Sulfonate (6).—A solution of **4a** (0.5 g, 1.38 mmol) in pyridine (25 ml) was refluxed for 10 hr. The crystalline precipitate was then collected and washed with pyridine to give 0.28 g (46%) of **6**: mp 279–280° dec (crystallization from methanol raised the melting point to 283–286° dec); $[\alpha]^{23}D$ −49.6°, $[\alpha]^{23}_{436}$ −104.8°, $[\alpha]^{23}_{365}$ −175.8° (c 0.5, H_2O); uv max[18] (water) 260 nm (ε 16,100), 235 (4100); nmr[19] (DMSO-d_6, poorly resolved) δ 11.41 (s, 1, δ-pyridine H), 9.45 (d, 2, β-pyridine H), 8.34 (d, 2, α-pyridine H), 7.73 (d, 1, H_6), 6.51 (m, 1, $H_{1'}$), 4.15 (q, 2, CH_2 of C_2H_5O), 3.34 (s, 3, CH_3SO_3), 1.83 (d, 3, CH_3 of thymine), 1.15 (t, 3, CH_3 of C_2H_5O); ir (KBr) ν_{CO} 1773 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}N_3O_8S$: C, 48.97; H, 5.25; N, 9.52; S, 7.26. Found: C, 48.70; H, 5.13; N, 9.81; S, 7.08.

Ethyl 3′-Deoxythymidine Uronate (17).—A solution of **5a** (0.2 g, 0.88 mmol) in dioxane–ethanol (2:3, 50 ml) was hydrogenated in a Brown apparatus[20] over 10% palladium on charcoal (0.2 g) for 3 hr at room temperature. The catalyst was filtered off and washed with ethanol, and the filtrate was evaporated. The residue on treatment with ether and petroleum ether gave 0.2 g of **17** (quantitative yield), mp 151–154°, homogeneous on tlc (S_1). A sample for analysis was crystallized from ethanol: mp 166–169°; $[\alpha]^{23}D$ +29.8°, $[\alpha]^{23}_{436}$ +79°, $[\alpha]^{23}_{365}$ +175.2° (c 0.5, $CHCl_3$); uv max (95% ethanol) 268 nm (ε 8900), 237 (1900); nmr ($CDCl_3$) δ 8.09 (d, 1, H_6), 6.18 (t, poorly resolved, 1, $H_{1'}$), 4.56 (m, 1, $H_{4'}$, poorly resolved), 4.24 (q, 2, CH_2 of C_2H_5O), 2.23 (m, 4, $H_{3'}$ + $H_{2'}$, poorly resolved), 1.94 (d, 3, CH_3 of thymine), 1.29 (t, 3, CH_3 of C_2H_5O); ir (KBr) ν_{CO} 1745 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.68; H, 6.07; N, 10.36.

1-(5-Hydroxymethylfur-2-yl)uracil (16).—The reduction of **12** (0.125 g, 0.5 mmol) followed the procedure described for 3′,4′-unsaturated nucleosides **15a–d**. Over a period of 8 hr, a total of 4 mmol of sodium bis(methoxyethoxy)aluminum hydride was added. Dry Dowex 50 WX (NH_4^+) 100–200 mesh (10 g) was introduced and the mixture was stirred at room temperature for 1 hr. The insoluble portion was filtered off and washed with tetrahydrofuran. The filtrate was evaporated and the residue was crystallized from tetrahydrofuran–methanol to give 38 mg of product (36% yield): mp 166–167°; uv max (95% ethanol) 251 nm (ε 8600), shoulder 298 (4400), min 240 (7900); nmr (CD_3CN) δ 7.48 (d, 1, H_6), 6.37 (s, 2, $H_{3'}$ + $H_{4'}$), 5.70 (d, 1, H_5), 4.47 (s, 2, CH_2); nmr (D_2O, external TMS) δ 8.13 (d, 1, H_6), 6.95 (s, 2, $H_{3'}$ + $H_{4'}$), 6.38 (d, 1, H_5), CH_2 overlapped with HDO signal.

Anal. Calcd for $C_9H_8N_2O_4$: C, 51.92; H, 3.87; N, 13.45. Found: C, 51.96; H, 3.95; N, 13.41.

3′-Deoxythymidine (18).—The reduction of **17** (0.402 g, 1.5 mmol) in THF (60 ml) was carried out in essentially the same manner as that described for the unsaturated nucleosides **15a–d**. The total amount of sodium bis(methoxyethoxy)aluminum hydride added in three portions during 3 hr at room temperature amounted to 4 mmol. The reaction mixture was worked up in the same way as that described for the preparation of **16** with the sole exception that in addition to THF, the resin was also washed with ethanol. Crystalline material was obtained after evaporation of the filtrate, which was collected after addition of ether to give 0.24 g (72%) of **18**, mp 132–133°, homogeneous on tlc (S_1). Recrystallization of the solid from ethyl acetate raised the melting point to 142–143° (lit. mp 145°,[15a] 147–149°,[15b] and 149–150°[2b]). The product **18** was identical with an authentic specimen according to uv, ir, and nmr spectra, tlc, and mixture melting point.

Registry No.—**2a**, 37781-47-8; **2b**, 29617-88-7; **2c**, 20105-71-9; **2d**, 37781-50-3; **4a**, 37781-51-4; **4b**, 37781-52-5; **4c**, 29673-92-5; **4d**, 29673-93-6; **4e**, 37781-54-7; **5a**, 29617-89-8; **5b**, 37781-56-9; **5c**, 37781-57-0; **5d**, 29617-92-3; **6**, 37782-84-6; **7**, 29617-91-2; **8**, 4603-70-7; **9**, 37782-86-8; **10**, 37782-87-9; **11**, 37782-88-0; **12**, 37782-90-4; **13**, 37782-91-5; **15a**, 37782-89-1; **15b**, 29617-90-1; **15c**, 37782-93-7; **15d**, 37818-74-9; **16**, 37782-95-9; **17**, 37782-94-8; dimethylformamide dimethyl acetal 4637-24-5.

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(18) Uv data[9] for a similar compound—*N*-[*trans*-4-(thyminyl)cyclopentyl]-pyridinium hydroxide (inner salt)—have been reported: λ_{max} 262 (shoulder), 267, and 280 (shoulder) (ϵ_{max} 13,300, 13,800, and 9180). The corresponding hydrochloride showed λ_{max} 262 (sh), 267, and 280 (sh), (ϵ_{max} 12,530, 13,040, and 8500).

(19) The positions of pyridine protons were assigned in analogy with the literature: L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p 64.

(20) C. A. Brown and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 2829 (1962).

The Chemistry of Carbanions. XXIV. Comparison of Stereochemistry in Alkylation and the Michael Reaction[1a]

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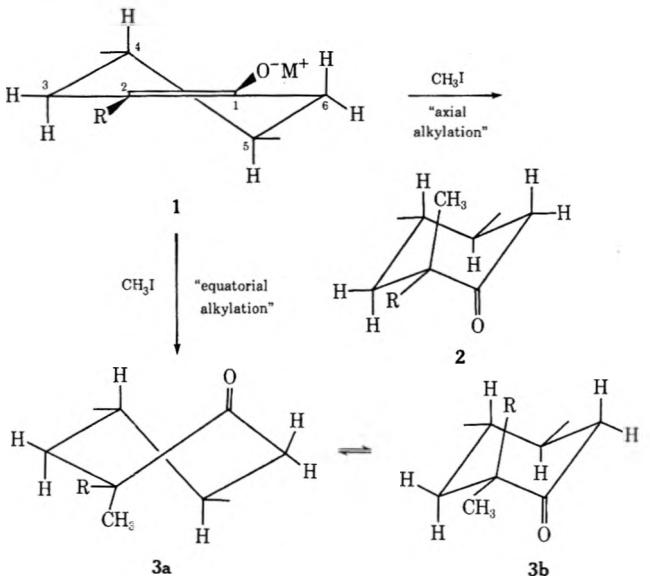
Reaction of the lithium enolate **9** from 2-methyl-5-*tert*-butylcyclohexanone (**4**) with trideuteriomethyl iodide yielded an alkylated product with 83% of the trideuteriomethyl group in an axial position. Reaction of the same ketone **4** with methyl acrylate produced a mixture of keto esters **14** and **15** with 82–86% of the β-methoxycarbonylethyl group in an axial position. These stereochemical results are suggested to result from deformation in the geometry of the starting metal enolate **9** that favors the introduction of a new axial substituent.

In the absence of substantial steric hindrance to attack from one side of an enolate anion **1** derived from a suitably substituted cyclohexanone derivative, the amounts of alkylated products formed with the new alkyl group axial (**2**) or equatorial (**3**) are influenced by the nature of the α substituent R. When this substituent is hydrogen, approximately equal amounts of axial and equatorial products are formed.[2a,b,f] However, when this substituent is alkyl, cyano, or carboalkoxy, the alkylated product is usually composed of 70–90% of the axial product **2** and 10–30% of the equatorial product **3**.

These sterochemical results could be explained in terms of a reactantlike transition state for enolates with hydrogen at the α carbon (**1**, R = H) and a productlike transition state with geometry similar to **2** or **3a** when some larger α substituent R is present. We

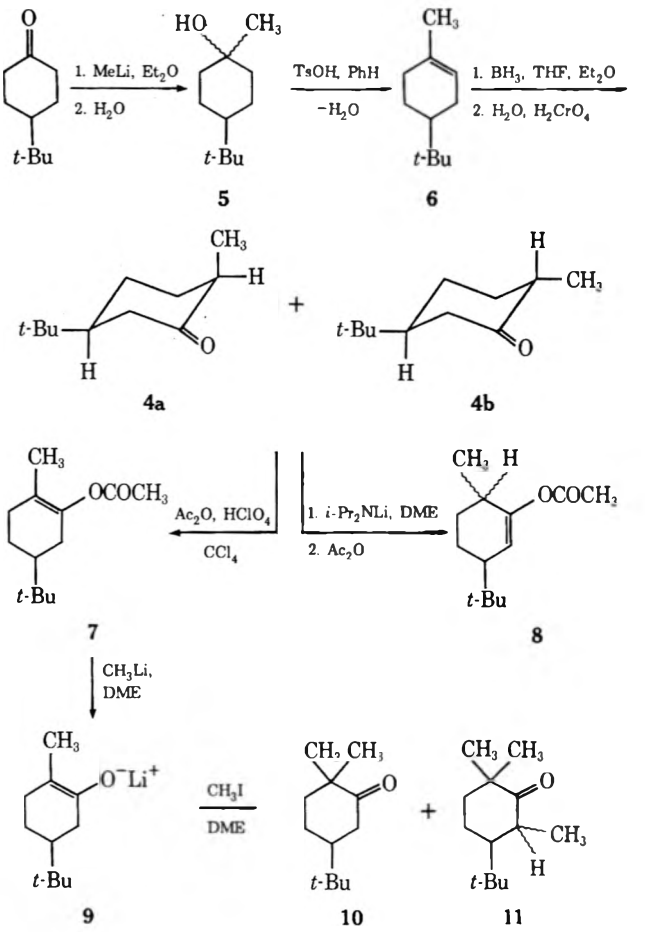


1 2 3a 3b

have described elsewhere[3] evidence indicating that early, reactantlike transition states are generally appropriate for both N- and C-alkylation reactions even though the relative rates of the alkylation reactions may differ by large factors.

In the present study we have compared the stereochemical results in two different reactions of an enolate anion: the alkylation with methyl iodide and the Michael reaction with methyl acrylate. The ketone **4**, selected for study, was prepared by the process summarized in Scheme I and converted into its lithium

SCHEME I



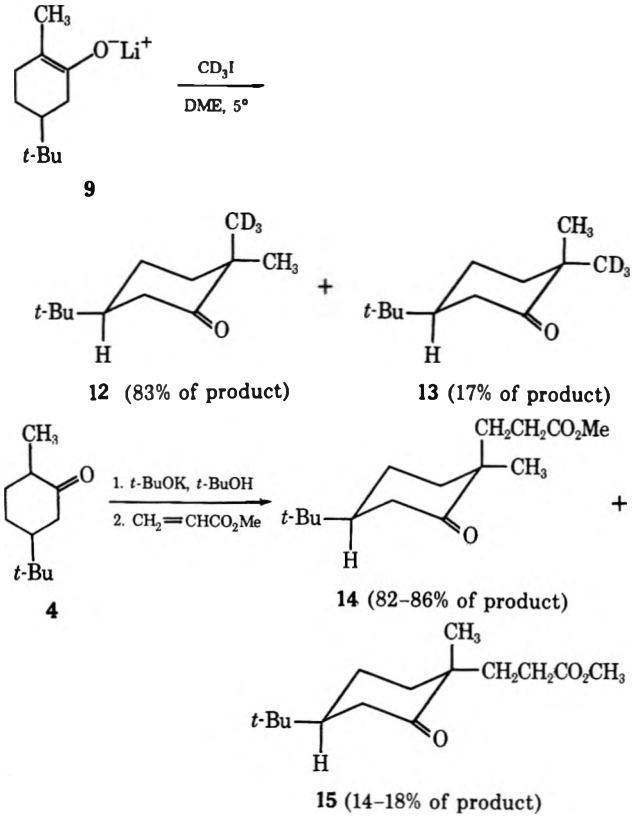
enolate **9** by way of the appropriate enol acetate **7**. The stereochemical results obtained from reaction of the lithium enolate **9** with trideuteriomethyl iodide and from Michael addition of the potassium enolate from ketone **4** to methyl acrylate are provided in Scheme II. Appropriate control experiments (see Experimental Section) were employed to demonstrate that the Michael products **14** and **15** were formed under conditions of kinetic control and that the proportions of these products were not being altered by further reac-

(1) (a) This research has been supported by Public Health Service Grant No. 7-RO1-CA-12634 from the National Cancer Institute. (b) This work is part of the Ph.D. Thesis of M. J. Umen done *in absentia* from the Department of Chemistry, Massachusetts Institute of Technology.

(2) (a) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968); (b) B. J. L. Huff, F. N. Tuller, and D. Caine, *ibid.*, **34**, 3070 (1969); (c) M. E. Kuehne and J. A. Nelson, *ibid.*, **35**, 161 (1970); M. E. Kuehne, *ibid.*, **35**, 171 (1970); (c) for a recent review of other examples, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Beniamin, Menlo Park, Calif., 1972, pp 586–615; (f) P. T. Lansbury and G. E. DuBois, *Tetrahedron Lett.*, **No. 32**, 3305 (1972).

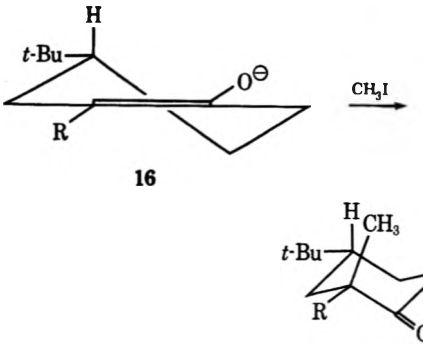
(3) (a) H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968); (b) T. M. Bare, N. D. Hershey, H. O. House, and C. G. Swain, *ibid.*, **37**, 997 (1972).

SCHEME II



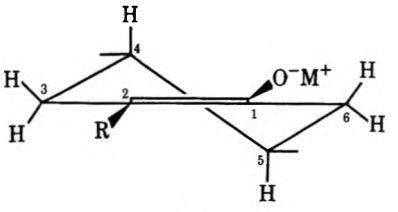
tion. The stereochemical assignments are based on the changes in nmr chemical shift values of the substituents α to the carbonyl group as the solvent was changed from CCl_4 to C_6D_6.[4] Thus in both of these reactions, one involving the nucleophilic displacement by the enolate anion at a tetravalent carbon and the second involving addition of the enolate to an unsaturated center, the stereochemical results are practically the same, namely *ca.* 85% reaction to introduce a new axial substituent. In a related study of the aldol condensation of the enolate **9** with benzaldehyde in the presence of Zn^{2+},[5] the initially formed aldol product contained 70% of the least stable stereoisomers with the added substituent axial. It is also appropriate to note that, in the methylation of the various enolates **16**[2b,c] with substituents of different character, the proportion of the major alkylated product, the axial isomer **17**, is remarkably similar.

It seems to us unlikely that the similar stereochemical results obtained in the various reactions studied should be ascribed to a series of productlike transition states, each of which involves approximately the same degree of new carbon–carbon bond formation. An alternative hypothesis, which we find more attractive, is that all of the enolate reactions described involve early reactantlike transition states with stereochemistry being deter-

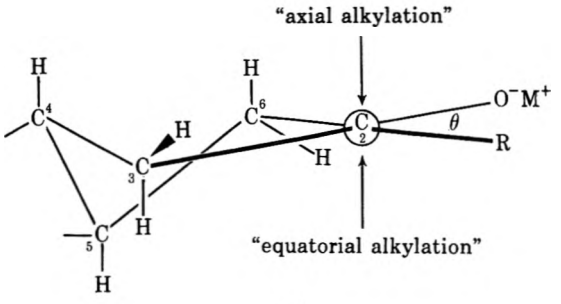


17a, R = CH_3 (with CD_3I) (~70% of product)
b, R = CN (77% of product)
c, R = CO_2CH_3 (83% of product)

mined primarily by the geometry of the starting enolates. Specifically, we suggest that the dihedral angle defined by C_1–O–M^+ and C_2–R (angle θ in structure **1b**) is not zero in order to avoid eclipsing of the C-1



1a



1b

and C-2 substituents.[6] This deformation is expected to occur in the direction illustrated in structure **1b** in order to avoid eclipsing the pseudoequatorial hydrogen at C-6 with the substituent O–M^+ and eclipsing the pseudoequatorial hydrogen at C-3 with the substituent R. Furthermore, this deformation of the planar enolate system would be expected to increase as the steric bulk of R (or the negative charge at R) is increased. Since the deformation suggested in structure **1b** would be accompanied by a partial rehydridization of the p orbital at C-2 toward an sp^3 orbital, the result of this deformation would be to favor axial attack both by allowing increased orbital overlap and by decreasing steric interference with an entering axial substituent. As has been noted in a different context,[2f] "equatorial alkylation" of the deformed enolate **1b** also will be accompanied by movement of the substituent R in a direction that will increase eclipsing of the substituents R and O–M^+ as the new C–C bond is formed, since the

(4) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–182. (b) Earlier studies of the stereochemistry of alkylation of 2-alkyl-4-*tert*-butylcyclohexanones [J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1966)] had suggested that the major products resulted from "equatorial alkylation" at C-2 and that the alkylated products did not follow the nmr solvent shift rule. Subsequent study [K. Dawes, N. J. Turro, and J. M. Conia, *Tetrahedron Lett.*, **No. 18**, 1377 (1971)] has established that the original stereochemical assignments were reversed and, in agreement with other studies,[2b] the major products resulted from axial alkylation at C-2 and all products obey the expected nmr solvent shift rule.

(5) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, to be published.

(6) A similar deformation of a carbon–carbon double bond has been suggested to minimize the energy of strained olefins: N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972). An example of this deformation is provided by an X-ray structure determination for 2,3-bis-(*cis*-4-chloro-1-methylcyclohexyl)-*trans*-2-butene: D. Mootz, *Acta Crystallogr., Sect. B*, **24**, 839 (1968). With polar α substituents (CN, CO_2CH_3), the suggested deformation could result in part from electrostatic rather than steric repulsion.

two substituents R and O^-M^+ must move past one another. This problem does not arise in "axial alkylation." Thus, we believe that the suggested deformation of the initial metal enolate can both account for the stereochemical differences observed in the alkylation when the α substituent (R in structure **1**) is changed from hydrogen to an alkyl group and account for apparent increases in the tendency to obtain axial alkylation when bulky substituents (which would increase the enolate deformation) are present in the pseudoequatorial positions at C-3[2f] and C-6.[7]

Experimental Section[8]

4-*tert*-Butyl-1-methylcyclohexene (6).—To a cold (−10°) solution of 0.94 mol of MeLi in 611 ml of Et_2O was added, dropwise and with stirring over 2 hr, 117.7 g (0.767 mol) of 4-*tert*-butylcyclohexanone in 120 ml of Et_2O. The reaction solution, maintained at −10 to +10° throughout the addition, was stirred for an additional 10 min at 5–10° and then partitioned between Et_2O and aqueous NH_4Cl. The Et_2O solution was washed successively with aqueous 1 *M* HCl and with aqueous NaCl and then dried and concentrated to leave the crude mixture of epimeric alcohols **5** as a white solid containing (glpc, silicone fluid 710 on Chromosorb P) the alcohols **5** (retention times 12.2 and 16.2 min) and a small amount of unchanged 4-*tert*-butylcyclohexanone (18.4 min). A solution of this solid and 2.55 g of *p*-toluenesulfonic acid in 1.1 l. of PhH was refluxed with continuous removal of H_2O for 64 hr at which time analysis (glpc) of an aliquot indicated that dehydration was essentially complete. The resulting PhH solution was washed with aqueous $NaHCO_3$, stirred with saturated aqueous $NaHSO_3$ for 2.5 hr, and then washed with aqueous NaCl, dried, and concentrated. Distillation separated 95.3 g (82%) of the olefin **6**, bp 71–72° (9 mm), $n^{25}D$ 1.4588 [lit. bp 74–75 (11 mm),[9] $n^{25}D$ 1.4578[10]], as a pale yellow liquid which contained (glpc, silicone fluid 710 on Chromosorb P) the olefin **6** (retention time 5.8 min) accompanied by traces of the starting ketone (17.7 min). A pure sample of this olefin **6** was obtained by collection (glpc): nmr (CCl_4) δ 5.32 (1 H, m, vinyl CH), 1.0–2.2 (10 H, m, aliphatic CH), and 0.85 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity), 152 (M^+, 46), 96 (75), 95 (53), 81 (95), 79 (34), 69 (45), 68 (83), 67 (80), 57 (84), 55 (46), 41 (100), and 39 (34).

5-*tert*-Butyl-2-methylcyclohexanone (4).—To a solution of 95.02 g (0.625 mol) of the olefin **6** in 300 ml of Et_2O, maintained at 15 to 34°, was added, dropwise and with stirring, 282 ml of a tetrahydrofuran solution containing 0.377 mol of BH_3. The resulting white slurry was stirred for 1 hr and then 100 ml of H_2O was added followed by the dropwise addition (during 35 min) of a solution of 137.5 g (0.460 mol) of $Na_2Cr_2O_7$ and 103 ml of concentrated H_2SO_4 in 495 ml of H_2O. The resulting mixture was refluxed with stirring for 1.5 hr and then partitioned between H_2O and Et_2O. The Et_2O solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. Distillation separated 66.0 g (63%) of a mixture of the epimeric ketones **4** [glpc, 1,2,3-tris(β-cyanoethoxy)propane on Chromosorb P, retention times 28.2 (major epimer **4b**) and 30.0 min (minor epimer **4a**)]: bp 99–105° (10 mm); $n^{25}D$ 1.4562 [lit.[10] bp 42–46° (0.3 mm), $n^{25}D$ 1.4557]; ir (CCl_4), 1711 cm^{-1} (C=O); nmr (C_6D_6) δ 0.8–2.5 (11 H, m, aliphatic CH) and 0.72 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity), 168 (M^+, 17), 112 (57), 111 (39), 83 (31), 57 (100), 55 (66), and 41 (74).

Preparation of the Enol Acetate 7.—A mixture of 18.32 g (0.109 mol) of the ketone **4**, 59.4 g (0.582 mol) of Ac_2O, 0.07 ml of aqueous 70% $HClO_4$, and 131 ml of CCl_4 was stirred at 25° for 3 hr and then stirred with 100 ml of pentane and 100 ml of cold (0–5°) aqueous $NaHCO_3$ for 2.5 hr. Additional solid $NaHCO_3$ was added during this period to complete the neutralization of the HOAc. The pentane layer and pentane extract of the aqueous phase were dried and concentrated. Distillation of the residual liquid separated 20.49 g (89%) of the crude enol acetate **7**, bp 70–76° (0.1 mm), $n^{25}D$ 1.4609, containing (glpc, silicone fluid QF_1 on Chromosorb P) the desired enol acetate **7** (*ca.* 92%, retention time 9.4 min) and the isomeric enol acetates **8** (*ca.* 8%, 7.2 and 7.6 min). Fractional distillation through a 60-cm spinning band column afforded the pure (glpc) enol acetate **7** as a colorless liquid: $n^{25}D$ 1.4629; ir (CCl_4), 1752 (enol ester C=O) and 1711 cm^{-1} (enol C=C); uv (95% EtOH), end absorption with ϵ 1410 at 210 mμ; nmr (CCl_4), δ 2.02 (3 H, s, CH_3CO), 1.0–2.2 (7 H, m, aliphatic CH), 1.47 (3 H, broad, vinyl CH_3), and 0.87 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity), 210 (M^+, 10), 169 (32), 168 (100), 153 (50), 111 (61), 84 (49), 69 (30), 57 (41), 43 (41), and 41 (34).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.27; H, 10.59.

Preparation of the Enol Acetates 8.—To a cold (−20 to −40°) solution of $(Me_2CH)_2NLi$ [from 94.2 mmol of MeLi and 9.51 g (94.0 mmol) of $(Me_2CH)_2NH$] in 200 ml of 1,2-dimethoxyethane was added, dropwise and with stirring, 15.03 g (89.3 mmol) of the ketones **4**. The resulting suspension was warmed to 20° and added to a mixture of 140.6 g (1.37 mol) of Ac_2O and 200 ml of pentane. The resulting mixture was partitioned between pentane and aqueous $NaHCO_3$ (excess solid $NaHCO_3$ added), and the pentane solution was washed successively with cold (5°), aqueous 0.5 *M* HCl and aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, distillation of the residue separated 14.66 g (78%) of the crude enol acetates **8**, bp 60–68° (0.5 mm), $n^{25}D$ 1.4580, contaminated (nmr and glpc) with several other components. Successive fractional distillations through a 60- and a 24-cm spinning band column separated a colorless liquid, bp 55–58° (0.5 mm), $n^{25}D$ 1.4600, which contained [glpc, 1,2,3-tris(β-cyanoethoxyl)propane on Chromosorb P] the epimeric enol acetates **8** (*ca.* 95%, retention times 22.5 and 24.6 min) accompanied by the enol acetate **7** (*ca.* 5%, 30.2 min): ir (CCl_4), 1752 (enol ester C=O), and 1680 cm^{-1} (enol C=C); nmr (CCl_4) δ 5.25 (1 H, m, vinyl CH) and 2.08 (3 H, s, CH_3CO), and two partially resolved singlets at δ 0.89 and 0.90 (9 H, *t*-Bu) superimposed on a multiplet at 0.8–2.0 (9 H, aliphatic CH); mass spectrum *m/e* (rel intensity) 210 (M^+, 1), 153 (38), 112 (23), 111 (100), 57 (20), 43 (42), and 41 (20).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.14; H, 10.51.

Reaction of the Ketone 4 with Methyl Acrylate.—To a solution of 6.09 g (36.2 mmol) of the ketones **4** and 0.4 g (4 mmol) of *t*-BuOK in 33 ml of *t*-BuOH was added, dropwise and with stirring and cooling, 3.46 g (40.2 mmol) of methyl acrylate while the reaction mixture was kept at 23–30°. The resulting solution was stirred at 25–28° for 2 hr and then acidified with 25 ml of aqueous 2 *M* HOAc, concentrated, and partitioned between Et_2O and aqueous $NaHCO_3$. After the Et_2O solution had been dried and concentrated, a portion of the residual pale yellow liquid (8.275 g) was mixed with an internal standard (*o*-terphenyl, retention time 6.6 min), and subjected to glpc analysis (silicone fluid QF_1 on Chromosorb P). The calculated yields were 58% of keto ester **14** (retention time 14.8 min) and 9% of keto ester **15** (retention time 18.4 min). A 2.793-g portion of the crude product was fractionally distilled with a 24-cm spinning band column to separate 1.604 g (48%) of fractions, bp 92–99° (0.2 mm), containing (glpc) mixtures of the keto esters **14** and **15** from which pure samples were collected (glpc).

The high-boiling liquid residue remaining after distillation of the keto esters **14** and **15** is believed to be dialkylated material. This crude material exhibits a single major glpc peak (60-cm silicone rubber on Chromosorb P) with ir absorption (CCl_4) at 1740 (ester C=O) and 1695 cm^{-1} (C=O) and prominent high-mass peaks in the mass spectrum at *m/e* 283, 277, and 251.

The major product, keto ester **14**, was obtained as a colorless liquid: $n^{25}D$ 1.4690; ir (CCl_4) 1740 (ester C=O) and 1705 cm^{-1} (C=O); uv $\lambda_{max}^{95\% EtOH}$ 290 mμ (ϵ 40); nmr (CCl_4) δ 3.58 (3 H, s,

(7) An example of the effect of substituents at C-6 is provided by R. E. Ireland, P. S. Grand, R. E. Dickerson, J. Bordner, and D. R. Rydjeski, *J. Org. Chem.*, **35**, 570 (1970).

(8) 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 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with 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 values (ppm) 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.

(9) B. Cross and G. Whitham, *J. Chem. Soc.*, 3892 (1960).

(10) N. LeBel and G. Ecke, *J. Org. Chem.*, **30**, 4316 (1965).

OCH_3), 1.0–2.5 (7 H, m, aliphatic CH), and 0.90 (12 H, s, CH_3 and *t*-Bu); in benzene-d_6 the singlets are found at δ 3.56 (CH_3O), 0.95 (CH_3), and 0.72 (*t*-Bu) corresponding to a solvent shift, $\delta_{CCl_4} - \delta_{C_6D_6}$, of −3 Hz for the equatorial methyl group;[4] mass spectrum *m/e* (rel intensity) 254 (M^+, 2), 168 (27), 137 (33), 109 (31), 95 (37), 69 (37), 67 (24), 57 (64), 55 (53), 43 (27), and 41 (100).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.54; H, 10.26.

A collected (glpc) sample of the minor product, keto ester **15**, was obtained as a colorless liquid: $n^{25}D$ 1.4713; ir (CCl_4), 1740 (ester C=O) and 1705 cm^{-1} (C=O); uv $\lambda_{max}^{95\% EtOH}$ 290 mμ (ϵ 35); nmr (CCl_4), δ 3.60 (3 H, s, OCH_3), 1.2–2.5 (7 H, m, aliphatic CH), 1.10 (3 H, s, CH_3), and 0.92 (9 H, s, *t*-Bu); in benzene-d_6 the singlets are at δ 3.43 (OCH_3), 0.83 (CH_3), and 0.70 (*t*-Bu) corresponding to a solvent shift, $\delta_{CCl_4} - \delta_{C_6D_6}$, of +16 Hz for the axial methyl group;[4] mass spectrum *m/e* (rel intensity) 254 (M^+, 2), 168 (40), 165 (25), 137 (38), 109 (33), 95 (39), 69 (38), 67 (25), 57 (65), 55 (55), 43 (24), and 41 (100).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.62; H, 10.24.

To demonstrate that keto esters **14** and **15** are not interconverted under the reaction conditions, a solution of 17.8 mg (0.16 mmol) of *t*-BuOK, 305 mg (1.20 mmol) of the keto ester **14**, and 116 mg (1.35 mmol) of methyl acrylate in 1.1 ml of *t*-BuOH was stirred at 25° for 2 hr and then quenched with aqueous 2 *M* HOAc. An Et_2O solution of the crude product was mixed with 121 mg of 1-methylnaphthalene (an internal standard), washed successively with aqueous $NaHCO_3$ and aqueous NaCl, dried, concentrated, and analyzed (glpc). The recovered ketone **14** amounted to 73% and no ketone **15** was detected. A collected (glpc) sample of the ketone **14** was identified with the previously described material by comparison of ir spectra and glpc retention times.

For quantitative studies of the reaction products, the glpc equipment was calibrated with known mixtures of the keto esters **14** (retention time 17.1 min) and **15** (21.5 min), the starting ketones **4** (3.0 min), and the internal standard *o*-terphenyl (7.4 min). A reaction of 1.627 g (9.71 mmol) of the ketones **4** and 115 mg (1.02 mmol) of KOBu-*t* in 6 ml of *t*-BuOH with 285 mg (3.31 mmol) of methyl acrylate at 25–31° was quenched after 57 sec in aqueous 1 *M* NH_4Cl. The organic product was extracted with Et_2O, mixed with an internal standard and analyzed (glpc). The calculated yields (based on methyl acrylate) were 58% of keto ester **14** and 9% keto ester **15**, and no polyalkylated product was detected (glpc). In a comparable reaction from which aliquots were removed at regular intervals from a reaction time of 45 sec to 19.2 hr, the composition of the alkylated product was within the range 82–86% of keto ester **14** and 14–18% of keto ester **15**, and no polyalkylated material was detected.

Reaction of the Lithium Enolate 9 with Methyl Iodide and Trideuteriomethyl Iodide.—A solution of the enolate **9** was prepared by the addition, dropwise and with stirring, of 1.485 g (7.07 mmol) of the enol acetate **7** to a cold (5–11°) solution of 15 mmol of MeLi in 15 ml of DME containing several milligrams of 2,2′-bipyridyl as an indicator to establish the presence of excess MeLi. After the resulting red solution had been treated with 6.26 g (44.2 mmol) of CH_3I, it was stirred for 4 min (during which time the temperature rose to 25° and separation of a white solid began after *ca.* 1 min) and then partitioned between pentane and aqueous NH_4Cl. The organic solution was washed with aqueous NaCl, dried, concentrated, and analyzed (glpc, TCEP on Chromosorb P) employing *n*-hexadecane as an internal standard and glpc equipment calibrated with known mixtures. The crude product contained *n*-hexadecane (4.4 min), trimethyl ketone **11** (36% yield, 12.0 min), dimethyl ketone **10** (48% yield, 13.7 min), and starting ketone **4** (<1%, 15.7 min). In a subsequent comparable run, performed at 9–15°, aliquots were removed, quenched, and analyzed at regular intervals. The following yields were obtained after the times indicated: 15 sec, <1% **11**, 73% **10**, and 4% **4**; 44 sec, 11% **11**, 62% **10**, and 3% **4**; 121 sec, 23% **11**, 59% **10**, and <1% **4**. Authentic samples of the ketones **10** and **11** were collected by glpc (Apiezon L on Chromosorb P).

The dimethyl ketone **10** was obtained as a colorless liquid: $n^{25}D$ 1.4567; ir (CCl_4) 1705 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity), 182 (M^+, 25), 139 (79), 126 (46), 125 (80), 123 (70), 111 (63), 97 (100), 83 (58), 57 (35), and 55 (42); nmr (CCl_4) δ 1.2–2.4 (7 H, m, aliphatic CH), 1.09 (3 H, s, axial CH_3), 0.97 (3 H, s, equatorial CH_3), and 0.90 (9 H, s, *t*-Bu). In C_6D_6 solution the high-field singlets are found at δ 1.12 (3 H, s, equatorial CH_3, shifted downfield 9 Hz), 0.89 (3 H, s, axial CH_3, shifted upfield 20 Hz), and 0.70 (9 H, s, *t*-Bu). The assignments of these peaks in the two solvents were established by measuring the nmr spectrum repeatedly as increments of C_6D_6 were added to the CCl_4 solution of the ketone **10**. A sample of the ketone **10** crystallized from pentane solution at Dry Ice temperatures as white plates, mp 32.5–34.5° (lit.[11] mp 33–35°).

A sample of the ketone **11** was obtained as a colorless liquid: $n^{25}D$ 1.4589; ir (CCl_4), 1693 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity), 196 (M^+, 8), 139 (38), 138 (44), 125 (32), 111 (100), 97 (37), 69 (42), 57 (45), 56 (43), 55 (53), and 41 (65); nmr (CCl_4) δ 1.2–2.4 (6 H, m, aliphatic CH), 1.20 (3 H, d, J = 7.2 Hz, CH_3 at C-6), 1.08 (3 H, s, CH_3 at C-2), 1.05 (3 H, s, CH_3 at C-2), and 0.91 (9 H, s, *t*-Bu). In C_6D_6 solution the high-field peaks are found at δ 1.14 (3 H, d, J = 7.2 Hz, CH_3 at C-6 shifted upfield 4 Hz),[12] 1.10 (3 H, s, CH_3 at C-2), 1.02 (3 H, s, CH_3 at C-2), and 0.75 (9 H, s, *t*-Bu).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.36; H, 12.30.

The alkylation reaction was repeated with the enolate **9**, prepared from 7.6 mmol of MeLi and 774 mg (3.68 mmol) of the enol acetate **7** in 7.5 ml of DME, and 3.29 g (22.7 mmol) of CD_3I. After a reaction period of 30 sec at 5–10°, the reaction mixture was partitioned between aqueous NH_4Cl and pentane. After the organic solution had been dried, concentrated, and mixed with an internal standard, glpc analysis indicated the product yields to be 68% of monoalkylated ketones **12** and **13**, 17% of dialkylated ketone (the d_6 analog of **11**), and 4% of the starting ketones **4**. A collected (glpc) sample of the monoalkylated ketones **12** and **13** was subjected to nmr analysis in both CCl_4 and C_6D_6 solution to measure the areas under the axial and equatorial C-2 methyl peaks. The composition was 83% of the axial deuteriomethyl ketone **12** and 17% of the equatorial deuteriomethyl ketone **13**. The mass spectrum of the mixture of ketones **12** and **13** indicated the presence of only d_3 species: *m/e* (rel intensity) 185 (M^+, 12), 141 (95), 128 (43), 100 (55), 69 (64), 59 (89), 58 (67), 57 (98), 56 (56), 55 (87), 53 (59), 44 (45), 43 (61), 42 (57), 41 (100), and 39 (51).

The same alkylation reaction was repeated with a reaction time of 11.7 hr at −64°. The cold reaction mixture was quenched in a MeOH–HOAc mixture, and the resulting mixture was neutralized with aqueous $NaHCO_3$ and then extracted with pentane. The crude product contained (glpc) the monoalkylated ketones **12** and **13** (35% yield) and the unalkylated ketones **4** (38% recovery). A collected (glpc) sample of the monoalkylated ketones was subjected to the previously described nmr analysis and found to contain 90% of the axial deuteriomethyl ketone **12** and 10% of the equatorial isomer **13**.

Registry No.—**4a**, 5951-22-4; **4b**, 5937-40-6; **6**, 3419-74-7; **7**, 37786-83-7; *cis*-**8**, 37818-69-2; *trans*-**8**, 37786-84-8; **9**, 37786-85-9; **10**, 17359-15-8; **11**, 37786-87-1; **12**, 37786-88-2; **13**, 37786-89-3; **14**, 37818-70-5; **15**, 37786-90-6; 4-*tert*-butylcyclohexanone, 98-53-3.

(11) J. Sicher and M. Tichy, *Collect. Czech. Chem. Commun.*, **32**, 3687 (1967).

(12) Because of the small magnitude of the upfield shift in a sterically congested molecule, we regard the configuration as uncertain.

Conformational Analysis by Nuclear Magnetic Resonance Spectroscopy. N′ Derivatives of *N*-Aminocamphorimides

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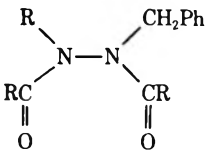
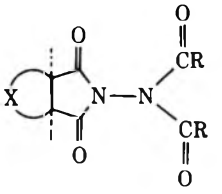
A series of N′ derivatives of *N*-aminocamphorimide has been prepared and characterized by ir and nmr spectroscopy. The nmr spectra studied at 44.5° provide evidence for the preferred conformations due to restricted rotation about the N–N′ or the N′–CO bond. The nonplanar "cage moiety," *i.e.*, the camphorimidyl system, has been used for the conformational study of the substituents at the exocyclic nitrogen atom. The spectra of *N*′-monoacyl derivatives which are characterized by the shielding constants of the β-methyl group of the "cage moiety" show restricted rotation about the N′–CO bond. N′-Disubstituted derivatives strongly prefer noneclipsed conformations due to restricted rotation about the N–N′ bond. Barriers to free energy of activation, $\Delta G^{\pm}$, have been determined by temperature-dependent spectral measurements.

It can be shown from the available experimental details that the conformations adopted by substituted hydrazines depend upon the nature of the substituents.[1-4] Preferred conformations of certain acyclic *N*,*N*′-diacylhydrazines (I)[3] and other related systems[1,2] have been reported to be due to restricted rotation about the N–N and N–CO bonds. Similar observations of restricted rotation about the N–N bond have been reported for tetraacylhydrazines (II).[4] The



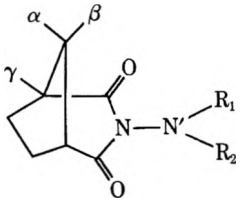
I



X represents a chain of four carbon atoms

II

existence of nonplanar ground states has been proposed in all these systems. The present study reports evidence for the conformations adopted by N′ substituents in a series of *N*-aminocamphorimide derivatives (IIIa–IIIm). Nmr spectra of some of the repre-



IIIa, $R_1 = R_2 = H$
b, $R_1 = COCH_3$; $R_2 = H$
c, $R_1 = COPh$; $R_2 = H$
d, $R_1 = m\text{-}COC_6H_4CH_3$; $R_2 = H$
e, $R_1 = CO_2C_2H_5$; $R_2 = H$
f, $R_1 = COC_2H_5$; $R_2 = H$
g, $R_1 = COCF_3$; $R_2 = H$
h, $R_1 = Ph$; $R_2 = H$
i, $R_1 = 2,4\text{-}C_6H_3(NO_2)_2$; $R_2 = H$
j, $R_1 = R_2 = COCH_3$
k, $R_1 = Ph$; $R_2 = COCH_3$
l, $R_1 = R_2 = CH_2Ph$
m, *N*,*N*′-Biscamphorimidyl

sentative derivatives recorded at 44.5° are discussed on the basis of slow rotation about the N′–CO and N–N′ bonds, the free energies of activation ($\Delta G^{\pm}$) being calculated from the variable-temperature spectra using Eyring's rate equation.[5]

Flautt and Erman,[6] in their studies on the stereochemistry of substituted bornanes with nmr spectroscopy, observed no clear pattern of the shielding constants of the three methyl groups with respect to the stereochemistry of the substituents. Nakagawa, *et al.*,[7] correlated the shielding constants of the three methyl groups of the pinane derivatives and the magnetic anisotropy of the cyclobutane system with the puckered structure. A similar approach in the present system has been made to correlate the shielding constants of the three methyl groups with the conformations of N′ substituents. The shielding constants of the β-methyl of the cage structure are affected by the N′ substituents, whereas those of α- and γ-methyls are not much affected. Chemical shifts of the three methyl groups (α, β, and γ) of the compounds IIIa–IIIm are recorded in Table I.

***N*′-Monoacyl-*N*-aminocamphorimides.**—The three methyl groups of camphorimide and *N*-anilinocamphorimides (IIIh and IIIi) appear as three signals, each of 3 H intensity, in the nmr spectrum (δ 1.00–1.25). On the other hand, monoacylsubstituted compounds (IIIb–IIIf) show a characteristic type of spectra: two sharp signals (each of 4.5 H intensity) around δ 1.00 and 1.25 in $CDCl_3$, accounting for nine protons of the three methyl groups of the camphorimidyl moiety (Figure 1, Table I). This behavior of monoacyl derivatives could not be explained on the basis of accidental overlap of the signals, as has been observed in some camphorimide derivatives. For example, the spectrum of the compound IIIa shows only two sharp signals for the three methyl groups with relative intensities of 3 H and 6 H (Table I). This type of accidental overlap could be removed by taking advantage of "solvent shifts" in aromatic solvents. Thus, in benzene the three methyl groups of IIIa resonate at δ 0.71 (3 H), 0.81 (3 H), and 1.10 (3 H), respectively.

The spectra of the compounds IIIb–IIIf indicate the possibility of two equally populated conformations, both being stable with respect to the nmr time scale. In the two conformations, the β-methyl (in III) point-

(1) J. C. Breliere and J. M. Lehn, *Chem. Commun.*, No. 18, 426 (1965); J. E. Anderson and J. M. Lehn, *J. Amer. Chem. Soc.*, **89**, 81 (1967); *Tetrahedron*, No. 1, **24**, 123, 137 (1968).

(2) B. J. Price, R. V. Smallman, and I. O. Sutherland, *Chem. Commun.*, No. 11, 319 (1966); B. J. Price, I. O. Sutherland, and F. G. Williamson, *Tetrahedron*, No. 10, **22**, 3477 (1966); R. Daniels and K. A. Roseman, *Tetrahedron Lett.*, No. 13, 1335 (1966); M. J. S. Dewar and W. B. Jennings, *J. Amer. Chem. Soc.*, **91**, 3655 (1967).

(3) G. J. Bishop, B. J. Price, and I. O. Sutherland, *Chem. Commun.*, No. 14, 672 (1967).

(4) B. H. Korsch and N. V. Riggs, *Tetrahedron Lett.*, **No. 47**, 5897 (1966).

(5) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); L. W. Reeves in "Advances in Physical Organic Chemistry," Vol. 3, V. Gold, Ed., Academic Press, New York, N. Y., 1965, Chapter 4.

(6) T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963).

(7) N. Nakagawa, S. Saito, A. Suzuki, and M. Itoh, *Tetrahedron Lett.*, **No. 11**, 1003 (1967).

Table I

Chemical Shifts of the Three Methyl Groups of N′ Derivatives of *N*-Aminocamphorimide (with Proton Count in Parentheses) in $CDCl_3$ at 44.5°

Compd	δ, ppm from internal TMS reference			
Camphorimide	1.00 (3 H)	1.05 (3 H)	1.20 (3 H)	
IIIa	0.98 (6 H)	1.25 (3 H)		
IIIb	1.00 (4.5 H)	1.25 (4.5 H)		
IIIc	1.00 (4.5 H)	1.25 (4.5 H)		
IIId	1.00 (4.5 H)	1.23 (4.5 H)		
IIIe	1.02 (4.5 H)	1.25 (4.5 H)		
IIIf	1.00 (4.5 H)	1.20 (4.5 H)		
IIIg	0.97 (3 H)	1.03 (1.5 H)	1.16 (1.5 H)	1.25 (3 H)
IIIh	1.00 (3 H)	1.05 (3 H)	1.22 (3 H)	
IIIi	1.15 (3 H)	1.18 (3 H)	1.31 (3 H)	
IIIj	1.05 (3 H)	1.30 (6 H)		
IIIk	0.80 (1.5 H)	0.99 (3 H)	1.23 (3 H)	1.43 (1.5 H)
IIIl	0.70 (3 H)	0.78 (3 H)	1.06 (3 H)	
IIIm	1.01 (6 H)	1.23 (6 H)	1.31 (6 H)	

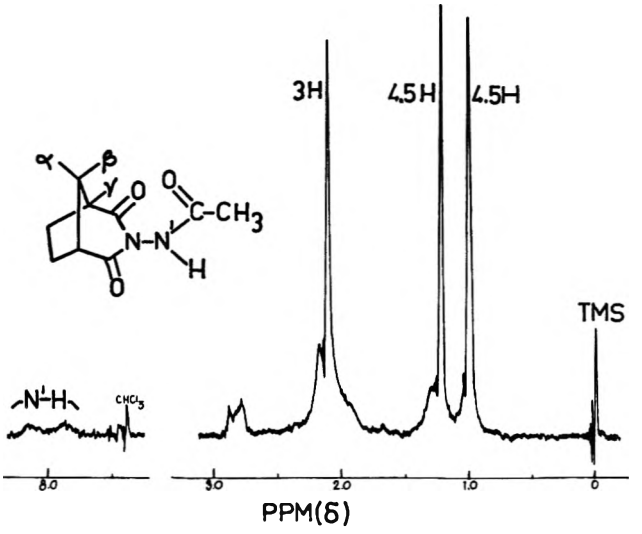


Figure 1.—60-MHz nmr spectrum of *N*′-acetyl-*N*-aminocamphorimide (IIIb) in $CDCl_3$ at 44.5°.

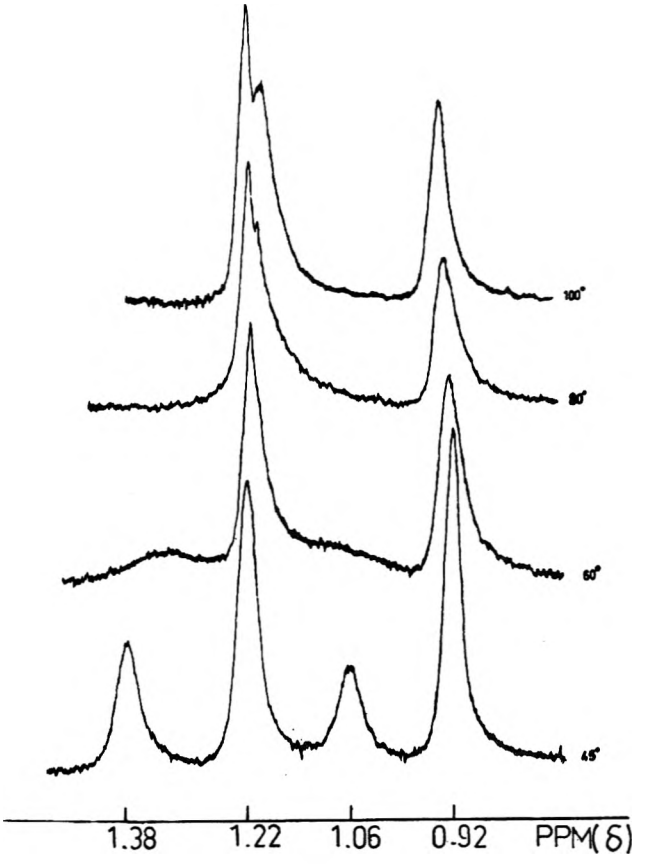


Figure 2.—Spectra of methyl signals of *N*′-acetyl-*N*-aminocamphorimide (IIIb) in nitrobenzene at different temperatures.

ing toward the N–N′ bond could acquire two different magnetic environments, more or less like those of α- and γ-methyls. In consequence, the β-methyl resonance distributes itself between those of α- and γ-methyls, giving rise to two singlets of equal intensity. The N′H resonance appearing as a broad doublet of equal intensity also supports the possibility of two conformations (Figure 1, Table II). This is further evidenced by the appearance of four signals of relative intensities 1.5:3:1.5:3 (Figure 2) for the three methyl groups when the spectra of these compounds are recorded in aromatic solvents. A more pronounced effect on the β-methyl is seen when the substituent is $COCF_3$ (compound IIIg) where it appears as two singlets, each of 1.5 H intensity even in $CDCl_3$.

The possibility of two conformations due to intramolecular hydrogen bonding[8] between N′–H and one of the imidyl carbonyls is excluded because such conformations would not allow the β-methyl to experience significantly different environments. Moreover, on this basis, other monosubstituted derivatives, *e.g.*, IIIh and IIIi, should also be expected to give similar observations but they show no multiplicity for any of the cage methyls (Table I).

(8) J. P. Chupp and A. J. Speziale, *J. Org. Chem.*, **28**, 2592 (1963).

Molecular models show that the magnetic environment of the β-methyl (syn to the N–N′ bond) would be sensitive toward the rotational changes in the substituents at the exocyclic nitrogen atom. Different conformations could arise due to some hindered internal rotation in the molecule which may be either (i) about the N–N′ bond or (ii) about the N′–CO bond. Two conformations due to restricted rotation about the N–N′ bond would very likely show two signals for the acetyl methyl (in IIIb), because of the nonsymmetric cage structure, which provides different magnetic environment for the acetyl methyl in the different conformations. It is evident from the spectrum of *N*′,*N*′-diacetyl-*N*-aminocamphorimide (IIIj), where two

TABLE II

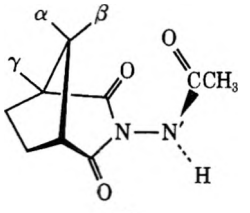
MELTING POINTS, CHARACTERISTIC INFRARED PEAKS, AND NMR OF IIIa–IIIm

No.	Compd	Mp °C	Ir data,[a] cm⁻¹ ν_{max} C=O	Ir data,[a] cm⁻¹ ν_{max} NH	Nmr data,[b] δ Methylene	Methyne	N′ substituents R_1	N′ substituents R_2
	Camphorimide	246–248	1690 (s) 1730 (s)	3080 (m) 3200 (m)	2.08 (4 H, m)	2.7 (1 H, m)		
IIIa	$R_1 = R_2 = H$	154–156	1665 (s) 1725 (m)	3240 (m) 3320 (m)	1.99 (4 H, m)	2.82 (1 H, m)	4.58 (1 H, s)	4.58 (1 H, s)
IIIb	$R_1 = COCH_3$; $R_2 = H$	82–83	1685 (s) 1695 (m)	3200 (m) 3420 (m) 3540 (m) 1575 (w) 1630 (m)	2.07 (4 H, m)	2.80 (1 H, m)	2.12 (3 H, s)	8.0 (1 H, d) $\Delta\nu$ = 17 Hz
IIIc	R_1 = COPh; $R_2 = H$	172 ± 0.5	1665 (s) 1705 (s) 1755 (m)	3240 (m) 1580 (w) 1600 (m)	2.08 (4 H, m)	2.80 (1 H, m)	7.70 (5 H, m)	8.50 (1 H, d) $\Delta\nu$ = 18 Hz
IIId	$R_1 = m$-$COC_6H_4CH_3$; $R_2 = H$	174–175	1660 (s) 1710 (s) 1755 (m)	3210 (m) 3290 (m) 1585 (m) 1605 (w)	2.13 (4 H, m)	2.83 (1 H, m)	2.36 (3 H, s) 7.65 (4 H, m)	8.75 (1 H, d) $\Delta\nu$ = 17 Hz
IIIe	$R_1 = CO_2C_2H_5$; $R_2 = H$	100 ± 0.5	1695 (s) 1730 (s) 1755 (m)	3300 (m)	2.08 (4 H, m)	2.85 (1 H, m)	1.30 (3 H, t) 4.28 (2 H, q) J = 7.2 Hz	8.48 (1 H, d) $\Delta\nu$ = 14 Hz
IIIf	$R_1 = COC_2H_5$; $R_2 = H$	70 ± 0.5	1700 (s) 1750 (s)	3200 (m) 1610 (w)	2.05 (4 H, m)	2.80 (1 H, m)	1.18 (3 H, t) 2.25 (2 H, q) J = 8 Hz	8.16 (1 H, d) $\Delta\nu$ = 10 Hz
IIIg	$R_1 = COCF_3$; $R_2 = H$	111–112	1660 (s) 1710 (s) 1760 (m)	3230 (w) 3280 (m) 1575 (m)	2.10 (4 H, m)	2.85 (1 H, m)		6.9 (broad signal)
IIIh	R_1 = Ph; $R_2 = H$	117–118	1680 (s) 1735 (m)	3310 (m) 1600 (m)	2.11 (4 H, m)	2.87 (1 H, m)	7.1 (5 H, m)	6.48 (1 H, s)
IIIi	R_1 = 2,4-$C_6H_3(NO_2)_2$; $R_2 = H$	246–248	1705 (s) 1745 (w)	3325 (m) 1600 (m) 1620 (m)	2.20 (4 H, m)	3.05 (1 H, m)	6.75 (1 H, d) 8.40 (1 H, q) 9.26 (1 H, d) J = 9, 3 Hz	9.70 (broad)
IIIj	$R_1 = R_2 = COCH_3$	115	1710 (s) 1730 (s) 1760 (m)		2.125 (4 H, m)	2.90 (1 H, m)	2.29 (3 H, s)	2.41 (3 H, s)
IIIk	R_1 = Ph; $R_2 = COCH_3$	106–107	1680 (s) 1700 (s) 1740 (m)		2.02 (4 H, m)	2.83 (1 H, m)	7.50 (5 H, m)	2.03 (3 H, s)
IIIl	$R_1 = R_2 = CH_2Ph$	151–152	1690 (s) 1740 (m)		1.37 (4 H, m)	2.48 (1 H, m)	4.28 (2 H, s)	4.44 (2 H, s)
IIIm	*N,N′*-Biscamphorimidyl	348–350	1700 (s)		2.16 (8 H, m)	2.83 (2 H, m)		

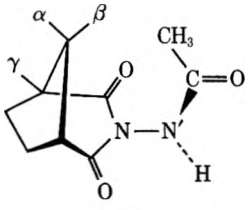
[a] Ir taken in Nujol medium. Abbreviations: s, strong; m, medium; and w, weak. [b] Nmr in $CDCl_3$ (30 mg in 0.3 ml) at 44.5° using TMS internal reference standard. Parentheses include proton count and the multiplicities are abbreviated as s, singlet; d, doublet; t, triplet,; q, quartet; and m, multiplet. Coupling constants and internal chemical shifts in hertz are indicated.

singlets for the acetyl methyl groups ($\Delta\nu$ = 7 Hz in $CDCl_3$) are observed. A singlet observed for the acetyl methyl protons (Figure 1) in IIIb eliminates the possibility of hindered rotation about the N–N′ bond.

A slow rotation about the N′–CO bond provides two different magnetic environments for the β-methyl: (i) deshielded as in IV and (ii) shielded as in V.[3] Under



IV



V

these conditions, the different magnetic environments experienced by the β-methyl in the two conformations IV and V are very nearly like those of the γ- and α-methyls, respectively. In the case of IIIg, the substituent $-COCF_3$ provides slightly different shielding and deshielding effects on the β-methyl, and, as a result, the latter is not allowed to become magnetically equivalent to either of the two methyls (Table I).

With slow rotation about the N′–CO bond, one might expect two different signals for the acetyl methyl protons corresponding to IV and V. However, as the shielding and deshielding effects on the acetyl methyl group due to the β-methyl and the carbonyls of the cage moiety are averaged out by a fast rotation about the N–N′ bond, a sharp singlet is observed for the acetyl methyl in IIIb (Figure 1).

The nmr spectra of these compounds are temperature dependent. The three methyl groups of IIIb appear as a set of four signals in nitrobenzene (Figure 2). The β-methyl signals of practically equal intensity (1.5 H), separated by 19 Hz at 44.5°, coalesce to a singlet at 70° and the three methyl groups appear as three sharp signals at higher temperatures. Free-energy barriers to

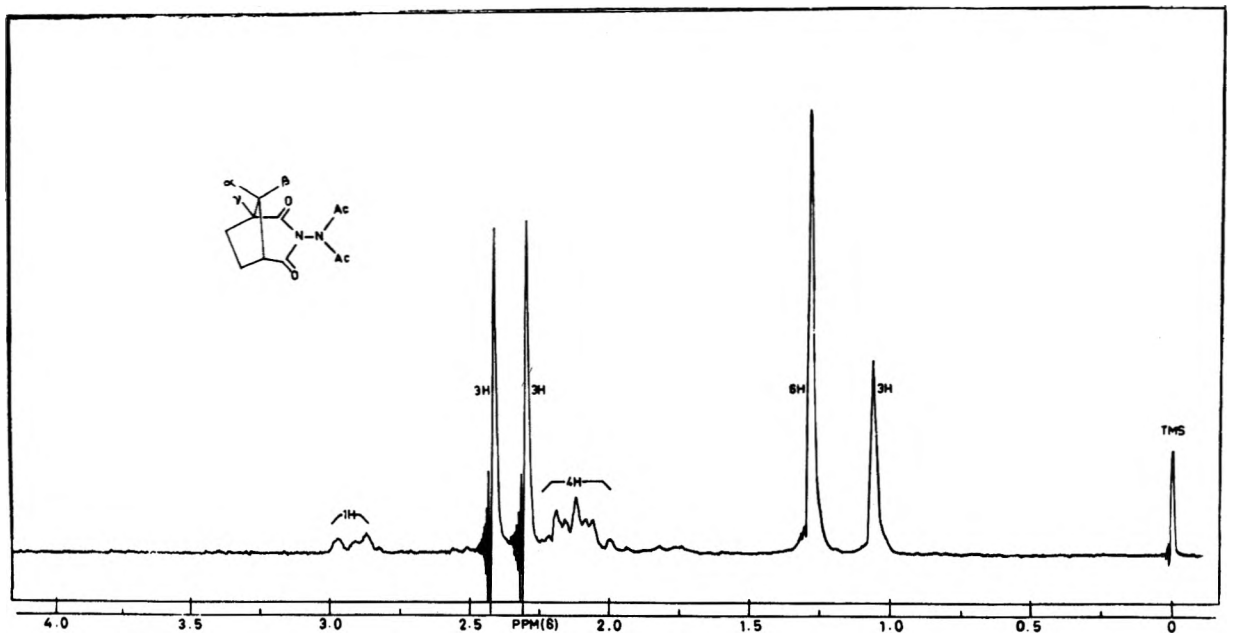


Figure 3.—60-MHz nmr spectrum of *N*′,*N*′-diacetyl-*N*-aminocamphorimide (IIIj) in $CDCl_3$ at 44.5°.

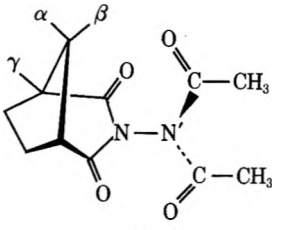
rotation about the N′–CO bond for the compound IIIb, calculated from the temperature-dependent methyl signals, $\Delta G_{70}^{\pm}$, was found to be 17.7 kcal/mol. This is in fair agreement with $\Delta G^{\pm}$ values reported for the N–CO hindered rotation in urethanes[2] and other systems.[1]

***N*′-Disubstituted *N*-Aminocamphorimides.**—The nmr spectra of the disubstituted *N*-aminocamphorimides indicate the possibility of slow rotation about the N–N′ bond. Conformational studies by nmr spectroscopy about the N–N single bonds are complicated by the possibility of partial double bond formation and the inversion at the trivalent nitrogen besides steric and nonbonding repulsive interactions. Tetra- and hexahydropyridazine systems[1] are further complicated by a ring inversion process. The present system is much simplified and provides unambiguous assignments for the spectral changes. The cage moiety, *i.e.*, the bicyclic camphorimidyl system, provides no scope for the ring inversion process. The possibility of inversion at the nitrogen, in the planar imide ring and also at the exocyclic nitrogen when attached to an acyl group, is eliminated. The "cage moiety" with a nonplanar structure provides a suitable basis for the study of the magnetic environment of N′ substituents.

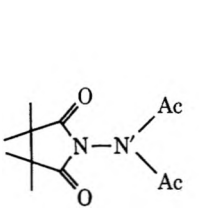
***N*′,*N*′-Diacyl-*N*-aminocamphorimide (IIIj).**—The three methyl groups (α, β, and γ) of the camphorimidyl system appear as two signals of 3 H (δ 1.05) and 6 H (1.30) and the acetyl groups as two singlets, each of 3 H intensity with an internal chemical shift of 7 Hz in $CDCl_3$ (Figure 3). The chemical shift of other protons (methylene and methyne) are recorded in Table II.

Preferred conformations about the N–N′ bond in tetraacylhydrazines[4] of type II have been rationalized through nmr studies in terms of nonbonded repulsions between the acyl substituents in the planar transition state; the two acyl groups attached to the exocyclic nitrogen atom would lie above and below the plane of the succinimidyl ring. X-Ray analysis of *N*,*N*′-bisuccinimidyl[9] shows that the two ring planes make a dihedral angle of 65°. Free-energy barriers to rotation about the N–N′ bonds estimated from the variable-temperature spectral measurements have been reported to be in excess of 18–20 kcal/mol.[3]

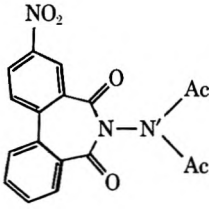
In the compound IIIj, the restricted rotation about the N–N′ bond seems to be responsible for orienting the two acetyl groups, one above and one below the common plane of the imide bridge, leading to a magnetic nonequivalence as represented in VI. Molecular



VI



VII



VIII

models show that in the noncoplanar conformation (VI) the two acetyl groups experience different magnetic environments due to the "cage moiety." In the absence of this property, compounds VII[4] and VIII[10] do not show different signals for the acetyl groups. A fixed noncoplanar conformation VI also allows for the magnetic equivalence of one of the *gem*-methyl groups (β-methyl, syn to the N–N′ bond) with that of the angular γ-methyl.

Variable-temperature spectral measurements of the compound in DMSO-d_6 show that acetyl signals move closer as the temperature is raised accompanied by a broadening of signals at 150° ($\Delta\nu_{30°}$ = 15 Hz and $\Delta\nu_{150°}$

(9) G. S. D. King, *J. Chem. Soc. B*, 1224 (1966).

(10) N. V. Riggs and S. M. Verma, *Aust. J. Chem.*, **23**, 1913 (1970).

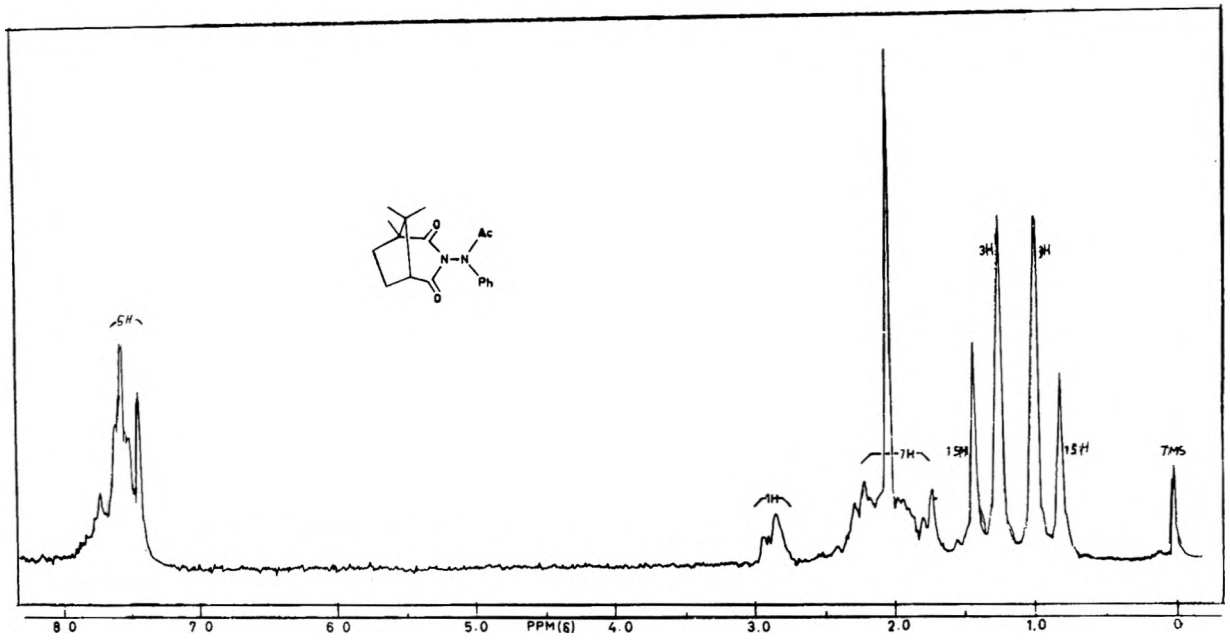
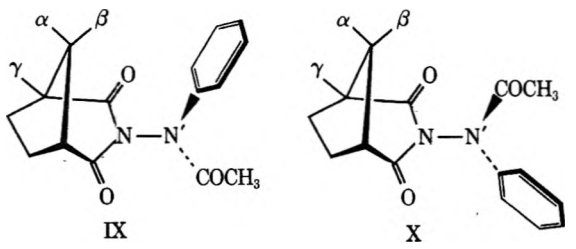


Figure 4.—60-MHz nmr spectrum of N'-acetyl-N-anilinocamphorimide (IIIk) in $CDCl_3$ at 44.5°.

= 8.8 Hz). The exact coalescence temperature, T_c, could not be determined due to the experimental limitations but one would expect that coalescence would not occur for at least another 30°. $\Delta G^{\ddagger}$ calculated on the basis of spectral analysis corresponds to 23.2 and 23.9 kcal/mol, respectively, for T_c = 170 and 180°.

N'-Acetyl-N-anilinocamphorimide (IIIk).—The nmr spectrum of the compound (Figure 4) in $CDCl_3$ shows a sharp singlet (3 H) for the acetyl group and a set of four signals for the three methyl groups of the camphorimidyl along with multiplets for the methylene, methyne, and aromatic protons. Appearance of two signals for the β-methyl, each of 1.5 H (at δ 0.8 and 1.43), provides evidence for the two different conformations of the compound. The shielding constant for the α-methyl (3 H singlet at δ 0.99) is not affected by the substituents at exocyclic nitrogen, while that of γ-methyl shows splitting at δ 1.23 (Figure 4).

As in tetraacyl compounds and IIIj, two different conformations for the compound IIIk are possible due to restricted rotation about the N–N′ bond, which could be represented as IX and X. The shielding and



IX

X

deshielding effects on β-methyl due to phenyl and acetyl groups, respectively, are indicated by the spectrum (Figure 4). In one of the conformations (IX), where the β-methyl is facing the phenyl group, a shielding effect is observed (δ 0.8) as compared to that in camphorimide, δ 1.05 (Table I). In the other preferred conformation (X), the acetyl group lies syn to the β-methyl, causing a deshielding effect (δ 1.43). From the proton intensity measurements of these signals, the two conformations appear in equal population in CDCl solution at 44.5°.

The spectrum of the compound IIIk in nitrobenzene, however, gives a slightly different picture. The two signals for the acetyl methyl group in the two conformations, which accidentally overlapped in $CDCl_3$, are observed with an internal chemical shift of 2 Hz. The proton intensities of the upfield and low-field signals are in the ratio of 3:4. Similarly, the proton intensity ratio of the two signals of the β-methyl is also changed from 1:1 to 3:4. Variable-temperature spectral measurements in nitrobenzene have shown that the signals due to the β-methyl and acetyl methyl, separated by 41 and 2 Hz, respectively, move closer when the temperature is raised, the values being 37 and 1.2 Hz at 100°. Based on the separation of the acetyl signals at 44.5 and 100°, a free energy of activation not less than 21 kcal/mol could be obtained.

N',N'-Dibenzyl-N-aminocamphorimide (IIIl).—In the nmr spectrum of the compound IIIl in $CDCl_3$ (Figure 5), the three methyl signals appear to be shielded by δ 0.2–0.3 as compared to that of camphorimide; in addition the ring methylene protons are also shielded. The four exocyclic benzylic methylene protons appear as two sharp singlets of equal intensity with an internal chemical shift of 9.5 Hz.

The absence of AB quartets for the geminal benzylic protons rules out the possibility of slow inversion at the exocyclic nitrogen atom[11] and that the degree of nonequivalence due to asymmetry of the cage moiety[12] is immeasurably small. Therefore the two singlets for benzylic protons in the nmr spectrum can easily be explained on the basis of a slow rotation about the N–N′ bond. For compounds XI[13] and XII,[14] one should not expect AB quartets for the geminal benzylic protons due to the symmetry properties of the molecules, but two singlets might have been expected. Compounds

(11) M. J. S. Dewar and W. B. Jennings, *Tetrahedron Lett.*, **No. 5**, 339 (1970).
(12) R. E. Lyle and J. J. Thomas, *ibid.*, **No. 11**, 897 (1969).
(13) N. V. Riggs and S. M. Verma, unpublished results.
(14) S. M. Verma and C. Koteswara Rao, *Tetrahedron*, **28**, 5029 (1972).

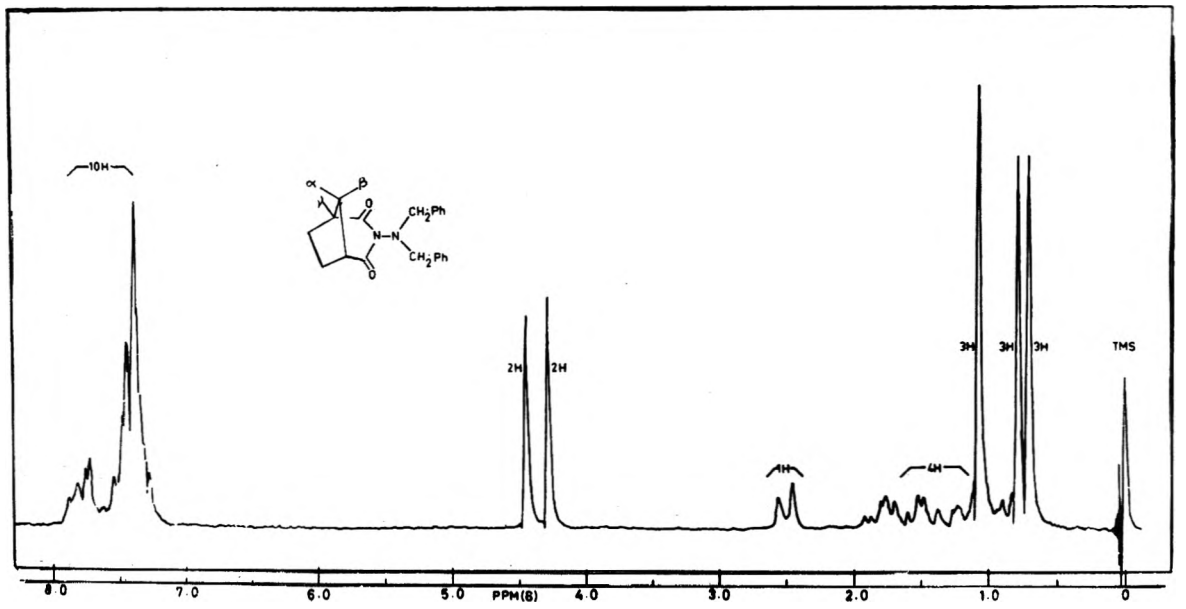
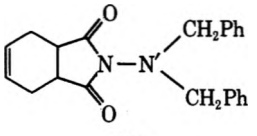
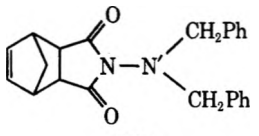


Figure 5.—60-MHz nmr spectrum of *N*′,*N*′-dibenzyl-*N*-aminocamphorimide (IIIl) in $CDCl_3$ at 44.5°.

XI and XII show only sharp singlets of 4 H intensities, which may be attributed to the imidyl system being far



XI



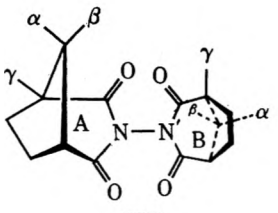
XII

away from the cage moiety. On the other hand, in IIIl, the imidyl system forms a part of the cage moiety leading to steric factors which play a significant role in hindering the N–N′ bond rotation at room temperature.

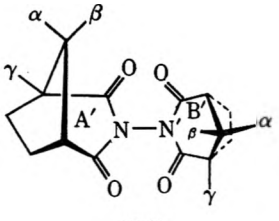
Variable-temperature spectral measurements in nitrobenzene show that the benzylic methylene signals, which are separated by 11.8 Hz at 44.5°, coalesce at 100°. $\Delta G^{\ddagger}$ calculated from $\Delta\nu$ and T_c values is found to be 19.7 kcal/mol, which is in good agreement with the values reported by Fletcher and Sutherland[15] for the *N*,*N*-diacyl-*N*′,*N*′-dibenzylhydrazine system ($\Delta G^{\ddagger}$ = 19.6 ± 0.5 kcal/mol).

***N*,*N*′-Biscamphorimidyl (IIIm).**—The appearance of the nmr spectrum of IIIm in $CDCl_3$ is very much similar to that of camphorimide except that all the protons undergo a slight paramagnetic shift due to the mutual interaction of the rings.

As in other tetraacyl hydrazines, two preferred conformations (XIII and XIV) about the N–N′ bond



XIII



XIV

could be expected. In XIII, all the chemically equivalent protons of the ring A and ring B are magnetically equivalent. Similarly, in XIV, the chemically equivalent protons of ring A′ and ring B′ are magnetically equivalent. Molecular models show that the magnetically equivalent protons of XIII are not equivalent to those in the other conformation, XIV. For example, the angular γ-methyls in XIII are facing the *gem*-methyls of the opposite rings, whereas in XIV the γ-methyls are facing the methylene bridges of the opposite rings. A complicated spectrum, thus, might have been expected, but the observed spectrum is simple (three sharp signals for the six methyls, each of 6 H intensity). This is probably because the difference in magnetic environments of the protons in the two conformations is insufficient to resolve the peaks. In nitrobenzene, however, the most downfield methyl signal, probably that of γ-methyl, appears broad due to "solvent shifts" supporting the above argument.

Studies on N′-substituted *N*-aminocamphorimides have indicated that the N′-monoacyl derivatives tend to show a partial double bond character about the N′–CO bond; $\Delta G^{\ddagger}$ is of the order of 18 kcal/mol. *N*′,*N*′-Diacyl derivatives prefer a noneclipsed conformation about the N–N′ bond and the high torsional barriers could be due to repulsive interactions between the carbonyls at the two nitrogens. In case of bulky substituents, *e.g.*, *N*′,*N*′-dibenzyl derivatives, steric factors could be responsible for the hindered rotation about the N–N′ bond.

Experimental Section

Preparation of Compounds.—Camphorimide,[16] *N*-aminocamphorimide (IIIa),[17] *N*-anilinocamphorimides (IIIh and IIIi),[18] and *N*′-acetyl-*N*-anilinocamphorimide (IIIk)[19] were prepared according to the methods already reported.

***N*′-Monoacyl derivatives (IIIb–IIIg)** were obtained by acylation of the *N*-amino compound (IIIa) with acyl chlorides (in equimolecular proportions) in the presence of pyridine at room temperature. Elemental analyses of the compounds were in good agreement with the calculated values. The melting points of the compounds are recorded in Table II.

(15) J. R. Fletcher and I. O. Sutherland, *J. Chem. Soc. D*, No. 13, 706 (1969).

(16) W. C. Evans, *J. Chem. Soc.*, **97**, 2237 (1910).

(17) V. Alexa and G. Gheorghin, *Bull. Soc. Chim. Fr.*, **49**, 1112 (1931).

(18) Chaplin, *Ber.*, **25**, 2566 (1892); Beilstein's Handbuch Band XXI, 420.

(19) Chaplin, *Ber.*, **25**, 2567 (1892); Beilstein's Handbuch Band XXI, 421.

N',N'-**Diacetyl-*N*-aminocamphorimide** (**IIIj**) was obtained by refluxing *N*-aminocamphorimide (IIIa) with acetic anhydride for about 2 hr, the excess of the latter being removed off under reduced pressure and the product being recrystallized from ethanol, mp 115°.

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.14. Found: C, 59.73; H, 7.49.

N',N'-**Dibenzyl-*N*-aminocamphorimide** (**IIIl**) was obtained by heating *N*-aminocamphorimide with 2 mol of benzyl chloride in the presence of pyridine at 120° for about 2 hr. The excess of benzyl chloride and pyridine were removed off under reduced pressure and the product was recrystallized from ethanol, mp 152°.

Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.59; H, 7.44. Found: C, 76.81; H, 7.62.

N,N'-**Biscamphorimidyl** (**IIIm**) was obtained by heating a mixture of 2 mol of camphoric anhydride and 1 mol of hydrazine hydrate at 240–250° for 3–4 hr. It was recrystallized from hot ethanol, mp 350°.

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.66; H, 7.77; mol. wt, 360. Found: C, 66.27; H, 7.83; mol wt, 362. The molecular weight of the sample was determined by an osmometer (Mechrolab Model 301 A).

The nmr spectra were recorded on a Varian A-60D spectrometer equipped with a variable-temperature controller Model V-6040. Ir spectra were recorded in Nujol on Perkin-Elmer spectrophotometers (Model 621 and 257). Ir and nmr data (excluding chemical shifts of the methyl groups listed in Table I) and the melting points are recorded in Table II.

Registry No.—IIIa, 37710-30-8; IIIb, 37710-31-9; IIIc, 37710-32-0; IIId, 37710-33-1; IIIe, 37710-34-2; IIIf, 37710-35-3; IIIg, 37710-36-4; IIIh, 37710-37-5; IIIi, 37780-36-2; IIIj, 37710-38-6; IIIk, 37710-40-0; IIIl, 37710-39-7; IIIm, 37710-41-1; acetyl chloride, 75-36-5; benzoyl chloride, 98-88-4; *m*-toluoyl chloride, 1711-06-4; ethyl chloroformate, 541-41-3; propionyl chloride, 79-03-8; trifluoroacetyl chloride, 354-32-5; acetic anhydride, 108-24-7; benzyl chloride, 100-44-7; camphoric anhydride, 76-32-4.

Acknowledgment.—Thanks are due to Professor G. B. Singh for his keen interest and to Professor N. V. Riggs, University of New England, Australia, for recording a variable-temperature spectra of the compound IIIj.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Tetramethylenehalonium Ions

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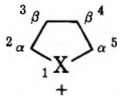
Received August 16, 1972

Carbon-13 nmr chemical shifts for the cyclic five-membered halonium ions and their precursors have been tabulated. Consistent downfield shifts of 30–35 ppm have been observed for the halo-substituted carbon (α carbon) in going from precursor to ion when the α carbon is primary. Addition of a methyl group to the α carbon of a substituted ion causes a 35-ppm downfield shift. The coupling constants for these ions have also been tabulated. A 10–15-Hz increase in the J values of the α carbons of halonium ions, compared to J values for precursors, was observed. These data suggest that highly electronegative heteroatoms give carbonium ion character to the attached carbons.

Since the preparation of the stable five-membered tetramethylenehalonium ions[2] **1** their reactions with various nucleophiles have been studied.[3] In the case of the tetramethylenechloronium ion, rate studies[4] with various carboxylic acids in SO_2 at $-65°$ gave rate constants which were significant as possible measures of the nucleophilicities of the carboxylic acids.



1

We have recently prepared halonuum ions with alkyl or halo substituents at the 3 position of the ring and have studied the direction of ring opening by a variety of nucleophiles. The relative percentages of products formed appeared to be affected by the inductive and steric effect of the ring substituent and the nucleophilicity of the nucleophile.[5]

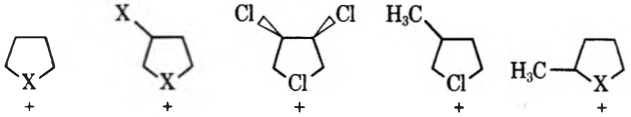
Olah and White have correlated the charge density on various carbons of positively charged species with the ^{13}C chemical shift.[6a] Among the species investigated were the ethylenebromonium (**2**) and tetramethylethylenebromonium (**3**) ions. Reported chemical

2

3

shifts of the ring carbons were 120.8 and 55.2 ppm, respectively, upfield from CS_2.[6a,7] It was shown that ^{13}C chemical shifts offer a possibility of distinguishing open chain, equilibrating, and bridged cationic species.[6]

We now wish to report ^{13}C nmr data (δ_{CS_2} and J_{CH}) for the five-membered halonium ions **4–13** and their



4, X = Cl; **5**, X = Br; **6**, X = I

7, X = Cl; **8**, X = Br

9

10

11, X = Cl; **12**, X = Br; **13**, X = I

precursors (Table I). Our study provides an illustration of the applicability of presently available instru-

(1) Postdoctoral Investigator.
(2) G. A. Olah and P. E. Peterson, *J. Amer. Chem. Soc.*, **90**, 4675 (1968).
(3) P. E. Peterson, P. R. Clifford, and F. J. Slama, *ibid.*, **92**, 2840 (1970).
(4) P. E. Peterson and F. J. Waller, *ibid.*, **94**, 991 (1972).
(5) P. E. Peterson and B. R. Bonazza, *ibid.*, **94**, 5017 (1972).
(6) (a) G. A. Olah and A. M. White, *ibid.*, **91**, 5801 (1969), and references cited therein; (b) G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *ibid.*, **92**, 4627 (1970).
(7) G. A. Olah and R. D. Porter, *ibid.*, **93**, 6877 (1971).

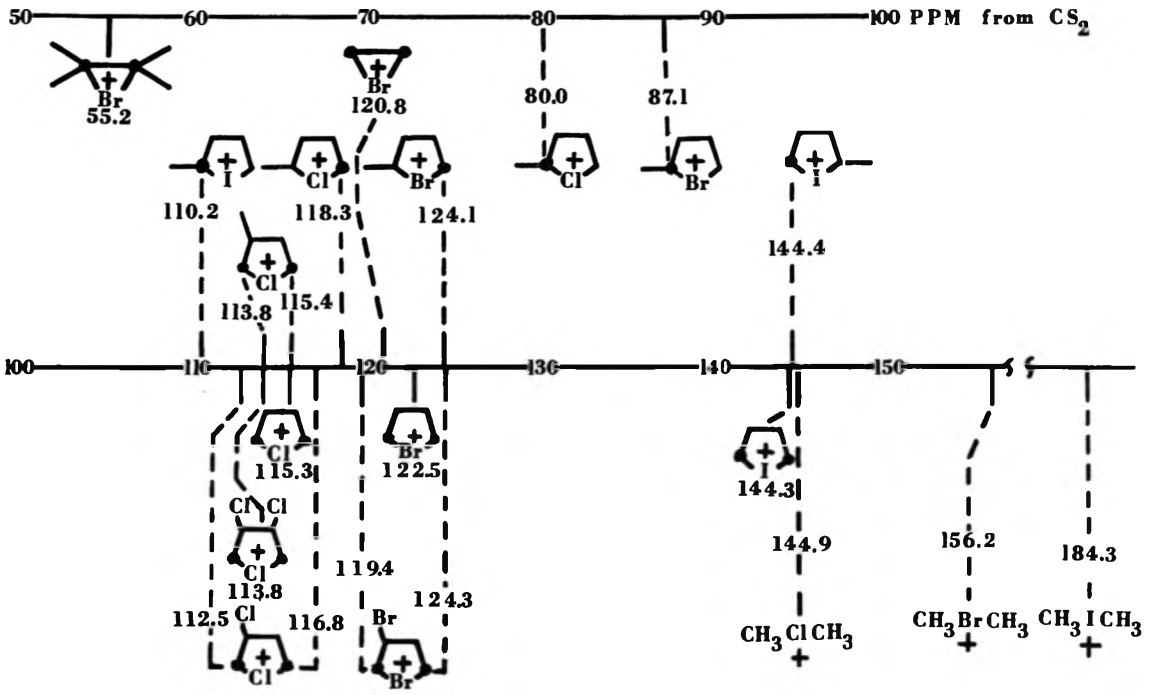


Figure 1.—Carbon-13 chemical shifts of the tetramethylenehalonium ion α carbons relative to 0.8 M CS_2 in SO_2 at $-65°$. Also plotted are Olah's values for the dimethylhalonium, the ethylenebromonium, and the tetramethylethylenebromonium ions.

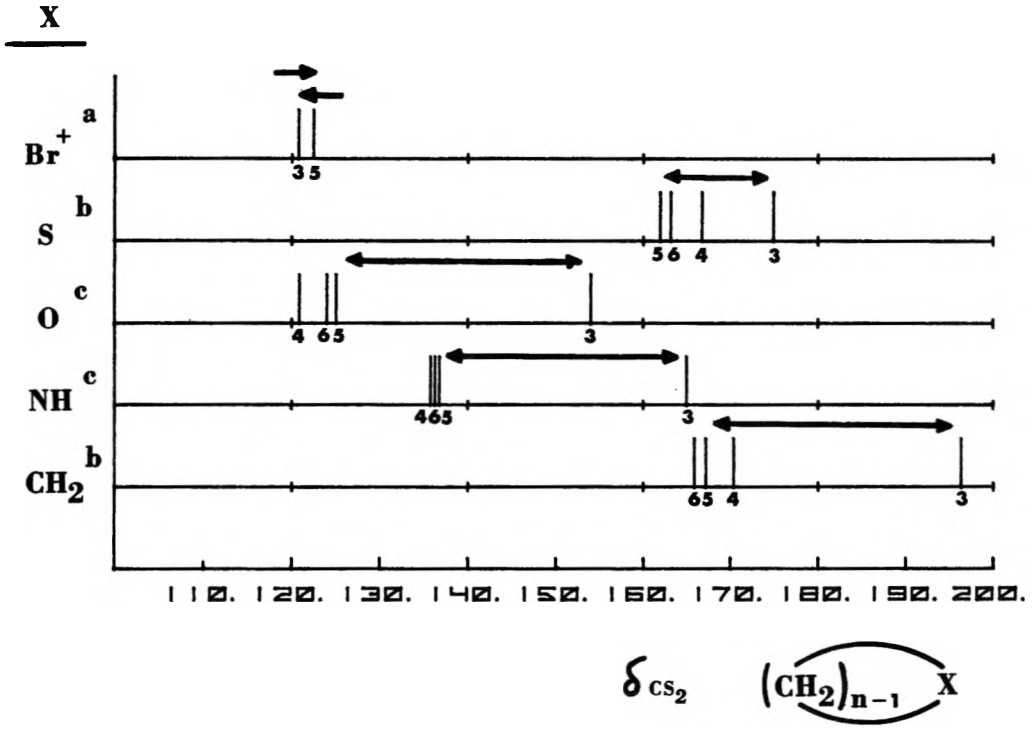


Figure 2.—Carbon-13 chemical shifts of heterocycles and cycloalkanes. For heteroycles the δ value for the heterosubstituted (α) carbon is plotted for the ring size indicated by the number. Arrows indicate the differences in chemical shifts between three- and five-membered rings. (a) Reference 6A and this work. (b) Values obtained in our laboratories. See Experimental Section for values. (c) Reference 12a.

mentation to practical organic problems.[8] The combination of large nmr sample tubes (12-mm spinning) and pulsed Fourier transform mode of operation allowed us to obtain both noise decoupled and coupled spectra from 0.6–0.8 M solutions in 12-mm tubes. Previously, coupling information for ions in SO_2 has been obtained from INDOR experiments in which side bands in the hydrogen spectra arising from coupling to ^{13}C are utilized. Owing to overlapping of hydrogen resonances, many of the results reported here possibly could not have been obtained by the INDOR method.

Chemical Shifts.—A plot of the chemical shifts relative to CS_2 is shown in Figure 1 and further comparisons are given in the plot of Figure 2, to be discussed later. By the use of 3000–5000-Hz sweep widths and centered 5-mm 1,2-dibromo-1,1,2,2-tetrafluoroethane ($C_2F_4Br_2$) lock capillaries the decoupled spectra shown in Figures 3 and 4 could be obtained in

(8) See Experimental Section for description of instrumentation.

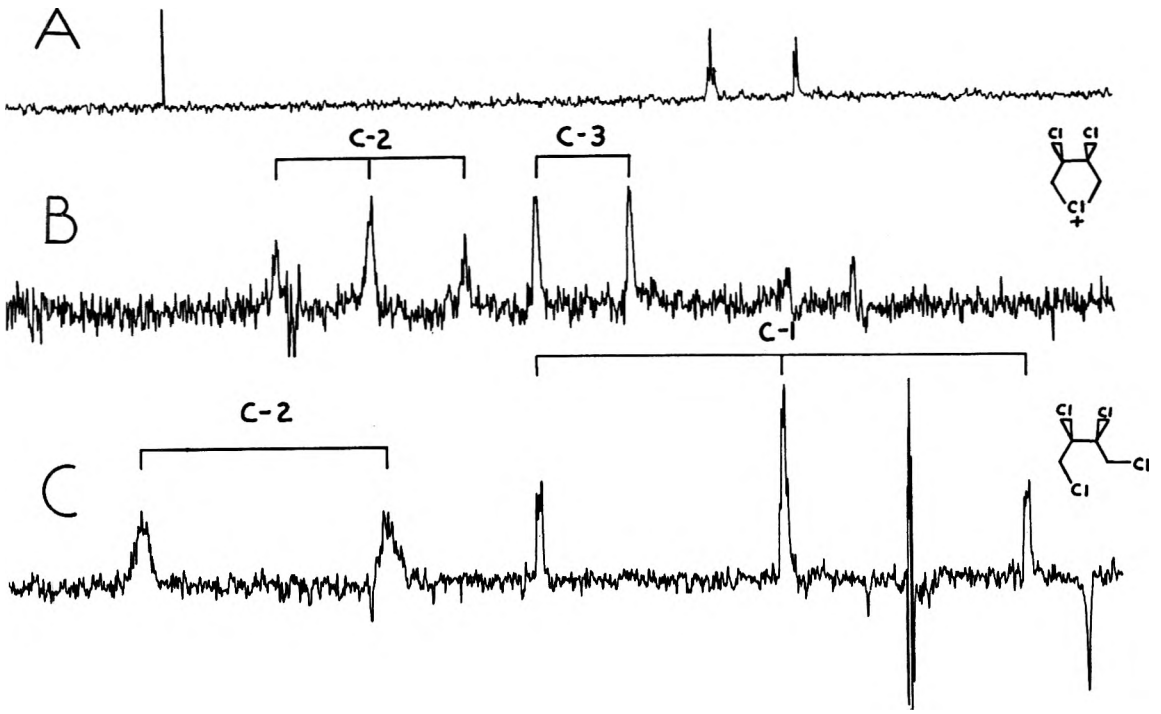


Figure 3.—(A) Off resonance decoupled ^{13}C spectrum of 0.6 *M* **9** in SO_2 at −65°; 5000-Hz sweep width; 238 pulses. (B) Coupled ^{13}C spectrum of 0.6 *M* **9** in SO_2 at −65°; 2000-Hz sweep width; 5400 pulses. (C) Coupled ^{13}C spectrum of 1.5 *M* precursor to ion **9** in CCl_4 at 25°; 700-Hz sweep width; 1300 pulses.

TABLE I

^{13}C NMR DATA FOR THE TETRAMETHYLENEHALONIUM IONS

	C-2		C-3		C-4[c]		C-5[c]		CH_3	
Ion	δ_{CS_2}[a]	J_{CH}[b]	δ_{CS_2}	J_{CH}	δ_{CS_2}	J_{CH}	δ_{CS_2}	J_{CH}	δ_{CS_2}	J_{CH}
4					159.2	137	115.3	165		
					(4.1)	(7)	(31.8)	(14)		
5					157.2	136	122.5	165		
					(4.8)	(7)	(35.0)	(11)		
6					155.0	135	144.3	160		
					(4.3)	(7)	(39.3)	(10)		
7	112.5	167	131.8	164	151.3	140	116.8	167		
	(31.1)	(13)	(1.9)	(12)	(4.6)	(10)	(33.5)	(14)		
8	119.4	167	141.4	166	148.9	138	124.3	168		
	(35.6)	(9)	(−0.9)	(9)	(5.7)	(9)	(35.3)	(13)		
9					128.9	168	113.8	170		
					(4.3)	(12)	(31.5)	(16)		
10	113.8		150.8		153.2		115.4		178.7	
	(27.4)		(9.8)		(4.0)		(33.5)		(−2.6)	
11[d]	80.0		152.2		158.2		118.3		171.1	
12[d]	87.1	165	149.5	135	156.9	137	124.1	165	170.1	132
	(51.0)	(15)	(4.2)	(5)	(5.1)	(8)	(33.0)	(13)	(−3.7)	(3)
13[d,e]	110.2	159	146.0	132	155.4	129	144.4	157	168.9	132

[a] Referenced to 0.8 *M* CS_2 in SO_2 at −55° by adding 78.1 to $\delta_{CF_2BrCF_2Br}$. To reference shifts to pure CS_2 at −65° add 0.5 ppm. To reference shifts to capillary CS_2 −65° add 1.6 ppm. Values in parentheses are $\Delta\delta$ precursor ion. [b] Values in parentheses are ΔJ ion precursor. [c] For symmetrical ions C-4 and C-5 are equivalent to C-3 and C-2, respectively. [d] Assignment of C-3 and C-4 may be reversed. [e] We are indebted to Dr. P. M. Henrichs for the data on ion **13**.

1.5–3 min (200–400 pulses). We referenced our chemical shifts to the easily recognized center peak of the triplet of triplets given by the $C_2F_4Br_2$ lock material (J_{CF} = 313 Hz, J_{CCF} = 39 Hz) contained in an inner concentric tube. The $C_2F_4Br_2$ capillary signal was separately shown to be 78.1 ppm upfield from CS_2 in SO_2 at −55°. Direct use of CS_2 as a reference was inconvenient because its weak intensity was easily confused with frequently encountered spurious singlets.[9]

(9) Singlets may be introduced by the computer or may be "foldovers." See Thomas C. Farrar and Edwin D. Becker, "Pulse and Fourier Transform NMR," Academic Press, New York, N. Y., 1971.

As seen in Figure 1, the chemical shifts of the primary α carbons of the five-membered ions **1** tend to fall in regions which are characteristic of the halogen. The characteristic regions are 112–119 (X = Cl), 119–125 (X = Br), and 144–145 ppm (X = I). Chemical shifts for the halo-substituted carbon atoms of ions are 30–35 ppm downfield from those for dihalide precursors (*cf.* Table I).

Substitution of a methyl group for hydrogen at C-2 in the five-membered halonium ion ring (ions **11**, **12**, and **13**) causes an unusually large downfield shift (~35 ppm) of C-2 relative to the shift of C-2 in the unsub-

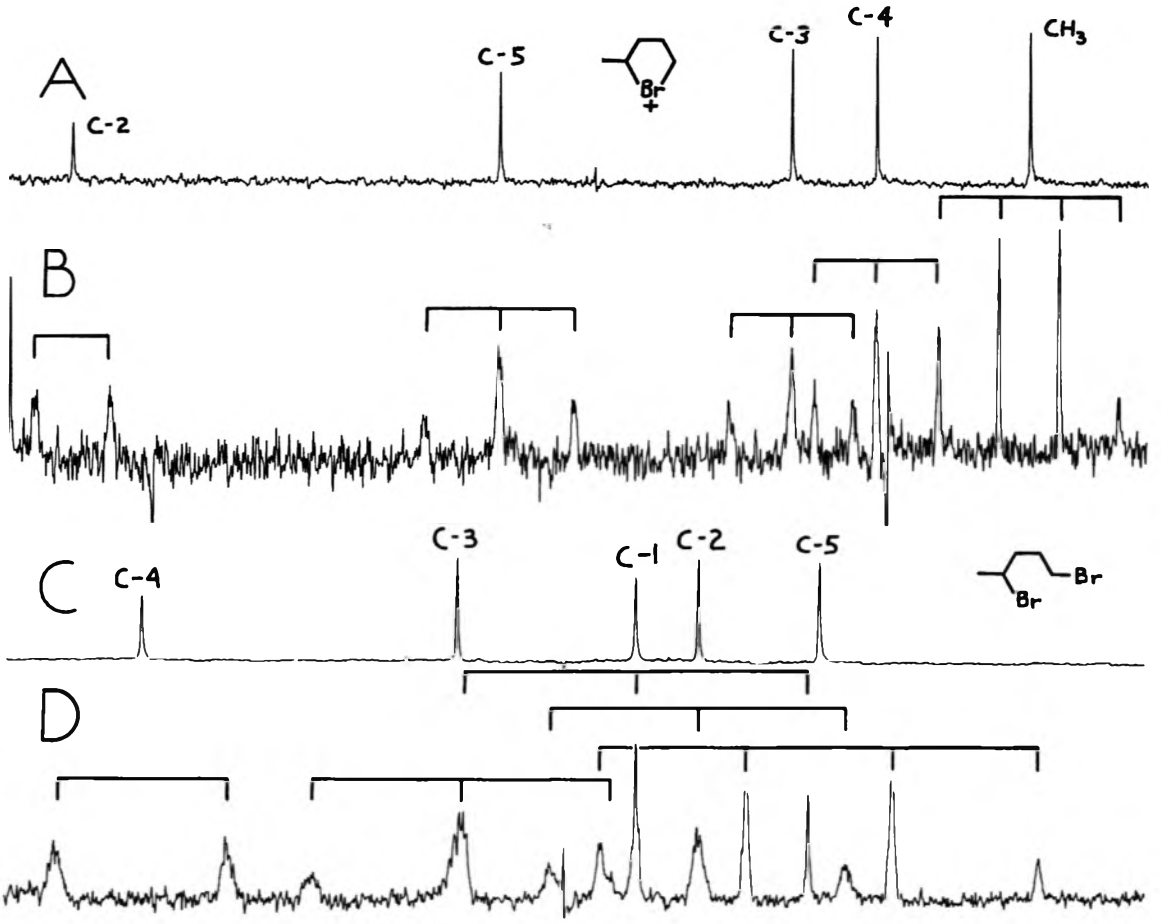


Figure 4.—(A) Noise decoupled (300 pulses) and (B) coupled (5200 pulses) ^{13}C spectra of 0.6 *M* **12** in SO_2 at −65°; both at 2500-Hz sweep widths and identical offsets. (C) Noise decoupled (22 pulses) and (D) coupled (150 pulses) ^{13}C spectra of the precursor to ion **12** neat at 25°.

stituted ions **4**, **5**, and **6**. We shall discuss this effect later. In contrast to the downfield shift of C-2 in methyl-substituted ions **11** and **12**, the primary carbon at C-5 tends to shift upfield slightly relative to the unsubstituted ions **4** and **5** (Figure 1). Substitution of chlorine at C-3 in ion **4** (giving **7**) tends to cause a downfield shift of C-2 with smaller upfield shift at C-5. When an alkyl group is substituted at C-3 (ion **10**) the shifts at C-2 and C-5 are seen to be much smaller but in the same direction as for 3-chlorosubstituted ion **7**. Similar shifts can be seen for halo-substituted ions **8** and **9** (Figure 1).

Dependence of the ^{13}C chemical shift on concentration for ion **4** and its precursor was determined in SO_2 at −65°. The effect of concentration over the range from 0.17 to 0.6 *M* was found to be negligible for both. Also the dependence of the chemical shift of ion **4** on excess SbF_5 was found to be negligible when solutions containing 0.16 *M* **4** prepared from 2:1 and 4:1 molar ratios of SbF_5 to 1,4-dichlorobutane were compared.

Although there does not appear to be any temperature dependence of $\delta_{C_2F_4Br_2}$ for the ion **4** over the range from −65 to −25°, there does seem to be a small dependence for the primary carbons in the precursor, 1,4-dichlorobutane. When $\delta_{C_2F_4Br_2}$ for the primary carbons in 1,4-dichlorobutane was plotted *vs.* temperature a straight line was obtained with a slope of 0.016 ppm/°C corresponding to a small downfield shift with decreasing temperature. A similar dependence of 0.031 ppm/°C was noted for the primary carbons of 1,4-diiodobutane (precursor to ion **6**). The temperature dependence of the spectra of precursors is probably due to conformational changes (C–C rotation) which are not possible for the ion. However, the lock material is in principle subject to temperature effects of conformational origin which would lead to modification of the above discussion.

Coupling Constants.—Owing to the absence of Overhauser enhancement and because of the greater multiplicity of the peaks, determination of coupled spectra (on 0.6–0.8 *M* solutions) required from 30 to 75 min (2000 to 5000 pulses). Coupled spectra for ions **9** and **12** are shown in Figures 3 and 4.

The fluorine lock material used to obtain coupled spectra was trichlorofluoromethane (CCl_3F), chosen because its carbon atom appears to have a long relaxation time, and, thus, its absorption is not seen in the coupled spectrum either directly or as a foldover.[9] The use of 1000–2000-Hz sweep widths was necessary to obtain coupling constants to the accuracy at ±2 Hz measured directly from the spectrum. Unresolved longer range ^{13}C–H coupling and concomitant dependence of the peak midpoint upon the phase control settings limit the accuracy of measurement.

Table I shows that J_{CH} values for C-2 and C-5 in the five-membered halonium ions range from 160 to 170 Hz, whereas the methylene carbons β to positive halogen (C-3 and C-4) have lower values, 130–140 Hz. This difference in J_{CH} between the two types of carbon atoms aided in the assignment of their resonances when

peak multiplicities were the same. The coupling constants for the C-2 and C-5 carbons in the five-membered ions are of the same magnitude as those obtained by Olah and DeMember for the dimethylhalonium ions.[10] The larger coupling constant observed for the ethylenebromonium ion (J_{CH} = 185 Hz) has been attributed to the effect of the three-membered ring.[6a]

Discussion

The factors which affect ^{13}C chemical shifts and coupling constants are not fully understood.[11] However, we shall discuss our results based on available empirical generalizations as follows, despite the well-recognized limitations of the approach. (1) Downfield shifts and increased J ^{13}C–H coupling constants occur as the charge on ^{13}C becomes more positive. (2) Downfield shifts and increased J ^{13}C–H coupling constants occur as the hybridization on carbon changes from p to sp^3 to sp^2 to sp. Whether electronegative substituents exert their effect directly or by changing the hybridization on carbon (with interorbital angles not equal to bond angles) is debatable.[11] (3) An effect is present which leads to upfield ^{13}C shifts as the atomic number of the element attached to carbon increases in a column of the periodic table. For example, δ ^{13}C for C–I is upfield from that for C–H, that of C–Br is near to that of C–H, and that of C–Cl is downfield from that of C–H.

Carbon-13 chemical shifts for five-membered ring bromonium ions are best interpreted by comparison with values of chemical shifts of cyclic alkanes, amines, ethers, and sulfides, along with the available[6a] value for the three-membered ethylenebromonium ion. When the shifts for carbon attached to the heteroatom in these compounds[12] are plotted, the values for the five-membered rings, compared to those for the three-membered rings, form a suggestive pattern, illustrated in Figure 2, where arrows connect δ values for the two ring sizes. As has been noted,[12a] for cyclopropane, ethylenimine, and ethylene oxide the carbons of the three-membered ring are strikingly more shielded than those for other ring sizes. For ethylene sulfide the chemical shift of the three-membered ring is closer to that of the other rings, whereas for the cyclic bromonium ions, the carbons of the three-membered ring are less shielded than those of the five-membered ring, whose δ value is reported in the present paper. The number of five-membered ring halonium ions which we have measured is large enough to assure that the range of δ values is small for primary carbons of this ring size and that the patterns of Figure 1 are not substantially influenced by unpredictable variations in δ. Even the presence of electronegative substituents on the carbon atom β to the positive halogen in ions **7**, **8**, and **9** results in only a slight deshielding effect (2–3 ppm) at the α carbon. This result is not surprising, since "β effects" for substituents at this distance from the carbon under examination have been found in aliphatic systems to be moderate in size (~6 ppm) and not markedly dependent on the electronegativity of the substituent.[13] The chemical shift effects of Figure 2 would be observed if the carbon atoms of the three-membered ring bromonium ion, and to a lesser extent of the corresponding sulfide, are unusually positive and/or if the geometry of the CH_2CH_2 system is displaced toward planarity corresponding to a hybridization more like that of ethylene. These observations suggest the possibility that the unfilled d orbitals of bromine and sulfur accept electrons from the filled molecular orbitals of the ring. This would give the ring carbon atoms a net positive charge and cause the downfield shifts observed. The positive bromine, although from a higher row in the periodic table, is presumed to be a better acceptor than uncharged sulfur because of the influence of the positive charge.

In a separate publication one of us has examined the possibility of transfer of charge from Walsh type ring orbitals to d orbitals. Based on the symmetry properties of the ring orbitals and the d orbitals, charge transfer may be favored in odd-sized rings,[14] although other properties of the orbitals could negate this postulate. Based on overlap considerations, the small rings are predicted to exhibit the postulated stabilization of odd-sized rings to the greatest extent. Accordingly, the three-membered ring bromonium ion chemical shift can be considered to reflect the substantial shielding exhibited by three-membered rings, in combination with a larger deshielding effect resulting from charge transfer to bromine to give the observed chemical shift 35 ppm downfield from the 1,2-dibromoethane. Based on a 30-ppm shielding effect ($\Delta\delta$, cyclohexane to cyclopropane), the deshielding effect resulting from charge transfer would be approximately 65 ppm. If the large heteroatom blocks some of the shielding effect in the three-membered ring, as has been hypothesized,[12] the estimates given here would be modified.

In the case of the five-membered ring halonium ions the 35-ppm downfield shift caused by introduction of a 2-methyl substituent is suggestive of charge transfer from the ring carbon orbitals to halogen. The methyl group may be postulated to promote increased carbonium ion character at the halo-substituted carbon, since the methyl substituent effect is much greater than that found for hydrocarbons (~8 ppm)[15] and other compounds.[16] The presently available data do not suggest whether the charge transfer from carbon arises from filling of d orbitals, mentioned above, or merely from σ-bond polarization, however. In any event, the 35-ppm effect may be compared with the approximate 290-ppm change in ^{13}C chemical shift attendant upon converting a hydrocarbon to a carbonium ion, to yield an estimate of $^{35}/_{290}$ or 12% increase in cationic character at the halo-substituted carbon upon methyl substitution.

Although the above discussion has been developed largely as a correlation of chemical shifts, it is to be noted that other evidence from the literature is con-

(10) G. A. Olah and J. R. DeMember, *J. Amer. Chem. Soc.*, **92**, 718 (1970).

(11) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 988.

(12) (a) G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, **69**, 3925 (1965). (b) We have remeasured some of the values, as indicated in the footnotes of Figure 2 and as described in the Experimental Section.

(13) (a) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971); (b) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970).

(14) P. E. Peterson, *J. Org. Chem.*, **37**, 4180 (1972).

(15) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

(16) T. F. Page, Jr., T. Alger, and D. M. Grant, *ibid.*, **87**, 5333 (1965).

sistent with the ring size effects and alkyl substituent effects which we discussed. Rerrangement reactions studied in Olah's group showed a strong preference for three- and five-membered ring halonium ion formation.[17] Larsen and Metzner[18] found 8–19 kcal/mol of stabilization in three-membered ring bromonium ions. These authors also found increased sensitivity to methyl stabilization in the three-membered ring, compared to five, indicative of the carbonium ion nature of carbons in the three-membered ring. Our work shows that ^{13}C nmr effects in five-membered rings are well accommodated within a framework which correlates the properties of the halonium ions and other cyclic compounds as a function of structure and ring size.

Experimental Section

Chemicals.—All dihalide precursors to the various ions were either commercially available materials or prepared as described previously.[5] The cyclic sulfides and alkanes whose nmr line positions are listed in Figure 2 also were commercially available.

Preparation of the Ions.—The ions were prepared at 0.6–0.8 *M* concentration levels by procedures mentioned previously.[2,3,5]

Nmr Spectra.—Nmr spectra were obtained on a Varian XL-100-15 spectrometer with accompanying VFT-100-X Fourier transform unit. The line positions for noise-decoupled spectra were read out of the accompanying Varian 620i computer and, after referencing, are accurate to ±0.2 ppm. All halonium ion spectral parameters were measured at −65 to −70° and referenced to carbon disulfide as described in the text. Chemical shifts for the cyclic sulfides and alkanes were measured on 1.0 *M* solutions in carbon tetrachloride at room temperature and were referenced to centered 5-mm tubes of $C_2F_4Br_2$. The $C_2F_4Br_2$ signal was separately shown to be 78.2 ppm upfield from CS_2 in CCl_4 at room temperature. The δ ^{13}C values obtained for the cyclic sulfides and alkanes follow: ethylene sulfide (thiirane), C-2 175.1; trimethylene sulfide (thietane), C-2 166.9, C-3 164.8; tetramethylene sulfide (thiolane), C-2 162.1, C-3 162.9; pentamethylene sulfide (thiane), C-2 163.3, C-3 164.1, C-4 165.7; cyclopropane, 195.4; cyclobutane, 170.0; cyclopentane, 166.9; and cyclohexane, 165.8.[19] Assignments of the various carbon shifts in the sulfur heterocycles was accomplished by heteronuclear hydrogen decoupling while observing the carbon spectrum.

Registry No.—**4**, 22211-89-8; **5**, 22211-90-1; **6**, 22211-91-2; **7**, 33740-96-8; **8**, 33740-97-9; **9**, 33740-98-0; **10**, 33740-99-1; **11**, 22211-92-3; **12**, 23595-67-7; **13**, 22211-93-4.

Acknowledgment.—Support by the National Science Foundation (Grant GP 30683) is gratefully acknowledged.

(17) G. A. Olah, J. M. Bollinger, Y. K. Mo, and J. M. Brinich, *J. Amer. Chem. Soc.*, **94**, 1164 (1972).

(18) J. W. Larsen and A. V. Metzner, *ibid.*, **94**, 1614 (1972).

(19) We are indebted to Dr. P. M. Henrichs for obtaining some of these values.

Uniparticulate Electrophilic Addition to Alkenylidenecyclopropanes[1]

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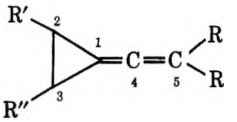
The reaction of a number of substituted isobutenylidenecyclopropanes with chlorosulfonyl isocyanate (CSI) have been investigated for comparison with the reactions of the alkenylidenecyclopropanes with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). In the previous article the cycloaddition reactions of alkenylidenecyclopropanes with PTAD were described, product formation being proposed to occur *via* a concerted process. A new molecular orbital description of the bonding in the alkenylidenecyclopropanes and the transition states for cycloaddition was advanced to account for the mode of reaction and high reactivity. In contrast to the singular mode of reaction of alkenylidenecyclopropanes with PTAD, the reactions with CSI produce both cyclopropane ring-retained (*N*-chlorosulfonyl-β-lactams formed by electrophilic attack at C_5) and ring-opened (five-membered ring



N-chlorosulfonylimino ethers and *N*-chlorosulfonyl-γ-lactams derived by attack at C_4) products. The ratio of cyclopropane-retained and -opened products is a sensitive function of the number and type of functions attached to the three-membered ring. Product formation is discussed in terms of stabilization of the cationic portion of the dipolar intermediates. It is proposed that the substituent effects on the mode of electrophilic attack arise from stabilization and delocalization of the positive charge developed in the p orbital of C_4 on electrophilic attack at C_5 (which is coplanar with the three-membered ring) with the molecular orbitals of the cyclopropane ring in a manner similar to that described for the ground-state electronic structure of alkenylidenecyclopropanes.

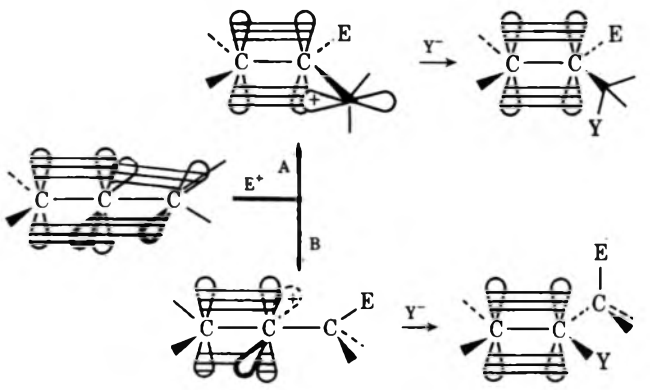
Attack by a nonbridging electrophile on an allene can occur either at the central or the terminal carbon of the cumulene system. Initial bonding at the central carbon produces a nonresonance-stabilized cationic species (path A),[3] the vacant orbital being orthogonal to the proximate π-electron system. Electrophilic attack at a terminal carbon leads to the formation of a vinyl cation (path B).[4] Competition between these two pro-

(1) (a) Cycloaddition Reactions of Cyclopropane-Containing Systems. IV. For the previous paper in this series see D. J. Pasto, A. F.-T. Chen, and G. Binsch, *J. Amer. Chem. Soc.*, **94**, 1553 (1973). Submitted by A. F.-T. C. in partial fulfillment of the requirements for the Ph.D., University of Notre Dame, 1972. (b) Unsaturated Heterocyclic Systems. LXXXVIII. For the previous paper in this series see L. A. Paquette and M. J. Broadhurst, *J. Amer. Chem. Soc.*, **94**, 632 (1972).

(2) Fullbright–Hayes Fellow on leave from the Institute of Chemistry, Cluj, Romania (1971–1972).

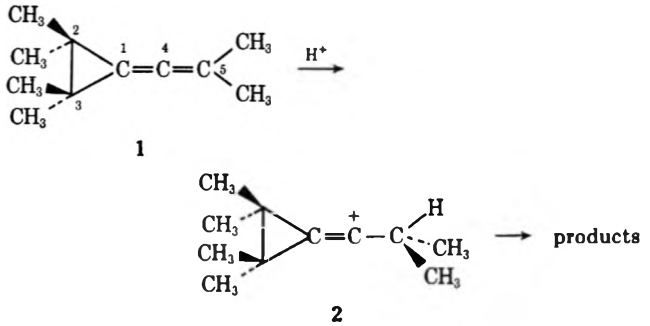
(3) T. L. Jacobs and R. N. Johnson, *J. Amer. Chem. Soc.*, **82**, 6397 (1960); K. Griesbaum, W. Naegele, and G. G. Wanless, *ibid.*, **87**, 3151 (1965); W. L. Waters and E. F. Kiefer, *ibid.*, **89**, 6261 (1967).

(4) For a recent review of this subject see M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970). See also S. A. Sherrod and R. G. Bergman, *J. Amer. Chem. Soc.*, **93**, 1925 (1971); D. R. Kelsey and R. G. Bergman, *ibid.*, **93**, 1941 (1971).



cesses is sensitive to the degree of substitution on the allene chromophore. For example, allene enters into reaction by preferential bonding at a terminal carbon,[5] while tetramethylallene exhibits reactivity predominantly at the central carbon.[6]

In this context it is interesting to note that electrophilic attack on alkenylidenecyclopropane **1** occurs preferentially at C_5.[7,8] Crandall[7] has attributed the

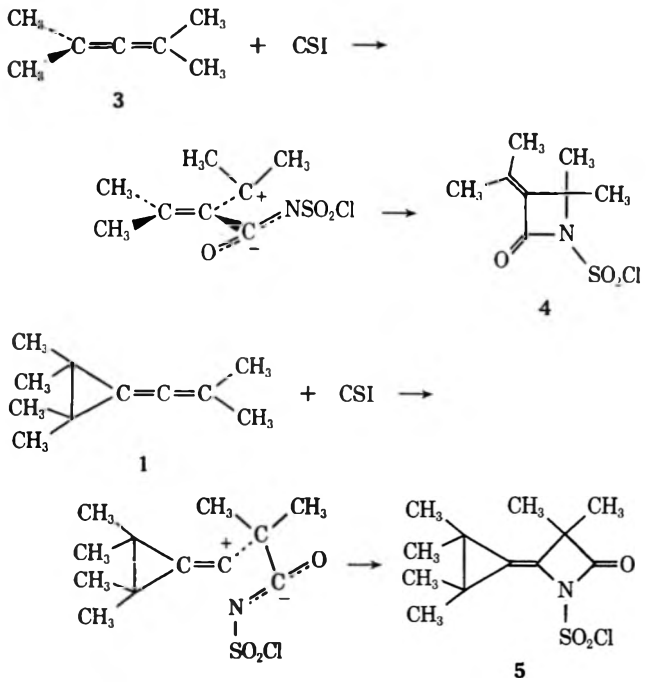


apparently enhanced stabilization of the cationic species **2** to its particularly unique geometry in which the σ bonds of the cyclopropane ring are perfectly bisected by the residual π orbitals, a particularly favorable orientation.[9] Production of cation **2** might also be due, at least in part, to steric hindrance to attack at the central carbon owing to the proximate cyclopropane methyl functions, and because of ground-state steric strain arising from the nonbonded interactions in **1**.[8]

Pasto, Chen, and Binsch have provided a theoretical basis for the differences in reactivity of alkenylidene- and methylenecyclopropanes in cycloaddition reactions,[10] and for the stability of cations such as **2**, based on an interaction of the C_4–C_5 π bond of an alkenylidene cyclopropane, or the in-plane p orbital on C_4 in **2**, with the appropriate Walsh orbitals of the cyclopropane moiety.[11]

The motivations for the present research were, in effect, twofold. It was anticipated that reactions of alkenylidenecyclopropanes of differing electronic, steric, and stereochemical features with chlorosulfonyl isocyanate (CSI) would provide product distributions from which information relating to mechanisms and the stability of intermediates would be available. Secondly, it was desired to investigate cycloaddition reactions of alkenylidene-, methylene-, and vinylcyclopropanes[12] proceeding *via* two-step, dipolar intermediate reactions for comparison with the reactivity and mode of reaction of these systems with 4-phenyl-1,2,4-triazoline-3,5-dione.[10,11] The choice of CSI[13] as the electrophilic reagent for use in these studies was based on past observations from one of these laboratories, which have demonstrated a number of discrete advantages which occur from the utilization of this uniparticulate electrophile[14] for the investigation of electrophilic additions.[15] In the present context, this type of reagent was anticipated to be an unusually effective probe for the elucidation of competitive rate situations surrounding the intramolecular capture of various transient carbonium ions.

Recent studies by Moriconi and Kelly[16] attest to the fact that the principal mode of CSI addition to a variety of allenes occurs at the central carbon to produce *N*-chlorosulfonyl-β-lactams such as **4**. Under similar conditions, **1** reacts with CSI to produce only **5**, in which the electropositive center of CSI has become attached to the terminal allenic carbon.[8] Consequently, the disparity in chemical behavior noted earlier for the protonation of **1** and **3** is carried over without apparent discrepancies into uniparticulate additions.



Results

2-Phenylisobutenylidenecyclopropane (6) with CSI. —The reaction of **6** with CSI produced a mixture of adducts (see Scheme I) as indicated by analysis of the nmr and ir spectra of the reaction product. Direct chromatographic separation of the CSI adducts on

(5) K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **5**, 933 (1966); **8**, 933 (1969).

(6) J.-P. Bianchini and A. Guillemonat, *Bull. Soc. Chim. Fr.*, 2120 (1968).

(7) J. K. Crandall, D. R. Paulson, and C. A. Bunnell, *Tetrahedron Lett.*, 5063 (1968).

(8) M. L. Poutsma and P. A. Ibarbia, *J. Amer. Chem. Soc.*, **93**, 404 (1971).

(9) For current views on this topic see M. Hanack and H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.*, **6**, 666 (1967); G. A. Olah, D. P. Kelley, C. L. Jeuell, and R. D. Porter, *J. Amer. Chem. Soc.*, **92**, 2544 (1970).

(10) D. J. Pasto and A. F.-T. Chen, *ibid.*, **93**, 2562 (1971); *Tetrahedron Lett.*, 2995 (1972).

(11) See reference in footnote 1a.

(12) D. J. Pasto and A. F.-T. Chen, *Tetrahedron Lett.*, in press.

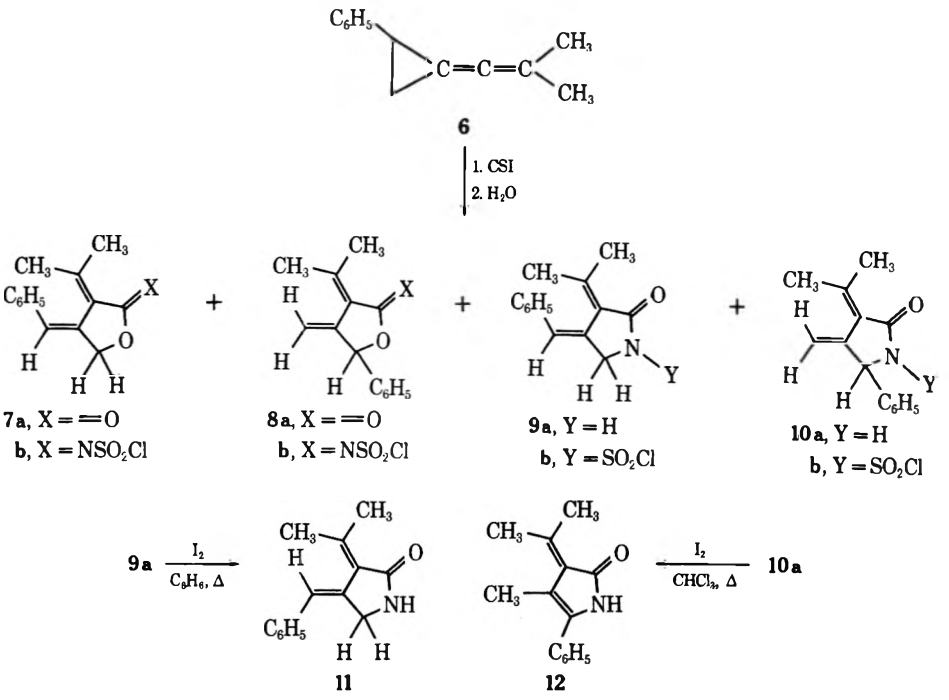
(13) R. Graf, *Chem. Ber.*, **89**, 1071 (1956).

(14) As previously defined,[15a] these reagents are those which are incapable of fragmentation during the course of bonding to an electron-rich system.

(15) For leading references, see (a) ref 1b; (b) L. A. Paquette, J. R. Allen, Jr., and M. J. Broadhurst, *J. Amer. Chem. Soc.*, **93**, 4503 (1971); (c) L. A. Paquette, M. J. Broadhurst, C. Lee, and J. Clardy, *ibid.*, **94**, 630 (1972).

(16) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).

SCHEME I



silica gel resulted in the isolation of pure fractions of adducts **7b–10b**. The structures of the adducts have been assigned on the basis of high-resolution mass spectral *m/e* measurements and ir and nmr spectral properties, and by identification of their hydrolysis products.

N-Chlorosulfonylimino ether **7b** displays characteristic absorption bands in the ir at 1640 ($\nu_{C=C}$), 1575 ($\nu_{C=N}$), and 1372 and 1172 cm^{-1} (ν_{SO_2}). The nmr spectrum of **7b** exhibits methyl singlets at δ 1.54 and 2.33, a doublet at 5.10 (J = 2.0 Hz), for the methylene hydrogens, and a triplet at 6.58 (J = 2.0 Hz, vinyl hydrogen), with the aromatic hydrogens appearing at 7.25. The high-field methyl resonance of **7b** is characteristic of the "inside" methyl of the isopropylidene function positioned directly over the face of the phenyl ring which is twisted perpendicularly to the plane of the diene chromophore.[17,18] Hydrolysis of **7b** produced lactone **7a**, identified by high-resolution mass spectral *m/e* measurements and the ir ($\nu_{C=O}$ at 1750 cm^{-1}) and nmr spectral properties. The nmr spectrum, for example, again displays the characteristic high-field methyl resonance at δ 1.47 (see Table I for the remainder of the spectrum).

The *N*-chlorosulfonylimino ether **8b** possesses ir spectral properties very similar to those of **7b**, the structural identification being based on the very definitive resonance patterns appearing in the nmr spectrum of **8b**. Hydrolysis of **8b** produced a lactone (**8a**) which possesses spectral properties commensurate with the proposed structure.

The *N*-chlorosulfonyl-γ-lactam **9b** was similarly identified by its chemical and physical properties. The ir spectrum of **9b** contains a carbonyl band at 1748 cm^{-1} along with the typical ν_{SO_2} bands at 1420 and 1197 cm^{-1}. The nmr spectrum of **9b** is very similar to that of **7b** (see Table I), clearly indicating the presence of the "inside" methyl and phenyl functions of **9b**. Hydrolysis of **9b** produces lactam **9a**, the nmr spectrum of which contains the high-field methyl resonance. Treatment of lactam **9a** with a catalytic quantity of iodine in refluxing benzene resulted in quantitative isomerization to **11**. The high-field methyl resonance of **9a** has shifted downfield to δ 2.22 in **11**, while the hydrogen of the benzylidene group has shifted 0.20 ppm to lower field owing to long-range deshielding by the isopropylidene double bond and the methyl group (see Table I for the nmr data for **11**). The quantitative isomerization of **9a** to **11** is dramatic evidence that this lactam suffers internal steric effects which are relieved on isomerization of the phenyl from the "inside" to the "outside" of the diene chromophore.

Adduct **10b** possesses ir spectral properties very similar to those of **9b**, and nmr chemical shifts very similar to those of **8b** (see Table I). Hydrolysis of **10b** produces a lactam (**10a**) which, on treatment with iodine in deuteriochloroform, underwent allylic rearrangement to lactam **12**. Migration of the double bond during the isomerization of **10a** to **12** was most clearly evidenced by the large bathochromic shift in the uv absorption spectra [$\lambda_{max}^{95\%\ C_2H_5OH}$ 263.5 nm (ϵ 10,100) for **10a** to 372.5 (5180) in **12**], and the appearance of a third sp^2 C-bound methyl resonance in the nmr spectrum.

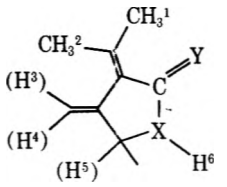
The assignment of nmr chemical shifts to the appropriate hydrogens in adducts **7b–10b** allows for the direct determination of the yields of **7b–10b** by integration of the aromatic hydrogen and δ 4–7 regions of the nmr spectrum of the crude reaction mixtures. Integration of the aromatic and δ 4–7 regions gives a ratio of 5.0:3.0, indicating that **7b–10b** are the only products formed (all resonances appearing in the nmr spectrum of the crude reaction mixture have been assigned as belonging to **7b–10b**), and that they are formed in essentially quanti-

(17) Similar shielding of the "inside" methyl by an "inside" phenyl has been observed in the adducts of phenyl-substituted alkenylidenecyclopropanes with 4-phenyl-1,2,4-triazoline-3,5-dione.[1a,10]

(18) Additional evidence that the phenyl ring of adducts such as **7b** is twisted out of the plane of the diene chromophore is provided by the uv absorption data of compounds possessing the stereochemistry present in **7b** and compounds in which the phenyl resides "outside" of the diene chromophore, the isomerization of the phenyl from the "inside" to the "outside" resulting in a substantial bathochromic shift (*vide infra*; see also ref 1a and 10).

TABLE I

NMR PARAMETERS FOR 7a–10a, 7b–10b, AND 11 (δ)



Compd	H¹	H²	H³	H⁴	H⁶	H⁶	Aromatic H
7a	2.30	1.47		6.44	4.77 (d, J = 2.0 Hz)		7.27
8a	2.52	2.17	5.32	4.98	5.66		7.27
9a	2.28	1.37		6.50 (t, J = 1.8 Hz)	3.98 (d, J = 1.8 Hz)	7.0	7.25
10a	2.54	2.10	5.04	4.97	5.30	6.15	7.25
7b	2.33	1.54		6.58 (t, J = 2.0 Hz)	5.10 (d, J = 2.0 Hz)		7.25
8b	2.56	2.28	5.45	5.10	6.09		7.32
9b	2.32	1.47		6.61	4.48		7.25
10b	2.54	2.17	5.37	5.11	5.50		7.30
11	2.47	2.22	6.72		4.22 (d, J = 2.1 Hz)	*a*	7.25

[a] Could not be unambiguously assigned.

tative yield. The ratios of the products (**7b–10b**) formed at −30 and 38° were measured by carrying out the reaction in the nmr probe. The product ratios remain constant with time at both temperatures, and are given in Table II.

TABLE II

YIELDS OF ADDUCTS **7b–10b** FROM **6** WITH CSI

7b	8b	9b	10b	Temp, °C
9	15	43	33	−30
19	17	33	31	38

trans-**2-Methyl-3-phenylisobutenylidenecyclopropane (13) with CSI.**—The ir spectrum of the crude product obtained from the reaction of **13** with CSI (Scheme II) indicated the presence of *N*-chlorosulfonylimino ether ($\nu_{C=N}$ 1570–1590 cm^{-1}) and *N*-chlorosulfonyl-γ-lactam ($\nu_{C=O}$ 1750 cm^{-1}) functions, and a major product(s) with $\nu_{C=O}$ 1788 cm^{-1} identified as belonging to a *N*-chlorosulfonyl-β-lactam (*vide infra*). The nmr spectrum of the product mixture similarly indicated the formation of a complex mixture of products. Furthermore, integration of the aromatic and δ 4–7 regions indicated that the major product(s) did not contain vinyl or other low-field hydrogens.

Chromatographic separation of the CSI adduct mixture provided a fraction with $\nu_{C=O}$ 1788 cm^{-1}. The nmr spectrum of this fraction indicated the presence of two isomeric compounds in an approximate 90:10 ratio, the principal component giving rise to methyl singlets at δ 1.15 and 1.47, a methyl doublet at 1.42, a double quartet at 1.97 (1 H), and a doublet at 2.41 (1 H) with the aromatic hydrogen resonances appearing at 7.14. Ozonolysis in dichloromethane–pyridine did not produce acetone, thus eliminating the possible presence of an isopropylidene function. The physical and chemical data are consistent with either structure **14** or **15** as the major component of this fraction. We tentatively assign structure **14** as the principal component based on the presence of a high-field methyl resonance arising from long-range shielding by the syn phenyl. Acid hydrolysis of the mixture of **14** and **15** produces an ~1:1 mixture of the ketones **16** and **17** ($\nu_{C=O}$ 1694 cm^{-1}, cyclopropyl ketone). The mass spectrum of the mixture of **16** and **17** clearly established the gross structure of the ketones as $C_{10}H_{11}CO_2C_3H_7$ (see Experimental Section). The nmr spectrum is entirely consistent with the assigned structures.

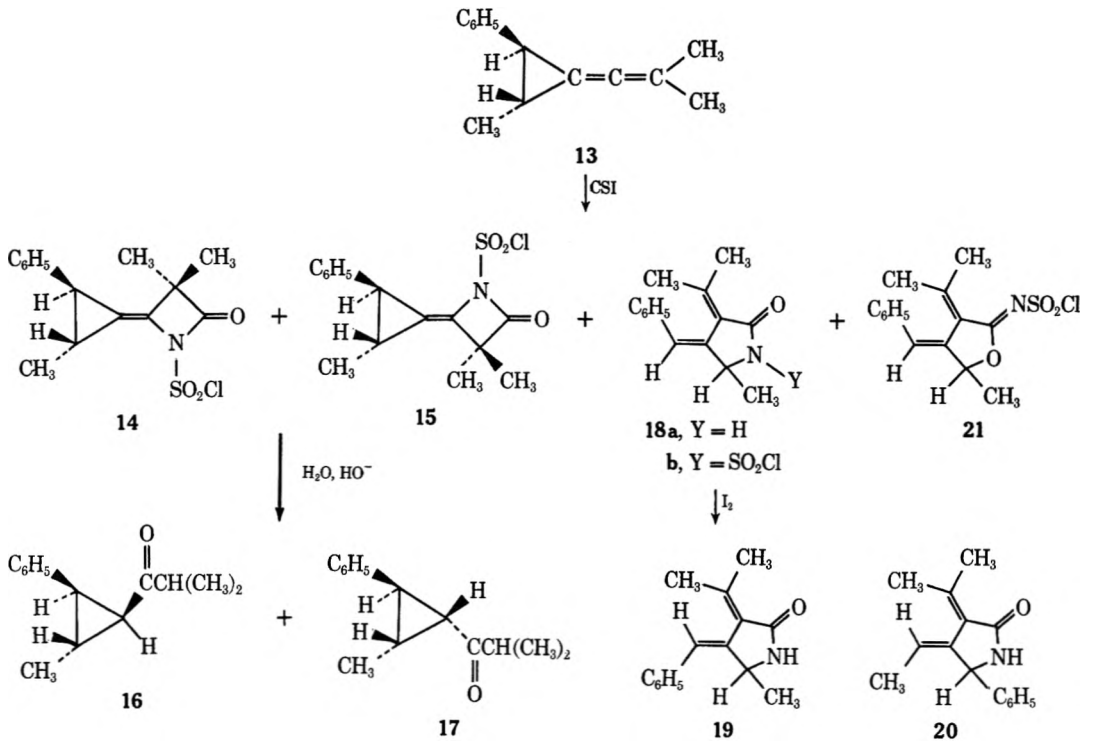
Also isolated from the initial reaction mixture were pure fractions of **18b** and **21**. Both adducts gave ir and nmr spectra fully consistent with the proposed structures.

Hydrolysis of the CSI adduct mixture followed by chromatographic separation led to the isolation of a mixture of ketones **16** and **17**, lactam **18a**, a mixture of lactams **18a** and **19**, and a small amount of lactam **20**. Identification of the structure of lactam **18a** is based on the presence of a high-field methyl resonance in the nmr spectrum, and the quantitative isomerization of **18a** to **19** by iodine in deuteriochloroform. The identification of lactam **19** in the mixture of **18a** and **19** is based on a comparison of the nmr spectral properties of **19** in the mixture with those of pure **19** obtained by isomerization of **18a**. The structure of lactam **20** is based on a comparison of the nmr spectral properties of **20** with those of lactam **25** isolated from the reaction of **22** with CSI (see Scheme III). In particular, the ethylidene hydrogen appears at lower field in **20** consistent with its being "inside" the diene chromophore, and the $CH_3CH=$ resonance appears at higher field owing to shielding by the phenyl.

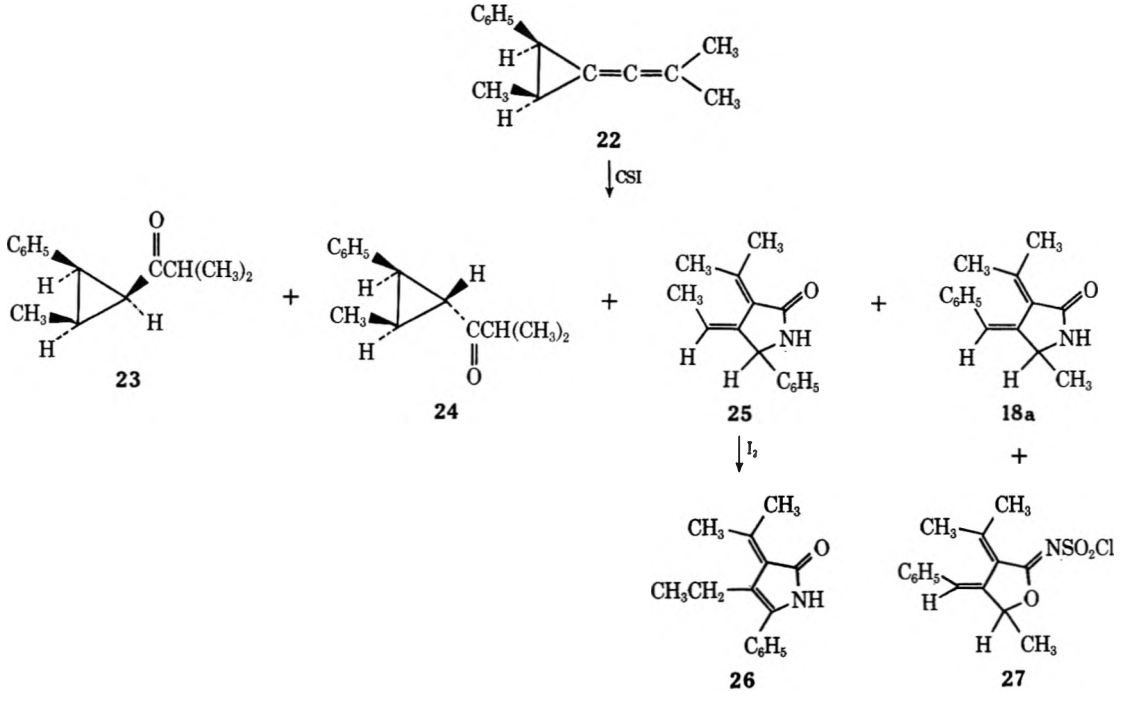
cis-**2-Methyl-3-phenylisobutenylidenecyclopropane (22) with CSI.**—The ir spectrum of the reaction mixture displayed intense absorption at 1778 cm^{-1} (*N*-chlorosulfonyl-β-lactam) along with very weak bands at 1751 and 1580 cm^{-1} (*N*-chlorosulfonyl-γ-lactam and *N*-chlorosulfonylimino ether, respectively). The nmr spectrum indicated that cyclopropane ring-opened products were formed in less than 20% yield.

Hydrolysis of the reaction mixture followed by chromatographic separation gave as the major fraction a mixture of the ketones **23** and **24** which were identified from ir, nmr, and mass spectral data (see Experimental Section). The major ring-opened product was identified as **25** on the basis of elemental analysis and comparison of nmr chemical shift data with that of **20** derived from **13** with CSI. Lactam **25** undergoes isomerization in the presence of iodine in deuteriochloroform to produce

SCHEME II



SCHEME III



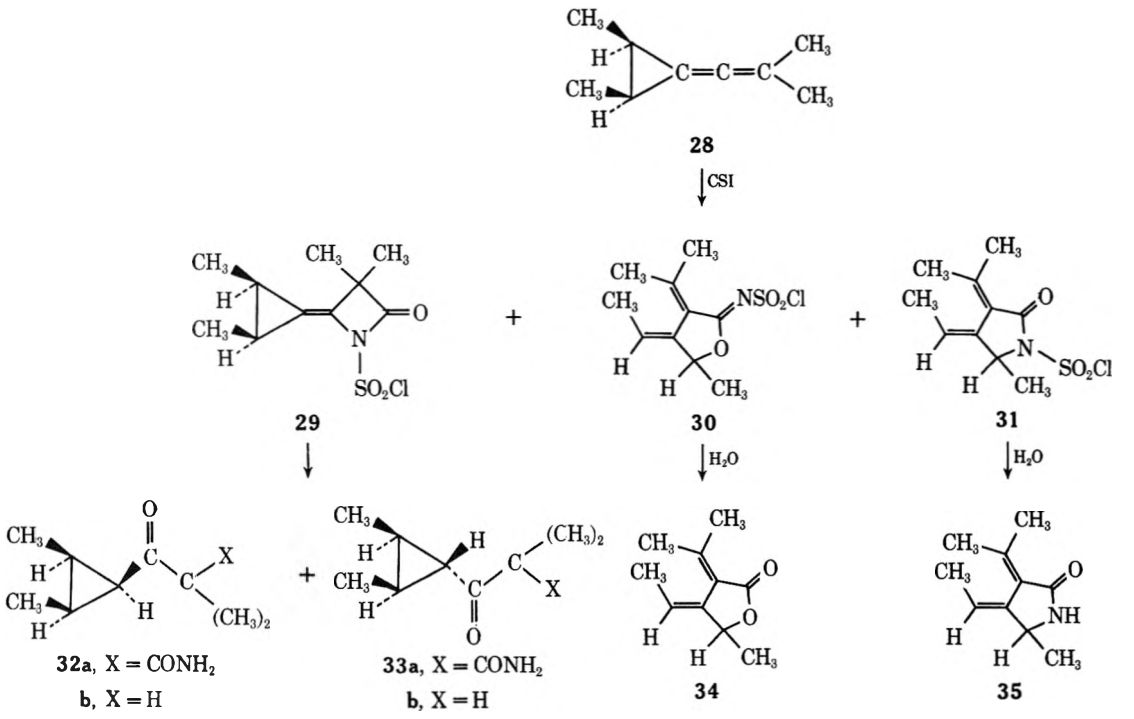
lactam **26**, the nmr spectrum of which displays very characteristic $CH_3CH_2C=$ resonances. A small quantity of lactam **18a** was also isolated, as well as a small quantity of the imino ether **27**. (The *N*-chlorosulfonylimino ethers hydrolyze rather slowly and sometimes survive the hydrolysis procedure. The lactone corresponding to **27** was not isolated.)

cis-**2,3-Dimethylisobutenylidenecyclopropane (28) with CSI.**—The nmr spectrum of the product mixture indicated the formation of a moderate quantity of cyclopropane ring-opened product(s) (Scheme IV). Direct chromatographic separation gave pure fractions of the *N*-chlorosulfonyl-β-lactam **29** (51%, $\nu_{C=O}$ 1793 cm^{-1}), *N*-chlorosulfonylimino ether **30** (8.5%, $\nu_{C=N}$ 1575 cm^{-1}), and the *N*-chlorosulfonyl-γ-lactam **31** (15.5%, $\nu_{C=O}$ 1748 cm^{-1}).

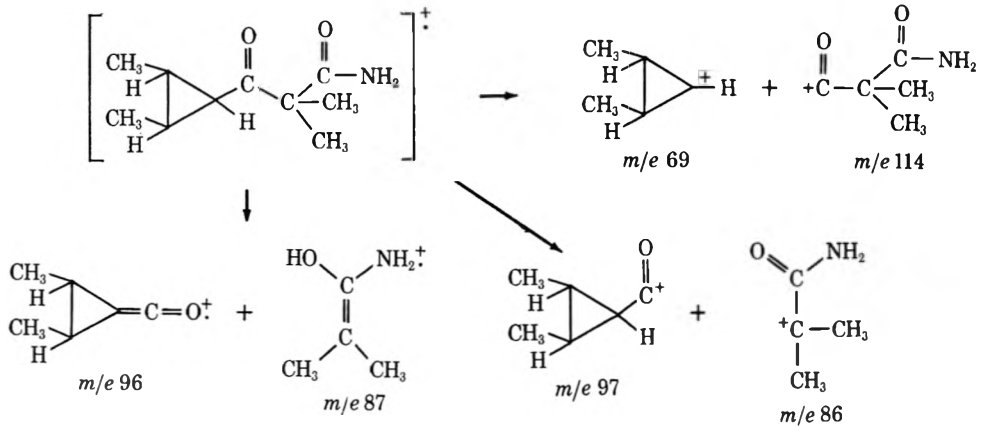
Basic hydrolysis of **29** produced a mixture of keto amides **32a** and **33a**, whereas acid hydrolysis produced a mixture of the ketones **32b** and **33b**.[19] The structures of the keto amides are clearly indicated by ir ($\nu_{C=O}$ 1691

(19) It is interesting to note the distinctly different behavior of the *N*-chlorosulfonyl-β-lactams toward acid- and base-catalyzed hydrolysis. The keto amides are stable under the conditions used for the acid-catalyzed hydrolyses of the *N*-chlorosulfonyl-β-lactams. It is clearly evident that the acid- and the base-catalyzed reactions proceed by grossly different mechanisms, the former proceeding *via* an enamino acid involving cleavage of the N–C=O bond, while the latter involves cleavage of the vinyl C–N bond.

SCHEME IV



SCHEME V



and 1672 cm^{-1}, ν_{NH_2} 3502 and 3398 cm^{-1}), nmr (see Experimental Section), and mass spectra. The mass spectrum of the mixture of **32a** and **33a** clearly indicated the gross structure $C_5H_9CO_2C(CH_3)_2CONH_2$ by the presence of appropriate fragment and metastable peaks (see Scheme V).

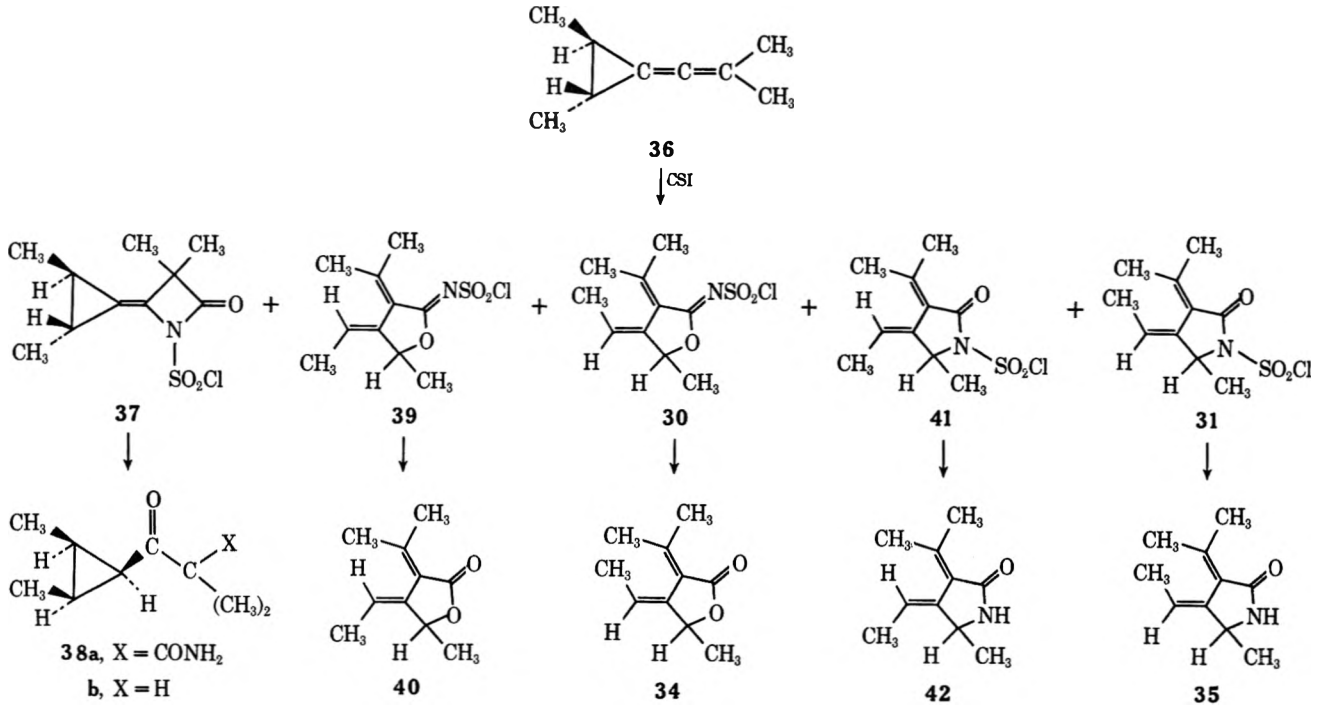
The structures of the ketones **32b** and **33b** were clearly indicated by the ir (1685 cm^{-1}) and mass spectra (see Experimental Section) of the mixture.

Hydrolysis of **30** and **31** produced the lactone **34** and lactam **35**, respectively. The stereochemistry about the ethylidene function was assigned by comparison of the nmr spectra of **34** and **35** with the spectra of the mixtures of lactones and lactams derived from **36**, the ethylidene vinyl hydrogens of **34** and **35** appearing at higher field than the "inside" hydrogens of **40** and **42** (see Scheme VI) as pointed out earlier.

trans-**2,3-Dimethylisobutenylidenecyclopropane (36) with CSI.**—Alkenylidenecyclopropane **36** reacts with CSI to give as the major product a *N*-chlorosulfonyl-β-lactam (~90% by ir and nmr analysis of the reaction product mixture). Chromatographic separation of the reaction mixture gave pure *N*-chlorosulfonyl-β-lactam **37**, and small quantities of a 3:1 mixture of the *N*-chlorosulfonylimino ethers **30** and **39** (6%, $\nu_{C=N}$ 1568 cm^{-1}) and a 4:1 mixture of the *N*-chlorosulfonyl-γ-lactams **31** and **41** (2%, $\nu_{C=O}$ 1743 cm^{-1}).

The structures of the adducts were assigned on the basis of their hydrolysis products. Basic hydrolysis of **37** produced a single, crystalline keto amide **38a** easily identified by its ir, nmr, and mass spectra (see Experimental Section), while acid hydrolysis produced a single ketone **38b**. Hydrolysis of the mixture of **30** and **39** produced a mixture of lactones, the major isomer possessing nmr chemical shifts identical with those of **34** derived from **28**. The ethylidene vinyl hydrogen of the minor isomer (**40**) appears at lower field than its counterpart in **34**, indicating the stereochemistry as shown in **40**. Similarly, hydrolysis of the mixture of **31** and **41** produced a mixture of lactams, the major isomer (**35**) being identical with the lactam derived from **28**. The stereochemistry about the ethylidene functions in the two amides was assigned as described for the lactones (see Experimental Section for details of the nmr spectra).

SCHEME VI



Discussion

Electrophilic attack by CSI on the alkenylidenecyclopropane can occur either at C_1, C_4, or C_5. Competition between these modes of reaction is expected to be sensitive to steric effects engendered by substituents on the alkenylidenecyclopropane with the approaching CSI, steric effects in the resulting dipolar intermediates, and stabilization afforded the cationic center. The factors affecting the stereochemistry about the benzylidene or ethylidene functions in the cyclopropane ring-opened products arise not only in the initial step of the reaction, but also in the second step, during which the dipolar intermediates collapse to products.

Although electrophilic attack at C_1 would be expected to be favorable owing to a decrease in bond-angle strain about C_1, it is expected to be less so than the other two modes because of steric hindrance to CSI approach by the substituents attached to the cyclopropane moiety, and because of less stabilization afforded the cationic center in the dipolar intermediate **43** (Scheme VII).

Bonding by CSI at C_5 results in the formation of the dipolar intermediate **44**. The vacant orbital thus formed on C_4 is perfectly aligned for interaction with the Walsh orbitals[20] of the cyclopropane ring similar to the interaction between the C_4–C_5 π system and the cyclopropane ring in the starting alkenylidenecyclopropane as discussed in an earlier article.[1a] The cationic portion of the dipolar intermediate may thus be compared in a limited sense to an allyl cation, for which the resonance structures illustrated in Figure 1 may be written. (The molecular orbital representation of the resulting hybrid is illustrated below the resonance contributing structures in Figure 1.) Alkyl and aryl substituents bonded to the cyclopropane ring should lend inductive and resonance stabilization, respectively, to the delocalized cation (akin to the well-known stabilization of allyl cations by alkyl and aryl functions).

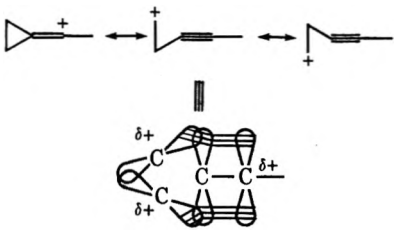


Figure 1.—Resonance structures and MO description of the cyclopropylmethylene cation.

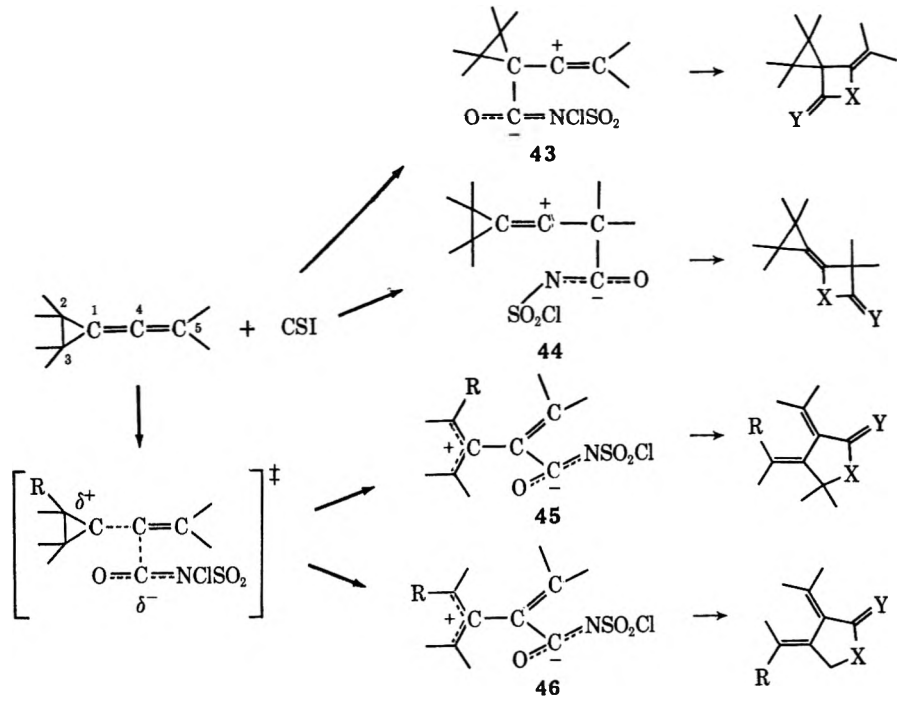
Electrophilic attack by CSI at C_4 can lead either to the development of a cyclopropyl cation, which is expected to undergo concerted disrotatory ring opening to produce a resonance-stabilized allylic cation,[21,22] or a nonresonance-stabilized tertiary cation at C_5. The former mode of reaction would appear to be quite favorable owing to the release of the strain energy of the three-membered ring and the stabilization of the incipient allylic cation. In this mode of reaction there are, in fact, two different pathways of disrotatory ring opening, one leading to **45** in which adverse steric effects are absent and the other leading to **46** in which severe steric interactions arise owing to the R function which is forced to reside "inside" the cavity of the allylic cation. In the present work, only the former mode of disrotatory ring opening is observed (except in the case of the trans 2,3-disubstituted alkenylidenecyclopropane in which one of the substituents must be placed in the "inside" of the allylic cation). Bonding by CSI at C_4 will suffer steric deceleration by functions attached to the cyclopropane ring which impede the approach of CSI to C_4, or which force a function to reside on the "inside" of the allylic

(20) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

(21) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

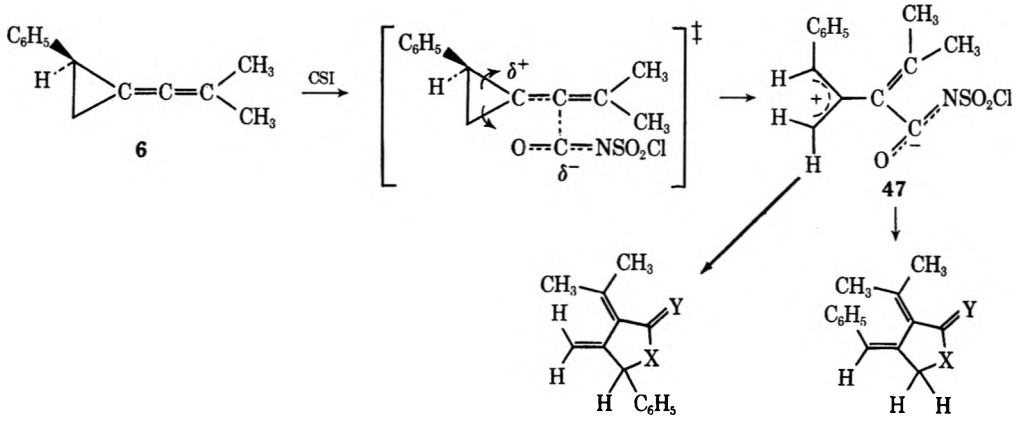
(22) For leading references see (a) P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schöllkopf, J. Paust, and K. Fellenberger, *J. Amer. Chem. Soc.*, **94**, 125 (1972); (b) W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972), and references contained in ref 22a.

SCHEME VII



X = O; Y = NSO_2Cl
Y = O; X = NSO_2Cl

SCHEME VIII



X = O; Y = NSO_2Cl
X = NSO_2Cl; Y = O

cation in the dipolar intermediate. Of the three possible modes of reaction of an electrophile (CSI) with an alkenylidenecyclopropane, only those occurring at C_4 (with generation of cyclopropyl cation character at C_1 and concomitant disrotatory ring opening) and C_5 are observed. The results of the present study reveal that the competition between these two modes is a sensitive function of the type, number, and stereochemical relationship of substituents attached to the cyclopropane ring.

Alkenylidenecyclopropane **6** suffers electrophilic attack by CSI only at C_4, resulting in the formation of cyclopropane ring-opened products. With **9** steric factors are minimal, and stabilization of the ring-opened allylic cation is maximal. Of two disrotatory modes of ring opening, only that producing the more stable allylic cation in **47** is observed (see Scheme VIII). Collapse of the dipolar intermediate to products occurs to an essentially equal extent at both ends of the allylic cation, C–N bond formation being slightly favored over C–O bond formation.

In contrast to the reaction of **6** with CSI, **13** and **22** suffer extensive electrophilic attack at C_5, leading to the formation of *N*-chlorosulfonyl-β-lactams. One might have anticipated that both steric hindrance to attack by CSI at C_4 and adverse steric effects generated in the disrotatory ring-opening process would disfavor attack at C_4 of **13**.[22] These steric interactions, however, are not present in the case of the reaction of the cis isomer **22** with CSI (approach trans to the phenyl and methyl functions is not sterically impeded compared to the case of **6**), which, nonetheless, undergoes extensive, albeit somewhat less, electrophilic attack at C_5.[23] The domi-

(23) A similar reduction in reactivity toward cyclopropane ring-opening reactions of cis- and trans-substituted cyclopropyl cations has been reported by Parham and Yong,[24] in which the silver ion assisted solvolysis of *cis*-2,3-di-*n*-propyl-1,1-dichlorocyclopropane occurs 24 times faster than with the *trans*-2,3-di-*n*-propyl isomer.

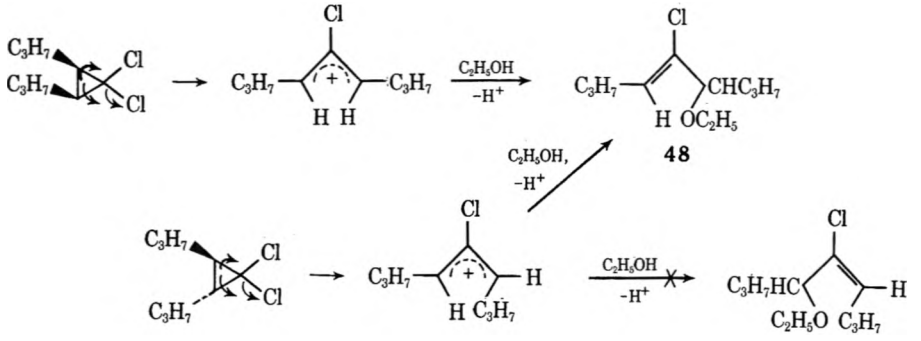
(24) W. E. Parham and K. S. Yong, *J. Org. Chem.*, **33**, 3947 (1968).

nant factor leading to more extensive attack at C_5 must be the stabilization of the intermediate cation (similar to **44** in Scheme VII) by the methyl group attached to the cyclopropane ring. Further evidence in support of this proposal is provided by the results derived with the 2,3-dimethylalkenylidenecyclopropanes **28** and **36**, both of which undergo even more extensive attack at C_5, and the results reported by Poutsma and Ibarbia[8] for **1** which produces exclusively **5**.

A closer analysis of the products derived from the cyclopropane ring-opened dipolar intermediates from **13** and **36** indicates that collapse of the dipolar intermediates occurs predominantly at the allylic carbon bearing the function constrained to the "inside" of the allylic cation structure.[25] This is consistent with the results of Parham and Yong[24] reported for the solvolysis of *cis*- and *trans*-2,3-di-*n*-propyl-1,1-dichlorocyclopropane, in which both substrates produce only (*Z*)-5-chloro-6-ethoxy-4-nonene (**48**). This behavior must be the result of a sterically enforced distortion of the allylic cation system resulting in a decrease in the stabilization of the positive charge afforded by the proximate double bond, thus inducing greater reactivity toward C–O and C–N bond formation at that carbon. Based on this rationale, it is possible to infer the structure of the dipolar intermediate derived from **13** with CSI from the structures of the cyclopropane ring-opened products. Collapse of intermediate **49** (see Scheme IX) produces **50** and **51**, which correspond in structure to adducts **18a** and **20**, and **21**. Collapse of intermediate **52** would be expected to give rise to **53** and **54**, neither of which are formed. This evidence strongly suggests that the only dipolar intermediate formed in the reaction of **13** and CSI is **49**. The greater stability, and thus preferential formation, of **49** must be due to the presence of the styrene chromophore in the twisted allylic cation portion of **49**.

A further aspect concerning the stereochemistry of the benzylidene and ethylidene functions merits comment. The isomers with phenyl or methyl residing "inside" the diene chromophore are the least thermodynamically stable. Although the stereochemistry of the final product is determined in the cyclopropane ring-opening step, the thermodynamic instability inherent in the product, however, does not arise in the first step, but arises in the subsequent collapse of the dipolar intermediates to the final products. The structure of the dipolar intermediates as initially formed is that illustrated in **55** of Scheme X in which there is very little steric interaction between the R and the subsequent "inside" methyl of the isopropylidene function (the rotational processes occurring in the collapse of **55** are indicated by arrows).

The relative amounts of C–O and C–N bond formation in the collapse of the dipolar intermediates varies with temperature (see Table II), the structure of the alkenylidenecyclopropane, and the structure of the product.[27] In the present studies the four-membered ring products are formed exclusively by C–N bond formation, while the five-membered ring products are formed by both C–N and C–O (the former dominating) bond formation. No trend in the preference for C–N *vs.* C–O bond formation is readily apparent.



Experimental Section

Melting points are corrected. Proton magnetic resonance spectra were obtained with Varian A-60A and XL-100 spectrometers. The reported coupling constants are derived by first-order analyses of the nmr spectra. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. High-resolution mass measurements and mass spectra were recorded on a Picker Nuclear MS-902 spectrometer.

Preparation of Alkenylidenecyclopropanes.—The procedure of Hartzler[31] was used to prepare the alkenylidenecyclopropanes[1a] by the addition of 3,3-dimethylallene carbene to the requisite alkene.

Reactions of Alkenylidenecyclopropanes with CSI. Procedure A.—To a solution of 0.01 mol of the alkenylidenecyclopropane in 15 ml of dichloromethane at −78° under a nitrogen atmosphere was added 0.01 mol of CSI in 10 ml of dichloromethane. After 5 hr at −78° the reaction mixtures were poured into 100 ml of water and shaken for 30 min. The organic layers were separated, dried, and evaporated, and the residues were chromatographed on Florisil.

Procedure B.—To a solution of the alkenylidenecyclopropane in dichloromethane (0.3 *M*) maintained at 0° was added a solution of CSI in dichloromethane (0.3 *M*). The reaction mixtures were allowed to warm to room temperature and stirred for 30 min. The solvent was then removed on a rotatory evaporator, and the ir and nmr spectra were immediately recorded. The

(25) The possible isomerization of allylic cations does not occur, as evidenced by the lack of isomerization crossover products from **22** and **28**, and the fact that the isomerization of allylic cations requires activation energies in excess of 15 kcal/mol,[26] which indicates that collapse of the dipolar intermediate must occur more rapidly than isomerization.

(26) P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, *J. Amer. Chem. Soc.*, **91**, 5174 (1969).

(27) Differences in the preference for C–N *vs.* C–O bond formation as a function of structure has been noted previously in the reactions of cyclooctatetraene,[28] cycloheptatriene,[29] and bullvalene.[30]

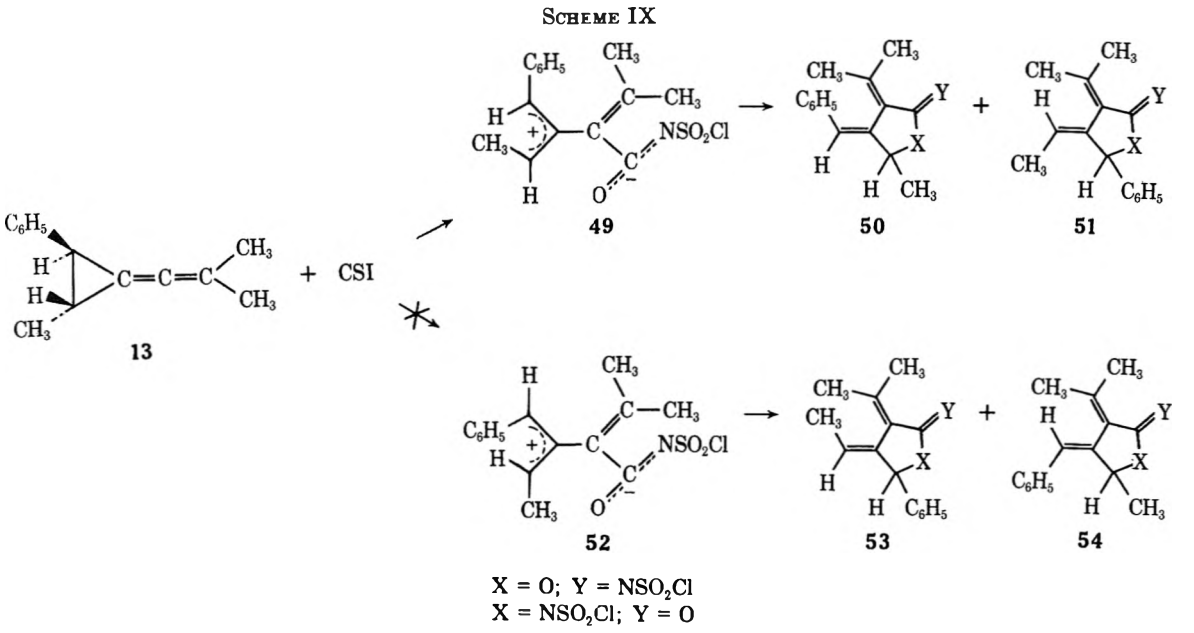
(28) L. A. Paquette, J. R. Malpass, and T. J. Barton, *J. Amer. Chem. Soc.*, **91**, 4714 (1969); L. A. Paquette and T. J. Barton, *ibid.*, **89**, 5480 (1967).

(29) E. J. Moriconi, C. F. Hummel, and J. F. Kelly, *Tetrahedron Lett.*, 5325 (1969).

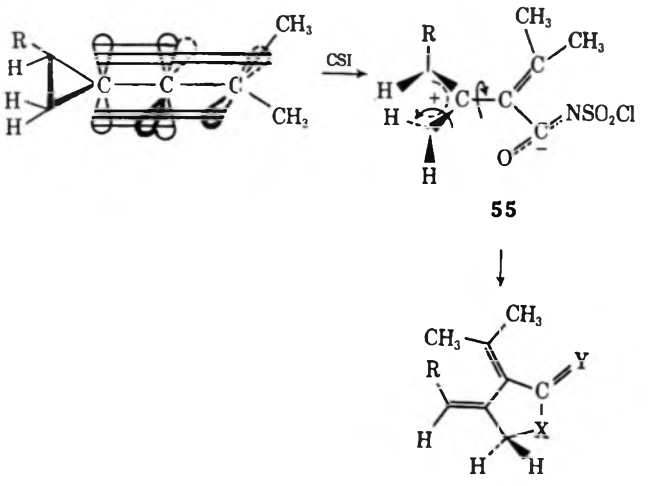
(30) L. A. Paquette, S. Kirschner, and J. R. Malpass, *J. Amer. Chem. Soc.*, **91**, 3970 (1969); **92**, 4330 (1970).

(31) H. D. Hartzler, *ibid.*, **83**, 4990 (1961).

SCHEME IX



SCHEME X



reaction mixtures were either separated directly by chromatography, or were hydrolyzed and then separated as described in the following paragraphs.

Separation of the CSI adducts was accomplished by column chromatography on silica gel.[32] Elution with hexane afforded the *N*-chlorosulfonyl-β-lactams, while elution with ~5% ether–hexane furnished separate fractions of the *N*-chlorosulfonyl-γ-lactams, and elution with ~10% ether–hexane afforded separate fractions of the *N*-chlorosulfonylimino ethers. The CSI adducts were further purified by recrystallization from ether.

The CSI adducts were hydrolyzed by dissolution in 20% aqueous acetone maintaining a pH of ~7–8 by titration with 0.2 *M* potassium hydroxide. After the hydrolyses were complete, the reaction mixtures were extracted with dichloromethane. The organic layers were dried ($MgSO_4$ for lactones, K_2CO_3 for lactams) and the solvent was removed under reduced pressure.

Reaction Products of 6 with CSI. **Adduct 9b** (30.5% isolated yield) had mp 115.0–115.5°; ir ($CHCl_3$) 1750 (C=O), 1608 (C=C), 1409 and 1189 cm^{-1} (SO_2); nmr, see Table I; mass spectrum (70 eV) *m/e* (calcd for $C_{14}H_{14}{}^{35}ClNO_3S$, 311.039) 311.042.

Adduct 10b (26.4%) had mp 108–110°; ir ($CHCl_3$) 1750 (C=O), 1630 (C=C), 1404, and 1196 cm^{-1} (SO_2); nmr, see Table I.

Adduct 7b (17%) was not obtained crystalline: ir ($CHCl_3$) 1613 (C=C), 1577 (C=N), 1367, and 1164 cm^{-1} (SO_2); nmr, see Table I.

Adduct 8b (19%) had mp 93–95°; ir ($CHCl_3$) 1613 (C=C), 1568 (C=N), 1370, and 1162 cm^{-1} (SO_2); nmr, see Table I.

Lactam 9a had mp 166–167.5[33] (from ether); ir 3440 (NH), 1690 (C=O), 1635 (amide II), and 1627 cm^{-1} (C=C); uv max (95% ethanol) 297.5 nm (ε 7220); nmr, see Table I; mass spectrum *m/e* (calcd for $C_{14}H_{15}NO$, 213.116) 213.115.

Lactam 10a had mp 167–168°[33] (from ether); ir 3441 (NH), 1690 (C=O), and 1630 cm^{-1} (amide II or C=C); uv max (95% ethanol) 263.5 nm (ε 10,000); nmr, see Table I; mass spectrum *m/e* (calcd for $C_{14}H_{15}NO$, 213.116) 213.116.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.67; H, 7.09; N, 6.70.

Lactone 7a was a viscous liquid: ir 1750 (C=O) and 1622 cm^{-1} (C=C); nmr, see Table I; mass spectrum *m/e* (calcd for $C_{14}H_{14}O_2$, 214.099) 214.097.

Lactone 8a was a viscous liquid: ir 1747 (C=O) and 1630 cm^{-1} (C=C); nmr, see Table I; mass spectrum *m/e* (calcd for $C_{14}H_{14}O_2$, 214.099) 214.099.

Isomerization of 9a to 11.—A solution of 120 mg of **9a** and 5 mg of iodine in 1.5 ml of benzene in a sealed ampoule was heated at 70–80° for 24 hr. The reaction mixture was directly chromatographed on silica gel, giving **11** on elution with 50% benzene–hexane: mp 199–202° dec; ir 3440 (NH), 1690 (C=O), and 1627 cm^{-1} (amide II and C=C); nmr, see Table I; mass spectrum *m/e* (calcd for $C_{14}H_{15}NO$, 213.116) 213.113.

Isomerization of 10a to 12.—Into an nmr tube were introduced approximately 40 mg of **10a**, an appropriate volume of deuteriochloroform, and a few crystals of iodine. The tube was sealed and heated at 70° for 3 hr, at which time the conversion to **12** was seen to be complete. Chloroform was added, and the solution was washed with aqueous sodium thiosulfate, dried, and evaporated. Recrystallization of the solid from acetone gave **12** as yellow crystals: mp 202–203°; ir 1682 cm^{-1} (C=O); uv max (95% ethanol) 372.5 nm (ε 5180); nmr ($CDCl_3$) δ 2.19, 2.28, 2.48 (s, 3 H each, $-CH_3$'s) and 7.40 (s, 5 H, aromatic H).

Anal.. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.78; H, 6.82; N, 6.64.

Reaction Products Derived from 13 with CSI. **Mixture of adducts 14 and 15** (56%) was a viscous liquid: ir ($CHCl_3$) 1867 (m), 1790 (C=O), 1422, and 1182 cm^{-1} (SO_2); nmr (CCl_4) δ 1.15 (s, $-CH_3$), 1.42 (d, $HCCH_3$), 1.45 (s, $-CH_3$), 1.97 (m, $HCCH_3$), 2.40 [d, $HC(C_6H_5)CH-$)], and 7.15 (m, aromatic H).

Adduct 18b (13%) had mp 133–134°; ir ($CHCl_3$) 1750 (C=O), 1620 (C=C), 1412, and 1179 cm^{-1} (SO_2); nmr (CCl_4) δ 1.45

(32) It is necessary to remove all of the unreacted CSI (under reduced pressure) prior to chromatographic separation on silica gel. Any remaining CSI hydrolyzes on the silica gel and results in destruction of the *N*-chlorosulfonylimino ethers.

(33) At temperatures above 150° the character of the sample begins to undergo noticeable changes. On heating at 180° for 10 min lactams **9a** and **10a** undergo significant rearrangement to mixtures of isomeric compounds, the nature of which have not been fully investigated. As a result the melting points of **9a** and **10a** are not highly reproducible.

(s, 3 H), 1.60 (d, J = 6.5 Hz, 3 H), 2.33 (s, 3 H), 4.80 (q, J = 6.5 Hz, 1 H), 6.50 (broad s, 1 H), 7.17 (m, 5 H).

Adduct 21 (3.5%) had mp 118–120° (acetone–water); ir ($CHCl_3$) 1614 (C=C) and 1575 cm^{-1} (C=N); uv max (95% ethanol) 320.5 nm (ϵ 4600); nmr ($CDCl_3$) δ 1.54 (s, 3 H, CH_3), 1.66 (d, J = 6.5 Hz, 3 H, >CHC**H**$_3$), 2.39 (s, 3 H, =CC**H**$_3$), 5.41 [q, J = 6.5 Hz, 1 H, –C**H**(CH$_3$)O], 6.56 (br s, 1 H, =CH), and 7.30 (s, 5 H, aromatic).

Anal. Calcd for $C_{15}H_{16}ClNO_3S$: C, 55.29; H, 4.95. Found: C, 55.52; H, 5.28.

Lactam 18a (7%) had mp 174–175° (aqueous acetone); ir ($CHCl_3$) 3425 (NH), 1692 (C=O), and 1629 cm^{-1} (amide II and/or C=C); uv max (95% ethanol) 297 nm (ϵ 8400); nmr ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.33 (d, J = 6.3 Hz, 3 H, >CH-C**H**$_3$), 2.29 (s, 3 H, CH_3), 4.17 (q, J = 6.3 Hz, 1 H, >C**H**CH$_3$), 6.31 (br s, 1 H, =CH), 6.81 (br, 1 H, NH), and 7.20 (s, 5 H, aromatic H); mass spectrum m/e (calcd for $C_{15}H_{17}NO$, 227.132) 227.137.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.24; H, 7.48; N, 6.30.

Lactam 19 was obtained in <1% yield as a mixture with **18a** and was identified by comparison with the nmr spectrum of **19** derived by isomerization of **18a** (*vide infra*).

Lactam 20 (0.5%) had mp 192–193° (aqueous acetone); ir ($CHCl_3$) 1690 cm^{-1} (C=O); uv max (95% ethanol) 287.5 nm (ϵ 10,800); nmr ($CDCl_3$) δ 1.60 (d, J = 7.3 Hz, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 5.13 (br s, 1 H, >CHN), 5.85 (br q, J = 7.3 Hz, 1 H, =CH), 6.30 (br, 1 H, NH), and 7.28 (s, 5 H, aromatic H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.03; H, 7.50; N, 6.04.

Base-Catalyzed Hydrolysis of Mixture of 14 and 15.—The base-catalyzed hydrolysis of the mixture of **14** and **15** (65 mg) was effected as described in procedure B. The product was purified by column chromatography on silica gel (hexane), giving a mixture of **16** and **17** as a viscous liquid: ir ($CHCl_3$) 1690 cm^{-1} (cyclopropyl ketone); nmr (CCl_4) 0.83 and 0.94 [d's, J = 6.0 Hz, 6 H, –CH(CH$_3$)$_2$ of two isomers], 1.22 (m, 4 H, >CHCH$_3$), 2.0–2.6 [m, 3 H, CHC(=O)CH and CHC$_6$H$_5$], and 7.11 (s, 5 H, aromatic H); mass spectrum m/e (calcd for $C_{14}H_{18}O$, 202.136) 202.137; m/e (rel intensity) 202 (50.8), 159 (51.9), 131 (100.0), and 71 (49.0).

Iodine-Catalyzed Isomerization of 18a.—Approximately 40 mg of **18a** in 0.5 ml of deuteriochloroform was treated with a few crystals of iodine. After standing at room temperature for 24 hr, the conversion to **19** appeared complete. Work-up as described earlier afforded **19** as colorless crystals: mp 126° (aqueous acetone); ir 1685 cm^{-1} ($\nu_{C=O}$); uv max (95% ethanol) 318.5 nm (ϵ 17,300); nmr ($CDCl_3$) δ 1.23 (d, J = 6.3 Hz, 3 H, –CH$_3$), 2.21 and 2.49 (s, 3 H each, –CH$_3$'s), 4.58 (d of q, J = 1.7 and 6.3 Hz, 1 H, –CH(CH$_3$)N–], 6.68 (br s, 1 H, =CH), and 7.32 (s, 5 H, aromatic H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.91; H, 7.51; N, 5.93.

Reaction Products Derived from 22 with CSI. Mixture of ketones 23 and 24 was a ~5:1 ratio of isomers in 30% isolated yield: ir ($CHCl_3$) 1690 cm^{-1} (C=O); nmr (benzene) δ 0.77 and 0.79 (d's, J ~ 6.2 Hz, ~3 H, >CHC**H**$_3$), 1.02 [d, J = 7.0 Hz, 6 H, –CH(CH$_3$)$_2$], 1.6 (m, 1 H, >CHCH$_3$), 1.98 (m, 1 H, >CHC$_6$H$_5$), ~2.65 (overlapping m, 2 H, O=CC**H**<); mass spectrum m/e (rel intensity) 202 (36.3), 159 (33.2), 131 (100.0), 71 (51.9), and 43 (91.3).

Lactam 25 (16–33%) was white needles: mp 168–170.5 (ether); ir ($CHCl_3$) 3450 (NH), 1690 (C=O), and 1630 cm^{-1} (C=C); uv max (95% ethanol) 258 nm (sh, ϵ 7500); nmr δ 1.60 (d, J = 7.0 Hz, 3 H, C**H**$_3$CH=), 1.81 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 4.98 (br s, 1 H, >CHN<), 5.25 (br q, J = 7.0 Hz, 1 H, =CHCH$_3$), 6.50 (br, 1 H, >NH), and 7.29 (s, 5 H, aromatic H); mass spectrum m/e (calcd for $C_{15}H_{17}NO$, 227.132) 227.131.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.31; H, 7.67; N, 6.16.

Adduct 27 (~0.3%) had ir ($CHCl_3$) 1575 cm^{-1} (C=N); nmr δ 1.68, 2.05, 2.43 (s, 3 H each, –CH$_3$'s), 5.48 (br q, 1 H, >CHO–), 6.09 (m, 1 H, =CH), 7.36 (s, 5 H, aromatic H).

Isomerization of 25.—A dilute chloroform solution of **25** (~40 mg) containing a few crystals of iodine was refluxed for 6 days. The usual processing gave in nearly quantitative yield the isomeric lactam **26** as a yellow solid: mp 169–170° (aqueous acetone); ir ($CHCl_3$) 1700 cm^{-1} (C=O); uv max (95% ethanol) 370 nm (ϵ 5800); nmr ($CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3 H, –CH$_2$C**H**$_3$), 2.25 and 2.50 (s, 3 H each, CH$_3$'s), 2.56 (q, J = 7.5 Hz, 2 H, –C**H**$_2$CH$_3$), and 7.43 (s, 5 H, aromatic H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.03; H, 7.50; N, 6.37.

Reaction Products Derived from 28 with CSI. Adduct 29 was a viscous liquid (51% isolated yield): ir ($CHCl_3$) 1871, 1846, 1831 (moderate intensity), 1794 (C=O), 1411, and 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 1.21 (overlapping d, J = 5.4 Hz, 6 H), 1.47 [s, 6 H, >C(CH$_3$)$_2$], and 1.85 (br m, 2 H, >CHCH$_3$).

Adduct 30 (8.5% isolated yield) had ir ($CHCl_3$) 1625 (C=C), 1565 (C=N), 1365 and 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 1.57 [d, J = 6.1 Hz, 3 H, –CH(C**H**$_3$)O–], 1.72 (d d, J = 7.3 and ~1.2 Hz, 3 H, =CHC**H**$_3$), 2.08 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 5.28 (br q, J = 6.1 Hz, CHO–), 5.68 (br q, J = 7.3 Hz, 1 H, =CH).

Adduct 31 (15.5% isolated yield) was a viscous oil: ir ($CHCl_3$) 1742 (C=O), 1630 (C=C), 1405, and 1159 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 1.49 [d, J = 6.5 Hz, 3 H, –CH(C**H**$_3$)N–], 1.68 (d, J = 7.4 Hz, 3 H, =CHC**H**$_3$), 1.94 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 4.65 (q, J = 6.5 Hz, 1 H, =CHN–), and 5.64 (q, J = 7.4 Hz, 1 H, =C**H**CH$_3$).

Mixture of keto amides 32a and 33a had mp 92–98°; ir ($CHCl_3$) 3507 and 3400 (–NH_2), 1695 (C=O), 1676 cm^{-1} (CO-NH_2); nmr ($CDCl_3$) δ 1.18 (distorted d, J ≅ 5.0 Hz, 6 H, cyclopropyl methyls), 1.40 [s, 6 H, >C(CH$_3$)$_2$], 1.50 (m, 2 H), 2.13 (m, 1 H, >CHCO–), and 5.7 (s, 2 H, –NH_2); mass spectrum (calcd for $C_{10}H_{17}NO_2$, 183.127) 183.122; m/e rel intensity) 183 (3.1), 114 (6.2), 97 (100), 96 (2.6), 87 (29.0), 86 (9.1), and 69 (17.8).

Mixture of ketones 32b and 33b was a liquid: ir ($CHCl_3$) 1685 cm^{-1} (C=O); nmr (CCl_4) δ 1.04 [d, J = 7.0 Hz, 6 H, –CH(CH$_3$)$_2$], 1.12 (br s, 6 H, cyclopropyl methyls), 1.1–1.5 (br m, 3 H), and 2.11 [h, J = 7.0 Hz, 1 H, –CH(CH$_3$)$_2$]; mass spectrum m/e (calcd for $C_9H_{16}O$, 140.120) 140.121; m/e (rel intensity) 140 (8.2), 97 (100.0), 71 (4.4), 69 (11.0), 43 (14.6).

Lactone 34 was a liquid: ir (neat) 1750 (C=O) and 1643 cm^{-1} (C=C); nmr (CCl_4) δ 1.37 [d, J = 6.3 Hz, 3 H, –CH-(CH$_3$)O–], 1.68 (d, J = 7.2 Hz, 3 H, =CHC**H**$_3$), 1.92 (s, 3 H, –CH$_3$), 2.31 (s, 3 H, –CH$_3$), 4.71 (q, J = 6.3 Hz, 1 H, >CHO–), 5.47 (q, J = 7.2 Hz, 1 H, =C**H**CH$_3$).

Lactam 35 had mp 113–114° (ether); ir ($CHCl_3$) 3425 (NH), 1690 (C=O), and 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.22 [d, J = 6.2 Hz, 3 H, –CH(C**H**$_3$)N–], 1.63 (d, J = 7.2 Hz, 3 H, =CHC**H**$_3$), 1.83 (s, 3 H, –CH$_3$), 2.34 (s, 3 H, –CH$_3$), 4.02 (q, J = 6.2 Hz, >CHN–), 5.42 (q, J = 7.2 Hz, 1 H, =C**H**CH$_3$), and 6.52 (br s, 1 H, NH).

Reaction Products Derived from 36 with CSI. Adduct 37 was a viscous liquid: 53% isolated yield; ir ($CHCl_3$) 1880, 1840 (medium), 1797 (C=O), 1415, and 1175 cm^{-1} (SO_2); nmr (CCl_4) δ 1.29 (m, 8 H, >CHCH$_3$), 1.48 (s, 3 H, –CH$_3$), and 1.50 (s, 3 H, CH$_3$).

Mixture of adducts 30 and 39 was a viscous liquid: ir ($CHCl_3$) 1630 (C=C), 1570 (C=N), 1370, and 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) (in addition to the peaks of the major isomer **30**) δ 1.53 (d, J = 6.1 Hz), 1.84 (d, J = 7.3 Hz), 2.28 (s, 3 H, =C-CH$_3$), 2.53 (s, 3 H, =CCH$_3$), 5.35 (q, J ≅ 6 Hz, >CHO–), and 5.81 (q, J ≅ 7 Hz, =CHCH$_3$).

Mixture of adducts 31 and 41 was a viscous oil: ir ($CHCl_3$) 1745 (C=O), 1630 (C=C), 1410, and 1170 cm^{-1} (SO_2); nmr (CCl_4) (in addition to the peaks of the major isomer **31**) δ 1.49 (d, J ≅ 6 Hz), 1.72 [d, J ≅ 7 Hz, >CH(CH$_3$)N–], 2.14 (s, CH$_3$), 2.42 (s, CH$_3$), 4.54 (q), and 5.77 (q, =CHCH$_3$).

Keto amide 38a had mp 92.0–93.5° (ether); ir ($CHCl_3$) 3504 and 3397 (–NH_2), 1690 (C=O), 1677 (–CONH_2), 1605 (C=C), 1580 (amide II); nmr ($CDCl_3$) δ 1.13 (m, 8 H, >CH-CH$_3$), 1.41 [s, 6 H, C(CH$_3$)$_2$], 1.97 (m, 1 H, >CHCO), and 5.75 (br s, 2 H, >NH_2); mass spectrum m/e (calcd for $C_{10}H_{17}NO_2$, 183.123) 183.127.

Ketone 38b was a liquid: ir (CCl_4) 1685 cm^{-1} (C=O); nmr (CCl_4) δ 1.06 (br s, 3 H, >CHCH$_3$), 1.08 [d, J = 7.0 Hz, 6 H, –CH(CH$_3$)$_2$], 1.13 (br s, 3 H, >CHCH$_3$), 1.25 (m, 2 H, >CHCH$_3$), 1.66 (m, 1 H, >CHCO–), and 2.62 [h, J = 7.0 Hz, 1 H, –CH-(CH$_3$)$_2$]; mass spectrum m/e (calcd for $C_9H_{16}O$, 140.120) 140.121; m/e (rel intensity) 140 (9.0), 97 (100.0), 71 (13.0), 69 (12.3), 43 (18.5).

Mixture of lactones 34 and 40 was an oil: ir ($CHCl_3$) 1741 (C=O) and 1632 cm^{-1} (C=C); nmr (CCl_4) (in addition to peaks of the major isomer **34**) δ 1.36 (d, J = 6.3 Hz), 1.82 (d, J ≅ 7 Hz), 2.13 (s, CH$_3$), 2.42 (s, CH$_3$), ~5.75 [q, –CH(CH$_3$)O–],

and 5.72 (q, $J \cong 7$ Hz, $=CHCH_3$); mass spectrum m/e (calcd for $C_{10}H_{14}O_2$, 166.099) 166.100.

Mixture of lactams 35 and 42 was an oil: ir ($CHCl_3$) 3430 (NH), 1689 (C=O), and 1634 cm^{-1} (C=C); nmr ($CDCl_3$) (in addition to peaks of the major isomer **35**) δ 1.22 (d, J = 6.2 Hz), 1.63 (d, J = 7.2 Hz), 2.07 (s, CH_3), 2.43 (s, CH_3), 4.28 [q, J = 6.2 Hz, $-CH(CH_3)N-$], 5.73 (q, J = 7.2 Hz, $=CHCH_3$), and 6.82 (br s, 1 H, NH); mass spectrum m/e (calcd for $C_{10}H_{15}NO$, 165.116) 165.112.

Registry No.—**6**, 4544-23-4; **7a**, 37817-10-0; **7b**, 37817-11-1; **8a**, 37817-12-2; **8b**, 37817-13-3; **9a**, 37817-14-4; **9b**, 37817-15-5; **10a**, 37817-16-6; **10b**, 37817-17-7; **11**, 37817-18-8; **12**, 37817-19-9; **13**, 33530-27-7; **14**, 37817-21-3; **15**, 37817-22-4; **16**, 37817-23-5; **17**, 37817-24-6; **18a**, 37817-25-7; **18b**, 37817-26-8; lactam **19**, 37817-27-9; adduct **21**, 37817-29-1; **22**, 33530-26-6; **23**, 37817-31-5; **24**, 37817-32-6; **25**, 37817-33-7; **26**, 37817-34-8; **28**, 37817-36-0; **29**, 37817-37-1; **30**, 37817-38-2; **31**, 37817-39-3; **32a**, 37817-40-6; **32b**, 37817-41-7; **33a**, 37817-42-8; **33b**, 37817-43-9; **34**, 37817-44-0; **35**, 37817-45-1; **36**, 37817-46-2; **37**, 37893-77-9; **38a**, 37817-48-4; **38b**, 37817-53-1; **39**, 37817-47-3; **40**, 37817-51-9; **41**, 37817-49-5; **42**, 37817-28-0; CSI, 1189-71-5.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy. The Spectra of the Linear Alkynes[1]

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The ^{13}C chemical shifts of a selection of linear alkynes are collected and correlated with structure. A system of empirical rules by which the ^{13}C nuclear magnetic resonance spectra of such compounds can be predicted is derived. The failure of the current point-dipole approximation to predict correctly the shifts due to the anisotropy of the triple bond is discussed.

Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra have been reported for a number of linear alkynes.[2-6] In most cases,[2-5] only the chemical shifts of the sp-hybridized carbons were reported, and in all cases spectra were measured using the adiabatic, rapid-passage technique, which generally yields experimental uncertainties of 0.5 ppm. While accuracy of this magnitude is adequate for many applications,[6] it is not sufficient to identify the more subtle chemical-shift differences associated with changes in substitution in remote sites in the molecule. Because such information is important in applications of ^{13}C nmr spectroscopy to problems in structure elucidation,[7] we have undertaken a brief survey of ^{13}C spectra of linear alkynes using the absorption mode and spectrum averaging. The present paper describes the results of this survey and compares them to those reported earlier.

Experimental Section

Carbon-13 chemical shifts were measured under conditions of full proton decoupling on the Varian digital frequency sweep spectrometer described previously.[8] Chemical shifts were measured relative to internal 1,4-dioxane and were then referenced to external carbon disulfide using the relation $\delta_{CS_2} = \delta_{1,4\text{-dioxane}} + 126.2$. Regression analyses were performed on an IBM 360/75 computer with the aid of a standard subroutine for stepwise multiple regression analysis.[9]

Results

The extant data for the linear alkynes and alkadiynes are presented in Table I. The spectrum of 1,7,13-tetradecatriyne[10] is also included for comparison. For the octynes, data from earlier workers and from these laboratories are both included in Table I. It is obvious that there are substantial differences between the spectra obtained by dispersion[6] and absorption modes. Indeed, the differences are often greater than the experimental errors of the two methods. These disparities are possibly partly due to solvent or concentration effects. The earlier data[6] were derived from neat solutions, while solutions in 1,4-dioxane were used in the present study. Throughout the remainder of this paper, only our own data for the octynes will be considered.

The spectra of the various alkynes are compared to those of the analogous alkanes in Table II. The values in this table were obtained by subtracting the shifts of the alkane from those of the alkyne in each case. From Table II it is evident that, within any particular subgroup of linear alkynes, the sp-hybridized carbons are shifted downfield from their positions in the saturated alkane by quite constant amounts. Thus, in the 1-alkynes, the terminal sp carbon is 54.5 ppm downfield from the corresponding methyl, while the other unsaturated carbon is about −61.0 ppm

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relative to its position in the alkane. The relative constancy of these shift differences suggest that the alkynes would yield a satisfactory regression analysis of the type noted earlier for the acyclic alkenes.[11] The effects of the triple bond upon the saturated carbons of the chain are, however, rather less regular than observed for the alkenes.[11] There is, of course, the large and relatively constant upfield shift which has been noted to occur at the α carbon,[6a] but the chemical-shift differences at the β, γ, $\cdots$ carbons are far less regular than observed for the alkenes.

The convention used in the regressional analysis is detailed in Figure 1. The chemical shift of each sp-hybridized carbon was expressed as a function of the number of α, β, γ, α', $\cdots$ carbons in the molecule. Thus, the expression for carbon 1 of 1-butyne is $125.5 = \alpha' + \beta'$, while that of carbon 3 of 2-heptyne is $114.9 = \alpha + \beta + \gamma + \alpha'$. It is important to note that because data are available only for linear alkynes, the coefficients of the substituent parameters α, β, $\cdots$ will be 1 or 0 in every case.

The results of the regressional analysis are shown in Table III. As for the alkenes,[11] the α and β parameters are large and negative, while the γ shift is smaller and positive. In contrast to the α shift, α' is upfield in nature, again as observed for the alkenes. The only difference in the qualitative comparison of the results for the regressional analyses of the alkenes and alkynes is that of the β' parameter. This shift was found to be upfield in the alkenes, while for the present compounds it is small and deshielding. The analysis yields a standard error of 0.3 ppm and a multiple correlation coefficient of 0.998. It is of interest to note that the chemical shift of ethyne itself is predicted by the analysis to be 120.9 ppm. Apparently, the carbon shift of this compound has not yet been measured.

Discussion

Throughout the common hydrocarbons which have been studied by ^{13}C nmr spectroscopy, chemical shifts have been found to fall within three broad ranges, depending on the hybridization of the carbon. The chemical shifts of saturated carbons generally fall into a range of 140–190 ppm upfield from the resonance of carbon disulfide, while sp^2 carbons occur between 45 and 85 ppm. As seen from this and previous studies, the present range of chemical shifts of sp-hybridized carbons can be taken to be within the bounds of 105 and 125 ppm. Within these broad ranges, the largest variations have been shown[11,12] to correlate well with the extent of direct substitution by carbon, as well as the substitution on adjacent carbons (the so-called α and β effects[11,12]). Within the hydrocarbons, other effects, such as electronegativity, seem to be minor. Thus, a saturated carbon which is attached to a double bond is deshielded at most by 2 ppm. A shift of this magnitude is small in ^{13}C nmr spectroscopy, amounting to only about 1% of the general range of carbon chemical shifts. In fact, the small downfield shift observed for the α carbons in the alkenes is frequently entirely outweighed by opposing shielding effects which are

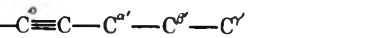

Figure 1.—The designation of the saturated carbons in the calculation of the chemical shift of C°.

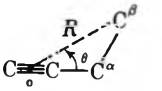

Figure 2.—A definition of the parameters in the McConnell equation, taking the β carbon as an example. The point o is the electrical center of gravity of the anisotropic group. The distance R is that between the point o and the nucleus in question, while θ is the angle between R and the axis of symmetry of the triple bond.

considered to be steric in nature.[11,13] To demonstrate the differences between carbon and proton chemical shifts, we may consider the methyl carbon chemical shifts in methylcyclohexane, 1-methylcyclohexene, and toluene. The chemical shifts of the methyl carbons in these three compounds are 170.6,[14] 169.9,[6b] and 171.8 ppm,[15] respectively. Thus, the chemical shift of a carbon bonded to a double bond is relatively unaffected by the increased electronegativity of the unsaturated system.

The three examples above serve to demonstrate another curiosity regarding carbon chemical shifts. The methyl carbon resonance of toluene is upfield of the analogous absorption in 1-methylcyclohexene, while protons attached to aromatic rings are strongly deshielded by the ring-current effect.[16] Furthermore, the chemical shifts of sp^2-hybridized carbons in alkenes and aromatic carbons are not very different.

With this in mind, we may approach the interpretation of the ^{13}C nmr spectra of the alkynes. One of the most striking shifts observed in these compounds is that of the α carbon, which is shielded by *some 10 to 14 ppm* relative to the analogous alkanes (see Table II). While this shielding effect might be attributable to the diamagnetic anisotropy of the triple bond, it is clear that the point-dipole approximation,[17] which was derived to rationalize quantitatively the proton chemical shifts in such systems, fails to predict correctly the chemical shifts of the α carbons of linear alkynes.[6a] In terms of the spatial parameters defined in Figure 2, the McConnell equation takes the form

$$\sigma_g = \frac{\Delta\chi}{3R^3}(1 - 3\cos^2\theta)$$

where σ_g is the screening due to anisotropic group g, and $\Delta\chi$ represents the anisotropy of the diamagnetic susceptibility. Using general bond lengths and angles observed in alkynes,[18] and a value of $\Delta\chi$, which was derived from proton nmr studies,[19] the point-dipole approximation predicts a shielding effect of about 4 ppm at the α carbon. The empirical shift is at least three times this magnitude. Unless there is a second,

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TABLE I

^{13}C CHEMICAL SHIFTS OF CARBONS OF LINEAR ALKYNES IN PARTS PER MILLION WITH REFERENCE TO CS_2

Registry no.	Alkyne	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	Ref
	1-Butyne	125.5	107.8											3
	1-Pentyne	125.5	110.1	173.6	171.6	180.6								6b
	1-Hexyne	125.1	107.4	175.1	162.6	171.3	179.6							6a
	1-Heptyne	125.1	109.6	174.8	164.4	161.8	170.1	178.5						6a
	1-Octyne	123.5	108.5	174.1	163.3	163.3	160.5	169.1	177.6					6a
629-05-0	1-Octyne	124.8	109.3	174.9	164.5	164.6	161.7	170.6	179.4					This study
	1-Dodecyne	124.9	109.0	174.4	163.5	163.5	163.5	163.5	163.5	163.5	160.9	170.2	178.9	6b
	2-Butyne		118.9	118.9										3
	2-Hexyne	190.8	118.8	115.6	172.9	170.9	180.4							6a
	2-Heptyne	190.2	118.3	114.9	174.8	161.3	170.7	179.0						6a
	2-Octyne	189.6	117.7	114.0	174.1	163.0	161.1	169.8	178.0					6a
2809-67-8	2-Octyne	190.7	118.5	114.5	174.6	164.2	162.0	170.9	179.6					This study
	2-Dodecyne	190.0	118.4	114.6	172.2	164.1	164.1	164.1	164.1	164.1	161.0	170.0	179.1	6b
	3-Hexyne	178.1	180.5	112.6										6a
	3-Heptyne	178.8	180.5	112.3	114.2	172.3	170.0	179.4						6a
	3-Octyne	177.4	179.5	111.5[a]	112.8[a]	173.8	160.6	169.7	177.9					6a
15232-76-5	3-Octyne	180.0	181.0	112.2	114.4	175.2	161.8	171.3	179.1					This study
	3-Dodecyne	178.6	180.3	112.0[a]	113.8[a]	174.0	163.4	163.4	163.4	163.4	160.9	170.1	178.6	
	4-Octyne	179.8	171.1	173.3	113.5									6a
1942-45-6	4-Octyne	180.2	170.6	173.6	113.6									This study
	4-Dodecyne	179.5	170.5	172.6	113.7	113.7	174.6	164.1	164.1	164.1	161.1	170.5	179.5	6b
	5-Dodecyne	179.4	171.1	161.6	174.6	113.7	113.7	174.6	164.0	164.0	161.6	171.1	179.4	6b
	6-Dodecyne	178.8	170.4	161.6	163.8	174.4	113.2							6b
871-84-1	1,7-Octadiyne	124.0	109.2	175.3	165.6									This study
16387-70-5	3,5-Octadiyne	180.0	180.6	115.2	128.3									This study
16287-71-6	4,6-Dicadiyne	180.1	171.1	172.2	117.0	127.3								This study
	5,7-Dodecadiyne					114.8	125.5							5
872-21-9	1,7,13-Tetradeca-triyne	124.6	109.6	175.2	165.1	165.5	174.9	112.7						This study

[a] The assignments of the indicated resonances have been reversed from those of the original study.

TABLE II

^{13}C SHIFT DIFFERENCES BETWEEN LINEAR ALKYNES AND ALKANES WITH THE SAME NUMBER OF CARBONS

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
1-Butyne	−54.8	−60.7										
1-Pentyne	−54.3	−60.8	+14.6	+0.7	+0.8							
1-Hexyne	−54.5	−60.9	+13.6	+1.1	+0.7	0						
1-Heptyne	−54.5	−60.9	+13.7	+0.4	+0.7	−0.4	−1.1					
1-Octyne	−54.8	−61.2	+13.8	+0.7	+0.8	+0.6	+0.1	−0.2				
1-Dodecyne	−54.0	−61.4	+13.5	+0.3	+0.3	+0.3	+0.3	+0.3	+0.3	0	−0.2	0
2-Butyne		−49.6										

2-Hexyne	+11.2	−51.8	−45.9	+11.4	+0.3	+0.8						
2-Heptyne	+10.6	−52.2	−46.2	+10.8	+0.2	+0.2	−0.6					
2-Octyne	+11.1	−52.0	−46.6	+10.8	+0.4	+0.9	+0.4	0				
2-Dodecyne	+11.1	−52.0	−46.3	+9.0	+0.9	+0.9	+0.9	+0.9	+0.1	−0.4	+0.2	
3-Hexyne	−1.5	+9.9	−48.9									
3-Heptyne	−0.8	+9.6	−48.8	−49.8	+11.2	−0.5	−0.2					
3-Octyne	+0.4	+10.5	−48.9	−49.4	+11.4	+0.7	+0.8	−0.5				
3-Dodecyne	−0.3	+9.9	−48.9	−49.4	+10.8	+0.2	+0.2	+0.2	0	−0.3	−0.3	
4-Octyne	+0.6	+0.1	+12.5	−50.2								
4-Dodecyne	+0.6	+0.1	+11.7	−49.5	−49.5	+11.4	+0.9	+0.9	+0.9	+0.1	+0.1	+0.6
5-Dodecyne	+0.5	+0.7	+0.7	+11.4	−49.5	−49.5	+11.4	+0.8	+0.8	+0.7	+0.7	+0.5
6-Dodecyne	−0.1	0	+0.7	+0.6	+11.2	−50.0						

TABLE III

CHEMICAL-SHIFT PARAMETERS IN PARTS PER MILLION OBTAINED FROM REGRESSIONAL ANALYSES[a]

Parameter	Value	F level	Parameter	Value	F level
α	−6.7	2.5	α'	+5.3	2.5
β	−6.3	2.5	β'	−0.6	0.6
γ	+1.6	2.0	γ'	−0.4	0.5

[a] Standard error of fit = ±0.3. Multiple correlation coefficient, 0.998; constant term, 120.9. The standard error of the parameters were uniformly ±0.2 ppm.

unrecognized shielding mechanism at the α carbon of these alkynes, these results indicate a clear failure of the point-dipole approximation. Further experiments designed to clarify this problem are in progress and will be reported separately.[10]

The shielding effect at the β and γ carbons is less regular and, in many instances, shows variations greater than expected from experimental errors. In the case of the γ carbons, as well as those more remote from the triple bond, these differences could be due to conformational differences. Thus, changes in the dihedral angles between the triple bond and the γ carbon could change the R and θ of Figure 2 significantly. The same is not true of the β carbon, the R and θ values of which are fixed. The variation at these centers cannot be explained in terms of neighboring-group effects. It is possible that some form of self-association of alkyne units is responsible for these variations, and a study of a more extended range of dilutions using pulse Fourier transform spectroscopy is badly needed.

Some additional insight regarding the effect of a triple bond upon neighboring carbon nuclei is available from the data for the diynes and single triyne in Table I. It is noteworthy, for example, that in the spectra of 3,5-octadiyne and 5,7-dodecadiyne the interior sp-hybridized carbons are upfield by 12 to 14 ppm from their positions in the corresponding monoalkynes. Hence, the effect of a triple bond at the neighboring α position is broadly independent of the hybridization of the α carbon. In the spectra of 1,7-octadiyne and 1,7,13-tetradecatriyne, the chemical shifts of the β and γ carbons are 0.6–1.1 ppm upfield from their positions in the spectrum of 1-octyne. It appears then that the magnitude of the shielding effect in these compounds is dependent upon the number of triple bonds present, even if these effects cannot be put in accurate quantitative terms.

The sp-hybridized carbons fall into a range intermediate between those of saturated carbons and alkene and aromatic carbons. It has been pointed out that the range of shifts for acetylenic carbons is more limited than those of the other two hybridizations,[6a] but it should be recognized that this results primarily from the lack of data regarding examples of alkynes which are branched at the α carbon. Thus, because both the α and β parameters are large and negative (see Table III), it would be expected that alkynes branched at the α position could show more extended ranges of shifts. There are, unfortunately, no data available for a branched alkyne at the present time.

It was pointed out above that the chemical shifts of sp-hybridized carbons are relatively constant within a given subgroup of alkynes. Thus, the shifts of carbons 1 and 2 of 1-alkynes are quite consistently about 124 and 109 ppm, respectively. It has been suggested[5] that the differences between the chemical shifts of the sp-hybridized carbons of an alkyne will be a diagnostic tool which allows differentiation of 1-alkynes, 2-alkynes, and midchain alkynes. Unfortunately, our results again indicate that these generalizations will break down when alkynes with chain branching at the α position are taken into account.

The γ parameter (Table III) for the alkynes is of the same sign and magnitude as observed for the alkenes.[11] This fact would seem to argue against

the earlier conclusion[11] that the γ effect is at least partially steric in nature, because the steric interactions of sp^2- and sp-hybridized carbons must surely be different. Except for the alkanes, the γ effect remains an important but poorly rationalized phenomenon. Further research into the mechanism of this effect is underway.[20]

Regardless of the origin of the γ effect, its identification has allowed us to assign the sp resonances uniquely in the spectra of 3-alkynes. In previous work, the unsaturated carbon resonances of such alkynes as 3-octyne were incorrectly assigned, or left unassigned.[6a] The derivation of the γ parameter, however, allows specific assignment in such examples. Alkynes which possess triple bonds which are removed by more than three sp^3-hybridized carbons from the end of a linear chain cannot, however, be assigned using our method. Fortunately, the chemical shifts of the sp-hybridized carbons in such systems are frequently so similar as to preclude the resolution of the peaks.[6a]

The similarities of the α' shifts of alkenes and alkynes tends to confirm the hypothesis[11] that this effect is derived in part from polarizations of the π electrons. Certainly, large chemical-shift differences have been demonstrated for unsaturated species and, where mesomeric polarizations can be expected, these lead to very large polarizations of both double[21,22] and triple[23] bonds. In the hydrocarbons, in which the polarizing effect can be due only to inductive and hyperconjugative effects, the polarizations lead to much smaller differences in the shifts of the unsaturated carbons. Thus, the chemical shifts of carbons 1 and 2 of ethoxyethyne are 104.6 and 170.8 ppm,[23] respectively. These shifts may be directly compared to those of 1-pentyne, in which the chemical shifts of the sp-hybridized carbons differ by only 15.4 ppm.

Both the β' and γ' shifts are small and negative. Furthermore, the lower F levels[9] indicate that these parameters are less important to the regressional analysis. In the alkenes,[11] the analogous β' effect was found to be approximately +2 ppm, and its origin was considered to be of a steric nature. The present results are consistent with such a formulation. In the rigidly linear alkynes, the β' carbon is precluded from coming into the proximity of the more distant sp-hybridized carbon and a steric effect would therefore be suppressed. Without such an influence, the presence of the β' effect becomes less important.

With the present analysis of the ^{13}C nmr spectra of alkynes, procedures are now available for the prediction of the spectra of all three major groups of acyclic hydrocarbons. We are therefore prepared to establish a set of rules through which the interpretation of carbon-13 chemical-shift data can lead to elucidation of structures. The development of such rules and their applications to compounds other than hydrocarbons are currently under investigation in these laboratories and will be reported later.[7]

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Registry No.—^{13}C, 14762-74-4.

Cycloaddition. XV. Competing Mechanisms in the Reaction of Cyclopentadiene with Trifluoroethylene and 2-Chloro-1,1-difluoroethylene

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Thermal cycloaddition of trifluoroethylene to cyclopentadiene competes unfavorably with diene dimerization (about 1:600 at 8°). At 210°, where the dimer dissociates thermally, a cross-cycloadduct is obtained consisting of about 99% of the two norbornenes (exo H/endo H, 2:1). 2-Chloro-1,1-difluoroethylene appears to be about four times as reactive a dienophile as trifluoroethylene, yielding a cycloadduct at 170° that is 99.5% norbornenes (exo H/endo H, 5:3). Photosensitized cycloaddition of trifluoroethylene to cyclopentadiene yields mixtures of six cross-cycloadducts, whose structures and configurations were established by proton and fluorine nmr spectroscopy and by independent synthesis. The product composition did not depend on the nature or triplet excitation energy of the sensitizer, but reflected competition, even at 2°, between slow thermal cycloaddition and the relatively inefficient photosensitized process. When thermal reaction was minimized, the photosensitized product consisted of 15.5% norbornenes and 84.5% bicyclo[3.2.0]heptenes from (2 + 2) cycloaddition. The latter showed major/minor regioselectivity of about 2.3, and in the major orientation the ratio of endo H/exo H was ~ 2. The photosensitized adduct of 2-chloro-1,1-difluoroethylene to cyclopentadiene differed from that of trifluoroethylene chiefly in showing a much greater regioselectivity in the bicyclo[3.2.0]-heptenes: the major/minor orientation = 42 and endo H/exo H = 3.2–3.4. These results are consistent in detail with competition in the thermal cycloaddition such that about 98.5% is concerted in the case of trifluoroethylene and 99.4% in the case of 2-chloro-1,1-difluoroethylene. The endo preference of halogen in the concerted (2 + 4) cycloaddition mechanism is absent or slightly reversed in the (2 + 4) products of the photosensitized reaction and is strongly reversed in the (2 + 2) product.

Photosensitized cycloadditions, proceeding through an excited triplet state of one of the reactants, have been used successfully as models indicating what may be expected of a *bona fide* biradical mechanism.[1,2] When one of the reactants is a conjugated diene and the other is unsymmetrically substituted, the product mixture is characterized by its relative content of

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cyclobutanes and cyclohexenes, resulting respectively from (2 + 2) and (2 + 4) addition, and by the orientation of the reactant molecules in the former (regioselectivity). If, in addition, there is geometrical configuration in either or both of the reactants, wide variations are possible in the extent of configurational loss, retention, or inversion during the cycloaddition. In the reaction between cyclopentadiene and 1,2-dichloroethylene,[3] on going from photosensitized to thermal reaction the four (2 + 2) cycloadducts disappear from the product and one observes only the Diels–Alder product (two isomers from the cis alkene and one from the trans) formed with retention of configuration, indicating that the thermal reaction is a concerted one with no biradical behavior. On the other hand, the cycloaddition of trifluoroethylene to butadiene photosensitized with biacetyl yields a mixture of the same four stereoisomeric vinyltrifluorocyclobutanes plus trifluorocyclohexene as is obtained by thermal cycloaddition, the only difference between these two mixtures being a regioselectivity factor of 1.35 for the photosensitized reaction and 2.16 for the thermal.[1] By detailed study of the dependence of product composition upon the triplet energy of the sensitizer it was possible to conclude that the thermal addition of trifluoroethylene to butadiene is chiefly a biradical reaction, but with about 9% occurring by a competing concerted mechanism.

If trifluoroethylene represents a compound in which the capabilities for biradical formation and for concerted Diels–Alder reaction are delicately balanced, the behavior of this olefin should be subject to variation as it reacts with dienes differing in their predisposition to be Diels–Alder donors or to yield biradicals. Accordingly we have, in the present study, compared the thermal and photosensitized cycloaddition of trifluoroethylene to cyclopentadiene, previously shown to be more than 1000 times as reactive as butadiene toward maleic anhydride in a concerted mechanism, but less reactive by a factor of 8 than butadiene toward the stepwise reagent 1,1-dichloro-2,2-difluoroethylene.[4]

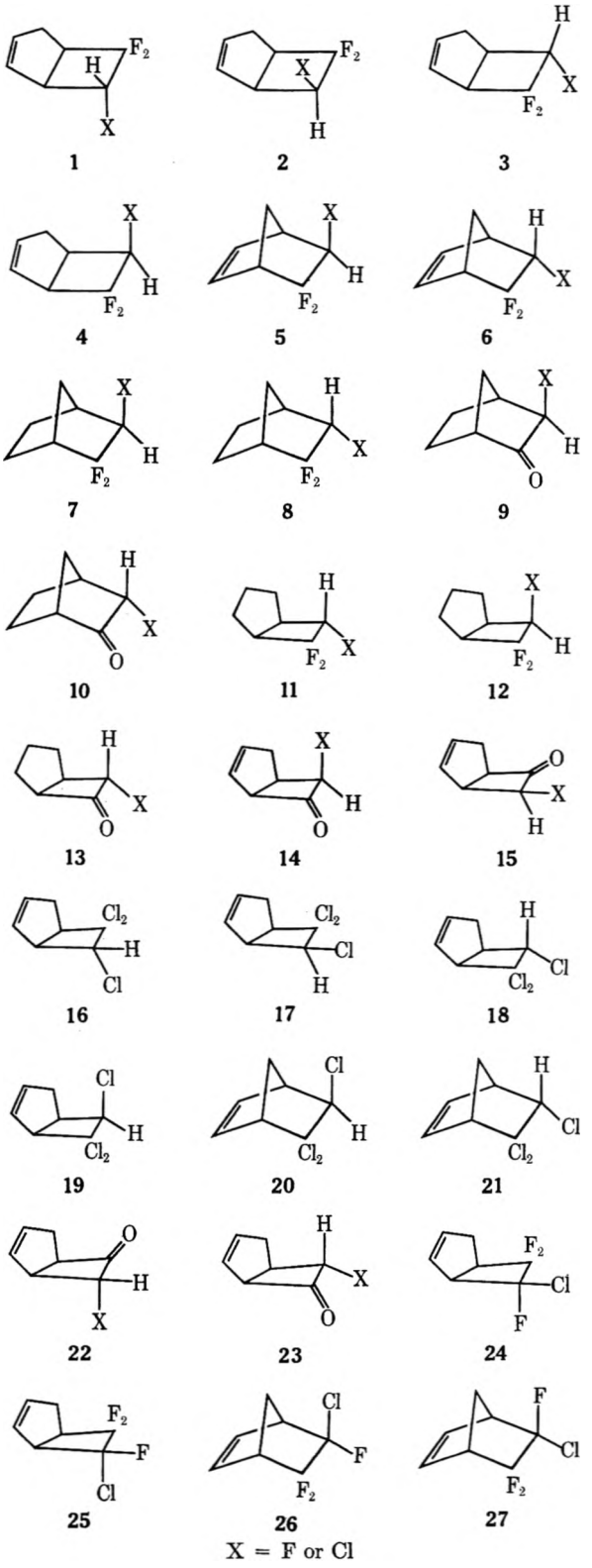
Results

Thermal Cycloadditions.—Although it was possible to obtain appreciable amounts of cycloadducts by protracted thermal reactions at temperatures as low as 8°, these preparations were made very inefficient by the strongly competing dimerization of cyclopentadiene. Thus, with a sixfold excess of trifluoroethylene over diene, after 30% reaction of the diene only 0.9% of the product was cross-cycloadduct, the rest being dicyclopentadiene. This indicates that the bimolecular rate constant for dimerization of cyclopentadiene must be at least 600 times as great as that for its cycloaddition with trifluoroethylene. For the practical purpose of obtaining higher yields of cross-cycloadducts, advantage was taken of the reversibility of cyclopentadiene dimerization; when the reaction was run with an excess of trifluoroethylene at 210° dicyclopentadiene was formed only temporarily and eventually the whole of the diene was converted into cross-cycloadducts.

(3) P. D. Bartlett, R. Helgeson, and O. A. Wersel, *Pure Appl. Chem.*, **16**, 187 (1968).

(4) P. D. Bartlett and L. K. Montgomery, *J. Amer. Chem. Soc.*, **86**, 628 (1964).

With only cis ring juncture being considered, the possible cross-cycloadducts are **1**-F to **6**-F. The char-



acterization and establishment of structure for these isomers and the corresponding ones where X = Cl are described below. Table I shows the product compositions indicated by vapor chromatography for the thermal cycloadditions. None of **3**-F or **4**-F could be detected in these mixtures; although there is interference from the overlapping of the relatively large peaks of **5**-F and **6**-F, we know from the butadiene adducts[1] and from the photosensitized products from cyclo-

TABLE I

PRODUCTS OF THE THERMAL REACTION OF TRIFLUOROETHYLENE AND CYCLOPENTADIENE

Temp, °C	Ratio of C_2F_3H/diene	1-F	2-F	5-F	6-F	Dicyclopentadiene yield, %	Diene converted, %
8 ± 3	6.0	<0.01	<0.01	0.2	0.7	99+	30
29.2 ± 0.1	4.0	<0.01	<0.01	1.1	3.0	96	55
64.5 ± 0.1	5.2	<0.01	<0.01	2.8	6.4	91	65
121.7 ± 0.1	4.9	<0.01	<0.01	5.0	10.0	85	95
210 ± 5	2.0	0.6	0.3	39.0	60.1		100

TABLE II

PRODUCTS OF THE THERMAL REACTION OF 2-CHLORO-1,1-DIFLUOROETHYLENE AND CYCLOPENTADIENE

Temp, °C	Ratio of C_2F_2ClH/diene	1-Cl	2-Cl	5-Cl	6-Cl	Dicyclopentadiene yield, %	Diene converted, %
8 ± 3	2.4	~0.02	~0.01	0.6	1.1	98	30
29.2 ± 0.1	6.0	~0.02	~0.01	1.8	3.1	95	55
64.5 ± 0.1	3.7	~0.02	~0.01	3.1	5.0	92	70
121.7 ± 0.1	3.9	~0.09	~0.05	9.5	15.6	75	95
170 ± 5	2.0	0.3	0.2	38.0	61.5		100

TABLE III

CROSS-ADDUCT DISTRIBUTIONS FROM THE PHOTOSENSITIZED REACTION OF CYCLOPENTADIENE AND TRIFLUOROETHYLENE

Sensitizer	1-F	2-F	3-F	4-F	5-F	6-F	Yield of all cross-adducts, %
None[a]	~1	<1	?	?	24	75	~0.5
None[b]	28	13	12	4	18	25	1.3
2-Acetonaphthone or benzophenone	42	19.5	20.5	5.0	6.5	6.5	6–12

[a] Cyclopentadiene treated with lithium aluminum hydride before use, all transfers done under vacuum. [b] No precautions taken to prevent oxidation of the cyclopentadiene.

pentadiene that the orientation of **1** and **2** is preferred over that of **3** and **4** by at least 2:1, which sets an upper limit of 0.45% for (**3** + **4**) in the product at 210° having the most (2 + 2) cycloadducts. This very strong preference for (2 + 4) cycloaddition by trifluoroethylene, when compared with the formation of 67% (2 + 2) product[5] by tetrafluoroethylene at 470–480° and of 16% (2 + 2) product[6] by 1122 at 80°, confirms the position of trifluoroethylene as a reagent in which the concerted mechanism competes strongly with the stepwise.

Table II shows that the thermal cycloaddition of 2-chloro-1,1-difluoroethylene to cyclopentadiene is similar to that of trifluoroethylene, with the small difference that the detectable (2 + 2) cycloadducts now represent only 0.5% of the whole. The regioselectivity introduced by a single chlorine atom in the alkene will reduce the products **3**-Cl and **4**-Cl to negligible proportions (see the photosensitized results in Table IV). Table II shows that 170° is a sufficient temperature to eliminate the cyclopentadiene dimer through its thermal dissociation and recapture of the cyclopentadiene by the halo olefin. There is a hint that the endo/exo ratio in the norbornenes, which favors endo halogen, chlorine somewhat more than fluorine, is determined by the secondary orbital-overlap effects often seen in the concerted Diels–Alder mechanism. This selectivity, amounting to as much as 2:1, is reversed in the (2 + 2) adducts, and also in all the products of photosensitized addition, indicating that secondary orbital overlap does not control the isomer distribution in the stepwise mechanism.

Photosensitized Cycloadditions.—After a few photosensitized cycloadditions had been run, it became apparent that the reactivity of cyclopentadiene in thermal dimerization and cross-cycloaddition was high enough to necessitate correction for competing thermal reaction even at 0°. In a series of reactions with seven different sensitizers it was noted that, as the total yield of cross adducts rose from 2 to 12%, the fraction of **5**-F and **6**-F in the product declined from 31 to 15.5%. Photochemical runs without sensitizer sometimes gave as much **1** + **2** as **5** + **6** and some of the (2 + 2) as well as (2 + 4) dimers of cyclopentadiene, but, if oxidation products were removed from the starting diene and air was excluded, only **5**, **6**, and the thermal diene dimer were formed. The absence of the tetracyclic dimer[3] showed that the reaction occurring under these conditions was thermal and not initiated by excited cyclopentadiene singlets. This conclusion is supported by the dark control in Table IV. Increasing the concentration of the sensitizer (using a little ether to increase sensitizer solubility) and using sensitizers of higher absorbance helped to increase the photosensitized reaction and decrease the correction for competing thermal reaction. There was no dependence of the composition of cyclopentadiene cycloadducts on the triplet energy of the sensitizer within the limits of those used here (biacetyl, E_T 54.9, to acetone >78 kcal/mol). Good photosensitized rates and reproducible product compositions were obtained with benzophenone or 2-acetonaphthone (Table III) at concentrations of about 15 mol %.

(5) J. J. Drysdale, W. W. Gilbert, H. K. Sinclair, and W. H. Sharkey, *J. Amer. Chem. Soc.*, **80**, 3672 (1958).

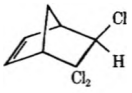
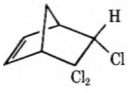
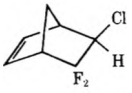
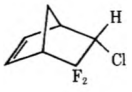
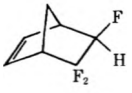
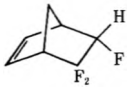
(6) P. D. Bartlett, L. K. Montgomery, and B. Seidel, *ibid.*, **86**, 616 (1964).

TABLE IV
CROSS-ADDUCT DISTRIBUTIONS FROM THE PHOTOSENSITIZED REACTION OF CYCLOPENTADIENE AND 2-CHLORO-1,1-DIFLUOROETHYLENE

Sensitizer	1-Cl	2-Cl	3-Cl	4-Cl	5-Cl	6-Cl	Yield of all cross-adducts, %
None[a]	5	6	?	?	42	47	0.8
None[b]	37	12	?	?	25	18	2.5
None, no light	<1	?	?	?	36	63	0.8
Acetophenone, benzophenone, 2-acetonaphthone	66	19.5	1.4	0.6	7.5	4.5	15–20

[a] No precautions taken to prevent air oxidation of the cyclopentadiene. [b] Cyclopentadiene treated with lithium aluminum hydride before use, all transfers done under vacuum.

TABLE V
PROTON NMR DATA FOR SOME 5,5,6-TRIHALOBICYCLO[2.2.1]HEPTENE-2 COMPOUNDS

		δ_{H_1}	δ_{H_4}	δ_{H_5}	δ_{H_2}, δ_{H_3}	δ_{H_7} (2 H)	$\Delta\delta_{H_5}$
20		3.03	3.48	4.20	6.32 (2 H)	1.95, 2.3	0.57
21		3.25	3.53	4.77	6.28 (2 H)	2.0 (2 H)	
5-Cl		2.96	2.96	3.80	6.2, 6.2	1.95, 2.15	0.44
6-Cl		3.10	3.10	4.24	6.2, 6.3	1.9 (2 H)	
5-F		2.9	2.9	4.33	6.2 (2 H)	2.0, 2.15	0.52
6-F		3.0	3.0	4.85	6.22 (2 H)	1.7, 1.8	

The photosensitized cycloaddition of 2-chloro-1,1-difluoroethylene to cyclopentadiene is similar to that of trifluoroethylene. Table IV shows that the main difference between the two cases is the much smaller fraction of **3** and **4** in the chlorodifluoroethylene adduct where these isomers together amount to only 2% of the product, as compared to 25.5% in the trifluoroethylene photoadducts. This difference is obviously appropriate to a biradical mechanism, where the high preference for forming an allylic radical from the diene and an α-chloroalkyl radical from the haloalkene produces a high regioselectivity in the reactant having a chlorine atom at one end. It is also noticeable that, between the two principal products, the less hindered stereoisomer is more highly favored where the disposition of a chlorine atom rather than a fluorine atom is involved (1-F/2-F 42:19.5, 1-Cl/2-Cl 66:19.5).

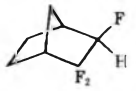
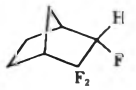
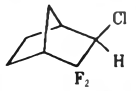
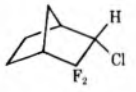
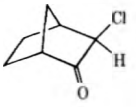
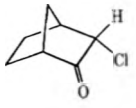
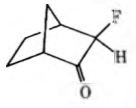
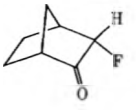
Identification of Products.—The analyses and preparative separations were accomplished by vapor chromatography as described in the Experimental Section. The proton nmr spectra of 5,5,6-trihalonorbornenes form a consistent pattern, as shown in Table V where the chemical shifts of **5** and **6** are compared with those of the trichloronorbornenes.[7] The assignments are consistent with the generalization that an endo hydrogen is shielded relative to a similarly situated exo hydrogen, and that hydrogen is shielded by an eclipsing chlorine atom.[8-11] The nmr spectra of the hydrogenated compounds shown in Table VI further illustrate the effect of endo or exo configuration and show that the effect can be as large in norbornanes (*e.g.*, **9**-Cl and **10**-Cl) as in the corresponding norbornenes.

The availability of all the cycloadducts from photosensitized cycloaddition made possible the nmr observations summarized in Tables VII, VIII and IX. The ethylenic proton absorptions of the bicyclo[3.2.0]-heptenes examined here fell in the range δ 5.7–6.0

(7) J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, **84**, 297 (1962).
(8) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).
(9) W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 2533 (1958).
(10) R. B. Fraser, *Can. J. Chem.*, **40**, 78 (1962).
(11) T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963).

TABLE VI

PROTON NMR DATA FROM SOME 2,2,3-TRIHALONORBORNANES AND RELATED COMPOUNDS

	[a]	δ_{H_1}	δ_{H_4}	δ_{H_6}	$\Delta\delta_{H_6}$	δ_{H_6} of dehydro compounds
7-F		2.1	2.4	4.28		4.33
					0.27	
8-F		2.5	2.5	4.55		4.85
7-Cl				3.80		3.80
					0.31	
8-Cl				4.11		4.24
9-Cl		2.65	2.65	3.75		3.75
					0.54	
10-Cl				4.29		4.28
9-F		2.6	2.6	4.17		
					0.48	
10-F		2.2	2.2	4.65		

[a] The numbering is made to correspond with that of the norbornenes to simplify comparisons to values in Table V.

ppm, while those of the norbornenes were at 6.2–6.3 ppm. The exo and endo assignments based on the hydrogen chemical shifts are confirmed by the ^{19}F chemical shifts, which also show fluorine more shielded when in the endo than in the exo position (Table X). The structural and configurational assignments based on the nmr spectra were made in a consistent manner by comparison with analogous compounds.[12] These assignments were confirmed by synthesis of several of the adducts or derivatives as well as of analogous compounds.

The trichloroethylene cycloadducts **16**, **17**, and **18** were prepared as shown in Scheme I. **15**-Cl was identical with the known main product of cycloaddition of monochloroketene to cyclopentadiene. The known endo configuration[13–16] of **15**-Cl establishes the exo configuration of the major and minor products, **22**-Cl and **23**-Cl, which yield a common hydrogenation product (**13**-Cl) whereas **15**-Cl yields a different one (**14**-Cl). The three unsaturated chloro ketones were converted by phosphorus pentachloride into the corresponding trichlorobicyclo[3.2.0]heptenes without loss of configuration.

Of the reactions used in approaching the bicyclo[3.2.0]heptene ring system, the addition of ketenes is more regio- and stereoselective than the addition of nitrosyl chloride. Compound **17**, accessible by both paths and almost the sole product by the ketene approach, is the isomer missing in the previous[3] photosensitized cycloaddition of trichloroethylene and cyclopentadiene. In a reexamination of such a cycloadduct mixture, a small peak was observed in the vapor chromatogram having the retention time of **17**; it represented 0.3% of the mixture.

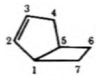
The configurations of the 2-chloro-1,1-difluoroethylene cycloadducts **1**-Cl, **2**-Cl, and **5**-Cl were independently established through their hydrogenation products **11**-Cl, **12**-Cl, and **7**-Cl which were prepared from the ketones **13**-Cl, **14**-Cl, and **9**-Cl, respectively, by reaction with sulfur tetrafluoride, the yield in the last case being 95% of a single product. The reaction of **13**-Cl, catalyzed with a few mole per cent of HF, and that of **14**-Cl, catalyzed by 30–40 mol % HF, gave 25% yields and neither the **11**-Cl nor the **12**-Cl was contaminated with the other.

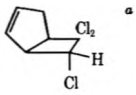
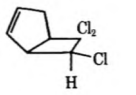
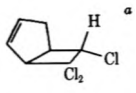
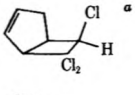
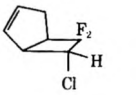
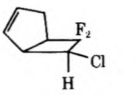
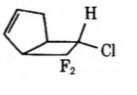
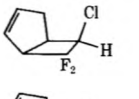
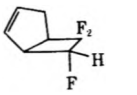
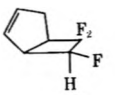
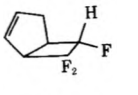
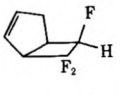
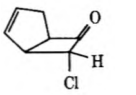
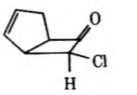
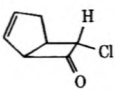
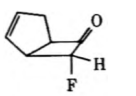
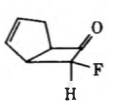
An attempt to synthesize the trifluoroethylene cycloadducts **1**-F to **6**-F by way of the corresponding fluoro

(12) B. M. Jacobson, Thesis, Harvard University, 1970.
(13) W. T. Brady and E. F. Hoff, Jr., *J. Amer. Chem. Soc.*, **90**, 6256 (1968).
(14) W. T. Brady, E. F. Hoff, Jr., R. R. Roe, Jr., and F. H. Parry, III, *ibid.*, **91**, 5679 (1969).
(15) P. R. Brook, A. J. Duke, and J. C. R. Duke, *Chem. Commun.*, 574 (1970).
(16) P. R. Brook, J. M. Harrison, and A. J. Duke, *ibid.*, 589 (1970).

TABLE VII

PROTON NMR ABSORPTIONS FOR SOME HALOBICYCLO[3.2.0]HEPT-2-ENES

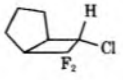
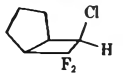
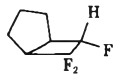
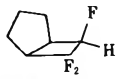
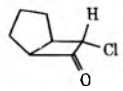
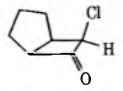
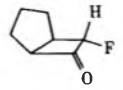
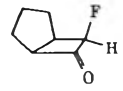


		δ_{H_1}	δ_{H_5}	$\delta_{H_1} - \delta_{H_5}$	δ_{H_6} or δ_{H_7}	$\Delta(\delta_{H_6}$ or $_{H_7})$
16	 [a]	3.34[b]	3.64	−0.30	4.28	
17		3.81[b]	3.60	0.21	5.01	0.73
18	 [a]	3.98	3.06[c]	0.92	4.30	
19	 [a]	4.01	3.50[c]	0.51	4.99	0.69
1-Cl		3.16	3.50	−0.34	4.00	
2-Cl		3.55	3.24[d]	0.31	4.65	0.65
3-Cl		3.8	2.7	1.1	4.02	
4-Cl		3.80	3.15	0.65	4.67	0.65
1-F		3.3	3.3	0.0	4.65	
2-F		3.58	3.00	0.58	5.08	0.43
3-F		3.68	2.75	0.93	4.65	
4-F		3.63	2.90	0.73	4.99	0.34
22-Cl		3.52	4.15	−0.63	4.32	
15-Cl		3.92	3.90	0.02	5.25	0.93
23-Cl		4.30	2.92	1.38	4.52	
22-F		3.54	3.96	−0.42	4.86	
15-F		3.84	3.48	0.36	5.56	0.07

[a] Reference 3. [b] Assigned by decoupling H-7. [c] Assigned by decoupling H-6. [d] Assigned by decoupling H-4.

TABLE VIII

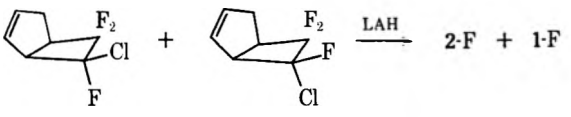
PROTON NMR ABSORPTIONS FOR SOME HALOKETO- AND TRIHALOBICYCLO[3.2.0]HEPTANES

		δ_{H_1}		δ_{H_4}	δ_{H_6}	$\Delta\delta_{H_6}$	δ_{H_6} of dehydro compounds
11-Cl		2.64		3.18	3.92		4.0, 4.2
						0.67	
12-Cl		2.22		2.90	4.59		4.65, 4.67
11-F		2.6	to	3.0	4.53		4.65, 4.65
						0.43	
12-F		2.1		2.9	4.96		4.99, 5.08
13-Cl		2.88		3.70	4.45		4.32, 4.52
						0.67	
14-Cl		3.28		3.72	5.12		5.25
13-F		2.8		3.5	4.98		4.86
						0.44	
14-F		3.3		3.3	5.42		5.56

ketones was unsuccessful. Sulfur tetrafluoride converted *exo*-3-fluoro-2-norbornanone (**9**-F) into an almost equal mixture of the stereoisomeric dihydro products **7**-F and **8**-F, offering no check on the configurations of the single fluorine atoms. In the case of **14**-F, sulfur tetrafluoride did not yield either **11**-F or **12**-F, but instead an isomer containing a $-CF_2H$ group and a single ethylenic hydrogen atom, evidently resulting from opening of the four-membered ring.

Incidentally to the preparation of the fluoro ketone **15**-F, we observed that the cycloadduct of fluoroketene and cyclopentadiene contains not only the endo isomer, recognized by Brady and Hoff,[13] but actually 14% of the exo isomer **22**-F, which is enough more water soluble than the endo to be easily lost in water washing during work-up unless special precautions are taken. A comparison of the endo/exo ratios in the cycloadducts of fluoroketene (6.1), chloroketene (24), methylketene (99),[17] and *tert*-butylketene (>99)[17] extends by about a log unit the field of plottable points in the correlation[18] between Taft's E_S and the endo/exo ratio in cycloaddition of substituted ketenes. The new points maintain the Brady–Roe slope of 1.5 within the limited precision of the relationship. The $(2_s + 2_a)$ mechanism provides the only general "masochistic steric effect" of which we are aware—one in which the requirements of the transition state and product are so completely reversed that a product predominates in direct proportion to its steric strain.

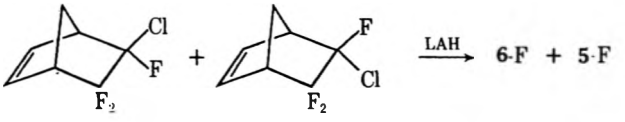
To establish the orientation of the major and minor pairs of the (2 + 2) products of trifluoroethylene with butadiene,[1] advantage had been taken of the high regiospecificity in cycloaddition of trifluorovinyl chloride. The same was now done with the cyclopentadiene adducts; a mixture of **24** and **25** in a 1:1 ratio was



24 **25**

1 : 1 97 : 3

completely dechlorinated by lithium aluminum hydride to yield a 97:3 mixture of 2-F and 1-F. Exactly the same endo/exo ratio was seen in the trifluoronorbornenes resulting from the LAH dechlorination of a 3:2 mixture of **26** and **27** after 80 and 100% reaction.



26 **27**

3:2 97 : 3

The mechanism of the LAH dechlorination, in cases where SN2 displacement is not favored, is not known, but the predominant delivery of the hydrogen on the exo side is in accord with any of the possible two-step mechanisms proceeding through an ionic or radical intermediate. The assignment of the orientations **1** and **2** to the major 1,2 adducts of trifluoroethylene

(17) L. A. Hull, unpublished work.

(18) W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **93**, 1662 (1971).

TABLE IX

COUPLING CONSTANTS IN THE BICYCLO[3.2.0]HEPTENE-2 SYSTEM AS DETERMINED BY DOUBLE IRRADIATION

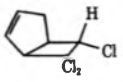
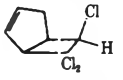
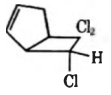
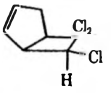
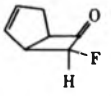
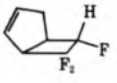
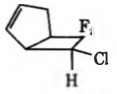
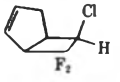
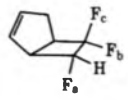
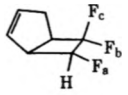
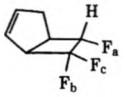
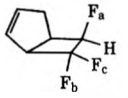
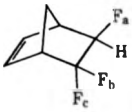
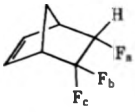
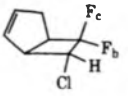
		$J_{1,7}$ or $J_{5,6}$, cps	$J_{5,7}$ or $J_{1,6}$, cps	$J_{4,5}$, cps
18		7	1	
19		8	3	
16		5	1	
17		8	<1	
15-F		8	3	
3-F		7	<1	
2-Cl				7
4-Cl				9

TABLE X

^{19}F NMR DATA FOR THE CYCLOPENTADIENE–TRIFLUOROETHYLENE ADDUCTS

		δ_{F_a}[a]	δ_{F_b}	δ_{F_c}	$J_{b,c}$, cps	J_{H,F_a}, cps
1-F		176	101	102	210	52
2-F		186	84	117	200	51
3-F		181	93	110	200	51
4-F		195	91	109	210	52
5-F		178	95	105	230	53
6-F		178	93	105	230	53
1-Cl			88	91	190	

[a] In parts per million upfield from $CFCl_3$ internal standard.

confirms the assignments made on the basis of nmr spectra.

Finally, **3**-F and **4**-F are assigned their configurations by hydrogenation, **1**-F and **3**-F both yielding the same product (**11**-F) while **2**-F and **4**-F yield **12**-F.

Discussion

The characteristics of typical thermal concerted cycloadditions (such as maleic anhydride and cyclopentadiene) and of typical thermal biradical cycloadditions (such as 1122 and butadienes) have been explored in detail and found to form two self-consistent patterns.

For (2 + 4) cycloaddition, both concerted and biradical mechanisms are equally "allowed." We first raised the question of possible biradical pathways for certain (2 + 4) cycloadditions when it was found that substitution of bulky groups in the 2 position of butadiene[19,20] made cyclohexenes prominent reaction products of 1122, which with butadiene gave 99% vinylcyclobutanes. A consistent explanation of this steric effect was that the 2 substituents forced a larger fraction of the dienes into the s-cis or the skew conformation, resulting in the kind of cis-allylic radical which was compatible with closure to a six-membered ring. It was found, however,[21] that the cis-fixed diene, 1,2-dimethylenecyclobutane, gave entirely (2 + 2) cycloaddition of 1122, and it was noted that two discernible differences between it and cyclopentadiene—C_1–C_4 distance and strain in the double bond of the (2 + 4) adduct—would operate similarly whether the mechanism of the cycloaddition were concerted or stepwise. Therefore other criteria of mechanism would be needed if any assignment to competing modes of (2 + 4) cycloaddition in such cases were to be made.

Our first attempt to resolve the cycloaddition of a borderline reagent into simultaneous competing pathways[22] was based on the stereochemistry of thermal addition of *cis*- and *trans*-1,2-dichloro-1,2-difluoroethylene ("1212") to cyclopentadiene. The (2 + 4) cycloadduct showed retained configuration with retention index[2,23] PQ > 10^4, while the (2 + 2) cycloadduct lost configuration to an extent normal (PQ = 9.5) for the stepwise mechanism. The ratio of rate constants for (2 + 4) and (2 + 2) addition was found to be 16 for *cis*- and 36 for *trans*-1212, and the rate constant ratio for the two mechanisms is presumably not far from this value.

For alkenes, such as trifluoroethylene, having no geometrical configuration to serve as an indicator of stepwise mechanism, a detailed comparison between thermal and photosensitized cycloaddition[1] to butadiene has indicated that the ratio k_{2+4}/k_{2+2} of 0.15 in thermal cycloaddition corresponds to $k_{\text{concerted}}$/

(19) P. D. Bartlett, *Science*, **159**, 833 (1968).

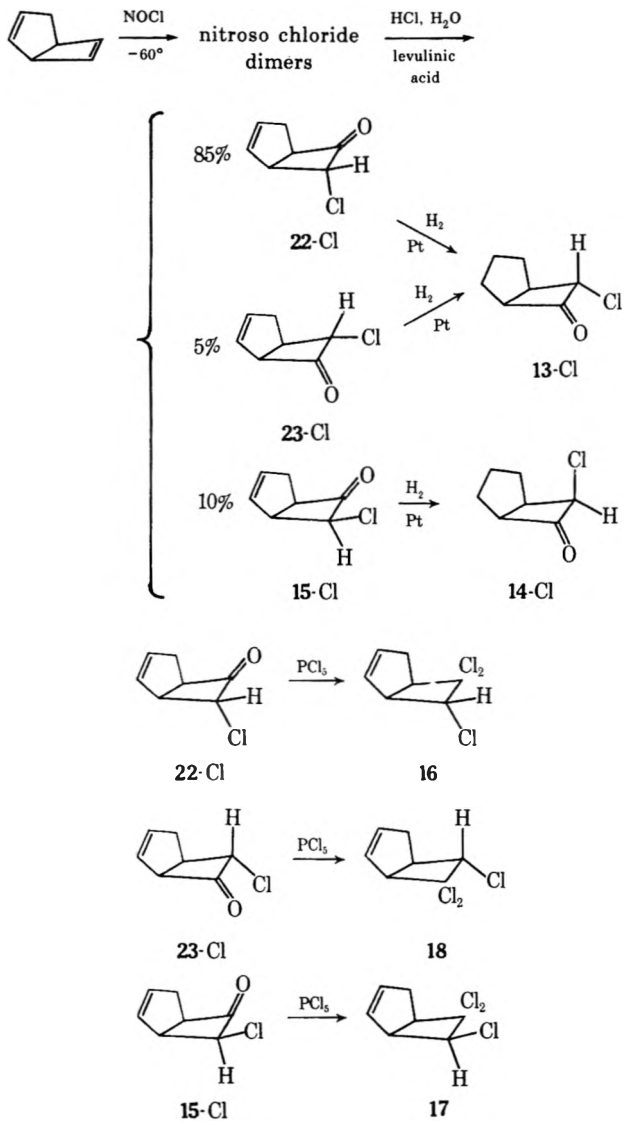
(20) P. D. Bartlett, G. E. H. Wallbillich, A. S. Wingrove, J. S. Swenton, L. K. Montgomery, and B. D. Kramer, *J. Amer. Chem. Soc.*, **90**, 2049 (1968).

(21) P. D. Bartlett, A. S. Wingrove, and R. Owyang, *ibid.*, **90**, 6067 (1968).

(22) R. Wheland and P. D. Bartlett, *ibid.*, **92**, 3822 (1970).

(23) L. K. Montgomery, K. E. Schueller, and P. D. Bartlett, *ibid.*, **86**, 622 (1964).

SCHEME I



$k_{stepwise}$ of 0.12, reflecting a mechanism that is mostly by the biradical path. The present results reflect the large preference of cyclopentadiene for the concerted process. The (2 + 4)/(2 + 2) ratio of 110 observed in the thermal reaction of trifluoroethylene at 210° should probably be corrected by assuming that the undetected 3-F and 4-F were formed thermally in a proportion to (1-F and 2-F) no greater than that (0.41) seen in the photosensitized reaction where all the (2 + 2) isomers are more abundant. This would make the ratio of (2 + 4)/(2 + 2) for trifluoroethylene greater than 78, and for 2-chloro-1,1-difluoroethylene about 195. To determine the ratio of concerted to stepwise mechanism we need to transfer from the numerator of this fraction to the denominator that part of the (2 + 4) adduct which arose from biradicals, as indicated by the photosensitized results. If N_C = amount of norbornenes in the thermal product from concerted reaction, N_R = amount of norbornenes in the thermal product from biradicals, and B = amount of bicyclo[3.2.0]heptanes in the thermal product, then for trifluoroethylene $(N_C + N_R)/B = (2 + 4)/(2 + 2) = 78$; $N_C + N_R = 78B$; $N_R/B = 13/87 = 0.15$; $N_R = 0.15B$; $N_C = 77.85B$; (concerted)/(stepwise) = $N_C/(N_R + B) = 77.85B/(0.15B + B) = 68$. Similarly for 2,2-difluoro-1-chloroethylene, (concerted)/(stepwise) = $N_C/(N_R + B) = (195 - 0.136)B/(0.136B + B) = 172$. These figures show that the 500-fold preference of cyclopentadiene for (2 + 4) rather than (2 + 2) cycloaddition, as compared to butadiene, is a matter of a strong predisposition to react by the concerted mechanism.

If we assume that the lack of a primary end to the conjugated system of cyclopentadiene leads to the same eightfold retardation for biradical formation with trifluoroethylene as with 1122, the concerted mechanism must be faster for cyclopentadiene by a factor of 566/8 or 71, corresponding to a $\Delta\Delta F^{\ddagger}$ of 4 kcal/mol. The ionization potential of cyclopentadiene is 0.10 V lower than that of butadiene,[24] which would account for a $\Delta\Delta F^{\ddagger}$ of 2.3 kcal in a reaction controlled by donor-acceptor interactions. The remaining 1.7 kcal could be provided as a $T\Delta\Delta S^{\ddagger}$ term, since to react concertedly butadiene must be brought into the s-cis conformation in which cyclopentadiene is permanently fixed. (Toward benzoquinone in benzene, the $\Delta S^{\ddagger}$ of reaction with cyclopentadiene is 5.9 eu more favorable than is that with butadiene.[25])

The results to date support the following generalizations. (1) The tendency to react *via* biradicals changes more rapidly with structure of the alkene than does the capacity for concerted Diels–Alder reaction.[19] (2) Geminal substitution on the double bond by fluorine or by a cyclopropane ring[26] increases the proneness to biradical formation. (3) Accommodation of an odd electron in a biradical is favored in the descending order: $-CCl_2 > -CHCl > -CHF > CF_2$. Regioselectivity is the greater, the farther apart the two ends of the alkene are in this series. (4) Relative to hydrogen or fluorine, most other substituents on a carbon–carbon double bond are favorable to the formation of a radical site, but unfavorable to initial bond formation at that position, in the biradical mechanism.[27] (5) Regioselectivity is the same in direction, and somewhat reduced in magnitude, when biradicals are formed in reaction of an excited triplet state of a diene compared to its ground state. (6) Despite incomplete correction for thermal effects, alkenes in photosensitized reaction with cyclopentadiene all yield ratios of k_{2+4}/k_{2+2} within the limits 0.15–0.78, even though the k_{2+4}/k_{2+2} ratios for thermal reaction vary in the same series from 5 to over 100. (7) The structural features predisposing alkenes and dienes to undergo cycloaddition thermally by concerted mechanisms are largely independent of those predisposing to biradical mechanisms. Nevertheless, the widely varying behavior of the borderline fluorinated alkenes in this regard is a predictable function of the structure of the diene.

Experimental Section

Thermal Reaction of Cyclopentadiene and Trifluoroethylene.—A 0.75-g sample of freshly cracked cyclopentadiene was placed

(24) 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 Positive Ions," National Standard Reference Data System.

(25) A. Wassermann, "Diels–Alder Reactions," Elsevier, Amsterdam, 1965, p 52, Table 14.

(26) P. D. Bartlett and R. Wheland, *J. Amer. Chem. Soc.*, **94**, 2145 (1972).

(27) P. D. Bartlett, K. Hummel, S. P. Elliott, and R. A. Minns, *ibid.*, **94**, 2898 (1972).

in a heavy walled (2 mm) tube, and 2–2.5 g of trifluoroethylene was condensed into the tube, which was then degassed and sealed. The tube was heated in the appropriately thermostated water or oil bath or tube oven. Reaction times for complete consumption of the diene were several weeks at or below 30°, 1 week at 65°, 2 days at 120°, and 36 hr above the cracking temperature of the diene dimer.

After being cooled in liquid nitrogen and opened, the tube was transferred to a Dry Ice–acetone bath with immersion as complete as possible. *n*-Decane (100 mg) was washed into the tube with ether, and the contents of the tube were poured into a flask previously cooled in a Dry Ice–acetone bath. The flask was allowed to warm to room temperature with vigorous stirring. The residue left after the excess trifluoroethylene had been removed was distilled trap-to-trap and analyzed on column K (Table XI) with flame detector response factor of 1.7 for the

TABLE XI

GAS-LIQUID PARTITION CHROMATOGRAPHY COLUMNS USED[a]

Index no.	Column[b]	Machine[c]
A	Apiezon J, 20 ft × 1/4 in. 45/60 Chromosorb P	90P-3
B	Carbowax 20M, 24 ft × 1/4 in. 60/80 acid-washed Chromosorb P	700
C	Tricresyl phosphate, 30 ft × 1/4 in. 60/80 Chromosorb P	700
D	1,2,3-Tris(2-cyanoethoxy)propane, 25 ft × 1/4 in. 60/80 Chromosorb P	700
E	Carbowax 20M, 20 ft × 3/8 in. 60/80 Chromosorb W	90P-3
F	β,β′-Oxydipropionitrile, 25 ft × 1/4 in. 45/60 Chromosorb P	90P-3
G	Carbowax 20M, 9 ft × 1/4 in. 60/80 Chromosorb W	1520
H	10% tricresyl phosphate, 30 ft × 1/8 in. 60/80 Chromosorb P	609, 7620A
J	10% 1,2,3-tris(2-cyanoethoxy)propane, 30 ft × 1/8 in. 60/80 Chromosorb P	609, 7620A
K	11% Carbowax 20M, 30 ft × 1/8 in. 60/80 Chromosorb P	609
L	10% β,β′-oxydipropionitrile, 30 ft × 1/8 in. 45/60 Chromosorb P	609

[a] Flow rates: 110 ml/min for 3/8 in. diameter columns; 75 ml/min for 1/4 in. diameter columns; 20–25 ml/min for 1/8 in. diameter columns. [b] 20% liquid phase unless noted otherwise. [c] Machines: F & M 700, T. C. detector, dual columns; F & M 609, flame detector, single column; F & M 7620A, flame detector, dual columns; Varian Aerograph 90P-3, T. C. detector, single column.

adducts. Preparative separation was carried out using column E. The first material eluted from the column other than solvent was **5**-F, mp 74.5–75.5°, a volatile waxy material (exact mass for $C_7H_7F_3$: calcd, 148.04998; found, 148.04964.) Compound **6**-F follows **5**-F, mp 73–75°, also a waxy volatile solid (exact mass found, 148.04935).

Precautions.—The glass tubing used for the thermal reaction was always annealed in an annealing oven before use (with a neck for the final seal already made) and the final seal annealed carefully. Tubes were not filled more than one-quarter full and tube diameters of more than 12 mm were avoided. A weak or over-full tube may explode violently upon heating.

Thermal Reaction of Cyclopentadiene and 2-Chloro-1,1-difluoroethylene.—The procedure, work-up, and analysis were the same ones used for the reaction of cyclopentadiene and trifluoroethylene. Compound **5**-Cl, *exo*-6-chloro-5,5-difluoronorbornene, a waxy material melting slightly below room temperature (exact mass for $C_7H_7F_2Cl$: calcd, 164.02035; found, 164.02071) was eluted from the column before the endo-chloro compound, **6**-Cl, a waxy solid, mp 34–36° (exact mass found, 164.0206). Both materials have retention times greater than that of cyclopentadiene dimer. The flame response factor is 1.7.

Photosensitized Reaction of Cyclopentadiene and Trifluoroethylene. Materials.—Acetophenone and biacetyl were distilled before use. Fluorene (Eastman White Label) was recrystallized before use from 95% ethanol. Benzophenone (Eastman White Label), acetone (Fisher reagent), and 2-acetonaphthone (Matheson Coleman and Bell) were all used as received. Triphenylene (Aldrich Chemical Co.) was recrystallized from CH_2Cl_2–pentane and phenanthrene was purified by heating with maleic anhydride in triglyme and recrystallization from 95% ethanol. Trifluoroethylene (Peninsular Chem-Research Co.) was used as received. Cyclopentadiene was freshly cracked or distilled before use, but in the blanks, additional purification was required. This consisted of placing the freshly cracked cyclopentadiene over a few grams of lithium aluminum hydride in a flask attached to a vacuum line. The flask was degassed and the mixture was stirred at room temperature for 2 hr. The cyclopentadiene was then distilled through the line into the previously prepared and degassed reaction tube which was then sealed *in vacuo*.

Irradiation.—This was performed in sealed heavy walled (2 or 3 mm) Pyrex tubes. The tube was charged with 0.5–2 g of cyclopentadiene, depending on its diameter (9 to 19 mm), a 3- to 15-fold excess of trifluoroethylene, and the sensitizer (1–15 mol % based on diene, with 2 or 3 ml of ethyl ether if more than 3 mol % of sensitizer was used, since trifluoroethylene is a very poor solvent and the sensitizer would fail to dissolve in most cases without added ether). The tube was given a final degassing and sealed under vacuum. Tubes were strapped to an immersion well placed in a water bath cooled to 3 ± 2° by a Lauda Ultra Kryomat TK-30 circulating methanol cooled to −10°. Irradiation was performed with a 450-W Hanovia medium pressure mercury lamp. Irradiation in analytical runs was from 10 to 100 hr. In preparative runs 72 hr of irradiation was used.

Analysis.—Following irradiation, the tubes were cooled in liquid nitrogen, opened, and transferred to Dry Ice and 100 mg of *n*-decane was washed into each tube. Each tube was immersed as deeply as possible in Dry Ice; the contents were then poured into a previously cooled flask. The excess trifluoroethylene was distilled off with vigorous stirring and the residue distilled trap-to-trap at 0.1 mm pressure. Glpc analysis of the distillate was carried out using column K at 90°. The order of elution of cross-adducts was **1**-F, **3**-F, **5**-F, **4**-F, **6**-F, and **2**-F. Retention times are 20, 23, 24, 27, 30, and 32 min, respectively.

Preparative Scale Reaction.—Following removal of the excess trifluoroethylene and trap-to-trap distillation, the distillate was injected 0.5 ml at a time on column A to yield a mixture of the six cross-adducts (retention time 20–30 min at 125°) free of the cyclopentadiene dimers (retention time approximately 2 hr, three spaced injections of distillate are made before clearing the column of dimers). The mixture of cross-adducts was then injected 30 μl at a time on column B at 90°. Collection at this stage yielded **1**-F and **2**-F in greater than 99% purity, and almost pure **6**-F. **5**-F, **3**-F, and **4**-F were not completely separated by one pass and a second pass of each of these materials, injected 10 μl at a time, was necessary. Nmr spectra of the separated adducts were taken in 50% $CFCl_3$ (both H and ^{19}F). Ir spectra were taken in CCl_4. Samples for mass spectra were collected by the method of Burson and Kenner[28] [exact masses for $C_7H_7F_3$: calcd, 148.04998; found, 148.04949 (for **1**-F), 148.04949 (for **2**-F), 148.05049 (for **3**-F)].

Photosensitized Reaction of Cyclopentadiene and 2-Chloro-1,1-difluoroethylene.—Materials and irradiation procedure were as for trifluoroethylene except that no added ethyl ether solvent was required.

Analysis.—The work-up used is the same used for the trifluoroethylene case. Column K at 110° or L at 90° may be used for glpc. The order of retention times is (for column K): **1**-Cl, 55 min; **3**-Cl, 61 min; **5**-Cl, 65 min; **6**-Cl, 77 min; **4**-Cl, 84 min; **2**-Cl, 98 min.

Preparative Scale Reaction.—Following the trap-to-trap distillation of the crude photoproducts, the distillate was injected 0.5 ml at a time on column A (retention time of cross-adduct mixture 40–55 min at 125°) yielding the six cross-adducts together freed from diene dimers. The adduct mixture was injected 50 μl at a time on column B at 110°. **5**-Cl, **6**-Cl, **1**-Cl, and **2**-Cl were collected essentially pure (99 +%). Fractions containing about 50% pure **3**-Cl contaminated with **1**-Cl and **5**-Cl and 50% pure **4**-Cl contaminated with **6**-Cl were reinjected to give 90% pure **3**-Cl and 99% pure **4**-Cl. Since the total yield

(28) K. R. Burson and C. T. Kenner, *J. Chromatogr.*, **7**, 63 (1969).

of 3-Cl at this point (200 hr of collecting time) was 19 mg, no further purification was attempted. The 10% impurity remaining is compound 5-Cl.

Nmr spectra were taken in 50% CCl_4. Ir spectra were also in CCl_4. Samples for mass spectra were collected in capillary tubes by the method of Burson and Kenner[27] [exact masses for $C_7H_7F_2Cl$: calcd, 164.02035; found, 164.02038 (for 1-C), 164.02055 (for 2-Cl)].

Hydrogenation of Trifluoro- and 2-Chloro-1,1-difluoroethylene–Cyclopentadiene Adducts. Hydrogenation of *exo*-5,5,6-Trifluoronorbornene (5-F).—A 150-mg sample of 5-F and 10 mg of PtO_2 in 500 μl of ethyl acetate were placed in a 5-ml flask with magnetic stirring bar, degassed with one freeze–thaw pumping cycle, and then stirred under hydrogen at atmospheric pressure until the calculated amount of hydrogen had been absorbed (approximately 30 ml). The mixture was then distilled trap-to-trap and injected 150 μl at a time on column B or G at 100°; 120 mg of *exo*-2,2,3-trifluoronorbornane was collected (80% yield).

Hydrogenation of the 11 other cross-adducts was done in the same manner, except that for 3-Cl only 15 mg of adduct and 2 mg of PtO_2 were used yielding 10 mg of product while 8 mg of 4-Cl and 2 mg of PtO_2 were used yielding 5 mg of hydrogenation product. In these two cases, the product was transferred from the collection trap in a minimum of CCl_4 to a 0.2-mm ir cell for the ir spectrum to be taken and then transferred, with a drop of tetramethylsilane added, to an nmr probe.

Reaction of Nitrosyl Chloride and Bicyclo[3.2.0]heptadiene-2,6. Preparation of Ketones 15-Cl, 22-Cl, and 23-Cl.—A 7.5-g sample of bicyclo[3.2.0]heptadiene-2,6[29] dissolved in 75 ml of chloroform was cooled in a Dry Ice–acetone bath. Nitrosyl chloride (Matheson) was bubbled in with rapid stirring until the deep blue-green solution turned a definite yellow-brown and remained so colored when the NOCl addition was stopped. The mixture, containing a thick semicrystalline precipitate, was allowed to warm to room temperature. The chloroform was removed on a rotary evaporator, and this residue was stirred with 200 g of levulinic acid (Aldrich Chemical Co., freshly distilled) and 17 ml of 2 *N* hydrochloric acid at 70° overnight. The cooled mixture was poured into 600 ml of water and the aqueous layer extracted ten times with 30-ml portions of ethyl ether. The original organic layer and combined ether fractions were washed once with 200 ml water, twice with 200 ml of saturated $NaHCO_3$ solution, and once with saturated NaCl solution, and dried over anhydrous $MgSO_4$; the ether was evaporated. The crude product was distilled through a 6-in. column of glass helices. The fraction, bp 80–90° (8 mm), 5.5 g (48% yield), consisted of nearly pure chloro ketones 15-Cl, 22-Cl, and 23-Cl and a few per cent of ethyl levulinate. All are separated on column E at 150°. The first ketone eluted from the column is 22-Cl, *exo*-7-chlorobicyclo[3.2.0]hepta-2-en-6-one. 23-Cl follows, then ethyl levulinate and then 15-Cl. The proportions of the three ketones were 17:1:2.

Preparation of *exo*-6,6,7-Trichlorobicyclo[3.2.0]heptene-2 (16).—A 1.0-g sample of 22-Cl was placed in 4.0 ml of PCl_3, and 3 g of PCl_5 was added. The mixture was stirred at room temperature for 8 days. It was poured on ice, a few milliliters of CH_2Cl_2 were added, and the solution was extracted with $KHCO_3$ solution, dried, and distilled trap-to-trap. Analytical glpc on column K indicates the presence of 16 and the absence of 17, 18, and 19. Preparative glpc on column E at 160° yielded 0.1 g of pure 16 having nmr and ir spectra matching those of material isolated from the photosensitized reaction of cyclopentadiene and trichloroethylene.[3]

Preparation of *endo*-6,6,7-Trichlorobicyclo[3.2.0]heptene-2 (17).—A 0.6-g sample of *endo*-7-chlorobicyclo[3.2.0]hept-2-en-6-one (15-Cl) was placed in 3 ml of PCl_3 containing 2 g of PCl_5 and stirred at room temperature for 2 weeks. It was poured onto ice and a few milliliters of CH_2Cl_2 were added. The organic layer was extracted with aqueous $KHCO_3$, washed once with water and once with saturated NaCl, dried over anhydrous $MgSO_4$, and filtered, and the CH_2Cl_2 was evaporated. The residue was distilled trap-to-trap. Analytical glpc indicated the absence of 16, 18, and 19. The major peak occurred with the retention time assigned to the previously unisolated 17 from the photosensitized reaction of cyclopentadiene and trichloroethylene. The photoreaction was repeated and preparative glpc using column E at 160° (two passes) allowed isolation of a few milligrams of 17. Nmr and ir spectra of the adduct collected in this way matched those at the product from the reaction with PCl_5.

Preparation of *exo*-6,7,7-Trichlorobicyclo[3.2.0]heptene-2 (18).—A 0.1-g sample of *exo*-6-chlorobicyclo[3.2.0]hept-2-en-7-one (23-Cl) was placed in 0.4 ml of PCl_3 containing 300 mg of PCl_5 and stirred at room temperature for 8 days. The product was worked up as in the case of 17. Analytical glpc on column K indicated a low yield of 18 and the absence of 16, 17, and 19. Preparative separation on column G at 150° afforded 10 mg of 18, with nmr and ir matching authentic samples obtained from the cyclopentadiene–trichloroethylene photoreaction.

Hydrogenation of 22-Cl and 23-Cl. Preparation of *exo*-7-Chlorobicyclo[3.2.0]heptanone-6 (13-Cl).—A 1-g sample of 22-Cl (or 100 mg of 23-Cl) with 5 mg of PtO_2 per 100 mg was hydrogenated at atmospheric pressure in ethyl acetate as solvent. Following absorption of 1 equiv of H_2, the mixture was filtered and distilled to yield 0.9 g (85 mg from 23-Cl) of 13-Cl.

Preparation of *exo*-3-Chloro-2,2-difluoronorbornane (7-Cl).—A 2.5-g sample of *exo*-3-chloronorcamphor[30] in 30 ml of CH_2Cl_2 and 0.35 g of water was cooled in a stainless steel pressure vessel to −70°. SF_4 (30 g, Matheson) was condensed into the vessel through Teflon tubing; the vessel was sealed and shaken overnight at 70°. After venting (through aqueous KOH), the solution was washed with aqueous $KHCO_3$, filtered, dried, and distilled trap-to-trap to give 2.6 g (95%) of *exo*-3-chloro-2,2-difluoronorbornane (7-Cl) after removal of the CH_2Cl_2.

Hydrogenation of 100 mg of 5-Cl (PtO_2, ethyl acetate) yielded the same material. Hydrogenation of the endo adduct 6-Cl (PtO_2, ethyl acetate) indicated that no detectable (on column K as well as by nmr) endo compound was produced in the reaction with SF_4.

Preparation of *exo*-7-Chloro-6,6-difluorobicyclo[3.2.0]heptane (11-Cl).—The reaction vessel used was a 20-cm length of 1/4 in. o.d. stainless steel tubing capped at each end by Swagelok fittings, union and plug, all 316-stainless steel. The internal volume of the vessel is approximately 7 ml.

A 200-mg portion of *exo*-7-chlorobicyclo[3.2.0]heptanone-6 (13-Cl) in 1 ml of CH_2Cl_2 was placed in the vessel. The volume of water appropriate to yield the desired amount of HF upon reaction with SF_4 was added, and the vessel was cooled in Dry Ice. Through Teflon tubing, 1 ml of SF_4 was condensed into the vessel (transferred from a calibrated polyethylene tube) and the vessel was sealed. It was placed in a water bath held at 39 ± 2° for 48 hr. It was inverted to mix the contents several times a day during this period. Upon removal from the bath, the vessel was cooled in Dry Ice and opened, 50 mg of *n*-decane was added as an internal standard, and the vessel was allowed to warm to room temperature, with all effluent gases being passed through a KOH solution. The remaining contents of the vessel were washed out with more CH_2Cl_2 into a dilute K_2CO_3 solution, washed twice with water, dried, and distilled trap-to-trap. Analysis was done on column K at 110°. There were several products besides the desired materal 11-Cl but no endo chloride 12-Cl was present. The yields ran up to 26% with 20 mol % HF catalyst. Preparative separation on column G yielded 20 mg of 11-Cl with ir and nmr matching those produced by the product of hydrogenation of adducts 1-Cl and 3-Cl (PtO_2, ethyl acetate).

Preparation of *endo*-7-Chloro-6,6-difluorobicyclo[3.2.0]heptane (12-Cl).—A 200-mg sample of *endo*-7-chlorobicyclo[3.2.0]-heptanone-6 (14-Cl) in 1 ml of CH_2Cl_2 was placed in the reaction vessel previously described, and the vessel was cooled in Dry Ice. SF_4 (1 ml) was condensed into the vessel after addition of the desired amount of water, and the vessel was sealed. It was placed in a water bath at 35 ± 2° for 48 hr with occasional inversion to mix the contents. Upon removal from the bath, the vessel was cooled in Dry Ice, opened, and allowed to warm to room temperature with all effluent gases being passed through a KOH solution. *n*-Decane (50 mg) was added; the contents of the vessel were washed into dilute K_2CO_3 solution with a few milliliters of CH_2Cl_2, washed with water twice, dried, filtered, and distilled. Analysis on column K indicated a maximum yield of 12-Cl with 40 mol % of HF present, and with no exo compound, 11-Cl, detectable. The highest yield attained was 13%. Separation using column G at 100° yielded enough material for ir and nmr spectra, which were found to match those of the hydrogenation product of 2-Cl as well as of 4-Cl.

(29) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **12**, 186 (1961).

(30) J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Amer. Chem. Soc.*, **86**, 4074 (1964).

Reaction of Monochloroketene with Cyclopentadiene.—Freshly distilled chloroacetyl chloride (10 g) and 100 ml of ethyl ether (dried over sodium wire) were placed in a 500-ml three-neck flask. Freshly cracked cyclopentadiene (100 ml) was added, and the flask was cooled with Dry Ice–acetone. An 8.5-g sample (slightly less than the equivalent amount needed to react quantitatively with the acid chloride) of freshly distilled triethylamine was dripped in slowly with vigorous stirring. The flask was allowed to warm to room temperature over several hours while stirring continued. A stream of dry nitrogen was passed over the solution throughout the reaction. After stirring 1 day at room temperature, the mixture was poured into 100 ml of water; the organic layer was washed once with dilute $KHCO_3$, once with saturated NaCl solution, and dried over anhydrous $MgSO_4$ and the ether evaporated. Distillation affords 6 g of material boiling at 94–96° (8 mm). Glpc on column G at 140° indicates that the product is 96% *endo*-7-chlorobicyclo[3.2.0]-hept-2-en-6-one (**15**-Cl) and 4% its exo epimer **22**-Cl. Separation using column E at 150° yields pure compounds whose spectra (ir, nmr) match those of the compounds prepared *via* the reaction of NOCl and bicyclo[3.2.0]heptadiene-2,6.

Reaction of Monofluoroketene and Cyclopentadiene.—A 1.0-g sample of fluoroacetyl chloride[31] in 10 ml of sodium-dried ethyl ether, 5 g of freshly cracked cyclopentadiene, and 100 mg of decane was cooled under a dry nitrogen atmosphere to −78°. Freshly distilled triethylamine (1 g) was added dropwise over a 5-min period with vigorous stirring. The flask was allowed to warm to 0° and stirred at this temperature for 6 hr. A 1-ml sample was withdrawn and quenched in water (1 ml); the organic phase was checked, with no further purification, by glpc on column K. A ratio of 14:86 was observed for the two ketones produced, and the size of the peaks relative to the decane standard was noted. The flask with the remaining reactants was allowed to warm to room temperature and stirring continued for 2 days. The contents were then poured into 5 ml of water and shaken, the organic phase was separated and dried over anhydrous $MgSO_4$, and the ether was removed. Glpc on column K at the same temperature used before, 140°, indicated that the product ratio had remained constant at 14:86 and that the earlier sample had been withdrawn at approximately 1% of complete reaction. If the volume of water used in the quench is increased or an additional water wash is used, the ratio of the two ketones changes markedly, with the minor component decreasing relative to the major. Isolation of the ketones free of cyclopentadiene dimer may be accomplished by chromatography on Florisil: elution with 95% petroleum ether–5% ethyl ether until cyclopentadiene dimer is completely eluted, then changing to 30% petroleum ether–70% ethyl ether to elute the ketone mixture. Preparative glpc is accomplished on column E at 150°. The first (the minor) ketone from the column is *exo*-7-fluorobicyclo-[3.2.0]hept-2-en-6-one, **22**-F (exact mass for C_7H_7OF: calcd, 126.04809; found, 126.04776). The second ketone is the endo epimer found by Brady and Hoff.[13] Identical results are achieved using fluoroacetyl bromide[32] in place of the chloride. If triethylamine is replaced with tributylamine, no precipitate is formed in the reaction and the yield of cross-adduct is very low. However, if the solvent is changed to tetrahydrofuran and 2 g of fresh cyclopentadiene is added to the refluxing reaction mixture every 12 hr for 2 days, a 70% yield of ketones in a 12:88 ratio is isolated. If the reaction using triethylamine is filtered before warming above 0° and the solid residue treated with cyclopentadiene in ether, the yield of ketones from the filtrate is found to be 1% or less—while the yield from the residue is 50–60%, indicating that the precipitate is not triethylamine hydrochloride, but a precursor to the ketene. Replacing triethylamine with ethyldiisopropylamine, which is nearly immune to alkylation[33] resulted in no significant difference in the rate of the reaction. A precipitate also formed immediately in this case, indicating that the intermediate may be an enolate rather than an acylammonium ion.[34]

Preparation of *exo*- and *endo*-3-Fluoronorcamphor (9-F and 10-F).—A 4.5-g sample of norbornene in 100 ml of $CHCl_3$ which had been freed of ethanol by elution through an alumina column was cooled to −60°. Approximately 3 g (2.2 ml) of nitrosyl fluoride (Ozark-Mahoning Co.) previously measured into a polyethylene tube was transferred into the cold solution with vigorous stirring over a 10-min period. (All vessels or tubing coming into contact with the FNO should be of Teflon or polyethylene since glass will be etched.) The reaction vessel was then allowed to warm to room temperature, the chloroform evaporated away, and the residue treated with 60 g of levulinic acid and 7 ml of 2 *N* HCl with stirring for several days. The mixture was poured into 300 ml of water and extracted 15 times with 25-ml portions of ether; the ether extracts were washed once with water, once with $NaHCO_3$ solution, and dried. The ether was then removed on a rotary evaporator. The residue was distilled and the distillate injected 150 μl at a time on column E at 150°. The major product (600 mg) was *exo*-3-fluoronorcamphor (9-F) followed by ethyl levulinate and then (60 mg) impure *endo*-3-fluoronorcamphor (10-F) (exac mass for 9-F: calcd 128.0637; found, 128.0628).

Preparation of *endo*-6,6,7-Trifluorobicyclo[3.2.0]hept-2-ene (2-F). Reduction of the Chlorotrifluoroethylene–Cyclopentadiene Adducts.—To 0.31 g (32 mequiv) of lithium aluminum hydride in 10 ml of freshly purified tetrahydrofuran (distilled from lithium aluminum hydride) was added 1.2 g (6.2 mequiv) of a 1:1 mixture of *endo*- and *exo*-7-chloro-6,6,7-trifluorobicyclo-[3.2.0]heptene-2 (**24** and **25**), and the mixture was refluxed at least 15 hr. The excess hydride was then destroyed by addition of 5 ml of ethyl acetate followed by dilute H_2SO_4. The organic phase was washed with water and dried over anhydrous $MgSO_4$. It was then distilled and injected 100 μl at a time on column B at 90°. The collected yield of **2**-F was 35%. If the reaction was quenched after 6 hr of reflux and 100 mg of decane added as internal standard, the reaction was found to be 65% complete with a 3:1 ratio of **24**/**25** and a 60% yield based on reacted material. In neither case does the *exo*-trifluoro compound **1**-F appear in more than 4% of the yield of the endo compound **2**-F.

Preparation of *endo*-5,5,6-Trifluorobicyclo[2.2.1]hept-2-ene (6-F).—To 0.3 g of lithium aluminum hydride in 10 ml of freshly purified tetrahydrofuran was added 1.2 g of a 3:2 mixture of *exo*- and *endo*-6-chloro-5,5,6-trifluorobicyclo[2.2.1]heptene-2 (**27** and **26**), and the mixture was refluxed at least 15 hr. The excess hydride was then destroyed by addition of 5 ml of ethyl acetate followed by dilute H_2SO_4. It was then dried over $MgSO_4$ and distilled. The distillate was injected 100 μl at a time on column B at 90°. The collected yield of **6**-F was 40%. Quenching of the reaction after 6 hr and addition of decane standard indicated 80% of the reaction was complete at that time with a 1:1 ratio of recovered starting materials and a 40% yield of products based on consumed material. In both the 6- and 16-hr reactions, the exo adduct **5**-F produced does not exceed 3% of the endo (**6**-F).

Registry No.—**1**-Cl, 37579-89-8; **1**-F, 37579-90-1; **2**-Cl, 37579-91-2; **2**-F, 37579-92-3; **3**-Cl, 37579-93-4; **3**-F, 37579-94-5; **4**-Cl, 37579-95-6; **4**-F, 37579-96-7; **5**-Cl, 37579-97-8; **5**-F, 37579-98-9; **6**-Cl, 37579-99-0; **6**-F, 37580-00-0; **7**-Cl, 37580-01-1; **7**-F, 37580-02-2; **8**-Cl, 37580-04-4; **8**-F, 37580-03-3; **9**-Cl, 10464-71-8; **9**-F, 37580-06-6; **10**-Cl, 30860-22-1; **10**-F, 37580-07-7; **11**-Cl, 37580-08-8; **11**-F, 37580-09-9; **12**-Cl, 37580-10-2; **12**-F, 37580-11-3; **13**-Cl, 37580-12-4; **13**-F, 37580-13-5; **14**-Cl, 37580-14-6; **14**-F, 37580-15-7; **15**-Cl, 25169-61-3; **15**-F, 25975-83-1; **16**, 37580-18-0; **17**, 37580-19-1; **18**, 37580-20-4; **19**, 37580-21-5; **20**, 37580-22-6; **21**, 37580-23-7; **22**-Cl, 37573-87-8; **22**-F, 37573-88-9; **23**-Cl, 37573-89-0; **24**, 37573-83-4; **25**, 37573-84-5; **26**, 37573-85-6; **27**, 37573-86-7; cyclopentadiene, 542-92-7; trifluoroethylene, 359-11-5; 2-chloro-1,1-difluoroethylene, 359-10-4; monochloroketene, 29804-89-5; monofluoroketene, 37580-39-5; norbornene, 498-66-8.

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Notes

Mass Spectrometry of 1-Substituted Adamantanes. The Effect of Functional Groups on the Primary Fragmentation Pathways[1]

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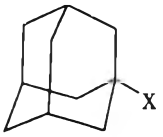
We wish to report on the primary fragmentation pathways of a number of 1-substituted adamantanes, **1** (abbreviated to 1-AdmX), in the light of current interest in mass spectral behavior of adamantanes.[2-8]



1

This analysis addresses itself to the origin of the most abundant ions only, Table I, since further fragmentations of these produce similar spectra of lower abundance ions.[9] The fate of the molecular ion of **1** is conveniently classified according to one of the three recognized processes: (a) loss of the substituent, X, as a radical to produce the even-electron ion at *m/e* 135, (b) loss of the neutral molecule, HX, to produce the odd-electron ion at *m/e* 134, and (c) loss of the C_4H_9 hydrocarbon radical to produce an M − 57 ion.

For compounds which produced their most abundant ions by paths a and b, low molecular ion abundance was characteristic, the average from 20 compounds being 10%. For compounds where the base peak arose *via* path c, much higher molecular ion abundance was found, the average from eight compounds being 40%.

Sulfur-Linked Substituents.—Our recent synthetic work on antiradiation drugs[8,10] provided a series of 1-adamantyl sulfides and related compounds[8] [**1**, X = SH,[4] SCH_3, $S(CH_3)_2{}^+I^-$,[11] $S(CH_2)_2NH_2$, $S(CH_2)_5NH_2$, $S(CH_2)_2NHCOC_6H_5$, $S(CH_2)_2NHSO_2C_6H_4CH_3$-*p*, $S(CH_2)_2NHC(=NH)CH_2Cl$, $SCOCH_3$,[11] and $SC(=NH)—NH_2$]. Members of this series exhibit a relatively weak molecular ion (2–15% of base peak) which loses the substituent X as a radical to form the stable 1-adamantyl ion, *m/e* 135 (100%).

With the introduction of nitrogen-containing groups into the side chain, other noteworthy ions appear. In the spectrum of **1**, X = $SCH_2CH_2NH_2$, an ion at *m/e* 182 (26%) appears due to the loss of $CH_2{=}NH$ from the parent ion to produce the equivalent to $[1\text{-Adm-}SCH_3]^+$. Conversion of the above amine to its benzamide, *p*-toluenesulfonamide, or amidine, represented by 1-AdmS$(CH_2)_2NHY$, produces an ion at *m/e* 194 (18–32%) indicative of the elimination of YNH_2 from the substituent to give $[1\text{-AdmSCH}{=}CH_2]^+$.

For sulfur-linked substituents, bond cleavage of either side of the sulfur atom can also occur, with the charge being retained by the substituent group. For example, in the spectrum of 1-AdmS$(CH_2)_5NH_2$, an abundant fragment at *m/e* 86 (95%) is accounted for by C–S bond cleavage with the loss of 1-adamantyl radical, the charge being retained by the substituent group to produce a $C_5H_{12}N$ ion. An ion also appears in less abundance at *m/e* 118 (18%), representing cleavage of the other C–S bond to produce the $C_5H_{12}NS$ ion. As the complexity of the side chain increases, other processes may lead to the base peak. For example, in 1-AdmS$(CH_2)_5NHCO$-C_6H_5, the base peak is *m/e* 105, ($C_6H_5CO^+$) which is not at all unusual, while the *m/e* 135 ion abundance diminished to 5%. However, cleavage of the bridgehead adamantane sulfur bond produces a strong $C_{12}H_{16}NOS$ ion, *m/e* 222 (M − 135, 31%). Among the few ions with 5% abundance or over in this spectrum was one for sulfur side chain cleavage to produce a $C_{12}H_{16}NO$ ion (*m/e* 190, 5%).

Oxygen-Linked Substituents.—Unlike the relatively simple 1-adamantanethiol derivatives for which only one of the major modes of molecular ion decomposition is observed, ethers and esters based on 1-adamantanol may follow any of the three pathways mentioned above. However, for a given compound, one mode usually predominates. 1-Adamantanol (**1**, X = OH), on electron bombardment, produces an M − 57 ion as the base peak and indeed with a very minor contribution from the 1-adamantyl ion at *m/e* 135 (5%).[2,4,7] A similar fragmentation is shown by the ethyl ether (**1**, X = OC_2H_5[8]) with the M − 57 ion as the base peak and the *m/e* 135 ion at 19% abundance. Apparently, the amine function in the ether side chain stabilizes the radical produced by substituent cleavage and reverses the above trend. Thus, when X in **1** is $O(CH_2)_2NH_2$,[8] $O(CH_3)_3NH_2$,[12] $OCH(CH_3)CH_2NH_2$,[12] and $O(CH_2)_2$-$NHC(=NH)CH_2Cl$,[8] the base peak was the *m/e* 135

(1) Partial support for this work by the U. S. Army Medical Research and Development Command (Research Contract DADA 17-60-C-9110) is gratefully acknowledged.

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(9) All ions in the 70-eV mass spectra (5% or over of the base peak) up to *m/e* 28 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-73-1042. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

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TABLE I
PRINCIPAL IONS IN FRAGMENTATIONS OF 1-ADMX

X	Mol ion *m/e* (rel int)	*m/e* 135 rel int	*m/e* 134 rel int	[M − 57] ion (rel int)	Registry no.
SH	168 (10)	100		111 (2)	34301-54-7
SCH_3	182 (13)	100			34895-33-5
$S(CH_2)_2NH_2$	211 (6)	100			30771-87-0
$S(CH_2)_2NHCOC_6H_5$	315 (4)	100			30771-90-5
$S(CH_2)_2NHSO_2C_6H_4CH_3$-*p*	365 (2)	100			30771-91-6
$S(CH_2)_2C(=NH)CH_2Cl\cdot HCl$	288 (<1)	100			37817-01-9
	286 (2)				
$S(CH_2)_5NH_2$	253 (4)	100			30771-89-2
$S(CH_2)_5NHCOC_6H_5$	357 (0)	4	5		37817-02-0
$SCOCH_3$	210 (7)	100			37817-03-1
$SC(=NH)NH_2\cdot HBr$	210 (8)	100			30771-94-9
$S(CH_3)_2{}^+I^-$	324 (0)	100			37818-84-1
OH	152 (25)	5		95 (100)	768-95-6
OCH_2CH_3	180 (40)	19		123 (100)	6221-75-6
$O(CH_2)_2NH_2$	195 (13)	100			25225-13-2
$O(CH_2)_3NH_2$	209 (<1)	100		152 (9)	21624-07-7
$OCH(CH_3)CH_2NH_2$	209 (1)	100	3	152 (2)	21623-91-6
$O(CH_2)_2NHC(=NH)CH_2Cl\cdot HCl$	272 (0)	100			30771-83-6
	270 (<1)				
$OCOCH_3$	194 (4)	21	100		22635-62-7
$OCOCH_2CH_3$	208 (5)	57	100		37818-91-0
NH_2	151 (65)			94 (100)	768-94-5
$NHCH_3$	165 (22)			108 (100)	3717-38-2
$N(CH_3)_2$	179 (80)	15		122 (100)	3717-40-6
$NH(CH_2)_2NH_2$	194 (2)	100			37821-93-2
$NH(CH_2)_2OH$	195 (4)	100		138 (26)	3716-66-3
$NH(CH_2)_3OH$	209 (23)	61	9	152 (100)	19984-59-9
$NHCOCH_3$	193 (30)	25	25	136 (100)	880-52-4
$NHCONH_2$	194 (38)	9		137 (84)	13072-69-0
N=C=S	193 (16)	100	2		4411-26-1
CH_2NH_2	165 (29)	100			17768-41-1
$CONH_2$	179 (24)	100			5511-18-2
C≡N	161 (62)	10	100	104 (18)	23074-42-2
C_6H_5	212 (80)	<1		155 (100)	780-68-7

ion and the M − 57 ion is either absent or in low abundance (10%).

The loss of HX as the chief fragmentation mode is observed in several 1-adamantyl esters. When X = $OCOCH_3$[13] or $OCOCH_2CH_3$[11] in **1**, elimination of the corresponding carboxylic acid molecule produces the parent ion at *m/e* 134, with a smaller loss of the X moiety alone to give the *m/e* 135 ion in 21 and 57% relative abundance, respectively.

Nitrogen-Linked Substituents.—For the nitro[2] and isothiocyanato compounds (**1**, X = NO_2 and N=C=S), *m/e* 135 is the base peak with little contribution from the other pathways (<2%).

Loss of the X substituent as a radical from the parent ion of simple amines [**1**, X = NH_2,[2,7] $NHCH_3$,[10] and $N(CH_3)_2$[2]] is not favored (<15%), and the base peak in each instance arises from the M − 57 ion. In some polyfunctional amines apparent stabilization of the substituent group as a leaving radical again occurred such that for **1**, when X = $NH(CH_2)_2OH$[13] and $NH(CH_2)_2NH_2$,[14] the parent ion was the adamantyl ion, *m/e* 135, and the contribution from the M − 57 ion was reduced to 26 and less than 2%, respectively. However, in the spectrum of an homologous amino alcohol, **1**, X = $NH(CH_2)_3OH$,[15] the M − 57 ion is restored as the base peak, with a *m/e* 135 fragment amounting to 61%.

Decomposition of the molecular ion of 1-acetamidoadamantane[2] (**1**, X = $NHCOCH_3$) involves all three modes of fragmentation, with the M − 57 ion as the base peak. The loss of X and HX also occurs since the *m/e* 134 and 135 ions are present, both in 25% relative abundance. 1-Adamantylurea (**1**, X = $NHCONH_2$) is unique in that neither the M − 57 ion (84%) nor the *m/e* 135 ion (9%) but an ion at *m/e* 94 represents the base peak. The ion can be attributed to the loss of 43 (HNCO) from the M − 57 ion.

Carbon-Linked Substituents.—The fragmentation results in *m/e* 135 ion as the base peak when the substituents, X, in **1** are alkyl,[2] cycloalkyl,[2] CH_2OH,[2] $COCH_3$,[2] $CO_2C_2H_5$,[2] CH_2COCH_3,[6] $(CH_2)_2CO_2H$,[16] and from the present study, CH_2NH_2[17] and $CONH_2$. In a surprising departure from this pattern the molecular ion from 1-adamantanecarbonitrile (**1**, X = CN) eliminates HCN to create *m/e* 134 (100%) and gives rise to a small M − 57 ion (18%), while the *m/e* 135 ion is completely absent.

Not all carbon-linked substituents conform to either of these two patterns, since 1-phenyladamantane[2] (**1**,

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X = C_6H_5) has the M − 57 ion as base peak and the *m/e* 135 and 134 ions are absent. Apparently, different types of carbon-linked substituents control fragmentation of the molecular ions, albeit paths a, b, and c are predominantly involved.

Phosphorus-Linked Substituents.—In a recent report,[18] the mass spectrum of methyl 1-adamantanephosphonate [1, X = $P(O)(OCH_3)_2$] indicates that the 1-adamantyl ion, *m/e* 135, is also the base peak.

Registry No.—1-AdmO$(CH_2)_2NH_2 \cdot HCl$, 21623-89-2; 1-AdmNH$CH_3 \cdot HCl$, 3717-39-3; 1-AdmNH$(CH_2)_2$-$NH_2 \cdot HCl$, 37819-00-4; 1-Adm$CH_2NH_2 \cdot HCl$, 1501-98-0.

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Kinetics of the Peracid Oxidation of Acetylenes. Electrophilic Attack on Phenylacetylenes[1]

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The peracid oxidation of phenyl- and diphenylacetylenes suggests the rate-determining primary formation of oxirenes.[2]

An oxirene intermediate was verified in the peracid oxidation of cyclodecyne,[3] the Wolff rearrangement,[4] and the reaction of methylene with carbon monoxide.[5] Earlier reports[6-8] postulated an electrophilic attack of peracid on a triple bond, but the higher reactivity of triple-bond carbon toward nucleophiles[9] might enable a nucleophilic attack of peroxide ion to occur. Contrary to the anticipation, our kinetic data on the perbenzoic acid (PBA) oxidation of phenylacetylenes showed an electrophilic attack alone as shown below and added an example of electrophilic addition to triple bond similar to the acid-catalyzed hydration.[10]

Results and Discussion

The rate of the reaction of phenylacetylene with perbenzoic acid (PBA) was measured in benzene at 25.0°. The rate was expressed as eq 1.

$$v = k[PhC{\equiv}CH][PBA] \quad (1)$$

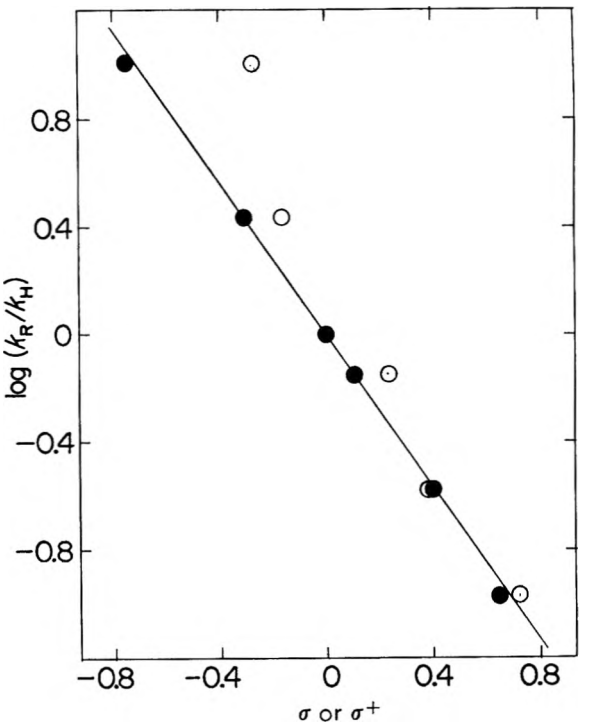

Figure 1.—Hammett plot for the reaction of substituted phenyl acetylenes with perbenzoic acid at 25.0°: open circle, σ; closed circle, σ+.

TABLE I

RELATIVE RATE CONSTANTS (k_R/k_H) FOR THE REACTION OF SUBSTITUTED PHENYLACETYLENES WITH PERBENZOIC ACID IN BENZENE AT 25.0° ± 0.1°[a]

Registry no.	R in $RC_6H_4C{\equiv}CH$	Relative second-order rate constant (k_R/k_H)
768-60-5	*p*-MeO	10.2[c]
766-97-2	*p*-Me	2.67[b]
536-74-3	H	1.00
873-73-4	*p*-Cl	0.680[b]
766-81-4	*m*-Br	0.263[c]
3034-94-4	*m*-NO_2	0.108[c]

[a] Initial concentrations: [$PhCO_3H$], 0.2–0.4 *M*; [$RC_6H_4C{\equiv}CH$], 0.06–0.25 *M*. [b] Probable error: ±1%. [c] Probable error: ±2%.

The second-order rate constant *k* (1.65×10^{-5} M^{-1} sec^{-1}) with excess phenylacetylene calculated from the pseudo-first-order rate constant agreed with that with excess PBA (1.44×10^{-5} M^{-1} sec^{-1}). This fact shows that phenylacetylene reacts with PBA in a molar ratio of *ca.* 1:1 under these conditions.[11]

Relative rates for substituted phenylacetylenes were determined by the competitive reaction as shown in Table I. The Hammett plot (Figure 1) gives a satisfactory straight line with σ^+ value[12] to give a ρ value of −1.40 with a correlation coefficient *r* of 0.999. The negative ρ value suggests an electrophilic attack of

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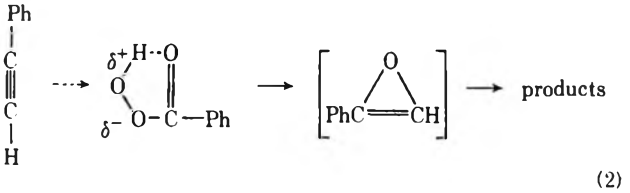
(9) E. Winterfeldt, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p 267.

(10) (a) D. S. Noyce and M. D. Schiavelli, *J. Amer. Chem. Soc.*, **90**, 1020 (1968); (b) D. S. Noyce, M. A. Matesich, M. D. Schiavelli, and P. E. Peterson, *ibid.*, **87**, 2295 (1965).

(11) The pseudo-first-order rate constant from the reaction with excess PBA remains constant within the experimental error in spite of the change of the molar ratio of stoichiometry (phenylacetylene:PBA) from 1:1 to 1:2. On the other hand, the pseudo-first-order rate constant from the reaction with excess phenylacetylene should change with the change in the molar ratio of the stoichiometry. Observed approximately identical values of the two second-order rate constants from the two methods with excess PBA and excess phenylacetylene show that the molar ratio of the stoichiometry is 1:1 rather than 1:2. In view of the literature[2a] together with our identification of phenylacetic acid, phenylketene may be an initial main product of this reaction of phenylacetylene with PBA.

(12) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **79**, 1913 (1957).

peroxidic oxygen to form the oxirene ring. Since PBA in benzene forms a five-membered intramolecular hydrogen bond, the mode of attack may be as follows.



(2)

The effect of substituents on the PBA epoxidation of styrenes[13] was reported to be correlated with the Yukawa–Tsuno equation[14] [$\log (k/k_0) = \rho (\sigma + r\Delta\sigma^+_R)$] ($\rho = -1.30$ and $r = 0.48$). The ratio of the ρ value for the PBA oxidation of phenylacetylenes to that for styrenes at 25.0° was 1.08. The ρ value (*vs.* σ^+) for acid-catalyzed hydration of phenylacetylenes[10] (−3.84) and that of styrenes[15] (−3.42) give a ratio of 1.12, which is close to the above ratio for the peracid oxidation. Hence, the attacks of peroxidic oxygen on triple and double bonds possess a polar effect analogous to that observed in protonation.

The r value in the Yukawa–Tsuno equation for our reaction is 1.0, which is larger than the r value of 0.48 for styrenes. The higher r value, *i.e.*, larger contribution of resonance for phenylacetylenes, shows that less (*ca.* $^1/_{60}$) reactive phenylacetylenes have a transition state stabilized more by conjugation between the reaction site and the phenyl group. One of the p orbitals of the triple bond, which is coplanar with the benzene ring, seems to participate in the reaction in the transition state. When its p-orbital electrons attack peroxidic oxygen, the positive charge generated on the reaction site is stabilized by delocalization to p orbitals of the benzene ring.

The solvent effect is shown in Table II. Addition of ethanol, a more basic solvent, to the nonpolar solvent benzene markedly decreases the rate. The peracid forms an intramolecular hydrogen bond in benzene.[16] The intramolecular bond changes to the intermolecular one by addition of more basic ethanol resulting in a decrease of rate. Strangely, the rate in aqueous ethanol is higher than that in benzene–ethanol. This suggests that the oxidation rate *via* an intermolecular hydrogen bonded peracid is increased by increasing solvent polarity as well as by decreasing solvent basicity. In fact, the same result has been obtained in the epoxidation of styrene.[17]

Peracid becomes its anion in aqueous ethanol buffered by Na_2CO_3, but the reaction of phenylacetylenes with perbenzoate ion was not appreciable, probably because the electrophilicity of acetylene is rather weak and the anion may spontaneously decompose faster than its attack on the triple bond.

TABLE II

SOLVENT EFFECT ON THE SECOND-ORDER RATE CONSTANTS (k) FOR THE REACTION OF PHENYL- AND *p*-METHYLPHENYLACETYLENES WITH PERBENZOIC ACID AT 25.0 ± 0.1°

Solvent (v/v)	$C_6H_5C{\equiv}CH$, $10^5\ k$, M^{-1} sec^{-1}	*p*-$MeC_6H_4C{\equiv}CH$, $10^5\ k$, M^{-1} sec^{-1}
C_6H_6	2.5[a]	6.8[a]
C_6H_6:EtOH (75:25)	1.1[a]	
C_6H_6:EtOH (50:50)	0.55[a]	
EtOH	0.1[a]	0.1[b]
EtOH:H_2O (80:20)	0.2[b]	0.5[b]
EtOH:H_2O (50:50)	1.2[b] (1.5)[a]	2.7[b]
EtOH:H_2O (40:60)	1.8[a]	
EtOH:H_2O (50:50) buffered by 0.1 *M* Na_2CO_3	Very small[a,b]	Very small[a,c]
EtOH:H_2O (40:60) buffered by 0.1 *M* Na_2CO_3	Very small[a,b]	

[a] Rate constants were calculated from a decrease of perbenzoic acid. [b] Rate constants were calculated from a decrease of $RC_6H_4C{\equiv}CH$. [c] *m*-Bromophenylacetylene was used instead of *p*-methylphenylacetylene.

(13) Y. Ishii and Y. Inamoto, *Kogyo Kagaku Zassi*, **63**, 765 (1960).
(14) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **32**, 965 (1959).
(15) W. M. Schubert, B. Lamm, and J. R. Keeffe, *J. Amer. Chem. Soc.*, **86**, 4727 (1964).

Experimental Section

Materials.—*p*-Methoxyphenylacetylene,[18a] bp 110–114° (24 mm), and *m*-nitrophenylacetylene,[18b] bp 120–123° (24 mm) [lit.[18b] bp 118–120° (20 mm)], were synthesized from the corresponding cinnamic acids. Other substituted phenylacetylenes were prepared from the corresponding acetophenones.[19] Substituent and melting point or boiling point were *p*-Cl, mp 46.5–47.0°; *m*-Br, 96–98° (22 mm); *p*-Me, bp 70.0–70.5° (23 mm) [lit.[19] bp 79–81° (31–33 mm)]; and unsubstituted, bp 46.5–47.0° (20 mm) [lit.[20] bp 137–139° (760 mm)]. They were identified by their ir spectra,[21] their purities being checked by glc. Perbenzoic acid was prepared by the reaction of benzoyl peroxide with hydrogen peroxide[22] and recrystallized from hexane.

Kinetics.—The rate of consumption of PBA was followed iodometrically. The rate of consumption of phenylacetylenes was determined by glc, using anisole as an internal standard with a column (2 m) of 3 wt % Apiezon grease L on Celite 545 (80–100 mesh) and N_2 as a carrier gas (20 ml/min) at the starting temperature of 50°, which was elevated at a rate of 6°/min. An aliquot was removed and added to a known amount of anisole, and the remaining PBA was decomposed by addition of dimethyl sulfoxide. The resulting benzene solution was washed with aqueous $NaHCO_3$ to remove acidic components, dried (Na_2SO_4), and analyzed by glc. This procedure was done for a mixture of two kinds of phenylacetylenes with the reaction time between 0 and 48 hr, the relative rate constant (k_R/k_H) being calculated from this competitive reaction. Assuming rate constants for two kinds of phenylacetylenes to be k_A and k_B, their initial concentrations, a and b, and their consumed concentrations at a given time, x and y, respectively, the relative rate constant (k_A/k_B) is given by eq 3.

$$k_A/k_B = \ln [(a - x)/a] / \ln [(b - y)/b] \quad (3)$$

Registry No.—PBA, 93-59-4

(16) R. Curci, R. A. DiPrete, J. O. Edwards, and G. Modena, *J. Org. Chem.*, **35**, 740 (1970).
(17) Y. Ogata and Y. Sawaki, unpublished results.
(18) (a) J. D. Fulton and R. Robinson, *J. Chem. Soc.*, 1463 (1933); (b) A. D. Allen and C. D. Cook, *Can. J. Chem.*, **41**, 1084 (1963).
(19) J. L. Jacobs, *Org. React.*, **5**, 50 (1949).
(20) H. Fiesselmann and K. Sasse, *Chem. Ber.*, **89**, 1775 (1956).
(21) A. D. Allen and C. D. Cook, *Can. J. Chem.*, **41**, 1084 (1963).
(22) Y. Ogata and Y. Sawaki, *Tetrahedron*, **22**, 3329 (1967).

Anodic Oxidations. V.[1] Aromatic Cyanation of Methoxydiphenylacetylenes

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We at first anticipated that, if the anodic oxidation of diphenylacetylene is conducted under the cyanation

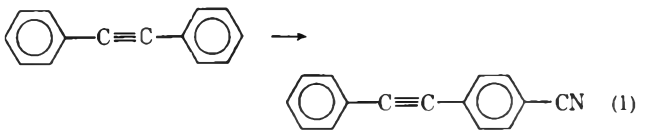
(1) Part IV: K. Yoshida, T. Saeki, and T. Fueno, *J. Org. Chem.*, **36**, 3673 (1971).

TABLE I
ANODIC CYANATION OF DIPHENYLACETYLENES[a]

Reactant	Electricity, F	Conversion, %	Product	Current efficiency, %	Yield,[b] %
Diphenylacetylene	0.023	59	4-Cyanodiphenylacetylene	31	60
2-Methoxydiphenylacetylene	0.007	34	2-Cyanodiphenylacetylene	11	12
			2-Methoxy-4-cyanodiphenylacetylene	4	5
3-Methoxydiphenylacetylene	0.037	81	3-Cyanodiphenylacetylene		Trace
			3-Methoxy-4-cyanodiphenylacetylene	9	23
4-Methoxydiphenylacetylene	0.014	57	4-Cyanodiphenylacetylene	15	18

[a] [NaCN] = 0.8 *M*; [diphenylacetylene] = 0.2 *M* (3-methoxydiphenylacetylene did not give a homogeneous solution owing to its limited solubility); platinum electrode; two-compartment cell; anode potential, 2.0 V *vs.* sce; temperature, 25°; reaction time, 24 hr; current density, *ca.* 0.003 A/cm². [b] Based on consumed acetylene compounds.

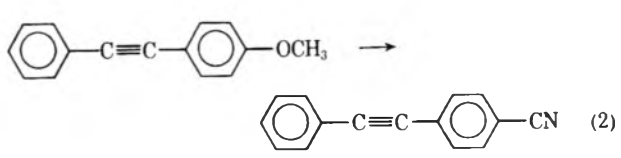
conditions, the cyanide ion would attack the acetylenic bond to yield α-phenylcinnamonitrile derivatives. However, the product formed was found to be exclusively 4-cyanodiphenylacetylene, an aromatic substitution product (reaction type 1).[2]



(1)

We have extended the work to methoxydiphenylacetylenes. Oxidations were carried out in methanolic sodium cyanide at an anode potential of +2.0 V *vs.* sce. The results are summarized in Table I.

4-Methoxydiphenylacetylene underwent replacement of the methoxyl group by the nitrile group to yield 4-cyanodiphenylacetylene (reaction type 2).[3] With 3-



(2)

methoxydiphenylacetylene, the product obtained was 3-methoxy-4-cyanodiphenylacetylene, which was formed by substitution of para hydrogen atom (reaction type 1). With 2-methoxydiphenylacetylene, both types of reactions, 1 and 2, occurred, the latter being somewhat prevalent. In all these cases, the yields of cyanated products were rather low, because of unavoidable side reactions giving a tarry residue.

By analogy with other anodic cyanations,[1,4] the primary electrode process is considered to be the oxidation of diphenylacetylene to a cationic species (most likely a cation radical) which subsequently reacts with cyanide ion.

Experimental Section

The electrochemical and spectroscopic instrumentation and techniques were as previously described.[4]

Materials.—Methanol was purified by fractional distillation from magnesium activated with iodine. Reagent grade sodium cyanide was used with no purification other than drying.

Acetylene compounds were prepared according to known procedures.[5,6] 3-Methoxydiphenylacetylene had mp 79–80° (from methanol); ir 2230 (C≡C), 1037 (COC), 866, 798, 770, and 686 cm⁻¹ (mono- and 1,3 substitution); nmr (CCl_4) τ 2.45–3.35 (9 H, m) and 6.27 (3 H, s). 2-Cyanodiphenylacetylene had bp 130° (1 mm). 3-Cyanodiphenylacetylene had mp 70–71°.

Procedure.—Acetylene compound (0.01 mol) in 50 ml of methanol–sodium cyanide (0.8 *M*) was electrolyzed at a controlled anode potential. The electrolyzed mixture was treated with water and the organic material was extracted with ether. The ether was removed by distillation and the residue was chromatographed on alumina using benzene as an eluent. Unreacted starting material was first eluted, followed by cyanated products.

Identification of Product.—Cyanated products were characterized by elemental analyses, by ir, nmr, and mass spectra, and by comparison with authentic samples.

2-Cyanodiphenylacetylene had bp 130° (1 mm); ir 2240 (CN and/or C≡C), 757, and 686 cm⁻¹ (mono- and 1,2 substitution); nmr (CCl_4) τ 2.3–2.8 (m).

Anal. Calcd for $C_{15}H_9N$: C, 88.64; H, 4.46; N, 6.89. Found: C, 88.89; H, 4.53; N, 6.83.

3-Cyanodiphenylacetylene had mp 70–71° (from ethanol); ir 2240, 2230 (CN and C≡C), 890, 795 (1,3 substitution), 758, and 677 cm⁻¹ (monosubstitution); nmr (CCl_4) τ 2.1–2.8 (m).

4-Cyanodiphenylacetylene had mp 108.5–109.5° (from ethanol); ir 2240, 2230 (CN and C≡C), 845 (1,4 substitution), 760, and 690 cm⁻¹ (monosubstitution); nmr (CCl_4) τ 2.40 (4 H, s) 2.4–2.7 (5 H, m). *Anal.* Calcd for $C_{15}H_9N$: C, 88.64; H, 4.46; N, 6.89; mol wt, 203.24. Found: C, 88.67; H, 4.47; N, 6.88; mol wt, 203 (mass spectroscopy).

2-Methoxy-4-cyanodiphenylacetylene had mp 106–107° (from ethanol); ir 2240 (CN and/or C≡C), 1172, 1115, 1030 (COC), 879, 823 (1,2,4 substitution), 756, and 688 cm⁻¹ (monosubstitution); nmr (CCl_4) τ 2.4–3.0 (8 H, m) and 6.7 (3 H, s). *Anal.* Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.35; H, 4.82; N, 5.90.

3-Methoxy-4-cyanodiphenylacetylene had mp 142.5–144.5° (from ethanol); ir 2240, 2230 (CN and C≡C), 1117, 1026 (COC), 859, 836 (1,2,4 substitution), 762, and 687 cm⁻¹ (monosubstitution); nmr (CCl_4) τ 2.44–3.02 (8 H, m) and 6.03 (3 H, s). *Anal.* Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00; mol wt, 233.27. Found: C, 82.26; H, 4.74; N, 6.01; mol wt, 233 (mass spectroscopy).

Registry No.—3-Methoxydiphenylacetylene, 37696-01-8; 2-cyanodiphenylacetylene, 32183-76-9; 3-cyanodiphenylacetylene, 37696-03-0; 4-cyanodiphenylacetylene, 29822-79-5; 2-methoxy-4-cyanodiphenylacetylene, 37696-05-2; 3-methoxy-4-cyanodiphenylacetylene, 37696-06-3.

Acknowledgment.—This work was partially supported by a grant (Shorei A) from the Ministry of Education.

(2) K. Yoshida and T. Fueno, *Chem. Commun.*, 711 (1970).

(3) A replacement of aromatic methoxyl by nitrile has been reported in the case of dimethoxybenzenes: S. Andreades and E. W. Zahnow, *J. Amer. Chem. Soc.*, **91**, 4181 (1969).

(4) K. Yoshida and T. Fueno, *J. Org. Chem.*, **36**, 1523 (1971).

(5) L. I. Smith and M. M. Falkof, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 350.

(6) R. D. Stephens and C. E. Castro, *J. Org. Chem.*, **28**, 3313 (1963).

4-Hydroxybenzenesulfonyl Chloride

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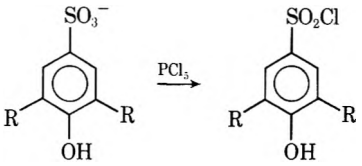
A variety of 3,5-disubstituted 4-hydroxybenzenesulfonyl chlorides have been reported in the literature.[1-4] They were obtained either from the reaction of the corresponding sulfonate salt with a chlorinating agent or by



R = CH_3, Cl, Br

direct chlorosulfonation of the corresponding phenol. The parent compound, 4-hydroxybenzenesulfonyl chloride (I), apparently resisted synthesis because of the reactive, unhindered phenolic group. Anschutz[5] reported in 1908 that treatment of potassium 4-hydroxybenzenesulfonate with phosphorus pentachloride yielded the dichlorophosphate ester of I.

We have reinvestigated this reaction and found that sodium 4-hydroxybenzenesulfonate (II) treated with phosphorus pentachloride under a variety of conditions gave product mixtures showing no hydroxyl absorption in the infrared. Reactions of chlorosulfonic acid with II or phenol gave complex reaction mixtures which failed to yield the desired sulfonyl chloride. When II was treated with thionyl chloride using dimethylformamide as solvent, small amounts of intractable oils were obtained which showed very little hydroxyl absorption.

We have found, however, that, if II is suspended in a substantial excess of thionyl chloride containing a catalytic amount of dimethylformamide for several hours at 60°, an 80–90% yield of I is obtained, mp 68–70°. A complicating feature of the work-up is the fact that this material absorbs sufficient water to form an oily layer when poured over ice, making filtration impossible. Extraction techniques result in a partitioning of the dimethylformamide between the aqueous and organic phases. The low melting point of I contributes to purification difficulties. Unsuccessful attempts were made to isolate I by sublimation, distillation, and conventional recrystallization. A technique[6] found to be useful for converting the oily reaction product to a more easily handled solid is to dissolve it in benzene, freeze the dry benzene solution, add hexane to the frozen solution, and collect the white precipitate produced as the mixture warms to room temperature. The hydroxysulfonyl chloride is then easily recrystallized from methylene chloride.

This material was found to be quite stable when stored at 0° under a nitrogen atmosphere. If all traces of dimethylformamide are removed, I is stable at room temperature when protected from atmospheric moisture. Conditions have been found[7a,b] for conversion of I into high molecular weight polymer.

A brief examination of other catalysts has shown[8] that some organophosphorus compounds (*e.g.*, triphenylphosphine, triphenylphosphine oxide, and hexamethylphosphoramide) can be used for the production of I. These reagents do not give as high conversions under the same conditions as dimethylformamide.

In 1965 King and Smith[9] published an article dealing with the sulfur–chlorine stretching band in sulfonyl chlorides. They reported the preparation of I from the reaction of phosphorus pentachloride and II. The similarity of their reported melting behavior (mp 90–92°) with that of Anschutz (mp 87–88°) combined with our observation that I has bands at 375 and 338 cm^{-1} compared with King's report of bands at 377, 354, and 343 cm^{-1}, has led us to believe that their product was incorrectly identified.[10]

Experimental Section

4-Hydroxybenzenesulfonyl Chloride (I).—A solution of 300 g (2.5 mol) of thionyl chloride and 3.0 g of dimethylformamide was quickly added to 98.1 g (0.5 mol) of sodium 4-hydroxybenzenesulfonate. The resulting mixture was stirred at 60° for 3.5 hr. At the end of this time, the mobile, nearly homogeneous reaction mixture was poured over 800 g of ice with vigorous stirring. An oily lower layer was produced and was dissolved in 300 ml of methylene chloride. The aqueous layer was extracted with 2 × 200 ml of methylene chloride and the combined organic solutions were washed with 200 ml of ice water. The organic solution was dried over $MgSO_4$ and solvent was removed *in vacuo*. The oil remaining was dissolved in 300 ml of benzene and dried over $MgSO_4$ and the solution was frozen. Hexane was added and the solution was allowed to warm to room temperature. The white precipitate was removed as it formed (3 × 30 ml of hexane used). The product was dried in a vacuum desiccator, yielding 80.7 g (84%) of crude I, mp 63–69°. Recrystallization from methylene chloride at −70° and twice at 0° yielded I: mp 68–70°; ir (Nujol mull) OH at 2.9 μ, SO_2 at 7.4 and 8.6 μ; nmr ($CDCl_3$) δ 6.70 (1 H, s, OH), 7.04 (2 H, d, J = 9 Hz, protons ortho to OH), 7.94 (2 H, d, J = 9 Hz, protons ortho to SO_2Cl). *Anal.* Calcd for $C_6H_5ClO_3S$: C, 37.5; H, 2.6; S, 16.7; Cl, 18.4. Found: C, 37.4; H, 2.7; S, 16.7; Cl, 18.4.

Registry No.—I, 4025-67-6; sodium 4-hydroxybenzenesulfonate, 825-90-1.

(1) T. Zincke and W. Glahn, *Ber.*, **40**, 3039 (1907).
(2) S. Oae and R. Kiritani, *Bull. Chem. Soc. Jap.*, **38**, 1543 (1965).
(3) W. L. Hall, *J. Org. Chem.*, **31**, 2672 (1966).
(4) W. L. Hall, U. S. Patent 3,530,177, issued to General Electric Co., 1970.
(5) R. Anschutz, *Justus Liebigs Ann. Chem.*, **358**, 92 (1908).
(6) R. W. Campbell, U. S. Patent 3,658,899, issued to Phillips Petroleum Co., 1972.
(7) (a) R. W. Campbell, U. S. Patent 3,549,595, issued to Phillips Petroleum Co., 1970; (b) R. W. Campbell and H. Wayne Hill, Jr., U. S. Patent 3,565,862, issued to Phillips Petroleum Co., 1971.
(8) H. Wayne Hill, Jr., and R. W. Campbell, U. S. Patent 3,673,247, issued to Phillips Petroleum Co., 1972.
(9) J. F. King and D. J. H. Smith, *Can. J. Chem.*, **43**, 1870 (1965).
(10) After this note was submitted for publication, it was learned by the authors *via* private communication that King had independently arrived at the same conclusion.

The Reaction of (Carbethoxymethylene)triphenylphosphorane with ω-Nitrostyrenes and Isatoic Anhydrides

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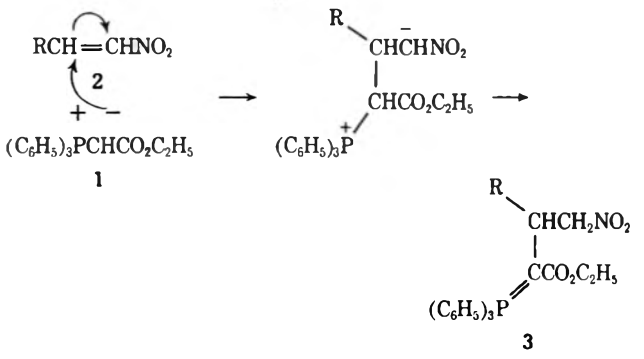
Our continuing interest in the reactions of phosphonium ylides for the production of novel, syntheti-

cally useful ylides[1] and new heterocyclic systems[1,2] led us to investigate the reaction of (carbethoxymethylene)-triphenylphosphorane (**1**) with ω-nitrostyrenes and isatoic anhydrides.

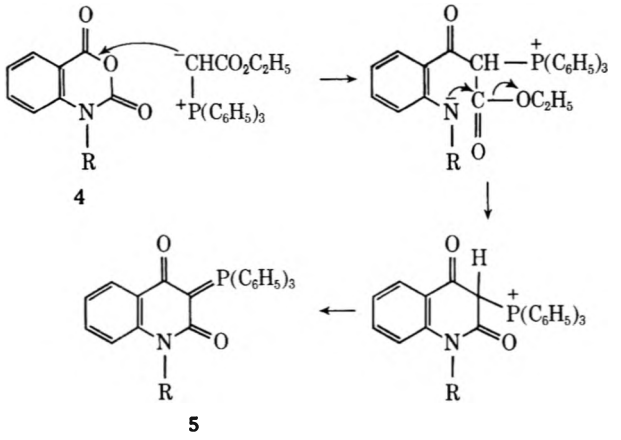
(Carbethoxymethylene)triphenylphosphorane (**1**) added to nitrostyrenes **2** (Scheme I) to give resonance-stabilized ylides **3**.

SCHEME I



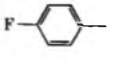
The reaction of **1** with isatoic anhydrides **4** to give resonance-stabilized ylides **5** is outlined in Scheme II.

SCHEME II



The products from the reactions are summarized in Table I. The analytical and spectral data are in agreement with the assigned structures.

TABLE I[a]

Compd	R	Mp, °C	Yield, %
3a		142–144	38
3b		156–157	30
3c		198–199	73
3d		170–171	18
5a	H	320 dec	50
5b	CH_3	252–253	44

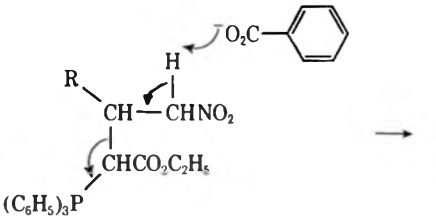
[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all new compounds listed in the table.

(1) M. von Strandtmann, M. P. Cohen, C. Puchalski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 4306 (1968).

(2) M. von Strandtmann, D. Connor, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **9**, 175 (1972).

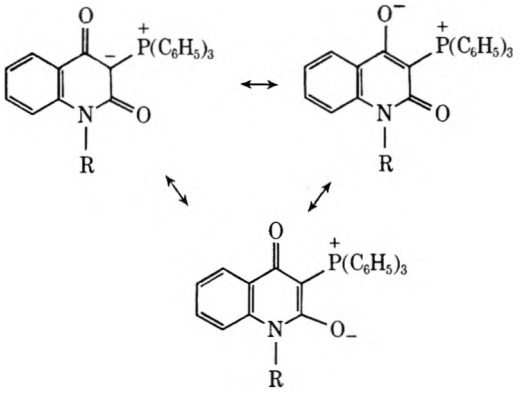
The products **3** exhibited a carbonyl band at 1620 cm^{-1} (Nujol) compared to 1600 cm^{-1} for the corresponding band in **1**. Their nmr spectra showed characteristic peaks at δ 0.41 (t, 3 H, CH_3 of ethyl) and 3.7 (q, 2 H, CH_2 of ethyl). The ir spectra of **5a** showed bands at 1625, 1610 (sh), and 1590 cm^{-1}. **5b** exhibited carbonyl bands at 1595 and 1580 cm^{-1} (sh) and showed a singlet (3 H) at δ 3.4 (NCH_3) in the nmr.

The phosphonium ylides **3** failed to undergo the Wittig reaction with aldehydes (benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde) under a variety of conditions. This contrasts with the behavior of the phosphonium ylides derived from **1** and Mannich bases[1] and can be attributed either to the steric effect of the trisubstituted carbon situated α to the carbanion carbon or to the presence of the nitro group. When benzoic acid, which is known to catalyze the reactions of **1** with ketones,[3] was added to the reaction between **3a** and *p*-chlorobenzaldehyde, the corresponding nitrostyrene was regenerated and no Wittig reaction product was detected by tlc.



$$R-CH=CHNO_2 + (C_6H_5)_3P=CHCO_2Et$$

The phosphonium ylides **5** also failed to react with aldehydes and were not affected by refluxing with alcoholic potassium hydroxide solution. This behavior reflects the extra stabilization (as compared to **1**) afforded by the second carbonyl group and the conjugation possible in the resonance forms.



Experimental Section

Melting points were taken in open capillary tubes and were not corrected. Nmr spectra were recorded on a Varian Model A-60 spectrometer using TMS as an internal standard ($CDCl_3$ solvent).

Phosphonium Ylides (3a–d).—A solution of the nitrosytrene (0.01 mol) and (carbethoxymethylene)triphenylphosphorane (0.01 mol) in dioxane (50 ml) was refluxed for 3 hr. The dioxane was evaporated under reduced pressure to give a brown gum, which crystallized from ethyl acetate–petroleum ether (bp 30–60°). One recrystallization from the same solvents gave analytically pure material.

Phosphonium Ylides (5a,b).—A solution of the isatoic anhydride (0.01 mol) and (carbethoxymethylene)triphenylphos-

(3) C. Ruchardt, S. Eichler, and P. Panse, *Angew. Chem.*, **75**, 858 (1963).

phorane (0.01 mol) in dioxane (50 ml) was refluxed for 17 hr The dioxane was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate–methylene chloride to give analytically pure material.

Attempted Reaction of Phosphonium Ylides (3a, 3c, and 5b) with Aldehydes.—The reaction of **3a**, **3c**, and **5b** with benzaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde was investigated in dioxane and benzene at reflux temperatures and room temperature for periods as long as 24 hr. In all cases the starting material was recovered. Extensive decomposition of the ylide took place when the reaction was run in DMF at 130°.

Registry No.—**1**, 1099-45-2; **2a** (R = Ph), 102-96-5; **2b** (R = *p*-F–Ph), 706,08-1; **2c** (R = 1-naphthyl), 4735-49-3; **2d** (R = 2-thienyl), 874-84-0; **3a** (R = Ph), 37709-90-3; **3b** (R = *p*-F–Ph), 37709-91-4; **3c** (R = 1-naphthyl), 37709-92-5; **3d** (R = 2-thienyl), 37709-93-6; **4a** (R = H), 118-48-9; **4b** (R = Me), 10328-92-4; **5a** (R = H), 37709-95-8; **5b** (R = Me), 37709-96-9.

Planarity of the Carbon Skeleton in Various Alkylated Olefins

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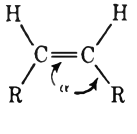
The planarity and extent of bond angle deformation in an alkene is of increasing interest to both the theoretical and the experimental chemist. In principle, a carbon–carbon double bond may experience both in-plane nonbonded repulsions, **1**, and out-of-plane "torsional strain,"[1] **2**, as a result of steric interactions. The



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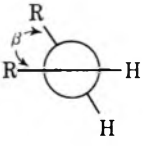

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strain in an alkene has traditionally been estimated experimentally from thermochemical data.[1,2] More recently, the force field method of calculation has been found to give reliable estimates of the strain energy and the structure of a variety of alkenes.[3]

Though the quantitative interpretation of photoelectron spectra almost always follows from a previous knowledge of the molecular geometry, in specific cases this can be reversed,[4] and we here offer several examples of this approach to the determination of certain gross geometric features of various alkylated olefins. Very briefly, the basic idea behind our work is that the π ionization potential of an olefin (or polyene) will depend strongly on the coplanarity of the $2p\pi$ AO's, and that twists in the π system of a particular molecule can be revealed by comparing its π-electron ionization potentials with that of a related standard molecule known to be planar. A semiquantitative estimate of the twist angle can be obtained if we then apply the theoretically determined curve of ionization potential *vs.* twist angle derived for ethylene.[5] According to this theoretical curve, the ionization potential of planar ethylene decreases by 3.24 eV on going to the form twisted by 90°.[6]

Recently, Harvey and Nelson[7] showed that the Raman spectrum of perfluoropropene was characteristic of a molecule having a plane of symmetry, in contrast to the report of Bauer and Chang,[8] who studied this molecule by electron diffraction and concluded that it is twisted by 40° about the C=C bond. Several other molecules of this sort were also reported to be twisted according to the diffraction study; the largest twist was reported for *cis*-perfluorobutene-2, 60 ± 2°. We can test this claim by comparing the ionization potentials of a series of cis and trans alkenes, which then leads indirectly to the degree of out-of-plane deformation of the double bond in the crowded isomer.

The photoelectron spectra of *cis*- and *trans*-butene-2 (Figure 1) understandably look very much alike since both molecules are planar[3,9] and differ only in the relative orientation of the ends, which are noninteracting. Note especially that the π ionization potentials at 9.29 and 9.32 eV (vertical) are very nearly equal. Extrapolating to the perfluorobutenes, the spectra will again resemble one another closely for the two planar isomers, but, at intermediate angles of twist about the central bond, the π-bond order is reduced, and the π ionization potential will decrease. According to the curves of Merer and Mulliken,[5] a twist of 60° will reduce the π ionization potential by 1.5 eV. In the same twisted olefin, the $\pi \rightarrow \pi^*$ interval in the optical spectrum will also decrease greatly over that in the planar configurations.

In Figure 1, we also show the photoelectron spectra of *cis*- and *trans*-perfluorobutene-2 and notice immediately that the two vertical π ionization potentials are again virtually identical at 11.46 and 11.55 eV, respectively. We take this result to show that both molecules are planar, or very nearly so (±10°). The optical spectra of the two isomers show $\pi \rightarrow \pi^*$ absorption maxima at 1640 (trans) and 1650 Å (cis) again indicating that the π-bonding strength is very nearly equal in the two systems. The π ionization potentials in the perfluoromethyl series seem to vary in a regular way, without any suggestion of nonplanarity in the carbon skeleton. Thus, the vertical π ionization potentials of perfluorotetramethylethylene, *cis*- and *trans*-perfluorobutene-2,

(1) For a general review of strained alkenes, see N. S. Zefirov and V. I. Sokolov, *Russ. Chem. Rev.*, **36**, 87 (1967).

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

(3) N. A. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972).

(4) See, for example, C. R. Brundle and M. B. Robin, *ibid.*, **92**, 5550 (1970).

(5) A. Merer and R. S. Mulliken, *Chem. Rev.*, **69**, 639 (1969).

(6) Actually, the Mulliken–Roothaan diagram relates the total energy to the angle of twist, always at the ground state C–C distance. The molecule, of course, will increase this distance in the excited ionic state, but, by the usual line of reasoning, the energy which most closely represents the transition in the fixed geometry of the ground state will have the maximum Franck–Condon factor, *i.e.*, the vertical ionization potential.

(7) A. B. Harvey and L. Y. Nelson, *J. Chem. Phys.*, **55**, 4145 (1971).

(8) S. H. Bauer and C. H. Chang, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, Paper Phys. 14.

(9) A. Almenningen, I. M. Anfinsen, and A. Haaland, *Acta Chem. Scand.*, **24**, 43 (1970).

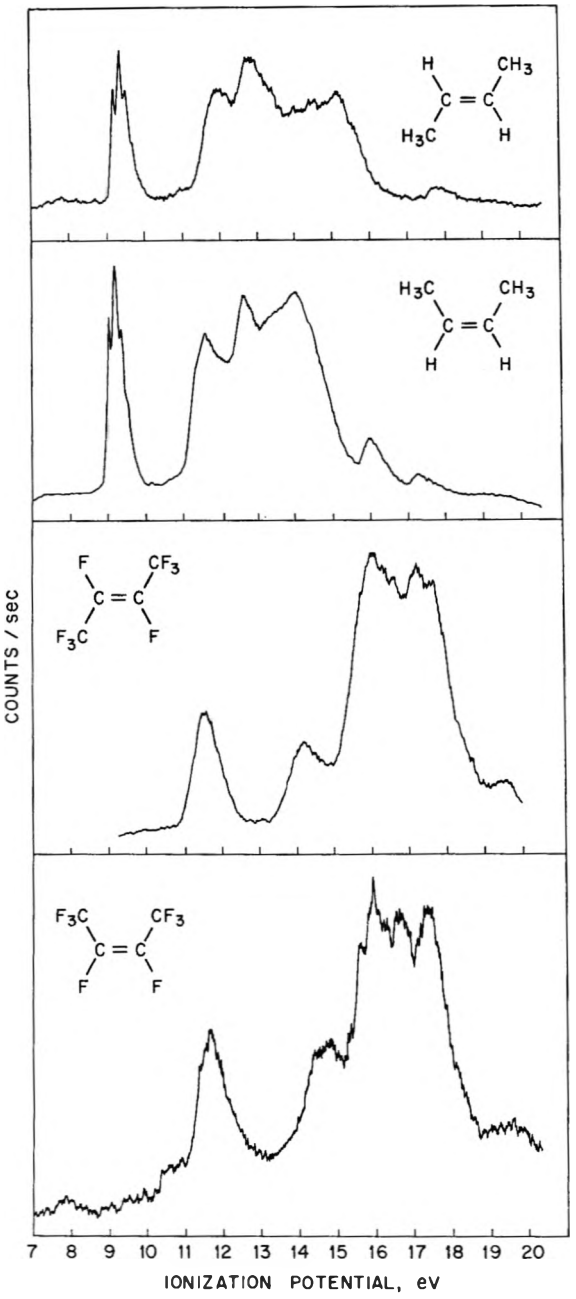

Figure 1.—Comparison of the He(I) photoelectron spectra of *cis*- and *trans*-butene-2 and their perfluoro derivatives.

and tetrafluoroethylene are 12.61, 11.46, 11.55, and 10.52 eV, respectively.

A second pair of molecules amenable to this type of study are *cis*- and *trans*-1,2-di-*tert*-butylethylene, the photoelectron spectra of which are shown in Figure 2. Offhand, we would expect the cis molecule to be sterically hindered and therefore twisted about the C=C double bond, whereas the trans isomer is expected to be planar. In fact, Demeo and El-Sayed[10] have already studied the photoionization thresholds of these molecules and having found that of the cis isomer to be 0.05 eV below that of the trans isomer concluded that the cis isomer was nonplanar. Our photoelectron spectra show the energetics of the ionization process more clearly (Figure 2, insert), from which it is seen that the vertical ionization potentials of the two isomers are essentially identical (8.95 eV, cis; 8.89 eV, trans), with

(10) D. A. Demeo and M. A. El-Sayed, *J. Chem. Phys.*, **52**, 2622 (1970).

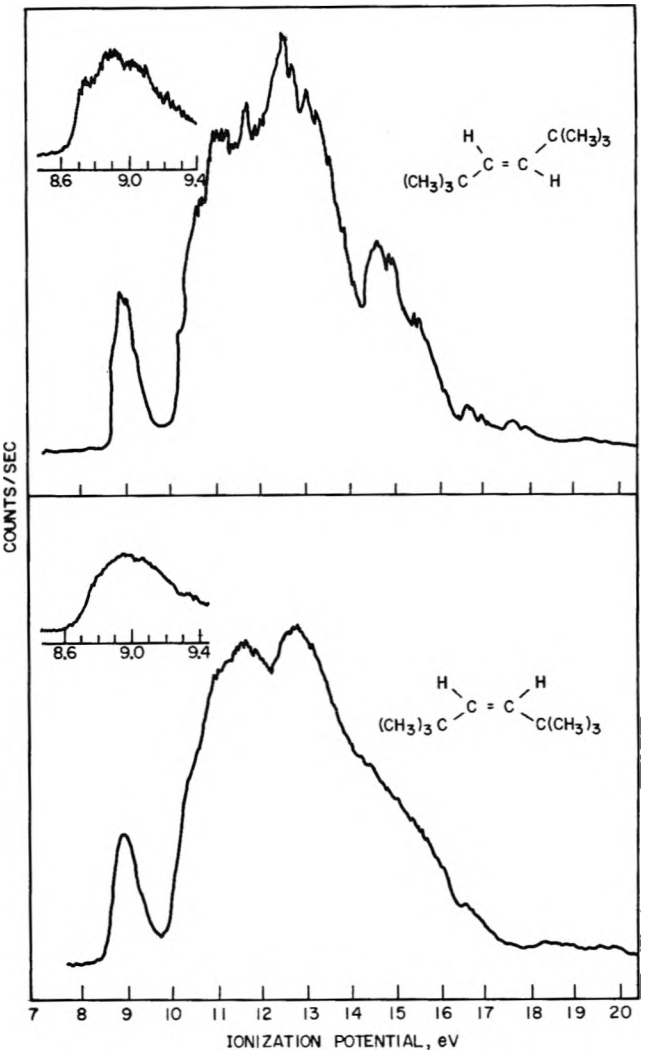

Figure 2.—He(I) photoelectron spectra of *cis*- and *trans*-di-*tert*-butylethylene.

that of cis actually somewhat higher than that of trans. It is also of interest that the $\pi \rightarrow \pi^*$ vertical excitation wavelengths are virtually identical in the two isomers of di-*tert*-butylethylene (1830 Å; cis; 1840 Å, trans).[11] We conclude that the strain in the cis molecule is not manifested as an appreciable twist (torsional strain) about the C=C double bond, but rather in the form of in-plane distortions. In support of this suggestion two calculations on the geometry of *cis*-1,2-di-*tert*-butylethylene have appeared[1,12] that agree on a value of 136° for the C=C—R bond angle (α in **1**). More recent force field calculations[3] also suggest that *cis*-1,2-di-*tert*-butylethylene is almost planar with the allylic carbon atoms being only 0.03 Å above and below the nodal plane of the π orbital.

Numerous earlier optical studies on *trans*-cyclooctene have been based on the assumption that the double bond is an inherently dissymmetric chromophore, the twist (β in **2**) typically being assumed to be in the range of 5–20°.[13] As a test of this idea, we have recorded the photoelectron spectra of *cis*- and *trans*-cyclooctene (Figure 3). The π ionizations in each of the isomers is a broad band, but with a clearly defined (0,0) spike

(11) G. J. Abruscato, R. G. Binder, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1787 (1972).

(12) E. H. Wiebenga and E. Bouwhuis, *Tetrahedron*, **25**, 453 (1969).

(13) C. C. Levin and R. Hoffmann, *J. Amer. Chem. Soc.*, **94**, 3446 (1972).

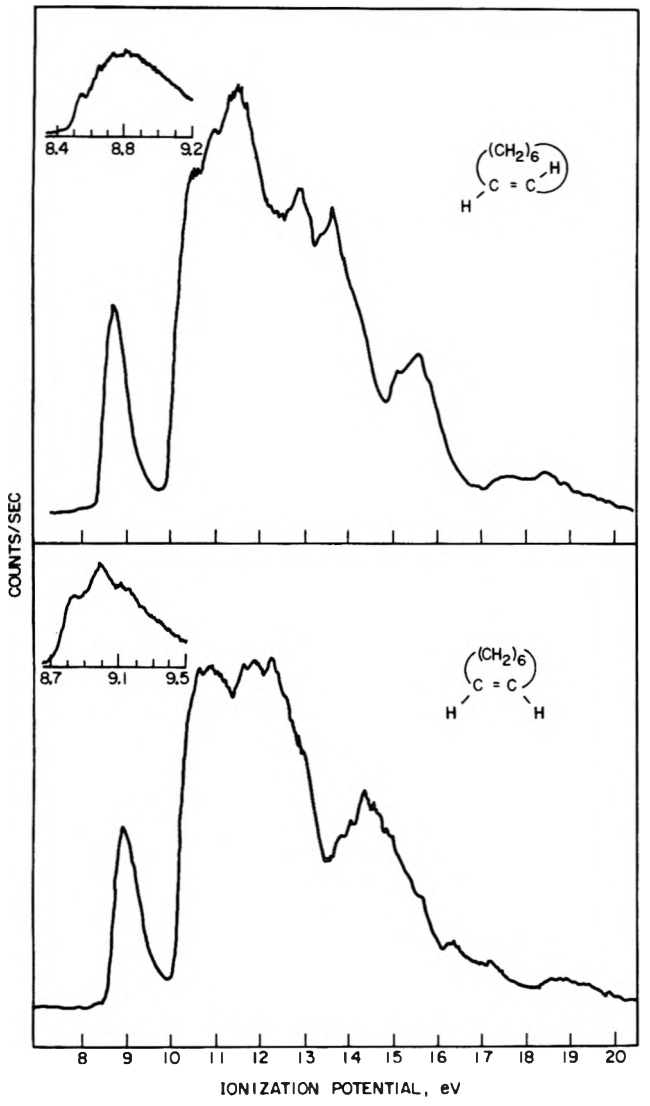

Figure 3.—He(I) photoelectron spectra of *cis*- and *trans*-cyeloctene.

(Figure 3, insert). The ionization potential of the trans isomer is 0.29 eV lower than that of the cis as measured by the positions of the (0,0) bands, and *ca.* 0.2 eV lower as measured by the approximate positions of the band maxima. Using the Mulliken diagram for ethylene and assuming that the 0.29 eV lowering of the trans ionization potential is due solely to twisting, we get a twist angle of 20 ± 3°, which is within the range of previous estimates for this quantity. This result is also in good agreement with the results of a force field calculation[3] in which the angle β between the π atomic orbitals is calculated to be 16.3°.

The present study demonstrates that the strain energies of *cis*-di-*tert*-butylethylene (10.5 kcal/mol)[14] and of *trans*-cyclooctene (9.2 kcal/mol)[15] are not necessarily indicators of the nonplanarity of these olefins. Consequently, any such structural assignments based solely on strain energies are suspect. The conclusions derived from these simple experiments must now be confirmed by more sophisticated measurements. If they are confirmed, and we think they will be, then medium resolution photoelectron spectroscopy will have been shown to be of unsuspected value in the gas phase structure determination of sterically crowded molecules such as olefins, dienes, biphenyls, etc.[16]

(14) J. D. Rockenfeller and F. D. Rossini, *J. Phys. Chem.*, **65**, 267 (1961).
(15) R. B. Turner and W. R. Meador, *J. Amer. Chem. Soc.*, **79**, 4133 (1957).

Registry No.—*trans*-2-Butene, 624-64-6; *cis*-2-butene, 590-18-1; *trans*-perfluorobutene-2, 1516-64-9; *cis*-perfluorobutene-2, 1516-65-0; *trans*-di-*tert*-butylethylene, 692-48-8; *cis*-di-*tert*-butylethylene, 692-47-7; *trans*-cyclooctene, 22770-27-0; *cis*-cyclooctene, 931-87-3.

Acknowledgment.—It is a pleasure to thank Professors S. H. Bauer, T. T. Tidwell, and L. S. Bartell for several of the samples used in this study.

(16) NOTE ADDED IN PROOF.—Professor Bauer has recently informed us that the electron diffraction work of his group on the fluorinated olefins in many cases yielded incorrect structures due to convergence to false minima. In *cis*-perfluorobutene-2, the revised dihedral angle is now quoted as equal to or less than 6°, in agreement with the photoelectron spectra. (S. H. Bauer Third Biannual Conference on Molecular Structure, Austin, Tex., Feb 1972).

2-Imino-4-methyleneoxazolidines from the Reaction of Propargyl Alcohols and Carbodiimides

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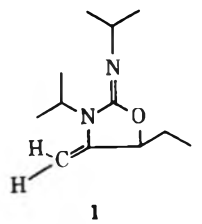
The formation of pseudoureas from the reaction of alcohols and carbodiimides, catalyzed by cuprous or cupric chloride, is well known.[1] Allyl alcohol and diisopropylcarbodiimide give *O*-allyl-*N*,*N*′-diisopropylpseudourea;[2] an analogous reaction of propargyl alcohol has not been reported. In the course of some earlier studies of propargyl alcohols, we investigated their reaction with carbodiimides.

The reaction of ethylethinylcarbinol with diisopropylcarbodiimide in the presence of cuprous chloride was slightly exothermic. Distillation gave a product which could be assigned structure **1** based on the spectral data. The presence of a terminal methylene group in the nmr spectrum (see Table I) and lack of an NH or C≡CH moiety in infrared or nmr spectra excludes several possible structures which could be written *a priori* except **1** and **2**. The intense uv absorption



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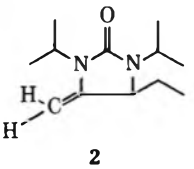

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maximum at 238 mμ, a pK_a of 9.4, and the ability to form salts lend support to structure **1**, 2-isopropylimino-3-isopropyl-4-methylene-5-ethyloxazolidine.

This facile reaction had thus provided a new entry into the iminooxazolidine class of compounds. Previous syntheses of iminooxazolidines and their deriva-

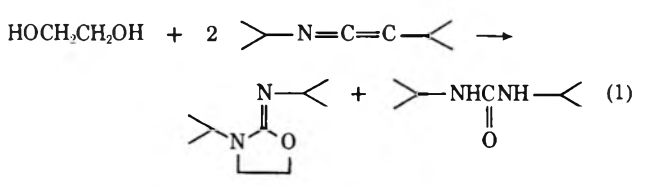
(1) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
(2) E. Schmidt, E. Dabritz, K. Thulke, and E. Grassmann, *Justus Liebigs Ann. Chem.*, **685**, 161 (1965).

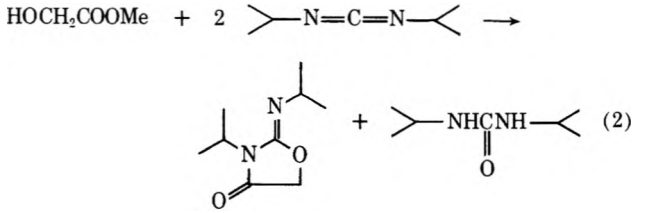
TABLE I
PHYSICAL DATA OF IMINOOXAZOLINE DERIVATIVES 7a–h[g]

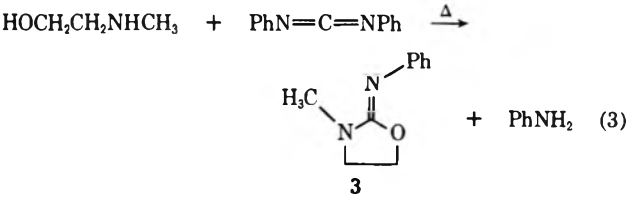
Oxazolidine	R	R_1	R_2	R_3	Mp,[a] °C	Yield, %	ν_{max}, cm^{-1}	λ_{max}, mμ (ε)	Nmr, δ, ppm
7a (1)	$(CH_3)_2CH$	H	H	Et	*b*	33	1700, 1660	238 (13,250) 288 (3410)	0.88, (3 H, t, J = 6.5 Hz), 1.03 (6 H, d, J = 6.5 Hz), 1.27 (6 H, d, J = 6.5 Hz), 1.4–1.95 (2 H, m), 3.63 (1 H, t, J = 2 Hz), 3.79 (1 H, septet, J = 6.5 Hz), 3.93 (1 H, t, J = 2 Hz), 4.27 (1 H, septet, J = 6.5 Hz), and 4.68 (1 H, m)
7b (*Z*)	$(CH_3)_2CH$	Ph	H	H	74–76	36.8	1720, 1670	225 (13,500) 284 (15,300)	1.07 (6 H, d, J = 6.5 Hz), 1.29 (6, H, d, J = 6.5 Hz), 3.77 (2 H, m), 4.72 (2 H, d), 5.21 (1 H, t), and 7.20 (5 H, broad singlet)
7c (*E*)	$(CH_3)_2CH$	H	Ph	H	43–44	50[c]	1710, 1645	224 (10,500) 289 (30,500)	1.07 (6 H, d, J = 6 Hz), 1.41 (6 H, d, J = 7 Hz), 3.76 (1 H, septet, J = 7 Hz), 4.52 (1 H, septet, J = 7 Hz), 4.96 (2 H, d, J = 2 Hz), 5.61 (1 H, t, J = 2 Hz), 6.9–7.4 (5 H, m)
7d (*E*)	C_6H_{11}	H	Ph	H	115–116	38.7[d]	1705, 1650	224 (10,750) 291 (32,250)	1.0–2.58 (20 H), 3.3–3.6 (1 H, m), 3.7–4.1 (1 H, m), 5.0 (2 H, d, J = 2 Hz), 5.64 (1 H, t, J = 1 Hz), 6.9–7.4 (5 H, m)
7e (*E*)	$(CH_3)_2CH$	H	*p*-C_6H_4Cl	H	66	63.2[e]	1715, 1650	256 (10,000) 299 (34,000)	1.07 (6 H, d, J = 6.5 Hz), 1.42 (6 H, d, J = 7 Hz), 3.78 (1 H, m J = 6.5 Hz), 4.42 (1 H, m, J = 7 Hz), 4.94 (2 H, d, J = 1 Hz), 5.56 (1 H, t, J = 2 Hz), 6.37 and 7.21 (4 H, A_2B_2 pattern)
7f (*E*)	C_6H_{11}	H	*p*-C_6H_4Cl	H	121–122	35[f]	1715, 1650	225 (10,200) 297 (34,300)	1.2–2.6 (20 H), 3.43 (1 H, m), 4.97 (2 H, d, J = 2 Hz), 6.92 and 7.25 (4 H, A_2B_2 pattern)
7g (*Z*)	$(CH_3)_2CH$	*p*-C_6H_4Br	H	H	88–89	41	1700, 1640	228 (16,000) 295 (16,400)	1.06 (6 H, d, J = 6.5 Hz), 1.30 (6 H, d, J = 6.5 Hz), 3.74 (2 H, 7 lines, J = 6.5 Hz), 4.71 (2 H, d, J = 2 Hz), 5.10 (1 H, broad singlet), 7.05 and 7.37 (4 H, A_2B_2 pattern)
7h (*E*)	$(CH_3)_2CH$	H	*p*-C_6H_4OMe	H	83–84	35	1710, 1660	225 (13,200) 280 (16,800)	1.10 (6 H, d, J = 7.0 Hz), 1.44 (6 H, d, J = 7.0 Hz), 3.76 (1 H, 7 lines, J = 7.0 Hz), 3.76 (3 H, s), 4.46 (1 H, m), 4.96 (2 H, d, J = 2 Hz), 5.61 (1 H, t, J = 2 Hz), 6.88–6.92 (4 H, m)

[a] The crystalline products were recrystallized from pentane. [b] Boiling point 46–48° (0.33 mm). [c] From distillation of 7b at 125° (0.25 mm). [d] From heating the corresponding *Z* isomer at 90° for 1 hr. [e] From heating the mixture of *E* and *Z* isomers at 80° for 1 hr [f] From heating the mixture of *E* and *Z* isomers at 125° for 1.5 hr. [g] Satisfactory microanalyses were obtained for all of the compounds.

tives include the reaction of 2 mol of a carbodiimide and 1 mol of a diol[2] (eq 1), the formation of 2-isopropylimino-3-isopropyloxazolidone-4 (isoelectronic with the basic ring structure of 1) from 2 mol of diisopropylcarbodiimide and 1 mol of the methyl ester of glycolic acid[3] (eq 2), and the formation of 2-phenylimino-3-methyloxazolidine (3) from *N*-methyl-2-hydroxyethylamine and diphenylcarbodiimide[4] (eq 3) or from reaction of the amino alcohol with phenyl isocyanide dichloride.[5] Thermal cyclization of acetylenic ureas has been reported[6] to give 5-methylene-2-iminooxazolidines of the

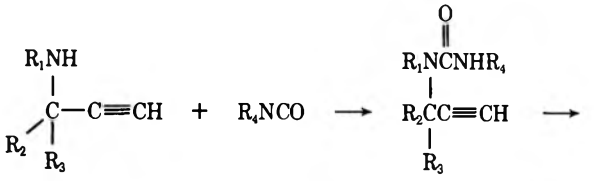


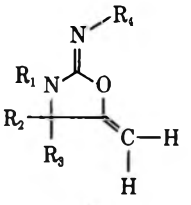




(3) E. Schmidt and W. Carl, *Justus Liebigs Ann. Chem.*, **639**, 24 (1961).
(4) B. Adcock, A. Lawson, and D. H. Miles, *J. Chem. Soc.*, 5120 (1961).
(5) (a) Belgian Patent 632,578 to Farbenfabriken Bayer A. G., May 20, 1963; (b) E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **8**, 20 (1969).
(6) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **29**, 1851 (1964).

general structure **4**, and iminooxazolidine **6** was obtained by allowing the urea **5** to rearrange in ethanol solution.[7]





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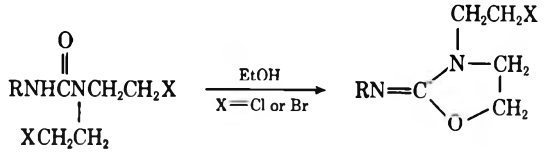
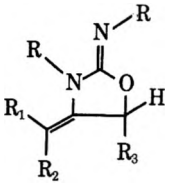


5 **6**

The present reaction provides an entry to the hitherto unknown 2-imino-4-methyleneoxazolidines by a method which permits introduction of a variety of substituents. Several compounds (**7a–h**) analogous to **1**



7a–h

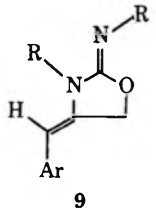
have been prepared and their physical data are given in Table I.

In the reaction of aryl propargyl alcohols of the type **8** with a carbodiimide, two geometrical isomers (*E* and

$$\mathrm{ArC{\equiv}CCH_2OH}$$

8

Z, **9** and **10**, respectively) about the double bond are possible. Pronounced shifts were noted in the nmr and ultraviolet spectra of the isomers **9** and **10**. The first-



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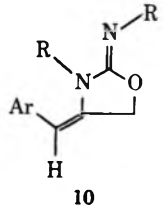
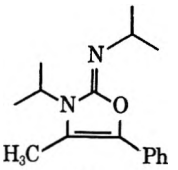


10

formed compound **10** undergoes isomerization to the more thermodynamically stable **9**, with relief of the steric crowding between the Ar and R groups of **10**. Thus, the ultraviolet spectra of compounds of the type **9**, in which coplanarity of the entire conjugated system can be achieved, exhibit longer wavelength, higher intensity maxima than those of structure **10**. The shifts to lower field in the nmr signals of **9** are consistent with this change in geometry.

The reaction of α-phenylpropargyl alcohol and diisopropylcarbodiimide afforded **11**, an iminooxazoline, in



11

which the double bond had undergone isomerization into the ring.

Experimental Section

General.—Melting points were taken on a Kofler hot stage and are uncorrected; boiling points are uncorrected. Infrared spectra were recorded on Beckman Model IR-9 or Perkin-Elmer Models 621 or 337 spectrophotometers; ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Nmr spectra were measured on a Varian Associates HA-100 or A-60 spectrometer or a Jeolco C60H instrument using tetramethylsilane as internal standard. Spectra and analyses were determined by our Physical Chemistry Department.

N,N'-Diisopropyl- and dicyclohexylcarbodiimide and ethylethynylcarbinol were purchased from Aldrich Chemical Co. and were redistilled prior to use. 3-Phenyl-2-propyn-1-ol was purchased from Farchan Research Laboratories; α-phenylpropargyl alcohol was obtained from K & K Laboratories. 3-*p*-Chloro- and 3-*p*-methoxyphenyl-2-propyn-1-ol[8] were prepared from the corresponding aryl acetylenes[9] according to known procedures.[10,11]

Procedure for Compounds 7a–h.—Freshly distilled acetylenic alcohol (0.05 mol) and 0.05 mol of carbodiimide were stirred with 50 mg of cuprous chloride overnight or longer if necessary for completion of the reaction. The product was distilled or recrystallized from the appropriate solvent. Physical data for compounds **7a–h** are given in Table I.

3-*p*-Bromophenyl-2-propyn-1-ol.—*p*-Bromophenylacetylene (1.4 g, 7.75 mmol), prepared according to the known procedure[9] from *p*-bromoacetophenone, was treated with equivalent amounts of butyllithium and dry paraformaldehyde as previously described.[11] Upon sublimation, the crude product (72%) afforded colorless crystals, which upon recrystallization from *n*-pentane had mp 68–69°; ν_{max}^{KBr} 3320–3200, 2225, 1480, 1070, 1020, 1010, 950, and 820 cm^{-1}; λ_{max}^{EtOH} 248 mμ (ϵ 25,080), 258 (23,050), 278 (1160), and 285 (610); nmr ($CDCl_3$) δ 1.52 (OH, broad), 4.43 (2 H, s) and 7.2–7.5 (4 H, m).

Anal. Calcd for C_9H_7BrO: C, 51.32; H, 3.34; Br, 37.61. Found: C, 51.22; H, 3.14; Br, 37.58.

2-Isopropylimino-3-isopropyl-4-methyl-5-phenyloxazoline (11).—A mixture of 6.6 g of α-phenylpropargyl alcohol, 6.3 g of diisopropylcarbodiimide, and 50 mg of cuprous chloride was heated at 70–80° under nitrogen for 4 days. Distillation at 105–109° (0.025 mm) afforded 27.5% yield of oxazoline **11**: $\nu_{max}^{CHCl_3}$ 1680 and 1655 cm^{-1}; λ_{max}^{EtOH} 221 mμ (ϵ 13,100) and 312 (12,800); pK_a 10.5; nmr ($CDCl_3$) δ 1.15 (6 H, d, J = 7 Hz), 1.41 (6 H, d, J = 7 Hz), 2.25 (3 H, s), 3.87 (1 H, 7 lines, J = 7 Hz), 4.39 (1 H, 7 lines, J = 7 Hz), and 7.2–7.5 (5 H, m).

Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.42; H, 8.52; N, 10.85. Found: C, 73.89; H, 8.49; N, 10.9.

Registry No.—**7a**, 37614-50-9; **7b**, 37681-83-7; **7c**, 37614-51-0; **7d**, 37614-52-1; **7e**, 37614-53-2; **7f**, 37614-54-3; **7g**, 37614-55-4; **7h**, 37614-56-5; **8b**, 1504-

(7) G. R. Pettit, D. S. Blonda, and R. A. Upham, *Can. J. Chem.*, **43**, 1798 (1965).

(8) F. Bohlmann, R. Enkelmann, and W. Plettner, *Chem. Ber.*, **97**, 2118 (1964).

(9) I. Iwai and Y. Yura, *Takamine Kenkyusho Nempo*, **10**, 30 (1958); *Chem. Abstr.*, **55**, 4400*d* (1961).

(10) H. Gilman and W. E. Catlin, "Organic Syntheses," Collect. Vol. 1, Wiley, New York, N. Y., 1958, p 188.

(11) A. Schaap, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **84**, 1200 (1965).

58-1; **8e**, 37614-57-6; **8g**, 37614-58-7; **8b**, 37614-59-8; **11**, 37614-60-1; dicyclohexylcarbodiimide, 538-75-0; diisopropylcarbodiimide, 693-13-0; *p*-bromophenylacetylene, 766-96-1; α-phenylpropargyl alcohol, 4187-87-5; propargyl alcohol, 107-19-7

Furazans and Furazan Oxides. III.[1] Acenaphtho[1,2-*c*]furazan

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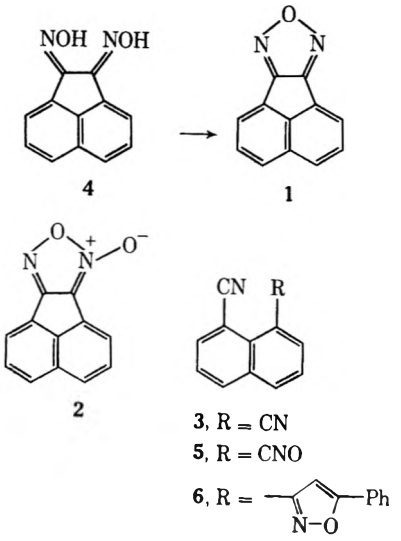
Received October 2, 1972

Some years ago, Boyer pointed out[2a] that very few representative furazans and furazan oxides fused to five-membered rings were known, and he also reported[2b] an unsuccessful attempt to prepare the title compound (**1**). Since that date, the number of strained furazan oxides known has increased,[3] but the only strained furazan has remained the rather doubtful example of Ingold and Shoppee.[4] Phosphite deoxygenation of acenaphtho[1,2-*c*]furazan oxide (**2**) has been found to occur under mild conditions, to form 1,8-dicyanonaphthalene (**3**), through the postulated intermediate furazan (**1**).[3] We now report the preparation of **1**, and some of its properties.



Dehydration of the dioxime **4** was effected by thionyl chloride in methylene chloride, a convenient modification of the method of Tokura, *et al.*,[5] who used sulfur dioxide as solvent. The product **1** was indefinitely stable at room temperature, but slowly decomposed to the nitrile oxide **5** on warming. The decomposition was followed by infrared, at 72° in toluene, and the appearance of two bands was observed, at 2285 (s, CNO) and 2210 cm^{-1} (m, CN). The nitrile oxide band reached a maximum after about 30 min, and then slowly decreased in intensity, falling to about 80% of its maximum after 2 hr. We were unable to isolate the expected furazan oxide dimer of **5**, after prolonged heating, and it is probable that other modes of polymerization had occurred, the product being oily and dark red in color.

The nitrile oxide **5** was not isolated in pure form, but brief (2–3 min) heating of the furazan **1** to 125° gave a product shown by infrared spectroscopy to contain largely the oxide. A number of stable 1-naphthonitrile oxides are known,[6a] although the examples quoted by Grundmann and Grünanger all have a 2 substituent.

The furazan **1** with phenylacetylene gave the adduct **6**, and with trimethyl phosphite formed 1,8-naphthalonitrile (**3**). These results tend to confirm the proposed scheme[3] for the phosphite deoxygenation of strained furazan oxides of type **2**, in that the furazan is now shown to ring open to the dinitrile monoxide under the conditions of the experiment. The finding that the reaction of the furazan oxide **2** with phosphite is rate dependent on phosphite concentration led us to attempt to prepare **1** from **2** using a high concentration of phosphite at temperatures at which **1** is stable. We did indeed isolate the furazan, but in poor yield.[6b]

A recent note[7] has reported that, under more forcing conditions (reflux in tri*phenyl* phosphite), even unstrained furazan oxides can be deoxygenated, with ring cleavage, to nitriles. We have found that 4,5,6,7-tetrahydrobenzofurazan and its oxide are slowly converted into adiponitrile on prolonged reflux in triethyl phosphite.[8] We also observe that the acenaphthofurazan oxide (**2**) is unchanged on heating alone to temperatures 20–30° higher than those at which the furazan **1** is converted into the dinitrile monoxide **5**. We suggest that this apparent greater thermal lability of the furazans, compared with their *N*-oxides, is a result of the greater thermodynamic stability of the nitrile group, compared with the nitrile oxide.[9] The lower energy of formation of the product of ring opening of the furazan oxide, compared with the furazan, is reflected in a slightly increased energy of activation for the ring opening. We have, however, been unable to trap any products of addition of phenylacetylene to 1,8-naphthalonitrile dioxide, which is expected to be formed by this ring opening, although the furazan oxide does decompose spontaneously at temperatures of 100° and above.

Experimental Section

Melting points are corrected. Nmr spectra are of $CDCl_3$ solutions, measured on a Perkin-Elmer R12 60-MHz instrument.

Acenaphtho[1,2-*c*]furazan (**1**). **A.**—Acenaphthoquinone dioxime[10] (5.0 g, 0.024 mol) was finely powdered and suspended in dry dichloromethane (20 ml). Thionyl chloride (3.1 g, 0.025 mol) was added, and the mixture was stirred at 20° for 24 hr. It was poured onto ice and extracted with dichloromethane (3 × 25 ml). The extracts were dried ($MgSO_4$) and the solvent was

(1) Part II: J. Ackrell and A. J. Boulton, *J. Chem. Soc., Perkin Trans. 1*, in press.

(2) J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., Wiley, New York and London, 1961, Chapter 6: (a) pp 466, 471; (b) p 508.

(3) J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton, and R. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1587 (1972).

(4) C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, **125**, 365 (1928).

(5) N. Tokura, R. Tada, and K. Yokoyama, *Bull. Chem. Soc. Jap.*, **24**, 270 (1961).

(6) (a) C. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag, West Berlin and Heidelberg, 1971. (b) The deoxygenation of furazan oxides to furazans by trialkyl phosphites has been observed: C. Grundmann, *Chem. Ber.*, **97**, 575 (1964).

(7) S. M. Katzman and J. Moffat, *J. Org. Chem.*, **37**, 1842 (1972).

(8) A. J. Boulton and S. S. Mathur, unpublished work (1971).

(9) Since we have been unable to locate any references to thermochemical data on nitrile oxides, this must remain an assertion unsupported by other than intuition.

(10) F. M. Rowe and J. S. H. Davies, *J. Chem. Soc.*, **117**, 1344 (1920).

removed (below 30°). Chromatography [Al_2O_3; eluent Et_2O (10%) in light petroleum] of the residue gave the furazan **1** (2.5 g, 55%) as pale buff needles: mp 140° (decomposing, depending on the rate of heating, above *ca.* 100°); ir (Nujol and $CHBr_3$) 1615 (w), 1600 (w), 1480 (m), 1410 (m), 1350 (m), 1315 (m), 1200 (m), 1150 (w), 1040 (w), 1020 (m), 940 (w), 820 (s), 810 (s), 770 (s); nmr τ_A 1.85, τ_B 2.00, τ_C 2.27 (J_{AC}, J_{BC} = 7 Hz).

Anal. Calcd. for $C_{12}H_6N_2O$: C, 74.2; H, 3.1; N, 14.4. Found: C, 74.5; H, 3.3; N, 14.1.

B.—Acenaphthofurazan oxide (**2**)[10] (0.1 g, 0.5 mmol) was allowed to stand for 48 hr with triethyl phosphite (5 g) at 20°. At the end of that period the solid had disappeared and the solution had become red-brown. It was poured into water (100 ml) containing 2–3 drops of HCl, and stirred until the smell indicated that the excess of phosphite had been hydrolyzed. Extraction (CH_2Cl_2) and chromatography on alumina as above gave the furazan **1** (0.01 g, 10%).

3-(8-Cyano-1-naphthyl)-5-phenylisoxazole (**6**).—The furazan **1** (0.1 g, 0.5 mmol) and phenylacetylene (0.07 g, 0.7 mmol) were heated to 125–130° for 15–20 min in xylene (3 ml). After cooling, the reaction mixture was chromatographed on alumina, eluting xylene and phenylacetylene with light petroleum, and then the adduct **6** with diethyl ether. The product formed needles (0.09 g, 55%): mp 142–143° (from ethanol); ir ($CHBr_3$) 3120 (m) (isoxazole CH), 2210 (m) (CN); nmr τ 3.22 (1 H, isoxazole), 1.8–2.6 (11 H).

Anal. Calcd for $C_{20}H_{12}N_2O$: C, 81.1; H, 4.05; N, 9.45. Found: C, 81.1; H, 4.25; N, 9.3.

1,8-Dicyanonaphthalene (**3**).—Heating the furazan **1** (0.1 g) to 80° for 4 hr with trimethyl phosphite (5 ml), followed by work-up in the usual way, gave the dinitrile **3** (95%), identical with a sample prepared previously[1] by reduction of the furazan oxide **2**.

Registry No.—**1**, 206-28-0; **3**, 5690-48-2; **4**, 1932-08-7; **5**, 37439-76-2; **6**, 37439-77-3; phenylacetylene, 536-74-3.

The Structure and Partial Synthesis of Fabacein[1a,b]

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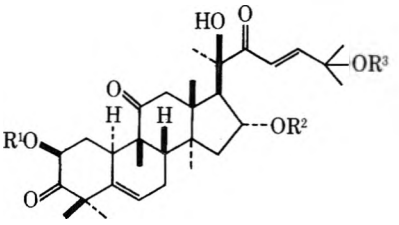
Received October 26, 1972

Fabacein is a bitter principle isolated from *Echinocystis fabacea* (Cucurbitaceae), and its isolation and preliminary characterization as a cucurbitacin diacetate derivative were described by Noller and coworkers.[2-4] In an extension of our recent studies of the structures of the cytotoxic cucurbitacins,[5-7] we have examined further the chemistry of fabacein. We report herein the structure elucidation and partial synthesis of fabacein (**1**), the first recognized naturally occurring cucurbitacin 16-acetate ester derivative.

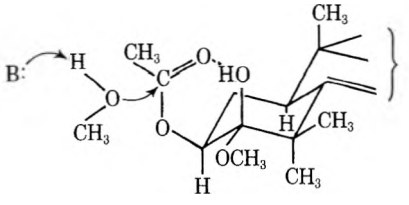


1, $R^1 = H$; $R^2 = R^3 = Ac$
2, $R^1 = R^2 = H$; $R^3 = Ac$
3, $R^1 = R^2 = R^3 = Ac$

Elemental analysis supported assignment of the molecular formula $C_{34}H_{48}O_9$[3] for fabacein (mp 198–201°, $[\alpha]^{25}D$ +36° absolute EtOH), and the spectral properties [$\lambda_{max}^{CHCl_3}$ 230 nm (ϵ 10,000); $\lambda_{max}^{CHCl_3}$ 2.91, 3.37, 3.43, 5.78, 5.91, 6.14, 6.84, 7.30, 8.00, 8.29, 8.87, 9.70, 10.2, and 10.8 μ; nmr ($CDCl_3$) τ 2.92 (1 H, d, J = 15 Hz), 3.68 (1 H, d, J = 15 Hz), 4.32 (1 H, m), 4.88 (1 H, b t, J = 8 Hz), 5.68 (1 H, d of d, J = 14, 6 Hz), 8.04 (3 H, s), 8.18 (3 H, s), 8.45 (3 H, s), 8.48 (3 H, s), 8.62 (3 H, s), 8.69 (3 H, s), 8.72 (3 H, s), 8.76 (3 H, s), 8.93 (3 H, s), and 8.99 (3 H, s); mass spectrum *m/e* 540, 445, 385, 369, 111, 96, and 43] supported its formulation as a cucurbitacin diacetate. The nmr signal at τ 4.88 (1 H, b t, J = 8 Hz) was characteristic of a C-16 proton in a 16-acetate derivative,[8] and, in view of the cooccurrence of fabacein with cucurbitacin B (**2**),[2] the hypothesis was entertained that fabacein is the 16-acetate ester (**1**) of cucurbitacin B (**2**).[3]

Interrelation of fabacein (**1**) with cucurbitacin B (**2**) was effected by acetylation of each to a common product, **3**. The triacetate **3** was obtained in a chromatographically homogeneous but amorphous form; the identity of the samples obtained from the respective precursors **1** and **2** was established by ir, uv, nmr, mass spectrum, mixed tlc, and optical rotation comparisons.

The synthesis of fabacein (**1**) from cucurbitacin B (**2**) was effected *via* selective base-catalyzed solvolysis of the C-2 acetate group of the triacetate **3**. Earlier studies in this laboratory have demonstrated a facilitation of the base-catalyzed solvolysis of the acetate esters of alcohols which bear carbonyl or hemiketal functions within hydrogen-bonding distance.[9] Accordingly, it was postulated that the alkaline solvolysis of the 2-acetate ester might be facilitated by the adjacent carbonyl group, possibly through hydrogen bonding of the acidic hydroxyl group of its hemiketal adduct with the carbonyl oxygen of the 2-acetate, as shown. In the event, treatment of **3** with triethylamine in 10% aqueous methanol for 12 hr at room temperature effected a smooth, selective solvolysis of the 2-acetate ester group, to yield fabacein (**1**).



(1) (a) Tumor Inhibitors. LXXXI. Part LXXX: S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Amer. Chem. Soc.*, **95**, 1335 (1973). (b) This investigation was supported by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (T-275). (c) National Institutes of Health Postdoctoral Fellow, 1972–.

(2) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958).

(3) W. Schlegel and C. R. Noller, *ibid.*, **26**, 1211 (1961).

(4) We thank Professor C. R. Noller cordially for a generous sample of fabacein.

(5) S. M. Kupchan, A. H. Gray, and M. D. Grove, *J. Med. Chem.*, **10**, 337 (1967).

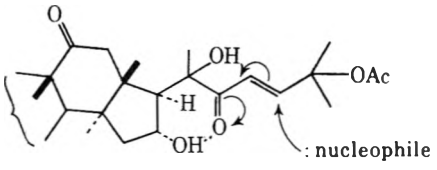
(6) S. M. Kupchan, R. M. Smith, Y. Aynehchi, and M. Maruyama, *J. Org. Chem.*, **35**, 2891 (1970).

(7) S. M. Kupchan, C. W. Sigel, L. J. Guttman, R. J. Restivo, and R. F. Bryan, *J. Amer. Chem. Soc.*, **94**, 1353 (1972).

(8) D. Lavie, Y. Shvo, O. Gottlieb, and E. Glotter, *J. Org. Chem.*, **28**, 1790 (1963).

(9) S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Amer. Chem. Soc.*, **88**, 343 (1966).

Fabacein showed relatively low cytotoxicity (ED_{50} = 1 μg/ml) toward human carcinoma of the nasopharynx in tissue culture (KB),[10] in contrast with the potent cytotoxicity shown by cucurbitacin B ($ED_{50} \cong 10^{-6}$ μg/ml).[5] Earlier studies in this laboratory have demonstrated the importance of highly electrophilic conjugated systems in relation to the cytotoxicity of several classes of terpenoids.[11] Saturation of the conjugated Δ^{23} double bond in the cucurbitacins is accompanied by a profound lessening in cytotoxicity of the resultant dihydrocucurbitacin derivatives.[5,6] Consequently, reactions of the side chain conjugated ketone with biological macromolecules may play an important role in the mechanism by which cucurbitacins exert their cytotoxic effects. The marked diminution in cytotoxicity which accompanies the acetylation of the C-16 hydroxyl group of cucurbitacin B suggests that the free hydroxyl group may be important for the reactivity of the conjugated ketone. Thus, hydrogen-bonding interaction between the C-16 hydroxyl group and the C-22 ketone could activate the α,β-unsaturated ketone toward nucleophilic attack by a biological macromolecule, as shown. The lessened cytotoxicity



of fabacein, then, may result from the diminished reactivity of the conjugated ketone in the C-16 acetate ester.

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Ultraviolet spectra were recorded on a Coleman Hitachi EPS-3T recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates HA-100 spectrometer using TMS as an internal standard. Mass spectra were recorded on either Hitachi Perkin-Elmer RMU-63 or AEI MS-902 spectrometers, equipped with direct insertion probes. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Acetylation of Fabacein to Triacetate 3.—A solution of fabacein[4] (1, 12 mg) in anhydrous pyridine (0.5 ml) was treated with acetic anhydride (0.5 ml). The reaction mixture was stirred overnight at room temperature under nitrogen. The solution was evaporated *in vacuo* and the residue was dissolved in ethanol and reevaporated. The oily residue (12 mg) was separated by preparative tlc on Brinkmann Silplates with 1% methanol–chloroform. The major band was eluted with ethyl acetate. Attempts to crystallize the product were unsuccessful. The amorphous product (**3**, 10 mg) showed R_f 0.68 on Brinkmann Silplates with 2% methanol–chloroform; R_f 0.80 on ChromAr plates with 1% methanol–ether; R_f 0.70 on polyamide plates with 70% methanol–water; uv ($CHCl_3$) 230 nm (ε 10,000); $[\alpha]^{25}D$ +2.5° (c 3.60, $CHCl_3$); ir ($CHCl_3$) 2.92, 3.36, 3.43, 5.76, 5.92, 6.15, 7.38, 8.09, and 9.70 μ; nmr ($CDCl_3$) τ 2.94 (1 H, d, J = 16 Hz), 3.66 (1 H, d, J = 16 Hz), 4.32 (1 H, m), 4.62 (1 H, d of d, J = 14, 5 Hz), 4.90 (1 H, b t, J = 8 Hz), 5.80 (1 H, s), 7.92 (3 H, s), 8.04 (3 H, s), 8.19 (3 H, s), 8.46 (6 H, s), 8.62 (3 H, s), 8.72 (3 H, s), 8.94 (3 H, s), and 9.01 (3 H, s); mass spectrum *m/e* 582, 412, 385, 325, 189, 112, 111, 96, and 43.

Acetylation of Cucurbitacin B to Triacetate 3.—Cucurbitacin B (**2**, 40 mg) was acetylated as above. The product obtained after preparative tlc (35 mg) showed the same rotation, ir, uv, nmr, mass spectrum, and R_f values as the product (**3**) of acetylation of fabacein (**1**).

Solvolysis of Triacetate 3 to Fabacein (1).—A solution of triacetate **3** (30 mg) in 10% aqueous methanol (0.5 ml) was treated with triethylamine (4 drops) and allowed to stand overnight at room temperature. The solution was evaporated *in vacuo*. The major component (21 mg), obtained by preparative tlc on Brinkmann Silplates with 2% methanol–chloroform, was crystallized from dichloromethane–absolute ethanol. The product (10 mg), mp 197–200°, was characterized as fabacein (**1**) by mixture melting point, ir, uv, nmr, mass spectrum, and tlc comparisons with an authentic sample.

Registry No.—**1**, 37710-13-7; **2**, 6199-67-3; **3**, 37710-14-8.

(10) Cytotoxicity was assayed, under the auspices of the National Cancer Institute, by the procedure described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(11) S. M. Kupchan, *Pure Appl. Chem.*, **21**, 227 (1970).

Benzo[*b*]thiophenes from Thiophenes. A Facile Approach

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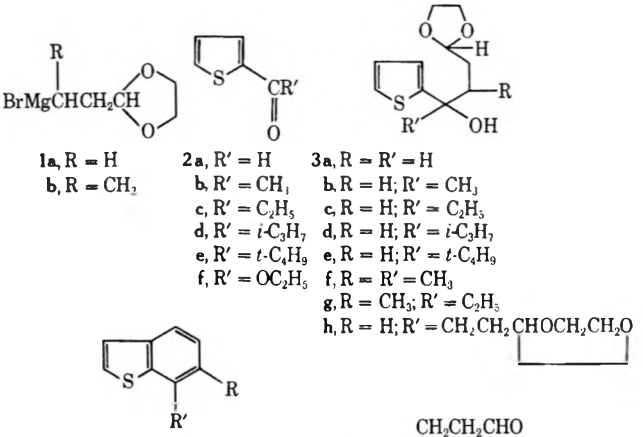
Benzo[*b*]thiophenes are generally synthesized by ultimate construction of the thiophene component onto thiophenol precursors. The alternative approach, *i.e.*, annellation of the benzene ring on preformed thiophenes, appears to have received scant attention.[1] Elaboration of such a route is herein described and is exemplified by the preparation of compounds **4a–d**, **4f–h**, and **5**.

Grignard reagent **1a** has recently attracted attention

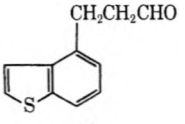


1a, R = H
b, R = CH_3

2a, R′ = H
b, R′ = CH_3
c, R′ = C_2H_5
d, R′ = i-C_3H_7
e, R′ = t-C_4H_9
f, R′ = OC_2H_5

3a, R = R′ = H
b, R = H; R′ = CH_3
c, R = H; R′ = C_2H_5
d, R = H; R′ = i-C_3H_7
e, R = H; R′ = t-C_4H_9
f, R = R′ = CH_3
g, R = CH_3; R′ = C_2H_5
h, R = H; R′ = $CH_2CH_2CHOCH_2CH_2O$

4a, R = R′ = H
b, R = H; R′ = CH_3
c, R = H; R′ = C_2H_5
d, R = H; R′ = i-C_3H_7
f, R = R′ = CH_3
g, R = CH_3; R′ = C_2H_5
h, R = H; R′ = CH_2CH_2CHO



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as a synthetic tool.[2] We chose to treat it with thiophenes **2a–e**. Products **3a–d** were subsequently submitted to the action of 10% refluxing H_2SO_4; this brought about hydrolysis, cyclization, and aromatization and produced benzo[*b*]thiophenes **4a–d** in 60–70%

(1) B. Iddon and R. M. Scrowston in "Advances in Heterocyclic Chemistry," Vol. 11, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1970, pp 177–381.

(2) G. Buchi and H. Wuest, *J. Org. Chem.*, **34**, 1121 (1969).

TABLE I
BENZO[b]THIOPHENES[a]

Compd	Yield,[b] %	Bp, °C (mm)	Deriv	Mp, °C	Empirical formula
4a	68	...[c]	Picrate	148–149	C_8H_6S
4b[d]	61	79–84 (4)	Picrate	140–144	C_9H_8S
4c	70	88–91 (5)			$C_{10}H_{10}S$
4d	64	106–109 (4)			$C_{11}H_{12}S$
4f[e]	42	110–115 (4)	Picrate	118–122	$C_{10}H_{10}S$
4g	44	116–122 (4)	Picrate	102–104	$C_{11}H_{12}S$
4h	90[f]	110–115 (0.05)[g]	Semicarbazone	176–178	$C_{11}H_{10}OS$

[a] Satisfactory analytical data (0.3 for C, H, N) for benzo[b]thiophenes 4c and 4d and the indicated derivatives of 4b, 4f, 4g, and 4h are reported. [b] Isolated material, purity >95% (nmr) and based on thiophene component. [c] Steam distilled out of reaction mixture. [d] A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A*, **32**, 390 (1950); *Chem. Abstr.*, **47**, 12346*d* (1953). [e] M. Pailer and E. Romberger, *Monatsh. Chem.*, **91**, 1070 (1960). [f] Yield based on purified 3h. [g] Nmr δ 2.5–3.3 (m, 4, aliphatic H), 6.80–7.57 (m, 5, aromatic H), 9.50 (t, 1, CHO); ir $\nu_{C=O}$ 1720 cm^{-1}.

overall yields. Attempts to effect such a transformation on **3e** gave complex mixtures of rearranged materials. Furthermore, variation of the Grignard component made possible the preparation of disubstituted systems. For example **1b**, upon reaction with **2b** and **e**, gave products **3f** and **g**, which, in turn, furnished **4f** and **g**.

Efforts aimed at extending the method led us to prepare benzo[b]thiophenes bearing ready-made functionalized side chains at C_4 and C_7. To this end, thiophene **2f** was treated with 2 equiv of **1a**, whereupon the product (**3h**) was cleanly converted in refluxing acid into aldehyde **4h**. Similarly, the 4-substituted isomer (**5**) was obtained by cyclization of the adduct of 2 equiv of **1a** and ethyl thiophene-3-carboxylate.

Experimental Section

General.—Melting points were determined on a Mettler apparatus and are uncorrected. Nmr data (Varian A-60, TMS as internal standard) were consistent with assigned structures. The intermediate crude oils **3a–g** were characterized solely by means of nmr and were converted as is into the products offered in Table I. Microanalyses were performed in our laboratories by Messrs. P. van den Bosch and H. Eding.

Starting Materials.—The required thienyl ketones were made by $SnCl_4$-promoted acylation of thiophenes as described for **2b**:[3] ethyl 2-thienyl ketone,[4] bp 102–104° (13 mm); isopropyl 2-thienyl ketone,[5] bp 104–106° (13 mm); and *tert*-butyl 2-thienyl ketone, bp 78–81° (3 mm), yield 61% (*Anal.* Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 64.23; H, 7.25.) [nmr δ 1.31 (s, 9, *tert*-butyl). 6.94, (m, 1, H_4 thienyl proton), 7.39 (d, 1, H_5 thienyl proton), 7.62, (d, 1, H_3 thienyl proton)]. Ethyl thiophene-3-carboxylate was prepared from 3-bromothiophene.[6a,b] 2-(2-Bromopropyl)-1,3-dioxolane was prepared from crotonaldehyde, ethylene glycol, and HBr[7] and was then converted into **1b** using conditions described for **1a**.[2]

The preparation of the benzo[b]thiophenes is illustrated by the synthesis of **4d**.

7-Isopropylbenzo[b]thiophene (4d).—To a solution of **1a**, prepared from 1.6 g (0.065 g-atom) of Mg and 12.3 g (0.065 mol) of 2-(2-bromoethyl)-1,3-dioxolane in 50 ml of THF,[2] was added dropwise a solution of 5.1 g (0.036 mol) of **2d** in 20 ml of Et_2O. After 2 hr the mixture was poured onto 10% NH_4Cl solution, which was extracted with Et_2O. The organic phase, upon drying (Na_2SO_4) and solvent removal left 8.3 g (90%) of oily **3d**: nmr δ 0.87 (2d, 6, i-C_3H_7), 2.93 (s, 1, OH), 3.80 (m, 4, dioxolane protons). It was added slowly to 150 ml of refluxing 10% H_2SO_4. After 1 hr, the product was extracted into Et_2O, which was then scrubbed ($NaHCO_3$), dried, and evaporated to leave an oily residue. Fractionation thereof afforded 3.6 g of **4d** (64% based on **2d**), bp 106–109° (4 mm).

1,5-Di(1,3-dioxolan-2-yl)-3-hydroxy-3-(2-thienyl)pentane (3h).—This compound, mp 48–49° [(i-Pr)$_2$O], was prepared in 80% yield by treating **2f** with 2 equiv of **1a** as described above, nmr δ 3.50 (s, 1, OH). *Anal.* Calcd for $C_{15}H_{22}O_6S$: C, 57.30; H, 7.05. Found: C, 57.32; H, 7.03.

3-(4-Benzo[b]thienyl)propionaldehyde (5).—This compound, prepared from ethyl thiophene-3-carboxylate and 2 equiv of **1a**, followed by acid treatment of the resulting oil, was obtained in 40% yield, bp 126–128° (0.01 mm): nmr δ 9.58 (t, 1, CHO); ir $\nu_{C=O}$ 1720 cm^{-1}. The semicarbazone was prepared in alcohol and melted at 186–187°. *Anal.* Calcd for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.93. Found: C, 57.91; H, 5.40; N, 16.93.

Registry No.—**1a**, 37610-80-3; **1b**, 37610-86-9; **2a**, 98-03-3; **2b**, 88-15-3; **2c**, 13679-75-9; **2d**, 36448-60-9; **2e**, 20409-48-7; **2f**, 2810-04-0; **3a**, 37610-85-8; **3b**, 37610-87-0; **3c**, 37610-88-1; **3d**, 37610-89-2; **3f**, 37610-90-5; **3g**, 37610-91-6; **3h**, 37610-92-7; **4a**, 95-15-8; **4a** picrate, 4500-67-8; **4b**, 14315-15-2; **4b** picrate, 37610-95-0; **4c**, 16587-42-1; **4d**, 37610-97-2; **4f**, 37610-98-3; **4f** picrate, 37610-99-4; **4g**, 37611-00-0; **4g** picrate, 37611-01-1; **4h**, 37611-02-2; **4h** semicarbazone, 37611-03-3; **5**, 37611-04-4; **5** semicarbazone, 37614-49-6.

Acknowledgment.—The authors wish to thank Professor C. Koningsberger for continued interest and encouragement and Mr. J. Lohmeyer for capable experimental assistance.

(3) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 8.

(4) W. Steinkopf and R. Schubart, *Justus Liebig Ann. Chem.*, **424**, 1 (1920).

(5) W. Krekeler, *Chem. Ber.*, **19**, 677 (1886).

(6) (a) S. Gronowitz, *Acta Chem. Scand.*, **13**, 1045 (1959); (b) S. Gronowitz and P. Moses, *Ark. Kemi*, **18**, 129 (1961).

(7) H. S. Hill and G. J. C. Potter, *J. Amer. Chem. Soc.*, **51**, 1509 (1929.)

Reactivity of First-Singlet Excited Xanthene Laser Dyes in Solution

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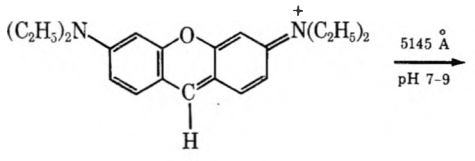
Received August 18, 1972

The useful lifetimes of xanthene laser dyes are limited primarily by an apparently irreversible photochemical reaction.[1] We report quantum efficiencies and photoproduct absorption spectra for this reaction.

(1) E. P. Ippen, C. V. Shank, and A. Dienes, *J. Quantum Electron.*, *QE-7*, 178 (1971).

The photochemical reaction was produced by irradiation of 4-ml samples of 2×10^{-4} *F* dye solution with 5145 Å excitation from a 1-W (cw) argon ion laser. At this wavelength, selective first-singlet excitation occurs for the fluorescent monomer form of the dye, producing excited states much lower in energy than those occurring in ultraviolet photochemistry. These excited states undergo chemical conversion as measured by fluorescent monomer absorbance decrease with quantum efficiencies in the range 10^{-6}–10^{-5}, under conditions of practical use—open solutions of dye in either ethanol or water containing a detergent.[1] We have observed a complication in this approach: the photoproducts arising from primary photobleaching enhance dye aggregation, which also reduces the fluorescent monomer concentration. Aggregation was more pronounced in water than in ethanol, was favored by basic conditions, and caused sharply increased rates of monomer decrease after 2–4-hr irradiation time.[2]

For Pyronin B (1), two photoproducts were observed, depending upon pH; these are not interconvertible by pH adjustment. At pH 7–9, a photoproduct with absorption bands centered at 332 and 382 nm was identified as the 9-xanthone (2) by comparison



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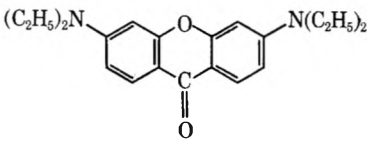

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with the spectrum of an authentic sample.[3] At pH 5.3, the absorption band of 1 at 552 nm decreases, and no absorption bands are observed at 332 and 382 nm. The pH 5.3 photoproduct absorbs in the 300–320-nm region. We find such absorption for the 9-xanthydrol, which may be formed from 1 by titration with base.[4] Neither the 9-xanthydrol nor the photoproduct air oxidize to 2, even in refluxing ethanol. The reactivity of first-singlet excited Pyronin B in solutions containing oxygen and hydroxyl donors then appears to be similar in kind, but different in degree, to ground-state reactivity. On the other hand, the dependence of photoproduct structure on solution pH is not predicted from studies on the ultraviolet photochemistry of xanthenes.[5]

The photoproduct of Rhodamine 6G shows strong absorption below 250 nm, a moderately strong absorption band at 260–270 nm, and an inflection point near 300 nm. The 9-hydrols of similar dye molecules have been studied, and possess absorption bands in the following regions: 232–238, 265–276, and 302–317 nm.[6,7] We infer that the 9-hydrol is the photoproduct observed at all pH values. (The C_9 carbon atom in Rhodamine 6G and disodium Fluorescein is tertiary, and ketone formation cannot occur *via* 5145 Å excitation.) The photoproduct of disodium Fluorescein shows only the trailing edge of a strong absorption band from 190 to 235 nm. Photobleaching of disodium Fluorescein occurs in the presence or absence of oxygen,[8] involves formation of an excited dye–solvent complex,[9] and leads to long-lived OH adducts in the presence of moisture.[10] It is therefore plausible that the 9-hydrol is the photoproduct of disodium Fluorescein also.

The photoproduct spectra indicated that, at the C_9-bridgehead position, conversion to an alcohol, and also oxidation to a ketone if secondary, took place. We therefore expected the quantum efficiencies to be comparable among the three dyes but strongly pH dependent, as is observed (Table I). For Pyronin B, the lowest bleaching rate occurs in acid solution, which may be explained by extensive reversion of the 9-xanthydrol to 1 under acid conditions.[4] The rate of formation of xanthone 2 increases with pH, up to the pH at which 1 is chemically converted to 9-xanthydrol. Disodium Fluorescein, which can be studied only in basic media, shows a definite but small pH effect. For all three dyes, an upper limit of *ca.* 10^{-5} in quantum efficiency is observed, and the nature of the pH dependence does not suggest a bimolecular, diffusion-controlled hydroxide attack. Rhodamine 6G, for example, shows sharp minima at pH 7 (ethanol) and 9 (water). From these results, given in Table I, we con-

TABLE I

THE pH DEPENDENCE OF PHOTOBLEACHING IN SOME XANTHENE DYES

Dye system	pH	Initial fluorescent monomer concn × 10^{-4} *M*[a]	Quantum efficiency × 10^{-5}
Pyronin B in ethanol (2×10^{-4} *F*)	5.3 (initial)	0.65	2.0
	7.1	0.86	4.9
	8.9	1.4	8.1
	9 and above	Chemical bleaching	
Disodium Fluorescein in ethanol (2×10^{-4} *F*)	7 and below	Chemical bleaching	
	8.9 (initial)	0.70	11
	11.2	1.2	13
	13.3	2.0	13
Rhodamine 6G in ethanol (2×10^{-4} *F*)	5.5 (initial)	1.6	8.1
	6.8	1.5	1.4
	9.3	2.0	11
	10.8	0.3	5.4
Rhodamine 6G in water containing 1.5% Triton X-100 (2×10^{-4} *F*)	5.5 (initial)	1.3	6.8
	7.1	1.4	6.8
	9.1	1.3	2.0
	11.1	1.0	7.3

[a] Based on $\epsilon_{552} = 8.3 \times 10^4$ (Pyronin B); $\epsilon_{497} = 9.7 \times 10^4$ (disodium Fluorescein); $\epsilon_{525} = 9.5 \times 10^4$ (Rhodamine 6G).

(2) A. D. Britt and W. B. Moniz, *J. Quantum Electron.*, *QE-8*, 913 (1972).
(3) P. Ehrlich and L. Benda, *Ber.*, **46**, 1931 (1913).
(4) K. Venkataraman, "The Chemistry of Synthetic Dyes," Vol. II, Academic Press, New York, N. Y., 1952, p 745.
(5) V. Zanker and E. Ehrhardt, *Bull. Chem. Soc. Jap.*, **39**, 1694 (1966).
(6) A. T. Vartanyan, *Zh. Fiz. Khim.*, **30**, 424 (1956).
(7) A. T. Vartanyan, *Russ. J. Phys. Chem.*, **36**, 1021 (1962).
(8) M. Imamura, *Bull. Chem. Soc. Jap.*, **31**, 962 (1958).
(9) S. Kato, T. Watanabe, S. Nagaki, and M. Koizumi, *ibid.*, **33**, 262 (1960).
(10) L. I. Grossweiner and A. F. Rodde, Jr., *J. Phys. Chem.*, **72**, 756 (1968).

clude that reaction occurs between the C_9 position in the excited dye molecule and oxygen-containing species in the immediate solvation sphere, the chemical nature of the latter being strongly predetermined by pH. The minima for Rhodamine 6G then are construed to represent the transition between acidic and basic solvation spheres, either of which favors hydrol formation. That hydrol may be formed in either acidic or basic media has been confirmed previously.[11]

Registry No.—1, 2150-48-3; disodium Fluorescein, 518-47-8; Rhodamine 6G, 989-38-8.

(11) L. Lindqvist, *Ark. Kemi*, **16**, 79 (1960).

Preparation of Uniformly ^{14}C-Labeled *p*-Hydroxybenzoic Acid[1]

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It was found that *p*-hydroxybenzoic acid (HBA) is converted to the benzoquinone nucleus of coenzyme Q (CoQ) in *Rhodospirillum rubrum*.[2-4] The conversion of HBA to CoQ also occurs in the rat.[2b,5] After these initial studies in 1963–1964, the biosynthetic significance of HBA was studied in several laboratories, and the following additional citations are representative and pertinent to interests in the availability of uniformly labeled [^{14}C]-*p*-hydroxybenzoic acid.

The complete sequence of biosynthesis from HBA to CoQ was elucidated for *R. rubrum*, and it was projected that the same sequence or a very closely related sequence would exist in mammalian tissue according to Friis, *et al.*[6]

Rudney[7] described studies on the biosynthesis of CoQ and polyprenylphenols in cell-free preparations of *R. rubrum*, *E. coli*, and rat tissue, and reported that the first two enzymatic systems in the biosynthetic pathway from HBA to CoQ were characterized. Trumpower, *et al.*,[8] utilized labeled precursors of CoQ, including HBA, in studies on liver slices and identified 5-demethoxy coenzyme Q_9 as an intermediate in the biosynthesis of CoQ_9 in the rat. Momose and Rudney[9] reported on the biosynthesis of 3-polyprenyl-4-hydroxybenzoate in the inner membrane of mitochondria from HBA and isopentenyl pyrophosphate.

Whistance, *et al.*,[10-12] have reported on the biosynthesis of CoQ in yeasts, gram-negative bacteria, and animals, and utilized tracer techniques with labeled HBA.

Nilsson, *et al.*,[13-15] utilized labeled HBA in the determination of precursors, in the biosynthesis of CoQ in genetically dystrophic mice, and in the biosynthesis of CoQ_{10} in beating cell cultures from heart tissue.

The preparation of [^{14}C]-*p*-hydroxybenzoic acid by the alkaline fusion of [^{14}C]tyrosine has been described.[2,16] However, this preparation from relatively expensive [^{14}C]tyrosine has given erratic and disappointing yields in our experience. Consequently, the procedure which has evolved from our many preparations of uniform ^{14}C-labeled HBA is described. The ready availability of [^{14}C]-HBA is essential to continuing studies on the biosynthetic conversion of HBA to CoQ in various systems, including normal and diseased tissues from experimental animals and humans.

Experimental Section

The fusion was carried out in a nickel crucible with a handle which was wrapped with asbestos for easy handling. The crucible was 44 mm deep, 44 mm in top diameter, 25 mm in bottom diameter, and 25 ml in capacity.

Uniformly labeled [^{14}C]-L-tyrosine (100 μCi) with a specific activity of 507 mCi/mmol was purchased from the Amersham-Searle Corp., Chicago, Ill. This tyrosine was received in an aqueous solution containing 2% ethanol. The solution was pipetted from its container into the crucible. The container and cap were washed thoroughly with 0.01 *N* HCl, and the washings were added to the crucible. The solution was evaporated by a warm-water bath under a stream of nitrogen. The inside surface of the crucible was well washed with 0.01 *N* HCl and the solution was evaporated. This washing was repeated about three times, and each time with a diminished volume to assure that the tyrosine was concentrated in one area of the bottom of the crucible. Approximately 150 mg of NaOH and 150 mg of KOH were finely crushed together and immediately added to the crucible in the region of the tyrosine. The NaOH and KOH were melted by placing the crucible in a Wood's Metal bath at 270°. The melted alkali was swirled around the crucible to encompass all the tyrosine. The temperature of Wood's Metal bath dropped about 15° on initial contact with the crucible and slowly climbed to 270°. After 10 min, the crucible was removed from the bath and allowed to cool. The melted residue solidified. Slowly, 1 ml of 10 *N* H_2SO_4 was added to dissolve the residue, and the solution was transferred to a small separatory funnel. The crucible was washed twice with 1 ml of water and the washings were poured into the separatory funnel.

The reaction mixture was extracted with 10 ml of ether. The extract was transferred into another small separatory funnel and extracted with 1 ml of H_2O. The extraction of the reaction mixture with ether followed by a water extraction of the ether was repeated ten times. The combined ether extract, 100 ml, was evaporated under vacuum. The residue was purified by thin layer chromatography on 1 mm silica gel G plates. The mobile phase for development was absolute methanol. Pure HBA was used as reference material. The area corresponding to the R_f value of HBA was removed and eluted four times with 50 ml of absolute methanol each time; this extraction was necessary to

(1) Coenzyme Q. CLVII.

(2) (a) H. Rudney and W. W. Parson, *J. Biol. Chem.*, **238**, PC 3137 (1963). (b) W. W. Parson and H. Rudney, *Proc. Nat. Acad. Sci. U. S.*, **51**, 444 (1964).

(3) W. W. Parson and H. Rudney, *J. Biol. Chem.*, **240**, 1855 (1965).

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(7) H. Rudney in "Natural Substances Formed Biologically from Mevalonic Acid." Biochemical Society Symposia, No. 29, T. W. Goodwin, Ed., Academic Press, New York, N. Y., 1970, p 89.

(8) B. L. Trumpower, A. S. Aiyar, C. E. Opliger, and R. E. Olson, *J. Biol. Chem.*, **247**, 2499 (1972).

(9) K. Momose and H. Rudney, *ibid.*, **247**, 3930 (1972).

(10) G. H. Spiller, D. R. Threlfall, and G. R. Whistance, *Arch. Biochem. Biophys.*, **125**, 786 (1968).

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(12) G. R. Whistance, F. E. Field, and D. R. Threlfall, *Eur. J. Biochem.*, **18**, 46 (1971).

(13) J. L. G. Nilsson, T. M. Farley, and K. Folkers, *Anal. Biochem.*, **23**, 422 (1967).

(14) J. L. G. Nilsson, T. M. Farley, J. Scholler, and K. Folkers, *Arch. Biochem. Biophys.*, **123**, 422 (1968).

(15) J. L. G. Nilsson, I. Nilsson, J. Scholler, and K. Folkers, *Int. J. Vitamin Res.*, **40**, 374 (1970).

(16) G. R. Whistance, D. R. Threlfall, and T. W. Goodwin, *Biochem. J.*, **105**, 145 (1967).

remove all the [^{14}C]-HBA. An aliquot was counted by liquid scintillation and showed that a yield of 55% of [^{14}C]-HBA was obtained. The purity of the HBA from fusion was tested by tlc in three additional systems: 1-propanol:H_2O:NH_4OH (8:1:1), benzene:methanol (1:4), and benzene:methanol:acetic acid (90:16:8). In all three systems, only one radioactive peak was detected by a Dünnschicht-Scanner, LB2721 (Berthold), and each had the same R_f value as reference HBA. Pauly's reagent was used to detect the areas of reference HBA.

Registry No.—[^{14}C]-*p*-Hydroxybenzoic acid, 33875-99-9; [^{14}C]tyrosine, 18875-48-4.

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Nitriles from Aldoximes. A New Reaction of Phosphonitrilic Chloride[1]

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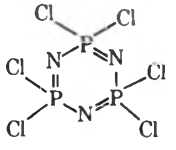
In previous work[2] we have reported that hexachlorocyclotriphosphazatriene (phosphonitrilic chloride) (**1**) can be used as an activator of the type RCOOX=Y[3] in the conversion of the carboxylic functions into amides and hydrazides in high yields and under very mild conditions.

Continuing the study of the chemical behavior of phosphonitrilic halides, we have examined the response of aliphatic, aromatic, and olefinic aldoximes toward phosphonitrilic chloride.[4]



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We found that nitriles are produced at room temperature in a process that is exceptionally mild, comparable to procedures recently reported, which involve dehydration of aldoximes.[5]

The method involves addition of a solution of triethylamine (3 mol) to a solution of phosphonitrilic chloride (1 mol) and oxime (1 mol) followed by isolation of the nitrile after 2–24 hr, usually by chromatography. Some results given by our process are shown in Table I,

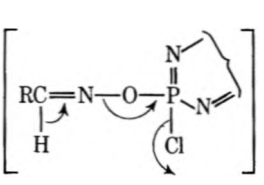
TABLE I

Oxime[a]	Yield of nitrile, %	Time of reaction, hr
(*E*)-Benzaldoxime	72 (88)[d]	24
(*Z*)-Benzaldoxime	74	24
(*E*)-*p*-Chlorobenzaldoxime	76 (60.8)[e]	18
(*Z*)-*p*-Chlorobenzaldoxime	78 (42.4)[e]	20
(*E*)-Cinnamaldoxime	98 (95)[d]	12
(*Z*)-Cinnamaldoxime	97	12
Undecaldoxime[b]	95	8
Heptaldoxime[b]	93 (42.7)[e]	8
(*Z*)-Furaldoxime	89 (60)[d]	18
p-Phenylbenzaldoxime	69	24
Pyridine-2-aldoxime	95	12
3,7-Dimethyl-2,6-octadienaldoxime	98	12
3-Indolecarboxaldehyde[c]	98	2

[a] Nomenclature of J. E. Blackwood, C. L. Gladys, K. L. Leoning, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968). [b] Stereochemistry unknown. [c] Reaction performed in THF. [d] Reference 5b. [e] Reference 5a.

in which the yields refer to analytically pure products obtained from reactions performed in diethyl ether. The yields given using other mild procedures are also reported.

Aldoximes react with phosphonitrilic chloride at room temperature to give nitriles, and no *O*-phosphonitrilic chloride derivative of type **2** has been observed during the reaction, whereas the cyclohexanone oxime reacts with compound **1** under the same conditions to give the compound **3** in 63% yield.



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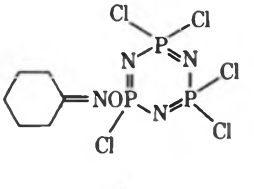

3

This fact induced us to hypothesize that aldoximes also react with phosphonitrilic chloride in the presence of triethylamine to give intermediates of type **2** that successively undergo 1,4 fast elimination of hydrogen chloride to form the corresponding nitriles.

Tlc analysis (silica gel, benzene as eluent) revealed the formation of nitrile and the disappearence of oxime during the time of the reaction, which was longer for the conversion of aromatic aldoximes (10–24 hr) than for the aliphatic and olefinic ones (2–8 hr). The stereochemistry of aldoximes (*E*, *Z*) has little effect on the reaction. The reaction can be performed in a variety of solvents (benzene, ethyl acetate, chloroform, THF) in very good yields.

The possibility of using a variety of solvents for the reaction, the simplicity of the operations involved, the high yields together with the mild conditions, and the ready availability of the reagent **1** recommend this new route to nitriles.

(1) This work was done with financial support from the Italian National Research Council (C. N. R.).

(2) L. Caglioti, M. Poloni, and G. Rosini, *J. Org. Chem.*, **33**, 2979 (1968); M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, p 206.

(3) J. Rudinger, *Pure Appl. Chem.*, **7**, 335 (1963).

(4) See, for recent reviews, R. A. Shaw, *Chem. Ind. (London)*, 1737 (1967); M. L. Paddock, *Quart. Rev., Chem. Soc.*, **18**, 168 (1964); R. A. Shaw, B. W. Fitzsimmons, and B. C. Smith, *Chem. Rev.*, **62**, 247 (1962).

(5) (a) D. L. J. Clive, *Chem. Commun.*, 1014 (1970); (b) P. J. Foley, Jr., *J. Org. Chem.*, **34**, 2805 (1969); (c) T. J. Bentley, J. F. McGhie, and D. H. R. Barton, *Tetrahedron Lett.*, 2497 (1965).

Work is in progress to extend the study of the chemical behavior of phosphonitrilic chloride toward ketoxime and amides.

Experimental Section

Materials.—Hexachlorocyclotriphosphazatriene (1) was purchased from Albright and Wilson, England, and used after purification by crystallization from petroleum ether (bp 30–60°). The oximes were prepared by standard methods. The nitriles were identified by comparison of their ir spectra and glc retention times with those of authentic samples and by their melting points in the case of solids. Pure-grade solvents were used without further purification.

General Procedure.—Triethylamine (3.0×10^{-2} mol) was added to a solution of the oxime (1.0×10^{-2} mol) and compound 1 (1.0×10^{-2} mol). The solution was allowed to stand at room temperature and the reaction was followed by tlc analysis (silica gel and benzene or cyclohexane–ethyl acetate as eluents). When the aldoxime had almost completely disappeared, triethylamine hydrochloride was removed by filtration and the filtrate was concentrated under reduced pressure. The mixture was taken up in 20 ml of benzene and the resulting nitrile was purified by chromatography on a silica gel column using benzene as eluent. Typical preparations follow.

Heptanenitrile.—To a solution of heptanealdoxime (1.29 g, 1.0×10^{-2} mol) and phosphonitrilic chloride (3.47 g, 1.0×10^{-2} mol) in 50 ml of diethyl ether in a 100-ml flask was added triethylamine (3.03 g, 3.0×10^{-2} mol) in 10 ml of diethyl ether. The solution was stirred for 8 hr at room temperature. The triethylamine hydrochloride was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel using benzene as eluent. Heptanenitrile (1.3 g), bp 54° (8 mm), was obtained in 93% yield; spectroscopic data are in agreement with those recorded on an authentic sample.

Anal. Calcd for $C_7H_{13}N$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.84; H, 11.62; N, 12.52.

3-Indolecarbonitrile.—To a solution of 3-indolecarboaldoxime (1.6 g, 1.0×10^{-2} mol) and phosphonitrilic chloride (3.47 g, 1.0×10^{-2} mol) in 50 ml of tetrahydrofuran in a 100-ml flask was added triethylamine (3.03 g, 3.0×10^{-2} mol). The solution was stirred for 2 hr at room temperature. The triethylamine hydrochloride was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel using benzene–ethyl acetate (7:3) as eluent. 3-Indolecarbonitrile (1.25 g, 98% yield) had mp 180–182° (lit.[6] mp 182–184°): spectroscopic data are in agreement with those recorded on a sample independently prepared.[6]

Anal. Calcd for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 75.89; H, 4.12; N, 19.54.

***O*-(Pentachlorocyclotriphosphazatriene)cyclohexanone Oxime (3).**—The reaction between cyclohexanone oxime and compound 1 was performed in diethyl ether as depicted in the general procedure and gave a compound (mp 74–75°, white crystals from pentane) in 63% yield, to which the structure of *O*-(pentachlorocyclotriphosphazatriene)cyclohexanone oxime (3) was assigned: ir (KBr) 2900 (w), 1470 (vw), 1430 (w), 1375 (m), 1360 (m), 1340 (m), 1325 (m), 1310 (m), 1280 (m), 1250 (s, shoulder), 1230 (vs, shoulder), 1200 (vs, broad), 1160 (vs, shoulder), 1122 (vs), 1095 (m), 1020 (w), 960 (m), 917 (m), 870 cm^{-1} (m).

Anal. Calcd for $C_6H_{10}Cl_5N_4OP_3$: C, 16.95; H, 2.37; Cl, 41.77; N, 13.23. Found: C, 16.70; H, 2.47; Cl, 41.81; N, 13.12.

Registry No.—1, 940-71-6; 3, 37709-15-2; heptanenitrile, 629-08-3; heptanealdoxime, 629-31-2; 3-indolecarbonitrile, 5457-28-3; 3-indolecarboaldoxime, 2592-05-4; cyclohexanone oxime, 100-64-1.

Acknowledgment.—The authors express their appreciation to Professor Luciano Caglioti for his interest in this project.

(6) H. M. Blatter, H. Lukaszewski, and G. de Stevens, *J. Amer. Chem. Soc.*, **83**, 2203 (1961); *Org. Syn.*, **43**, 58 (1963).

The Synthesis of 1,3,5-Trimethylbicyclo[4.4.1]undecan-11-one by Intramolecular Alkylation[1]

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Received October 31, 1972

In our approach toward the synthesis of molecules resembling the methymycin antibiotics, we recently reported the low yields found thus far in the acid-catalyzed cyclization–dehydration of 2,4,6-trimethyl-7-(4′-hydroxybutyl)cycloheptanone (1) to 2.[2]

In an attempt to overcome this problem, the following alternate pathway to 2 was developed. The alkylation of *cis,cis*-2,4,6-trimethyl-7-carbethoxycycloheptanone (3)[2] *via* its sodium enolate with 1,4-dibromobutane (4) gives a 60:40 mixture of the desired 2,4,6-trimethyl-7-carbethoxy-7-(4′-bromobutyl)cycloheptanone (5, as a mixture of stereoisomers) and the O-alkylated product 6. Since 3 is a highly hindered β-keto ester,[2] it had been anticipated that some O-alkylation might occur.[3] The corresponding alkylation of the sodium enolate of carbethoxycycloheptanone (7) with 4 occurs mainly on carbon.[4] Treatment with acid results in the hydrolysis of 6 to leave 5, which is then internally alkylated (with sodium hydride in hexamethylphosphoramide) to give a 60:40 mixture of the desired enol ether 9 and the bridged keto ester 8. Decarboxylation of this mixture with lithium iodide–collidine gives 1,3,5-trimethylbicyclo[4.4.1]undecan-11-one (10), a mixture of the enol ethers 2, and a small amount of 2,4,6-trimethyl-7-(3′-butenyl)cycloheptanone (11, derived from 2 with lithium iodide). Ketone 10 (and a minor amount of 11) is obtained by acid hydrolysis, which converts 2 to the easily separable 1.

The intramolecular alkylation of 5a had been expected to occur at the presumably less hindered oxygen site of the enolate ion, especially in highly polar hexamethylphosphoramide as solvent. Indeed, the sodium enolate of 2-carbethoxy-2-(4′-bromobutyl)cycloheptanone (i) gives 9:1 O/C intramolecular alkylation (ii, iii) in the less polar medium toluene–dimethylformamide.[4] The unexpected C-alkylation in 5a may be due to enhancement of the normally greater nucleophilicity of the enolate carbon by the 2-methyl[5a] and possibly by inhibition of solvation at the crowded enolate carbon.[6]

(1) This investigation was supported by Public Health Service Research Grant AI 07455 from the National Institute of Allergy and Infectious Diseases.

(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).

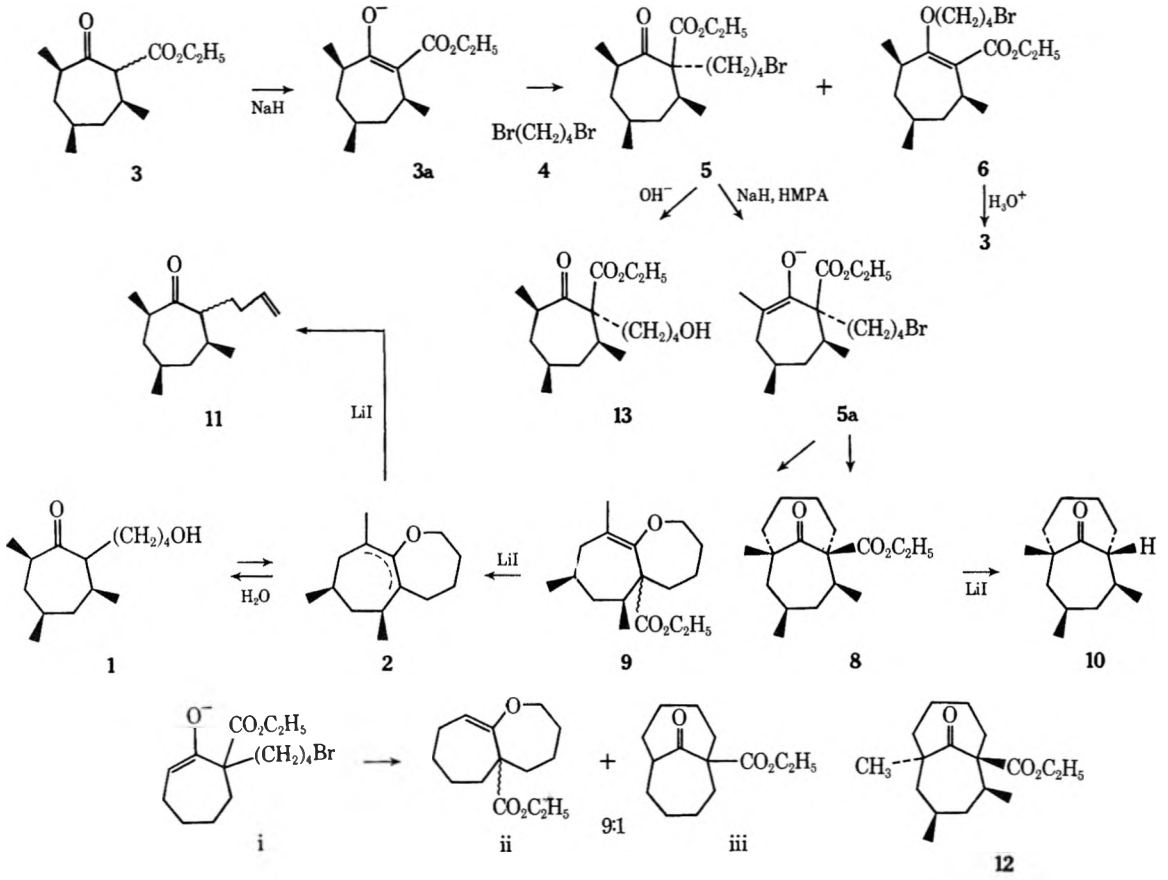
(3) The related alkylation of the sodium enolate of 3 with 1-bromo-4-acetoxybutane also gives some O-alkylation.[2]

(4) Professor John Wiseman, University of Michigan, private communication.

(5) (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 560; (b) pp 586–595.

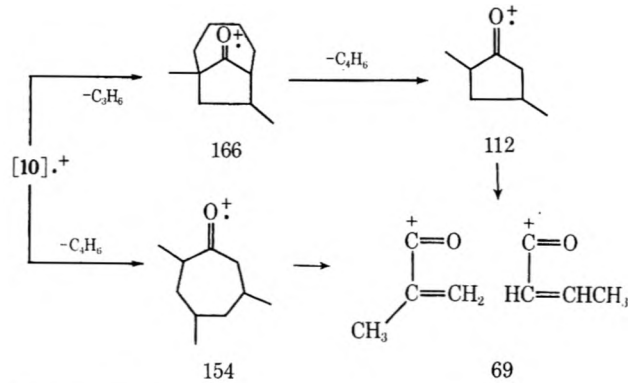
(6) Keto ester 5 may represent a borderline system wherein various factors can cause C- or O-intramolecular alkylation to predominate. The sodium enolate of 2-carbethoxy-2-(4′-bromobutyl)cyclododecanone (a large ring system approaching the behavior of acyclic enolates) gives intramolecular C-alkylation only.[7]

(7) H. Nozaki, H. Yamamoto, and T. Mori, *Can. J. Chem.*, **47**, 1107 (1969).



The stereochemistry suggested for the major isomer of **5**, for **8**, and for **10** (as illustrated) is based on the following assumptions. Introduction of the alkyl group from the less hindered side in **3a** *via* a transition state resembling the starting enolate[5b] should give **5**. Intramolecular cyclization of **5a** should give the all-cis isomer **8** as the less strained product (in comparison to the trans isomer **12**). Decarboxylation of **8** should give the all-cis **10**, again as the less strained isomer when compared to the alternate isomer with trans bridgehead methyl and proton groups.

Ketone **10** represents one of the few available examples of the bicyclo[4.4.1]undecane system.[8] Support for its structure is found in its mass spectrum, which includes peaks at *m/e* 112, 154, and 166. The latter two (among others) are not found in the mass spectra of the enol ether isomers of **2**. Suggested structures are as follows.



(8) See T. L. Westman and R. D. Stevens, *Chem. Commun.*, 459 (1965), and references cited therein.

It is interesting to note that intramolecular acid-catalyzed aldol condensation in cyclohexanones, leading to the bicyclo[3.3.1]nonane system, is favored by 2,6-dimethyl substitution.[9] The reasons for this "methyl group effect" differ, however, from those pertaining to enolate alkylation.

Experimental Section[10]

Alkylation of β-Keto Ester 3.—Alkylation of the sodium enolate of 2,4,6-trimethyl-7-carbethoxycycloheptanone [from **3** and sodium hydride in toluene–dimethylformamide (4–5:1) at reflux for 30 min] with 1,4-dibromobutane (**4**, 1 equiv, at reflux for 24 hr) gave a neutral solution which was filtered, concentrated, and treated with 1 *N* HCl in methanol–water (6:1) for 24 hr at 25°. Neutralization with $NaHCO_3$, evaporation of the methanol, and extraction of the organic layer into diethyl ether, followed by drying ($MgSO_4$) and evaporation *in vacuo*, gave 2,4,6-trimethyl-7-carbethoxy-7-(4′-bromobutyl)cycloheptanone (**5**, 26%): bp 150–160° (0.15 mm); ir (CCl_4) 1710, 1700 cm^{-1}; nmr (CCl_4) τ 5.83 (m, 2, $CO_2CH_2CH_3$), 6.67 (t, 2, CH_2Br), 7.9–9.1 (m, 16), 8.7 (t, 3, CH_3CH_2), and 8.95 (broad d, 6, CH_3CH); vpc (10% SE-30 at 200°) two peaks with close retention times (*ca.* 12 min).

Anal. Calcd for $C_{17}H_{29}O_3Br$: C, 56.51; H, 8.10; Br, 22.12. Found: C, 56.26; H, 7.92; Br, 21.86.

Similar alkylation of **3** with NaH and **4** in toluene–DMF without acid treatment gave a mixture of **5** and **6** in 60:40 ratio (28–38%), vpc (1% SE-30 at 165°) retention time 11 and 7 min, respectively. The use of toluene–DMF in 2 or 3:1 ratio gave a C-

(9) J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965).

(10) Infrared spectra were recorded on Perkin-Elmer 257 and 700 spectrophotometers. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Boiling points are uncorrected. Mass spectra were done on a Varian Atlas CH-5 vpc-inlet mass spectrometer by Mr. Jack Landis, City University of New York. Solvents were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions involving carbanions were conducted under prepurified nitrogen. Gas chromatograms were done on a Varian Aerograph A-700 employing columns packed with 5 or 10% SE-30 on Chromosorb W (5 or 10 ft × 0.25 in.).

vs. O-alkylated product ratio of 1:1 (35%). Reaction in toluene gave **5** in 8% yield. Reaction of **5** with aqueous NaOH gave 2,4,6-trimethyl-7-carbethoxy-7-(4′-hydroxybutyl)cycloheptanone (**13**) identical (by vpc, ir, and nmr) with a genuine sample [from the base hydrolysis of 2,4,6-trimethyl-7-carbethoxy-7-(4′-acetoxybutyl)]cycloheptanone].[2]

Intramolecular Alkylation of 5.—To a suspension of 52% NaH (washed with hexane, 1.31 g, 0.028 mol) in hexamethylphosphoramide (75 ml), **5** (10 g, 0.028 mol) was added with stirring at room temperature. The resultant mixture was stirred for 24 hr at 140° to give a neutral solution which was filtered and distilled to give a mixture containing **8** and **9** in 40:60 ratio (2.94 g, 0.011 mol, 39% if only **8**, **9**): bp 130–150° (0.15 mm); ir (CCl_4) 1680 (vinyl ether), 1725 (ketone), and 1740 cm^{-1} (ester); nmr (CCl_4) τ 5.88 (2, m, $CO_2CH_2CH_3$), 6.40 (m, CH_2O), 8.33 (s, vinyl CH_3), 8.8 (t, 3, CH_2CH_3), 8.2–8.8 (m), 8.95–9.2 (m, 6, CH_3); vpc–mass spectrum (5% SE-30, 75 eV) *m/e* peak 1 (minor isomer of **8**) 280, peak 2 (major isomer of **8**) 280, peak 3 (minor isomer of **9**) 280, peak 4 (major isomer of **9**) 280, peak 5 (minor amount, **1**) 298. Preparative tlc (on silica, extracted with $CHCl_3$) gave a mixture of fractions 1–4 (**1** was left behind) which was analyzed. *Anal.* Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.62; H, 10.03.

Decarboxylation of 8 and 9.—A mixture of lithium iodide dihydrate (4.4 g, 0.026 mol) and the above mixture of **8** and **9** (5.20 g, 0.019 mol) in dry collidine (25 ml) was heated at reflux for 30 hr. The cooled mixture was then poured into ice water (40 ml)–diethyl ether (40 ml) and carefully acidified with cold 1 *N* HCl. The resultant organic layer was then washed with 2 *N* Na_2CO_3 (30 ml) and saturated NaCl (2 × 30 ml), dried (Na_2SO_4), and distilled to give **2** and **10** in 60:40 ratio (0.7 g, 0.0034 mol, 18%): bp 75° (0.15 mm); ir (neat) 1700 cm^{-1}, no OH; nmr (CCl_4) τ 6.45 (m, CH_2O), 8.0–8.8 (m, CH_2, CH), 8.4 (s, vinyl CH_3), 8.95–9.2 (m, 6, CH_3CH); vpc–mass spectrum (5% SE-30, 70 eV) *m/e* (rel intensity) peak 1 (**10**) 208 ($M\cdot^+$, 27), 193 (25), 166 (28), 155 (38), 154 (98), 139 (98), 126 (34), 125 (48), 112 (98), 111 (100), 109 (35), 97 (40), 95 (60), 84 (42), 83 (98), 69 (98), 55 (98), M + 1 = 16.1 (calcd for $C_{14}H_{24}O$, M + 1 = 15.6),[11] peak 3 (isomer of **2**) 208 ($M\cdot^+$, 60), 193 (62), 179 (10), 165 (68), 151 (37), 139 (34), 137 (35), 126 (98), 112 (67), 111 (73), 109 (52), 95 (78), 81 (65), 69 (93), 55 (100), and similar fragmentation for peak 4 (isomer of **2**). Also obtained was a fraction consisting mainly of **1** (identical vpc, ir, and nmr with those of a genuine sample)[2] and small amounts of **2** and **10** (0.6 g, 0.0027 mol, 14% if all **1**), bp 125° (0.15 mm). Peak 2 (*m/e* 208) is probably **11** (see below).

Treatment of the mixture of **2**, **10**, and **11** (0.4 g, *ca.* 0.002 mol) with 1 *N* HCl (2 ml) in methanol (5 ml) gave a mixture of **1**, **10**, and **11** (minor amount). Distillation gave 1,3,5-trimethylbicyclo[4.4.1]undecan-11-one (**10**, *ca.* 0.15 g, 0.0007 mol, 35%): bp 70° (0.15 mm); ir (film) 1700 cm^{-1}; nmr (CCl_4) τ 7.0–8.8 (m, 15), 9.02 [s, 3, bridgehead CH_3, shifted downfield by Eu(DPM)$_3$], 9.01 (d, 6, CH_3CH, J = 7 Hz); vpc retention time for **10** as in above sample. About 10% (by vpc area of a separate peak) of **11** was present: ir 1640 cm^{-1}; nmr τ 4–4.5, 5.05 (br d), 5.3 ($CH=CH_2$).[2]

Registry No—**2** (10-ene), 33015-94-0; **2** (5a-ene), 37931-56-9; **3**, 37931-57-0; **4**, 110-52-1; **5**, 37931-58-1; **8** (major isomer), 37931-59-2; **8** (minor isomer), 37931-60-5; **9** (major isomer), 37931-61-6; **9** (minor isomer), 37931-62-7; **10**, 37931-63-8.

(11) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1963, p 37.

Communications

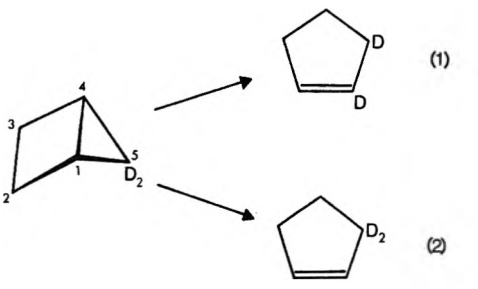
See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

Thermal Rearrangement of 5,5-Dideuteriobicyclo[2.1.0]pentane[1]

Summary: Through a deuterium-labeling study the thermal rearrangement of bicyclo[2.1.0]pentane to cyclopentene has been shown to involve a hydrogen rather than a carbon migration.

Sir: 5,5-Dideuteriobicyclo[2.1.0]pentane has been prepared and employed by Gassman, Atkins, and Lumb[2] in their investigations of the rhodium dicarbonyl chloride dimer catalyzed isomerization of that bicyclic system to cyclopentene. The rearrangement product indicated extensive scrambling of deuterium label at some stage of the reaction.

We have used this dideuterio compound to study the gas phase thermal isomerization of bicyclopentane to cyclopentene.[3-5] The results obtained provide the first experimental distinction between mechanistic options requiring C(1)–C(4) bond cleavage and C(5)–H hydrogen migration (eq 1), and others postulating C(1)–C(5) bond cleavage with C(3) carbon migration (eq 2).



Isomerizations analogous to each of these alternatives, and others consistent with either, have been observed in some acetyl- and ethoxycarbonyl-substituted bicyclopentanes.[6-9]

The deuterated substrate was prepared through reaction of cyclobutene[10] with 60% deuterated benzylmercuriiodomethane,[11] secured in turn from partially

(1) Supported by the National Science Foundation through Grant GP-31415.

(2) P. G. Gassman, T. J. Atkins, and J. T. Lumb, *Tetrahedron Lett.*, 1643 (1971); *J. Amer. Chem. Soc.*, **94**, 7757 (1972).

(3) R. Criegee and A. Rimmelin, *Chem. Ber.*, **90**, 414 (1957).

(4) M. L. Halberstadt and J. P. Chesick, *J. Amer. Chem. Soc.*, **84**, 2688 (1962).

(5) C. Steel, R. Zand, P. Hurwitz, and S. G. Cohen, *ibid.*, **86**, 679 (1964).

(6) T. H. Kinstle, R. L. Welch, and R. W. Exley, *ibid.*, **89**, 3660 (1967).

(7) M. J. Jorgenson and T. J. Clark, *ibid.*, **90**, 2188 (1968).

(8) M. J. Jorgenson and A. F. Thatcher, *Chem. Commun.*, 1030 (1969).

(9) E. Baggiolini, K. Schaffner, and O. Jeger, *ibid.*, 1103 (1969).

(10) A. C. Cope, A. C. Haven, Jr., F. L. Ramp, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **74**, 4867 (1952).

(11) R. Scheffold and U. Michel, *Angew. Chem., Int. Ed. Engl.*, **11**, 231 (1972).

deuterated diazomethane[12] and benzylmercuric iodide in tetrahydrofuran.[11]

The 5,5-dideuteriobicyclo[2.1.0]pentane was purified through preparative glpc on a 5 m × 6 mm 20% tris(cyanoethoxy)propane on Chromosorb P column at 30°. The purified sample, shown by analytical glpc to be free (<0.2%) of cyclopentene, was pyrolyzed at 300° for 63 min to give labeled cyclopentene, which was purified by glpc and analyzed by proton nmr. The data gathered from analyses of labeled and unlabeled samples on 2 days are given in the Table I; the standard deviations given stem from averages over nine integrations.

TABLE I

INTEGRATED ABSORPTION INTENSITIES FOR CYCLOPENTENE-d_x

Run	Compd	Vinyl H	Allylic H	Methylene H
1	d_0	1.79 ± 0.06	3.73 ± 0.09	2.00 ± 0.03
1	d_2[a]	1.28 ± 0.05	3.22 ± 0.08	2.00 ± 0.02
2	d_0	1.88 ± 0.04	3.94 ± 0.07	2.00 ± 0.02
2	d_2[a]	1.34 ± 0.05	3.27 ± 1.02	2.00 ± 0.02

[a] By nmr, 14.2 atom % deuterium content.

These data indicate 1.43 ± 0.05 vinyl protons and 3.44 ± 0.06 allylic protons in the labeled product. The predicted pairs of values for cyclopentene having 14.2 atom % deuterium content would be, according to eq 1 and 2, 1.43, 3.43, and 2.00, 2.86. The rearrangement thus clearly involves a hydrogen shift from C(5), and bicyclopentane and cyclopropane may share a common mechanism for isomerization to the corresponding olefins.

Assuming a statistical distribution among d_0, d_1, and d_2 bicyclopentane molecules, calculations suggest that a k_H/k_D ratio larger than 1.5 would have given detectably different integrated absorption intensities for the cyclopentene product.

Whether the isomerization to cyclopentene is a reaction best ascribed to the stabler folded bicyclopentane molecule[13] or to the easily accessible planar closed-shell 1,3-ethano-π-cyclopropane molecule[14] is a question demanding additional work on less symmetrical analogs. Such an effort now seems justified.

(12) S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, 1501 (1972).

(13) R. D. Suenram and M. D. Harmony, *J. Chem. Phys.*, **56**, 3837 (1972); **57**, 2597 (1972).

(14) J. E. Baldwin, A. H. Andrist, and R. K. Pinschmidt, Jr., *Accounts Chem. Res.*, **5**, 402 (1972), and references cited therein.

(15) National Science Foundation Predoctoral Trainee, 1972.

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GERALD D. ANDREWS[15]

RECEIVED DECEMBER 29, 1972

FROM
THE
BEGINNING . . .
ESTERIFICATION
REAGENTS

It has been well known that esterification of carboxylic acids can be accomplished with diazoalkanes.[1a] Our first Aldrich chemical "catalog" published some twenty years ago consisted of only one page and described a single compound, **N-methyl-N'-nitro-N-nitrosoguanidine** (MNNG), a diazomethane precursor. We soon added **Diazald®** and **N,N'-dimethyl-N,N'-dinitrosoterephthalamide** and have become the largest supplier of diazomethane precursors. While MNNG is still one of the most convenient and widely used diazomethane reagents, the low cost of Diazald® makes it the reagent of choice for methyl ester preparation on any scale.[1b] The generation of diazomethane from Diazald® is described in our Technical Information Brochure, which can be obtained upon request. For the experimentalists who are interested in using deuteriodiazomethane, we offer a **Deutero Diazald® Prep Set** that provides detailed instructions and sufficient chemicals to generate 50 mmoles of CD_2N_2.[2] For **safety** and **convenience** many chemists have found our **Diazald® Kit** superb for generating diazomethane as well as diazomethane-d_2. In addition to esterification of carboxylic acids, diazomethane is useful in the Arndt-Eistert reaction, for ring enlargements, for methylation of alcohols, etc.[1] Other diazoalkane precursors, of course, are also available from Aldrich: **N-ethyl-, N-propyl-** and **N-butyl-N'-nitro-N-nitrosoguanidine** for **diazoethane, diazopropane** and **diazobutane,** respectively.

We now offer a new class of alkylating reagents for carboxylic acids, the **3-alkyl-1-p-tolyltriazenes.** These triazenes are stable crystalline materials and react directly with carboxylic acids in ether or other organic solvents to form esters in high yields.[3] Esterification with 3-alkyl-1-p-tolyltriazenes involves a carbonium ion[4] but not a

R = Alkyl or Aryl **R' = Me, Et, Pr, i-Pr, Bu, Allyl, $PhCH_2$**

diazomethane intermediate, and therefore is unlikely to be accompanied by side reactions, such as addition to strained or conjugated double bonds. The simple reaction and workup procedure and high yield of the ester make this triazene method useful not only for preparative but also for analytical work, such as identification of carboxylic acids by gas or liquid chromatography. **3-Benzyl-1-p-tolyltriazene** is of special value in the protection of carboxylic acids as benzyl esters, because the latter can be readily converted to the carboxylic acids by hydrogenolysis or by means of sodium in liquid ammonia, as well as by acid or alkaline hydrolysis.[5] Please send for the free Technical Information Brochure on 3-alkyl-1-p-tolyltriazenes, which describes typical esterification procedures. 3-Alkyl-1-aryltriazenes also alkylate **phenols**[6,7] and **succinimide**[8] without a catalyst, and **alcohols,**[8] **enols**[8] and **mercaptans**[9] in the presence of $Al(OBu)_3$.

In addition our more powerful alkylating reagents, **Magic Methyl*** and **Magic Ethyl***, convert these esters to oxonium salts.[10] Amines, amides and carbamates are readily alkylated; and ethers, nitriles, sulfoxides and sulfides yield oxonium, nitrilium, sulfoxonium and sulfonium salts.[10,11]

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